Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds

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Received 24 December 2002; revised 24 March 2003

Abstract: Following the increased interest from the pharmaceutical industry for the generation of diverse libraries of heterocyclic compounds, scientific efforts have become more and more focused on the development of novel multi-component procedures as a means of gaining rapid access to such compounds. Initially, the development of solid-phase procedures received considerable attention. However, current efforts are increasingly concerned with the development of solution-phase procedures. The latter will be the subject of discussion in this review, which aims to give an overview of the progress made in the past decade.

After a general introduction, non-catalyzed, acid-catalyzed, and transition metal-catalyzed solution-phase multi-component procedures for the preparation of a wide range of heterocycles will be discussed. The last chapter discusses the role of cycloaddition reactions in the development of novel MCRs for the synthesis of heterocyclic compounds.

In spite of their important role in the synthesis of heterocyclic compounds, MCRs involving isocyanides are not discussed in this review, since the topic has been exhaustively reviewed several times.

1 Introduction

Since the synthesis of urea in 1828 by Friedrich Wöhler, increasingly sophisticated synthetic methodology has led to impressive achievements being made over the past two centuries.1 Ongoing development of novel synthetic concepts and methodologies has opened up the way to the construction of many complex and challenging synthetic targets (Figure 1).

However, in spite of its scientific merits and its profound influence on the progress of organic chemistry, it has become clear that much of the present synthetic methodology does not meet the constraints, which will be imposed on syntheses in the future. Increasingly severe economic and environmental constraints force the synthetic community to think about novel procedures and synthetic concepts to optimise efficiency. In an ideal synthetic route, the target molecule is prepared from readily available starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield.²

Figure 1 Synthetic sophistication has evolved tremendously over the past two centuries.

Inspired by the mode of action of nature, numerous groups reported the multi-step, single operation construction of complex molecules, in which several bonds are formed in one sequence without isolating the intermediates.3–8 Such processes, which are commonly referred to as tandem reactions,⁵ allow ecologically and economically favourable production of a wide range of organic compounds and brought the concept of ideal synthesis closer to reality.³

Multi-Component Reactions (MCRs)

Multi-component reactions, an important sub-class of tandem reactions,³ are one-pot processes that react at least three easily accessible components to form a single product, which incorporates essentially all of the atoms of the starting materials.⁷ MCRs are highly flexible, (chemo-)selective, convergent and atom efficient processes of high exploratory power (Eₜ).⁸–¹⁵ As such they closely approach the concept of ideal synthesis.

The growing interest for (novel) multi-component procedures is closely related to developments in combinatorial chemistry.⁴,⁷,⁸ Large combinatorial compound libraries (10⁶ to 10⁸ compounds) play an important role in drug dis-
covery. Their high $E_N$ and simple experimental set-up make MCRs convenient tools for easy and rapid access to such large libraries of organic compounds.

Some of the traditional combinatorial targets have lost importance and current developments are tending to move away from peptide and other biopolymer libraries. Scientific efforts focus more and more on the development of multi-component procedures for the generation of libraries of heterocyclic compounds. This growing interest is stimulated by the interesting pharmaceutical properties that are associated with many heterocycles. Furthermore, the rigid well-defined structures make heterocycles ideal candidates for detailed Structure Activity Relationship (SAR)-studies.

**History of Multi-component Chemistry**

The concept of MCRs to prepare complex structures is not new in chemistry or in fact nature. It may well have played a crucial role in evolution since adenine (1), one of the major constituents of DNA and RNA, prebiotically seems to originate from five molecules of hydrogen cyanide, once abundantly present in earth’s atmosphere (Scheme 1). The process clearly represents the essential features of a MCR: five simple starting materials react in a well-defined manner to afford a complex reaction product, which incorporates essentially all of the atoms of the starting materials.

However, it was not until 1850 that Strecker first contributed to the development of multi-component chemistry. He achieved a multi-component synthesis of $\alpha$-amino nitriles 3 by simply reacting hydrogen cyanide, aldehydes 2, and ammonia in one-pot (Scheme 2).

Some of the progress of multi-component chemistry has been related to the development of procedures for the synthesis of heterocyclic compounds. In 1882, Hantzsch achieved the synthesis of symmetrically substituted dihydropyridines 7 by reacting ammonia, aldehydes 5, and two equivalents of $\beta$-ketoesters 6 (Scheme 3). The reaction is still a popular tool for the construction of many, structurally diverse, members of this class of heterocycles.

