Recent Developments in the Isonitrile-Based Multicomponent Synthesis of Heterocycles

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Dedicated to Professor I. Ugi, the pioneer of modern MCR

Keywords: Combinatorial synthesis / Domino process / Heterocycles / Isonitrile / Multicomponent reactions

Although the synthesis of β-lactams by means of tethered Ugi reactions has been known since the early 1960s, the 1995 report from Ugi's group could be regarded as a turning point in the development of novel multicomponent reactions (MCRs) for heterocycle syntheses. Indeed, the number of articles describing isocyanide-based multicomponent syntheses of heterocycles has increased steadily since then. Although most of these novel MCRs still exploit the archetypal reactivity of isocyanide, its pronounced ability to undergo α-addition with electrophiles (sp^2- and sp-carbon atoms) and nucleophiles, new MCRs have also been discovered as a consequence of exploiting the different secondary reactions of this α-adduct. Since most of these MCRs were devised on the basis of known bimolecular reactions, judicious combination of reactive functional groups within substrates is of fundamental importance. While the combinatorial principle can help in finding and exploring new MCRs, we would advocate a "substrate-design approach" in searching for novel MCRs. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2003)

1. Introduction

A multicomponent reaction (MCR) is a process in which three or more reactants are combined in a single reaction vessel to produce a product that incorporates substantial portions of all the components.[1−4] The MCR is a sequence of bimolecular events that proceeds according to the domino principle: subsequent transformations are a consequence of the functionalities produced in the previous one.[5] A MCR is thus a domino process by definition.

Domino process can be unimolecular [Scheme 1 (a)],[6] bimolecular [Scheme 1 (b)],[7] or multicomponent [Scheme 1 (c)].[8] All these processes are highly efficient, for they create molecular complexity by generating more than two chemical bonds per operation. However, the multicomponent variant also has following added bonuses: a) it is more convergent than the uni- and bimolecular domino processes, b) the structure of the reaction product is easily diversified by systematic variation of each input, c) the starting materials are either commercially available or easily prepared, and d) the number of theoretically accessible compounds is extremely large. Conversely, the high level of structural complexity generated from a unimolecular domino process can sometimes be counter-balanced by the efforts associated with the synthesis of the linear precursor.

Many important named reactions, among others Strecker's amino acid synthesis (1850),[9] Hantsch's dihy-

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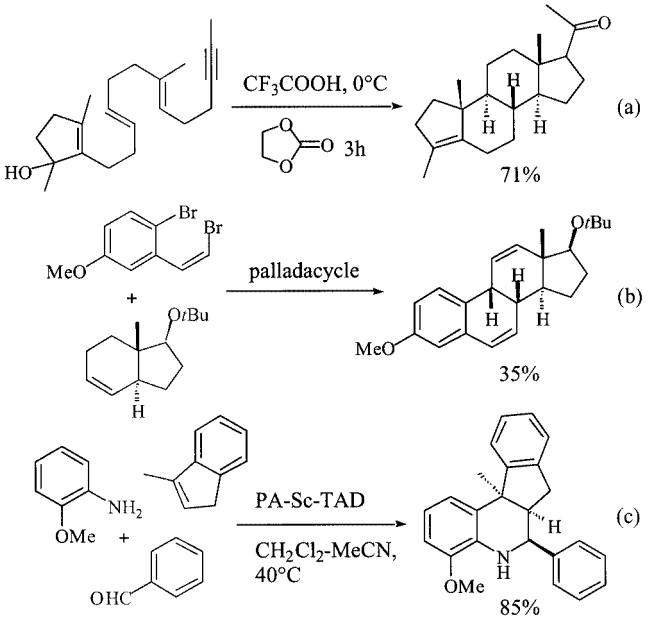
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 1. PA-Sc-TAD = (polyallyl)scandium trifylamide ditriflate

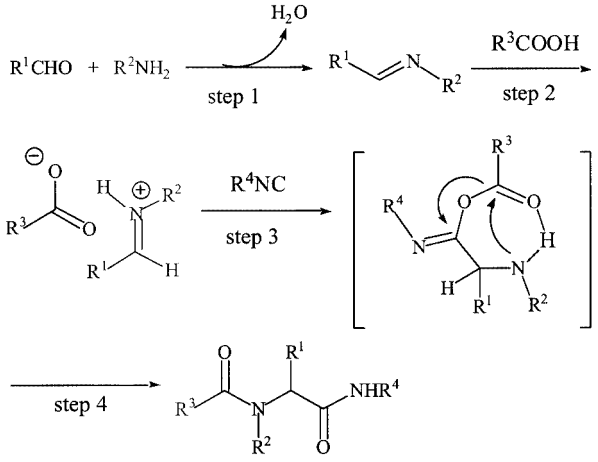
dropyridine synthesis (1882),[10] Biginelli's dihydropyrimidine synthesis (1891),[11] and Mannich's (1912)[12] and Passerini's reactions (1921),[13] were discovered about a century ago and remain the methods of choice in the syntheses of designated compound categories. The Ugi 4CR (1959),[14] a relatively "recent" and probably one of the most utilized MCRs during the last decade, is now almost 45 years old! In spite of the significant useful attributes of MCRs for modern organic chemistry and their potential use in complex organic synthesis, little attention has been paid to the development of novel MCRs[15] for the past half a century, although notable exceptions are the development of the Pauson–Khand reaction[16,17] and domino vicinal difunctionalization of α,β-unsaturated carbonyl substrates.[18] However, with the introduction of high throughput biological screening and the advent of genomics and proteomics, the demands on the *number* and the *quality* of compounds for drug discovery have increased enormously. By virtue of its inherent high exploratory power,[4] research on MCRs has naturally became a rapidly evolving field and since 1995 has attracted attention from both academic and industrial researchers.

This microreview focuses on the recent development of *isocyanide-based* one-pot multicomponent syntheses of *heterocycles*.[19,20] Combinations of MCR and subsequent transformations — such as Armstrong's elegant work on convertible isocyanide[21] and Hulme's highly versatile UDC (Ugi, 4CR/Deprotection/Cyclization) methodology[22] — are not included here.

2. The Ugi 4CR and Its Variants

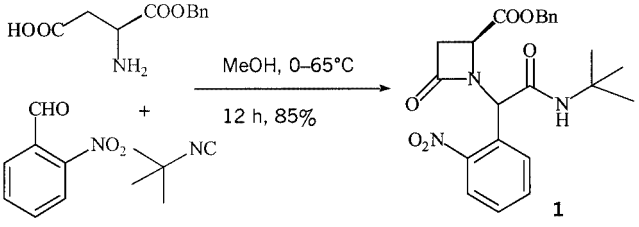
2.1. The Tethered Ugi 4CR

A Ugi 4CR converts an aldehyde, an amine, an acid, and an isocyanide into an α-acetamidoamide in one step, with good to excellent yields. It was postulated that the reaction involved a sequence of a) imine formation, b) protonation of imine by acid, c) α-addition of the electrophilic iminium cation and the nucleophilic carboxylate anion to isocyanide, and d) intramolecular acyl transfer (Scheme 2). The reaction is both ecologically benign and atom-economic, since only one molecule of water is lost in an entire process creating four chemical bonds. The conversion of a high-energy "formally divalent" isocyanide carbon atom into the tetravalent amide carbon atom provides the driving force for this truly versatile and powerful reaction.



