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Access to molecular complexity. Multicomponent reactions involving five or more components

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The evaluation of the significance of a chemical transformation addresses many factors, including such important characteristics as the number of chemical bonds formed in one step, the reaction time, labour intensity, the cost of reactants and catalysts and so on. The amount of waste produced in the reaction has also gained increasing importance in recent years. Multicomponent reactions (MCRs) occupy a special place as a synthetic tool in modern organic chemistry. These reactions allow the synthesis of target products with complex structures, minimizing labour costs. This review summarizes the literature on multicomponent reactions involving five or more components. The data in the review are classified according to the number of reactants participating in the reaction and the types of reactions. It is worth noting that in some cases, these transformations can be a part of a domino process, making this classification difficult, if not impossible. The structural diversity of the reaction products greatly increases with increasing number of components involved in the MCR, which becomes virtually unlimited when using combinations of MCRs. This review highlights the main trends of past decades in the field of MCRs. The last two decades have witnessed an explosive growth in the number of publications in this area of chemistry.
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1. Introduction

With the growing interest for biologically active small molecules, the application of multicomponent reactions (MCRs) for the synthesis of compound libraries has been extensively developed in recent years.[1–6] According to the commonly accepted definition,[7] multicomponent reactions are a class of reactions where three or more starting molecules react to afford a product sharing most of the atoms of the original reactants. Multicomponent reactions involving several molecules of a single or several starting compounds are called pseudo-multicomponent reactions (Fig. 1).[8] It is worth noting that one-pot MCRs, for example, when one or several reactants are added to the reaction mixture after a while, without the isolation of intermediates, also belong to multicomponent processes, which increases the diversity of such transformations.[9–12] Multicomponent reactions have obvious advantages over conventional multistep syntheses. The 'ideal synthesis' should afford the desired product *via* a minimum number of steps in a high yield and in the absence of environmentally hazardous chemicals.[13] The efficiency of a chemical reaction depends on different factors: the reaction time and labour intensity, the cost of reactant, the overall product yield, operational simplicity and eco-friendliness.[14] Hence, the efficiency of multistep syntheses significantly decreases with increasing number of steps, whereas MCRs generally overcome most of the drawbacks inherent in multistep transformations. Multicomponent reactions are advantageous for the design of the synthesis due to high atom economy. Besides, MCRs require much smaller amounts of solvents and are energy-effective, thereby complying with principles of green chemistry.[15]

In terms of efficiency, MCRs represent a powerful tool for the construction of compounds with great structural diversity and high molecular complexity in one synthetic step. As applied to the design of biologically active compounds, this structural diversity allows for the high-throughput screening of large data arrays. It is no wonder that in the past decades, chemists developed MCRs which can be used to synthesize drugs and natural products,[16]

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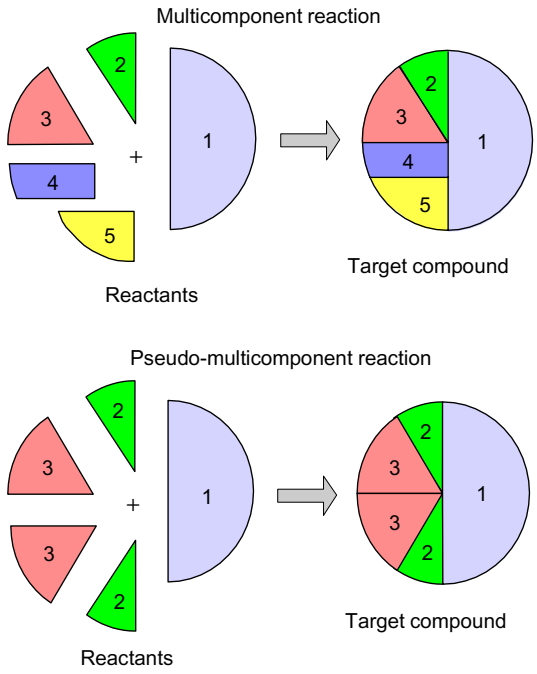


Figure 1. Schematic representation of multicomponent and pseudo-multicomponent reactions. 1 – 5 are starting reactants or their moieties.[6]

various heterocyclic compounds,[17 – 21] components for functional materials[22] and to design compound libraries with a high chemical diversity.[23 – 25]

Although molecular compound libraries can easily be produced using MCRs, these transformations generally afford the same molecular scaffolds. To overcome this drawback, MCR products are subjected to post-modification using click reactions, Diels – Alder cyclization, cross-coupling, *etc*.[26 – 29] An increase in the number of reaction components evidently leads to an increase in the structural diversity and makes it possible to address this issue.[30] For example, when varying one component in a three-component reaction, a combination of ten different starting reagents of each type results in the formation of 10^3 different compounds. Meanwhile, the variation of ten different starting compounds in a six-component reaction leads to an increase in the number of different products up to 10^6. The most important three- and four-component MCRs are Passerini and Ugi reactions. These reactions are well studied and described in numerous monographs and reviews.[1 – 36] The present review is devoted to MCRs involving five and more components.

The following abbreviations are used in the review:
All — allyl,
bmim — 1-n-butyl-3-methylimidazolium,
Boc — *tert*-butoxycarbonyl,
CAN — cerium(IV) ammonium nitrate,
Cat — catalyst,
Cbz — benzyloxycarbonyl,
CuAAC — copper(I)-catalyzed azide – alkyne cycloaddition,
DABCO — diazabicyclo[2.2.2]octane,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCM — dichloromethane,
DLP — dilauroyl peroxide,
dr — diastereomeric ratio,
Fc — ferrocenyl,
Fmoc — (fluoren-9-yl)methoxycarbonyl,
Fu — furyl,
HMDS — hexamethyldisilazide,
Hmim — 1-methylimidazolium,
Ind — indolyl,
MW — microwave irradiation,
Naph — naphthyl,
NCS — *N*-chlorosuccinimide,
NIS — *N*-iodosuccinimide,
NPs — nanoparticles,
PEG — polyethylene glycol,
Py — pyridyl,
rt — room temperature,
TFA — trifluoroacetate,
TfOH — trifluoromethanesulfonic acid,
TFP — tri(2-furyl)phosphine,
Th — thienyl,
TMS — trimethylsilyl,
Ts — *p*-toluenesulfonyl (tosyl),
US — ultrasonic irradiation.

2. Five-component reactions

2.1. Cycloaddition

A series of highly functionalized spirocyclic pyrrolidines were synthesized by a five-component reaction, involving [3 + 2]-cycloaddition of azomethine ylides to various bis(arylmethylidene)cycloalkanone derivatives as the key step (Scheme 1).[37] The reaction of bis(arylmethylidene)cycloalkanones, *o*-phenylenediamine, sarcosine, ninhydrin and hydrazine proceeds in methanol at reflux giving compounds **1** in 80% – 88% yields. The reaction is a complex sequence of transformations, the first step of which results in the formation of indenoquinoxalin-11-one **2** from ninhydrin and phenylenediamine (see Scheme 1). This is followed by the condensation of intermediate **2** with sarcosine and thermal decarboxylation of the latter giving 1,3-dipole — azomethine ylide **3**. The subsequent cycloaddition at one of the double bonds of the dipolarophile affords intermediate **4**, which reacts with hydrazine to give product **1** as a single diastereomer.

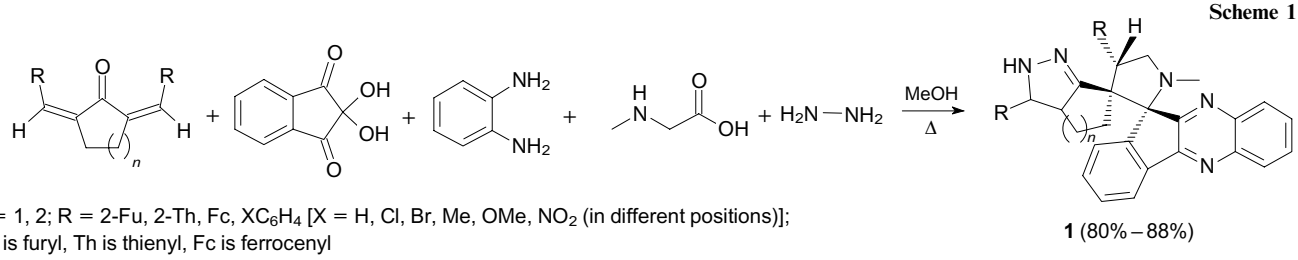
A similar approach to the synthesis of spiropyrrolidines **5** (Scheme 2)[38, 39] was based on the [3 + 2]-cycloaddition of azomethine ylides to a dipolarophile generated by the Knoevenagel reaction involving a malonic acid derivative and aryl carbaldehyde. Upon heating of a solution of the reactants in ethanol to 100 °C, products **5** were isolated in 55% – 92% yields. The reaction mechanism is similar to that described above with the difference that the latter reaction stops at the [3 + 2]-cycloaddition step. The use of indane-1,3-dione instead of cyanoacetic acid derivatives provides a route to derivatives with a spiropyrrolidine skeleton **6** (see Scheme 2), which were synthesized in high yields as single diastereomers.[40]

Recently, the first example of five-component reactions was reported, which involved two unstabilized azomethine ylides generated *via* decarboxylation of oxazolidin-5-ones. The double 1,3-dipolar cycloaddition was used in the diastereoselective synthesis of pyrrolidine-containing tetra-

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Current research interests: organofluorine chemistry, chirality, peptide synthesis, cyclic imines, click chemistry, multicomponent reactions, olefination, heterocyclic compounds.

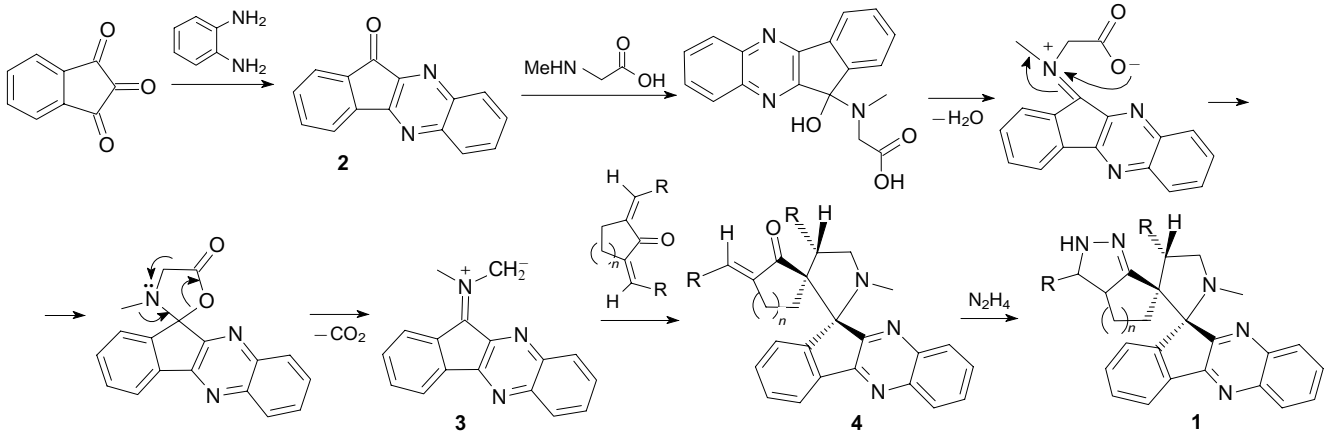
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Scheme 1



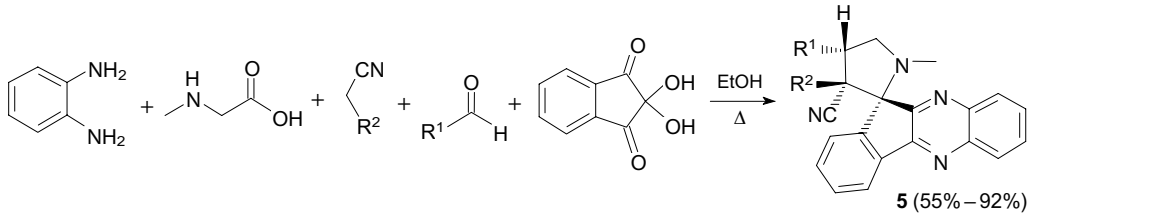
n = 1, 2; R = 2-Fu, 2-Th, Fc, XC_6H_4 [X = H, Cl, Br, Me, OMe, NO_2 (in different positions)];
Fu is furyl, Th is thienyl, Fc is ferrocenyl

1 (80% – 88%)

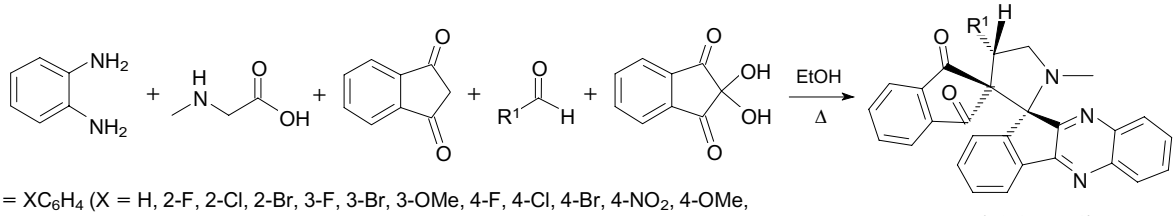


2 **3** **4** **1**

Scheme 2



5 (55% – 92%)



6 (80% – 92%)

R^1 = XC_6H_4 (X = H, 2-F, 2-Cl, 2-Br, 3-F, 3-Br, 3-OMe, 4-F, 4-Cl, 4-Br, 4-NO_2, 4-OMe, 4-Me), 2,4-$Cl_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 2-Fu, 2-Th, 1-Naph; R^2 = CN, CO_2Et, C(O)Ind-3; Naph is naphthyl, Ind is indolyl

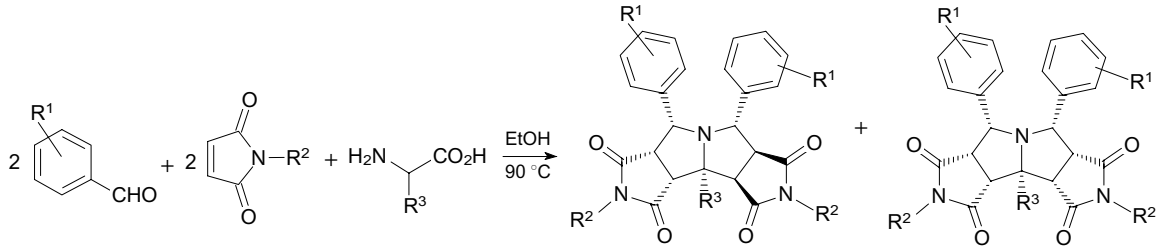
cyclic compounds (Scheme 3).[41] These compounds were isolated in yields of up to 93%. The diastereomeric ratio (*dr*) of products **7a** (major) and **7b** (minor) varies from 1 : 1 to 100 : 0. Apart from symmetrical structures, this reaction can afford unsymmetrical products when using two different aldehydes and different maleimide derivatives, thereby significantly extending the synthetic potential of this approach.

The five-component [3 + 2]-cycloaddition of azomethine ylides can be applied to prepare another type of interesting polycyclic compounds — triazolyl spirocyclic oxindole derivatives **8** (Scheme 4).[42] The reaction between acetylacetone, aryl azides, aromatic aldehydes, isatin and L-proline in the presence of 1,8-diazabicyclo[5.4.0]undecen-7-ene (DBU) as the catalyst in polyethylene glycol (PEG-400) at 80 °C affords desired products **8** in yields of up to 93%. The reaction mechanism can be represented as follows. Triazole **9**, which is generated from acetylacetone and azide in the presence of DBU (Dimroth reaction), undergoes aldol condensation with aromatic aldehyde giving chalcone derivative **10** (see Scheme 4). The condensation of isatin with L-proline affords spiro compound **11**; this is followed by decarboxylation to form dipole **12** and [3 + 2]-cycloaddition giving spirocyclic oxindoles **8**.

A similar pseudo-five-component reaction was performed using a chalcone component, which was synthesized in advance from terephthalaldehyde and acetophenone rather than was derived *in situ* (Scheme 5).[43] After the condensation of isatin derivatives with α,β-unsaturated ketone, two amino acid components (L-proline and sarcosine) were added to the reaction mixture, resulting in the formation of two series of bis(spirooxindolopyrrolidines) **13** and **14**, respectively, in high yields.

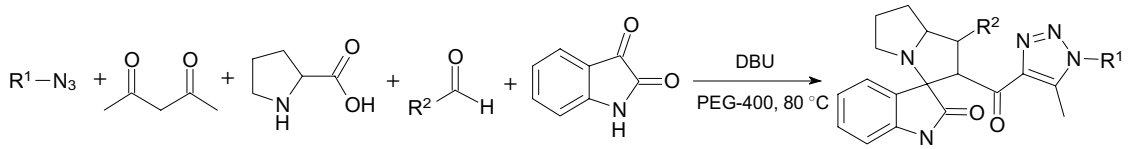
An efficient method for the synthesis of spirooxindolopyrrolizidine-linked 1,2,3-triazoles was based on the Cu^I-catalyzed five-component reaction of indane-1,3-diones, aldehydes, sarcosine, N-propargylated isatin and azides in PEG-400 as the reaction medium. The synthesis proceeds in a regio- and stereoselective manner and involves the Knoevenagel condensation giving alkene **15** and two

Scheme 3

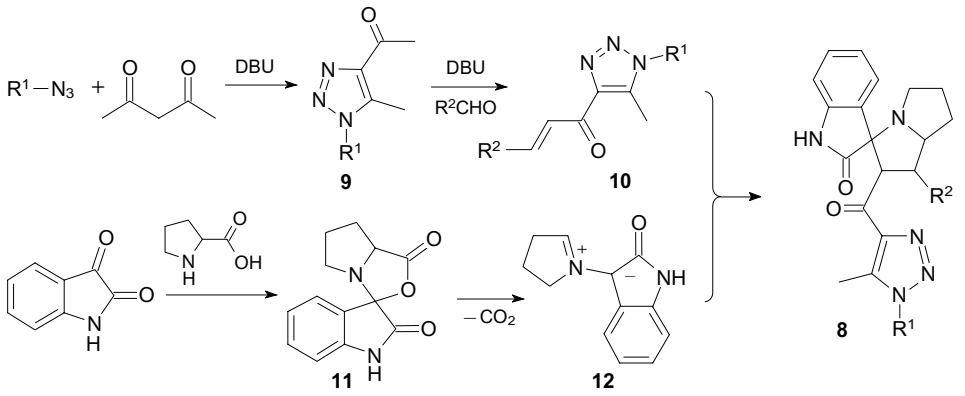


$R^1 = XC_6H_4$ (X = H, 4-Br, 4-CF_3, 4-F), 3-MeO-4-FC_6H_3, 2-Th, 4-Py; 3,4-$(MeO)_2C_6H_3$, 2-Fu, 2-Th, 1-Naph; R^2 = Me, Et, Bn; R^3 = H, Me, Pr^i, Bu^i, Ph, CH_2OH; Py is pyridyl

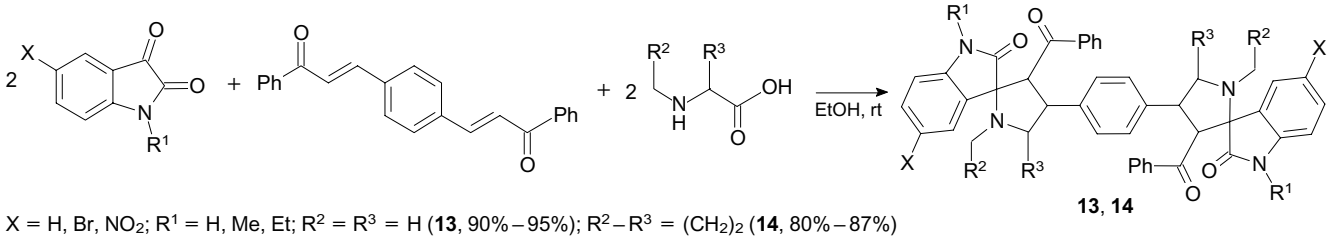
Scheme 4



$R^1 = 4\text{-}MeC_6H_4$, 4-$O_2NC_6H_4$, 4-BrC_6H_4, 3-Cl-4-FC_6H_3, 7-chloroquinoline;
$R^2 = 4\text{-}MeC_6H_4$, 4-$O_2NC_6H_4$, 4-BrC_6H_4

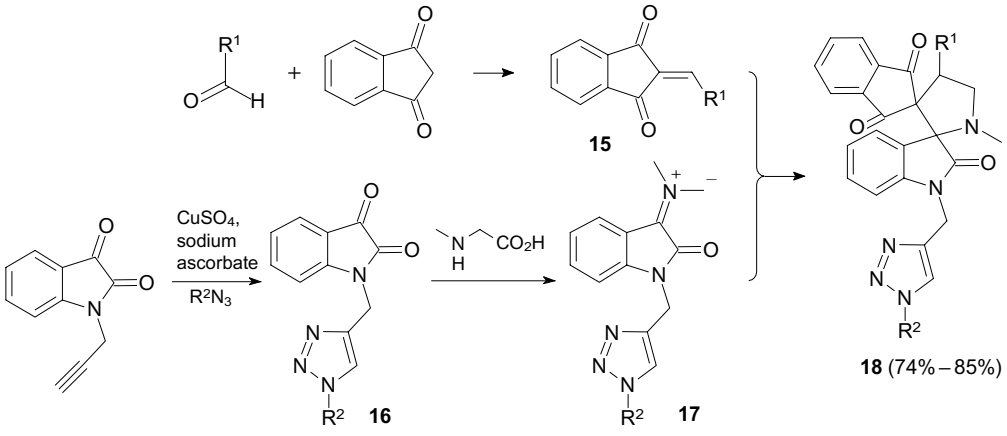


Scheme 5



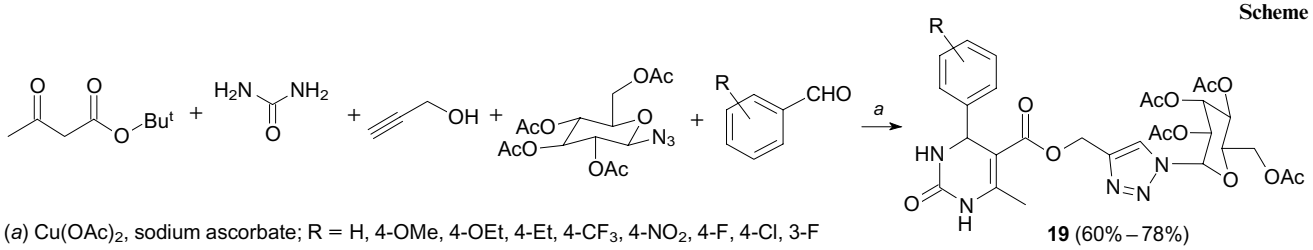
X = H, Br, NO_2; R^1 = H, Me, Et; $R^2 = R^3$ = H (**13**, 90% – 95%); $R^2 – R^3 = (CH_2)_2$ (**14**, 80% – 87%)

Scheme 6



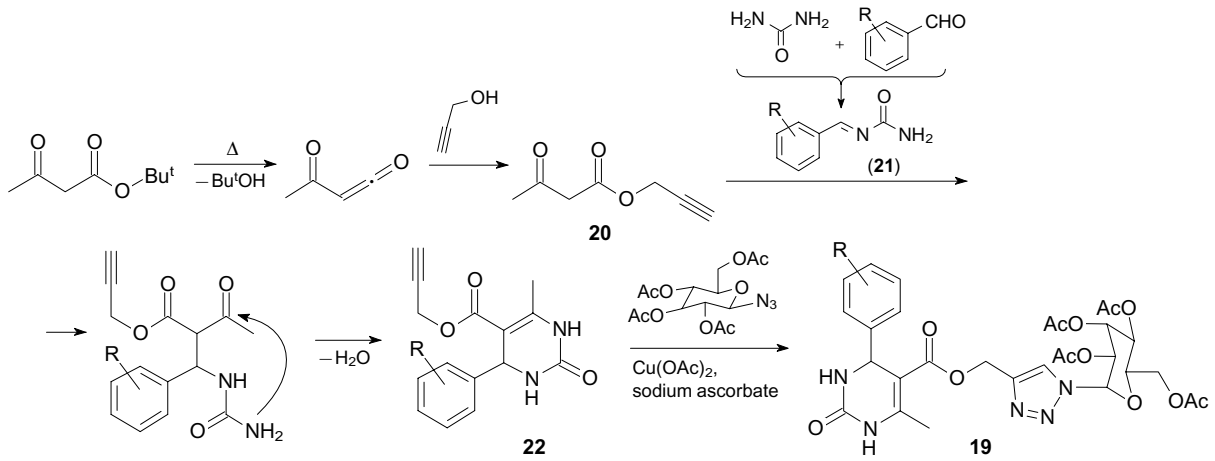
$R^1 = XC_6H_4$ (X = 4-Me, 4-F, 4-Cl, 4-Br, 4-CF_3, 4-NO_2), Bu^i, 3,4-$(CH_2OCH_2)C_6H_3$, 2-Fu;
$R^2 = YC_6H_4$ (Y = 4-Me, 4-F, 4-Cl, 4-OMe, 4-NO_2), Bu^n, 7-chloroquinoline

Scheme 7

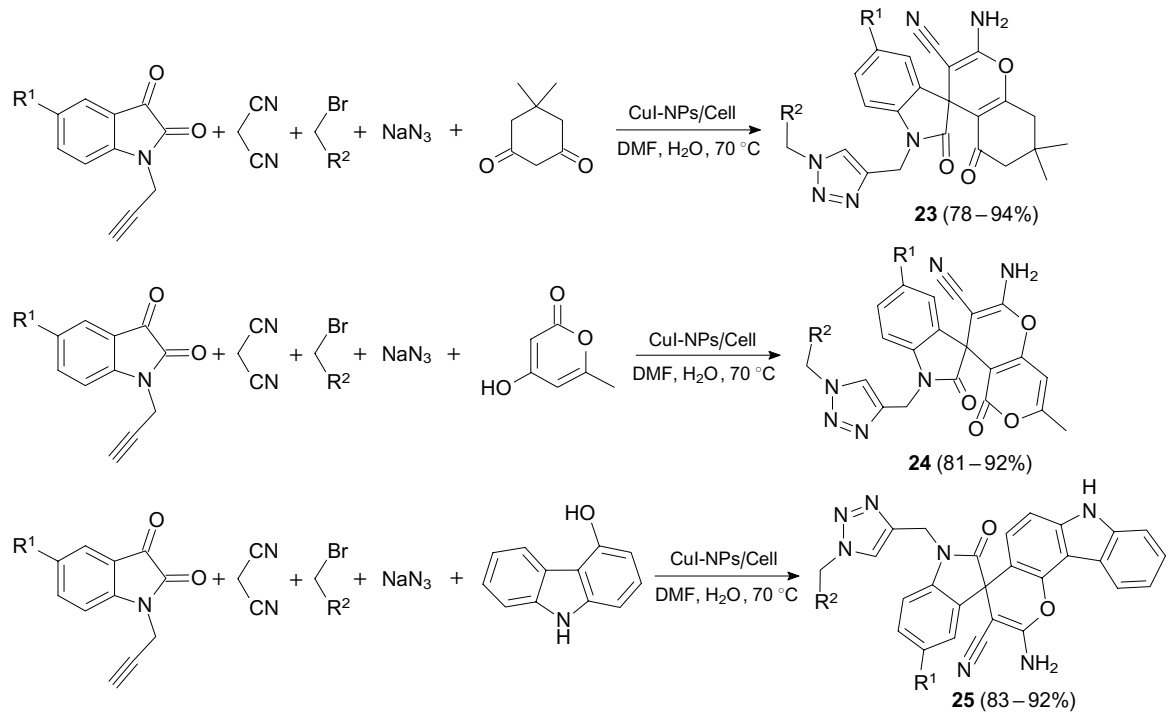


(*a*) $Cu(OAc)_2$, sodium ascorbate; R = H, 4-OMe, 4-OEt, 4-Et, 4-CF_3, 4-NO_2, 4-F, 4-Cl, 3-F

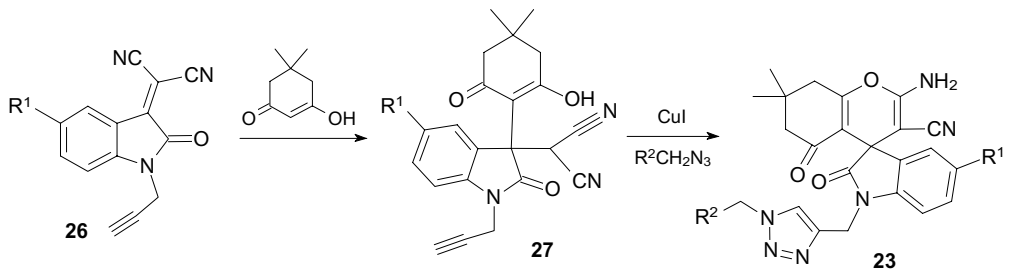
19 (60% – 78%)



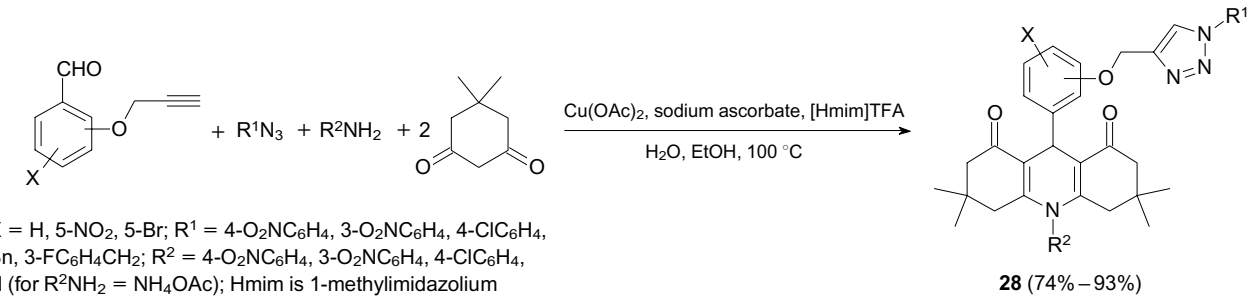
Scheme 8

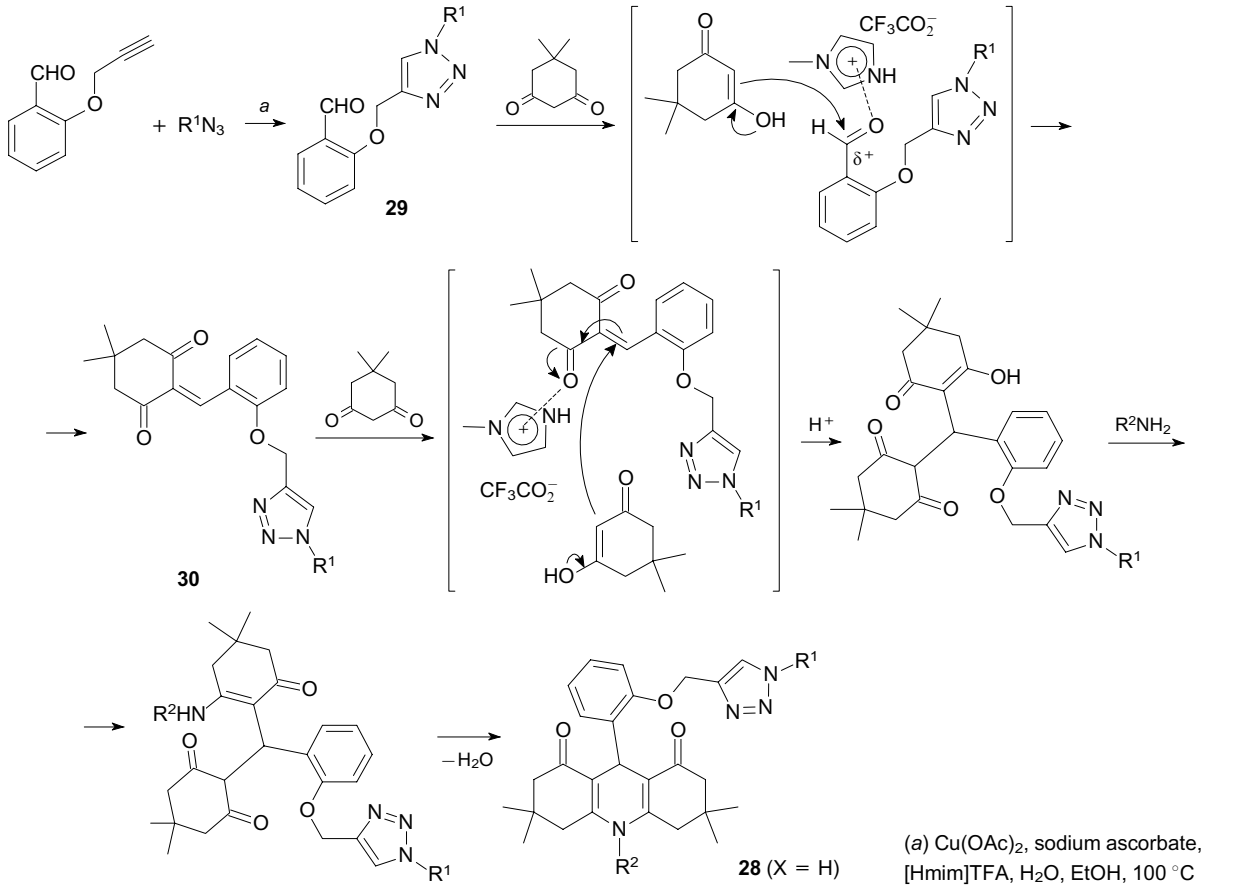


R^1 = H, F, Cl, Br, Me; R^2 = XC_6H_4 (X = H, 4-Me, 4-F, 4-Cl, 4-Br, 4-CN, 4-CF_3), 3,4,5-$(MeO)_3C_6H_2$, EtO_2C, Bu^s, n-C_5H_{11}



Scheme 9



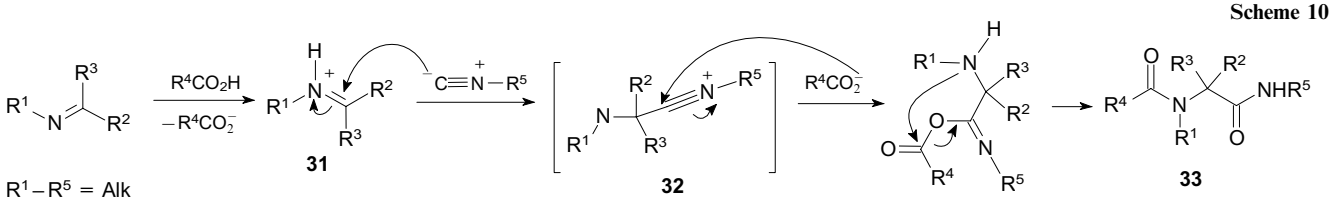


sequential 1,3-dipolar cycloaddition reactions.[44] The first reaction affords triazole derivatives of isatin **16** followed by the formation of dipole **17** and reaction of the latter with alkene **15**. Target spirocyclic derivatives **18** were synthesized in high yields (Scheme 6).

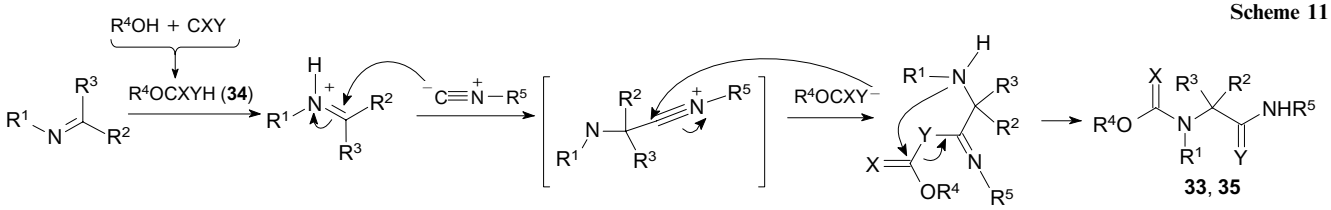
The copper(I)-catalyzed azide – alkyne cycloaddition (CuAAC) is a convenient method for the construction of the 1,2,3-trizole ring and is commonly used for the introduction of linkers into biologically active molecules. This advantage of CuAAC was employed by Dharma *et al.*[45] to produce glycoside-containing dihdropyrimidinone derivatives **19** by a five-component reaction (Scheme 7). The reaction between acetoacetic ester, urea, propargyl alcohol, substituted benzaldehyde and glucoside in aqueous medium in the presence of copper(II) acetate and sodium ascorbate gave target products **19** in good yields. The reaction involves the following sequence of transformations: transesterification – Biginelli reaction – CuAAC (see Scheme 7). The authors suggested that the first step affords propargyl acetoacetate **20**. Imine **21**, generated from urea and benzaldehyde, reacts with keto ester **20** to form dihdropyrimidinone derivative **22**, and the moiety of **22** containing the terminal triple bond is involved in the CuAAC reaction giving final product **19**.

The five-component approach to the synthesis of antitumour and antituberculosis drugs based on spirochromenocarbazoles **23** – **25** bearing the 1,2,3-triazole moiety was proposed by Sarkar and co-workers[46,47] (Scheme 8). The key step is CuAAC catalyzed by cellulose-supported CuI nanoparticles (7.4 mol.%) (CuI-NPs/Cell). The multicomponent reaction of R^1-substituted propargylisatins, malononitrile, bromides R^2CH_2Br and sodium azide in the presence of dimedone, 4-hydroxy-6-methylpyran-2(2*H*)-one or 3-hydroxycarbazole affords spirochromenocarbazoles **23**, **24** or **25** containing the 1,2,3-triazole moiety in yields of up to 94%. The following reaction mechanism was proposed (see Scheme 8 for the reaction with dimedone). Product **26** is initially generated *via* the Knoevenagel condensation of propargylisatin with malononitrile and then reacts with the enolic form of dimedone to form intermediate **27**. The latter enters into the CuAAC reaction with alkyl azide, generated *in situ* from R^2CH_2Br and sodium azide, giving final product **23**.

Scheme 10



Scheme 11



Another type of five-component reactions involving CuAAC refers to the synthesis of acridine derivatives **28** from propargyloxybenzaldehydes, azides, amines and dimedone in the presence of copper(II) acetate and sodium ascorbate (Scheme 9).[48] 1-Methylimidazolium trifluoroacetate ([Hmim]TFA) was used as the acid catalyst, which accelerated the assembly of the acridine skeleton. Target products **28** were prepared in high yields. It is worth noting that in the absence of [Hmim]TFA, the five-component reaction did not occur; under these conditions, the reaction afforded triazole as the addition product of azide to propargyloxybenzaldehyde. The process involves the formation of triazole **29**, which undergoes Knoevenagel condensation with dimedone in the presence of [Hmim]TFA to form compound **30** (see Scheme 9). This is followed by the Michael addition of the second dimedone molecule to unsaturated ketone **30** and the nucleophilic addition of amine. Finally, the cyclization and dehydration furnish desired product **28**.

2.2. Reactions involving isocyanides

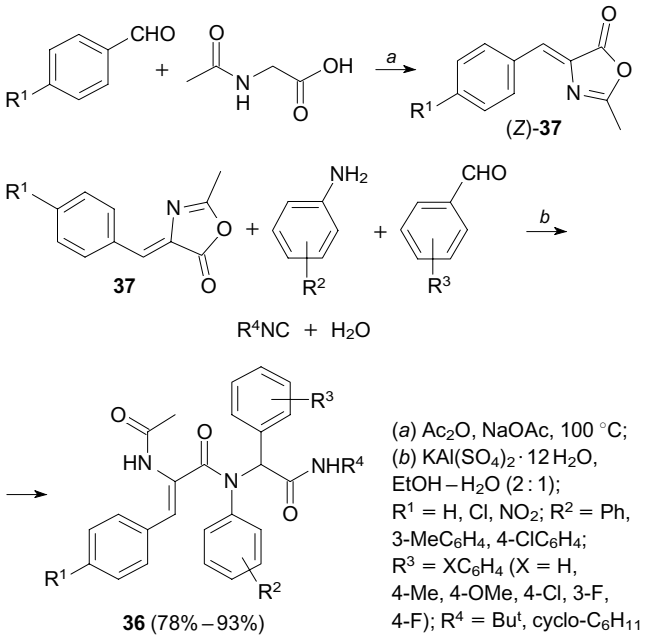
Multicomponent reactions involving isocyanides are among the most important types of MCRs. Due to the presence of a highly stable and reactive divalent carbon atom in the isocyano group, such compounds are very attractive building blocks. Despite the fact that isocyanides can be involved in radical reactions and undergo metallation, the most typical reactions with their participation are nucleophilic and electrophilic addition processes. This property underlies commonly used MCRs as the Ugi reaction, azido-Ugi reaction, Passerini and Michael reactions and some other.[49]

2.2.1. Ugi reaction

The four-component reaction of amine, a carbonyl compound (or imine), isocyanide and acid was discovered by Ivar Ugi in 1959 and, for more than 60 years, became one of the most commonly used multicomponent reactions.[50–55] The mechanism of the Ugi reaction involves the formation of iminium salt **31**, the addition of isocyanide to the latter and the subsequent addition of a carboxylate ion to intermediate **32** (Scheme 10). Finally, the acyl group migrates from the oxygen atom to nitrogen giving diamide **33** as the final product. Imine is generated *in situ* from amine and a carbonyl compound or can be prepared in advance.

The five-component version of the Ugi reaction was proposed back in 1961.[56] In this approach, CO_2 and alcohols form carbonic ester **34**, serving as a carboxyl component. This transformation proved to be a useful tool

Scheme 12

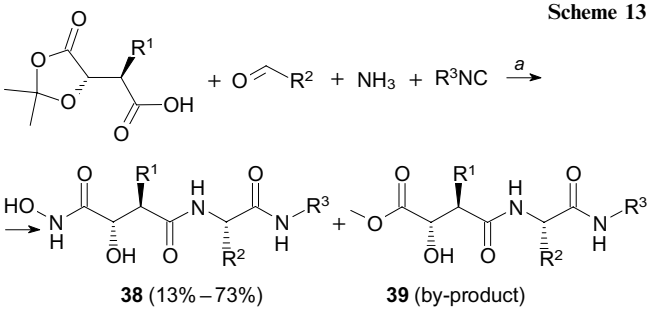


in the synthesis of *N*-(alkoxylcarbonyl)aminoamides, which can be synthesized in high yields using the most nucleophilic methanol. Other alcohols give products in much lower yields. Besides, it was shown that the utilization of CS_2 and COS in this reaction gave an unexpected result. The reaction with COS proceeds in a similar way giving thioamides **35** (Scheme 11); however, the use of CS_2 makes it impossible to accomplish this five-component transformation.[57]

The Ugi five-component reaction was applied to synthesize triamide derivatives **36** in an aqueous medium using oxazolones **37** as an acid component (Scheme 12).[58] Oxazolones **37** with a *Z* configuration were pre-synthesized from substituted benzaldehydes and 2-acetamidoacetic acid in acetic anhydride in the presence of sodium acetate. The Ugi reaction was performed in a mixture of ethanol and water in the presence of potassium alum; target triamides **36** were isolated in high yields. The role of potassium alum was not discussed in the cited publication. Apparently, they serve as an acid catalyst.

The synthetic potential of the Ugi reaction can be significantly increased by combining this reaction with other transformations in a one-pot manner. For example,

Scheme 13

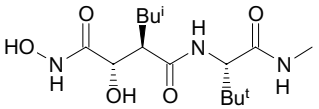


38 (13% – 73%) **39** (by-product)

(*a*) 1) MeOH, rt; 2) NH_2OH, rt; R^1 = Bu^t, $CH_2CH{=}CHPh$; R^2 = Bu^t, CMe_2All; R^3 = Pr^i, Bu^n, Bu^t, cyclo-C_6H_{11}, CH_2CO_2Me, Bn; All is allyl

analogues of marimastat **38**, serving as endothelial cell proliferation inhibitors, were synthesized using a five-component approach based on the Ugi reaction (Scheme 13).[59] The synthesis included the four-component reaction of alkylated malate acetonide, ammonia, aldehyde and isocyanide followed by the addition of hydroxylamine to the reaction mixture. The resulting hydroxamic acids **38** were isolated in yields from 13% to 73% as a mixture of diastereomers in a ratio of 1 : 1. In the reaction in the presence of excess ammonia, the ring opening of acetonide partially occurs *via* methanolysis and the formation of target compounds **38** is accompanied by the formation of methyl esters **39** as by-products. The formation of the latter can be suppressed using an exactly equivalent amount of ammonia.

Structure of marimastat

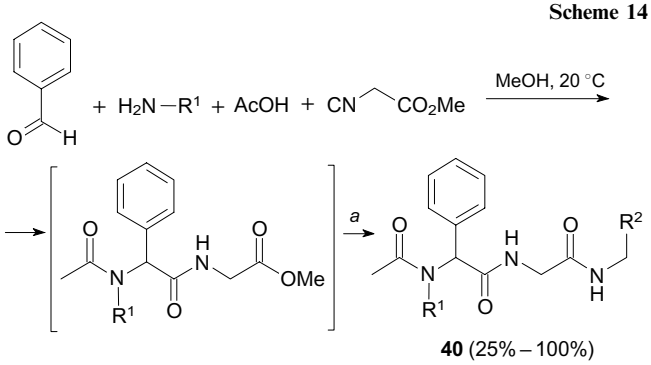


Marimastat

A combination of the Ugi four-component reaction with catalytic aminolysis was employed to synthesize diamides **40** (Scheme 14).[60] The aminolysis was performed at room temperature and catalyzed by Novozyme 435, immobilized lipase B from *Candida antarctica*. Target triamides **40** were isolated in moderate to quantitative yields using sufficiently nucleophilic amines.

Gesse and Müller[60] suggested combining this approach and the copper-catalyzed azide – alkyne cycloaddition or the Suzuki cross-coupling to prepare more complex triamide derivatives **41** and **42** (Scheme 15). For this purpose, the aminolysis was accomplished using amines containing an acetylene or *p*-iodophenylene moiety. Triamides **41** and **42** were synthesized by this six-component one-pot Ugi reac-

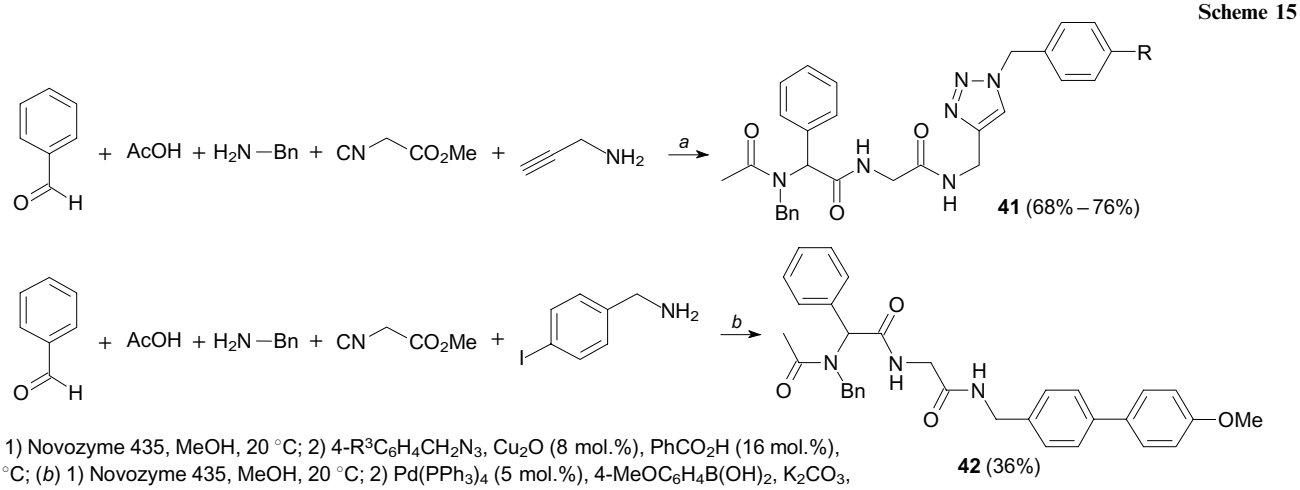
Scheme 14



40 (25% – 100%)

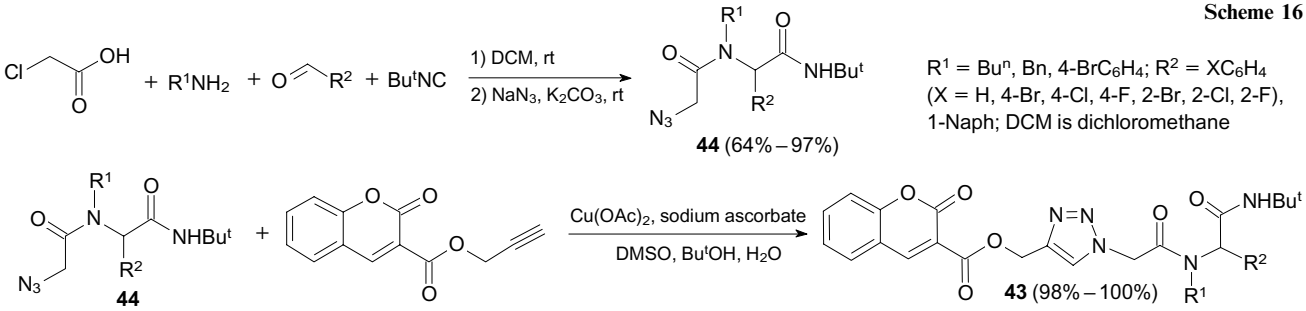
(*a*) $R^2CH_2NH_2$, Novozyme 435, MeOH, 20 °C; R^1 = XC_6H_4 (X = 3-Pr^i, 4-F, 4-Cl, 4-Br, 4-I), 3,5-$Me_2C_6H_3$, 2,6-$Pr^i_2C_6H_3$, 4-$YC_6H_4CH_2$ (Y = H, F, Cl, Br, I, OMe); R^2 = Bu^n, $HC{\equiv}CCH_2$, 4-$ZC_6H_4CH_2$ (Z = H, F, Cl, Br, I)

Scheme 15



(*a*) 1) Novozyme 435, MeOH, 20 °C; 2) 4-$R^3C_6H_4CH_2N_3$, Cu_2O (8 mol.%), $PhCO_2H$ (16 mol.%), 45 °C; (*b*) 1) Novozyme 435, MeOH, 20 °C; 2) $Pd(PPh_3)_4$ (5 mol.%), 4-$MeOC_6H_4B(OH)_2$, K_2CO_3, H_2O, 80 °C; R = H, F, Cl, Br, I

Scheme 16



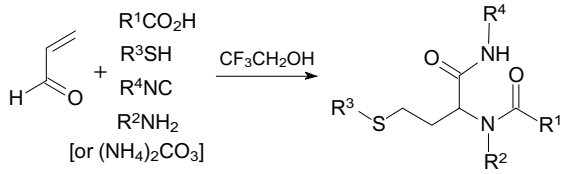
R^1 = Bu^n, Bn, 4-BrC_6H_4; R^2 = XC_6H_4 (X = H, 4-Br, 4-Cl, 4-F, 2-Br, 2-Cl, 2-F), 1-Naph; DCM is dichloromethane

tion – aminolysis – CuAAC and Ugi reaction – aminolysis – Suzuki reaction sequences, respectively.