Hantzsch made another contribution to the progress of multi-component chemistry. Pyrroles 10 were prepared from primary amines 8, $\beta$-ketoesters 6, and $\alpha$-halogenated $\beta$-ketoesters 9 (Scheme 4). After initial condensation of 8 and 6, the resulting intermediates 11 can react with $\alpha$-ha-

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**Biographical Sketches**

**Romano V. A. Orru** was born in 1965 in Heerlen (The Netherlands) and studied Molecular Sciences at the Agricultural University in Wageningen (NL) where he got his degree in 1990. Subsequently he obtained, in 1994, his PhD on natural products in the group of Prof. A. de Groot, also in Wageningen. From 1996 till 2000 he worked as a postdoc and as an assistant at the Technical and Karl-Franzens Universities (Graz, Austria), on the synthetic application of biotransformations in the group of Prof. K. Faber. In early 2000 he was appointed assistant professor (UD) at the Vrije University in Amsterdam. His current research focuses on the development of novel, diversity aimed, methodology for the asymmetric synthesis of pharmaceutically relevant natural products and their analogues.

**Michiel de Greef** was born 1979 in Velsen, The Netherlands. He studied chemistry at the Vrije Universiteit Amsterdam and received his M.Sc. in 2002 under the supervision of Dr. R. V. A. Orru on the synthesis of 14-membered cyclopeptide alkaloids. He subsequently joined the laboratory of Professor S. Z. Zard as a Ph.D. student at the Ecole Polytechnique, France. His current research interest is focused on the development of xanthate-based synthetic methodology and its application on natural product synthesis.
Recent Advances in Solution-Phase Multicomponent Methodology

In 1934, Bucherer and Bergs were the first to describe a four-component reaction to obtain hydantoins 17. They modified Strecker’s synthesis by reacting in one-pot hydrogen cyanide, aldehydes 2, ammonia, and carbon dioxide (Scheme 7). Hydantoins 17 are valuable compounds that are easily transformed into α-amino acids by simple hydrolysis.

![Scheme 7](image1)

An interesting MCR for the synthesis of thiazolines 20 was reported by Asinger in 1958. After in situ generation of thiols 18 from their corresponding α-halogenated carbonyl compounds and sodium hydrogen sulfide, thiazolines 20 are obtained by addition of ammonia and carbonyl compounds 19 to the reaction mixture (Scheme 8). The Asinger reaction has successfully been generalized and gives access to many heterocyclic compounds including oxazolines 21, imidazolines 22, oxazines 23, pyrimidines 24, and thiazines 25.

![Scheme 8](image2)

Most of the MCRs discussed in this review rely on the intervention of imines or iminium ions generated in situ from commercial carbonyl compounds and amines. Both imines or iminium ions are reactive electrophiles and often play an essential role in bond-forming processes. Another valuable class of MCRs relies on the ambiphilicity of isocyanides towards electrophilic and nucleophilic starting materials. The first MCR involving isocyanides was discovered in 1921 by Passerini who achieved the synthesis of α-acyloxy carboxamides 29 by reacting carboxylic acids 26, oxo-compounds 27, and isocyanides 28 (Scheme 9).

![Scheme 9](image3)

Although initially resulting in linear peptide-like compounds, the reaction has successfully been used for the one-pot synthesis of heterocyclic compounds. For example, Maruccini et al. recently demonstrated the potential of the Passerini reaction for the efficient synthesis of 30...
from cinnamic acid, chloroacetone and tert-butyl isocyanide.\(^{27}\)

In 1959, Ugi et al. probably discovered the most versatile MCR involving isocyanides.\(^{4b}\) They achieved the synthesis of \(\alpha\)-acylamino amides \(^{33}\) by reacting aldehydes \(^{5}\), primary amines \(^{31}\), carboxylic acids \(^{32}\), and isocyanides \(^{28}\) in a simple one-pot process (Scheme 10).\(^{4,7}\) Next to a wide range of amine and oxo components, the Ugi reaction tolerates many acid components.

\[ \text{Scheme 10} \quad \text{Ugi four-component reaction.} \]

The use of bifunctional starting materials in the Ugi reaction allows formation of heterocyclic products. Thus, \(n\)-butyl isocyanide, benzylamine, and bifunctional \(^{34}\) are efficiently combined to \(^{35}\).\(^{28}\) In spite of their important role in the synthesis of heterocyclic compounds, MCRs involving isocyanides will not be dealt with in the remainder of the text, since the topic has been exhaustively reviewed several times.\(^{4,7,29}\)

\section{Non-Catalyzed MCRs}

The MCRs applied to modern heterocyclic chemistry often owe their mild and highly efficient nature to the use of a catalyst. Brønsted-acid, Lewis-acid as well as transition metal catalyzed multi-component processes have been successfully applied. However, multi-component procedures do not necessarily require a catalyst and recently several such procedures were reported for the synthesis of a wide range of five- and six-membered biologically important heterocycles.\(^{30-32}\) Some of these procedures required stoichiometric amounts of base, while others involved microwave irradiation under solvent-free conditions.