Scheme 2

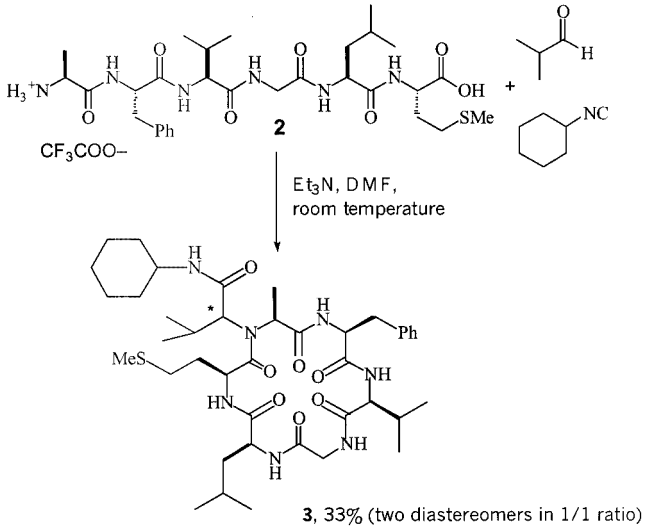
The Ugi 4CR provides a linear, peptide-like adduct. A conceptually simple approach to the cyclic structure is to tether two out of four inputs and to perform a three-component/four-center condensation (Ugi, 3CR/4centers). Indeed, various bifunctional components have been employed, and lactams with different substitution pattern have been synthesized by using ω-oxo acids,[23–25] ω-amino acids,[26–28] and ω-amino aldehydes[29] as inputs. The functionalized β-lactam **1**, for example, was readily prepared in excellent yield simply by mixing a β-amino acid, an aldehyde, and an isocyanide (Scheme 3).[30]



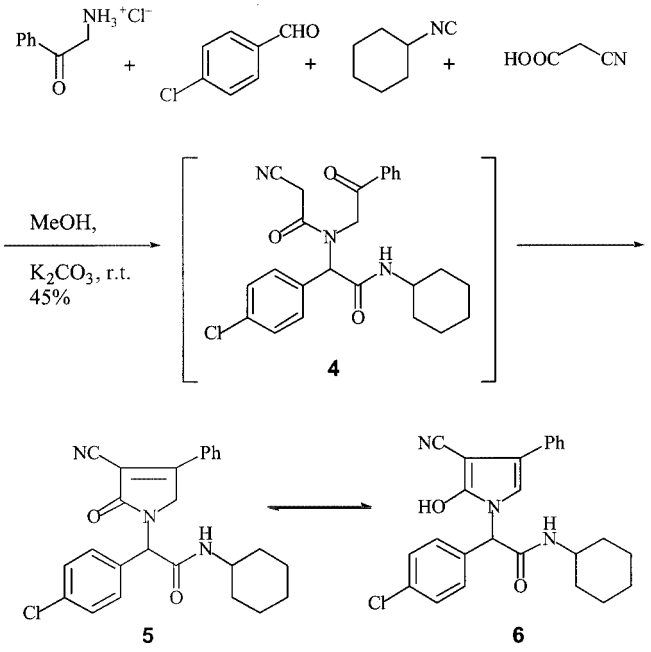
Scheme 3

Significantly, the same principle has also been applied to the synthesis of macrocycles. Thus, stirring of a DMF solution of linear hexapeptide **2**, isobutyraldehyde, and cyclohexyl isocyanide at room temperature provided the 18-

membered cyclohexapeptide **3** as a mixture of two diastereomers in 33% yield (Scheme 4).[31]



Scheme 4



Scheme 5

2.2. Combination of Ugi 4CR with Other Transformations

The Ugi 4CR gives α-acetamido amides, with four points of diversity. If one or two of the starting materials were to bear additional functional groups susceptible to reaction with each other after formation of the Ugi adduct, then cyclic structures should be produced. While such a union concept represents a simple yet very attractive approach to heterocycle synthesis, it does have some technical constraints. Since the preferred reaction medium for the Ugi reaction is a polar protic solvent, there are two options to develop the combination concept: a) to select a programmed post-transformation that is compatible with the protic solvent, or b) to develop novel conditions for the Ugi 4CR compatible with the projected in situ transformation. While the first option is simpler, the second, though requiring significant investigation, would open new avenues for the development of novel MCRs. Both approaches have indeed been examined and have produced fruitful results.

2.2.1. Combination of Ugi 4CR/Knoevenagel Condensation

Marcaccini and co-workers developed a novel four-component synthesis of pyrroles by combination of the Ugi 4CR and the Knoevenagel reaction (Scheme 5).[32] Mixing of the hydrochloride salt of phenacylamine, cyanoacetic acid, cyclohexyl isocyanide, and 4-chlorobenzaldehyde in MeOH in the presence of potassium carbonate directly gave the pyrrole **5**, in equilibrium with its 2-hydroxy tautomer **6**. The intramolecular Knoevenagel reaction was a relatively fast process, since the Ugi adduct **4** was not isolated. Five examples were given, with the yield ranging from 38 to 48%.

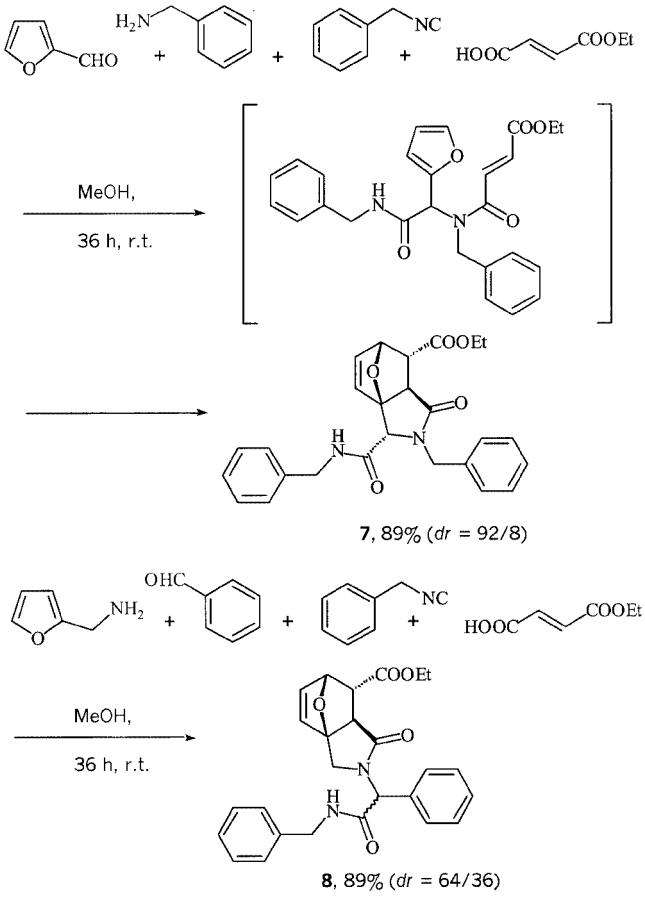
2.2.2. Combination of Ugi 4CR/Intramolecular Diels−Alder Cycloaddition