The one-pot tandem of the Ugi reaction and nucleophilic substitution was applied to synthesize precursors of bio-hybrid amphiphiles of coumarin derivatives **43** (Scheme 16).[61] The five-component transformation provides a route to azide-containing amides **44** in high yields. The latter compounds were utilized as substrates in the CuAAC reaction for the synthesis of products **43**.

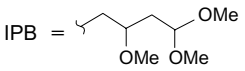
Peptides **45** and peptidomimetics **46** containing the methionine moiety were synthesized by the Ugi five-component reaction (Scheme 17).[62] The reaction of thiol, acid, isonitrile and acrolein with isopropylamine and aniline gave methionine-containing peptidomimetics **46**, whereas peptides **45** were prepared using ammonium carbonate as a source of ammonia.

Scheme 17



45: R^2 = H (24% – 33%);
46: R^2 = Pr^i, Ph (18% – 78%)

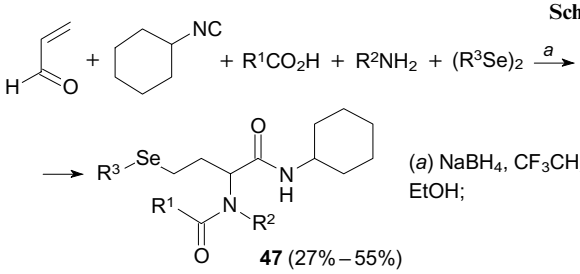
R^1 = Me, $CbzNHCH_2$; R^2 = H [for $(NH_4)_2CO_3$], Pr^i, Ph; R^3 = Et, Pr^n, All; R^4 = IPB, cyclo-C_6H_{11}; Cbz is benzyloxycarbonyl;

IPB = 

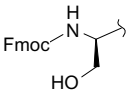
Peptidomimetics **47** containing a selenomethionine moiety were synthesized in moderate yields by a similar strategy (Scheme 18), but their yields were somewhat lower. In this case, selenols were generated *in situ* by the reduction of diselenides with sodium borohydride.

Another version of the five-component process, involving the nucleophilic addition and the Ugi reaction, was used to synthesize urea derivatives (Scheme 19).[63] Under solvent-free conditions, a series of diamides **48** containing a urea moiety were prepared in high yields.

Scheme 18



47 (27% – 55%)

R^1 = Me, $BocNHCH_2$,  ,  ; R^2 = H, Ph;

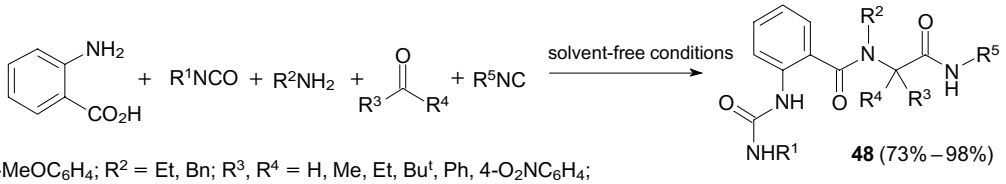
R^3 = Me, Ph; Boc is *tert*-butoxycarbonyl, Fmoc is (fluoren-9-yl)-methoxycarbonyl

S-Dipeptidouracil derivatives **49** were synthesized *via* a five-component domino process involving the nucleophilic addition and the Ugi reaction (Scheme 20).[64] This method complies with principles of green chemistry, because the process was performed in an ionic liquid — 1-n-butyl-3-methylimidazolium bromide ([bmim]Br). Besides, the authors significantly simplified the synthesis of *S*-dipeptidouracil derivatives **49** compared with the earlier approaches and reduced the reaction time to 30 min. Target products **49** were prepared in good yields. This transformation involves the alkylation of uracil with chloroacetic acid and the subsequent Ugi four-component reaction.

The reverse sequence, involving the Ugi reaction followed by the nucleophilic addition, was applied to synthesize 1,4-disubstituted piperazines **50** as potent transmembrane guanine nucleotide-binding regulatory protein receptor antagonists (Scheme 21).[65] The reaction was performed in a one-pot fashion. Target 1,4-disubstituted piperazines **50** were isolated as *E* isomers in high yields. The same approach was used to synthesize other enaminones.[66]

The five-component domino transformation based on the Ugi reaction – nucleophilic addition sequence proved to be

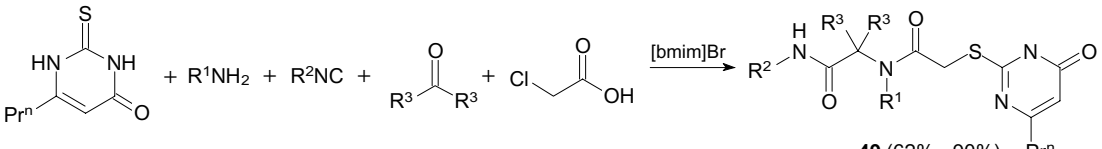
Scheme 19



48 (73% – 98%)

R^1 = Ph, 4-$MeOC_6H_4$; R^2 = Et, Bn; R^3, R^4 = H, Me, Et, Bu^t, Ph, 4-$O_2NC_6H_4$; $R^3 – R^4$ = $(CH_2)_4$, $(CH_2)_5$; R^5 = $Bu^tCH_2CMe_2$, cyclo-C_6H_{11}

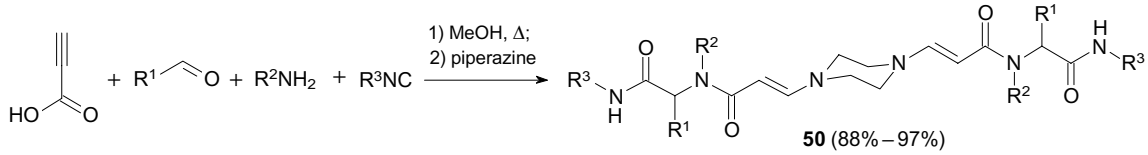
Scheme 20



49 (62% – 90%)

R^1 = Et, Pr^i, Bn; R^2 = Bu^t, cyclo-C_6H_{11}; R^3 = Me, Et; $R^3 – R^3$ = $(CH_2)_4$

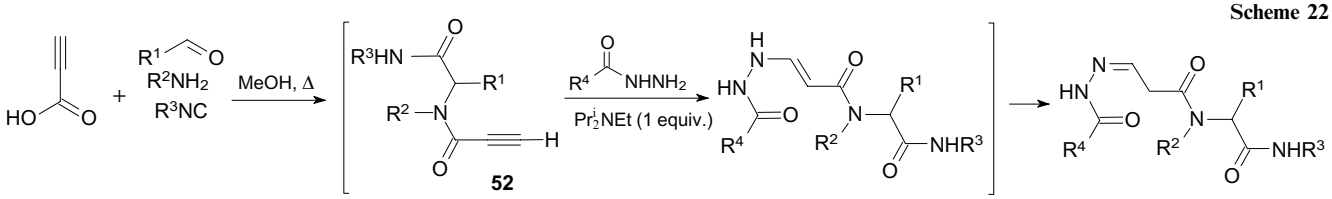
Scheme 21



50 (88% – 97%)

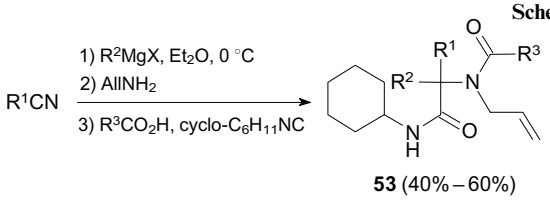
R^1 = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 2-Th; R^2 = Ph, 4-BrC_6H_4, All; R^3 = Bu^t, cyclo-C_6H_{11}

Scheme 22



R^1 = Ph, 2-Th; R^2 = Ph, 4-Pr^{i}C$_6$H$_4$; R^3 = Bu^t, cyclo-C$_6$H$_{11}$; R^4 = Me, Ph, 2-Th

Scheme 23



R^1 = Et, Ph; R^2 = Ph, Bu^n; R^3 = Pr^i, CH = CHPh; X = Cl, Br

successful for the synthesis of highly functionalized pseudopeptides **51** using propiolic acid. The addition of hydrazides at the activated triple bond of Ugi intermediates **52** was performed in the presence of diisopropylethylamine as the activator (Scheme 22).[67] The corresponding hydrazones, generated through tautomeric conversion of primary Michael addition products, were isolated in moderate yields.

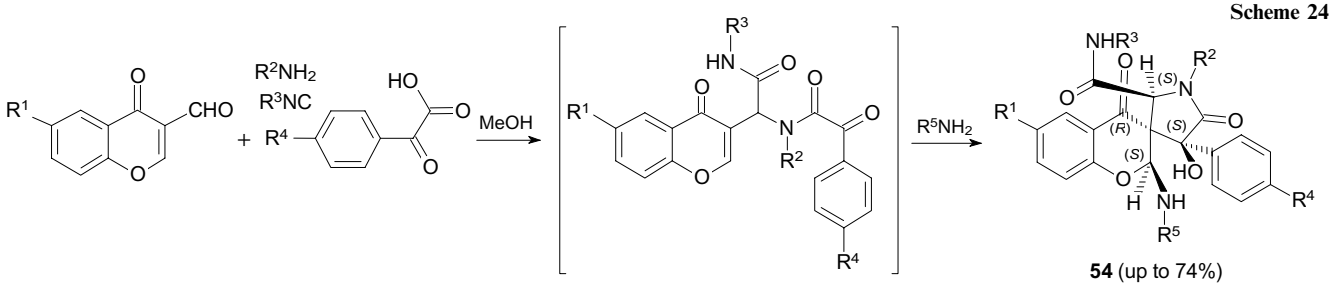
A range of substrates in the Ugi reaction was increased using addition products of Grignard reagents to nitriles (Scheme 23).[68] In one-pot conditions, an organomagnesium compound first reacted with nitrile then allylamine was added to the reaction mixture and then carboxylic acid and isocyanide were added. Diamides **53** were prepared in moderate yields.

The Ugi four-component reaction followed by one-pot amination was adapted to the synthesis of highly functionalized polycyclic compounds (Scheme 24). Spiropyrrolidinonechromanone derivatives **54** were isolated as a mixture of two of eight possible diastereomers.[69]

A five-component combination of the Knoevenagel and Ugi reactions was successfully applied to synthesize coumarin derivatives **55** (Scheme 25).[70] In this procedure, Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) and salicylaldehyde were first mixed in ethanol to prepare coumarin-3-carboxylic acid **56** and then amine, aldehyde and isocyanide were added. The resulting coumarin-containing diamides **55** were isolated in high yields. Some of these compounds exhibit high antimicrobial activity.

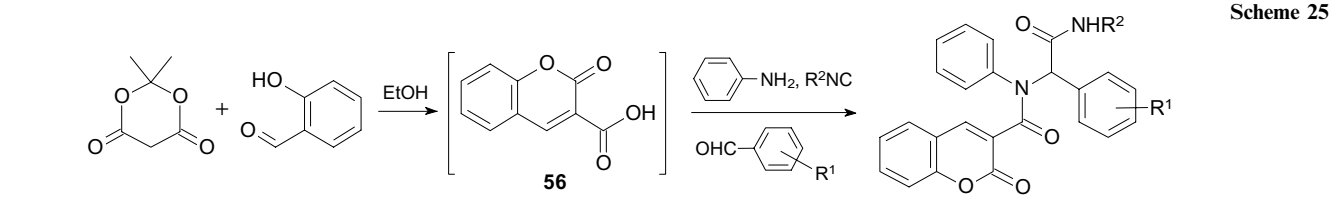
3-Triazolylquinolin-2-(1*H*)-ones **57** were synthesized using a more complex combination of the Ugi and Knoeve-

Scheme 24



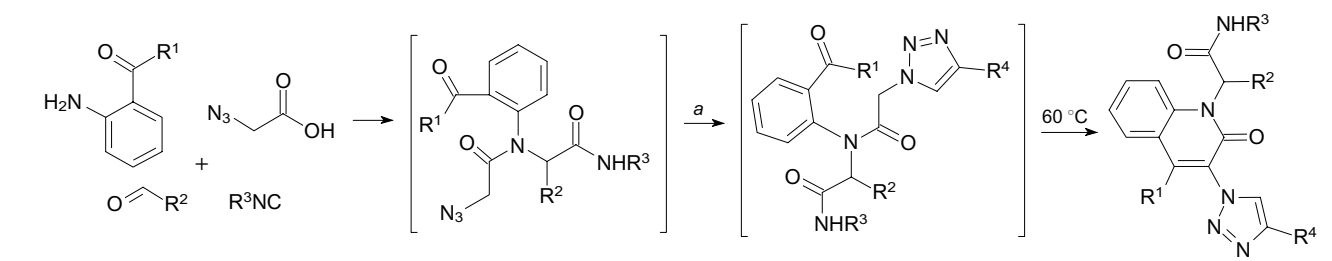
R^1 = H, Me; R^2 = Ph, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, Bn; R^3 = Bu^t, cyclo-C$_6$H$_{11}$, 2,6-Me$_2$C$_6$H$_3$; R^4 = H, MeO; R^5 = Bn, 3-ClC$_6$H$_4$CH$_2$, 4-ClC$_6$H$_4$CH$_2$, cyclo-C$_5$H$_9$OCH$_2$, (*S*)-PhCH(Me), 3,4-(OCH$_2$O)C$_6$H$_3$CH$_2$

Scheme 25



R^1 = H, 2-OMe, 4-Me, 4-OH, 3-OH, 2-OH, 2-NO$_2$; R^2 = Bu^t, cyclo-C$_6$H$_{11}$

Scheme 26

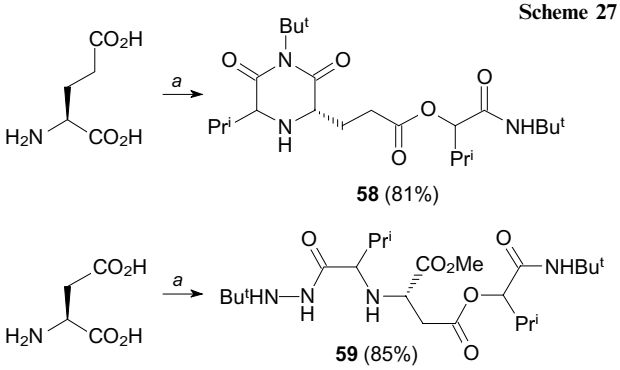


(*a*) R^4C≡CH, Cu(OAc)$_2$, Et$_3$N, sodium ascorbate; R^1 = Me, Ph; R^2 = 4-XC$_6$H$_4$ (X = H, CN, Cl, OMe), cyclo-C$_6$H$_{11}$; R^3 = Bu^t, cyclo-C$_6$H$_{11}$; R^4 = 4-YC$_6$H$_4$ (Y = H, NO$_2$, Cl, OMe), cyclo-C$_6$H$_{11}$

nagel reactions, involving the click condensation to form the triazole ring (Scheme 26).[71] This approach consists of the one-pot sequence of the Ugi four-component reaction, acetylene – azide cycloaddition in the presence of copper(II) acetate and sodium ascorbate and the intramolecular Knoevenagel-type condensation (Camps cyclization).

The Ugi and Passerini domino reaction using L-glutamic or L-aspartic acid, isobutyraldehyde and *tert*-butyl isocyanide as the starting compounds affords depsipeptides **58** and **59** in 81% and 85% yields, respectively (Scheme 27).[72] The reaction with glutamic acid was accompanied by lactamization giving piperazine-2,6-dione **58**, while compound **59** was isolated as a mixture of four diastereomers in a ratio of 5.0 : 2.7 : 1.3 : 1.0.

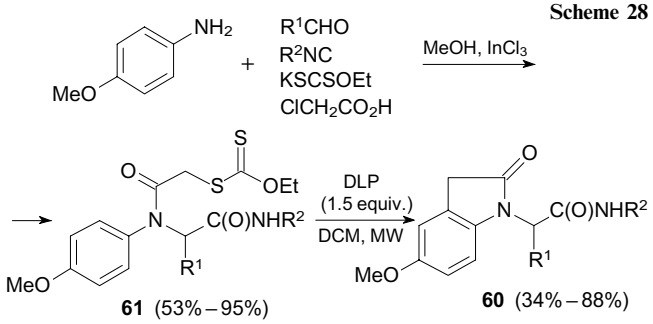
Scheme 27



(*a*) Pr^iCHO (2 equiv.), Bu^tNC (2 equiv.), MeOH

2-Oxindole derivatives **60** were synthesized *via* radical *ortho*-cyclization of products of the sequential Ugi five-component reaction and nucleophilic substitution with potassium ethyl xanthate (Scheme 28). The use of chloroacetic acid opens up a possibility to perform nucleophilic substitution in the resulting Ugi adducts giving target sulfur-containing derivatives **61** in yields of up to 95%. The subsequent radical cyclization occurs in the presence of dilauroyl peroxide (DLP) in dichloromethane or under microwave irradiation (MW). This transformation occurs in a selective manner and generally with high product yields.[73]

Scheme 28

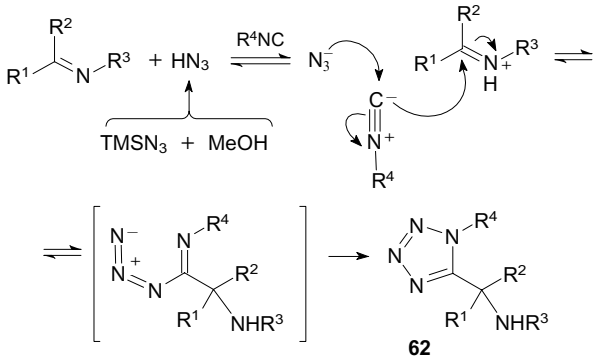


R^1 = Pr^i, Bu^t, Ph, 4-ClC_6H_4; R^2 = Bu^t, cyclo-C_6H_{11}, 2,6-$Me_2C_6H_3$

2.2.2. Azido-Ugi reaction

The azido-Ugi reaction is a modification of the classical Ugi reaction, in which hydrazoic acid is used instead of carboxylic acid (Scheme 29). This reaction affords the corresponding 1,5-disubstituted tetrazole **62**. Generally, the azido-Ugi reaction is performed in alcohols and, therefore, hydrazoic acid is generated *in situ* from trimethylsilyl azide ($TMSN_3$) and alcohol (methanol is used most often).

Scheme 29

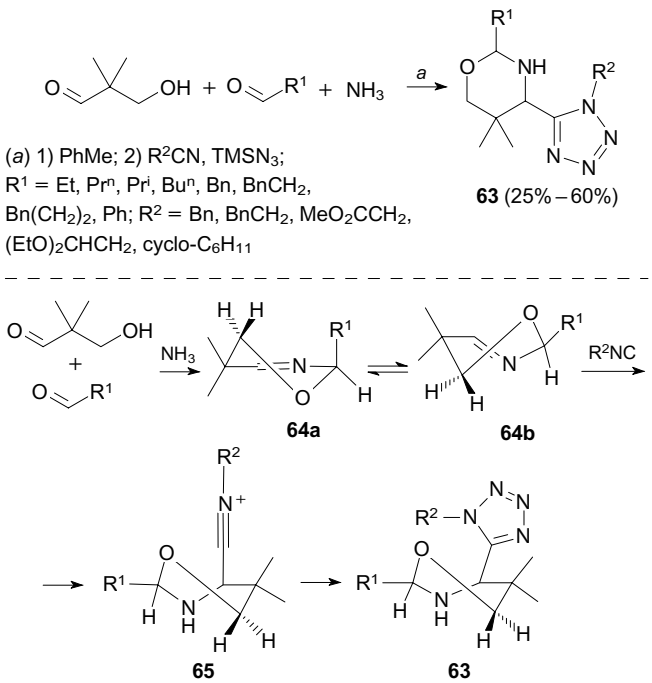


62

Tetrazoles are bioisosteres of carboxylic acids, and 1,5-disubstituted tetrazoles are bioisosteres of the *cis*-amide bond in peptides, possessing much higher metabolic stability and comparable biological activity.[74] Due to this property, tetrazoles are in high demand in medicinal chemistry.[75] Multicomponent reactions, in particular the azido-Ugi reaction, are the simplest and most generally applied approaches to the assembly of the tetrazole ring.[76–80]

Dömling and co-workers[81] used the azido-Ugi five-component reaction to synthesize tetrazole-containing 1,3-oxazines (Scheme 30). They prepared 4-(tetrazol-5-yl)-1,3-oxazines **63** in moderate yields and with high diastereoselectivity (the diastereomeric ratio varied from 78 : 22 to 96 : 4). High diastereoselectivity is attributed to the reaction mechanism. The first step is the reaction of aldehyde, ammonia and 3-hydroxypivaldehyde (see Scheme 30). This is followed by the transformation of asymmetrically substituted 5,6-dihydro-2*H*-1,3-oxazine adopting a half-chair conformation **64a**,**b**, conformer **64a** being energetically more favourable. Then isocyanide attacks 5,6-dihydro-2*H*-1,3-oxazine from the axial side to form intermediate **65** and the latter reacts with an azide ion giving target product **63**. The diastereomeric ratio directly depends on steric hin-

Scheme 30

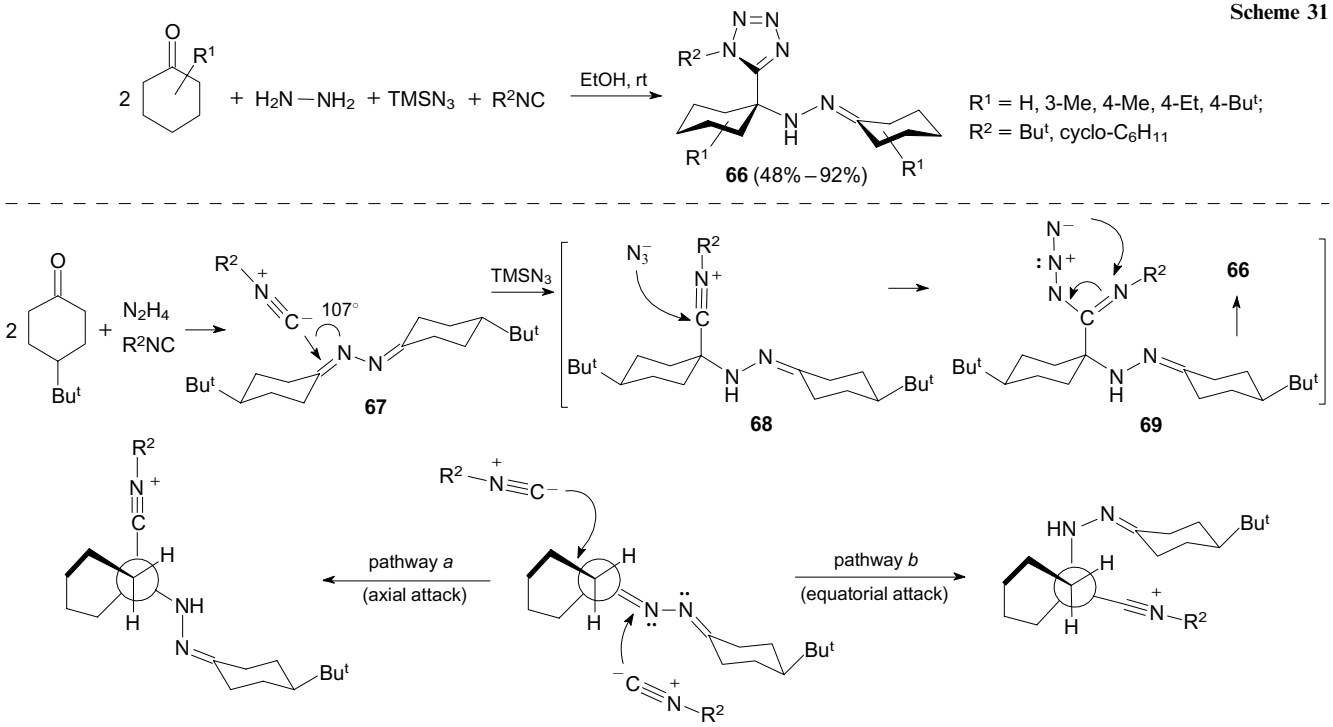


(*a*) 1) PhMe; 2) R^2CN, $TMSN_3$;
R^1 = Et, Pr^n, Pr^i, Bu^n, Bn, $BnCH_2$, $Bn(CH_2)_2$, Ph; R^2 = Bn, $BnCH_2$, MeO_2CCH_2, $(EtO)_2CHCH_2$, cyclo-C_6H_{11}

63 (25% – 60%)

64a **64b** **65** **63**

Scheme 31

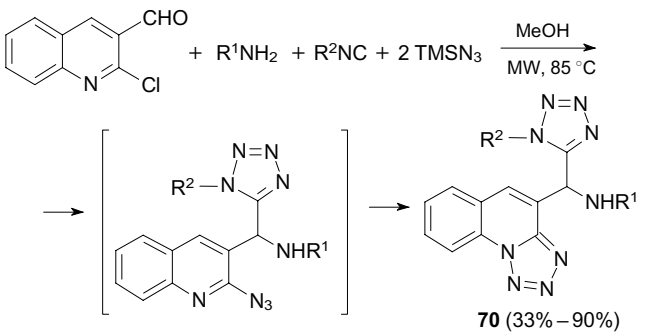


drance of the starting aldehyde and isocyanide molecules. Attempts to utilize ketones as a carbonyl component failed.

Another example of the diastereoselective azido-Ugi pseudo-five-component reaction was described by Rominger and co-workers [82] (Scheme 31). α-Hydrazine-substituted tetrazoles **66** were prepared as single diastereomers in good yields by the reaction of substituted cyclohexanones (2 equiv.), hydrazine (1 equiv.), isocyanide (1 equiv.) and trimethylsilyl azide (1 equiv.) as a source of hydrazoic acid in ethanol. It was noted that the use of sodium azide instead of TMSN leads to a significant decrease in the product yield, whereas methanol can be used instead of ethanol with equal success. The reaction mechanism involves the formation of azine **67** in the first step followed by its protonation and sequential attacks of isocyanide (to form compound **68**) and an azide ion. The resulting intermediate **69** undergoes cyclization giving final product **66** (see Scheme 31). All products adopt an *S*,*E* configuration, which was confirmed by X-ray diffraction. The key step responsible for the spatial structure of the target α-hydrazine tetrazole is the attack of isocyanide on azine either from the axial (pathway *a*) or the equatorial side (pathway *b*) (see Scheme 31). The authors stated that the equatorial attack is accompanied by increased torsion strain due to the interaction between the hydrazone moiety and β-C—H protons in the eclipsed conformation and also due to lower thermodynamic stability of the product. Hence, this attack is unlikely, and the axial attack takes place. Besides, according to Cieplak's model,[83] the axial addition of isocyanide is more favourable due to a stabilizing orbital interaction (the C—H bond is more donating compared to the C—C bond).

Tetrazole derivatives of quinoline **70** were synthesized *via* the pseudo-five-component azido-Ugi reaction – aromatic nucleophilic substitution (S_NAr) – azido tautomerization sequence (Scheme 32).[84] The microwave-mediated synthesis at 85 °C affords target tetrazolo[1,5-*a*]quinolines in yields of up to 90%.

Scheme 32



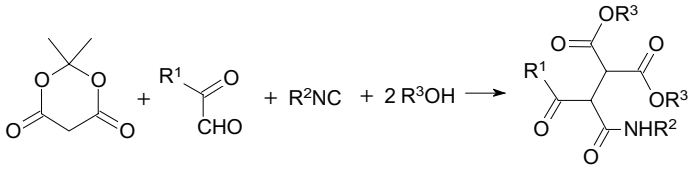
R^1 = Bu^n, cyclo-C_6H_{11}, All, $CH{\equiv}CCH_2$, Bn, 4-$MeOC_6H_4CH_2$, Ph, 2-$FuCH_2$; R^2 = Bu^t, cyclo-C_6H_{11}, Bn, 4-$MeC_6H_4(CH_2)_2$, 3,4-$Me_2C_6H_3(CH_2)_2$

2.2.3. Reactions with Michael acceptors

A large class of organogelators based on dialkyl 2-[1-(alkylamino)-1,3-dioxo-3-phenylpropan-2-yl]malonates **71** was synthesized by the pseudo-five-component reaction involving Meldrum's acid (Scheme 33).[85] Alcohols containing a long unbranched alkyl substituent are mainly used as nucleophilic components because they proved to be the best gelling agents. Target products **71** were isolated in yields of up to 83%. The plausible reaction mechanism (see Scheme 33) involves the Knoevenagel condensation of aryl glyoxal and Meldrum's acid giving α,β-unsaturated derivative **72** followed by the formation of intermediate **73**, resulting from the addition of isonitrile to an activated double bond, and the cyclization to iminolactone **74**. The subsequent transformation of **74** into unstable aminofuran **75** followed by the attack of an alcohol affords intermediate **76**. The substituted furan ring in **76** is cleaved to form compound **77**, which reacts with the second alcohol molecule and undergoes tautomerization giving final product **71**.

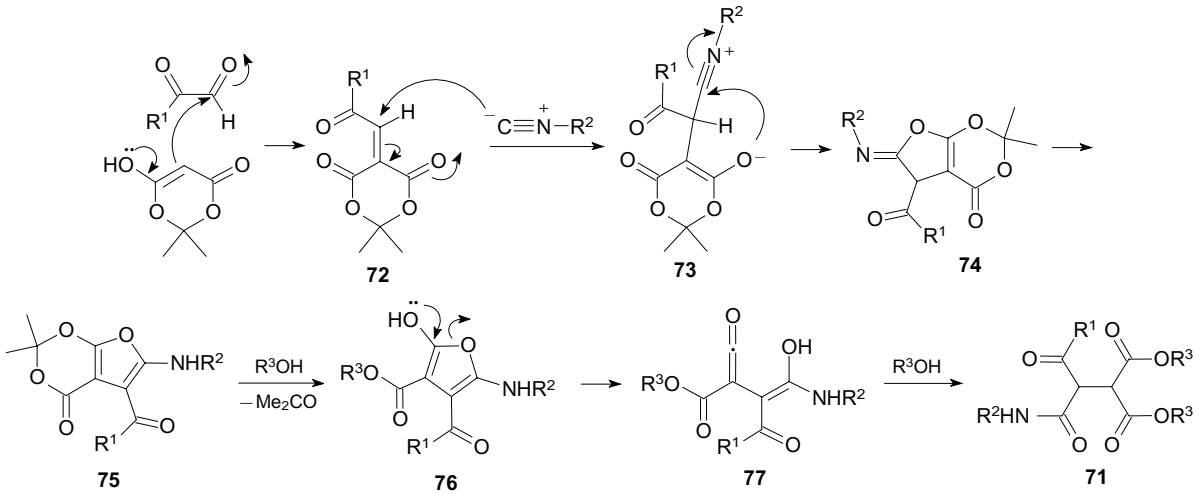
A similar pseudo-five-component reaction with Meldrum's acid was used to synthesize pseudopeptides **78** based on malonic ester, which were also studied as gelators

Scheme 33



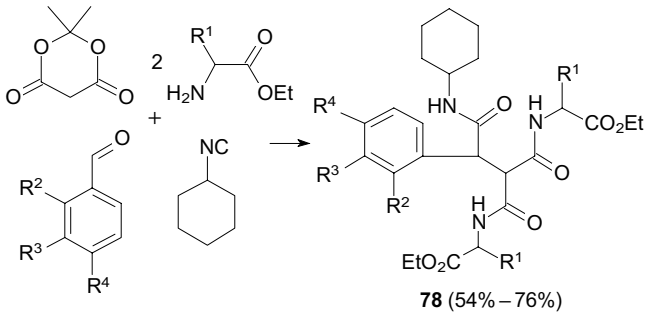
71 (24% – 83%)

R^1 = Bn, 4-$MeOC_6H_4$, 4-(cyclo-C_6H_{11})C_6H_4; R^2 = cyclo-C_6H_{11}, $Bu^tCH_2CMe_2$; R^3 = Me, Et, Pr^i, Bu^n, Bu^t, n-C_5H_{11}, n-C_6H_{13}, n-C_8H_{17}, n-$C_{12}H_{25}$, n-$C_{14}H_{29}$, cyclo-C_6H_{11}, All, 9-fluoryl



72 **73** **74** **75** **76** **77** **71**

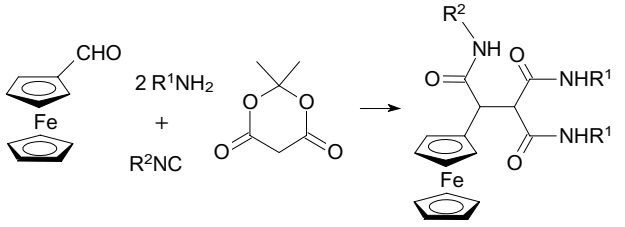
Scheme 34



78 (54% – 76%)

R^1 = H, Bn; R^2 = H, Cl; R^3 = H, OMe; R^4 = H, Cl, OMe

Scheme 35



79 (73% – 95%)

R^1 = XC_6H_4 (X = H, 2-Me, 4-Me, 4-Et, 3-NO_2, 4-OH), Bn, All, 1-Naph, 2-Naph, BzNH, 4-$ClC_6H_4C(O)NH$; R^2 = Bu^t, cyclo-C_6H_{11}, $Bu^tCH_2CMe_2$, $Ph(CH_2)_3$, 2,6-$Me_2C_6H_3$, 1-Naph, MeO_2CCH_2, Ts; Ts is *p*-toluenesulfonyl (tosyl)

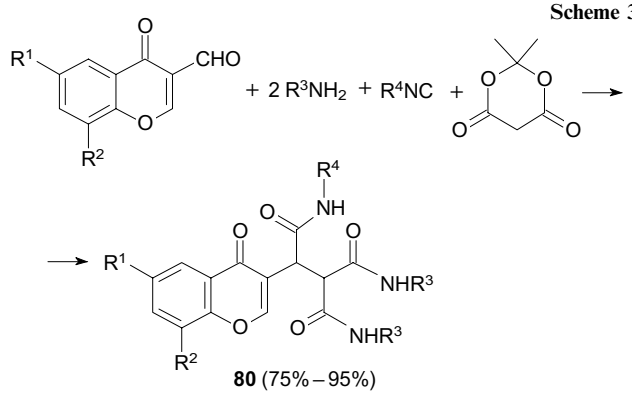
(Scheme 34).[86] In this case, the amino acids glycine and phenylalanine served as nucleophiles. Target products **78** were isolated in moderate yields. The reaction mechanism is similar to that described above with the difference that the addition of amino acids at the amino group occurs instead of the addition of alcohol.

The synthesis of ferrocene – triamide conjugates **79** by the pseudo-five-component reaction involving Meldrum's acid was described by Teimouri and Akbari-Moghaddam [87] (Scheme 35). The general character of the reaction was demonstrated for a wide range of aliphatic and aromatic isocyanides and amines. Ferrocene – triamide conjugates **79** were obtained in high yields regardless of the steric and electronic factors in the reactants.

A similar pseudo-five-component reaction was examined using 3-formylchromones (Scheme 36),[88] and a series of chromone-containing peptidomimetics **80** were synthesized in high yields. These compounds are of interest in drug design.

Another modification of the five-component reaction using Meldrum's acid involved substituted 2-benzylidenemalononitrile (Scheme 37).[89] The efficiency of this trans-

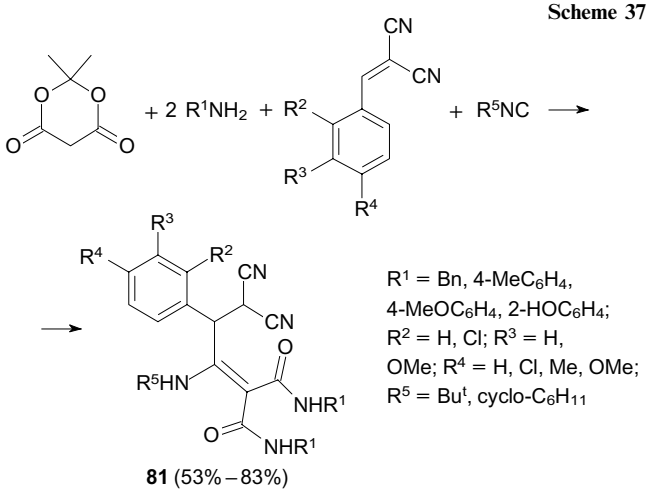
Scheme 36



80 (75% – 95%)

R^1 = H, Me, Cl; R^2 = H, Cl; R^3 = XC_6H_4 (X = H, 2-Me, 4-Me, 4-Et, 2-NO_2, 3-NO_2, 4-F), 2,6-$(MeO)_2C_6H_3$, 1-Naph; R^4 = Bu^t, cyclo-C_6H_{11}, $Bu^tCH_2CMe_2$, $Ph(CH_2)_3$, 2,6-$Me_2C_6H_3$, MeO_2CCH_2, Ts

Scheme 37



formation was demonstrated in relation to maleimide derivatives; target products **81** were isolated in high yields.

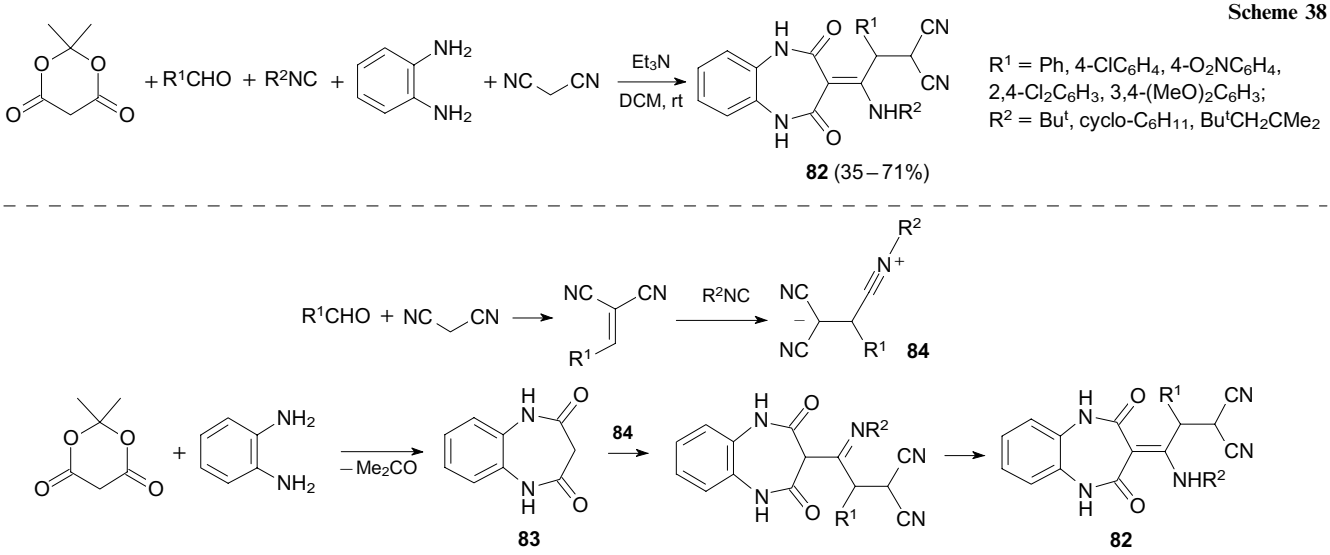
The five-component synthesis of diazepine derivatives was performed based on the reaction of Meldrum's acid, benzaldehyde, isonitrile, malononitrile and *o*-phenylenediamine (Scheme 38).[90] The treatment of the reaction mixture with triethylamine affords target heterocycles **82** in yields of up to 71%. The plausible mechanism of the synthesis involves the formation of intermediate **83** from *o*-phenylenediamine and Meldrum's acid. This intermediate reacts with zwitterion **84**, which is generated *via* sequential Knoevenagel and Michael reactions. Finally, the tautomerization affords target benzodiazepine **82** (see Scheme 38).

Alkylidene-substituted Meldrum's acid was used in the synthesis of spirocyclic structures (Scheme 39).[91] The reaction of this activated alkene, isocyanide and bisaniline in a molar ratio of 2 : 2 : 1 affords the corresponding symmetrical carboxamides **85** in yields of up to 81%. The first step is the addition of isocyanide to a Meldrum's acid derivative to form spirocyclic intermediate **86** (see Scheme 39). Then compound **86** (2 equiv.) reacts with dianilide and, after the elimination of acetone, gives product **85.**

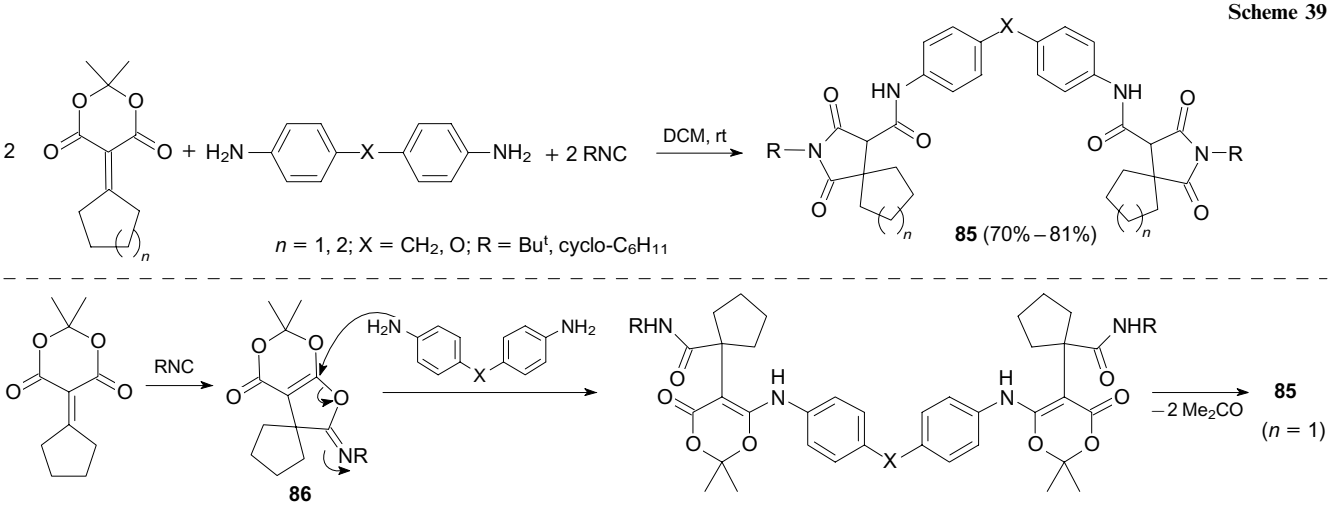
2.2.4. Miscellaneous reactions with isocyanides

Apart from the synthesis of diamides, tetrazoles and malononitrile derivatives, multicomponent reactions based on isocyanides are extensively used in the synthesis of polycyclic compounds. Adib *et al.*[92] described the pseudo-five-component approach to the diastereoselective synthesis of substituted 3-oxacyclobuta[*cd*]pentalenes **87** (Scheme 40), which were isolated in moderate yields. Such highly strained

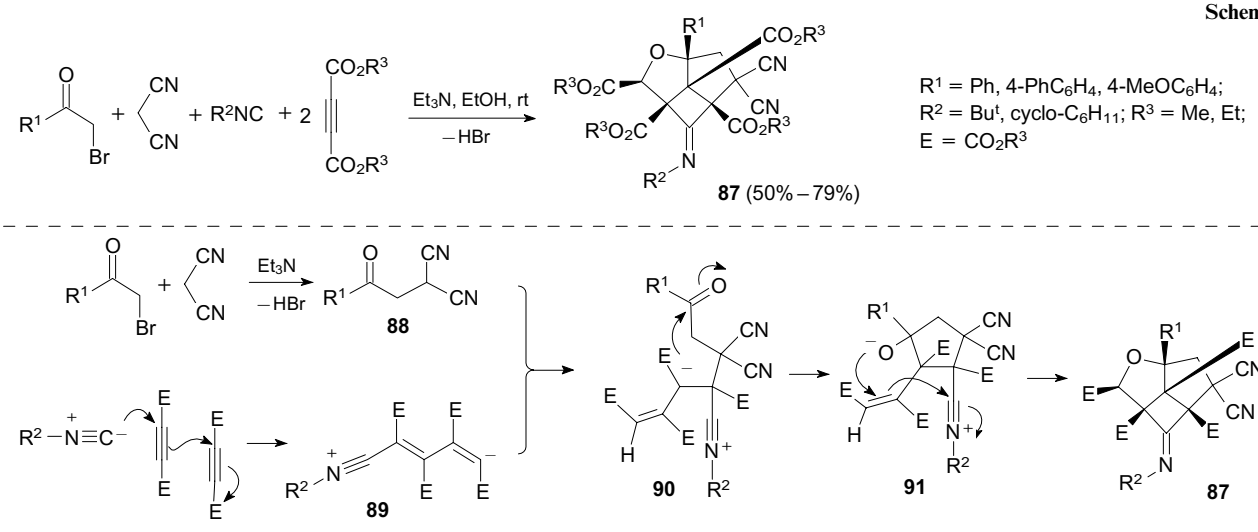
Scheme 38



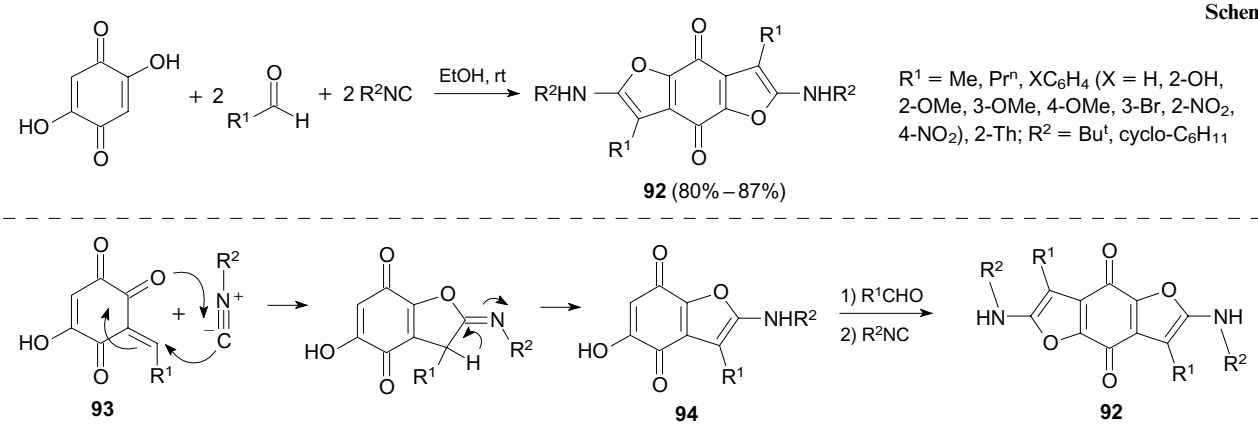
Scheme 39



Scheme 40

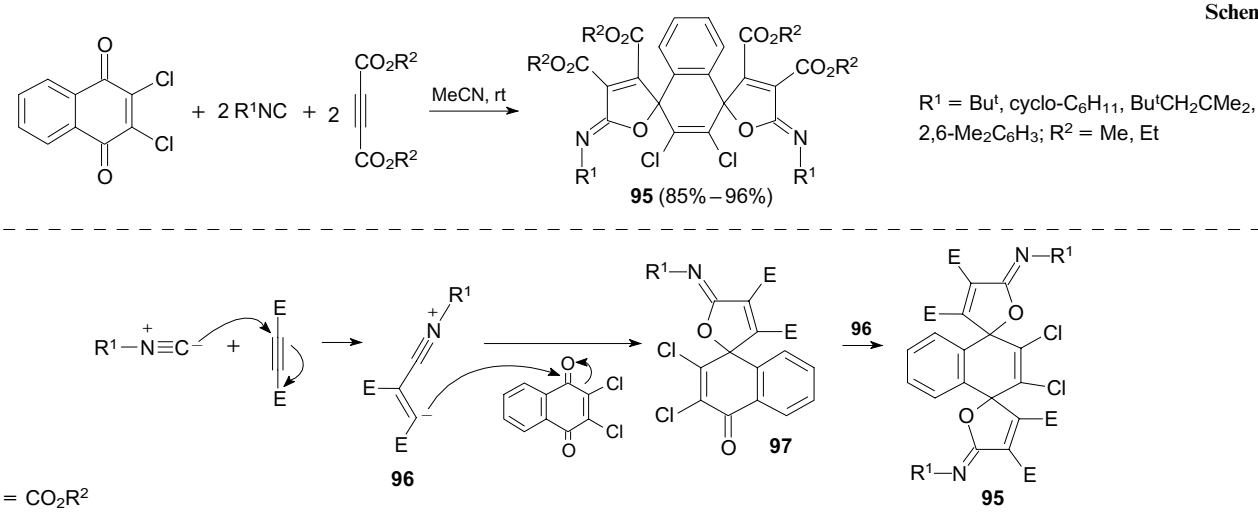


Scheme 41



compounds contain five chiral centres. However, the reaction affords one of the sixteen possible diastereomers, which was confirmed by X-ray diffraction. Therefore, the reaction is highly stereoselective and affords bowl-like structures, in which all carboxyl and aryl substituents at five chiral centres are located on one side of the tricyclic skeleton. The mechanism of the process can be represented as follows (see Scheme 40). In the first step, malononitrile reacts with phenacyl bromide in the presence of triethylamine with elimination of a hydrogen bromide molecule to give 2-(2-aryl-2-oxoethyl)malononitrile **88**. Then reactive zwitterionic intermediate **89**, generated *in situ via* the addition of two dialkyl acetylenedicarboxylate molecules to isonitrile, reacts with derivative **88** to form adduct **90**. The latter undergoes cyclization to cyclopentoxide **91** through intramolecular nucleophilic addition of the stabilized allyl anion at the carbonyl group. The conjugated addition of an alkoxide ion to the adjacent α,β-unsaturated system and the subsequent

Scheme 42

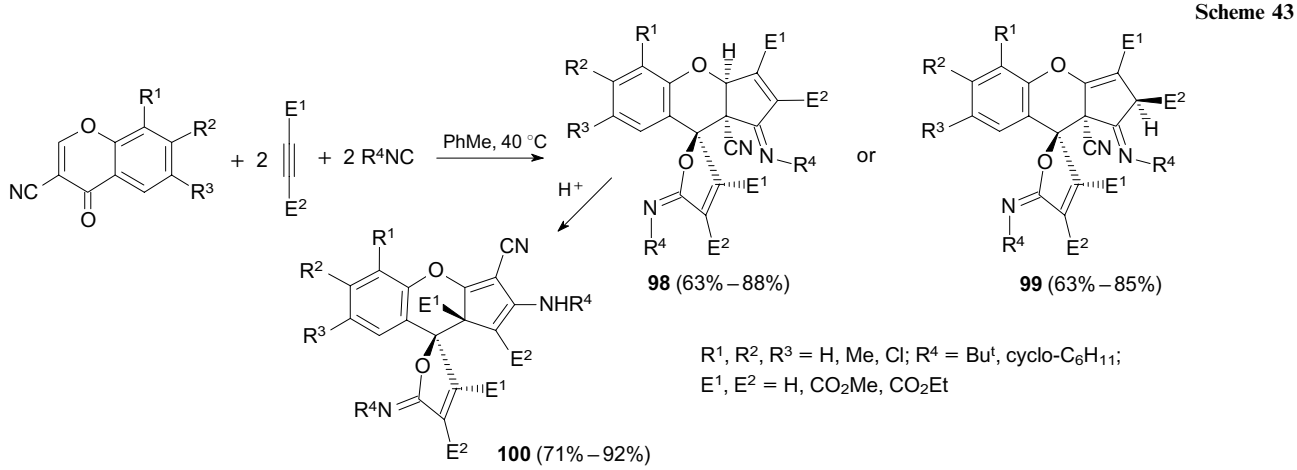


reaction of the resulting enolate with the nitrilium moiety afford 3-oxacyclobuta[*cd*]pentalenes **87**.