Paulvannan and co-workers reported an elegant synthesis of bridged tricyclic compounds in a combination of the Ugi 4CR and the intramolecular Diels−Alder cycloaddition (IMDA).[33] Key to this process is the incorporation of a diene and a dienophile in two of the four components of the Ugi reaction. As shown in Scheme 6, stirring of a solution of furaldehyde, benzylamine, benzyl isocyanide, and a fumaric acid derivative in methanol at room temperature for 36 h provided the cycloadduct **7** in 89% yield (*dr* = 92:8). The relative stereochemistry of the major isomer, undetermined at that time, was deduced in the light of the X-ray structure of a similar compound obtained by Schreiber and co-workers.[34]

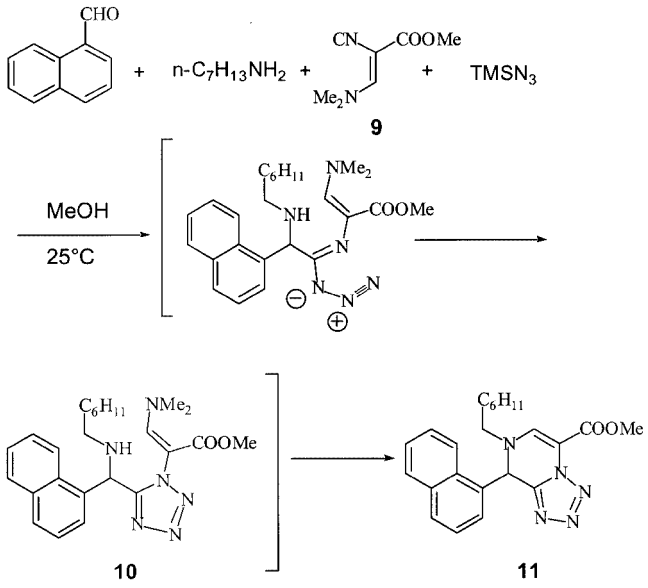
Alternatively, condensation of furylamine, benzaldehyde, benzyl isocyanide, and fumaric acid derivative gave compound **8** in excellent yield. As anticipated, the diastereoselectivity (*dr* = 64:36) was less in this case. The sequence seems to be quite general and has been performed on polymer support with both acid-labile ArgoGel-Rink[33] and high-capacity polystyrene resins.[34]

2.2.3. Combination of Ugi 4CR/Intramolecular 1,4-Addition and Elimination

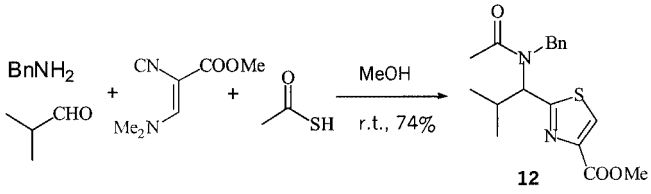
At the very earliest stage of its development, it had already been noticed that nucleophiles other than carboxylic acid, such as hydrazoic acid, would participate in the Ugi 4CR.[35] By judicious selection of starting materials, Bienaymé and co-workers devised an elegant synthesis of bicyclic tetrazole as shown in Scheme 7.[36] Thus, the reaction between 1-naphthaldehyde, heptylamine, methyl β-(*N*,*N*-dimethylamino)-α-isocyanoacrylate (**9**), and trimethylsilyl azide in MeOH afforded the stable bicyclic tetrazole **11** in good to excellent yield through a sequence of Ugi 4CR/intramolecular 1,4-addition and β-elimination of dimethylamine. In a control experiment, the intermediate tetrazole **10** was isolated and was found to cyclize to bicyclic tetra-



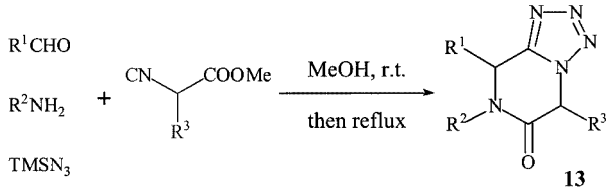
Scheme 6



Scheme 7



Scheme 8



Scheme 9

zole **11** in essentially quantitative yield. In this one-pot process, the exploitation of the different reactivities of the densely functionalized methyl β-(*N*,*N*-dimethylamino)-α-isocyanoacrylate (**9**) was maximized. Thus, the isocyanide (for α-addition), the enoate (as Michael acceptor), and the β-dimethylamino group (as leaving group) participated in the reaction sequence in a highly ordered fashion to deliver the final bicyclic compound.

Both aliphatic and aromatic aldehydes − and even ketones − participated in this process. In the amine part, both aliphatic and aromatic amines (anilines) were tolerated. The presence of an ester function should, in principle, provide an additional handle for further transformations.

Using thiocarboxylic acid and methyl β-(dimethylamino)-α-isocyanoacrylate as inputs, Dömling and coworkers reported an efficient synthesis of highly functionalized thioazole (**12**) by a similar reaction sequence (Scheme 8).[37]

2.2.4 Combination of Ugi 4CR/Lactamization

Hulme and co-workers developed a one-pot synthesis of 7,8-dihydrotetrazolo[1,5-*a*]pyrazin-6-one (**13**) by a sequence of an Ugi 4CR and a lactamization process (Scheme 9).[38] Thus, condensation of an aldehyde, a primary amine, methyl isocyanoacetate, and trimethylsilyl azide in methanol provided the bicyclic compound **13** in excellent yield.

Various aldehydes and amines have been used, and the MCR worked well for the synthesis of (5−6)-fused ring systems. However, the yield decreased significantly for the preparation of a (5−7)-fused bicyclic compound from methyl β-isocyanopropionate.

3. Novel Isocyanide-Based Multicomponent Reaction

It is fair to say that a multicomponent reaction was rarely devised with the goal of exploring new chemical reactivity in an individual functional group. Rather, the process is designed on the basis of well-known bimolecular reactions. The novelty of an MCR resides in how these individual reactions are combined and the outcome of the overall reac-

tion sequence. A suitable combination of a sequence of already existing reactions may result in a new MCR. The following section details some novel isocyanide-based multicomponent reactions. As highlighted mechanistically, most of these novel MCRs still exploit the archetypal reactivity of isocyanide, its pronounced ability to undergo α-addition with electrophiles (sp^2- and sp-carbon atoms) and nucleophiles. What makes the difference is the subsequent transformation of this α-adduct. In the classic Ugi 4CR and the Passerini 3CR, formation of this α-adduct was followed by an intramolecular acyl transfer as an irreversible step giving rise to linear adducts. In the MCRs described in the following section, two types of design principles can be recognized: a) the α-adduct is transformed into a heterocycle by simple tautomerization (usually a [1,*n*]-H shift), and b) the α-adduct formed is a reactive intermediate that can be engaged in subsequent reactions, other than acyl transfer, with the predisposed functionalities giving rise to complex heterocycles.

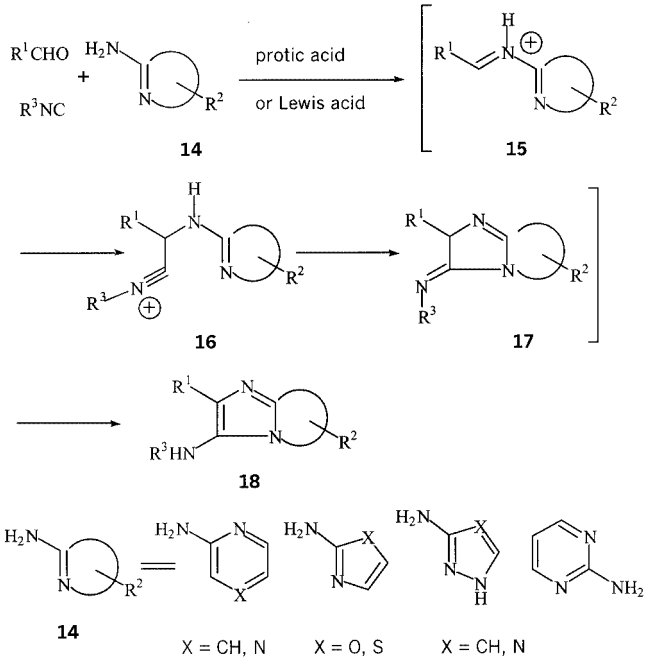
3.1 Three-Component Synthesis of Heterocyclic Fused 3-Aminoimidazoles

Three industrial research groups, led by Bienaymé at Rhone−Poulenc,[39] Blackburn at Millennium Pharmaceuticals,[40] and Groebke at Hoffmann−La Roche,[41] independently reported a three-component synthesis of imidazo[1,2-*a*]-annulated heterocycles **18** from aldehydes, isocyanides, and 2-aminoazenes **14** by a formal [4+1] cycloaddition process. The reaction is catalyzed (promoted) by protic acids [$HClO_4$ (0.05 equiv.), HOAc (2 equiv.)] and by Lewis acids [$Sc(OTf)_3$, 0.05 equiv.]. It is particularly noteworthy that the normal Ugi adduct was not produced even in the presence of two equivalents of acetic acid. The result indicates that intramolecular trapping of the nitrilium function in **16** by a nitrogen atom, a 5-*exo*-*dig* cyclization producing **17**, is highly competitive relative to intermolecular addition of a carboxylate anion onto **16** (Scheme 10).

There seems to be no major limitation regarding the selection of aldehydes and isocyanides. For the 2-aminoazene part, both heteroaromatic amidines and heteroaromatic guanidines participated in this novel 3CR, although aliphatic amidines were found to be inactive. A library of 30,000 different compounds has been prepared by solution-phase parallel synthesis, and the methodology has been transferred to solid-phase synthesis on supported aldehyde[42] or universal Rink-isocyanide resin.[43]

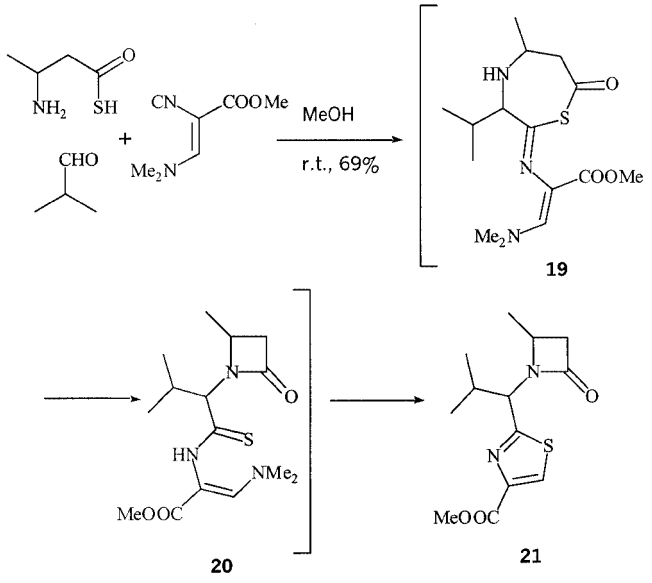
3.2 Three-Component Synthesis of 1-[(Thiazol-2-yl)methyl]-azetin-2-ones

Union of the tethered Ugi 4CR and a Michael addition/β-elimination sequence allowed Dömling and co-workers to develop a novel three-component synthesis of 1-(thiazol-2-ylmethyl)azetin-2-ones (Scheme 11).[44] Condensation of a β-aminothiocarboxylic acid, an aldehyde, and methyl β-(*N*,*N*-dimethylamino)-α-isocyanoacrylate gave the seven-membered thiolactam intermediate **19**. Ring-contraction by way of intramolecular acyl migration afforded β-lactam **20**,



Scheme 10

with concomitant generation of the thioamide function. Subsequent intramolecular Michael addition, followed by β-elimination of dimethylamine, provided the title compound **21**. In this experimentally simple procedure, five chemical bonds (one C−C, two C−N, and two C−S bonds) were formed with concurrent generation of two medicinally relevant heterocycles under mild conditions.

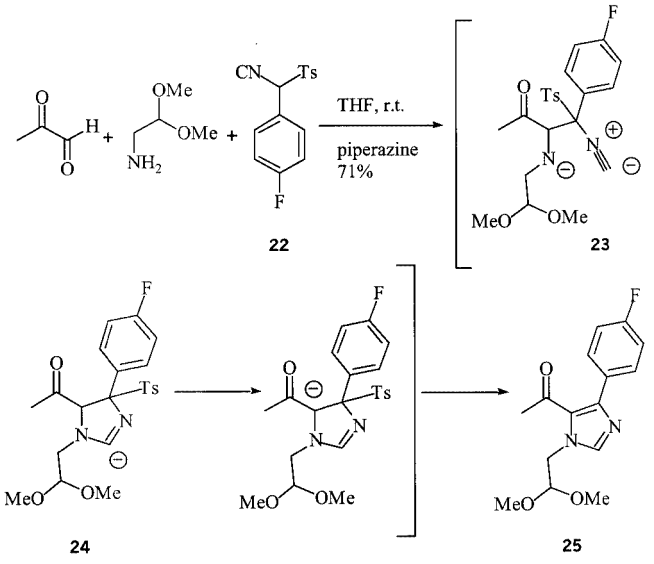


Scheme 11

It is interesting to note that in this three-component condensation, six functional groups participated in the reaction manifold in a highly ordered fashion without any external instruction (reagent).