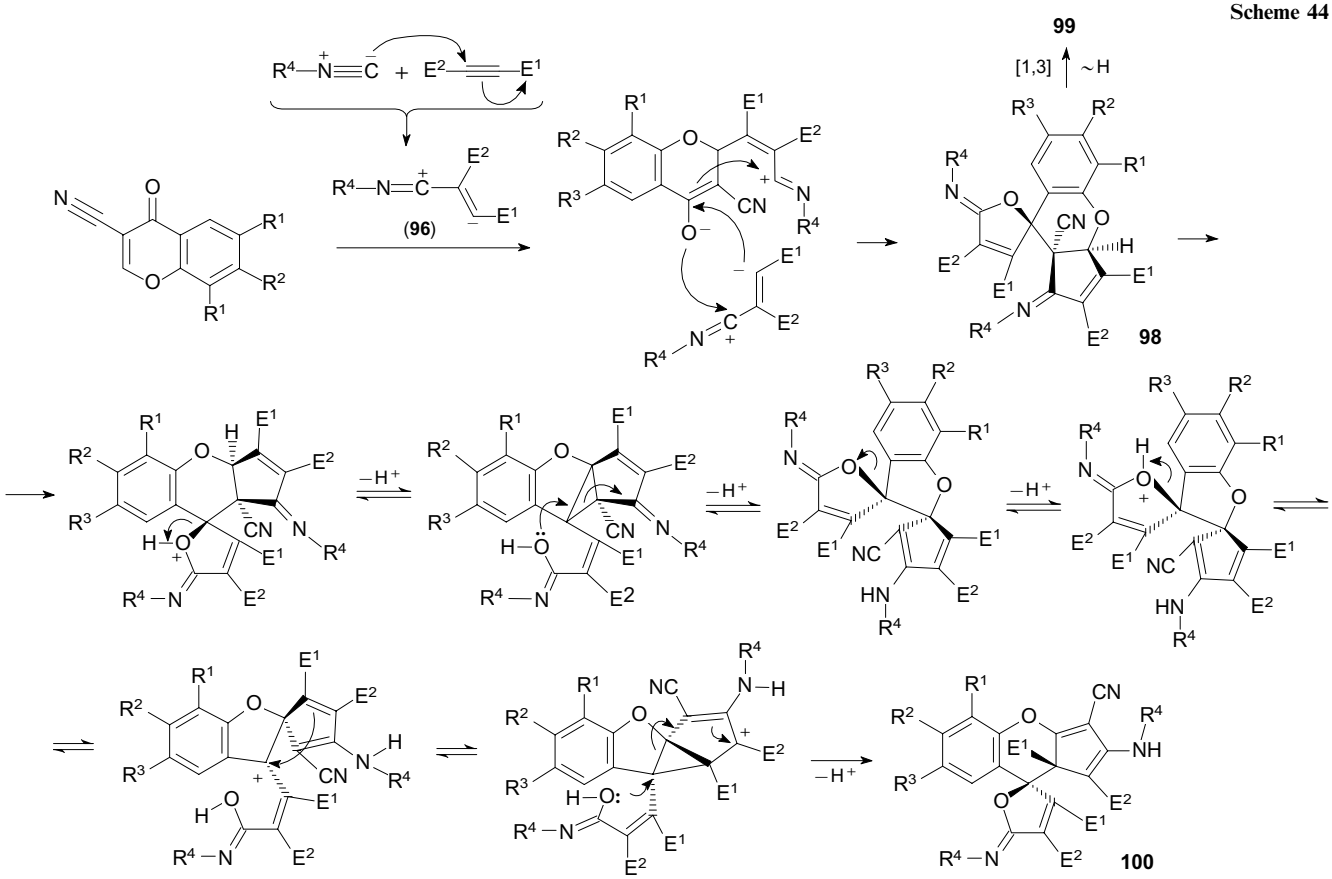
Other polycyclic derivatives **92** were synthesized in high yields by the pseudo-five-component reaction of 2,5-dihydroxy-1,4-benzoquinone with aliphatic and aromatic aldehydes and isonitriles (Scheme 41).[93] The reaction mechanism was not studied in detail. Nevertheless, the authors proposed the following scheme as a plausible mechanism. 2,5-Dihydroxy-1,4-benzoquinone reacts with an aldehyde molecule to form intermediate **93**, which is highly reactive *o*-quinone methide. This electron-deficient heterodiene **93** undergoes [1 + 4]-cycloaddition with isocyanide giving intermediate **94** *via* tautomerization. Then this transformation sequence is repeated to form target compound **92**.

Sadabad *et al.*[94] described the synthesis of polycyclic compounds, dispiro[furan-2,1′-naphthalene-4′,2-furan] derivatives **95**, by a pseudo-five-component reaction (Scheme 42). The reaction of dialkyl acetylenedicarboxylate (2 equiv.), 2,3-dichloronaphthalene-1,4-dione (1 equiv.) and isocyanide (2 equiv.) in acetonitrile affords spiro derivatives **95** in high yields. It is worth noting that the desired products were not isolated upon the reaction with *tert*-butyl acetylenedicarboxylates. The reaction mechanism involves the formation of zwitterionic intermediate **96** from isocyanide and dialkyl dicarboxylate in the first step followed by the reaction of compound **96** with 2,3-dichloronaphthalene-1,4-dione to give intermediate **97** (see Scheme 42). Then the described reaction sequence takes place at the second

Scheme 43



Scheme 44



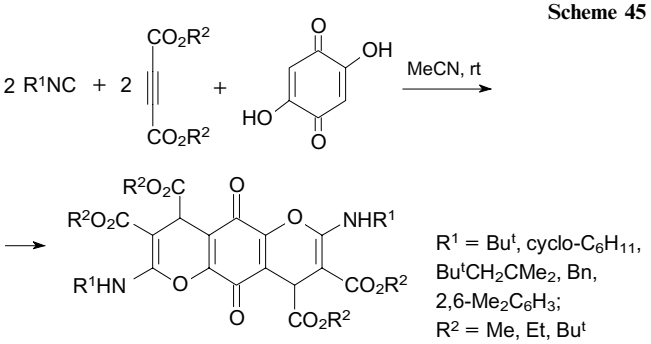
carbonyl group. The stereochemistry of the transformation is not discussed in the original publication.

A similar pseudo-five-component synthesis of polycyclic compounds, spirocyclopenta[*b*]chromenes **98**, was accomplishes using the reaction of 4-oxo-4*H*-chromene-3-carbonitrile with dialkyl dicarboxylates or methyl propiolate and also with isocyanides. Spirocyclopenta[*b*]chromenes **98** or their tautomers **99** were synthesized in good yields (Scheme 43).[95] Besides, some spirocyclopenta[*b*]chromenes **98** undergo a rearrangement to products **100** in high yields (see Scheme 43). Catalytic amounts (2 mol.%) of *p*-toluenesulfonic acid were added to accelerate the synthesis. It should be noted that the rearrangement did not occur with $R^4 = Bu^t$.

The reaction mechanism involves the formation of zwitterion **96** in the first step. This zwitterion adds twice to chromone to give stable product **98**. The transformation of the latter into tautomer **99** *via* the [1,3]-hydride shift is energetically favourable (structure **99** is calculated to be energetically more favourable by 7.5 kcal mol^{-1}). The acid-catalyzed isomerization of intermediate **98** to compound **100** begins with the protonation of the furan oxygen atom. After the cleavage of the C–O bond and the proton abstraction, the repeated protonation and the C–O bond cleavage, sequential isomerizations take place. Finally, the proton abstraction and rearrangement afford product **100** (Scheme 44).

A similar scheme of transformations was adapted to the synthesis of highly functionalized bis(4*H*-chromenes) **101** (Scheme 45).[96] Pseudo-five-component reactions involving 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione give target products in high yields. The stereochemistry of bis(4*H*-chromenes) **101** is not discussed in the original publication, but the authors emphasized that the reaction occurs with excellent (100%) diastereoselectivity.

Scheme 45



101 (62% – 86%)

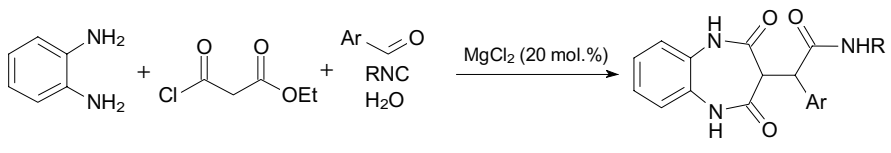
The multicomponent reaction based on isocyanides was successfully applied to synthesize substituted benzodiazepine **102** (Scheme 46).[97] The benzodiazepine ring is often involved in drugs, *e.g.*, some peptide hormone receptor antagonists, such as cholecystokinin,[98] interleukin-1B-converting enzyme (ICE) inhibitor and some other.[99] The reaction is performed in the presence of magnesium chloride as the catalyst (20 mol.%). The target functionalized benzodiazepines **102** were isolated in yields of up to 95%. The mechanism of the transformation involves the formation of benzodiazepinedione **103** from *o*-phenylenediamine and a chloro derivative of malonic ester in the first step followed by the Knoevenagel reaction with benzaldehydes to produce compound **104** (see Scheme 46). The addition of isocyanide to the latter and subsequent hydrolysis afford product **102**.

2.3. Reactions based on the Michael addition

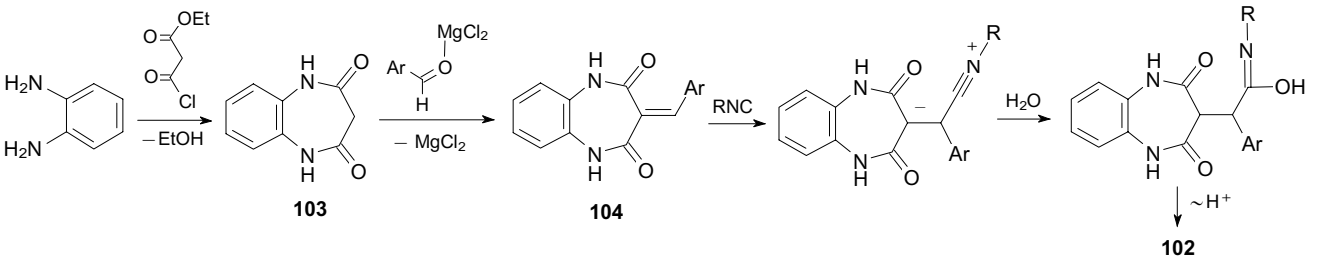
Due to versatility and simplicity, the Michael reaction is commonly used in laboratory practice, industry and biological processes and can easily be utilized as a step in complex multicomponent transformations. Thus, the pseudo-five-component iodination – Kornblum oxidation – Michael addition domino sequence was applied to synthesize dihydrooxepines **105** (Scheme 47).[100] The reaction of acetophenone, arylhydrazine and acetoacetic ester in a molar ratio of 1 : 2 : 2 in the presence of molecular iodine and trifluoromethanesulfonic acid (TfOH) in DMSO at reflux gave pyrazole-containing dihydrooxepines **105** in moderate yields. The possible mechanism of this transformation involves the formation of aryl glyoxal **106** from acetophenone *via* iodination – Kornblum oxidation as the first step followed by protonation of **106** with trifluoromethanesulfonic acid (see Scheme 47). The competitive reaction of arylhydrazine with acetoacetic ester gives pyrazolone **107**. Then sequential Michael additions of activated protonated aryl glyoxal **106** to two pyrazolone **107** molecules afford intermediate **108**, which is iodinated *in situ* to form compound **109**, and the latter is transformed *via* intramolecular cyclization to final dihydrooxepine **105**.

A unique example of the application of a pseudo-five-component reaction in the biomimetic total synthesis of polyketide natural product **110** was reported by Spence and George[101] (Scheme 48). *ent*-Penilactone A **110** that is present in *Penicillium crustosum* PRB-2, a fungus found in an Antarctic deep sea sediment, was prepared in 46% yield

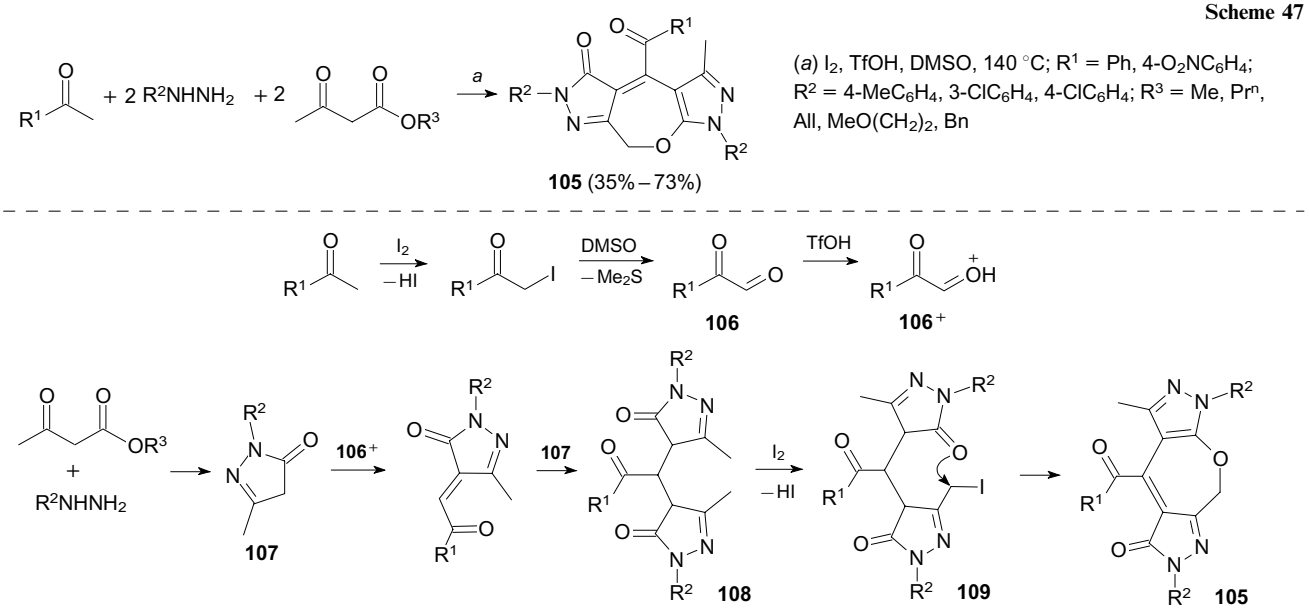
Scheme 46



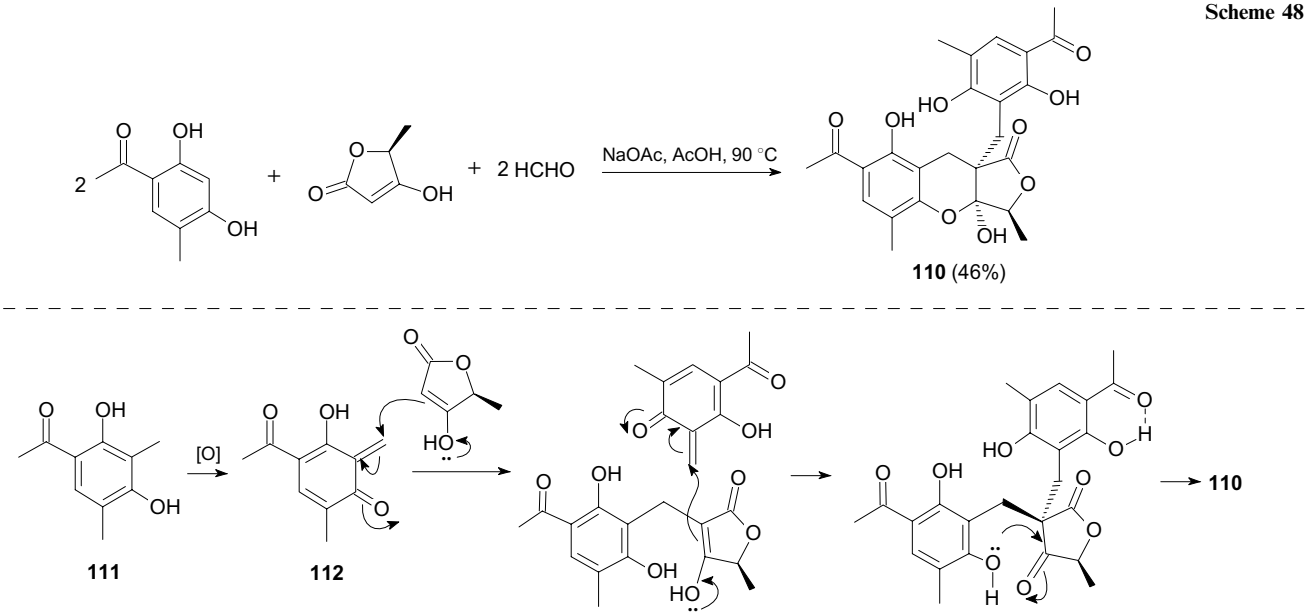
102 (80% – 95%)



Scheme 47



Scheme 48

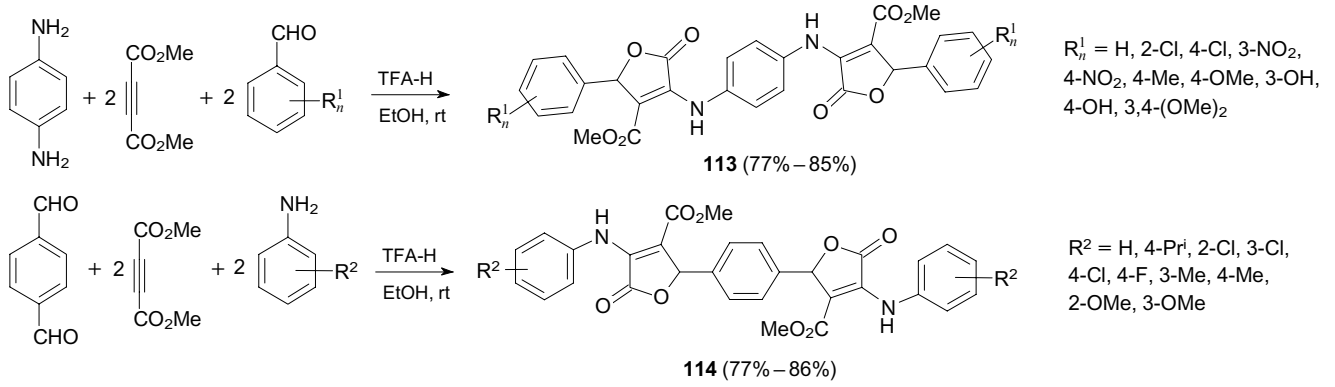


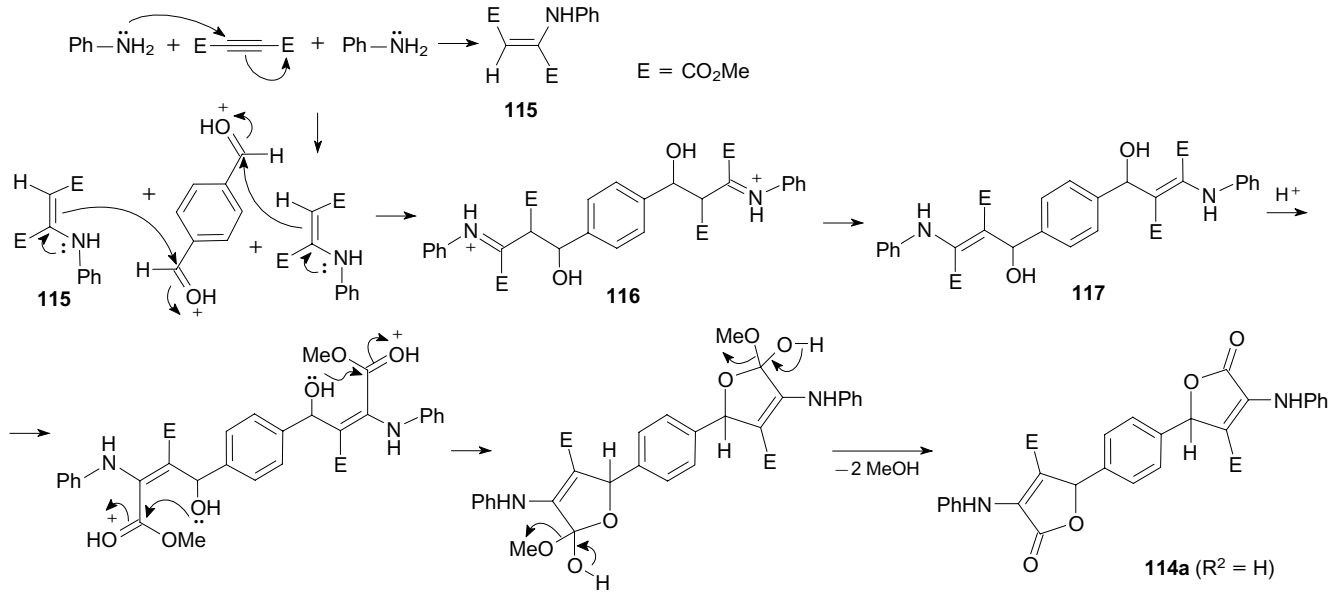
by heating tetronic acid, formaldehyde and a resorcinol derivative in an acetate buffer. The mechanism of both the biosynthesis and the laboratory approach involves the following sequence of transformations (see Scheme 48). In the first step, the reaction of 1-(2,4-dihydroxy-5-methylphenyl)ethanone and formaldehyde affords clavatol **111**, isolated from *Penicillium griseoroseum*.[101] This compound is oxidized to *o*-quinone methide **112**. Then two *o*-quinone methide **112** molecules sequentially undergo Michael condensation with tetronic acid, which is also present in the fungus *Penicillium griseoroseum*, to give *ent*-penilactone A **110**. The reaction leads to the stereoselective formation of two new C—C bonds and one C—O bond.

The double pseudo-five-component Michael reaction was used in the synthesis of polyfunctionalized bis(2,5-dihydrofuran-3-carboxylates) **113** and **114** (Scheme 49).[102] The variation of the amine and aldehyde components in trifluoroacetic acid (TFA-H) allows the preparation of isomeric 2- and 3-amino-substituted compounds. The reaction of *p*-phenylenediamine, dimethyl acetylenedicarboxylate and benzaldehyde in a ratio of 1 : 2 : 2 gives symmetrical products **113** in high yields. By contrast, the reaction of terephthalaldehyde, dimethyl acetylenedicarboxylate and aniline in a ratio of 1 : 2 : 2 affords derivatives **114**. Both reactions proceed by a similar mechanism (see Scheme 49). The first step is the Michael addition of acetylenedicarboxylic ester to aromatic amine (*e.g.*, aniline) giving enaminone **115**. This is followed by the reaction of the latter with terephthalaldehyde to form bisiminium intermediate **116** and transformation of **116** into compound **117**. Finally, the γ-lactonization of compound **117** affords target bis(2,5-dihydrofuran-3-carboxylate) derivative **114a**.

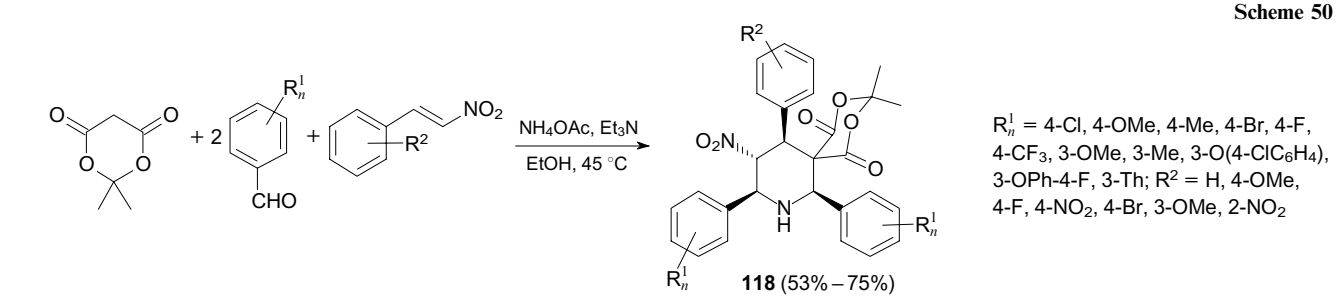
A series of polysubstituted piperidines **118** were synthesized from β-nitrostyrenes, Meldrum's acid, aromatic aldehydes and ammonium acetate by a pseudo-five-component reaction (Scheme 50).[103] This cascade process provides a route to 2,4,6-triaryl-3-nitropiperidines **118** containing a wide range of substituents on the aromatic rings under

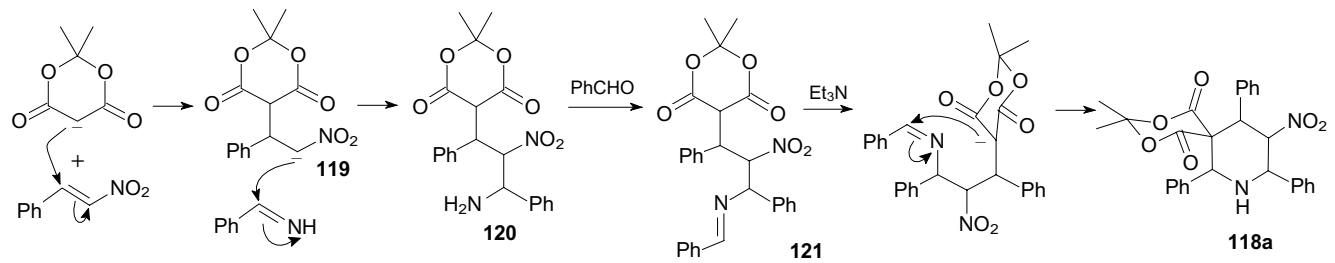
Scheme 49





Scheme 50

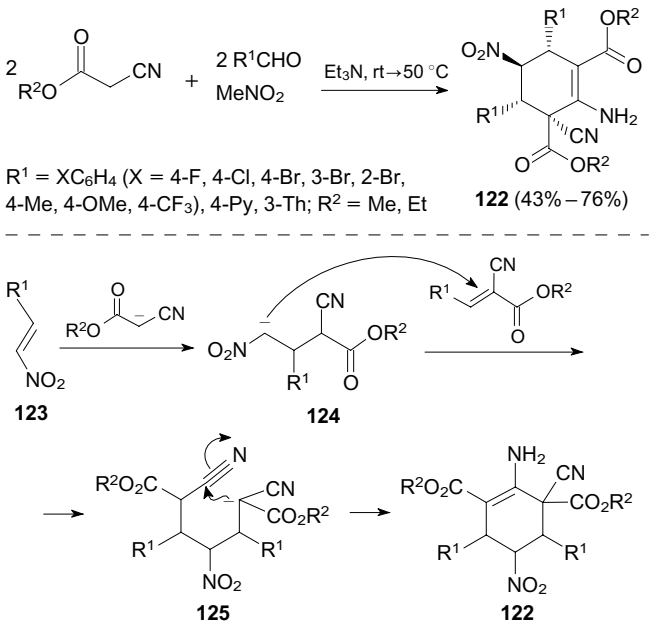




mild conditions. In the first step, the addition of Meldrum's acid to nitrostyrene occurs under basic conditions (see Scheme 50). Then Michael product **119** reacts with imine (generated from benzaldehyde and ammonium acetate) to give nitroamine **120**. This is followed by the formation of imine **121**, which undergoes the intramolecular nitro-Mannich reaction giving polysubstituted piperidine **118a** (R^1_n = R^2 = H).

This procedure was applied to synthesize a series of functionalized cyclic β-amino esters **122** (Scheme 51).[104]

Scheme 51



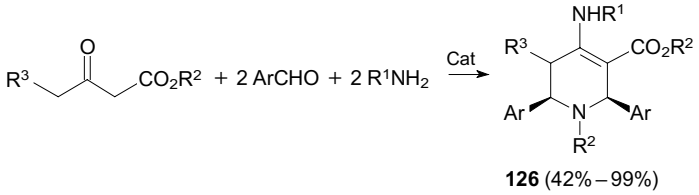
Compounds **122** were prepared in yields of up to 76% upon heating of a mixture of cyanocetate, aryl carbaldehyde and nitromethane in a ratio of 2 : 2 : 1 in the presence of triethylamine in ethanol. The proposed reaction mechanism involves the formation of β-nitrostyrene **123** as the first step. The subsequent addition of the cyanoacetate anion affords intermediate **124** (see Scheme 51). This is followed by the Michael reaction of intermediate **124** with the Knoevenagel product involving cyanoacetate and aryl carbaldehyde. The intramolecular nucleophilic addition of the resulting anionic intermediate **125** to the cyano group gives final product **122**.

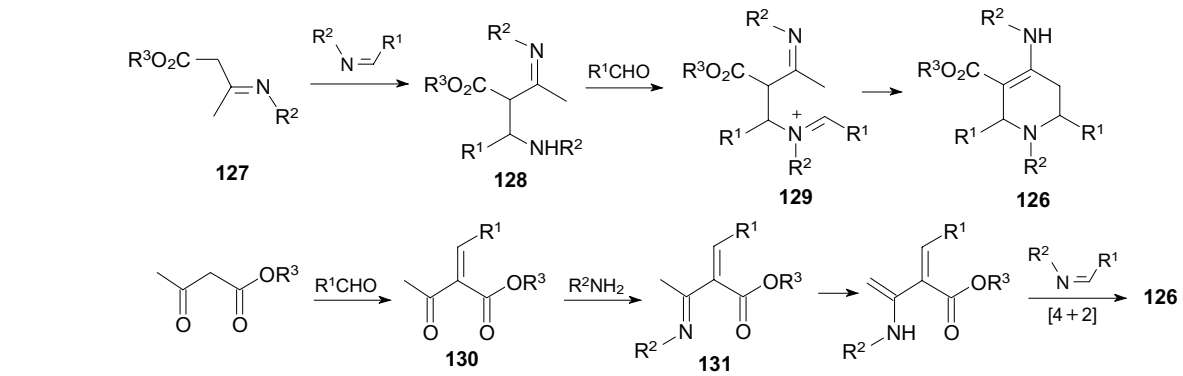
2.4. Transformations based on the Mannich reaction

The Mannich reaction is commonly used to form new C – C bonds. Apart from the classical Mannich reaction, there are diverse versions of this reaction, which expands its synthetic potential. A five-component tandem double Mannich reaction is widely applied in the synthesis of polyfunctionalized tetrahydropyridines and their derivatives **126**. Examples of such reactions catalyzed by silica sulfuric acid $SiO_2-OSO_3H_2$,[105,106] sulfamic acid,[107] lactic acid,[108] oxalic acid dihydrate,[109] ethylenediammonium diformate,[110] cyanuric chloride,[111] molecular iodine,[112] nanocrystalline ZrP_2O_7,[113] indium(III) chloride,[114] bismuth(III) complexes,[115] proline nitrate,[116] camphor-10-sulfonic acid,[117] ionic liquids,[118] BF_3-treated nanocellulose[119] and reactions under catalyst-free conditions[120] were reported (Scheme 52). Despite the fact that generally the double Mannich condensation affords 2,6-diaryltetrahydropyridines containing *cis*-aryl groups, some catalytic systems [for example, $PbCr_xFe_{12-x}O_{19}$,[121] dioctyl sodium sulfosuccinate[122] and 1,1′-bi(2-naphthol) (BINOL) derivatives][123] allow the preparation of *trans* isomers. The reaction mechanism involves the formation of imine **127**, which undergoes the Mannich reaction to form **128**. The subsequent reaction with aldehyde gives iminium salt **129** (see Scheme 52). The sequential tautomerization of this intermediate and the intramolecular Mannich reaction afford product **126**. On the other hand, some researchers consider this transformation as a domino transformation, involving the Knoevenagel condensation and the aza-Diels – Alder reaction (see Scheme 52). According to this concept, the first step is the Knoevenagel condensation followed by the addition of aniline to intermediate **130** to form compound **131**. After tautomerization, the latter undergoes [4 + 2]-cycloaddition with imine.

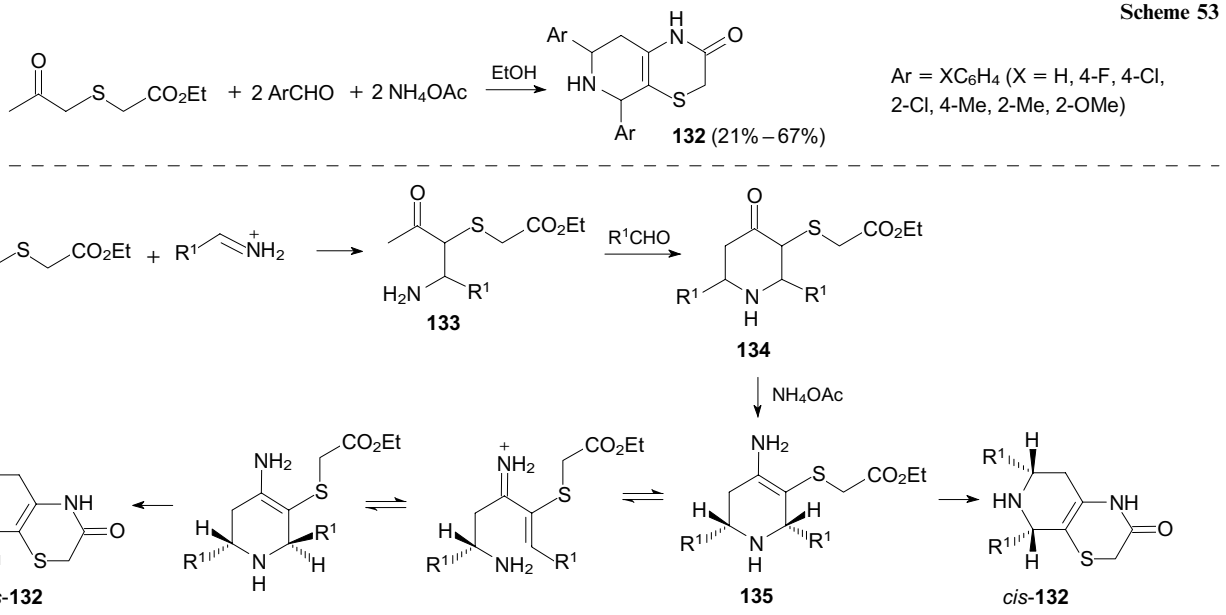
The pseudo-five-component synthesis of 5,6,7,8-tetrahydro-1*H*-pyrido[3,4-*b*][1,4]-thiazin-2(3*H*)-one derivatives **132** involves the double Mannich reaction and intramolecular cyclization (Scheme 53).[124] The reaction of ethyl 2-[(oxopropyl)thio]acetate, benzaldehyde and ammonium acetate proved to be sensitive to the nature and position of the substituent in benzaldehyde. Thus, thiazinones **132** were isolated as a mixture of *cis* and *trans* isomers (in the case of *para*-substituted benzaldehydes, where R^1 = H, Cl, Me, F, the *trans* : *cis* ratio was ~1 : 0.7) or as a pure *trans* isomer (for *ortho*-substituted benzaldehydes, where R^1 = Cl, Me, MeO) in a total yield of up to 67%. The possible reaction

Scheme 52





Scheme 53



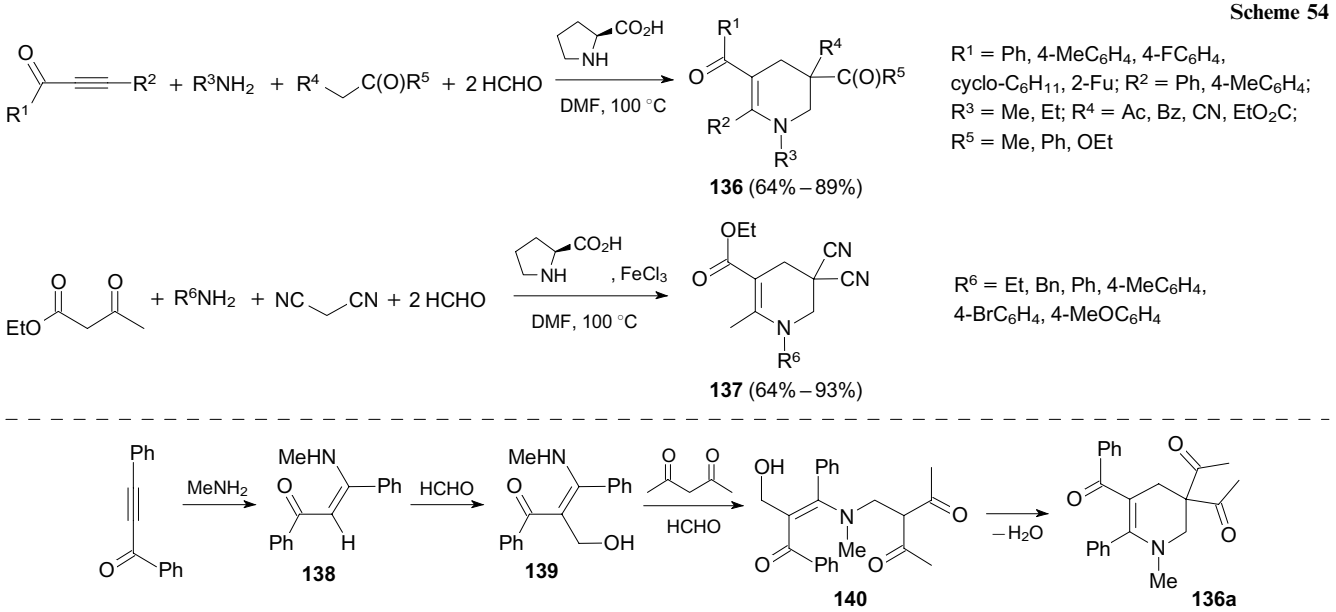
mechanism involves two sequential Mannich reactions giving intermediates **133** and **134** and the subsequent formation of enamine **135**, which is transformed into the *cis* isomer or is isomerized into the *trans* isomer through the cleavage and repeated closure of the ring (see Scheme 53).

The organocatalytic pseudo-five-component approach was used in the synthesis of polyfunctionalized 1,2,3,4-tetrahydropyridines **136** and **137** (Scheme 54).[125] The L-proline-catalyzed reaction of alkynones, primary aliphatic amines, carbon acids and formaldehyde gave tetrahydropyridine derivatives **136** in high yields. Related compounds **137** were prepared by the reaction using acetoacetic ester in the presence of L-proline and iron(III) chloride. The reaction mechanism (for $R^1 = R^2 = Ph$, $R^3 = R^5 = Me$, $R^4 = Ac$) involves the formation of enamine **138** and the Prins reaction giving product **139**. This is followed by the Mannich reaction involving intermediate **139**, carbon acid and formaldehyde. Finally, the intramolecular condensation of compounds **140** affords product **136a** (see Scheme 54).

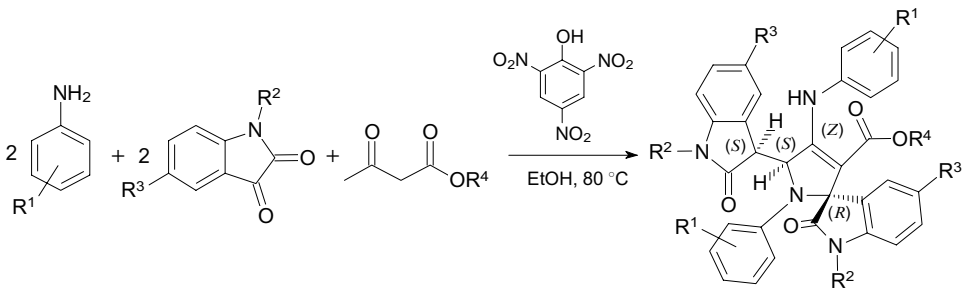
A series of cage spiro[indole-3,2′-pyrrole] **141** were synthesized by the diastereoselective pseudo-five-component reaction (Scheme 55).[126] The reaction of an ethanolic solution of aniline, isatin and acetoacetic ester (2 : 2 : 1 ratio) in the presence of 10 mol.% wet picric acid affords spiro[indole-3,2′-pyrroles] **141** as *syn* isomers. The first step is the aldol condensation of isatin at the less sterically crowded moiety of acetoacetic ester followed by the addition of aniline to intermediate **142** and the Mannich reaction giving molecules **143** and **144** (see Scheme 55). In this synthesis, picric acid not only provides the required pH value of the medium but also stabilizes transition state **145** through stacking interactions between aromatic systems, resulting in the formation of the *syn* isomer.

The pseudo-five-component Michael reaction – elimination – Mannich reaction domino sequence was successfully applied in the synthesis of 5-aroyl-1,3-diarylhexahydropyrimidines **146** (Scheme 56).[127] Heating of a mixture of α,β-unsaturated ketone, formaldehyde and aniline (1 : 2 : 2 ratio)

Scheme 54

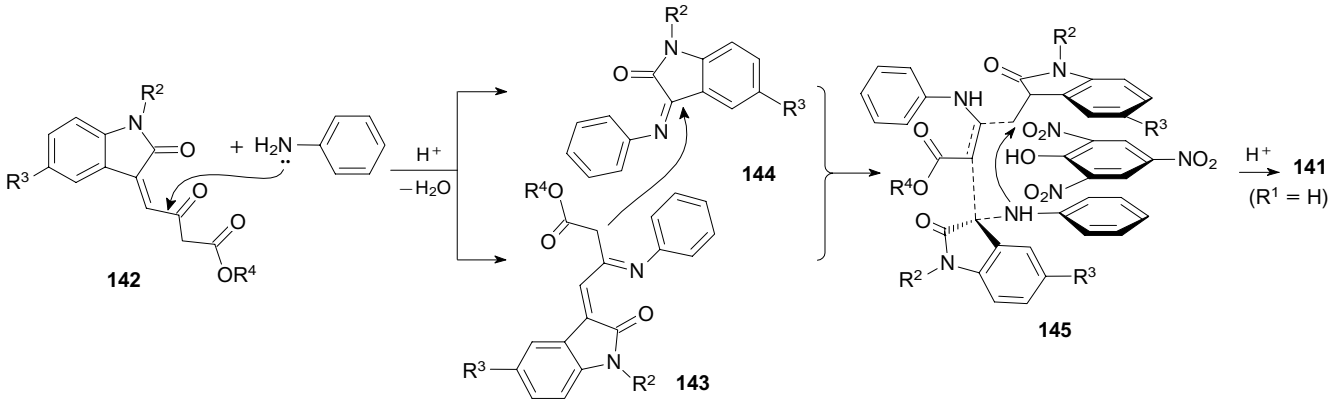


Scheme 55



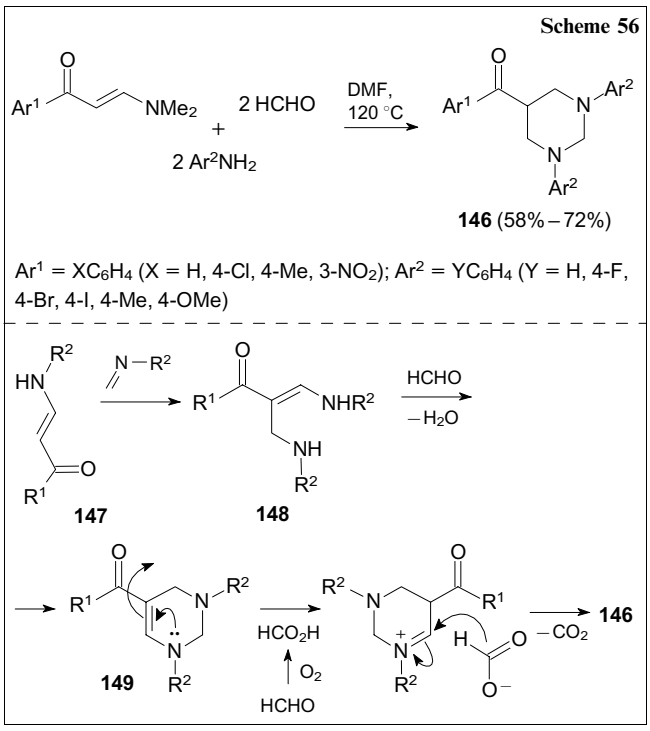
R^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4, cyclo-C_6H_{11}, 2-Fu; R^2 = Ph, 4-MeC_6H_4; R^3 = Me, Et; R^4 = Ac, Bz, CN, EtO_2C

syn-**141** (45% – 91%)



in DMF produces 1,3-disubstituted hexahydropyrimidines **146** in moderate yields. In the first step of this domino process, the addition – Michael elimination involving α,β-unsaturated ketone and aniline affords compound **147** with elimination of dimethylamine (see Scheme 56). The key step of the synthesis is the Mannich reaction giving intermediate **148**. This is followed by annulation – condensation and protonation of the resulting 1,2,3,4-tetrahydropyrimidine **149** and its reduction with formaldehyde accompanied by decarboxylation.

Scheme 56

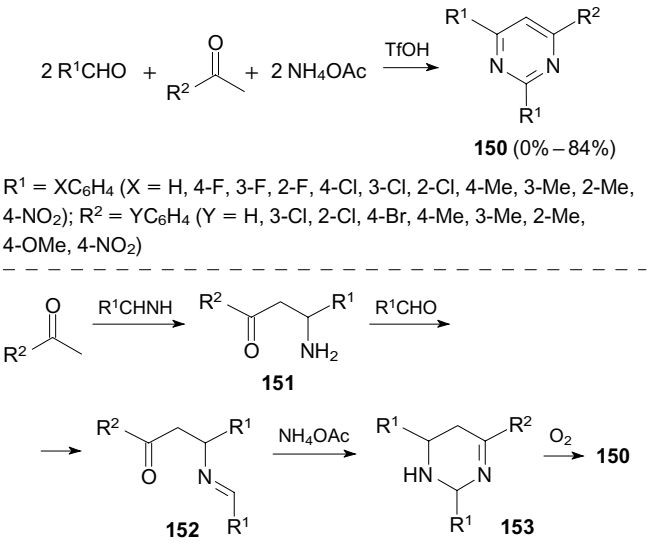


146 (58% – 72%)

Ar^1 = XC_6H_4 (X = H, 4-Cl, 4-Me, 3-NO_2); Ar^2 = YC_6H_4 (Y = H, 4-F, 4-Br, 4-I, 4-Me, 4-OMe)

The general synthesis of 2,4,6-triarylpyrimidines **150** was developed based on the TfOH-catalyzed pseudo-five-component annulation of methyl ketones, aldehydes and NH_4OAc. The oxidative cyclization resulted in the formation of one C – C bond and four C – N bonds. Based on experimental data, the following reaction mechanism was proposed (Scheme 57).[128] In the presence of a catalytic amount of TfOH, the Mannich reaction affords aminoketone **151**, which reacts with the second aldehyde molecule to form intermediate **152**. The intramolecular condensation of the latter produces tetrahydropyrimidine **153**, which undergoes aromatization in the presence of atmospheric oxygen to give final 2,4,6-triarylpyrimidine **150**. The yields of products are generally high, except for *ortho*-substituted

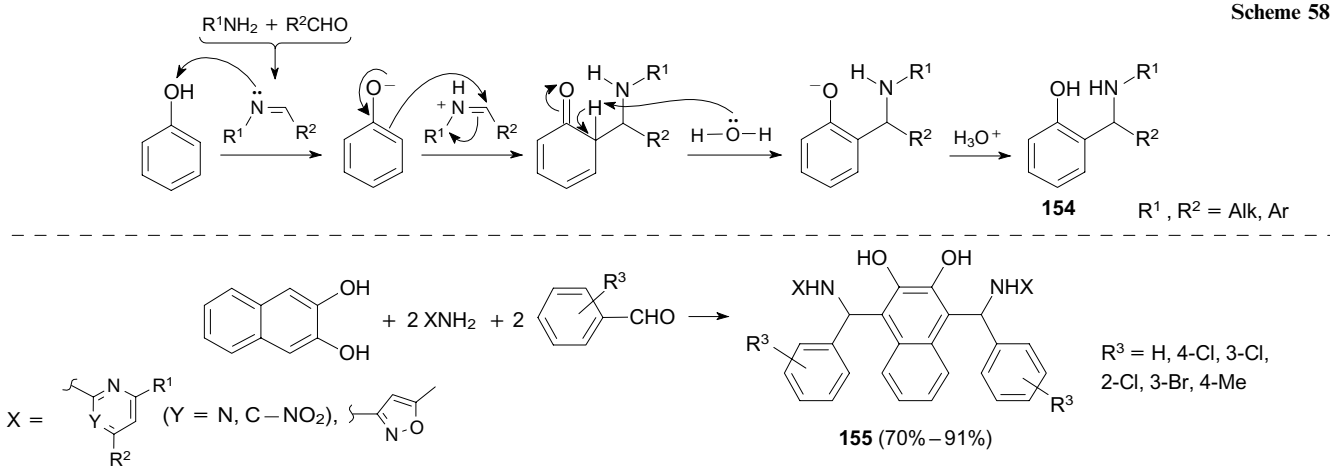
Scheme 57



150 (0% – 84%)

R^1 = XC_6H_4 (X = H, 4-F, 3-F, 2-F, 4-Cl, 3-Cl, 2-Cl, 4-Me, 3-Me, 2-Me, 4-NO_2); R^2 = YC_6H_4 (Y = H, 3-Cl, 2-Cl, 4-Br, 4-Me, 3-Me, 2-Me, 4-OMe, 4-NO_2)

Scheme 58

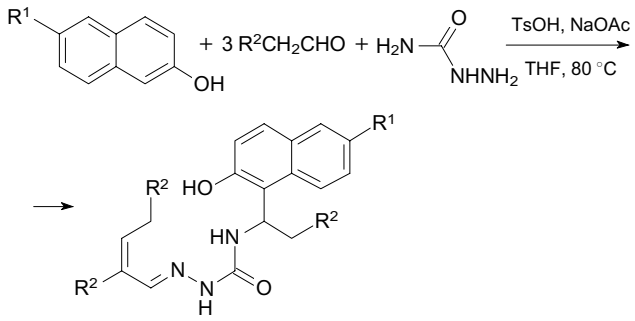


aldehydes and ketones. In the latter case, the formation of trace amounts of compounds **150** was observed.

The Betti reaction is a Mannich-type condensation. In this reaction, aromatic aldehydes are utilized instead of formaldehyde and phenols serve as nucleophiles. In the first step, phenol protonates imine; this is followed by the regioselective addition of iminium salt at the *ortho* position of the phenoxide ion to form product **154** (Scheme 58). Thus, the pseudo-five-component aminobenzylation of naphthalene-2,3-diol, where pyridine, pyrimidine and oxazole derivatives serve as an amine component (see Scheme 58), affords target products **155** in high yields under solvent-free conditions.[129, 130]

The pseudo-five-component domino transformation, involving the Betti reaction and crotonic condensation, was observed as a side process when using aliphatic aldehydes in the synthesis of 1-(3-semicarbazonoalkyl)-2-naphthols **156** (Scheme 59).[131] Although investigation of this process was not initially the main aim of the cited work, the authors succeeded in optimizing the conditions and achieved good yields of compounds **156**.

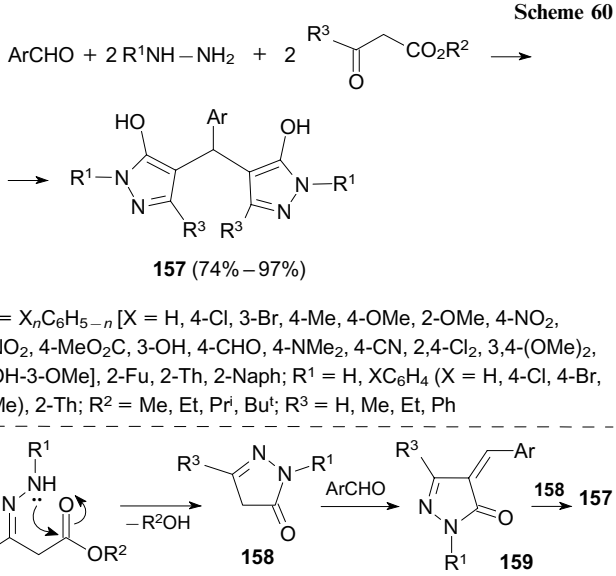
Scheme 59



2.5. Transformations involving the Knoevenagel reaction

The five-component cyclocondensation – Knoevenagel – Michael domino reaction is extensively used for the synthesis of symmetrical bis(pyrazol-5-ol) derivatives **157** (Scheme 60). The reaction of aryl carbaldehyde, (aryl)hydrazine and acetoacetic ester in a ratio of 1 : 2 : 2 affords bispyrazole derivatives in yields of up to 97%. This reaction can be performed in diverse ways, and often does not require a catalyst;[132 – 134] however, some reactions are catalyzed by 1,4-diazobicyclo[2.2.2]octane hydrochloride,[135]

Scheme 60

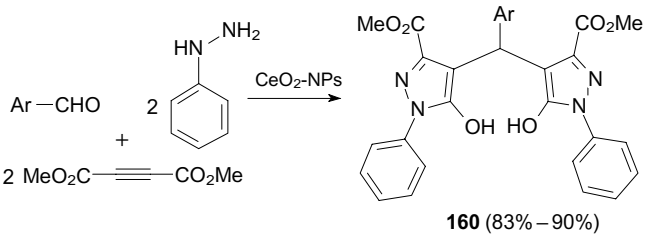


functionalized pyridinium salts,[136] *N*,2-dibromo-6-chloro-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide (DCDBTSD),[137] *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium-*N*,*N*′-disulfonic acid hydrogen sulfate,[138] potassium carbonate,[139] $CuCr_2O_4$ nanoparticles,[140] $ZnAl_2O_4$ nanoparticles,[141] guanidine hydrochloride[142] or palladium compounds.[143] The first step affords 1*H*-pyrazol-5-one **158** (see Scheme 60), which undergoes Knoevenagel condensation to form compound **159**. The Michael addition of the second 1*H*-pyrazol-5-one **158** molecule gives bis(1*H*-pyrazol-5-one) **157**.

This transformation can be performed with the use of acetylenedicarboxylates instead of keto esters (Scheme 61).[144] The reaction of benzaldehydes, dimethyl acetylenedicarboxylate and phenylhydrazine in a ratio of 1 : 2 : 2 in the presence of nanosized cerium dioxide particles (CeO_2-NPs) affords bis(pyrazol-5-ols) **160** in high yields. The reaction mechanism is similar to that described above for the cycloaddition – Knoevenagel – Michael domino sequence (see Scheme 61). In this process, the catalyst accelerates the Knoevenagel condensation.

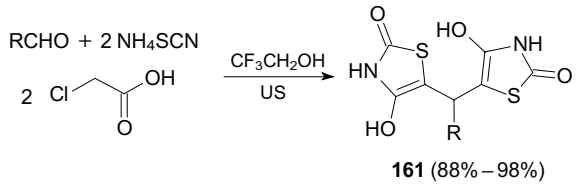
The versatility of Knoevenagel and Michael reactions and the diversity of the substrates provide the variability of the reaction products. This approach is used to synthesize various heterocyclic structures. A combination of such

Scheme 61

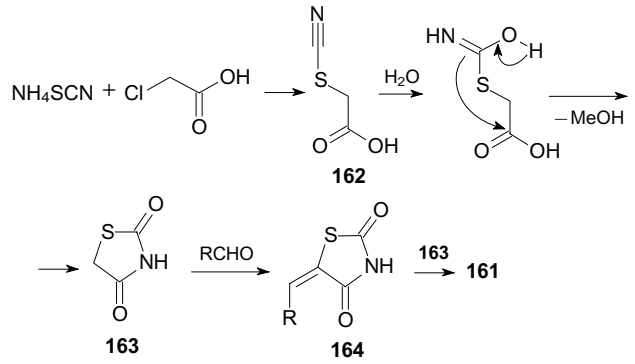


Ar = $X_nC_6H_{5-n}$ (X = H, 4-Cl, 2-Cl, 4-Me, 3-Me, 4-NO_2, 2,4-Cl_2)

Scheme 62



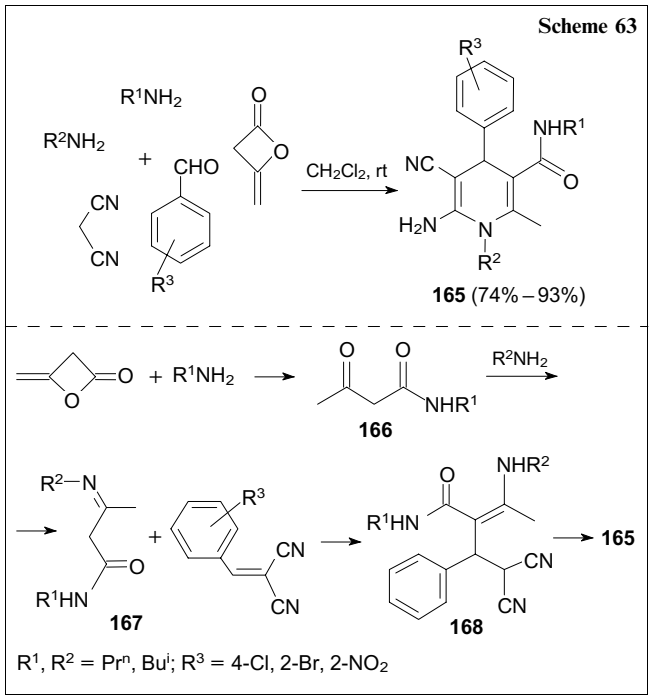
R = $X_nC_6H_{5-n}$ [X = H, 4-F, 4-Cl, 3-Cl, 2-Cl, 4-Br, 4-NO_2, 3-NO_2, 4-Me, 4-OMe, 4-OH, 2,4-Cl_2, 2,4-$(OMe)_2$], 2-Naph, 4-Py;
US is ultrasonic irradiation



transformations was applied in the synthesis of bis(4-hydroxythiazol-2-ones) **161** (Scheme 62).[145] The ultrasonic irradiation of a mixture of aryl carbaldehyde, ammonium thiocyanate and chloroacetic acid in trifluoroethanol gave target heterocycles **161** in yields of up to 98%. First, the reaction of ammonium thiocyanate and chloroacetic acid affords 2-thiocyanoacetic acid **162**, which is hydrolysed to thiazolidine-2,4-dione **163** (see Scheme 62). The subsequent steps are the Knoevenagel condensation and Michael addition of the second equivalent of compound **163** to alkene **164**.

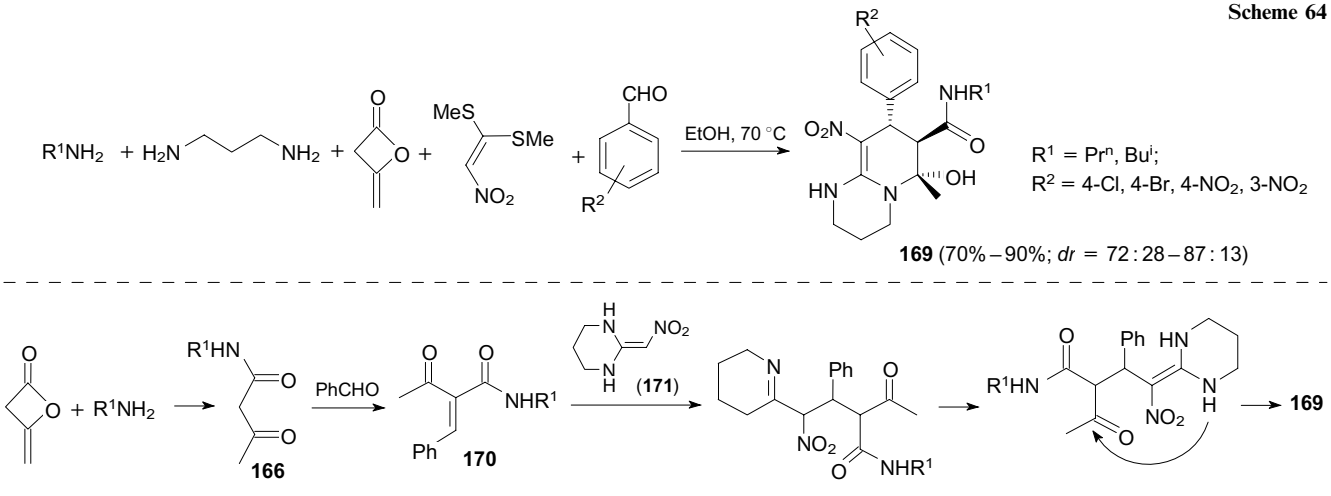
A five-component strategy for the synthesis of highly functionalized 1,4-dihydropyridines **165** in high yields was developed based on the commercially available diketene (4-methyleneoxetan-2-one), malononitrile, primary amines and substituted benzaldehydes (Scheme 63).[146] The reaction mechanism involves the sequential ring opening of diketene giving reactive methylene component **166**, the formation of imine **167**, the Knoevenagel reaction, Michael addition, 6-*exo-tet* cyclization of compound **168** and tautomerization to final product **165** (see Scheme 63). The transformation results in the formation of two new C—C bonds and three C—N bonds.

Scheme 63

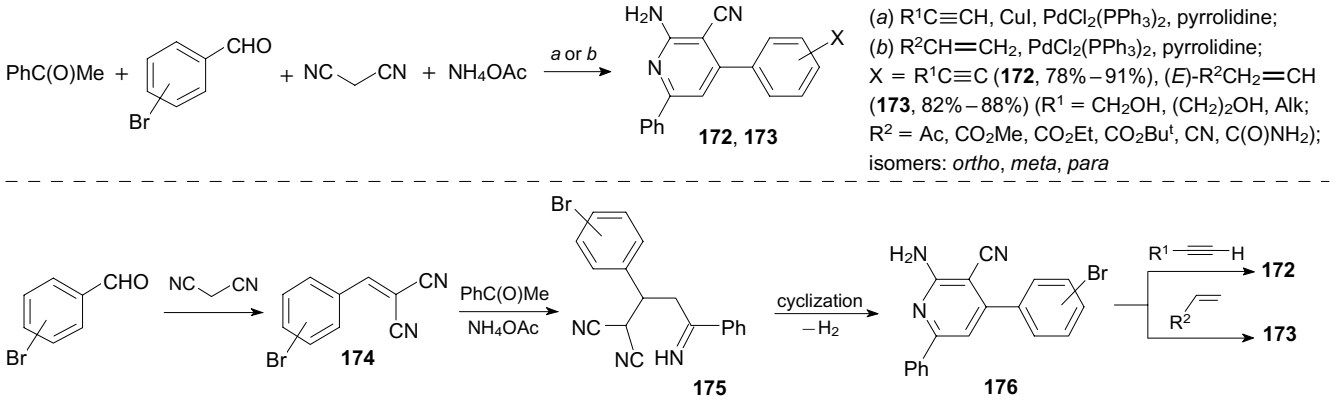


The same principle underlies the diastereoselective synthesis of pyrido[1,2-*a*]pyrimidines **169** (Scheme 64).[147] The five-component reaction provides a route to the target compounds in yields of up to 90% with high diastereoselectivity (the 6*R*,7*R*,8*S* isomer is the major product). This transformation involves the sequential formation of aceto-

Scheme 64



Scheme 65



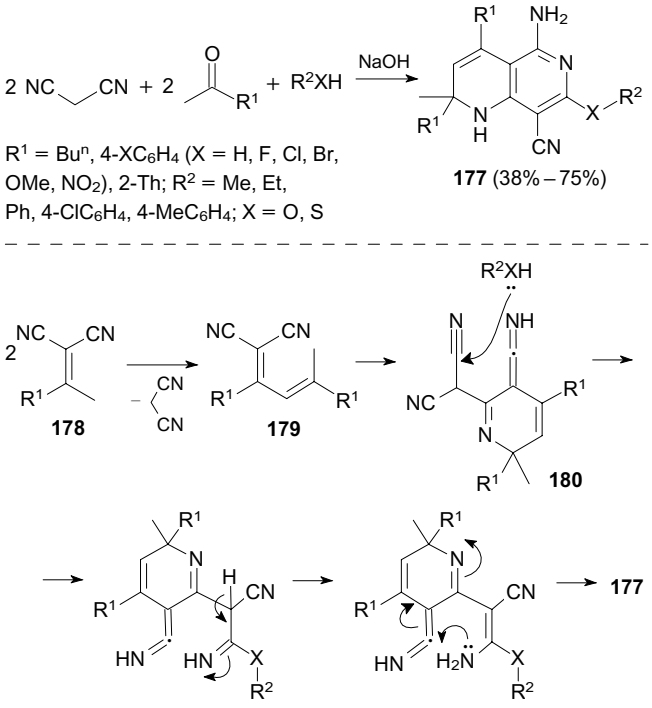
acetamide **166**, the Knoevenagel reaction, Michael addition of ketene aminal **171**, generated from propanediamine and nitroketene dithioacetal, to alkene **170** and intramolecular cyclization (see Scheme 64). Apart from three stereocentres, the reaction gives rise to four new C – N bonds and two C – C bonds.

The multicomponent reaction of bromobenzaldehydes, malononitrile, acetophenone, NH_4OAc and a series of terminal alkynes or alkenes in the presence of pyrrolidine and a Pd catalyst can be used to synthesize pyridines followed by palladium-catalyzed transformations in a one-pot manner. The Sonogashira and Heck reactions afford target compounds containing acetylene (**172**) or alkene moieties (**173**), the Heck reaction giving exclusively *E* isomers (Scheme 65).[148] The Knoevenagel condensation resulting in the formation of intermediate **174**, subsequent Michael addition and the formation of imine **175**, cyclization and aromatization to substituted pyridine **176** are the main steps of the process, which involves the palladium-catalyzed C – C bond formation as the final step.

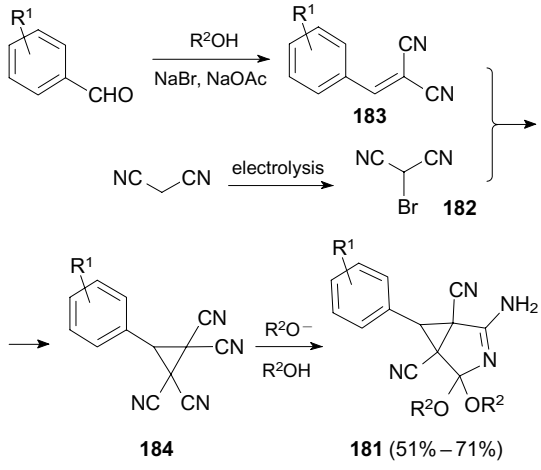
The versatile one-pot approach to the synthesis of polysubstituted 1,6-naphthyridines **177** was developed based on the reaction of methyl ketones, malononitrile and alcohols or thiols. Target 1,6-naphthyridines were synthesized in moderate to high yields. It is worth noting that the reactions with thiols give target products in somewhat lower yields compared to the reactions with alcohols (Scheme 66).[149] This multicomponent transformation involves the Knoevenagel condensation of ketones with malononitrile giving unsaturated dinitrile **178** and the subsequent condensation of two molecules of **178** accompanied by the elimination of malononitrile and the formation of intermediate **179**. This is followed by the attack of a malononitrile anion, resulting in the intramolecular cyclization to compound **180**. Naphthyridine **177** is formed through the closure of the second ring and aromatization (see Scheme 66).

The one-step synthesis of bicyclic pyrrolines **181** conjugated with the cyclopropane moiety was accomplished *via* electrolysis of a mixture of malononitrile and aromatic aldehydes in alcohol in the presence of sodium bromide and acetate. In terms of classical organic chemistry, this process involves the following four steps: halogenation of malononitrile giving bromide **182**, the formation of arylidenemalononitrile **183** *via* the Knoevenagel reaction, the formation of tetracyanocyclopropane **184** and its reaction with alkoxide ions. Target compounds **181** were synthesized in yields of up to 71% (Scheme 67).[150]

Scheme 66

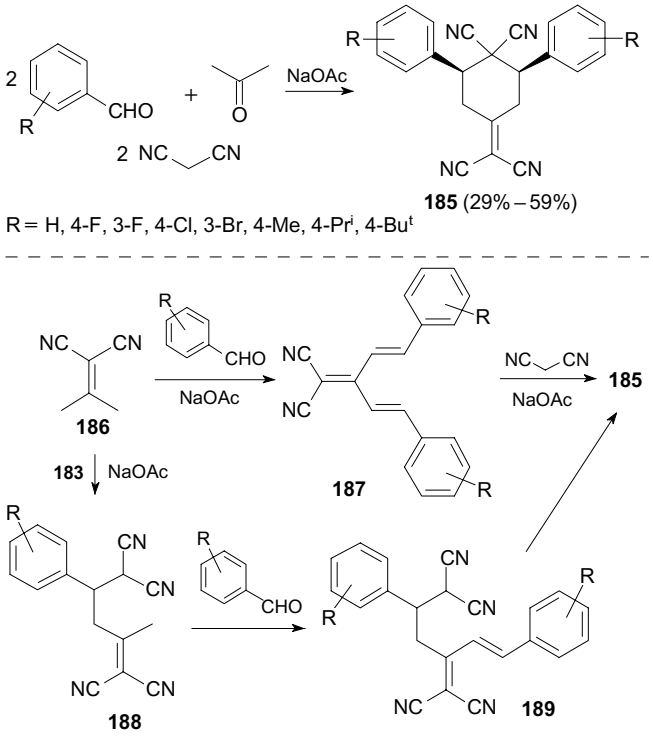


Scheme 67



Another multicomponent reaction involving malononitrile was used in the pseudo-five-component synthesis of cyclohexane derivatives. The transformation is based on the reaction of benzaldehydes, malononitrile and acetone in the presence of a catalytic amount of sodium acetate. The reaction results in the stereoselective formation of *cis*-2,6-diaryl-4-dicyanomethylidenecyclohexane-1,1-dicarbonitriles **185** in moderate yields (Scheme 68).[151] Two mechanisms were proposed for this process. Both mechanisms involve the Knoevenagel condensation giving compounds **183** and **186**. Then, in one mechanism, the reaction of intermediate **186** with two aldehyde molecules affords triene **187** followed by the addition of malononitrile as the final step. In an alternative mechanism, the reaction of compounds **183** and **186** gives product **188**, and its subsequent reaction with aldehyde affords intermediate **189**, which undergoes cyclization to derivative **185**.

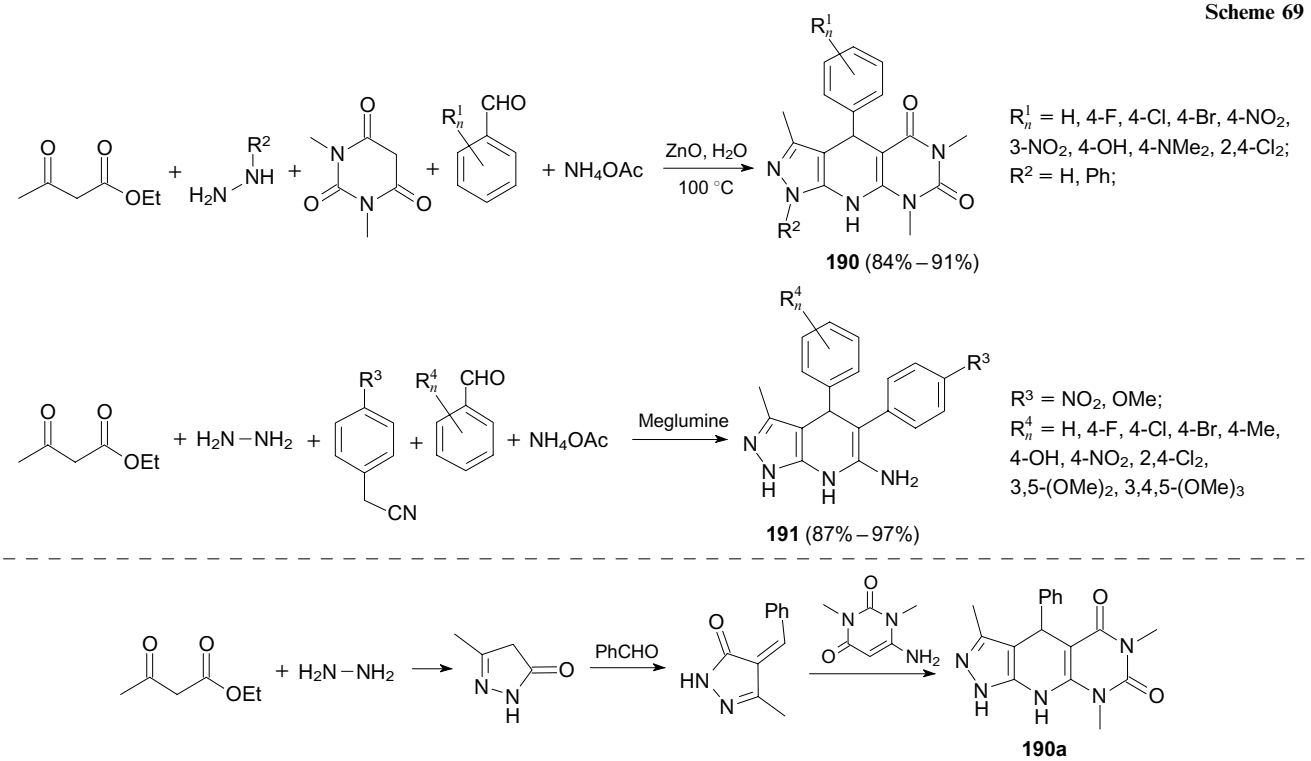
Scheme 68



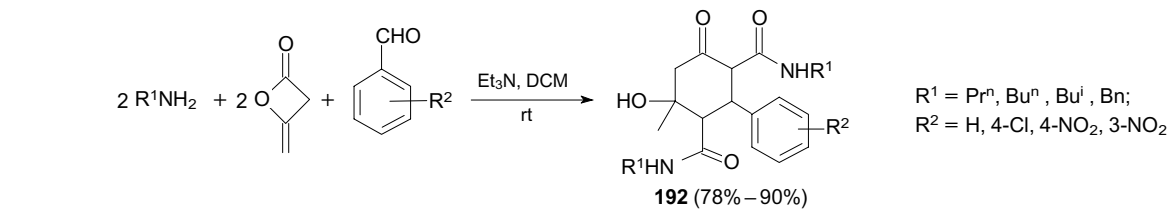
The synthesis of 4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine derivatives **190** was described[152, 153] (Scheme 69). These compounds were prepared in aqueous medium using zinc oxide nanoparticles. The process using 2-arylacetonitrile occurred in a similar way. The reaction was catalyzed by the aminosaccharide meglumine and gave heterocyclic products **191** in yields of up to 97%. Recently, a similar transformation was performed in the presence of nanosized neodymium catalysts.[154] The reaction mechanism involves the cyclocondensation of acetoacetic ester with hydrazines, the Knoevenagel reaction and the Michael addition of an amino pyrimidine derivative, generated by the reaction with ammonium acetate (see the synthesis of compound **190a** presented in Scheme 69). The second reaction occurs in a similar way.

Diketene was also used in the synthesis of cyclohexane-1,3-dicarboxamide derivatives **192** (Scheme 70).[155] The pseudo-five-component reaction of amine, diketene and benzaldehyde in a ratio of 2 : 2 : 1 takes place under mild conditions and affords products **192** in yields of up to 90%. The reaction mechanism involves the following reaction sequence: the ring opening of diketene by amine giving diketone **166**, Knoevenagel condensation yielding intermediate **193**, the Michael addition of diketone **166**, resulting in the formation of bis-product **194**, and intramolecular aldol condensation of product **195** to form target cyclohexane-1,3-dicarboxamide **192** (see Scheme 70). The transformation gives rise to five new C – C bonds and four chiral centres.

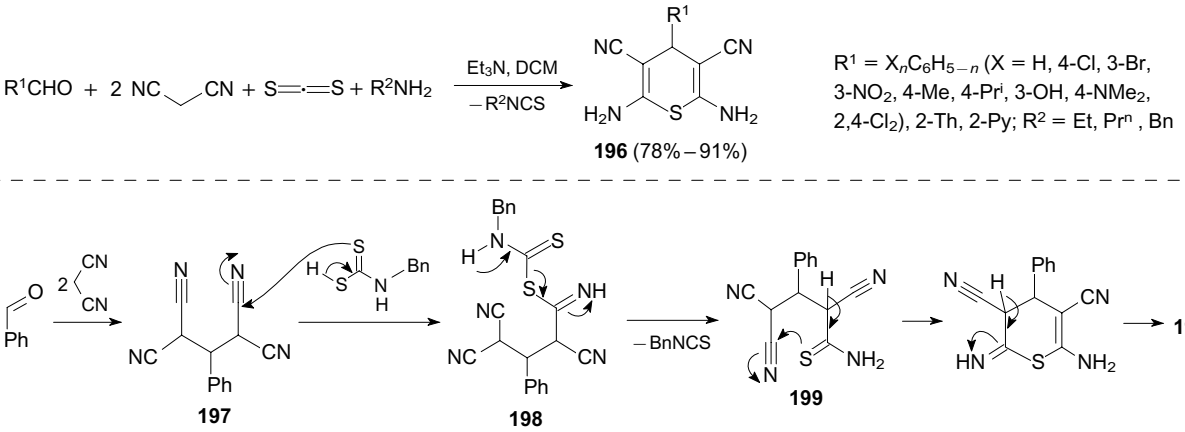
Scheme 69



Scheme 70



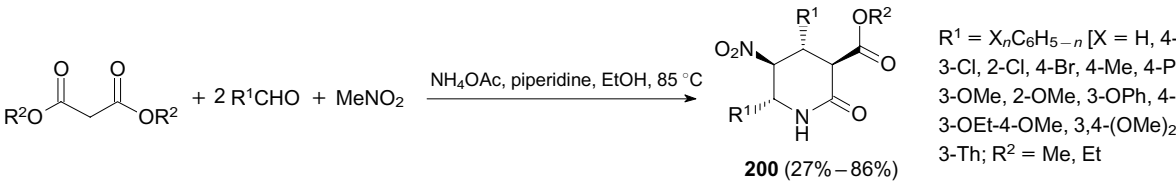
Scheme 71

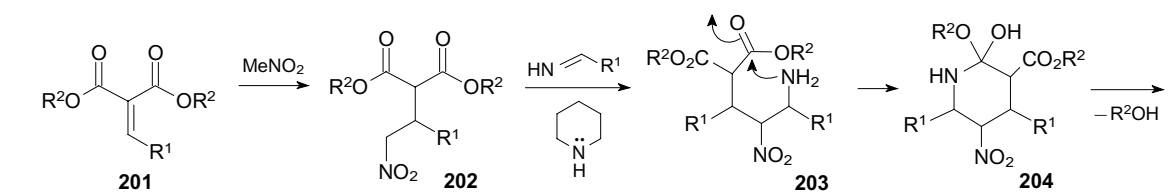


A convenient method for the synthesis of 4*H*-thiopyran derivatives **196** is based on the pseudo-five-component reaction of aryl carbaldehydes, malononitrile, primary amines and carbon disulfide. This reaction affords polyfunctionalized 4*H*-thiopyrans **196** in high yields (Scheme 71).[156] The first step is the Knoevenagel reaction involving benzaldehyde and malononitrile, which is followed by Michael addition of the second malononitrile molecule to form intermediate **197**. The successive steps include the formation of compound **198** through the nucleophilic addition of benzylcarbamodithioic acid, generated from benzylamine and carbon disulfide, the elimination of benzyl thiocyanate giving intermediate **199**, intramolecular condensation and tautomerization (see Scheme 71; exemplified by the reactions using benzaldehyde and benzylamine).[157]

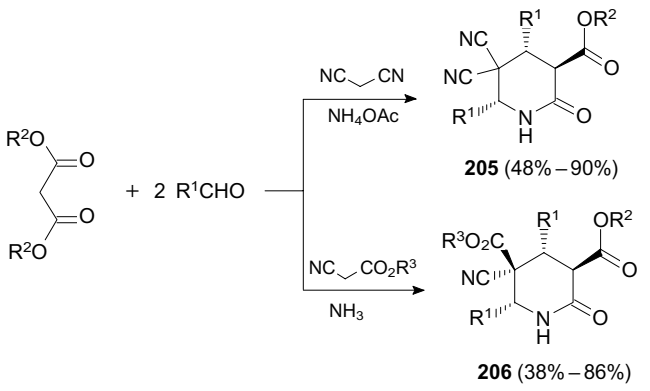
A similar reaction sequence was used in the diastereoselective synthesis of polysubstituted 2-piperidinones **200** (Scheme 72).[158] The pseudo-five-component reaction of malonic ester, aryl carbaldehyde, nitromethane and ammonium acetate affords compounds **200** as single diastereomers in moderate to high yields. The reaction mechanism involves the Michael addition of nitromethane to Knoevenagel product **201** giving diester **202**, the addition of arylimine to form intermediate **203** (see Scheme 72), its intramolecular cyclization to compound **204** and the elimination of alcohol, resulting in the formation of final product **200**. High diastereoselectivity of the reaction is

Scheme 72





Scheme 73



$R^1 = XC_6H_4$ (X = H, 4-Cl, 3-Cl, 4-Br, 4-Me, 3-Me, 2-Me, 4-OMe, 4-NO_2, 3-NO_2), 3-Py, 2-Fu; R^2, R^3 = Me, Et, Pr^n

attributed to the favourable equatorial orientation at the positions 3, 4 and 6 of the resulting 2-piperidinone ring and the thermodynamically controlled conditions of the reaction.

Malononitrile and cyanoacetic esters can be used instead of nitromethane as carbon acids. In this case, target piperidinones **205** and **206** are produced as single diastereomers in yields of up to 90% (Scheme 73).[159]

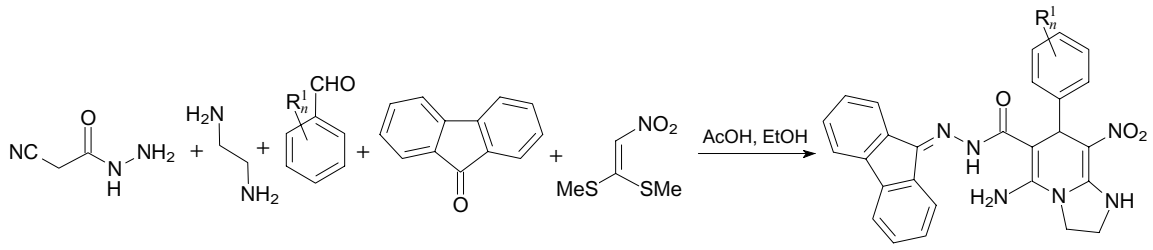
Imidazopyridine derivatives **207** and **208** were synthesized based on 2-(nitromethylene)imidazolidine (Scheme 74).[160] The five-component reaction of 2-cyanoacetohydrazide and ethylenediamine (or other diamines) with benzaldehydes, 9-fluorenone (or 4-nitroacetophenone) and 1,1-bis(methylthio)-2-nitroethylene affords target products in yields of up to 90%.[161] The process is a domino sequence, involving the formation of hydrazone **209**, the Knoevenagel condensation giving product **210**, Michael addition of heterocyclic ketene aminal, generated from ethylenediamine and bis(methylthio)-2-nitroethylene, and intramolecular cyclocondensation of compound **211** giving imine **212**, which undergoes isomerization to product **207** (see Scheme 74).

The synthesis of highly functionalized pyranopyrazoles **213** catalyzed by copper iodide nanoparticles was accomplished using the five-component reaction, involving malononitrile, hydrazine, Meldrum's acid, aromatic aldehydes and acid chlorides (Scheme 75).[162] Pyranopyrazoles **213** were isolated in moderate yields by heating the reaction mixture in aqueous medium in the presence of the catalyst. According to the proposed mechanism, compound **214** is generated *in situ* from Meldrum's acid and acid chloride and is then transformed into pyrazolone **215**. The subsequent Michael reaction with dicyanostyrene, generated from aldehyde and malononitrile, and the Thorpe – Ziegler condensation of intermediate adduct **216** afford target pyranopyrazole **213**.

A combination of a similar approach and the Suzuki reaction was applied in the synthesis of biphenyl-containing pyranopyrazoles **217** (Scheme 76).[163] The heating of the reaction mixture with palladium on carbon and potassium fluoride results in the formation of target products **217** generally in high yields (up to 92%).

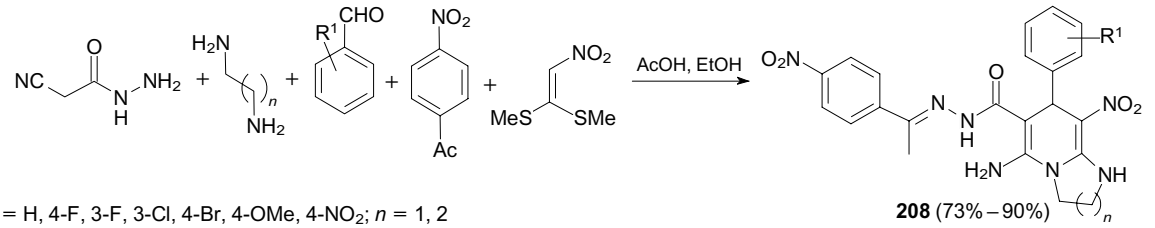
The five-component one-pot synthesis of hexahydrobenzofurans **218** and sulfenylimine chromene derivatives **219** was performed based on the reaction of benzaldehydes, malononitrile and dimedone followed by the treatment of the reaction mixture with aniline (or thiophenol) and *N*-chlorosuccinimide (NCS) (Scheme 77).[164] This approach was used to synthesize target five- and six-membered

Scheme 74



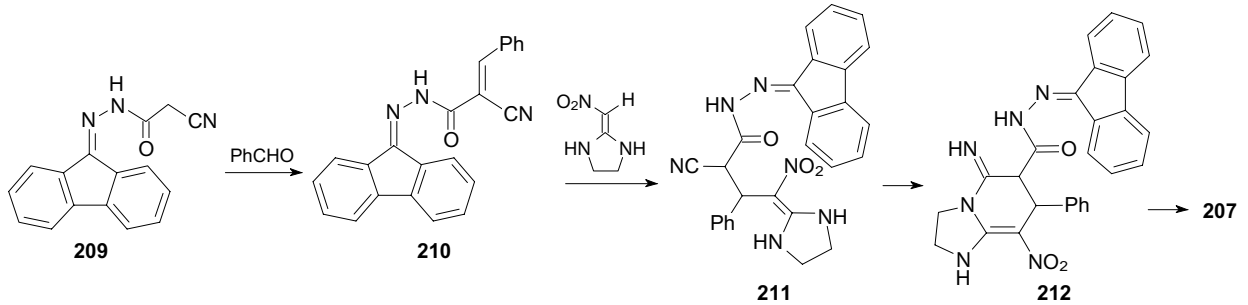
R^1_n = H, 4-F, 3-F, 3-Cl, 4-Br, 3-OMe, 4-NO_2, 4-CF_3, 3,4-$(OMe)_2$

207 (65% – 87%)

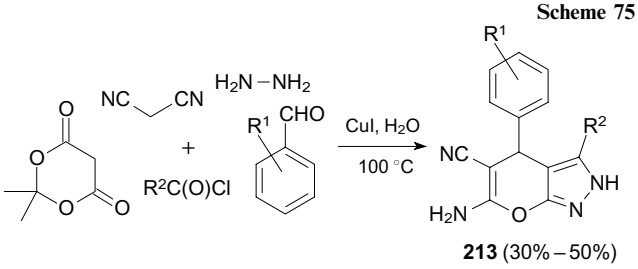


R^1 = H, 4-F, 3-F, 3-Cl, 4-Br, 4-OMe, 4-NO_2; n = 1, 2

208 (73% – 90%)

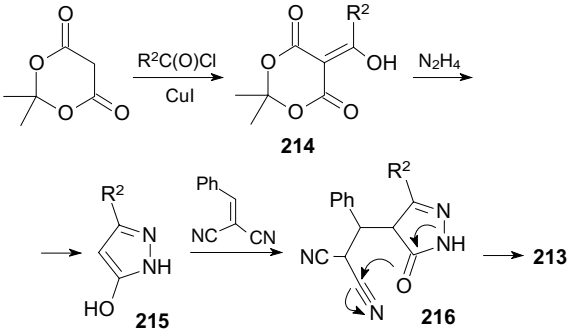


Scheme 75

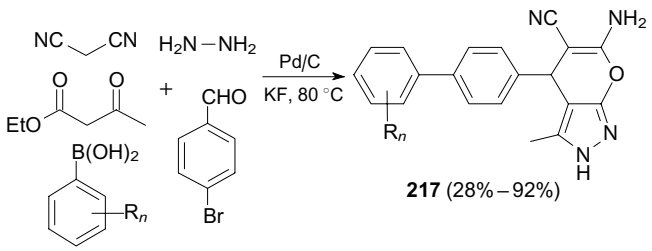


213 (30% – 50%)

R^1 = H, 4-Cl, 4-Br, 4-Me, 3-Me, 4-NO_2, 3-NO_2, 4-OH; R^2 = Me, Et



Scheme 76



217 (28% – 92%)

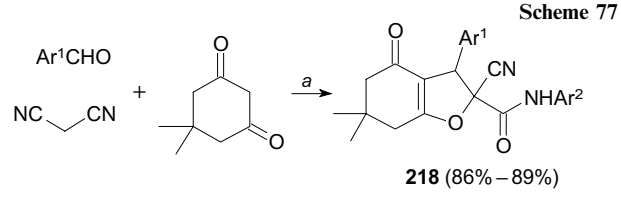
R_n = H, 4-F, 3-F, 4-Cl, 3-Cl, 4-Br, 4-Me, 3-Me, 4-Et, 4-Bu^t, 4-OMe, 4-CF_3, 2,4-F_2

heterocyclic compounds in yields of up to 93%. The first steps of the transformation are the sequential Knoevenagel condensation, nucleophilic Michael addition of dimedone giving compound **220** and intramolecular cyclization (see Scheme 77). After the addition of NCS and a nucleophilic component (aniline or thiol) to substituted tetrahydrochromenecarbonitrile **221**, the chlorination, ring opening and recyclization take place to form products **218** in the case of anilines; sulfenylation occurs in the case of thiophenol. Structures **222** – **224** are considered as intermediates.

Polycyclic bis(2-amino-4*H*-pyrans) **225** were synthesized by the pseudo-five-component domino reaction (Scheme 78).[165] The reaction of terephthalic and isophthalic aldehydes with malononitrile and 4-hydroxycoumarin in the presence of potassium alum afforded products **225** in yields of up to 79%. In this case, alum facilitated coagulation of the product. This transformation involves the sequential Knoevenagel reaction with malononitrile, Michael addition of 4-hydroxycoumarin and intramolecular cyclization.

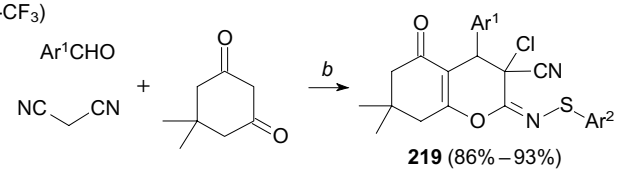
The five-component synthesis of bis(spiro-2-amino-4*H*-pyrans) **226** from isatin derivatives, malononitrile and 1,3-dicarbonyl compounds is based on similar reactions (Scheme 79).[166] The use of silica-coated magnetic Fe_3O_4 nanoparticles and ultrasonic irradiation of the reaction mixture allowed the preparation of target spiroheterocycles **226** in high yields.

Scheme 77



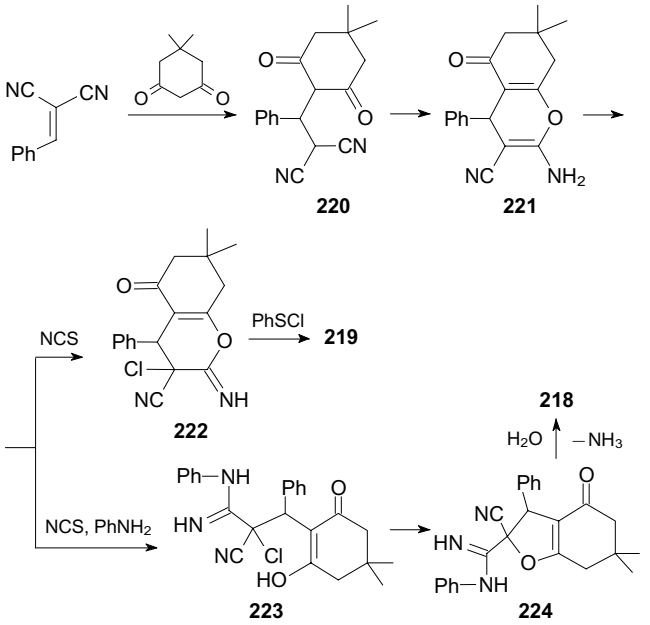
218 (86% – 89%)

(*a*) 1) PhMe, Δ; 2) Ar^2NH_2, NCS; Ar^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-Fu, 2-Th; Ar^2 = XC_6H_4 (X = H, 4-F, 4-Me, 4-NO_2, 2-CF_3)



219 (86% – 93%)

(*b*) 1) PhMe, Δ; 2) Ar^2SH, NCS; Ar^1 = 4-XC_6H_4 (X = H, Cl, Br, Me, OMe); Ar^2 = YC_6H_4 (Y = H, 4-F, 4-Cl, 4-I, 3-CF_3, 4-OCF_3)

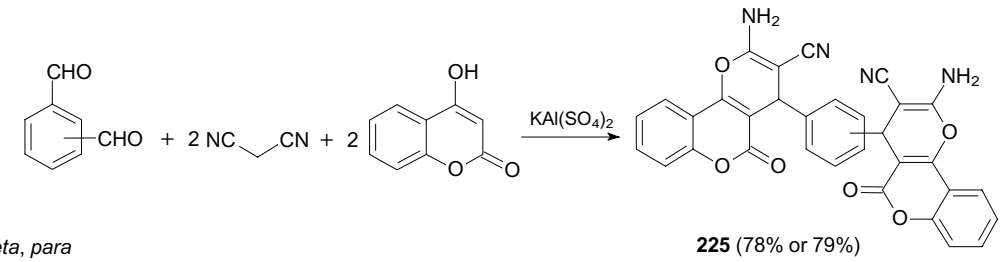


The one-step pseudo-five-component synthesis of bis(1*H*-indazolo[1,2-*b*]phthalazine-trione) derivatives **227** in the presence of a magnetic nanocatalyst was accomplished in a similar way. The condensation of bisaldehydes with dimedone affords activated alkenes **228** and the reaction of the latter with phthalazine gives intermediates **229**. The final step of the cascade process is the heterocyclization (Scheme 80). The target products were obtained in yields of up to 95%.[167]

An interesting diastereoselective synthesis of tetrahydrobenzodifuran-4,8-dione derivatives **230** is based on the reaction of 2-[2-oxo-2-(4-chlorophenyl)ethyl]isoquinolinium bromide, benzaldehyde and 2,5-dihydroxy-1,4-benzoquinone in a ratio of 2 : 2 : 1. This transformation affords compound **230** as a single diastereomer in high yield (Scheme 81).[168] The reaction mechanism involves the attack of the double Knoevenagel product by isoquinolinium ylide (2 equiv.) giving zwitterionic adduct **231**. The subsequent intramolecular cyclization and elimination of two isoquinoline molecules afford product **230**.