3.3 Three-Component Synthesis of Imidazoles

The reaction between imines and tosyl methyl isocyanides (TosMICs) was known to produce imidazoles, thanks to Van Leusen's pioneering work.[45,46] However, no systematic study on the reactivity of substituted TosMIC derivatives had been performed in the intervening years. In a series of papers, Sisko and co-workers demonstrated that use of isolated imines was not necessary and that the three-component condensation between aldehyde, amine, and an α-aryl-substituted TosMIC (**22**) provided 1,4,5-trisubstituted imidazole in good to excellent yields (Scheme 12).[47]



Scheme 12

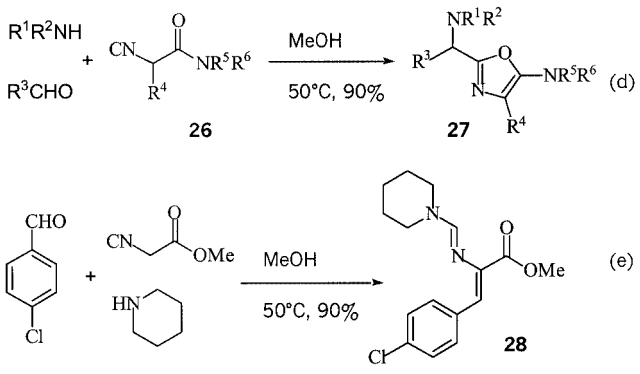
In contrast to the Ugi-type condensation, the reaction sequence was initiated by the nucleophilicity of the TosMIC's α-carbon anion, Mannich-type addition of the α-carbanion to the imine generated in situ affording the adduct **23**. Intramolecular nucleophilic addition of a nitrogen atom to the isocyanide carbon atom generated the carbanion **24**, which, after 1,3-proton transfer and tosyl group elimination, resulted in the formation of the observed imidazole **25**.

Aldehydes and amines bearing various functional groups participated in this reaction, and the overall transformation was essentially racemization-free when enantiomerically pure amino acid and *N*-Boc-amino aldehyde were used as inputs. However, the reaction seems to be limited to α-aryl-substituted TosMICs, both α-alkyl-substituted TosMICs and TosMIC itself failing to undergo this one-pot transformation.

1,4-Disubstituted imidazoles were prepared in excellent yields by employment of glyoxylic acid as the aldehyde component. The reaction outcome is accounted for by an in situ decarboxylation, followed by β-elimination of the tosyl group. Alternatively, 4,5-disubstituted imidazoles were readily prepared by use of ammonium hydroxide as amine input in conjunction with a variety of aldehydes.

3.4 Three-Component Synthesis of 5-Aminooxazoles

We have recently reported a three-component synthesis of 5-aminooxazoles, taking advantage of the dual reactivity of α-isocyanoacetamide [Scheme 13 (d)].[48] Thus, simply heating a methanol solution of an aldehyde, an amine, and an α-isocyanoacetamide **26** provided the 5-aminooxazole **27** in good to excellent yield. The condensation can be performed with approximately equimolar quantities of three components, simplifying the purification step. Use of α-isocyanoacetamide rather than α-isocyanoacetate is essential to channel the reaction sequence towards oxazole formation. If, in fact, α-isocyanoacetate is used as input, the predominant reaction pathways will be aldol (Knoevenagel) and Mannich-type condensation, giving rise to imidazolines or amidines [Scheme 13 (e)].[49,50]



Scheme 13

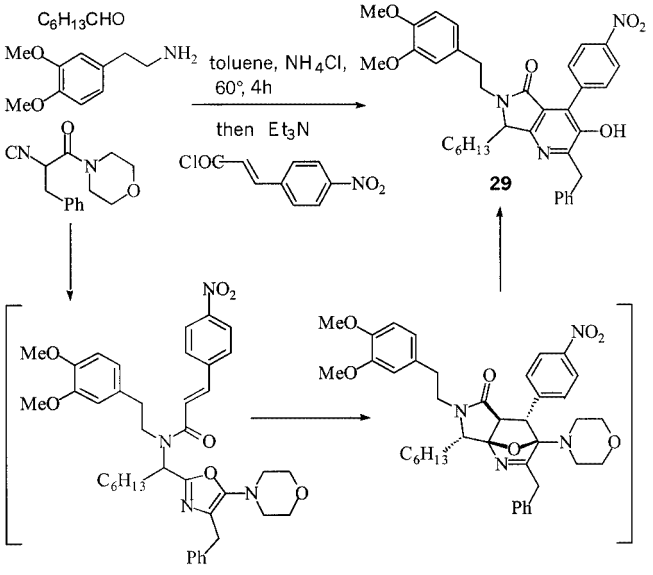
A variety of amines, aldehydes, and isocyanoacetamides have been used for the preparation of the corresponding oxazole **27**. No racemization was detected when enantiomerically pure amino ester was used as amine component.

As with Ugi-type condensations, the solvent of choice for this reaction was methanol. To enlarge the scope of application of this process, we examined other nonpolar aprotic solvents and found that in the presence of a weak Lewis acid (LiBr) or protic acid (ammonium chloride, catalytic amount of camphorsulfonic acid), the same condensation took place efficiently in toluene.[51] This result opened a new avenue for the development of novel MCRs by exploring the potential reactivity of 5-aminooxazole.

3.5 Four-Component Synthesis of Pyrrolo[3,4-*b*]pyridin-5-ones

5-Aminooxazole (**27**) has an electron-rich azadiene that is susceptible to reaction with electron-poor dienophiles. Moreover, it contains a secondary amine (R^1 or R^2 = H) that provides a useful handle for further functionalization. Consequently, combination of this oxazole with another suitably bifunctionalized substrate should in principle trigger a domino process, affording new heterocycles with significantly increased molecular complexity. If the conditions for this post-functionalization were compatible with the three-component synthesis of 5-aminooxazoles, then a four-component process would be created. This was illustrated

by the performance of a four-component synthesis of pyrrolo[3,4-*b*]pyridin-5-ones **29** (Scheme 14). A solution of an aldehyde, an amine, and an isocyanide in the presence of 1.5 equiv. of ammonium chloride was stirred at 60 °C. Once the oxazole formation was deemed complete by TLC analysis, an appropriate unsaturated acyl chloride and triethylamine was added at 0 °C. Heating to reflux produced pyrrolo[3,4-*b*]pyridin-5-ones in good yield through a domino process involving a three-component condensation, an intermolecular acylation, an intramolecular Diels−Alder cycloaddition, and a retro-Michael cycloreversion.[51]

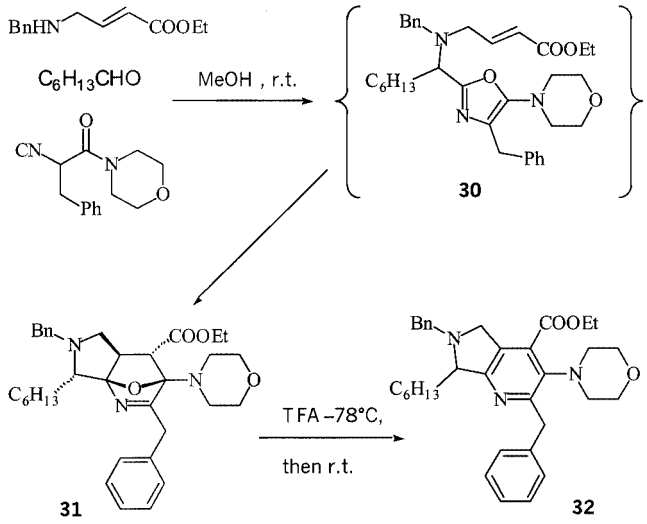


Scheme 14

Both aromatic and aliphatic aldehydes readily participated in this reaction. Amino esters took part in this reaction effectively, producing the functionalized pyrrolopyridines as separable mixtures of two diastereomers. The conditions were sufficiently mild that no epimerization of chiral centers was observed.

3.6 Three-Component Synthesis of Pyrrolo[3,4-*b*]pyridines and Tetracyclic Tetrahydroisoquinolines, with Diversity Deriving from the Workup Procedure

Encouraged by the results of the four-component synthesis of pyrrolo[3,4-*b*]pyridin-5-ones described above, we set out to explore the alternative three-component synthesis of pyrrolo[3,4-*b*]pyridines by tethering amine and dienophile into a single component. With an appropriately predisposed dienophile, we surmised that the intramolecular Diels−Alder cycloaddition should occur immediately after the formation of oxazole **30** under appropriate conditions. Indeed, the reaction between an aminocrotonate, an aldehyde, and an α-isocyanoacetamide in methanol at room temperature provided oxa-bridged tricycle **31** as a single diastereoisomer in 92% yield (Scheme 15).[52] It is worth noting that one C−N, one C−O, and three C−C bonds were formed with concomitant creation of five asymmetric centers in this one-pot multicomponent process.



Scheme 15

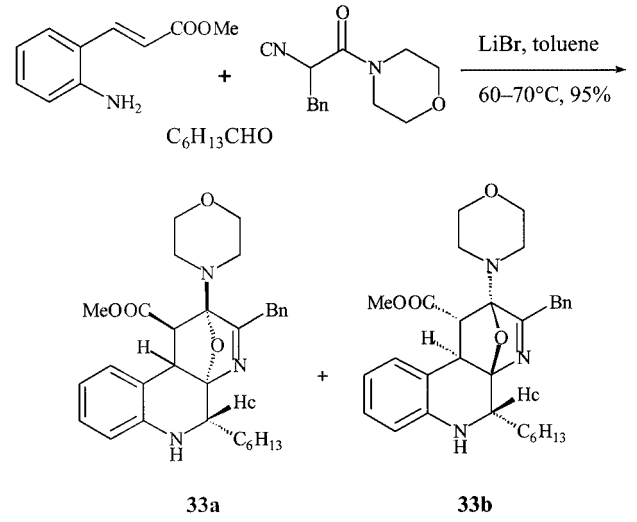
The oxa-bridged tricycle was found to be fairly stable and could be isolated by column chromatography. However, it is readily fragmented to pyrrolo[3,4-*b*]pyridine (**32**, Scheme 15) under acidic conditions (MeOH, TFA, −78 °C, 85% yield). In contrast to the four-component synthesis of pyrrolo[3,4-*b*]pyridin-5-one, in which a retro-5-*endo*-*trig* process occurred to give the phenolic compound (cf. **29**, Scheme 14), this fragmentation was assisted by the nitrogen atom lone pair, producing the morpholinyl-substituted pyrrolopyridine.

These results allowed us to prepare two structurally distinct libraries simply by modifying the workup procedure. A three-component condensation of an aminocrotonate, an aldehyde, and an α-isocyanoacetamide in methanol followed by the usual aqueous workup provided oxa-bridged polyheterocycle **31**, while acidic treatment before aqueous workup furnished the pyrrolopyridine **32** (Scheme 15).

We have also developed a three-component synthesis of tetracyclic tetrahydroquinolines **33** by condensation of an aldehyde, an *ortho*-aminocinnamate, and an α-isocyanoacetamide (Scheme 16).[53] The best conditions consisted of use of toluene as solvent in the presence of a stoichiometric amount of lithium bromide as a promoter. Under these conditions, two pairs of diastereomers were produced, out of 16 possible isomers, in 95% yield. The relative stereochemistry of the major isomer was determined by X-ray analysis.

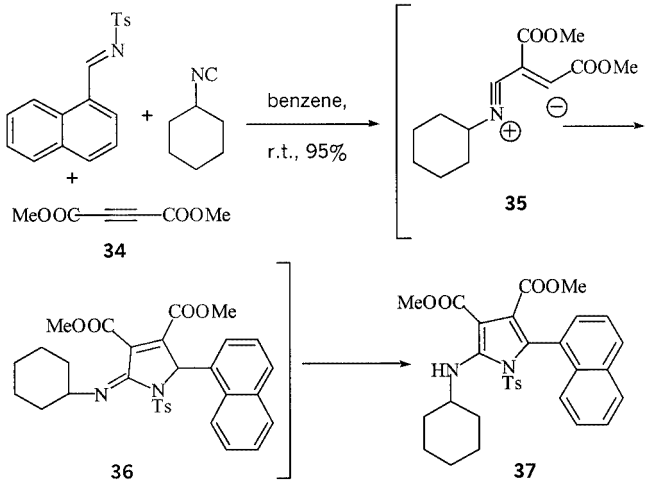
3.7 Multicomponent Synthesis of 2-Aminopyrroles, 2-Aminofurans, and Furoquinolines

Most of the multicomponent reactions discussed involve nucleophilic addition of isocyanide onto the imine (or aldehyde) function. Nair and co-workers found that when an isocyanide was mixed with an imine and dimethyl acetylenedicarboxylate (DMAD, **34**) in benzene, a sequence of reac-



Scheme 16

tions took place, initiated by nucleophilic addition of isocyanide onto the DMAD and producing 2-aminopyrrole in excellent yield (Scheme 17).[54] A formal [3+2] cycloaddition between zwitterionic intermediate **35** and imine followed by a [1,5]-H shift was proposed to explain the formation of 2-aminopyrrole (**37**).

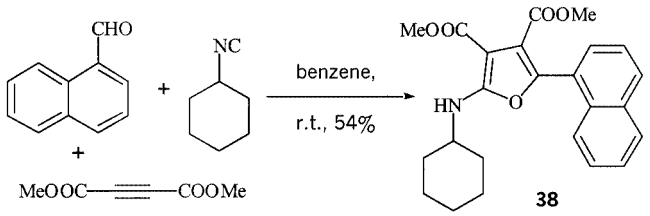


Scheme 17

The reaction seems to be limited to DMAD, since other electron-deficient acetylenes such as dibenzoylacetylene, methyl propiolate, and tetracyanoethylene did not produce the corresponding 2-aminopyrroles.

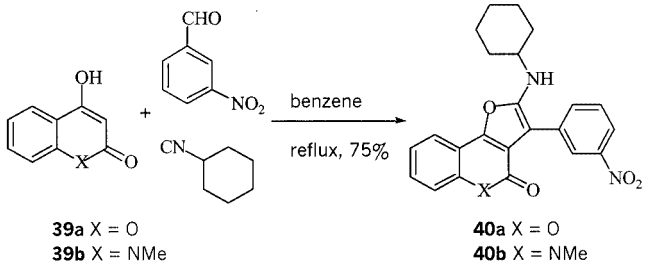
When an aromatic aldehyde was used instead of an imine under otherwise identical conditions, 2-aminofuran **38** was produced in good yield (Scheme 18).[55]

An alternative three-component synthesis of furan-annulated heterocycles was developed by Nair and co-workers (Scheme 19).[56] Heating of a benzene solution of 4-hydroxycoumarin (**39a**, X = O), 3-nitrobenzaldehyde, and cyclohexyl isocyanide at reflux delivered the furocoumarin **40a** (X = O) in 75% yield. These results would be



Scheme 18

accounted for by a sequence consisting of Knoevenagel condensation followed by a formal [4+1] cycloaddition between the intermediate enone and isocyanide and a [1,3]-H shift.