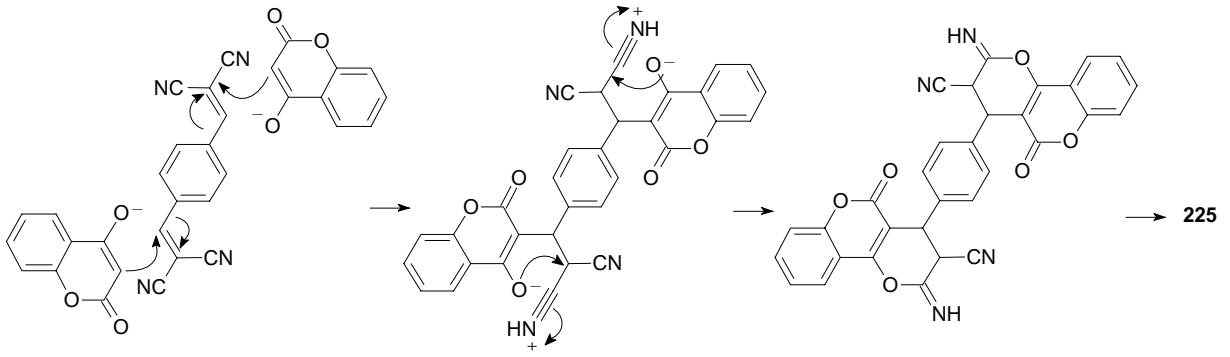
A similar transformation, in which dimedone serves as a carbon acid, was applied in the pseudo-five-component synthesis of fused chromene derivatives **232** in high yields

Scheme 78

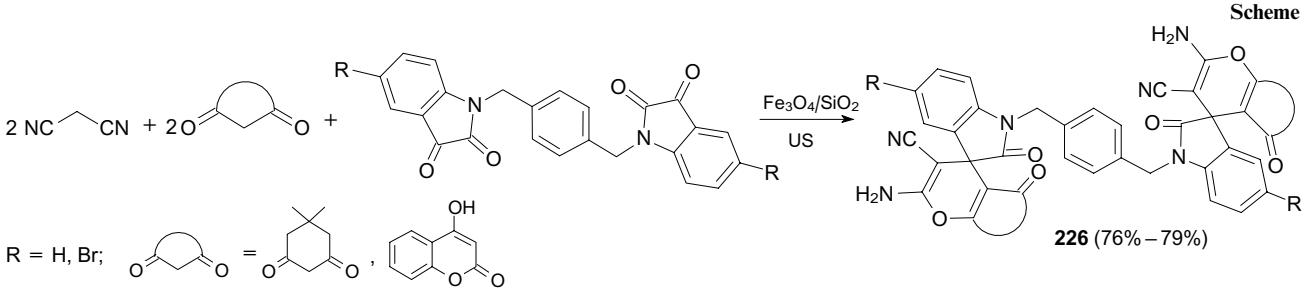


Isomers: *meta*, *para*

225 (78% or 79%)

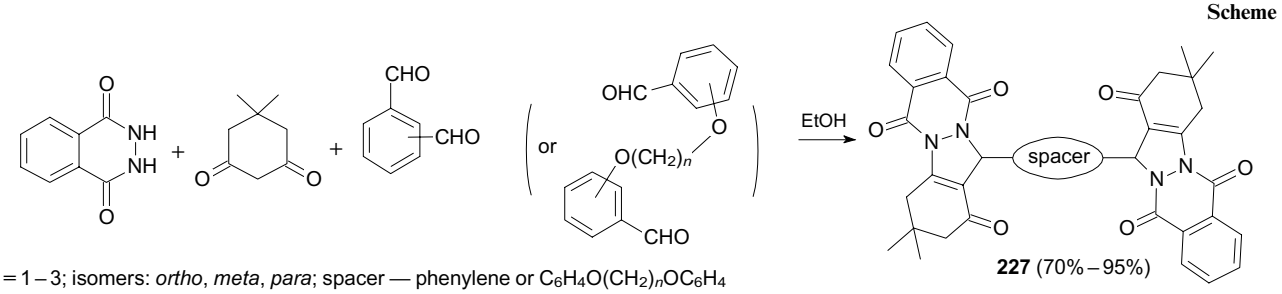


Scheme 79



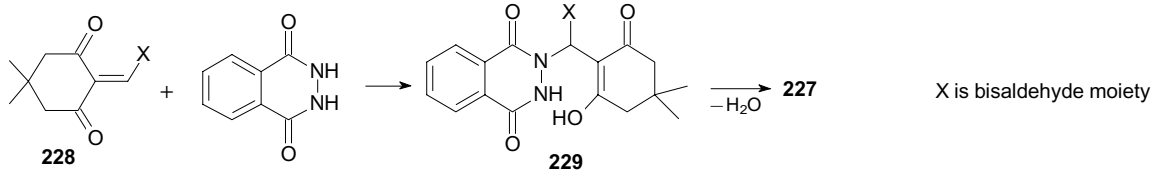
226 (76% – 79%)

Scheme 80



n = 1 – 3; isomers: *ortho*, *meta*, *para*; spacer — phenylene or $C_6H_4O(CH_2)_nOC_6H_4$

227 (70% – 95%)



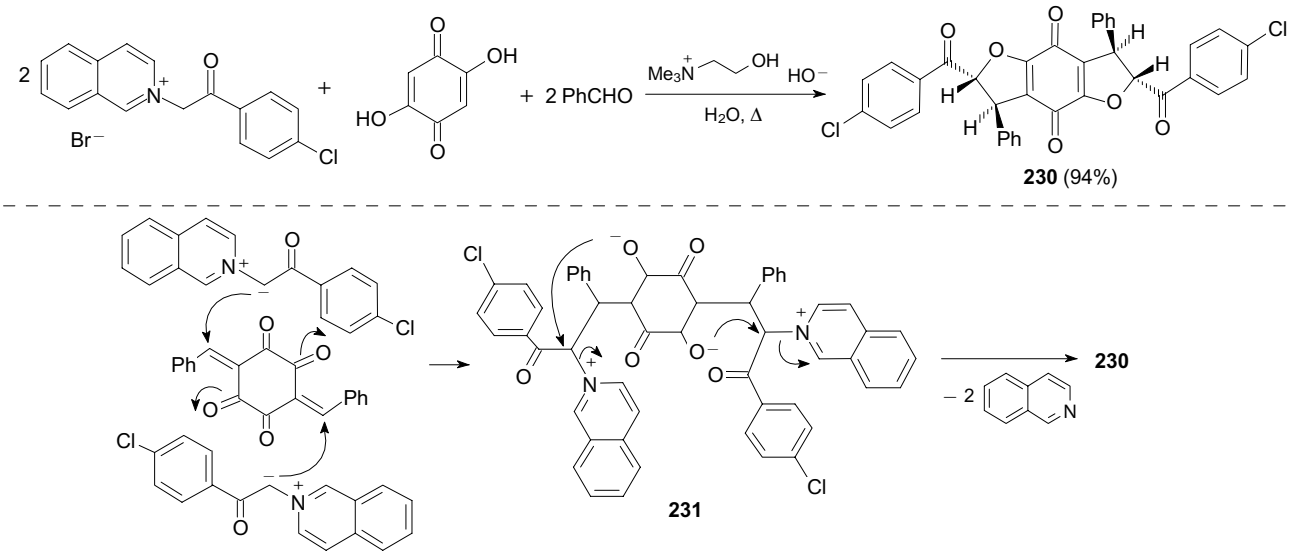
228 **229**

(Scheme 82).[169] This reaction was performed in the presence of aluminium-containing mesoporous molecular sieves (AlHMS) as the catalyst and iron-containing nanocatalysts.[170] The use of malononitrile as a carbon acid in a similar process resulted in the formation of dihydropyrano[2,3-*g*]chromene derivatives **233**.[171]

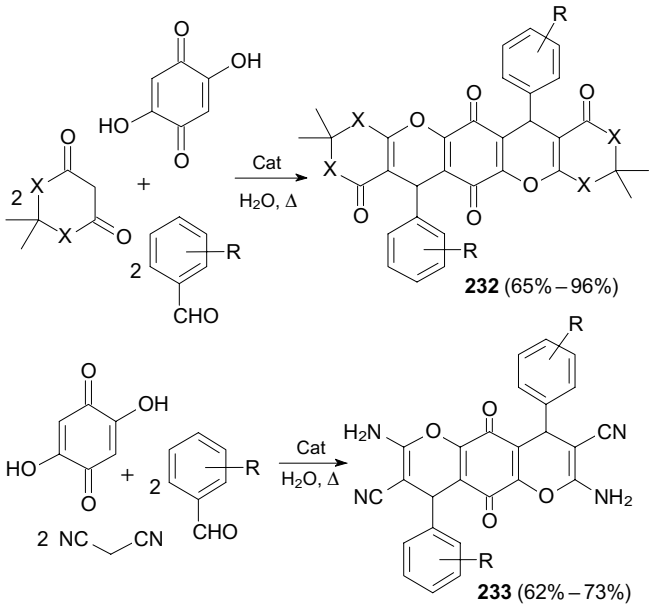
Heterocyclic sulfonyl[3,3,3]heteropropellanes **234** were synthesized by the five-component reaction from trichloroacetonitrile, sodium arylsulfinate, primary amine, ninhydrin and malononitrile (Scheme 83).[172] The reaction of primary amine, trichloroacetonitrile and sodium arylsulfinate affords arylsulfonylmethane iminoamide, which undergoes Michael condensation with a ninhydrin – malononitrile adduct (**235**) to form compound **236**. The subsequent intramolecular condensation gives target product **234**.

A method for the green synthesis of C(3)-pyranopyrazolyl-substituted coumarins **237** was developed based on the five-component reaction of 4-hydroxypyranone, hydrazine,

Scheme 81



Scheme 82

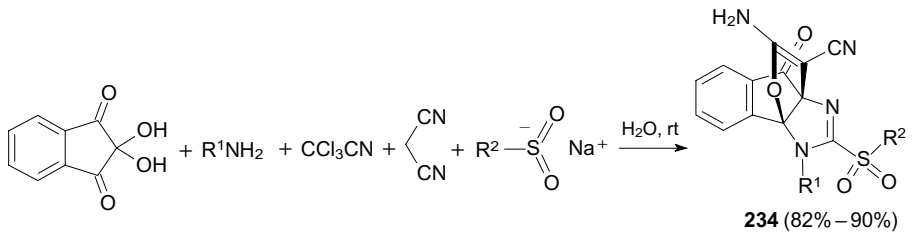


R = H, 4-Cl, 3-Br, 4-Me, 4-OMe, 4-NO_2, 3-NO_2; X = CH_2, O

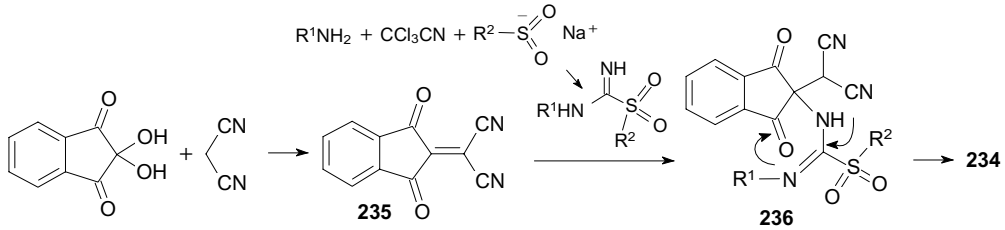
salicylaldehydes, acetoacetic ester and benzaldehydes (Scheme 84).[173] Coumarin derivatives **237** were prepared in high yields by the treatment of the reaction mixture in the presence of triethylamine with microwave irradiation. This reaction is a combination of two sequential Knoevenagel condensations. The reaction between hydroxypyranone and salicylaldehydes occurs as a cascade transformation through the formation of intermediate **238** to give diketones of coumarin series **239**. The second Knoevenagel reaction involves benzaldehydes and pyrazolones generated from acetoacetic ester and hydrazine. The Michael addition giving adduct **240** and intramolecular cyclocondensation are the final steps of the domino process.

An unusual example of the pseudo-five-component cycloaddition reaction using molecular iodine was described by Alizadeh *et al.*[174] (Scheme 85). This approach is based on the ability of iodine to activate imine bonds.[175] 1,2,4-Triazolo[1,5-*a*]pyridines **241** were prepared in yields of up to 76% by heating hydrazone (generated *in situ*), dialkyl acetylenedicarboxylate, aldehyde, malononitrile and molecular iodine in ethanol at reflux. The key step of the domino process (in relation to 4-chlorobenzaldehyde and benzaldehyde hydrazone) is the attack of compound **242**, generated from benzylidenehydrazine and dimethyl acetylenedicar-

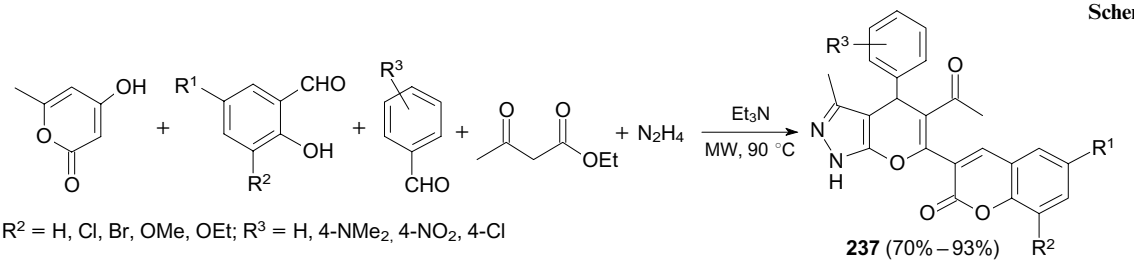
Scheme 83



R^1 = Bn, 4-$MeC_6H_4CH_2$, 4-BrC_6H_4, 4-ClC_6H_4; R^2 = Ph, 4-MeC_6H_4

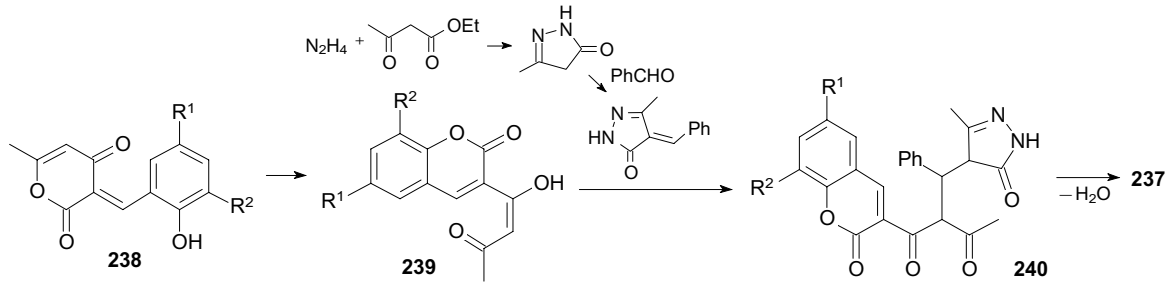


Scheme 84

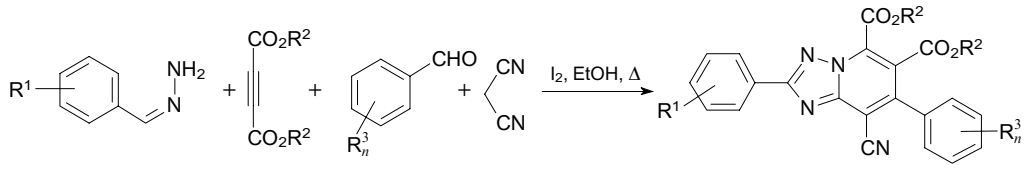


R^1 = H, Cl, Br; R^2 = H, Cl, Br, OMe, OEt; R^3 = H, 4-NMe_2, 4-NO_2, 4-Cl

237 (70% – 93%)

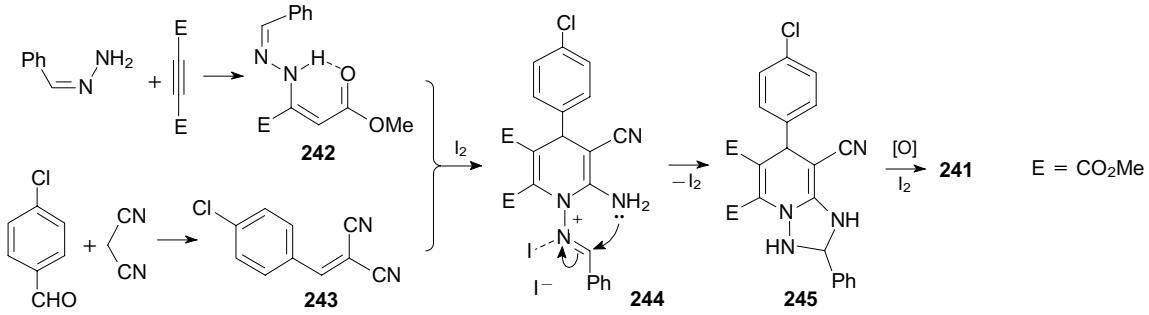


Scheme 85



R^1 = H, Cl, Me;
R^2 = Me, Et; R^3_n = 4-Cl, 3-Br, 4-Me, 2,6-Cl_2

241 (68% – 76%)



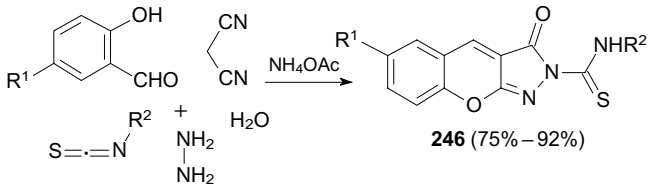
E = CO_2Me

boxylate, by Knoevenagel reaction product **243** (see Scheme 85) giving intermediate **244**. The imine moiety of the latter undergoes intramolecular nucleophilic attack by the NH_2 group in the reaction with an I_2 molecule. The oxidative aromatization of intermediate **245** affords target product **241**.

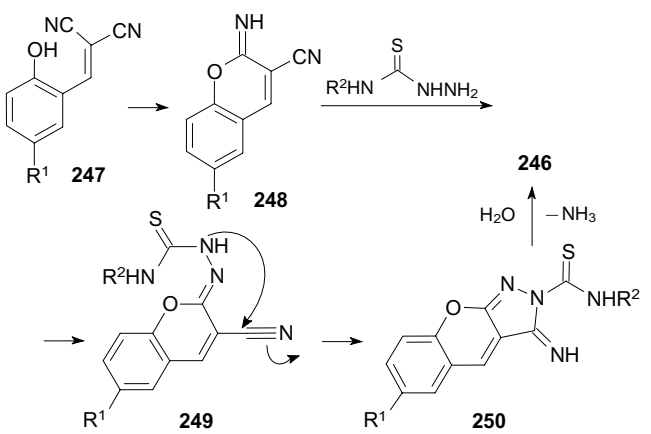
A five-component approach to the synthesis of *N*-aryl-3-oxochromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide derivatives **246** is based on the reaction of salicylaldehydes with malononitrile, hydrazine, isothiocyanates and water (Scheme 86).[176] A series of heterocyclic compounds **246** were prepared in yields of up to 92%. The transformation involves the Knoevenagel condensation of salicylaldehyde with malononitrile giving compound **247**, heterocyclization to imine **248**, the reaction with aryl thiosemicarbazide (generated from isothiocyanate and hydrazine) giving intermediate **249** and hydrolysis of heterocyclization product **250** to form the target heterocyclic system **246** (see Scheme 86).

Other polyfused heterocyclic compounds — benzo[*a*]phthalazino[2′,3′:1,2]pyrazolo[3,4-*c*]phenazines **251** — were synthesized by the five-component reaction catalyzed by magnetic Fe_3O_4 nanoparticles (Fe_3O_4-MNPs) (Scheme 87).[177] This approach provides a route to target products **251** from available starting compounds. Magnetic Fe_3O_4 nanoparticles facilitate the condensation of

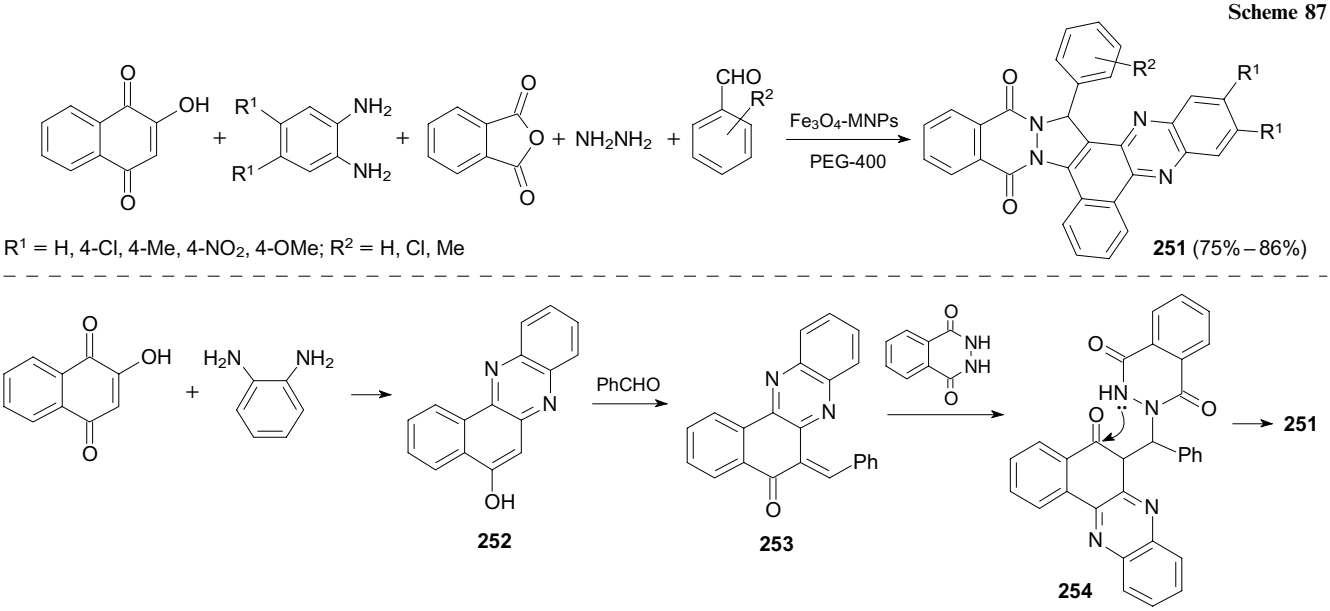
Scheme 86



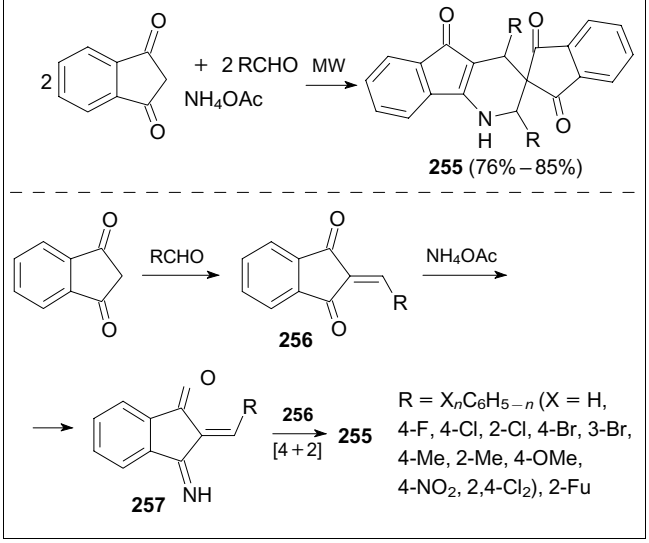
R^1 = H, Br, NO_2, OMe; R^2 = Ph, 4-FC_6H_4, 4-ClC_6H_4



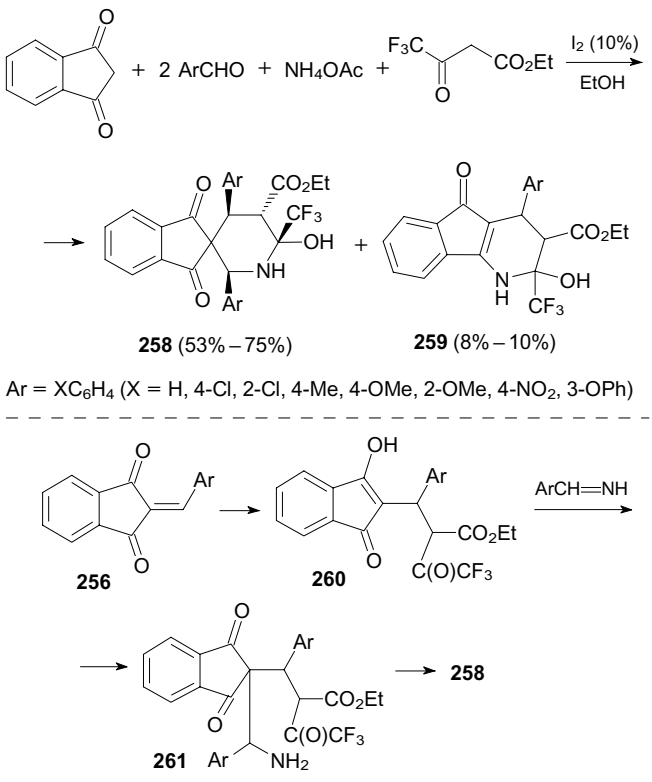
Scheme 87



Scheme 88



Scheme 89



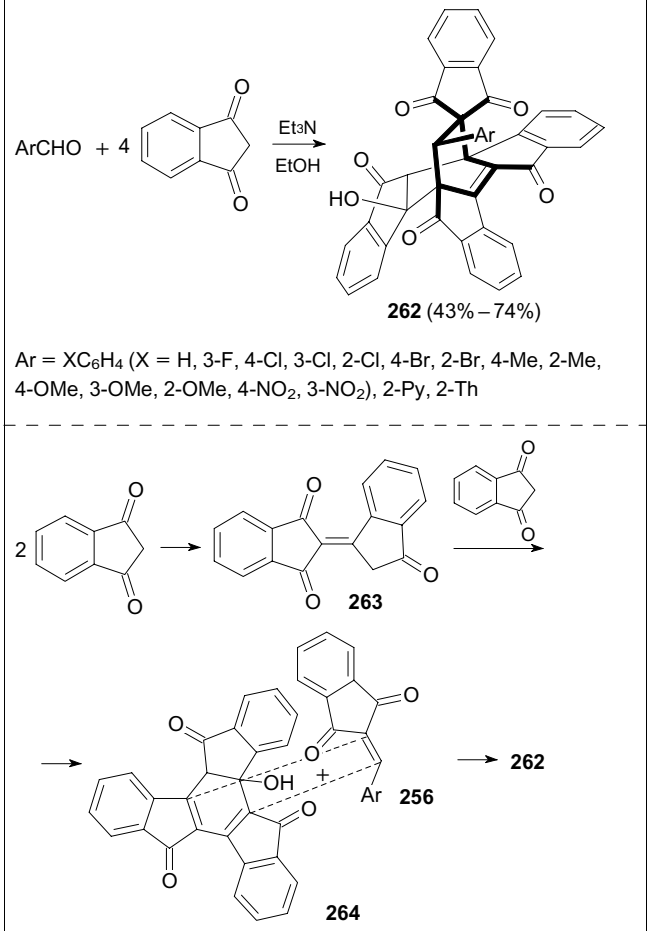
2-hydroxynaphthalene-1,4-dione with phenylenediamine giving product **252**, which undergoes the Knoevenagel reaction with benzaldehydes. The subsequent addition of intermediate **253** to phthalhydrazide gives adduct **254** and the latter undergoes intramolecular cyclocondensation to form compound **251**.

The pseudo-five-component Knoevenagel – aza-Diels – Alder reaction sequence was used in the synthesis of spiropyridines **255** (Scheme 88).[178] The microwave-assisted reaction under solvent-free conditions affords products **255** in yields of up to 85%. The reaction mechanism involves the Knoevenagel condensation of indane-1,3-dione and benzaldehydes giving unsaturated ketones **256**. The final steps are the subsequent transformation to imine **257** under the action of ammonium acetate and the aza-Diels – Alder reaction with the second molecule of unsaturated ketone **256** (see Scheme 88).

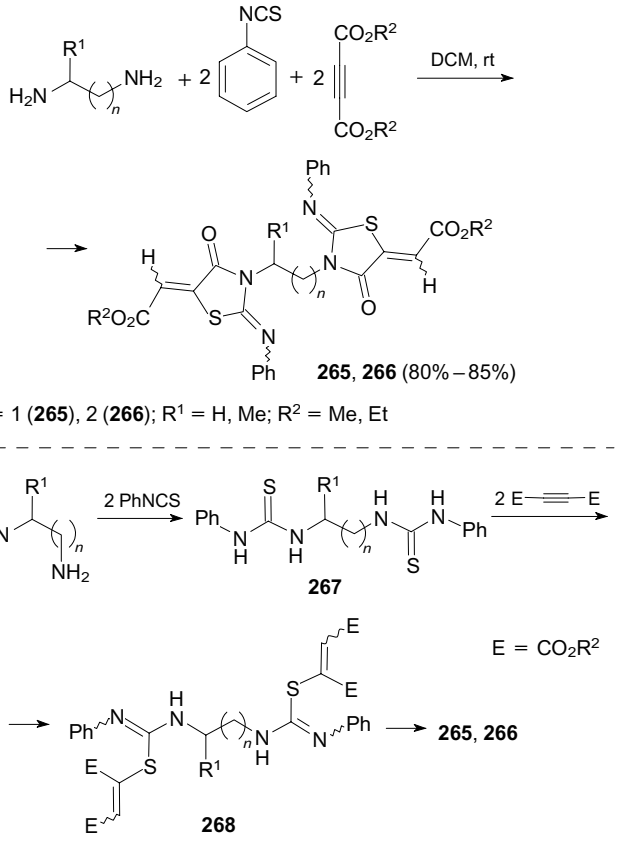
Trifluoromethyl-containing spiro[indene-2,3′-piperidines] **258** (see Ref. 179) were synthesized by the pseudo-five-component reaction of ethyl trifluoroacetoacetate, indane-1,3-dione, ammonium acetate and benzaldehydes in the presence of a catalytic amount of molecular iodine (10%) under mild conditions (Scheme 89).[180] The reaction occurs with complete diastereoselectivity under thermodynamic control to give compound **258** containing all bulky substituents in equatorial positions. Compounds **259** were isolated as by-products. The reaction mechanism involves the formation of Knoevenagel product **256**, the subsequent addition of ethyl trifluoroacetoacetate, the Mannich reaction of intermediate **260** giving compound **261** and its cyclization to spirocyclic product **258**.

Aromatic aldehydes react with four indane-1,3-dione molecules (a pseudo-five-component reaction) in ethanol

Scheme 90



Scheme 91



at reflux in the presence of triethylamine giving unique polycyclic bicyclo[2.2.2]octane derivatives **262** containing bridged- and spiro-indanone scaffolds. The reaction involves the base-catalyzed cyclotrimerization of indane-1,3-dione through the formation of dimer **263** to form active cyclic diene **264** and the subsequent Diels – Alder reaction with 2-arylideneindane-1,3-dione **256** generated *via* condensation (Scheme 90).[181] The reaction occurs in a stereoselective manner through the *endo* transition state.

2.6. Reactions based on heterocyclization

The pseudo-five-component one-pot synthesis of bis[2-(arylimino)-1,3-thiazolidin-4-ones] **265** and **266** was accomplished using the reaction of substituted ethylene- or propylenediamines, benzyl isothiocyanate and dialkyl acetylenedicarboxylate in a ratio of 1 : 2 : 2, which afforded target products in high yields (Scheme 91).[182] The plausible mechanism of the transformation involves the reaction of aliphatic diamine with two benzyl isothiocyanate molecules to form bis(thiourea) **267**, which is transformed into intermediate **268** in the reaction with dialkyl acetylenedicarboxylate (see Scheme 91). The final step is the intramolecular cyclization of compound **268** to bis[2-(arylimino)-1,3-thiazolidin-4-ones] **265** and **266**.

The pseudo-five-component cyclocondensation of isatin anhydride, benzaldehydes and diamines occurs in the presence of potassium alum (Scheme 92).[183] The use of substituted benzaldehydes and diamines made it possible to prepare a series of bis(dihydroquinazolinones) **269** in yields of up to 96%.[184] These compounds exhibit antioxidant, antitumour and electrochemical properties. According to the reaction mechanism, the reaction of isatin anhydride with diamine affords diamide **270**, which reacts with benzaldehyde (2 equiv.) to form diimine **271**. The intramolecular cyclization of the latter gives products **269** (see Scheme 92).

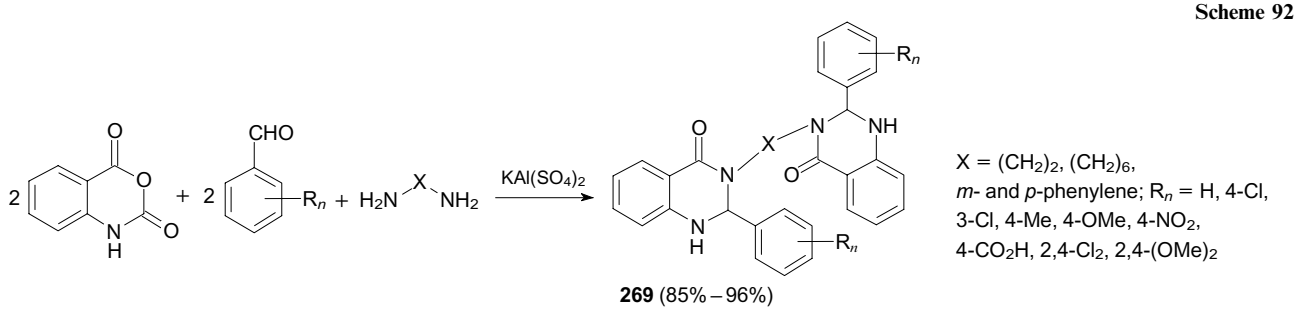
A similar approach was applied to synthesize bis[spiro(quinazoline,oxindole)] derivatives **272** (Scheme 93).[185] The use of 5-substituted isatins as a carbonyl component resulted in the formation of spiro compounds **272** in yields of up to 91%.

The cascade pseudo-five-component reaction of isatins and acetoacetic acid amides was employed to synthesize pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione derivatives **273**, which were isolated in yields of up to 90% (Scheme 94).[186] The reaction cascade starts with the acid-catalyzed reaction of two amide molecules with isatin giving compound **274**. The subsequent Knoevenagel reaction with the next two isatin molecules affords intermediate **275**, which is sequentially cyclized to compound **276**. The latter undergoes the ring opening to form product **277** followed by the protonation, resulting in the formation of quinoline moieties.

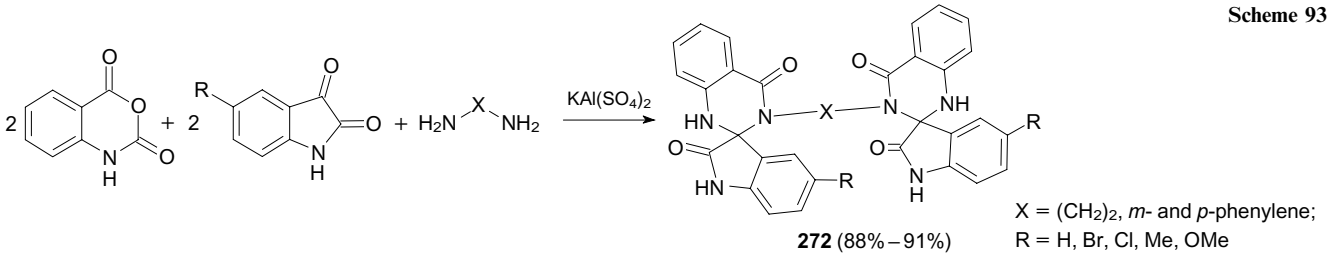
The pseudo-five-component one-pot synthesis of bisfuramides **278** was accomplished using the reaction of diamine (1 equiv.), diketene (2 equiv.) and dibenzoylacetylene (2 equiv.).[187] Target products were isolated in yields of up to 90%. The reaction mechanism involves the formation of dioxobutanamide **279**, the addition of betaine, which is generated from triphenylphosphine and dibenzoylacetylene, to form compound **280** and heterocyclization (Scheme 95).

The cyclocondensation of diamines with aryl carbaldehydes and 2-sulfanylacetic acid was utilized in the pseudo-five-component process (Scheme 96).[188,189] The use of

Scheme 92

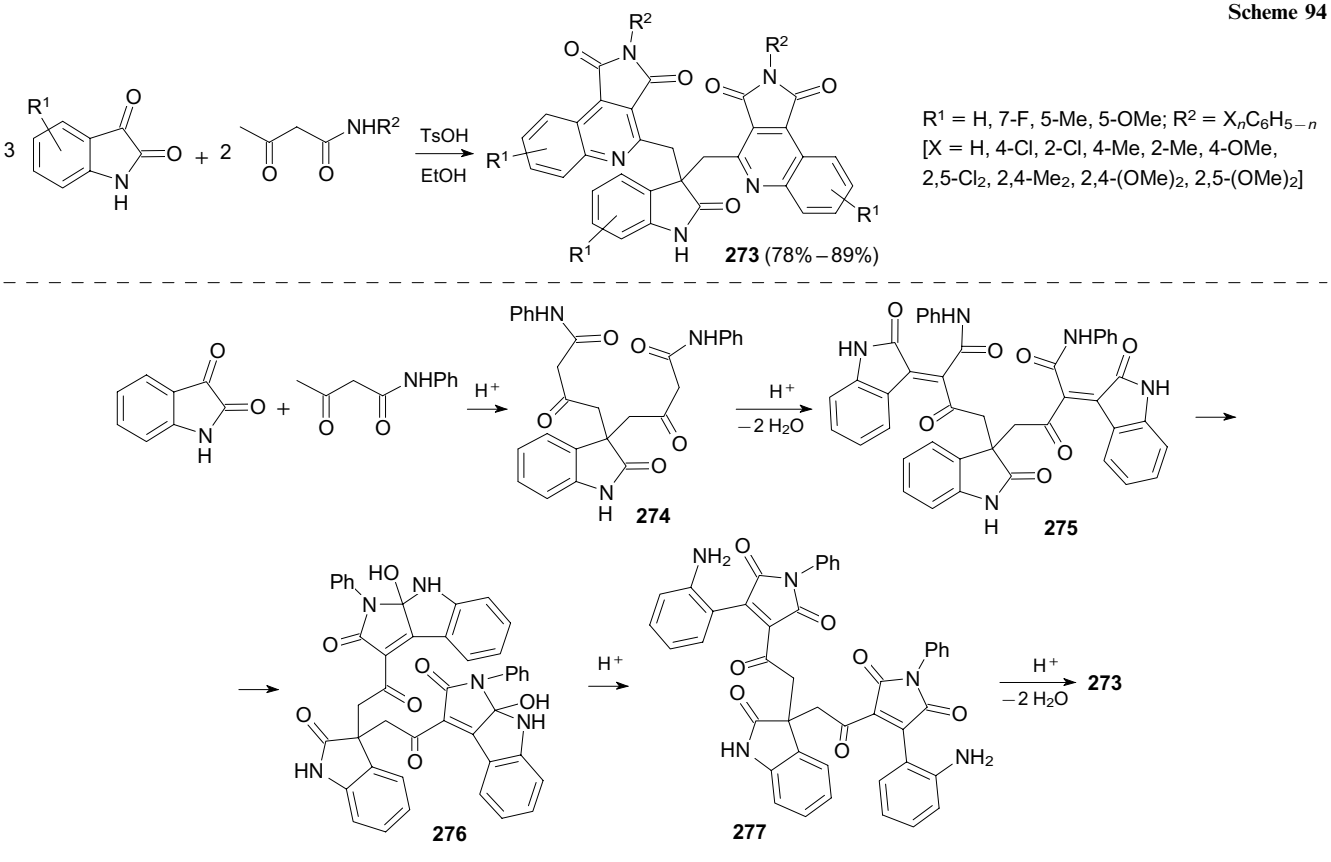


Scheme 93

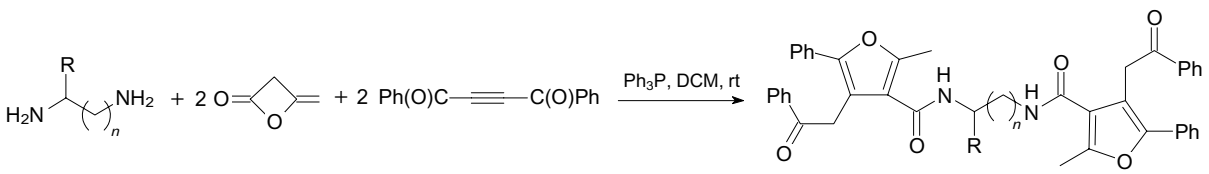


nano-colloidal polyhedral oligomeric silsesquioxanes and $CdZr_4(PO_4)_6$ nanoparticles as catalysts increases the yield of bis(thiazolidinones) **281** to 96% compared to the non-catalytic process, which afforded products in yields of not higher than 34%. This process involves the nucleophilic

Scheme 94

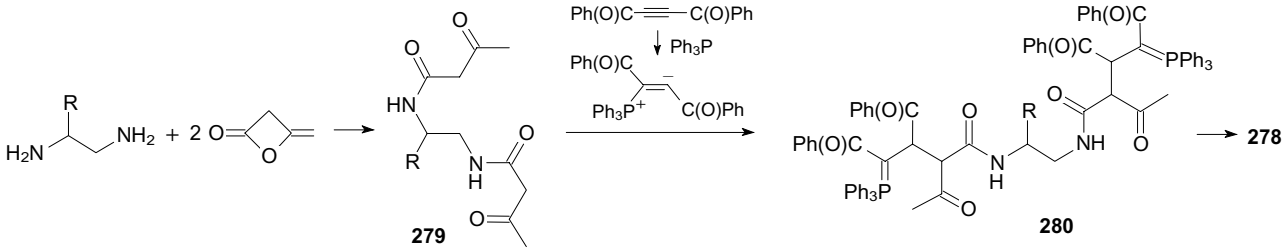


Scheme 95



n = 1, 3, 5, 7; R = H, Me

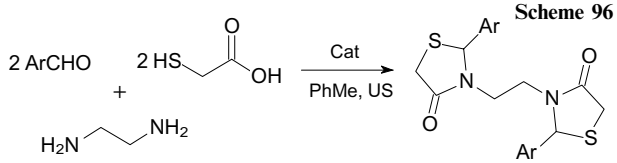
278 (82% – 90%)



279

280

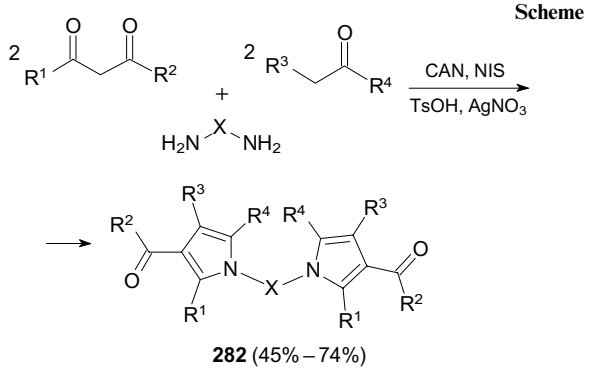
Scheme 96



281 (75% – 96%)

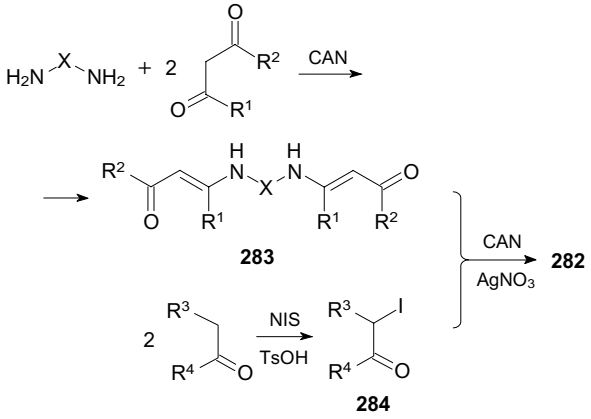
Ar = XC_6H_4 (X = H, 4-Cl, 2-Cl, 4-Me, 4-Pr^i, 4-NO_2, 3-NO_2), 2-Py, 3-Py

Scheme 97



282 (45% – 74%)

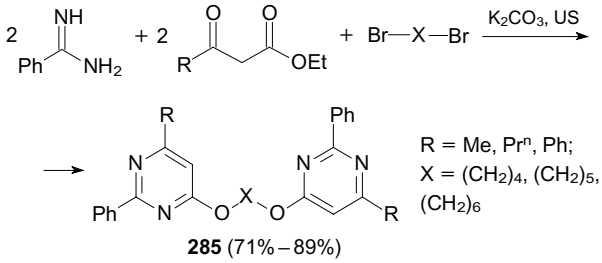
R^1 = Me, CH_2CO_2Me, CH_2CO_2Et; R^2 = Me, OMe, OEt, CH_2CO_2Me, CH_2CO_2Et; R^3 = H: R^4 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 2-Fu, 2-Th; $R^3 – R^4$ = $(CH_2)_3$; X = CH_2, $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_6$, $(CH_2)_7$, $(CH_2)_{11}$, $(CH_2)_2NH(CH_2)_2$, $(CH_2)_2N[(CH_2)_2]_2N(CH_2)_2$, $(CH_2)_2SiMe_2OSiMe_2(CH_2)_2$



283

284

Scheme 98



285 (71% – 89%)

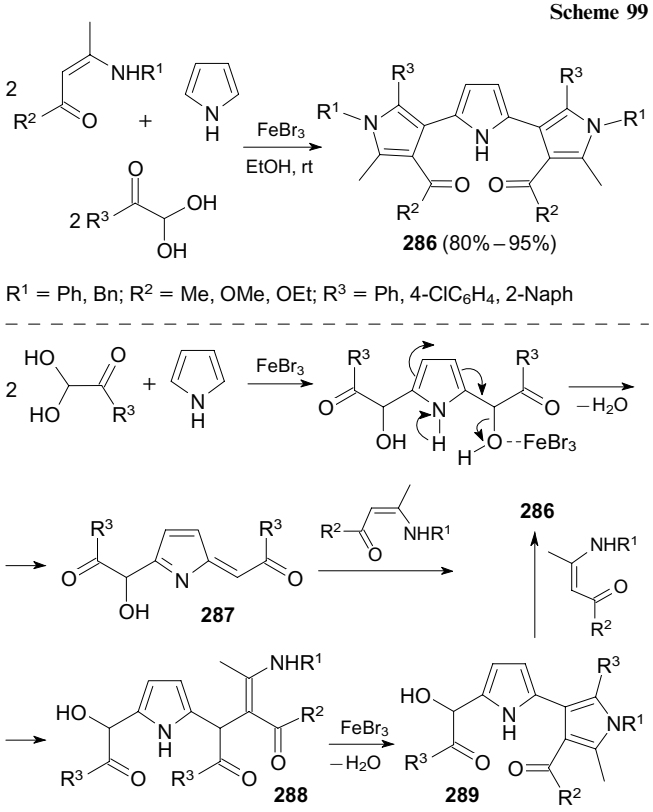
addition of 2-sulfanylacetic acid to diimine and subsequent intramolecular lactamization.

A method for the synthesis of symmetrical molecules **282** containing two pyrrole moieties was described by Leonardi *et al.*[190] (Scheme 97). The condensation of ketones, di- or triketones and diamines in the presence of cerium(IV) ammonium nitrate (CAN), *N*-iodosuccinimide (NIS), *p*-toluenesulfonic acid and silver nitrate resulted in the formation of diverse bis(pyrroles) **282** in yields of up to 74%. This process involves two competitive reactions: the CAN-catalyzed addition of two diketone molecules to diamine to form enamine **283** and the iodination of ketone with NIS to form compound **284**. The condensation of molecules **283** and **284** affords target product **282**. This approach was adapted to the synthesis of macrocyclic derivatives with different architecture.[191]

A facile method for the synthesis of bis-pyrimidines **285** is based on the pseudo-five-component heterocyclization and the linking of the resulting pyrimidine rings (Scheme 98).[192] A mixture of dibromoalkane (1 equiv.), acetoacetic ester (2 equiv.) and benzamidine (2 equiv.) was subjected to ultrasonication, resulting in the formation of products **285** in high yields.

Substituted terpyrroles **286** were synthesized by the reaction of pyrrole, β-enaminocarbonyl compounds and aryl glyoxals in a ratio of 1 : 2 : 2 using iron(III) bromide (Scheme 99).[193] The pseudo-five-component transformation affords target heterocycles **286** in yields of up to 95%. The plausible mechanism involves the alkylation of pyrrole with aryl glyoxal (2 equiv.) in the presence of $FeBr_3$. The subsequent $FeBr_3$-promoted elimination of a water molecule affords **287**, and the addition of enaminone gives pyrrole **288**. The cyclization to bipyrrole **289** and the

Scheme 99

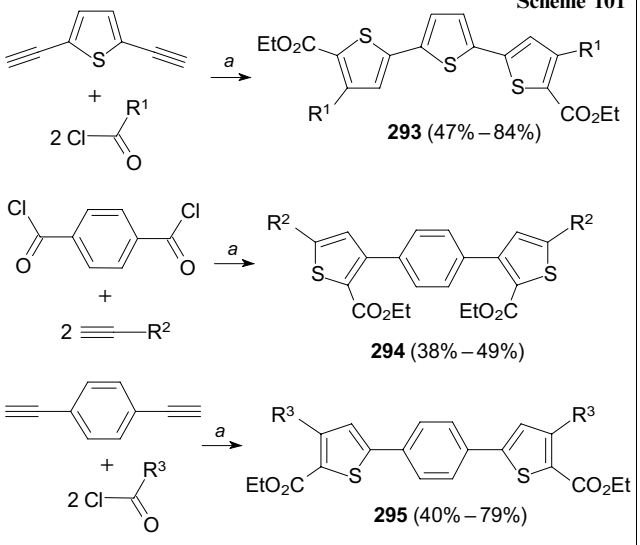


repeated sequence of transformations with this compound and enaminone afford product **286**.