Scheme 19

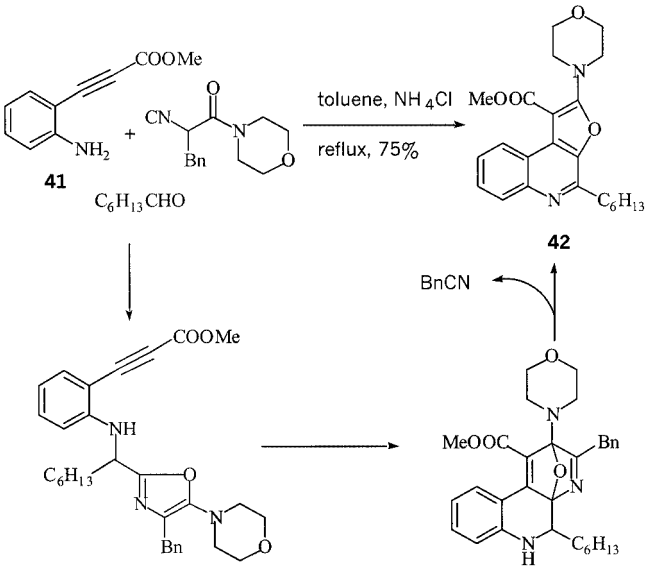
From 4-hydroxy-1-methylquinolinone (**39b**, X = NMe), the same three-component reaction resulted in the formation of furoquinolone **40b** (X = NMe) in 84% yield.

We have developed a mechanistically distinct three-component synthesis of furoquinolines (Scheme 20).[57] Thus, simply by heating a toluene solution of methyl 3-(2-aminophenyl)prop-2-ynoate (**41**), heptanal, and isocyanoacetamide at reflux in the presence of ammonium chloride, the furoquinoline **42** was produced in 75% yield. At least six distinct reactions, including condensation between aldehyde and amine, nucleophilic addition of isocyanide to imine, ring-chain tautomerization of nitrilium intermediate, intramolecular Diels–Alder (D–A) cycloaddition of oxazole, retro-D–A, and oxidation, occurred in this one-pot process.

Anilines bearing both electronically poor and electronically neutral acetylene units participated in the reaction. For aldehyde input, aliphatic (including sterically hindered isobutyraldehyde) and aromatic aldehydes bearing electron-donating or -withdrawing groups all took part in this reaction. Incorporation of various substituted amino functions was easily attainable simply by varying the isocyanoacetamide input.

3.8 Five-Component Synthesis of Polyheterocycles with Hexasubstituted Benzene Cores

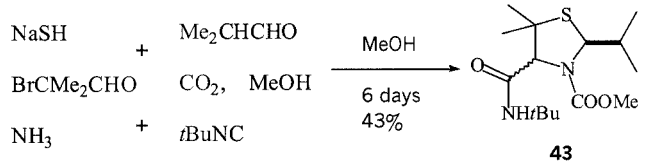
One-pot reactions involving more than four components have scarcely been reported in the literature. In 1961, Ugi reported a five-component synthesis of α-acetamido amides by mixing an amine, an aldehyde, an alcohol, carbon dioxide, and an isocyanide.[58,59] It was a variation of the Ugi



Scheme 20

4CR with a carboxylate anion generated in situ between CO_2 and alcohol. Recently, a five-component reaction involving an Ugi 4CR followed by hydroxyaminolysis of an acetonide to afford a linear matrix metalloproteinase (MMP) inhibitor was reported by Whittaker and co-workers.[60]

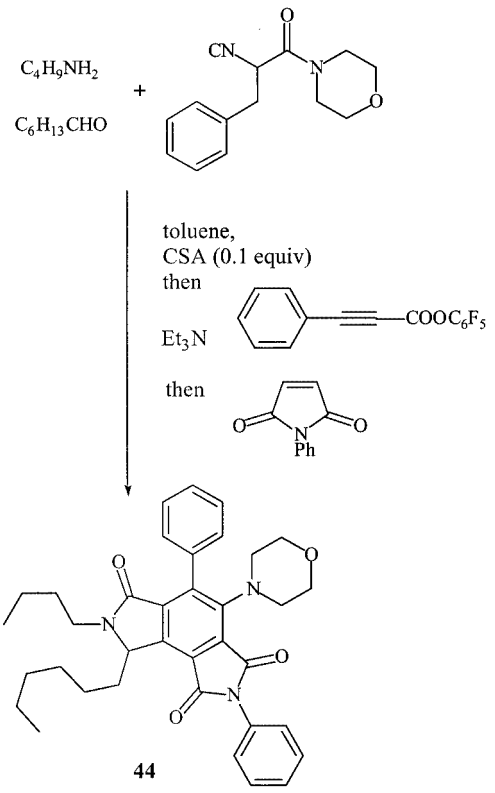
What is the highest number of different starting materials that can be involved in an MCR? The answer of Dömling and Ugi was seven.[61] Through a combination of Assinger and Ugi MCRs, they discovered a seven-component synthesis of thiaoxazolidines **43** as shown in Scheme 21.



Scheme 21

We have recently developed a five-component synthesis of polyheterocycles with hexasubstituted benzene cores (**44**, Scheme 22).[62]

A possible reaction scenario is shown in Scheme 23. Three-component condensation of an amine, an aldehyde, and an isocyanoacetamide provided the 5-aminooxazole **45**. Reaction between **45** and pentafluorophenyl 3-arylprop-2-ynoates **46** delivered the pyrrolofuran **47** by a sequence consisting of acylation, intramolecular Diels–Alder cycloaddition, and retro-Diels–Alder cycloreversion. The subsequent cycloaddition between the furan unit of **47** and the dienophile **48** (*N*-phenylmaleimide, quinone, etc.) followed by fragmentation of the oxa-bridged amino ether would then provide the observed product **44**. In this one-pot transformation, seven functional groups reacted with one another in a highly ordered fashion, resulting in the creation



Scheme 22

of seven chemical bonds and a polyheterocyclic scaffold with a hexasubstituted benzene core. Not fewer than nine reactions were involved in this experimentally simple MCR.