2.7. Transformations involving the Sonogashira reaction

A pseudo-five-component one-pot process involving the Sonogashira reaction was used to synthesize terthiophenes **290** (Scheme 100).[194] The reaction using thiophene-2,5-dicarbonyl dichloride, aroylacetylene and ethyl 2-sulfanylacetate as the starting compounds gave β,β′-terthiophenes **290** in yields of up to 84%. This approach is the consecutive Sonogashira reaction – Fiesselmann thiophene synthesis sequence that proceeds *via* the following mechanism (see Scheme 100). The reaction begins with the cross-coupling of thiophene-2,5-dicarbonyl dichloride with aroylacetylene (2 equiv.) in the presence of the $Pd(PPh_3)_4 - CuI - Et_3N$ catalytic system, resulting in the formation of acetylenic diketones **291**. Target oligothiophenes **290** are generated *via* the subsequent Michael addition of two ethyl 2-sulfanyl-

Scheme 101



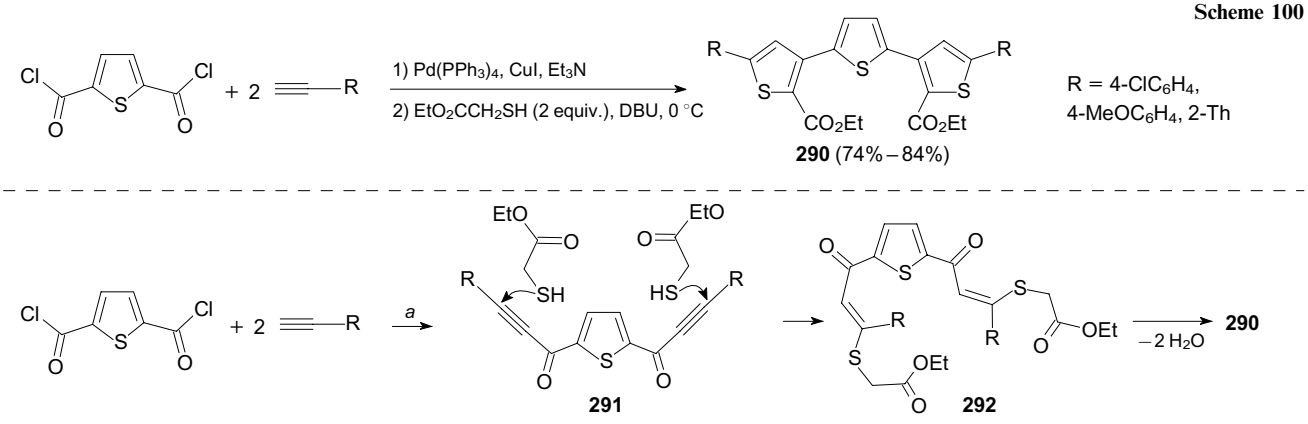
(*a*) 1) $Pd(PPh_3)_4$, CuI, Et_3N; 2) EtO_2CCH_2SH (2 equiv.), DBU, 0 °C;
R^1 = cyclo-C_3H_5, Bu^t, 4-FC_6H_4, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 2-Th;
R^2 = 4-MeC_6H_4, 2-Th; R^3 = 4-MeC_6H_4, 2-Th

acetate molecules giving adduct **292** and intramolecular aldol condensation.

A pseudo-five-component Sonogashira – Fiesselmann sequence was modified for the synthesis of β,β′-terthiophenes **293** and oligoaryls **294**, **295** (Scheme 101).[195] β,β′-Disubstituted thiophenes **293** were prepared from 2,5-diethynylthiophene. Target products **293** – **295** were isolated in yields of up to 84%.

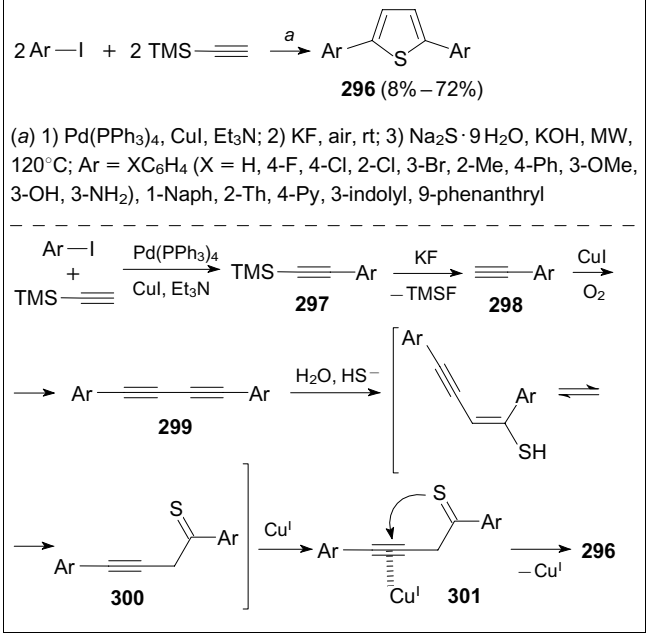
Another approach to the synthesis of polythiophenes and other polyarylated compounds **296** was applied to prepare 2,5-di(het)arylthiophenes from available reactants in one step (Scheme 102).[196] The Sonogashira – Glaser – heterocyclization domino sequence provides a route to oligoaryl compounds **296** in moderate to high yields; however, the reaction with 3-iodoindole gives target product in very low yield (8%). This synthesis is a three-step one-pot process, the mechanism of which can be described as follows (see Scheme 102). The reaction starts with the cross-coupling of trimethylsilylacetylene and (het)aryl iodide in the presence of the $Pd(PPh_3)_4 - CuI - Et_3N$ catalytic system giving alkyne **297**. The removal of the TMS protecting group with a fluoride ion affords terminal alkyne **298**, which undergoes Glaser oxidative coupling promoted by

Scheme 100



(*a*) 1) $Pd(PPh_3)_4$, CuI, Et_3N; 2) EtO_2CCH_2SH (2 equiv.), DBU, 0 °C

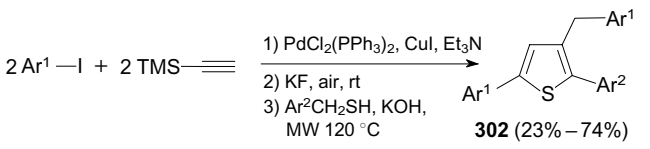
Scheme 102



copper(I) iodide and atmospheric oxygen to form diyne **299**. The addition of a hydrosulfide ion affords unsaturated thione **300**, which is coordinated to the copper(I) ion. Finally, complex **301** undergoes cyclization to product **296**.

Interestingly, an attempt to adapt this method to the synthesis of 2,3,5-trisubstituted thiophenes using benzyl thiol instead of sodium sulfide led to the formation of isomeric 3-(het)arylmethyl-2,5-di(het)aryl-substituted thiophenes **302** (Scheme 103) [197] isolated in yields of up to 74%. The addition of thiolate to butadiyne should afford a regioisomer with the most resonance-stabilized anion; in this case, the *E* to *Z* isomer ratio is 1 : 2. The *E* isomer is known to be completely transformed into the *Z* isomer when indirectly exposed to sunlight over a year. Since only the *Z* isomer can undergo cyclization to thiophene for steric reasons, it is assumed that microwave irradiation significantly accelerates isomerization.[198]

Scheme 103

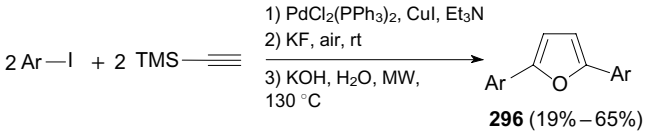


Ar^1 = XC_6H_4 (X = H, 4-F, 4-Cl, 4-Me, 3-Me, 2-Me, 3-OMe), 2-Th;
Ar^2 = Ph, 4-FC_6H_4, 4-MeC_6H_4, 2-Fu, 2-Th

The above-described approach to the preparation of 2,5-di(het)arylthiophenes was adapted to the synthesis of 2,5-di(het)arylfurans **296** (Scheme 104).[199] The consecutive pseudo-five-component Sonogashira – Glaser coupling – cyclization sequence afforded target 2,5-di(het)arylfurans **296** in moderate to good yields.

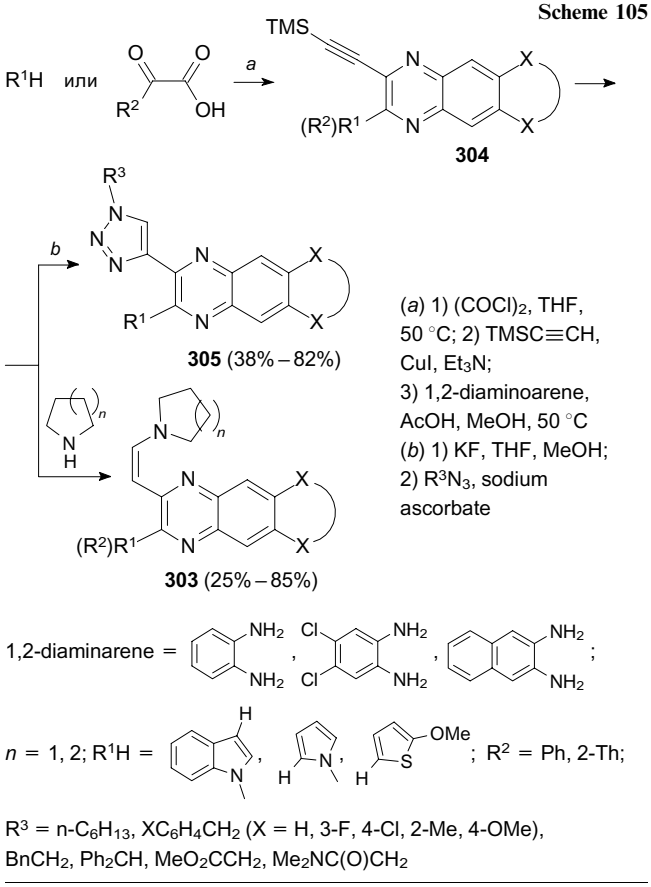
Gers-Panther *et al.*[200] developed a synthesis of 3-pyrrolidine- and 3-piperidinevinylquinoxaline derivatives **303** based on the five-component domino process involving the Sonogashira reaction (Scheme 105). This synthesis is a complex one-pot process, which can utilize heterocyclic compounds and arylglyoxylic acids as the starting substrates. In the first step, the reaction with oxalyl chloride affords the corresponding acid chlorides, which are involved in the copper-catalyzed Sonogashira reaction followed by cyclocondensation with 1,2-diaminoarene. Then pyrrolidine or piperidine is added to the resulting 3-ethynylquinoxaline **304**. The yields of target products **303** vary from 25% to 85%. An alternative modification of compounds **304** was accomplished based on the copper-catalyzed synthesis of 1,2,3-triazoles. The removal of the silyl moiety and the subsequent reaction with alkyl azides afford target derivatives **305** in yields of up to 82%.[201]

Scheme 104



Ar = $X_nC_6H_{5-n}$ (X = H, 4-F, 4-Me, 3-Me, 2-Me, 3-OMe, 3-CH_2OH, 3,5-Me_2, 3,4,5-Me_3, 2-OMe-5-Me), 1-Naph, 2-Naph, 3-Th

Scheme 105



1,2-diaminarene =

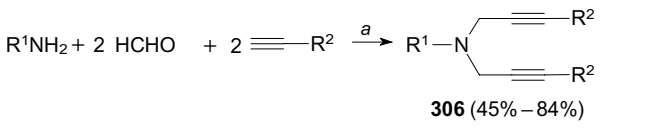
n = 1, 2; R^1H = ; R^2 = Ph, 2-Th;

R^3 = n-C_6H_{13}, $XC_6H_4CH_2$ (X = H, 3-F, 4-Cl, 2-Me, 4-OMe), $BnCH_2$, Ph_2CH, MeO_2CCH_2, $Me_2NC(O)CH_2$

2.8. A^3-Coupling reactions

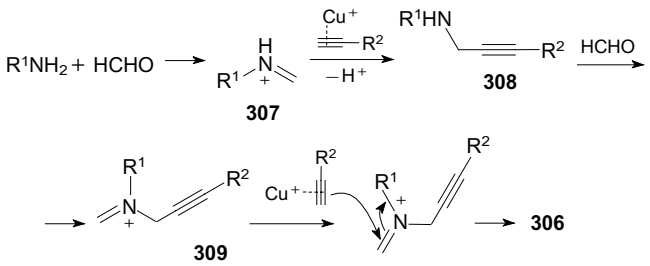
The three-component reaction of aldehydes, primary or secondary amines and terminal acetylenes is commonly called A^3-coupling.[202] More rare multicomponent reactions involving non-terminal acetylenes are also known.[203] A pseudo-five-component approach to the synthesis of bis(propargyl)amines **306** was described by Bonfield and Li [204] (Scheme 106). The reaction of primary amine, formaldehyde and terminal alkyne proceeded in aqueous medium in the presence of a ruthenium – copper co-catalyst. This method was used to prepare a series of N-substituted

Scheme 106



306 (45% – 84%)

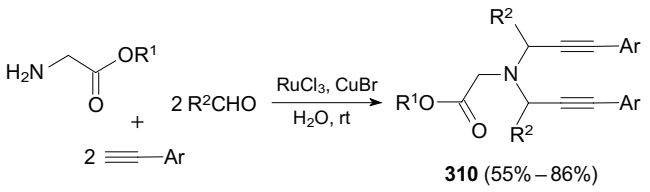
(*a*) $RuCl_3$, CuBr, H_2O, rt; R^1 = Bu^n, cyclo-C_5H_9, All, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, Ph$(CH_2)_3$; R^2 = Bu^n, Ph



bis(propargyl)amines **306** in yields of up to 84%. The reaction mechanism involves the formation of iminium salt **307** followed by the addition of a copper(I) acetylene complex. Then propargylacetylene **308** reacts with a second equivalent of formaldehyde and the copper acetylene complex to give sequentially compounds **309** and **306**.

Biologically active compounds were synthesized using glycine esters and diverse aldehydes as substrates in the pseudo-five-component A^3-coupling reaction (Scheme 107).[205] Target bis(propargyl)amines **310** were prepared in yields of up to 86%. Besides, in the case of 4-methyl- and 4-chlorobenzaldehydes, the reaction proved to be diastereoselective (the diastereomeric ratio was 88 : 12 and 72 : 28, respectively).

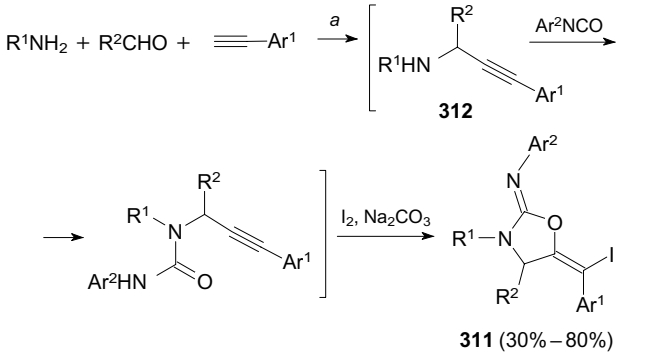
Scheme 107



310 (55% – 86%)

R^1 = Me, Et, Bu^t, Bn; R^2 = Bu^i, cyclo-C_6H_{11}, 4-ClC_6H_4, 4-$MeOC_6H_4$; Ar = Ph, 4-MeC_6H_4, 4-$Bu^tC_6H_4$

Scheme 108



311 (30% – 80%)

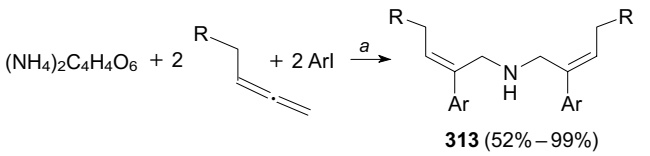
(*a*) CuI, 1,4-dioxane, 80 °C; R^1 = Bn, 4-$ClC_6H_4CH_2$, 4-$MeC_6H_4CH_2$, 3,4,5-$(MeO)_3C_6H_2$; R^2 = Pr^i, Bu^n, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-NCC_6H_4, 2-Cl-5-$O_2NC_6H_3$; Ar^1 = Ph, 2-MeC_6H_4; Ar^2 = Bn, 4-MeC_6H_4

A similar approach provides the basis for the one-pot synthesis of iodomethylideneoxazolidin-2-imines **311** (Scheme 108).[206] The reaction started with the CuI-catalyzed A^3-coupling. Then intermediate **312** was sequentially treated with isocyanate and a mixture of molecular iodine and sodium carbonate. This approach allows the preparation of desired heterocyclic derivatives **311** in moderate to high yields.

2.9. Palladium-catalyzed reactions

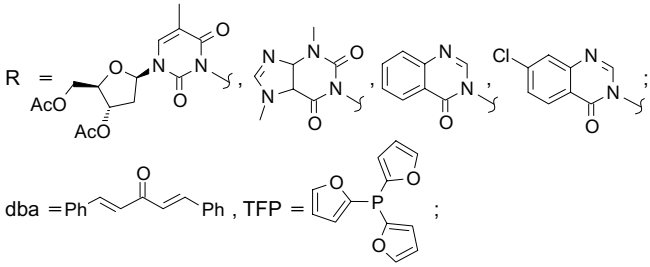
A palladium(0)-catalyzed synthesis of (*Z*,*Z*)-bis(allyl)-amines **313** was developed by Grigg *et al.*[207] (Scheme 109).

Scheme 109

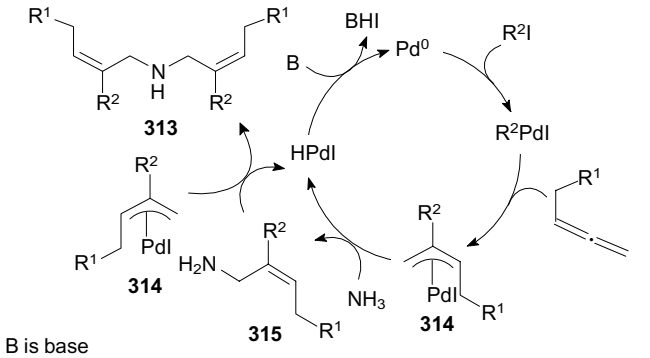


313 (52% – 99%)

(*a*) $Pd_2(dba)_3$, TFP, K_2CO_3, 1,4-dioxane – DMF (5 : 1), 100 °C;



Ar = $X_nC_6H_{5-n}$ [X = 4-NO_2, 4-CO_2Me, 4-Ac, 3-CF_3, 3,5-$(CF_3)_2$, 2,4-Cl_2, 3,5-Cl_2, 3,4-F_2], 2-Th, 3-Py

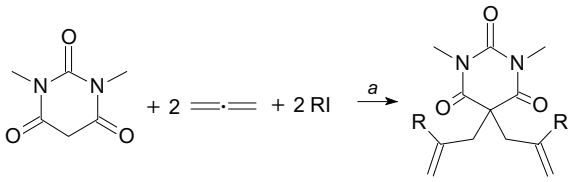


B is base

A series of allene derivatives of thymine, xanthine and quinazolinone as well as a wide range of aryl iodides were subjected to the reaction with ammonium tartrate as a source of ammonia to prepare (*Z*,*Z*)-bis(allyl)amines **313** in up to quantitative yields. The catalytic cycle for the synthesis is presented in Scheme 109. After the addition to the starting allene, the organopalladium compound forms π-complex **314**, which reacts with ammonia to form allylamine **315**, which is converted to **313** upon the reaction with a second equivalent of **314**.

This transformation can be performed with carbon acids instead of ammonia (Scheme 110).[208] Target α-substituted styrenes **316** were synthesized in high yields from *N*,*N*-dimethylbarbituric acid, allene and aryl iodides.

Scheme 110



316 (89% – 95%)

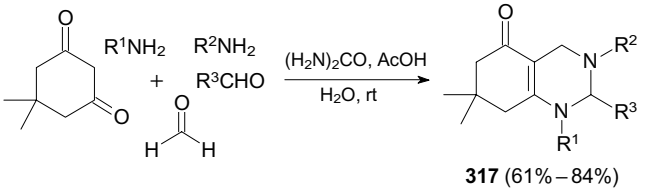
(*a*) $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 80 °C; R = $X_nC_6H_{5-n}$ [X = 4-Br, 4-CO_2Me, 4-CF_3, 3,5-$(CF_3)_2$, 3-Cl-4-F], 3-Py

2.10. Aza-ene-type reactions

A five-component synthesis of octahydroquinazolin-5-ones **317** was accomplished based on the reaction of dimedone, two different amines, benzaldehyde and formaldehyde under very mild conditions (30 mol.% urea as the catalyst, 2 equiv. of acetic acid, aqueous medium, room temperature) (Scheme 111).[209] This method affords target compounds **317** in yields of up to 84%. The first step in the synthesis is the condensation of dimedone and the most nucleophilic amine giving enamine **318**, which is involved in the aza-ene-type reaction with imine, generated from formaldehyde and another amine, resulting in the formation of diaminoketone **319** (see Scheme 111). The authors argue that this process involves exactly the aza-ene-type reaction rather than the Mannich reaction because the stepwise synthesis using secondary amine instead of a primary one would not afford a Mannich product, whereas adduct **319** was experimentally detected. Target compounds **317** were produced *via* the nucleophilic addition of adduct **319** to benzaldehyde giving diamine **320** and intramolecular condensation accompanied by the elimination of a water molecule.

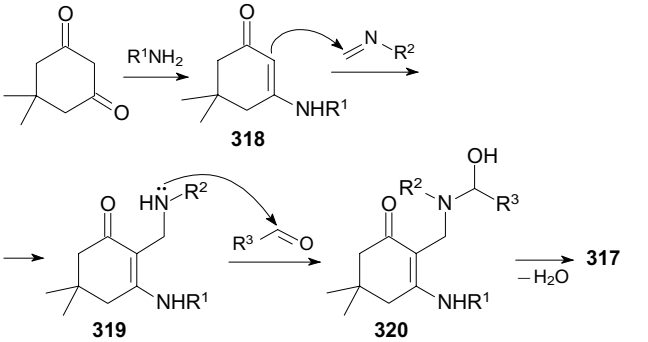
A similar five-component process was accomplished in the presence of diketene. This synthesis provides a route to another type of heterocycles. The reaction of diketene, arylamines, dimedone, primary amines and aryl aldehydes affords 3,4-dihydropyran-3-carboxamide derivatives **321** under mild conditions. This process gives rise to three stereocentres, but the reaction takes place with high diastereoselectivity under thermodynamically controlled conditions and gives products **321** in high yields (Scheme 112).[210] In this case, iodine serves as the catalyst. In the first step, the most nucleophilic amine reacts with diketene to form sequentially intermediate **322** and enamine **323**. The addition of the latter to activated alkene **324**, generated through the condensation of dimedone and aldehyde, affords adduct **325**, which undergoes cyclization in the final step.

Scheme 111



317 (61% – 84%)

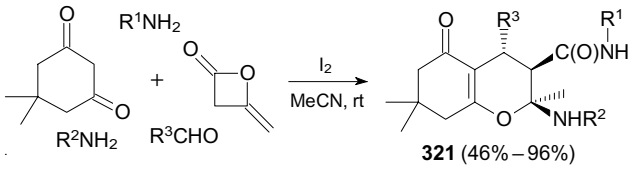
R^1 = Bn, Ph, 4-BrC_6H_4, 4-$PhNHC_6H_4$, 1-Naph; R^2 = Pr^i, Bu^n, $X_nC_6H_{5-n}$ [X = H, 4-Br, 4-OH, 4-OMe, 4-CF_3, 4-CN, 4-NO_2, 3-OH-4-OMe, 3,5-$(OMe)_2$-4-OH], 2-Th; R^3 = Bn, Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$



318

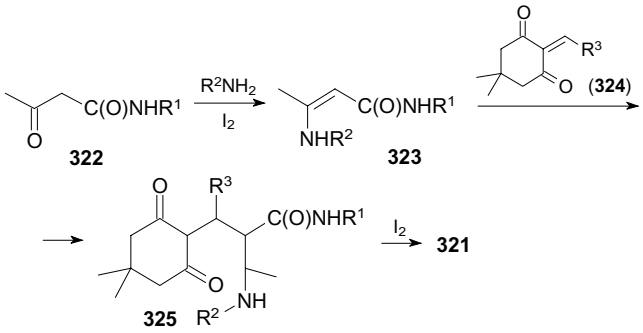
319 **320**

Scheme 112



321 (46% – 96%)

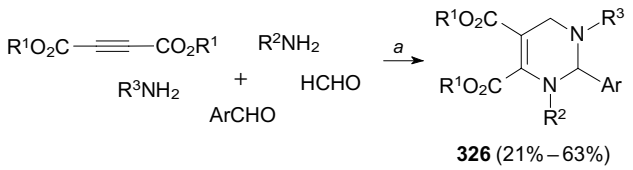
R^1 = Bu^n, Bn, 4-$FC_6H_4CH_2$, 2-$FC_6H_4CH_2$, 4-$MeC_6H_4CH_2$, 4-$MeOC_6H_4CH_2$, 4-MeC_6H_4; R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 2-MeC_6H_4; R^3 = XC_6H_4 (X = H, 4-Cl, 4-Br, 4-OMe, 4-OH, 4-NO_2, 4-CN), 2-Naph



322 **323** **325**

Tetrahydropyrimidines **326** were synthesized by the five-component reaction (Scheme 113).[211] The reaction using dialkyl acetylenes, primary amines, formaldehyde and benzaldehydes as the starting compounds in the presence of urea produced a series of heterocycles **326** in moderate to high yields. The plausible mechanism of this process repeats the above reaction mechanism with the only difference that the enamine component is synthesized beforehand by the addition of amine to acetylenedicarboxylate, thereby providing the selectivity of the reaction.

Scheme 113



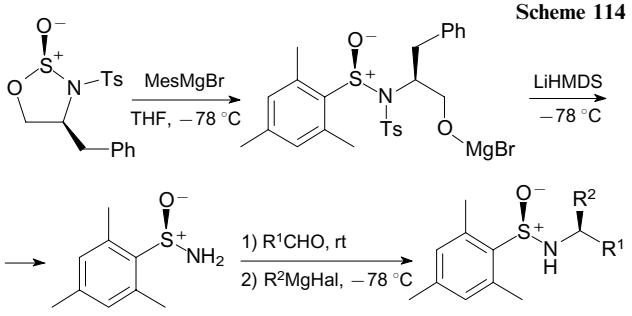
326 (21% – 63%)

(*a*) $(H_2N)_2CO$, AcOH, H_2O, rt; R^1 = Me, Et; R^2, R^3 = Bn, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4, 3-$F_3CC_6H_4$; Ar = Ph, 4-BrC_6H_4, 3-Me-4-HOC_6H_3

2.11. Miscellaneous transformations

A five-component one-pot approach was used to synthesize non-racemic sulfinamides **327** (Scheme 114).[212] For this purpose, a chiral oxathiazolidine oxide derivative was

Scheme 114



327 [34%–58%, *dr* = (84 : 16)–(> 99 : 1)]

R^1 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, Mes, 6-methoxy-2-naphthyl, PhC≡C, 2-Fu, 1-benzofuran-2-yl, 5-bromo-2-thienyl; R^2 = Et, Pr^n, Pr^i, Bu^t, cyclo-C_5H_9, n-C_6H_{13}, All, Bn

sequentially treated with mesitylmagnesium bromide (MesMgBr) and lithium hexamethyldisilazide (HMDS) at −78 °C. Then the reaction mixture was heated to room temperature followed by the addition of aldehyde and Grignard reagent. This gives the target sulfinamides in yields of up to 58% with very high diastereomeric purity.

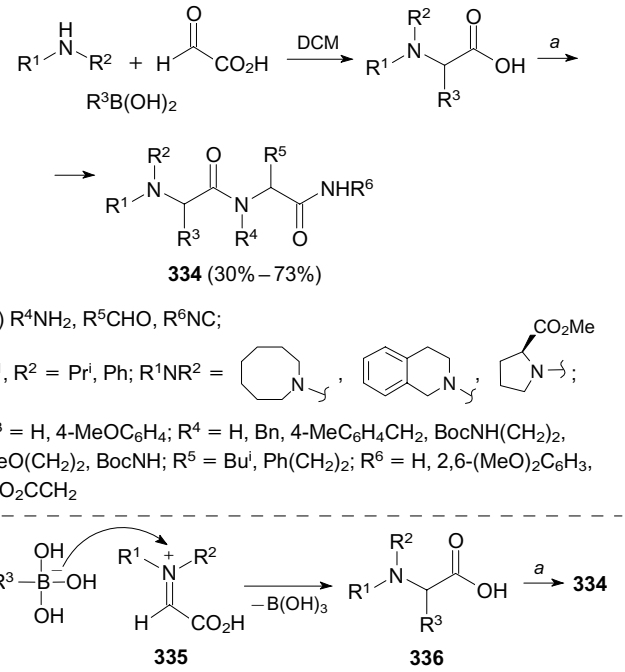
3. Six-component reactions

3.1. Reactions with isocyanides

The Ugi pseudo-six-component reaction using ammonium salts as an amine component was described by Pick *et al.*[213] (Scheme 115). Despite relatively moderate yields and inefficiency of the reaction with *p*-tolylacetic and trifluoroacetic acids, corresponding target diamide **328** was prepared even in the case of sterically overcrowded aldehydes, such as isobutyraldehyde. Although methanol is a classical solvent in the Ugi reaction, the authors chose aprotic acetonitrile, because the formation of compounds **328** was observed in this solvent (see Scheme 115). After the replacement of the solvent, the following reaction mechanism was proposed based on the experimental data. Imine **329**, generated from ammonia and aldehyde, does not directly undergo Ugi condensation but reacts with methanol and the second aldehyde molecule or carboxylate as nucleophiles to form intermediates **330** and **331**, and the latter also gives imine **332**. The subsequent Ugi reaction affords products **323** and **328**.

Dipeptides **334** were synthesized by the six-component Petasis–Ugi domino sequence (Scheme 116).[214, 215] A solid-phase synthesis using resin-immobilized amines or isonitriles in the Ugi reaction opens up a route to NH-diamides **334**.[216] The reaction mechanism involves the attack of iminium cation **335** by boronate, giving rise to bifunctional intermediate **336** (see Scheme 116). The Ugi reaction involving the carboxyl group of compound **336** results in the formation of products **334** in moderate yields.

Scheme 116



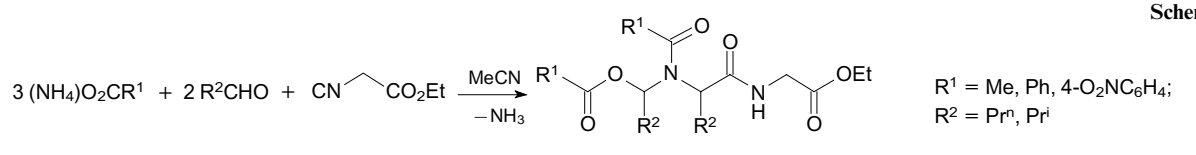
(*a*) R^4NH_2, R^5CHO, R^6NC;

R^1, R^2 = Pr^i, Ph; R^1NR^2 =

R^3 = H, 4-$MeOC_6H_4$; R^4 = H, Bn, 4-$MeC_6H_4CH_2$, $BocNH(CH_2)_2$, $MeO(CH_2)_2$, BocNH; R^5 = Bu^i, $Ph(CH_2)_2$; R^6 = H, 2,6-$(MeO)_2C_6H_3$, EtO_2CCH_2

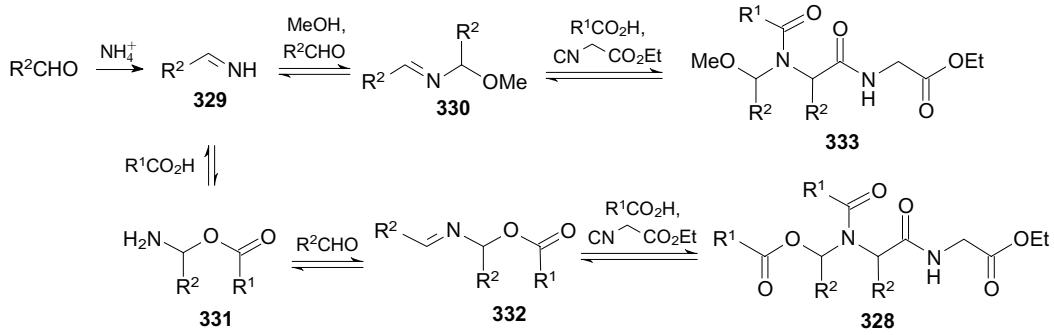
The synthesis of pseudopeptides **337** containing a rhodanine moiety (4-oxo-2-thioxo-1,3-thiazine) was accomplished based on the Ugi reaction (Scheme 117).[217] The reaction was performed in aqueous medium under ultrasound irradiation and gave target products in yields of up to 85%. The reaction with propiolic acid instead of maleic anhydride furnishes related derivatives containing a dithio-

Scheme 115

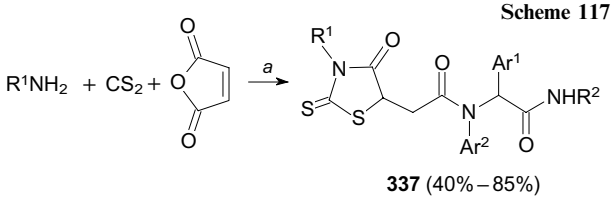


328 (17%–64%)

R^1 = Me, Ph, 4-$O_2NC_6H_4$;
R^2 = Pr^n, Pr^i

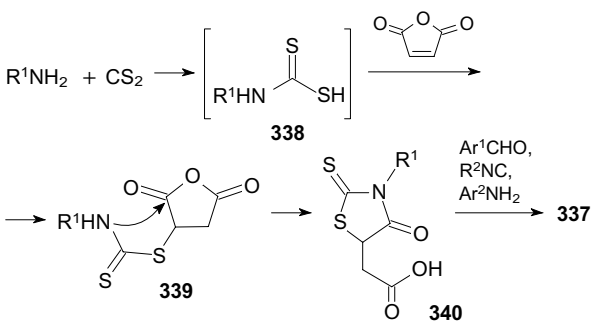


Scheme 117



337 (40% – 85%)

(*a*) 1) H_2O, US; 2) Ar^1CHO, R^2NC, Ar^2NH_2; R^1 = Me, Et, Pr^n, Pr^i, Bu^t, cyclo-C_6H_{11}, All, Bn, 4-$ClC_6H_4CH_2$, 2-$FuCH_2$, $Ph(CH_2)_2$; R^2 = Bu^t, Bn, cyclo-C_6H_{11}, 2,6-$Me_2C_6H_3$; Ar^1 = $X_nC_6H_{5-n}$ (X = 4-Cl, 2-Cl, 4-Br, 4-OMe, 4-OBn, 4-NO_2, 3-NO_2, 2,4-Cl_2); Ar^2 = $Y_nC_6H_{5-n}$ (Y = H, 2-Cl, 4-Me, 4-Bu^t, 4-OMe, 3,4-Cl_2, 3,4-Me_2)



carbamate moiety. The reaction mechanism involves the formation of carbamodithioic acid **338** from primary amine and disulfide (see Scheme 117). The subsequent Michael addition to maleic anhydride gives intermediate **339**, which undergoes intramolecular formation of an amide bond through the nucleophilic attack by an anhydride nitrogen atom to form rhodanine-5-acetic acid **340**. The classical Ugi reaction of **340** gives depsipeptide **337**.

Recently, a similar process was performed using acetylenedicarboxylic esters. The process involves similar initial steps, but the reaction affords rhodanine conjugates with a furan moiety — compounds **341** (Scheme 118).[218] This process gives rise to eight new bonds. The target products were prepared in yields of up to 70%. The initial steps are similar to those presented in Scheme 117 and involve the formation of rhodanine-5-acetic acid **340** and the subsequent addition of the latter to zwitterionic intermediate **342**, generated from acetylenedicarboxylic ester and isonitrile, to give compounds **343**. After the rearrangement to derivative **344**, the reaction with the next isocyanide molecule occurs *via* [1 + 4]-cycloaddition to form final structure **341**.

A stereoselective synthesis of 3-arylidene-2-oxindoles **345** was described by Bararjanian *et al.*[219] (Scheme 119). The stabilization *via* stacking interactions between phenyl groups results in the formation of *trans*,*trans*-**345** as a single product in high yield. The first step affords Ugi product **346** and is followed by the carbopalladation – Sonogashira cross-coupling domino sequence (see Scheme 119). The nucleophilic addition of secondary amine at the triple bond affords product **345**.

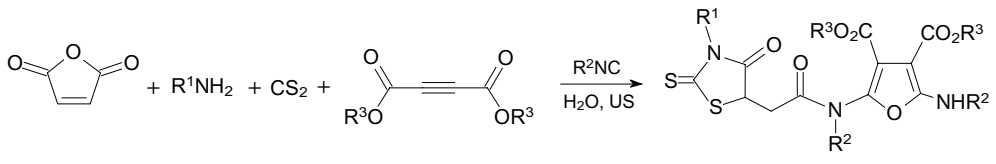
The six-component Knoevenagel – Ugi – CuAAC domino reaction was used to synthesize coumarin-3-carboxamides **347** containing a triazole moiety (Scheme 120).[220] A series of target products **347** were prepared in high yields by the reactions using salicylaldehyde derivatives, propargyl salicylaldehyde, aniline, Meldrum's acid, isocyanide, aliphatic and aromatic azides as substrates. The Knoevenagel product generated in the first step involving salicylaldehyde and Meldrum's acid (**348**) produces acid **349** *via* the elimination of an acetone molecule. The Ugi reaction of acid **349** with aniline, *O*-propargyl salicylaldehyde and isocyanide furnishes diamide **350** (see Scheme 120). Then the alkyne group of compound **350** undergoes 1,3-dipolar cycloaddition to form final product **347**.

Rahmati *et al.*[90] developed a pseudo-six-component synthesis of maleimide derivatives **351** (Scheme 121). The reaction of Meldrum's acid, aryl carbaldehyde, amine, isocyanide and malononitrile in a ratio of 1 : 1 : 2 : 1 : 1 gives diamides **351** in moderate to high yields.

The pseudo-six-component azido-Ugi reaction was modified[221] for the synthesis of tetrazolospiroquinazolinone derivatives **352** (Scheme 122). The first step is the nucleophilic attack of the carbonyl group of isatin anhydride by hydrazine followed by the ring opening and decarboxylation to form hydrazide **353**. The latter is transformed into intermediate **354** containing hydrazone and iminium salt moieties. The six-membered ring closure affords spirocyclic aminal **355**, which undergoes sequential attacks by isocyanide and azide ions followed by intramolecular cyclization to product **352a** (see Scheme 122).

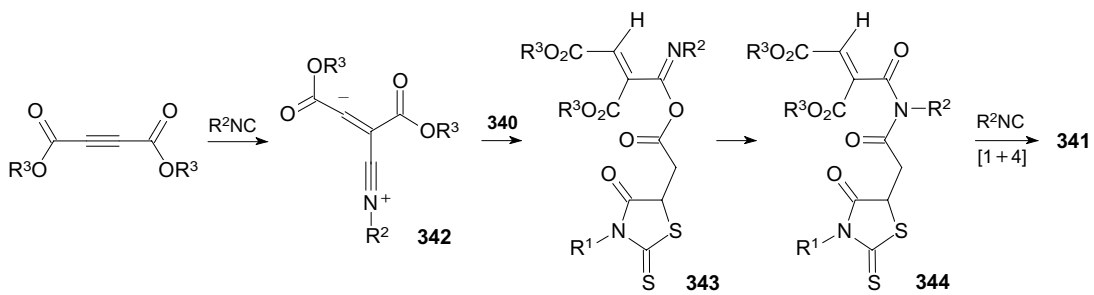
A combination of the azido-Ugi reaction and other multicomponent processes opens up a route to various tetrazole-containing compounds. The reaction sequence of *o*-aminobenzoic acid, isobutyraldehyde, *tert*-butyl isocya-

Scheme 118

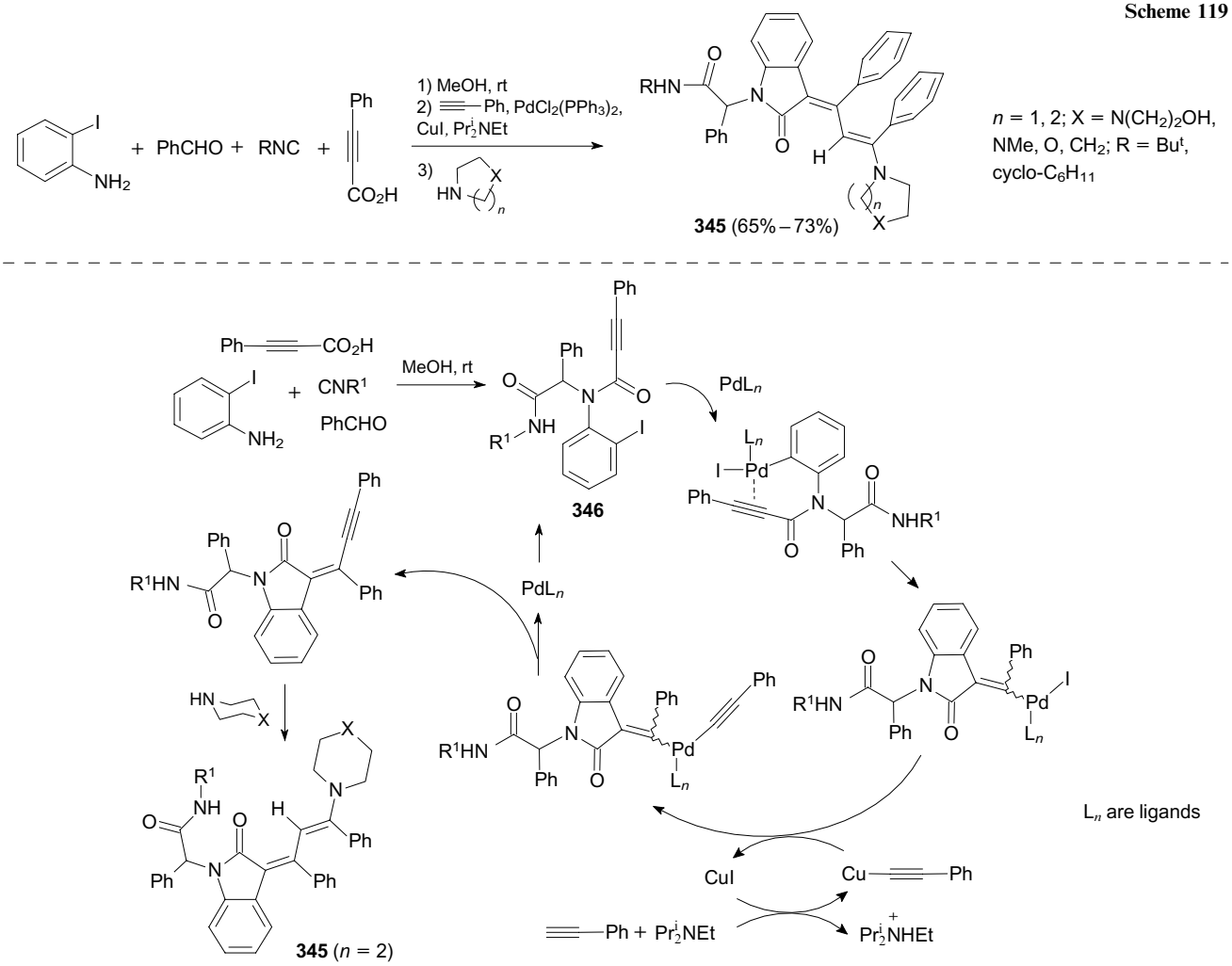


341 (42% – 70%)

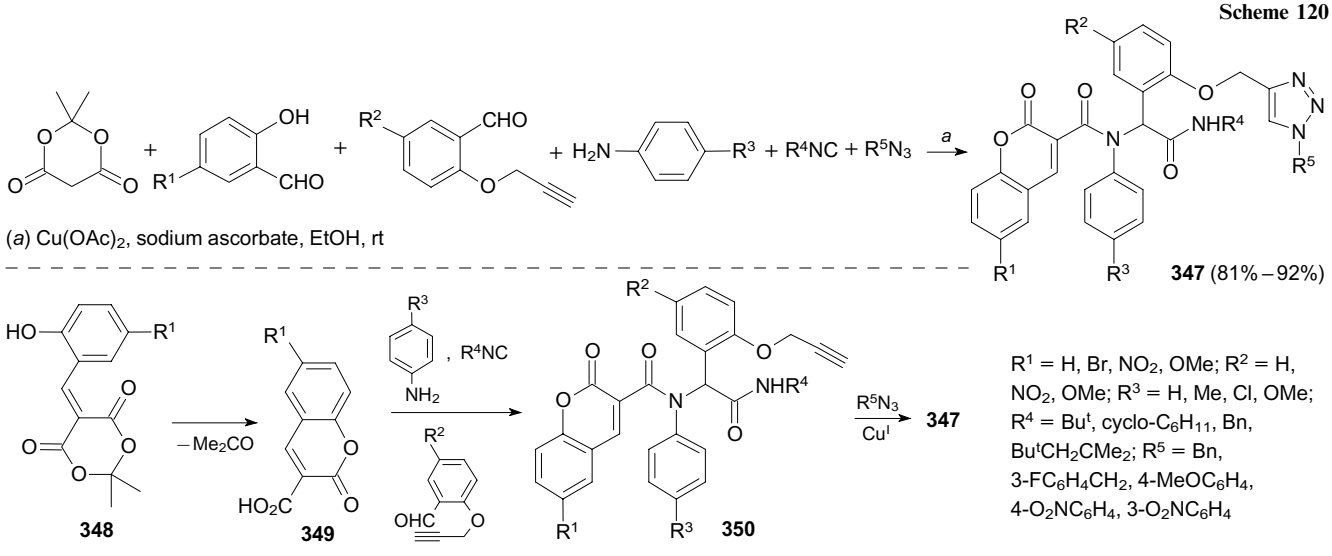
R^1 = Me, Pr^n, Pr^i, Bu^n, Bu^3, All, Bn; R^2 = Bu^t, tert-C_8H_{17}, 2,6-$Me_2C_6H_3$; R^3 = Me, Et



Scheme 119



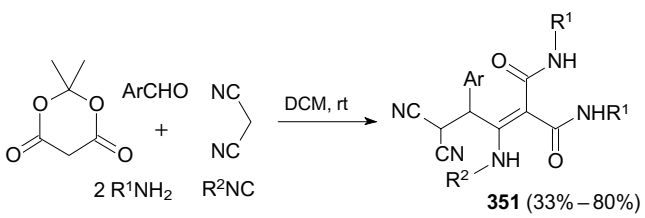
Scheme 120

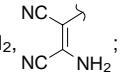


nide and hydrogen azide in a ratio of 1 : 2 : 2 : 1, involves the azido-Ugi reaction at the amino group and the Passerini reaction at the carboxyl group and affords product **356** as a mixture of diastereomers (Scheme 123).[222] A similar reaction of glycine in the presence of the Dowex ion-exchange resin gives 2,6-diketopiperazine **357** in 50% yield. The stereochemical aspect of the reactions was not discussed.