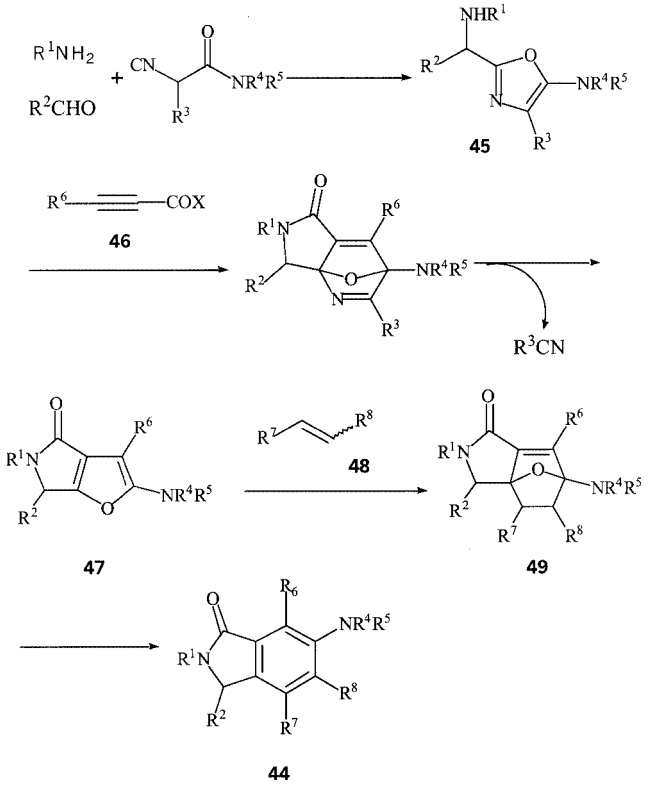
4. Novel Isocyanide-Based Multicomponent Reaction Catalyzed by Transition Metals

The last few years have witnessed the development of metal-catalyzed multicomponent reactions for the synthesis of complex molecules, including heterocycles.[63–70] Here we will limit ourselves to the metal-catalyzed multicomponent synthesis of heterocycles based on the dual reactivity of isocyanides.

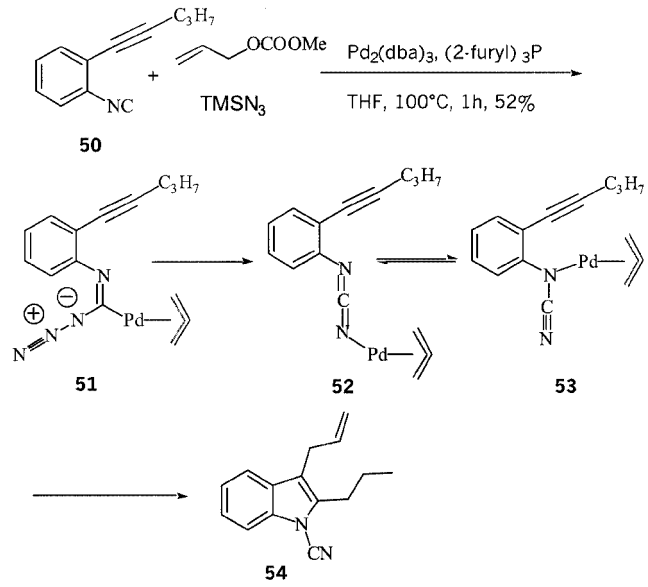
4.1 Three-Component Synthesis of *N*-Cyanoindoles

Building on their earlier works on the three-component synthesis of allyl cyanamides,[71] Yamamoto and co-workers developed a novel three-component synthesis of *N*-cyanoindoles (Scheme 24).[72] The reaction between the 2-alkynylisocyanobenzene **50**, allyl methyl carbonate, and trimethylsilyl azide in the presence of $[Pd_2(dba)_3]$ (2.5 mol %) and tris(2-furyl)phosphane (10 mol %) at 100 °C afforded *N*-cyanoindoles **54** in good yield.

The key steps of this reaction involved the formation of π-allylpalladium complex **51**, its Curtius-like rearrangement to intermediate **52**, and its subsequent isomerization to the π-allylpalladium cyanamide complex **53**. A wide range of functional groups is tolerated at the *para*, *meta*, and even *ortho* positions of the aromatic ring.



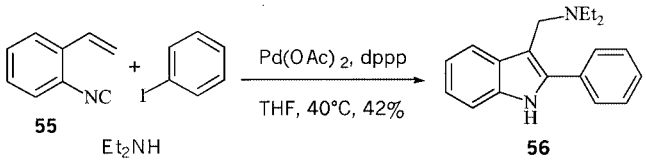
Scheme 23



Scheme 24

4.2 Three-Component Synthesis of Indoles

Takahashi and co-workers reported an alternative three-component synthesis of indoles (Scheme 25).[73] The reaction between an aryl iodide, an *ortho*-alkenylphenyl isocyanide **55**, and a secondary amine in the presence of a palladium catalyst produced 2,3-disubstituted indoles in moderate yields. Chelating ligands such as dppp were found to be superior to monodentate ligands such as PPh_3. Five examples were given in this preliminary communication.



Scheme 25

5. Conclusion

Small polyfunctionalized heterocyclic compounds have played important roles in the drug discovery process[74,75] and in the isolation and structural identification of biological macromolecules.[76,77] On the other hand, bioactive natural products can be regarded as chemical entities that have been evolutionarily selected and validated for binding to particular protein domains.[78–80] It is therefore not surprising that research in the field of combinatorial synthesis of heterocycles and natural product analogues has received special attention over the last few years.[19,20,81] With the advent of functional genomics and proteomics, more information about the structures and functions of biologically active macromolecules is becoming available. It was to be expected that a high-throughput synthesis program should not only help in improving the known biological and pharmacokinetic properties of drugs, but also help in the discovery of molecules exhibiting biological effects beyond those associated with previously known macromolecules. By virtue of its inherent convergence, high productivity, its exploratory and complexity-generating power, the multicomponent reaction approach is undoubtedly well suited for the drug discovery program.[82,83] Indeed, a highly active calcium antagonist, nifedipine (Adalat®) was synthesized by Hantsch multicomponent reaction methodology long before the nascence of the now fashionable combinatorial technology.[84]

The Hantsch dihydropyridine synthesis (1882)[10,84] and the Biginelli dihydropyrimidine synthesis (1891),[11,85] two of the most useful multicomponent heterocycle syntheses, have been known for more than a century. With critical mechanistic insight into various classic bimolecular reactions, the development of new reactive chemical entities, new activation methods for otherwise "inactive" functional groups, and enthusiasm of chemists for the subject, we may be optimistic that many new and synthetically useful MCRs will be developed in the coming years.[86–88] As in any discovery process, there are many ways, such as combinatorial methods, to approach this challenging problem, and we would advocate the "*substrate design approach*" in the search for new MCRs. The design of an appropriate substrate incorporating suitable functional groups is an essential departure point in planning novel MCRs. If polyfunctionalized substrates are designed and programmed in such a way that they will react in a highly ordered and productive fash-

ion merely on mixing them together, to produce an interesting scaffold in high yield, then a novel MCR will have been uncovered. We conclude this microreview by quoting Professor Echenmoser's analysis on the biosynthesis of vitamin B_{12}:[89] "*These outwardly complex structural elements are found to 'self assemble' with surprising ease under structurally appropriate preconditions; the amount of 'external instruction' required for their formation turns out to be surprisingly small in view of the complexity and specificity of these structural elements.*" The ultimate goal in organic synthesis will be "mix and add up reaction components" with anything else needed only catalytically and with minimal loss of atoms.[90]

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