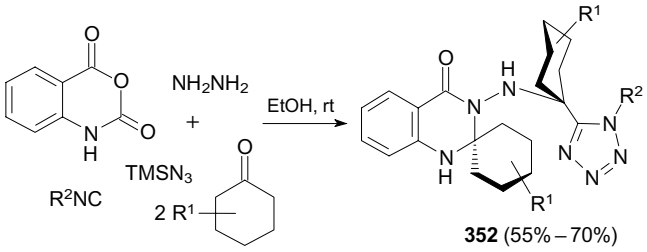
A broad range of depsipeptides **358** containing the dihydropyridine moiety were synthesized by a six-component one-pot process (Scheme 124).[223] The first step is based on the Horner – Wadsworth – Emmons reaction giving 1-azadiene intermediate **359**, which reacts *in situ* with isocyanide. The subsequent Passerini reaction of the resulting isocyanodihydropyridinone **360** furnishes target prod-

Scheme 121

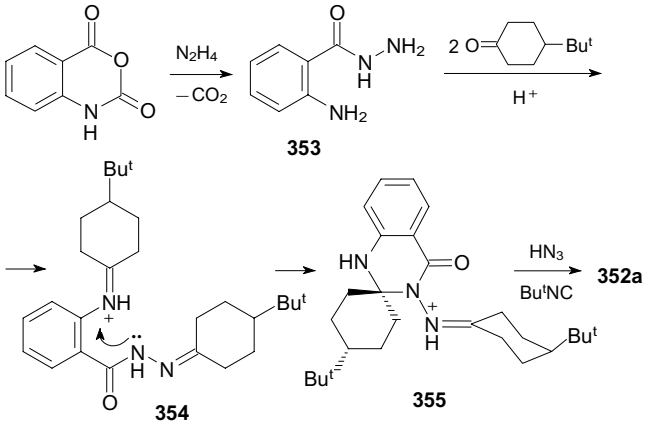


Ar = $X_nC_6H_{5-n}$ [X = 4-F, 3-Br, 4-Me, 4-OMe, 4-NMe_2, 3,4-$(OMe)_2$], 2-Naph; R^1 = 4-$H_2NC_6H_4$, 2-$H_2NC_6H_4$, 4-H_2N-4,5-$Cl_2C_6H_2$, ; R^2 = Bu^t, cyclo-C_6H_{11}, $Bu^tCH_2CMe_2$

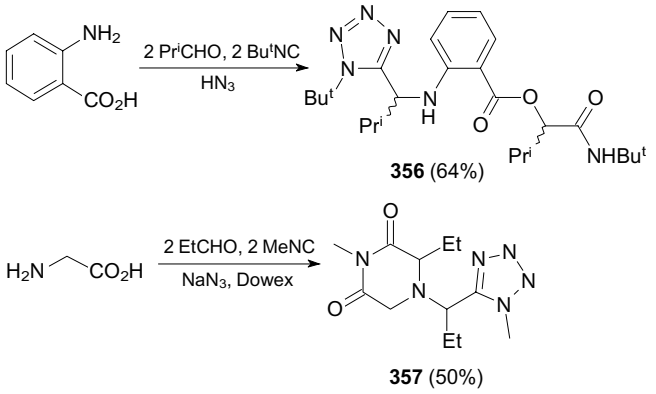
Scheme 122



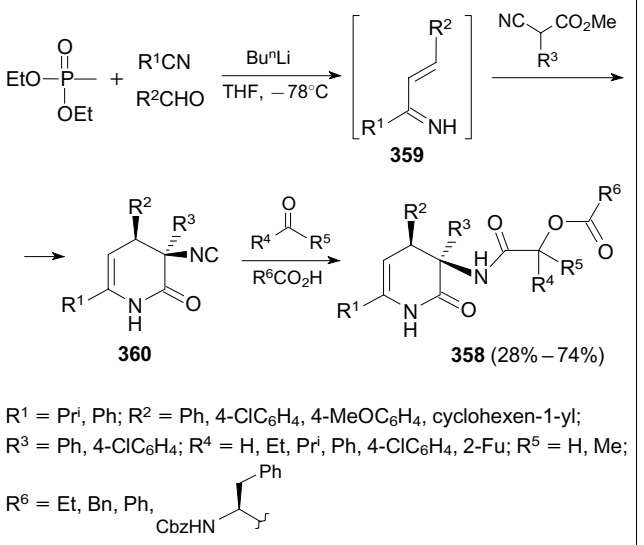
R^1 = H, 4-Me, 3-Me, 4-Et, 4-Bu^t; R^2 = Bu^t, cyclo-C_6H_{11}



Scheme 123



Scheme 124

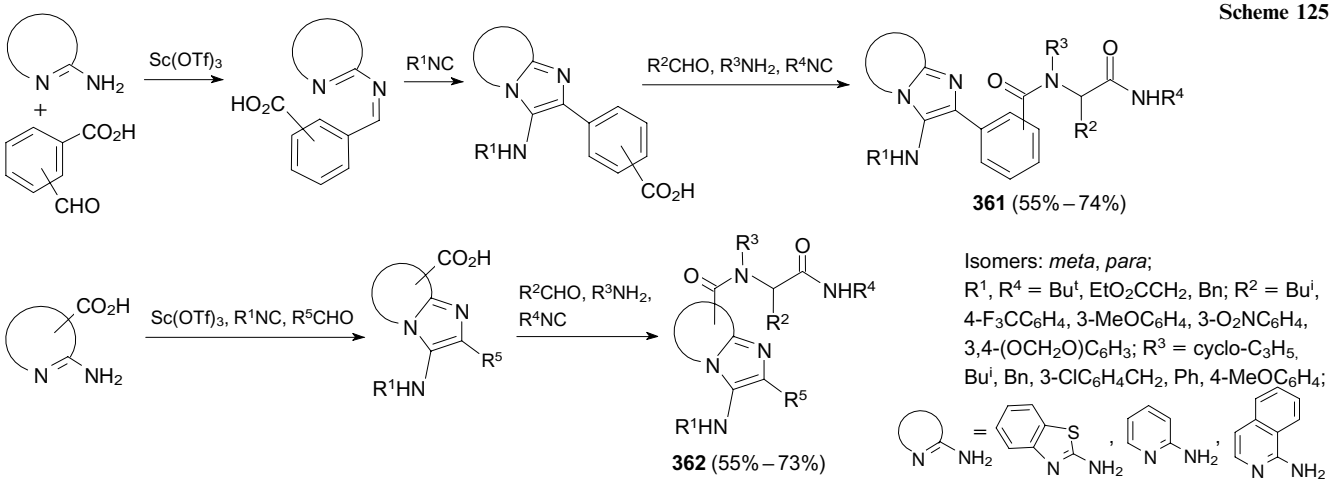


R^1 = Pr^i, Ph; R^2 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, cyclohexen-1-yl; R^3 = Ph, 4-ClC_6H_4; R^4 = H, Et, Pr^i, Ph, 4-ClC_6H_4, 2-Fu; R^5 = H, Me; R^6 = Et, Bn, Ph,

ucts **358** in moderate to high yields with full diastereoselectivity in favour of the *cis* isomer.

A six-component Groebke – Blackburn – Ugi process was applied in the synthesis of polyfunctional structures **361** and **362** (Scheme 125).[224] A wide range of substrates were examined in the reaction. Target diamides bearing a heterocyclic moiety were obtained in yields of up to 74%. The reaction mechanism involves the formation of imine,

Scheme 125



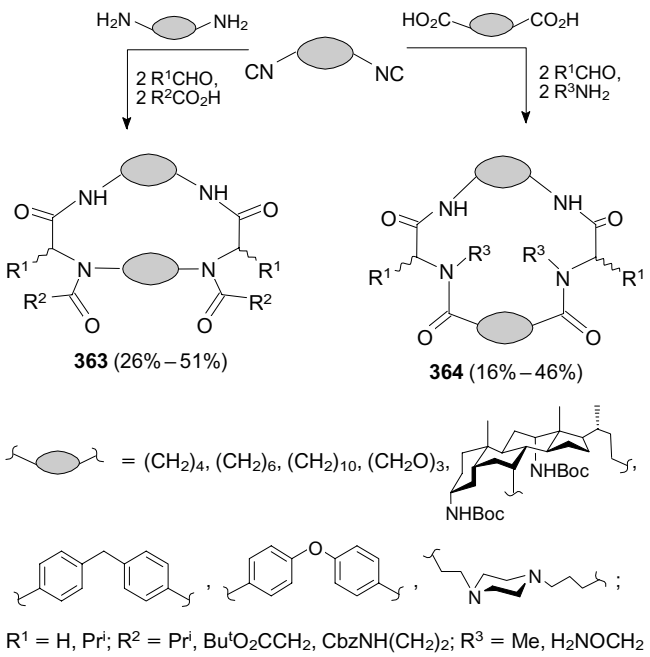
Isomers: *meta*, *para*;
R^1, R^4 = Bu^t, EtO_2CCH_2, Bn; R^2 = Bu^i, 4-$F_3CC_6H_4$, 3-$MeOC_6H_4$, 3-$O_2NC_6H_4$, 3,4-$(OCH_2O)C_6H_3$; R^3 = cyclo-C_3H_5, Bu^i, Bn, 3-$ClC_6H_4CH_2$, Ph, 4-$MeOC_6H_4$;

the addition of isocyanide accompanied by heterocyclization to an imidazole moiety and the Ugi reaction.

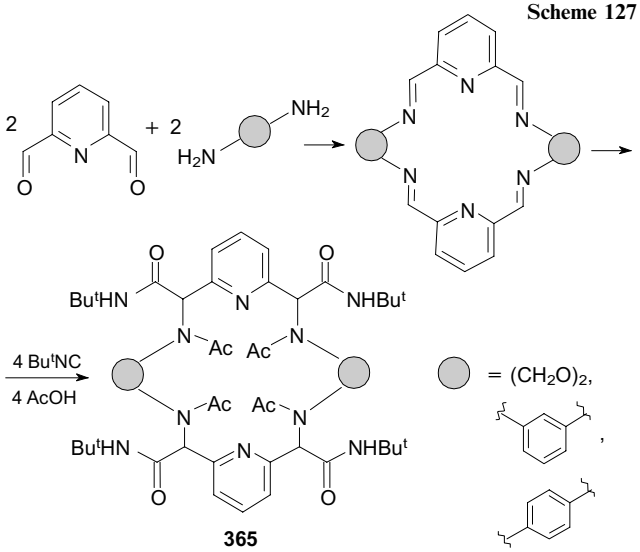
A one-step synthesis of various macrocyclic pseudopeptides was developed based on the Ugi pseudo-six-component reaction (Scheme 126).[225–227] Dipeptide macrocycles **363** and **364** were prepared in yields of up to 51% using diisocyanides, diamines and dicarboxylic acids. Aliphatic, aromatic or heterocyclic moieties and also structures containing a steroid core can serve as spacers in bifunctional reagents.

A similar process with bifunctional aldehydes involves two pseudo-six-component reactions and affords macro-

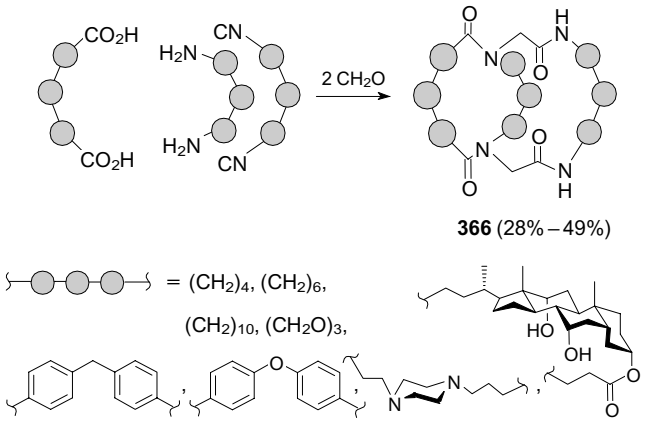
Scheme 126



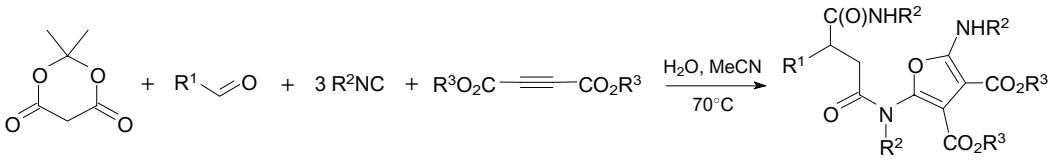
Scheme 127

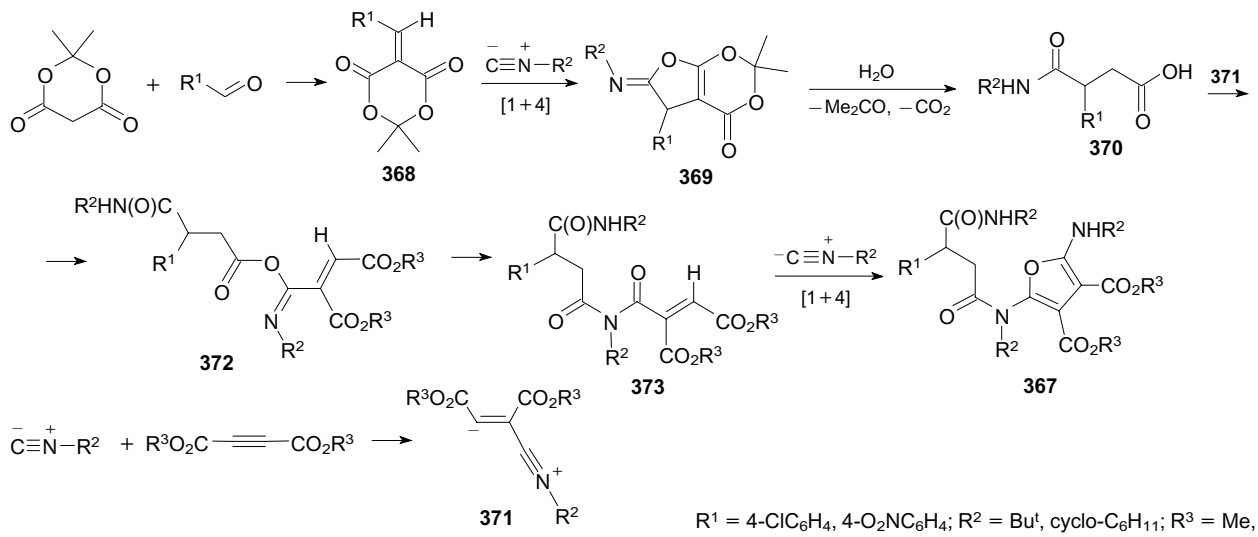


Scheme 128



Scheme 129



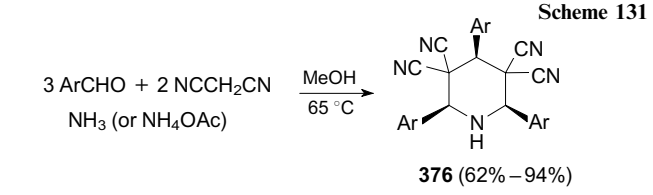


cycles **365** consisting of 24 atoms (Scheme 127).[228] To increase the efficiency of the process, Wessjohann *et al.*[228] used the template synthesis and added barium chloride to the reaction mixture, which allowed them to increase the yield of products **365** from 2% – 21% to 23% – 61%.

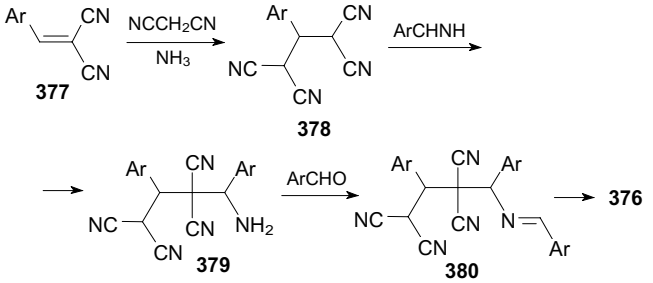
More complex cage structures **366** were synthesized by the simultaneous addition of diisocyanide, diamine and dicarboxylic acid to the reaction mixture (Scheme 128).[229] This approach enables the preparation of macrocyclic cages **366** in yields of up to 49%.

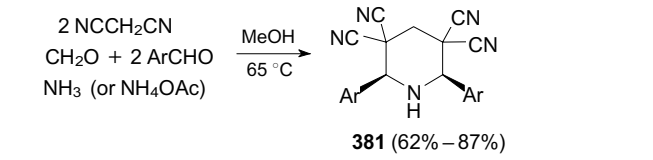
The pseudo-six-component reaction of Meldrum's acid, benzaldehydes, two different isocyanides and dialkyl acetylenedicarboxylates in a mixture of water and acetonitrile at 70 °C affords pseudopeptides **367** containing the fully substituted furan moiety (Scheme 129).[230] Target products were prepared in yields of up to 75%, thereby demonstrating high efficiency of the reaction. The reaction mechanism involves the condensation of aromatic aldehyde and Meldrum's acid to form compound **368**, the subsequent [1 + 4]-cycloaddition of isocyanide giving iminolactone **369**, the water-mediated elimination of acetone and decarboxylation giving acid **370**. Zwitterionic intermediate **371**, generated *in situ* in the reaction of dialkyl acetylenedicarboxylate with isocyanide, is protonated by acid **370** and adds the anion of this acid to form dicarboxylate **372**. The subsequent Mumm rearrangement and [1 + 4]-cycloaddition of another isocyanide molecule to intermediate **373** furnishes final product **367**.

Scheme 131



Ar = XC_6H_4 (X = H, 4-F, 2-F, 3-Br, 4-Me), 4-Py, 3-Py





Ar = XC_6H_4 (X = H, 4-F, 3-F, 3-Br, 4-Me, 4-Et, 3-NO_2), 3-Py

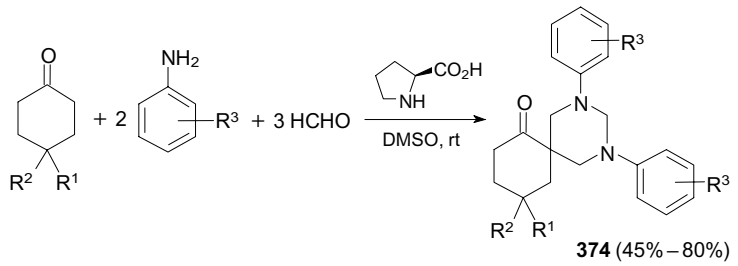
3.2. Miscellaneous six-component reactions

The L-proline-catalyzed pseudo-six-component Mannich reaction was successfully applied in the synthesis of 1,3-diaryl-5-spiro[hexane,hydropyrimidines] **374** (Scheme 130).[231] Cyclohexanone derivatives, anilines and formaldhyde were used in a ratio of 1 : 2 : 3. Spirocyclic products **374** were obtained in yields of up to 80%. The reaction mechanism involves the sequential α-aminomethylation reactions at the same carbon atom to form 1,3-diamine **375**. The condensation of compound **375** with formaldehyde affords final product **374** (see Scheme 130).

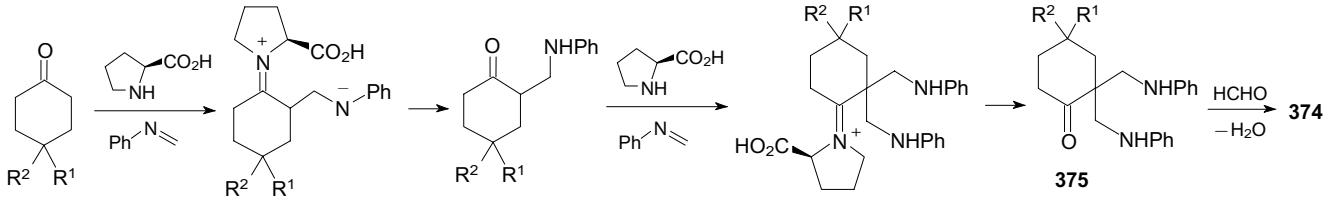
The Mannich reaction is one of the key steps in a pseudo-six-component process giving 2,4,6-triaryl-3,3,5,5-tetracyanopiperidines **376**. This process affords target products in high yields as single diastereomers (Scheme 131). The Knoevenagel – Michael – Mannich cascade reaction results in the piperidine ring formation and the formation of six new bonds.[232] The first step is the Knoevenagel condensation giving dicyanostyrenes **377**. The subsequent addition of malononitrile affords adduct **378**, which undergoes the Mannich reaction to form intermediate **379**. The final steps are the reaction of **379** with another aldehyde molecule and the Mannich cyclization of compound **380**. The reaction using 3 instead of 2 equiv. of aromatic aldehyde and 1 equiv. of formaldehyde furnishes piperidines **381** containing only two aryl rings. These products are also formed in a diastereoselective manner.[233]

Recently, a pseudo-six-component process, involving the Mannich reaction, was used to synthesize more complex spiropiperidine-based structures **382** (Scheme 132).[234] Target spiropiperidine derivatives **382** were prepared in high yields (83% – 95%) in the presence of a polystyrene (PS)-immobilized iron(III) complex as the catalyst. In terms of

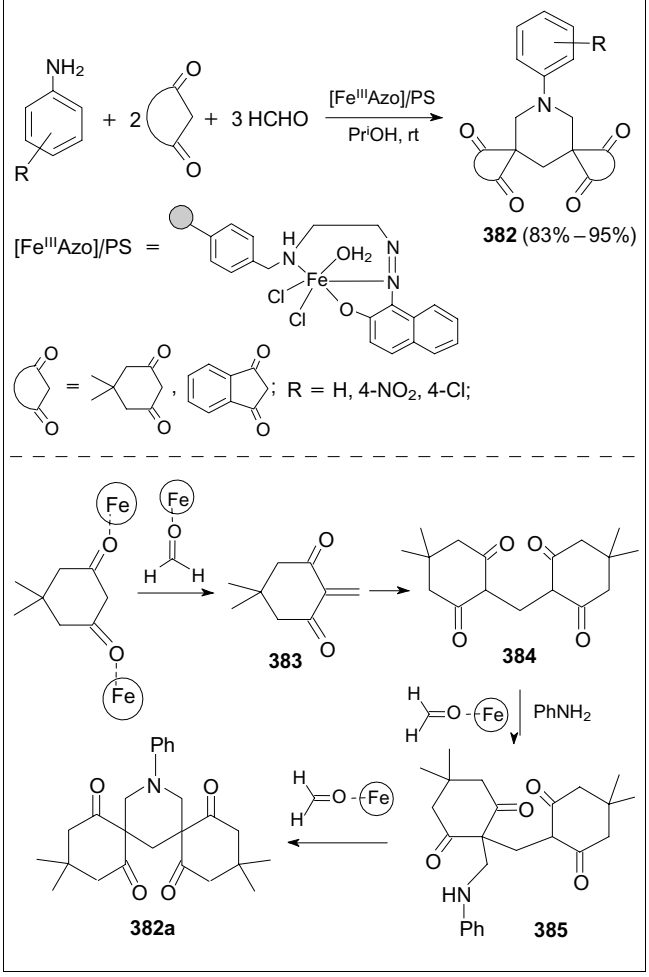
Scheme 130



R^1, R^2 = H, Me; $R^1 – R^2$ = OCH_2CH_2O;
R^3 = H, 3-Cl, 4-Br, 4-Pr^i, 4-NMe_2



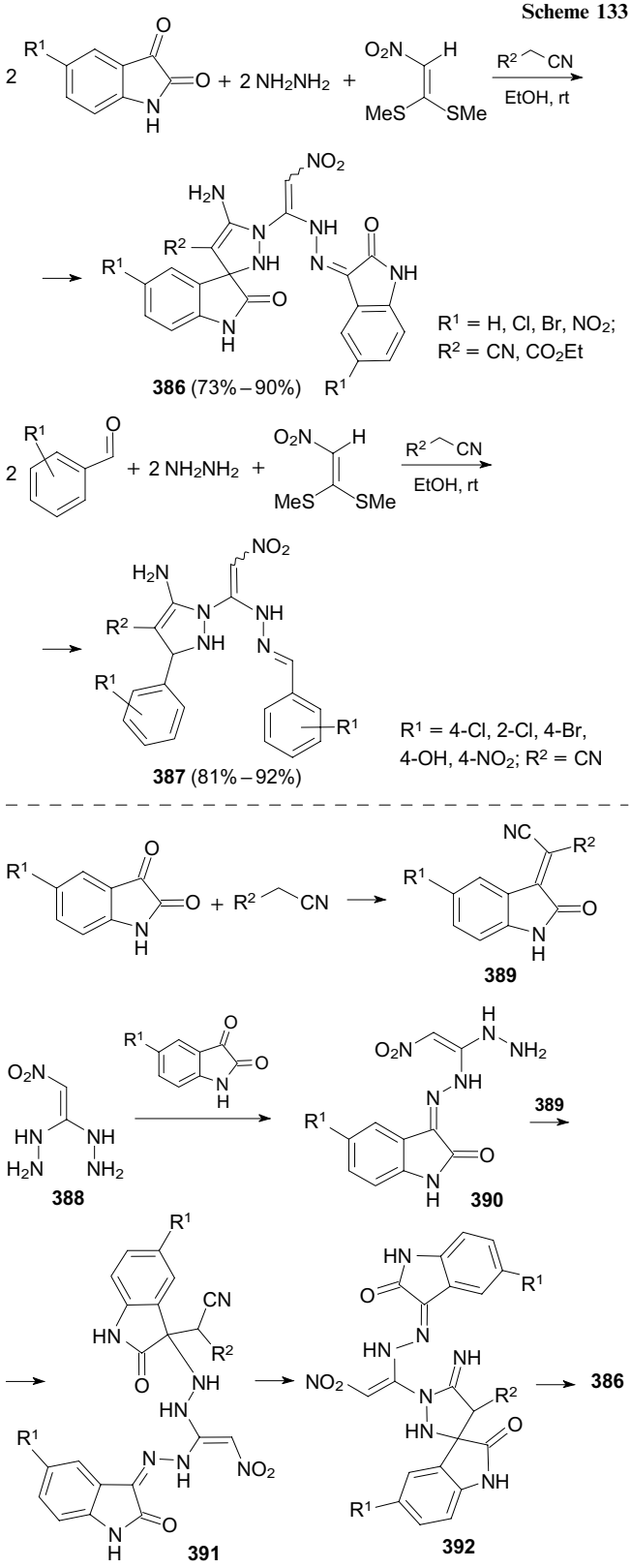
Scheme 132



the reaction mechanism, the process is the Knoevenagel condensation – Michael addition — double Mannich reaction sequence (see the synthesis of product **382a** in Scheme 132). In the first step, the catalyst [Fe^{III}Azo]/PS activates formaldehyde and dimedone, thereby promoting the Knoevenagel reaction giving compound **383**. Then the Michael reaction of a second equivalent of dimedone with intermediate **383** affords bis-product **384**. The subsequent Mannich reaction with activated formaldehyde and aniline furnishes amine **385**. In the final step, the second Mannich reaction with a third equivalent of activated formaldehyde takes place. The heterogeneous catalyst can be repeatedly used. A simpler modification of this process is based on the utilization of acetic acid or the DMSO – TsOH system as the solvent.[235, 236]

Another type of spirocyclic compounds — spiropyrazolines — can be prepared by the pseudo-six-component Michael reaction from isatins, hydrazine, nitro ketene dithioacetal and malonic acid derivatives (Scheme 133).[237] Target spiroheterocycles **386** were synthesized in high yields under mild conditions (ethanol, room temperature). This reaction can be performed using different benzaldehydes instead of isatins to prepare products **387**.[238] In the first step (see Scheme 133; the reaction with isatin), nitro derivative **388** is produced from hydrazine and nitro ketene dithioacetal. The sequential condensation of nitrile with isatin gives compound **389** and the Michael addition of **389** to intermediate **390** affords compound **391**. The intramolecular

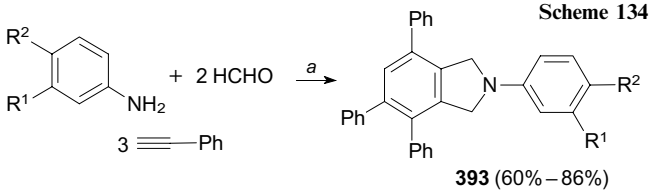
Scheme 133



cyclocondensation and tautomerization of the resulting compound **392** furnishes spiropyrazoline **386**.

The synthesis of isoindole derivatives **393** by the tandem double A^3-coupling and [2 + 2 + 2]-cycloaddition reaction was developed by Bonfield and Li[239] (Scheme 134). For this purpose, a mixture of aniline, formaldehyde and phenylacetylene in a ratio of 1 : 2 : 3 was heated in the presence

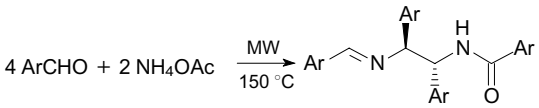
Scheme 134



393 (60% – 86%)

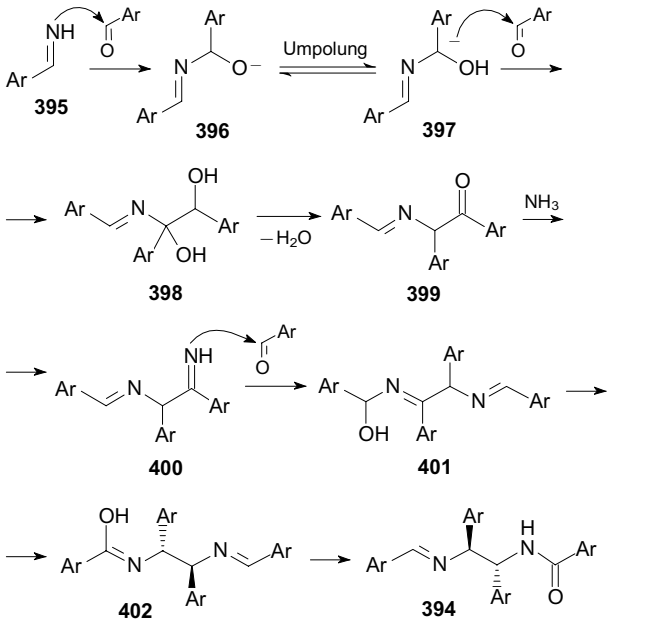
(*a*) $RuCl(PPh_3)_3$, CuBr, H_2O, 40 – 80 °C; R^1 = H, F, Cl, Me; R^2 = H, Cl, I, Ph, CF_3

Scheme 135



394 (80% – 92%)

Ar = $X_nC_6H_{5-n}$ [X = H, 4-F, 3-F, 2-F, 4-Cl, 2-Cl, 4-Br, 4-Me, 4-OMe, 3,4,5-$(OMe)_3$]

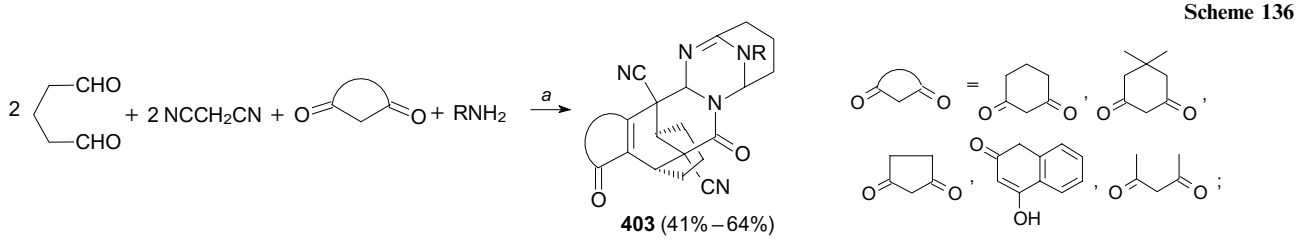


of rhodium and copper catalysts. Target heterocycles **393** were prepared in yields of up to 86%. Bis(propargyl)amine, which is generated in the course of the reaction, undergoes [2 + 2 + 2]-cycloaddition with ethynylbenzene to form the final product.

Jiang *et al.*[240] described an interesting synthesis of *anti*-1,2-diarylethylbenzamides **394** by the pseudo-six-component reaction (Scheme 135). The heating of a mixture of substituted benzaldehyde (4 equiv.) and ammonium acetate (2 equiv.) using microwave irradiation under solvent-free conditions gave ten *anti*-1,2-diarylethylbenzamides **394** in high yields. Based on the experimental data, the authors proposed a mechanism involving the formation of imine **395**, the addition of aldehyde, umpolung during the transformation of compound **396** into **397**, the nucleophilic addition of the second aldehyde molecule, dehydration of adduct **398** giving ketone **399** and the reaction of the latter with ammonia to form derivative **400** (see Scheme 135). The final steps are the formation of imine **401** and the 1,3-hydride shift giving intermediate **402**. The keto – enol tautomerization furnishes thermodynamically stable product **394**.

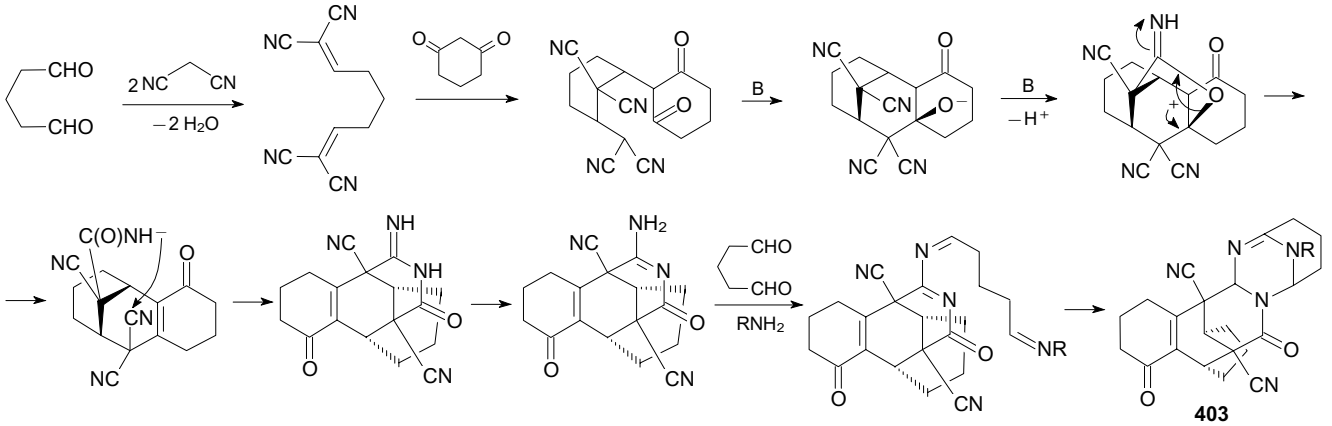
The six-component domino reaction involving glutaraldehyde, malononitrile, cyclic 1,3-dicarbonyl compounds and amines affords bridged pentacyclic derivatives **403** containing several stereocentres (Scheme 136). This reaction is accomplished by mixing four readily available reagents and piperidine as a base in ethanol under microwave irradiation and can be applied to prepare complex alkaloid-like products in yields of up to 64%. The proposed

Scheme 136



403 (41% – 64%)

(*a*) piperidine, EtOH, MW, 100 °C;
R = Bu^n, $X_nC_6H_{5-n}$ (X = H, 4-Cl, 4-Me, 2-Et, 4-Bu^t, 4-OMe, 4-OEt, 3-Pr^iO, 3-Cl-4-Me, 2,3-Me_2, 2,5-Me_2), 2-Py, 3-Py

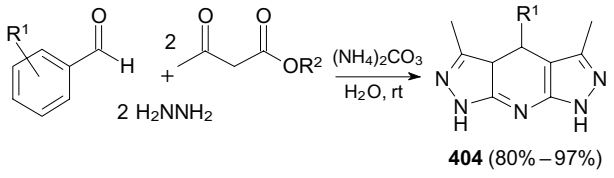


403

mechanism involves a complex sequence of transformations presented in Scheme 136. [241]

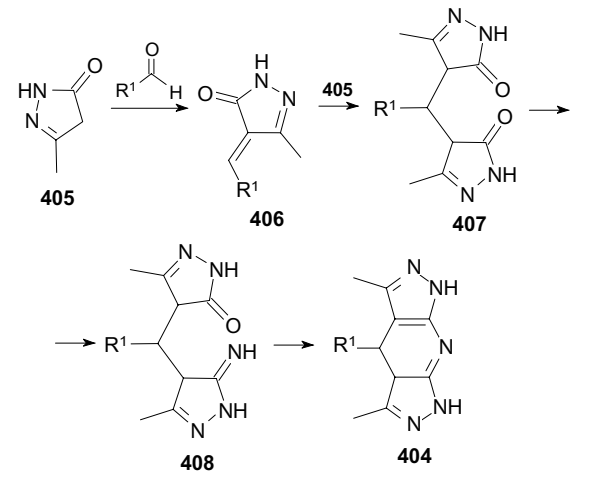
A pseudo-six-component synthesis of tetrahydrodipyrazolopyridines **404** based on acetoacetates, hydrazine hydrate, ammonium carbonate and aldehydes in a ratio of 2 : 2 : 1 : 1 occurs at room temperature. The products were isolated by filtration.[242] Alternatively, this process was performed using an ionic liquid immobilized on a $FeNi_3$ nanocatalyst.[243] The reaction mechanism involves the formation of pyrazolone **405**, the subsequent Knoevenagel condensation with aldehyde to form intermediate **406** and the Michael addition of the second pyrazolone molecule. Then an oxygen atom in the pyrazolone moiety of molecule **407** is replaced by nitrogen to give derivative **408**, which undergoes intramolecular cyclization to product **404** (Scheme 137).

Scheme 137



404 (80% – 97%)

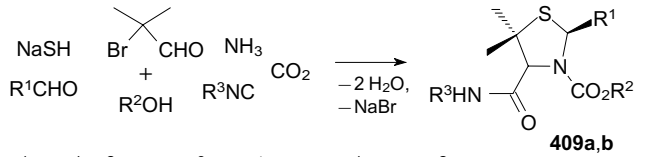
R^1 = H, 4-Cl, 2-Cl, 2-Br, 4-Me, 2-Me, 4-MeO, 4-OH, 4-NO_2, 3-NO_2, 4-NMe_2; R^2 = Me, Et



4. Seven-component reactions

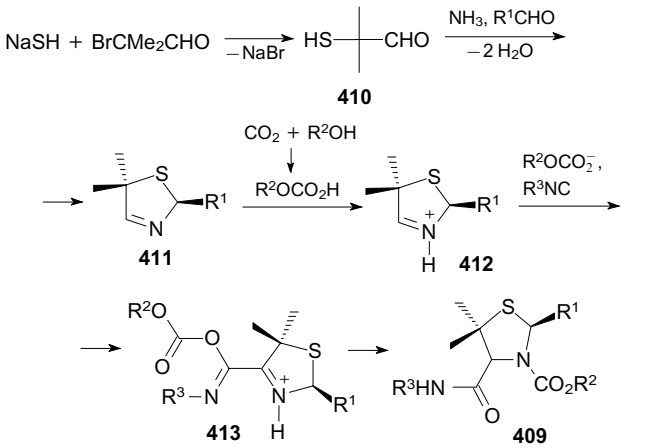
The Asinger – Ugi reaction (Scheme 138) was the first seven-component one-pot reaction, which was described in 1993 by Dömling and Ugi.[9] The mixing of sodium hydrosulfide, 2-bromo-2-methylpropanal, ammonia, isobutyraldehyde, carbon dioxide and *tert*-butyl isocyanide in methanol afforded thiazolidine-3-carboxylate **409a** in 43% yield (the diastereomeric ratio was 2 : 1). A similar process involving ferrocenecarbaldehyde and isocyanoacetic ester in ethanol gave product **409b** in a low yield (18%, *dr* = 14 : 9). In the first step, the Asinger condensation of α-sulfanyl aldehyde **410**, generated from sodium hydrosulfide and α-bromaldehyde, with ammonia and aldehyde affords cyclic imine **411** (see Scheme 138). The protonation of **411** gives iminium salt **412**, which undergoes the Ugi reaction with monoalkyl carboxylate, generated *in situ* from carbon dioxide and alcohol, and isocyanide. The subsequent rearrangement of compound **413** furnishes final product **409**.

Scheme 138



409a,**b**

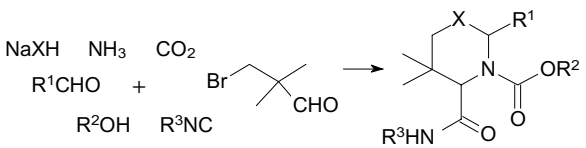
R^1 = Pr^i, R^2 = Me, R^3 = Bu^t (**409a**); R^1 = Fc, R^2 = Et, R^3 = EtO_2CCH_2 (**409b**)



The reaction occurs in a stereoselective manner and gives the major diastereomer, in which substituents in positions 2 and 4 are *trans* to each other.

Later, this method was modified for the synthesis of six-membered heterocycles (Scheme 139).[244] The reaction using 3-bromo-2,2-dimethylpropanal and sodium hydrosulfide or hydroxide gave the corresponding racemic 1,3-thiazinane- and oxazinane-3-carboxylates **414** in yields of up to 40%.

Scheme 139



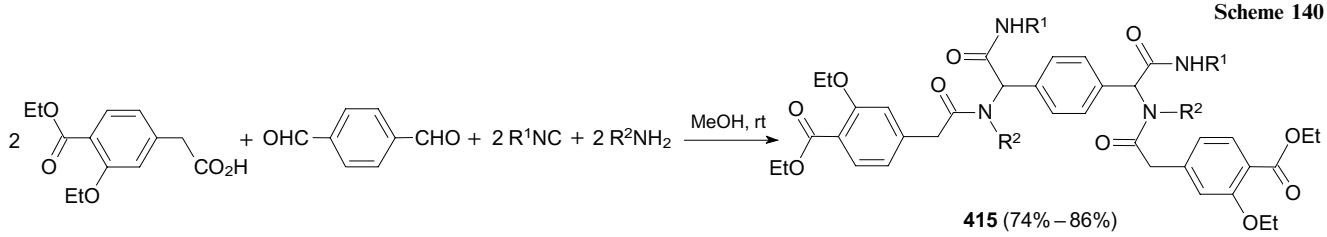
414 (19% – 40%)

X = O, S; R^1 = H, Me, Et, $HOCH_2CMe_2$; R^2 = Me, Et; R^3 = Bu^t, All, MeO_2CCH_2

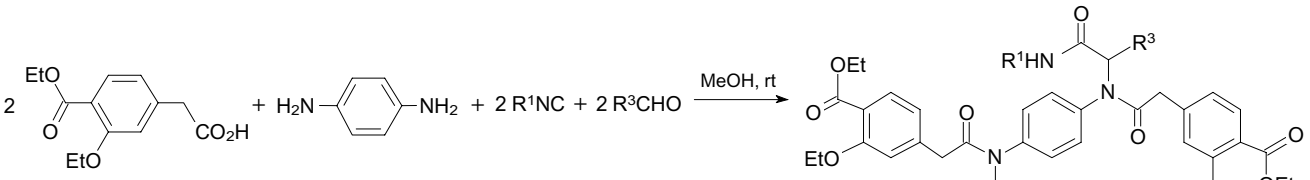
Recently, the pseudo-seven-component double Ugi reaction was applied in the synthesis of potential maltase-glucoamylase inhibitors **415** and **416** (Scheme 140).[245] A number of acid catalysts (*p*-toluenesulfonic acid, potassium alum) were tested in this process; however, the best results were obtained in methanol under catalyst-free conditions. Target tetraamides **415** and **416** were isolated in 74% – 86% and 65% – 90% yields, respectively.

A pseudo-seven-component domino process involving the sequential Ugi – Mumm and Ugi – Smiles reactions was studied by Brauch *et al.*[246] (Scheme 141). This process was found to have high tolerance to aromatic *para*-hydroxy acids, amines and isocyanides (products **417** were obtained in 52% – 98% yields). The use of sterically hindered isobutyraldehyde instead of formaldehyde leads to a decrease in the product yield to 34%. The reaction mechanism involves the Ugi reaction at the phenol OH group, inter-

Scheme 140



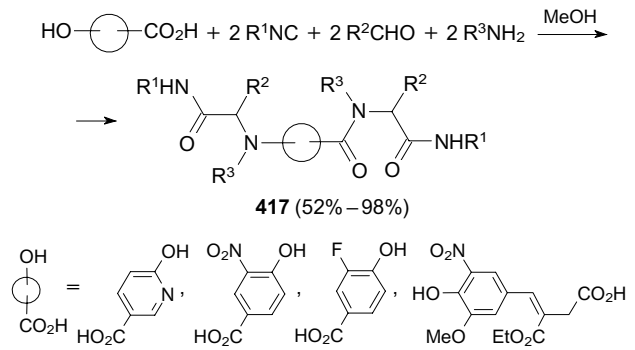
415 (74% – 86%)



416 (65% – 90%)

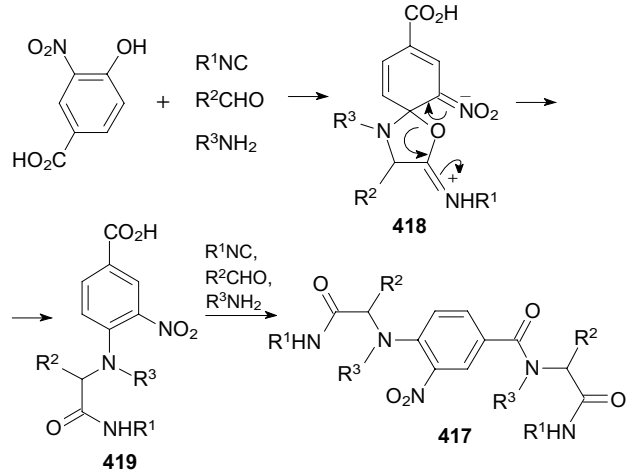
R^1 = Bu^t, cyclo-C_6H_{11}; R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4; R^3 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4, 4-$Pr^nC_6H_4$, 3-indolyl

Scheme 141



417 (52% – 98%)

R^1 = Bu^n, Bu^t, cyclo-C_6H_{11}; R^2 = H, Pr^i; R^3 = Pr^i, Bn



418

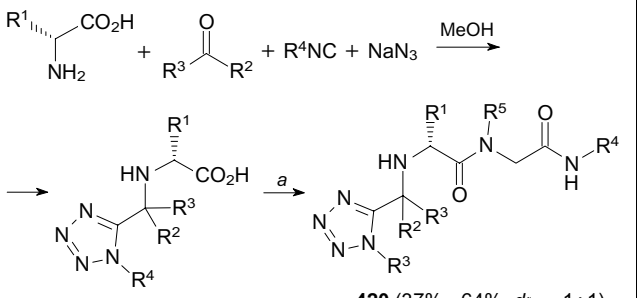
419

417

mediate **418** undergoing the Smiles rearrangement into intermediate **419**. The subsequent Ugi reaction at the carboxylic acid moiety of **419** and the Mumm rearrangement afford compound **417** (see Scheme 141).

A series of tetrazole-containing peptidomimetics **420** were synthesized by the azido-Ugi – Ugi reaction sequence (Scheme 142).[247] The azido-Ugi reaction was performed using amino acid, a carbonyl compound, isocyanide and sodium azide. The reaction mixture was kept for 12 h and then formaldehyde, isocyanide and amine were added. After the completion of the process, target tetrazole-containing

Scheme 142



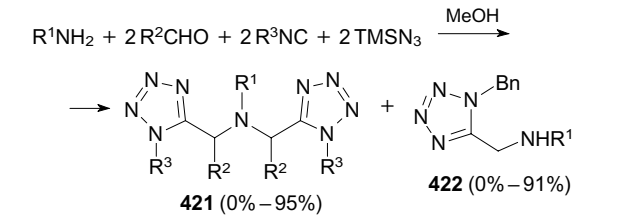
420 (37% – 64%, *dr* = 1 : 1)

(*a*) CH_2O, R^4NC, R^5NH_2, MeOH;
R^1 = H, Pr^i, Bn; R^2, R^3 = H, Me, Bu^i, 2-$MeOC_6H_4$;
R^4 = Bu^t, cyclo-C_6H_{11}, Bn, $Ph(CH_2)_2$, 3,4-$(MeO)_2C_6H_3$, MeO_2CCH_2;
R^5 = Pr^n, cyclo-$C_3H_5CH_2$, 4-$ClC_6H_4(CH_2)_2$

peptidomimetics **420** were isolated as a mixture of diastereomers in yields of up to 64%.

The pseudo-seven-component[248] (six-component, if cyclic imines are used as the starting compounds[249]) azido-Ugi reaction[250] was shown to provide a route to symmetrical and unsymmetrical bis-tetrazoles **421** (Scheme 143). The reaction in methanol at room temperature furnishes products **421** in yields of up to 95%. In the case of low-nucleophilic amines and weakly reactive carbonyl compounds, the reaction stops at the formation of 5-aminomethyltetrazoles **422**. The benzyl moiety can be quantitatively removed *via* hydrogenolysis in the presence

Scheme 143



421 (0% – 95%)

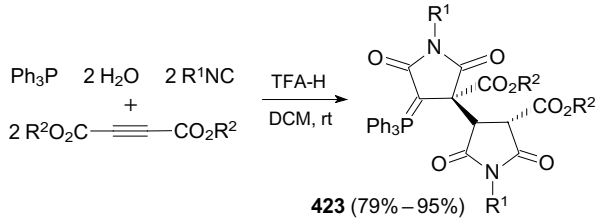
422 (0% – 91%)

R^1 = Pr^i, cyclo-C_3H_5, Bu^t, n-C_6H_{13}, cyclo-C_6H_{11}, Bn, 4-$MeOC_6H_4(CH_2)_2$; R^2 = H, Me, Pr^i; R^3 = Bu^t, cyclo-C_6H_{11}, All, Bn, 3,4-$Me_2C_6H_3$, $N_3(CH_2)_2$

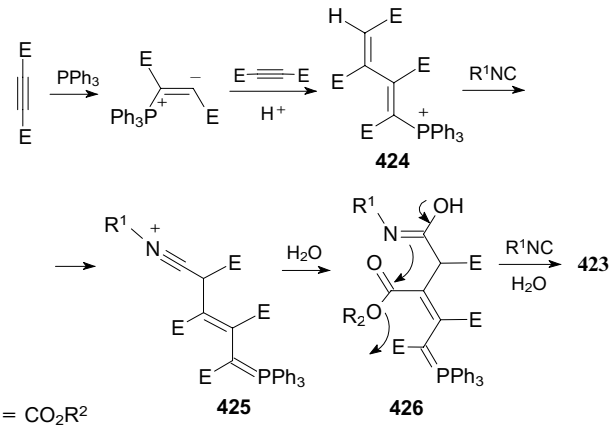
of HCl. This opens up a route to NH-derivatives of tetrazole, which are of interest in coordination chemistry.

A pseudo-seven-component diastereoselective synthesis of phosphorus-containing succinimide derivatives **423** was proposed by Alizadeh *et al.*[251] (Scheme 144). The treatment of a mixture of triphenylphosphine, water, isocyanide and dialkyl acetylenedicarboxylate with trifluoroacetic acid affords compounds **423** as single diastereomers in yields of up to 95%. This reaction can be considered as the sequential addition of two dialkyl dicarboxylate molecules to triphenylphosphine, the protonation giving intermediate **424** and the addition of isocyanide to form adduct **425** (see Scheme 144). Final product **423** is formed after the addition of isocyanide and water, intramolecular cyclocondensation and a hydride shift in intermediate **426**.

Scheme 144



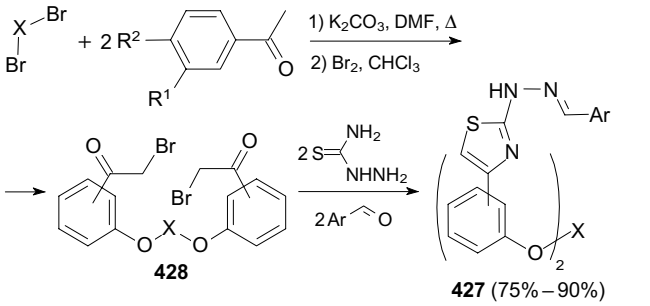
R^1 = Bu^t, cyclo-C_6H_{11}, EtO_2CCH_2; R^2 = Me, Et



Parvizi *et al.*[252] described a sequential pseudo-seven-component one-pot synthesis of bis-thiazoles **427** and evaluated their antibacterial and antioxidant activity (Scheme 145). A mixture of dibromide and hydroxyacetophenone in a ratio of 1 : 2 was refluxed with potassium carbonate in DMF and then treated with a solution of bromine in chloroform. Then thiosemicarbazide (2 equiv.) and aryl carbaldehyde (2 equiv.) were added to the resulting bromo ketones. Target bis-thiazole derivatives **427** were isolated in 75% – 90% yields. The reaction involves the alkylation of the phenol moiety, the bromination of the acetophenone derivative giving intermediate **428** and its condensation with thiosemicarbazide followed by intramolecular heterocyclization.

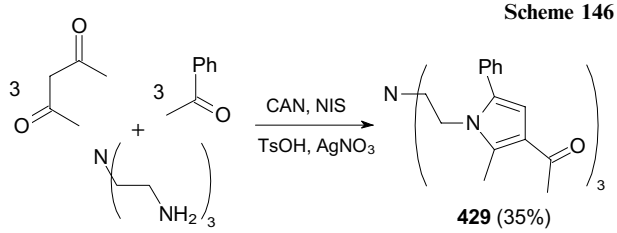
The pseudo-seven-component reaction with N^1,N^1-bis(2-aminoethyl)ethylene-1,2-diamine was performed similarly to the five-component construction of symmetrical molecules **429** bearing two pyrrole moieties, which was described by Leonardi *et al.*[190] The corresponding tripyrrole was isolated in 35% yield (Scheme 146).

Scheme 145



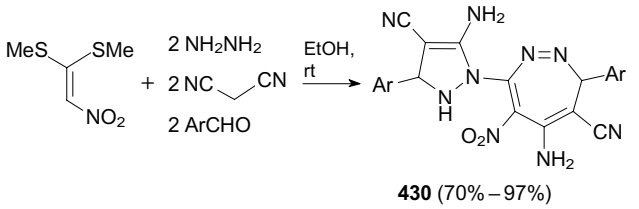
X = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$, $CH_2C_6H_4CH_2$ (in different positions); R^1, R^2 = H, OH; Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-Fu

Scheme 146

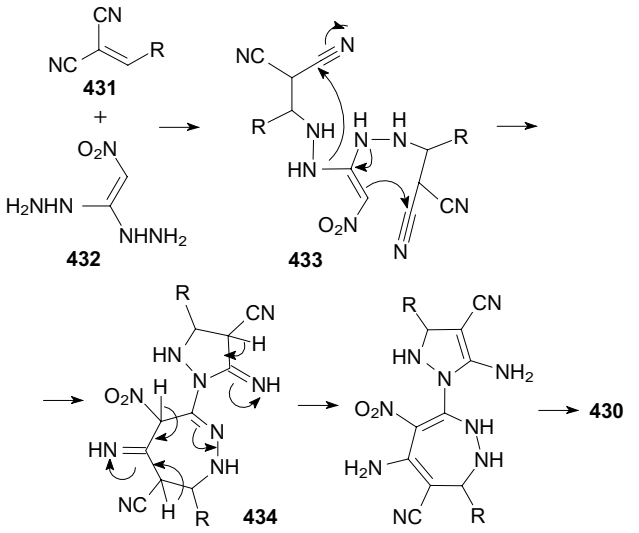


The highly efficient synthesis of polysubstituted pyrazolyl-1,2-diazepine derivatives **430** was based on the pseudo-seven-component one-pot reaction of 1,1-bis(methylthio)-2-nitroethylene, hydrazine, aryl carbaldehyde and malononitrile in a ratio of 1 : 2 : 2 : 2 under mild conditions (Scheme 147).[253] This process involves the Michael addition of two molecules of Knoevenagel product **431** to 1,1-

Scheme 147



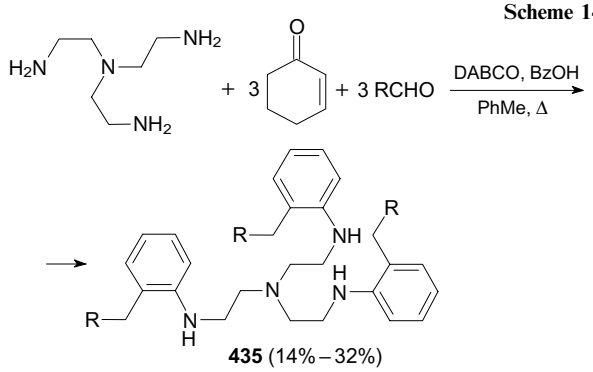
Ar = $X_nC_6H_{5-n}$ (X = H, 4-Cl, 2-Cl, 2-Br, 4-Me, 3-OMe, 3-OH, 4-NO_2, 2-NO_2, 4-CN, 2,6-Cl_2), 2-Naph



dihydrazino-2-nitroethylene **432**. The intramolecular cyclocondensation of adduct **433** affords compound **434** followed by tautomerization and oxidation with atmospheric oxygen to form final heterocycle **430**.

Almesåker *et al.*[254] prepared nitrogen-containing ligands based on tris(2-aminoethyl)amine derivatives **435** using N^1,N^1-bis(2-aminoethyl)ethylene-1,2-diamine as the starting compound (Scheme 148). The triple Michael α-aminomethylation followed by aromatization affords products in moderate yields.

Scheme 148

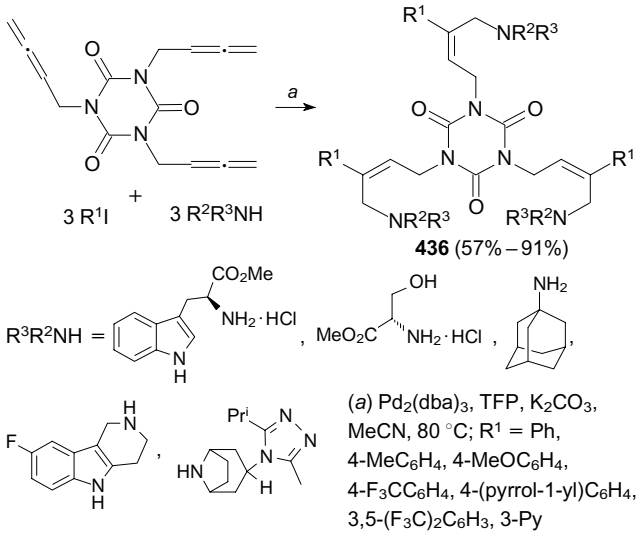


435 (14% – 32%)

R = 4-$F_3CC_6H_4$, 4-$O_2NC_6H_4$, 2-Fu; DABCO is diazobicyclo[2.2.2]-octane

Recently, Gültekina *et al.*[255] proposed the pseudo-seven-component cascade reaction involving trisallenyl isocyanuric acid derivatives (Scheme 149). The heating of triallene, which was synthesized from cyanuric acid, aryl iodide and a nucleophile in a ratio of 1 : 3 : 3 in the presence of a palladium catalyst, resulted in the formation of target heterocycles **436** in yields of up to 91% as single *Z*,*Z*,*Z* isomers.

Scheme 149



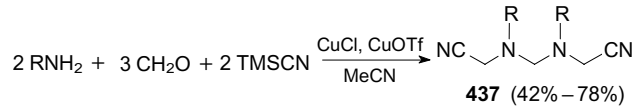
436 (57% – 91%)

(*a*) $Pd_2(dba)_3$, TFP, K_2CO_3, MeCN, 80 °C; R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 4-(pyrrol-1-yl)C_6H_4, 3,5-$(F_3C)_2C_6H_3$, 3-Py

The $CuCl-Cu(OTf)_2$ cooperative catalytic system provided efficient catalysis for the pseudo-seven-component coupling of primary aliphatic or aromatic amines, formaldehyde and trimethylsilyl cyanide giving N,N'-bis(cyanomethyl)methylenediamines **437** (Scheme 150).[256]

Another type of aminomethylation was accomplished as a pseudo-seven-component process[257] based on cyano-

Scheme 150

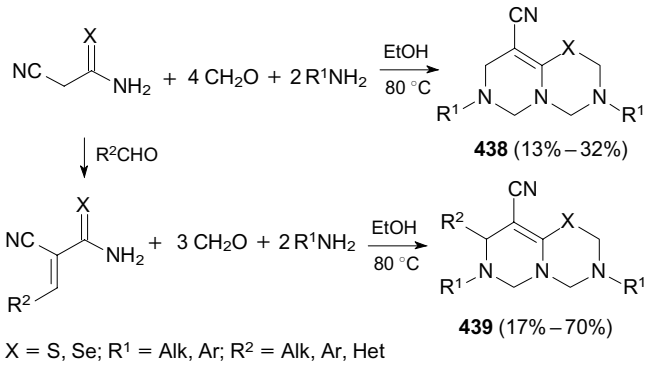


437 (42% – 78%)

R = Bn, 4-$MeOC_6H_4CH_2$, $BnCH_2$, Bu^n

thioacetamide and cyanoselenoacetamide.[258] These polyfunctional compounds undergo aminomethylation simultaneously at three different reaction centres, the methylene group, the sulfur atom and the amino group, to form bicyclic heterocycles **438**. The reaction can be performed using condensation products of cyanothioacetamide and cyanoselenoacetamide with aldehydes; in this case, substituted derivatives **439** are produced in yields of up to 70% (Scheme 151).

Scheme 151



438 (13% – 32%)

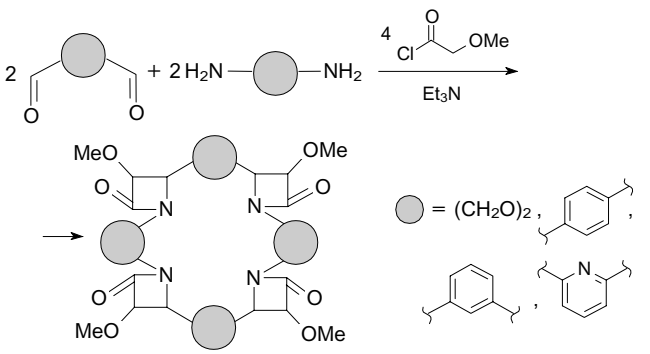
439 (17% – 70%)

X = S, Se; R^1 = Alk, Ar; R^2 = Alk, Ar, Het

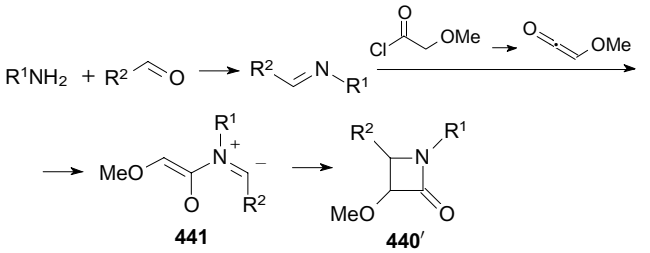
5. Eight-component reactions

Macrocyclic tetra-β-lactams **440** can be synthesized based on the pseudo-eight-component Staudinger process (Scheme 152).[259] The treatment of a mixture of dialdehydes,

Scheme 152

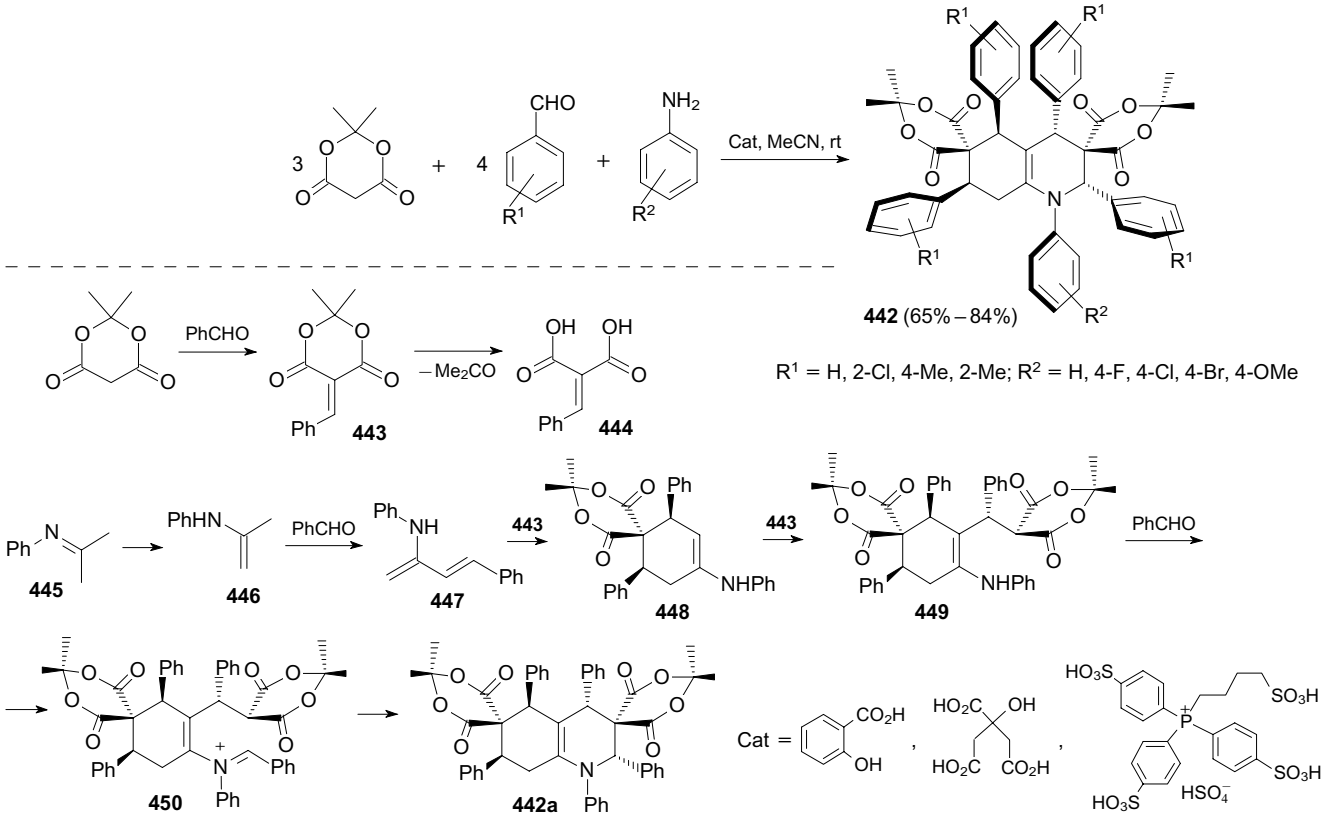


440 (33% – 82%)



441 **440′**

Scheme 153

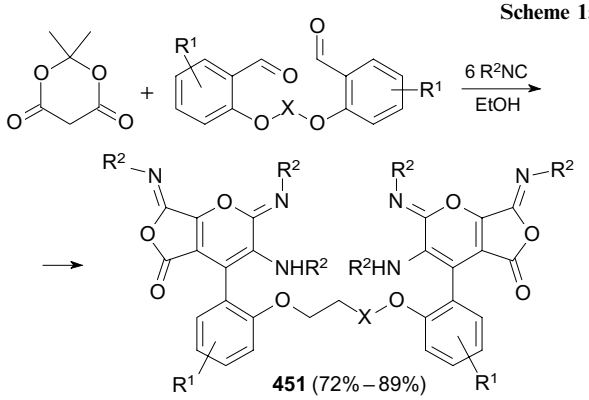


diamines and 2-methoxyacetyl chloride in a ratio of 2 : 2 : 4 with triethylamine affords 24-, 26- and 30-membered macrocyclic products **440**. The reaction mechanism implies the cycloaddition of imine and ketene giving zwiterionic intermediate **441** followed by the electrocyclic ring closure of the latter to form target β-lactam (structure **440′** presents one of the four moieties in Scheme 152).

The diastereoselective synthesis of dispirohydroquinolines **442** catalyzed by salicylic or citric acid was accomplished by a pseudo-eight-component reaction (Scheme 153).[260, 261] The reaction of Meldrum's acid, benzaldehyde and aniline in a ratio of 3 : 4 : 1 affords heterocyclic products **442** in yields of up to 84%. It is worth noting that in the absence of salicylic acid, the target product was not obtained. Later, Salahi *et al.*[262] discovered a more eco-friendly catalyst for this process — the ionic liquid (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulfate. The process is based on the domino Knoevenagel – aza-Diels – Alder reaction (see Scheme 153). The first step gives Knoevenagel condensation product **443**, which is converted to 2-benzylidenemalonic acid **444** *via* the elimination of an acetone molecule. Then acetone reacts with aniline to form imine **445**, which is transformed into enamine **446**. The reaction of the latter with benzaldehyde affords amino-substituted diene **447**. The latter undergoes [4 + 2]-cycloaddition with adduct **443** to give enamine **448**. The nucleophilic Michael addition of a second equivalent of compound **443**, the reaction of intermediate **449** with benzaldehyde and intramolecular cyclocondensation of iminium salt **450** furnish dispirohydroxyquinoline **442a**. The detailed investigation of the structural and energy characteristics of these spiro compounds was performed by Hazeri *et al.*[263]

Dimeric furopyran derivatives **451** linked by polyether spacer groups were synthesized by the pseudo-eight-compo-

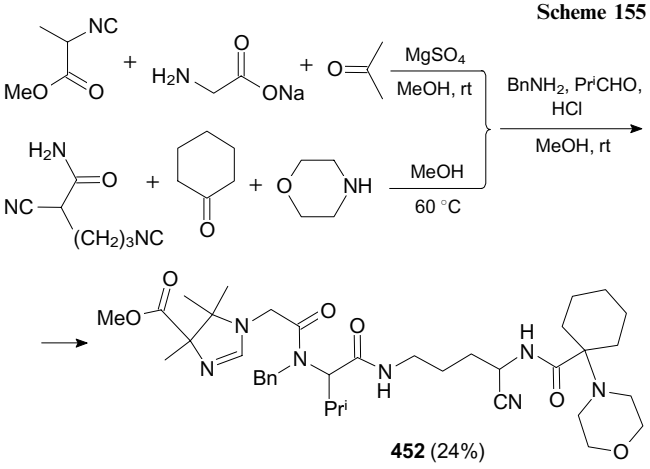
Scheme 154



nent reaction of bis(arylidene) Meldrum's acid derivatives with isocyanides in dichloromethane at room temperature with no catalysts. The reaction sequence involves the condensation of bisaldehydes with Meldrum's acid and [4 + 1]-cycloaddition of isocyanides giving iminolactone intermediate. Two subsequent reactions with isocyanide produce furopyran derivatives **451**.[264] Despite a large number of elementary steps, target products **451** were obtained in high yields (Scheme 154).

An eight-component synthesis of imidazoline-containing pseudopeptides **452** was described by Orru and co-workers[265] (Scheme 155). The process was accomplished in three steps. First, two three-components reactions involving ketone, amine and isonitrile were performed. Then the reaction mixtures were combined, and isobutyraldehyde

Scheme 155



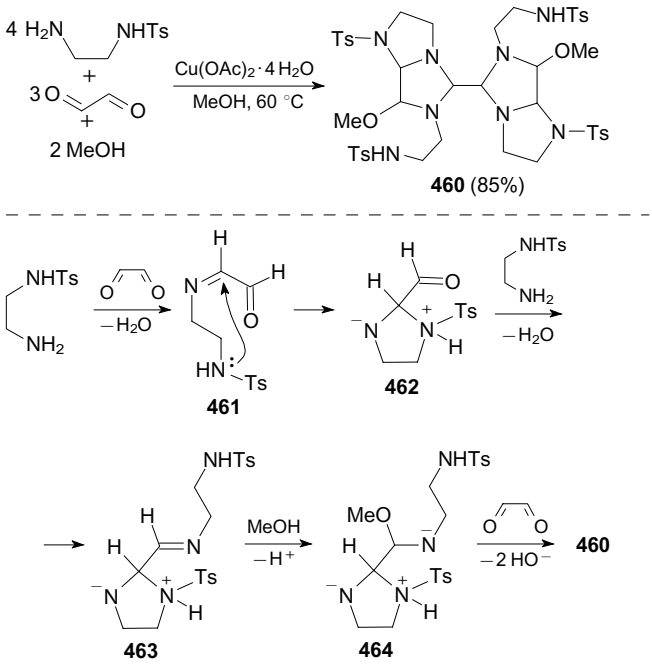
and benzylamine were added. Racemic product **452** was formed in the Ugi four-component reaction.

6. Reactions with nine and more components

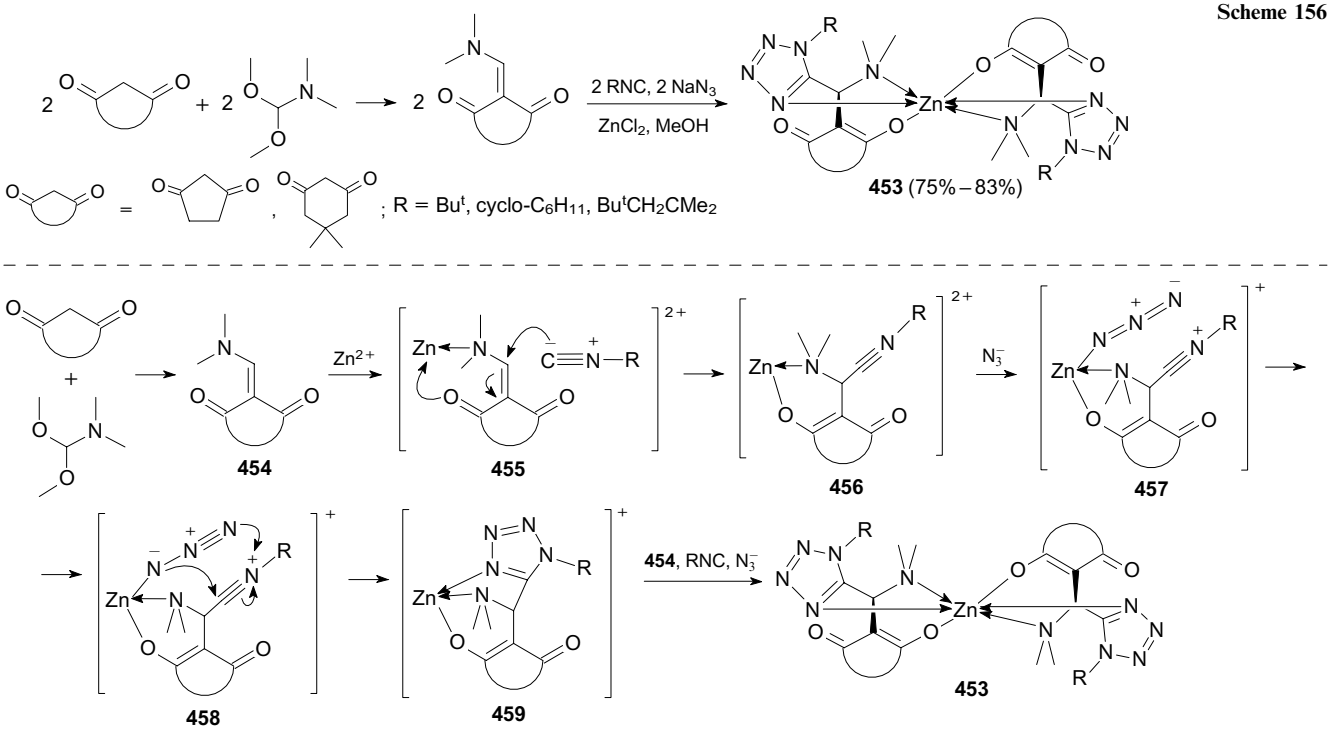
Higher-order multicomponent reactions are used, in particular, in coordination chemistry and are extensively applied in the synthesis of metal complexes. A method for the preparation of zinc 1,5-disubstituted 1*H*-tetrazol-5-yl complex **453** by the pseudo-nine-component reaction was proposed by Shaabani *et al.*[266] (Scheme 156). The synthesis was performed in a one-pot two-step manner. In the first step, dimedone (or cyclopentane-1,3-dione) and dimethylformamide dimethyl acetal (DMF-DMA) were mixed under solvent-free conditions. Then a solution of isocyanide, sodium azide and zinc chloride in methanol was added. Target zinc complexes **453** were isolated in 75% – 83% yields. The plausible reaction mechanism involves the formation of intermediate **454** from 1,3-diketone and DMF-DMA and its coordination to the Zn^{2+} ion to form complex **455** followed by the Michael addition of an isocyanide molecule (see Scheme 156). The subsequent nucleophilic attack of an azide ion on the nitrilium moiety of complex **456** followed by the 1,3-dipolar cycloaddition involving zinc azide derivative **457** produces intermediate **458**. The latter is transformed into complex **459**. The repeated reaction of complex **459** with intermediate **454**, isocyanide and azide ion furnishes target product **453**.

Unusual nitrogen heterocycles **460** were synthesized by the pseudo-nine-component reaction of *N*-tosylethylenediamine with glyoxal and methanol (Scheme 157).[267] The heating of the reactants in a ratio of 4 : 3 : 2 in the presence

Scheme 157



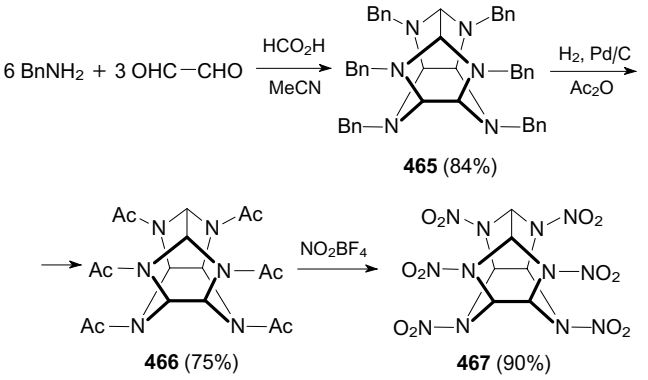
Scheme 156



of copper(II) acetate tetrahydrate affords target polyfused imidazoline derivative **460** in high yield. In the first step, the reaction of glyoxal with *N*-tosylethylenediamine gives imine **461**, which undergoes cyclization to imidazolidine **462** followed by the addition reaction of the latter with a second equivalent of *N*-tosylethylenediamine giving intermediate **463** (see Scheme 157). The subsequent attack of methanol on the unsaturated carbon atom of compound **463** and the proton abstraction give intermediate **464**. The reaction of this intermediate (2 equiv.) with glyoxal (1 equiv.) affords final product **460**.

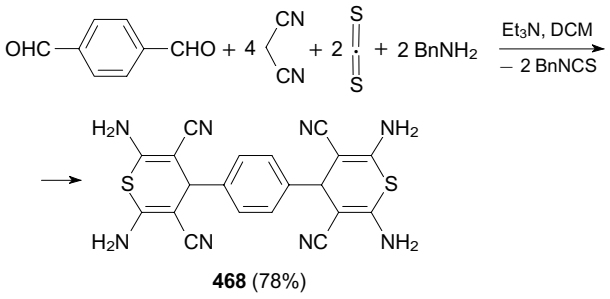
The condensation of benzylamine and glyoxal in a ratio of 6 : 3 furnishes hexabenzylhexaazaisowurtzitane **465** in high yield (Scheme 158), the reaction mechanism being similar to that described above.[268] The subsequent removal of benzyl protecting groups and acylation, followed by nitration of derivative **466** produce the nitramine explosive hexanitrohexaazaisowurtzitane **467**, commonly known as CL-20.[269 – 272]

Scheme 158



Bis(2,6-diamino-4*H*-thiopyran-3,5-dicarbonitrile) **468** was synthesized in good yield by a pseudo-nine-component process involving terephthaldehyde, malononitrile, carbon disulfide and benzylamine (Scheme 159).[156] The reaction mechanism in shown in Scheme 71.

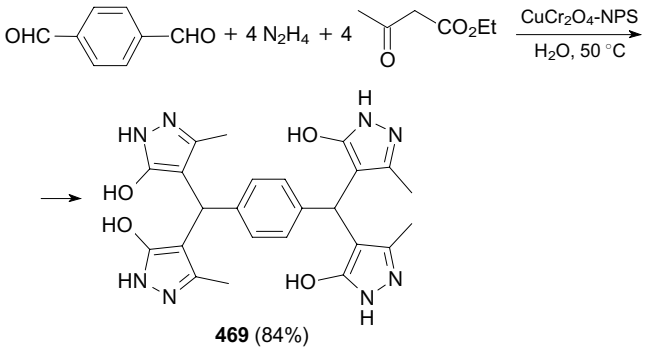
Scheme 159



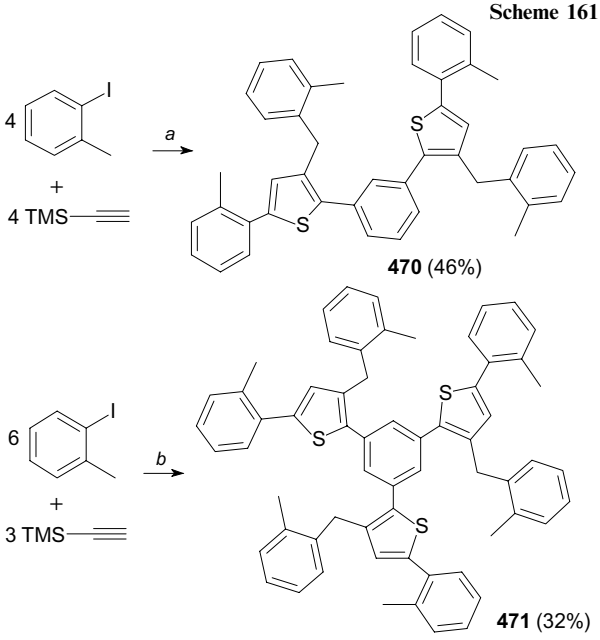
The domino cyclocondensation – Knoevenagel – Michael reaction using terephthaldehyde was implemented in a pseudo-nine-component process (Scheme 160). The reaction catalyzed by copper chromite nanoparticles ($CuCr_2O_4$-NPs) gave highly symmetrical pyrazol-5-ol derivative **469**.[140]

The Sonogashira – Glaser cyclization sequence[197] used in the synthesis of 2,3,5-trisubstituted thiophenes was applied to 1,4- and 1,3-di(sulfanylmethyl)benzenes and 1,3,5-tri(sulfanylmethyl)benzene (Scheme 161). However,

Scheme 160



Scheme 161



(*a*) 1) $PdCl_2(PPh_3)_2$, CuI, Et_3N; 2) KF, air, rt; 3) 1,3-$(HSCH_2)_2C_6H_4$, KOH, MW, 120 °C; (*b*) 1) $PdCl_2(PPh_3)_2$, CuI, Et_3N; 2) KF, air, rt; 3) 1,3,5-$(HSCH_2)_3C_6H_3$, KOH, MW, 120 °C

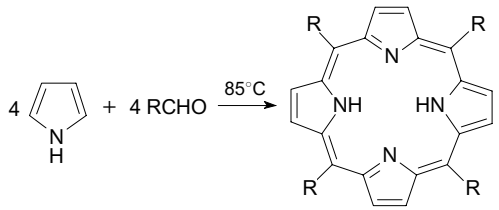
the formation of target branched molecules **470** and **471** was observed only with the *meta* derivatives (the yield of dithiophene **470** in the pseudo-nine-component reaction was 46%; the yield of trithiophene **471** in the pseudo-eleven-component reaction was 32%). In the case of 1,4-di(sulfanylmethyl)benzene, 2,5-diphenylthiophene was isolated as a sole product. The authors attributed this result to the fact that a superbasic medium promotes the elimination of carbon disulfide, thereby providing a source of sulfide ions for the synthesis of the by-product.

7. Oligo- and polymerization reactions

The biosynthesis of numerous oligomeric and polymeric natural products often involves six or more molecules. Natural products of the porphyrin series (porphyrin, chlorin, bacteriochlorin, *etc.*), corroles, phthalocyanines, cyclodextrins, as well as synthetic crown ethers, calixarenes, macrocyclic cavitands and many other compounds were thoroughly studied. Therefore, the preparation of sequence-defined oligomeric macrocycles and polymers can be considered as higher-order pseudo-multicomponent reac-

tions. The synthesis of porphyrin **472**, which was first reported by Rothemund,[273–276] is based on the pseudo-eight-component reaction of pyrrole with aldehydes on heating (Scheme 162).[277, 278] Modern methods for the synthesis of porphyrins **472**, involving microwave irradiation[279] and the use of the TFA-H – $Zn(OAc)_2$ catalytic system,[280] allow an increase in the product yield to 23%.

Scheme 162

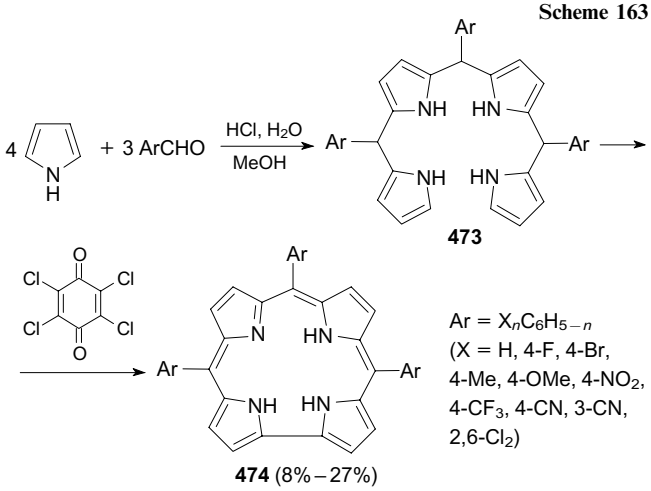


472 (4% – 23%)

R = H, n-C_5H_{11}, 4-XC_6H_4 (X = H, Cl, Me, Pr^i, Bu^t, SMe), 4-Py

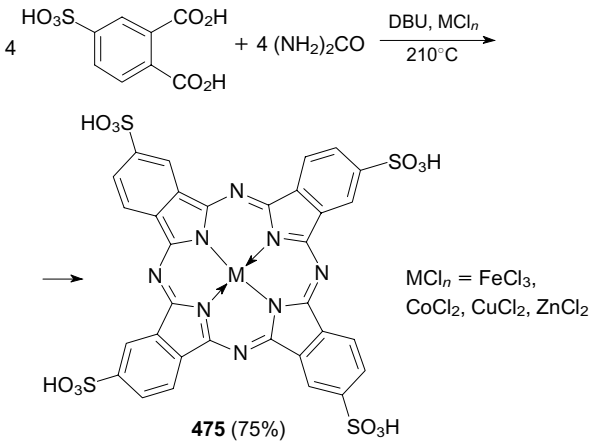
Such natural products as corroles **474** (see Refs 281 and 282) can be synthesized by a pseudo-multicomponent reaction (Scheme 163).[283] Tetrapyrrane **473**, initially formed *via* the reaction of pyrrole with benzaldehyde (4 : 3 ratio), is oxidized by chloranil giving compounds of the corrin series **474** in yields of up to 27%.

Scheme 163



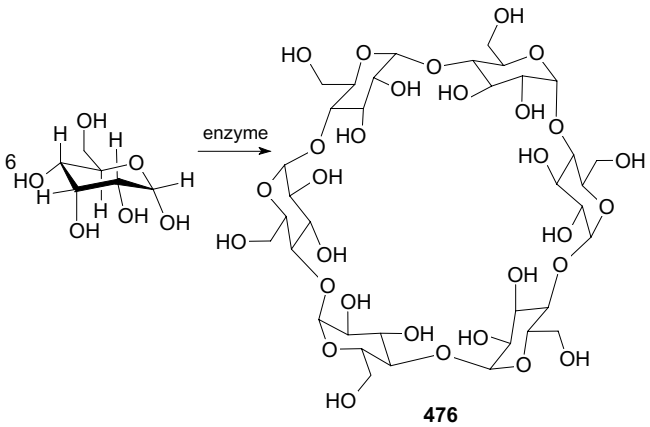
474 (8% – 27%)

Scheme 164



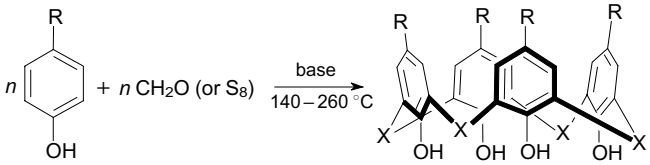
475 (75%)

Scheme 165



476

Scheme 166



477 (50% – 82%)

X = CH_2, S; *n* = 4, 6, 8; R = Br, Bu^t; base = NaOH, KOH, RbOH

Phthalocyanines **475**,[284, 285] which are analogues of porphyrins **472**, can also be synthesized by a pseudo-eight-component reaction (Scheme 164).[286] The reaction of 4-sulfophthalic acid with urea in the presence of DBU and iron(III), copper(II), cobalt or zinc chlorides furnishes metal phthalocyanine complexes **475** in 75% yield.

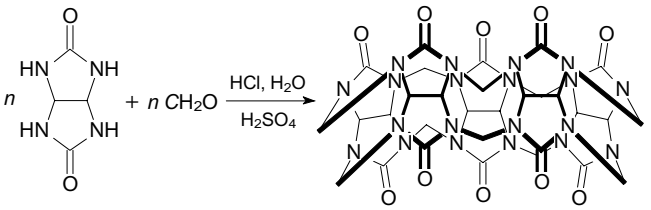
The enzymatic oligomerization of α-D-glucopyranose affords cyclodextrins **476** (see Refs 287 and 288) containing 6 to 32 glycoside residues (Scheme 165).[289, 290] The most common compounds of this class are α-, β- and γ-cyclodextrins **476** containing six, seven and eight monomer units, respectively.

Calixarenes and thiacalixarenes **477** (see Refs 291 and 292) are macrocyclic products of oligomerization of phenols with formaldehyde or sulfur (Scheme 166).[293] Compounds **477** are generally prepared by heating phenol and formaldehyde (or molecular sulfur) in the presence of a base, the base providing the template control over the macrocycle size. The reaction using NaOH affords calix[4]arenes, whereas KOH and RbOH give calix[6]- and calix[8]arenes, respectively. Calixarenes **477** containing up to 20 monomer units were studied in detail.[294]

Cavitands are a large class of macrocyclic oligomers with a cage structure.[295] The common property of these molecules is the ability to encapsulate metal cations. Cucurbituril **478**. (see Refs 296 and 297) is a bright representative of macrocyclic cavitands. This compound is generally prepared by the condensation of glycoluril and formaldehyde in an acidic medium (Scheme 167).[298]

The condensation of ammonia and formaldehyde in a ratio of 4 : 6 affords hexamethylenetetramine **479**, also known as hexamine or urotropin (Scheme 168). This pseudo-ten-component process was described for the first time by Butlerow[299] in 1859.

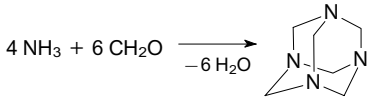
Scheme 167



478 (40% – 70%)

n = 5 – 10

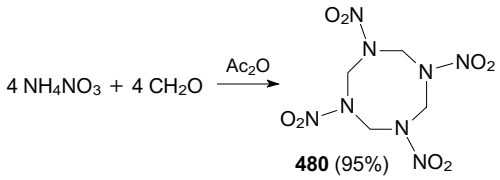
Scheme 168



479

A synthesis of a series of polynitropolyazinanes was developed based on urotropin. These compounds are structurally similar to urotropin **479**.[300] The powerful explosive octagen **480** is the most well-known representative of this class. Octagen is generally prepared by the reaction of ammonium nitrate with formaldehyde in the presence of acetic anhydride (Scheme 169).

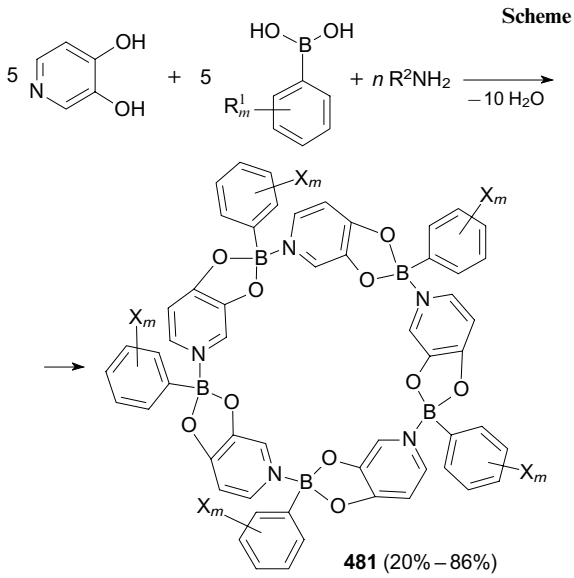
Scheme 169



480 (95%)

A large class of boron-containing dendritic oligomers **481** was synthesized based on pseudo-ten-, pseudo-fifteen- and pseudo-twenty-five-component reactions (Scheme 170).[301] Cyclic oligomeric products **481** containing five units were isolated in yields of up to 86%.

Scheme 170



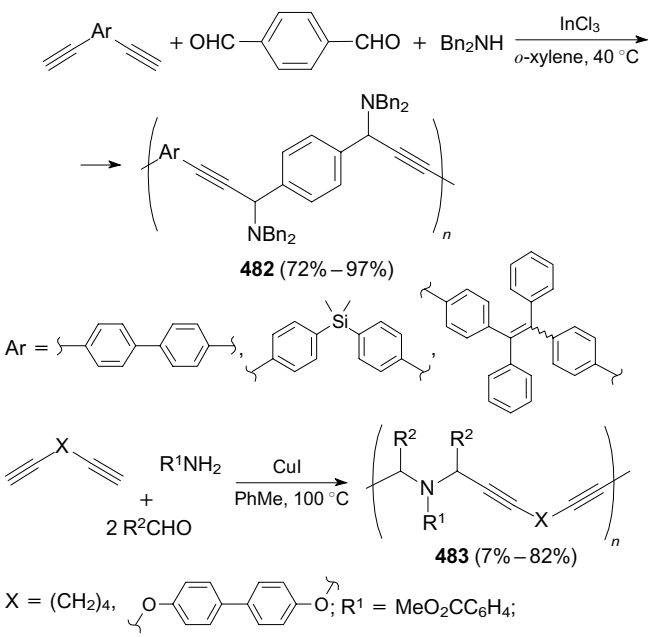
481 (20% – 86%)

n = 0, m = 1: R^1 = X = 3-F, 4-Me, 4-Bu^n, 4-Bu^i, 3-NH_2; n = 5, 10: m = 1, R^1 = 3-CHO, X = 3-(CH=NR^2); m = 2, R^1_2 = 3,5-$(CHO)_2$, X_2 = 3-(CH=NR^2)$_2$; R^2 = cyclo-C_6H_{11}, Bn, Ph, 4-BrC_6H_4

Most of synthetic polymers consist of randomly distributed monomer units. However, the monomer sequence regularity greatly affects the supramolecular and macroscopic properties of polymer materials. Hence, the precise molecular encoding of polymer chains is a challenging problem.[302] A convenient approach to the synthesis of sequence-controlled polymers is provided by pseudo-multicomponent reactions, in particular, the most commonly used metal-catalyzed transformations, and also Ugi and Passerini pseudo-multicomponent reactions.[303] Polycondensation catalyzed by indium(III) chloride [304] or copper(I) chloride [305] allows the preparation of chiral dendritic (**482**) and polymeric (**483**) structures (Scheme 171). A^3-Coupling reactions furnish target polymers **482** and **483** in yields of up to 97%.

Another type of copper-catalyzed polycondensation was applied in the synthesis of poly(*N*-sulfonylimidates) **484**.[306]

Scheme 171



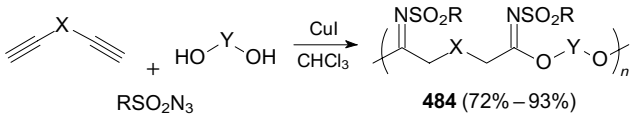
482 (72% – 97%)

483 (7% – 82%)

X = $(CH_2)_4$, ; R^1 = $MeO_2CC_6H_4$;

R^2 = H, 4-$MeOC_6H_4$

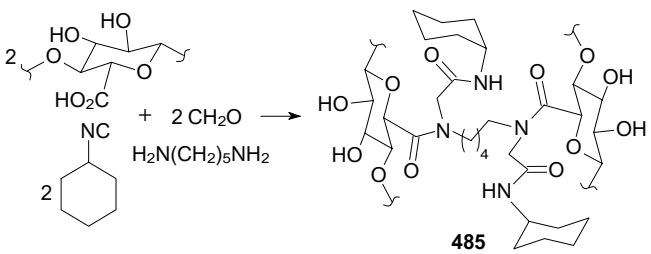
Scheme 172



484 (72% – 93%)

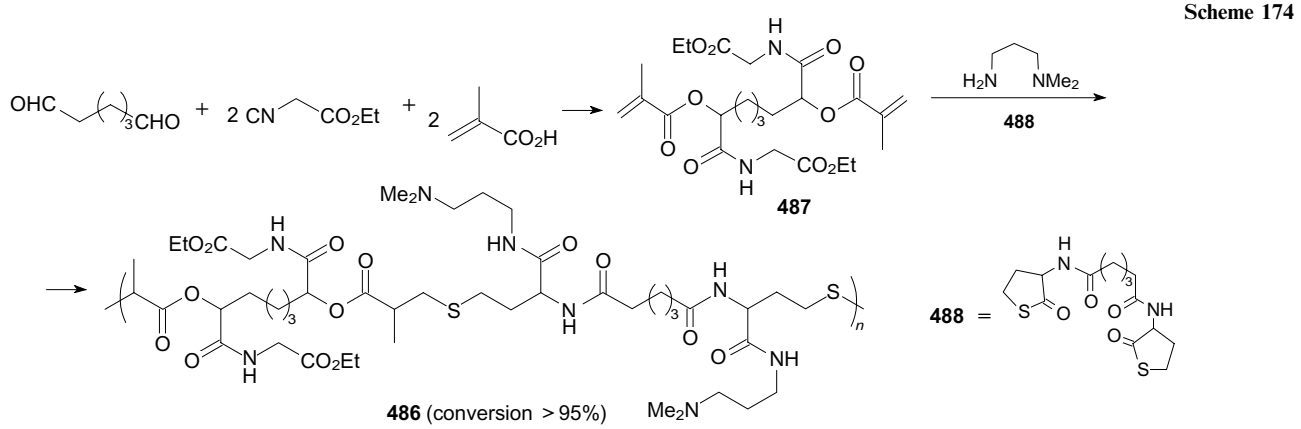
X = $(CH_2)_3$, $(CH_2)_5$, $(CH_2O)_n$; R = cyclo-C_6H_{11}, XC_6H_4 (X = 4-Me, 4-CF_3, 4-NO_2, 3-NO_2, 2-NO_2); X = $(CH_2)_5$, $(CH_2)_6$, $(CH_2O)_3$, C_6H_4 and C_6H_4 – C_6H_4 (in different positions)

Scheme 173



485

Scheme 174



This approach proved to be very efficient and can be used to prepare diverse target polymer materials **484** under mild conditions in high yields (Scheme 172).

A series of alginate-based hydrogels **485** were synthesized by the Ugi reaction (Scheme 173).[307, 308] The reaction of L-mannuronic acid, 1,5-diaminopentane, formaldehyde and cyclohexyl isocyanide in a ratio of 2 : 1 : 2 : 2 affords target biopolymers. The conversion and yields of products **485** were not reported by the authors.

Sequence-controlled polymers **486** were synthesized using a Passerini-based multicomponent process (Scheme 174).[309] The *in situ* prepared product of the reaction of adipic aldehyde, methacrylic acid and isocyanoacetic ester (1 : 2 : 2 ratio) — compound **487** — was treated with *N*,*N*-dimethyl-1,3-propanediamine and adipic acid amide **488** to form polymer **486** with an average molecular weight of 49.8 kDa and polydispersity of 2.03. The conversion of methacrylic acid was higher than 95%.

8. Conclusion

Higher-order multicomponent reactions are a powerful tool for the construction of complex carbon cages, the synthesis of various polyfunctionalized heterocycles, peptides, depsipeptides and biologically active compounds. The number of structural fragments introduced into the target molecule in one step by means of MCRs is limited only by the number of starting components and increases with increasing reaction order. This review demonstrates that, despite a great progress in this area, there are not many higher-order MCRs. It is worth noting that the number and diversity of five-component reactions are much larger compared to other higher-order MCRs. Moreover, many processes are pseudo-multicomponent. However, it can be seen that no other approach can provide such efficiency of the synthesis as MCRs. Consequently, any study devoted to multicomponent reactions involving more than six components is at the forefront of scientific research in this area of chemistry. Products prepared according to this approach have very high molecular complexity. Moreover, the chemical space of products becomes virtually unlimited with increasing number of components in MCRs. Isocyanide-based reactions especially stand out among all approaches considered in the review. These unique functional derivatives serve as linking units, thereby opening up a very efficient route to molecules with high complexity.

Hence, the data covered in this review provide evidence that investigations of multicomponent reactions are of great interest. Many research teams from all over the world are working in this area. An even more rapid progress in this field of chemistry would be expected to occur in the near future.

Acknowledgement

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