\section{Base-Promoted MCRs}

Despite its moderate \(E_N\), the Gewald process is the most convenient method for the preparation of functionalized thiophenes.\(^{33}\) In this three-component condensation reaction, \(\beta\)-ketoesters \(^{12}\), cyanoacetates \(^{36}\), and elemental sulfur condense in the presence of an organic base to yield tetrasubstituted thiophenes \(^{37}\) (Scheme 11).

\[ \text{Scheme 11} \quad \text{Gewald process for the preparation of functionalized thiophenes.} \]

Classically, the reaction is carried out in tert-butanol at 70 °C in the presence of an equimolar amount of diethylamine. However, work-up of the resulting reaction mixture is laborious under these conditions and yields are often unsatisfactory. Recently, McKibben et al. reported optimized reaction conditions.\(^{34}\) When pyridine instead of tert-butanol was used as a solvent, the reaction was successfully carried out at room temperature and product isolation was less tedious. Further optimization was achieved by using tert-butyl cyanoacetate \(^{36b}\) instead of ethyl cyanoacetate \(^{36a}\). Although a slower reaction rate was observed, the overall yield increased substantially and tetrasubstituted thiophenes \(^{37}\) were isolated in a reproducible 70% yield on a 60 g scale. Differentiating the ester groups of \(^{12}\) and \(^{36}\) (\(R^2\) and \(R^3\), respectively) revealed that branched alkyl\(\beta\)-ketoesters, benzyl isobutyrylacetate, and benzyl benzoylacetic acid were not tolerated. Furthermore, it was found that the structural nature of \(R^1\) was limited to either methyl, or methoxymethyl.

In an attempt to prepare a series of serine protease inhibitors \(^{40}\), Pinto et al. modified the original Gewald process.\(^{35}\) Thus, by reacting alkoxy methyl ketones \(^{38}\), cyanoacetates \(^{36}\) and elemental sulfur, with an equimolar amount of morpholine in ethanol as a solvent, thiophenes \(^{39}\), bearing an alkoxy group at C-5, were obtained (Scheme 12). Various alkoxy methyl ketones \(^{38}\) were used and the reaction was found to be of general applicability.

The use of arylxoy- instead of alkoxy methyl ketones \(^{38}\) led to the discovery of a novel four-component reaction that allowed the synthesis of various 5-aminothiophenes \(^{45}\) (Scheme 13). It is assumed that the arylxoy group is displaced by morpholine after formation of the initial condensation product \(^{41}\). Insertion of sulfur, cyclization and aromatization complete the process and lead to the formation of \(^{45}\). Morpholine could be replaced by a variety of other cyclic secondary amines, but the use of pyrrolidine,
Synthesis of serine protease inhibitors.

The thiazole ring system is a frequently occurring structural element in natural products and pharmacologically active substances. Although several approaches to thiazoles have been developed since Hantzsch’s synthesis in 1887, the need for more general procedures still exists. Recently an efficient method for the preparation of 2-amino- and 2,4-diamino thiazoles 52a and 52b was reported starting from either amidines 46a or thiouronium salts 46b, isothiocyanates 47 and α-bromo ketones 49 (Scheme 14). The reaction sequence starts with base-induced condensation followed by S-alkylation. The fate of the resulting intermediate 50 depends on the nature of R1. Thus, when R1 = Ar 50 undergoes intramolecular nucleophilic addition to give 52a after final loss of NH3. Since thiols are good leaving groups, use of 46b (R1 = ArCH2S) leads to intramolecular nucleophilic addition-elimination of 50 to afford thiazoles 52b after aromatization.

4-Thiazolidinones are most commonly prepared by condensing primary amines, aldehydes, and mercapto carboxylic acids. This approach can be used to prepare pyridyl substituted thiazolidin-4-ones 56, potential chiral ligands for copper(I)-catalyzed addition of diethylzinc to enones. When equimolar amounts of aniline 53, α-mercapto carboxylic acids 54, and 2-pyridine-carboxaldehydes 55, are mixed with azeotropic removal of water, thiazolidinones 56 were obtained in quantitative yield (Scheme 15).

Scheme 12 Preparation of serine protease inhibitors.

Scheme 13 Formation of 5-aminothiophenes by means of a novel four-component reaction.

Scheme 14 Three-component synthesis of 2-amino and 2,4-diamino thiazoles.
Diastereoselective formation of 56 is successfully promoted (de = 21–91%) by using optically active α-mercapto carboxylic acids derived from the corresponding α-amino acids. The major isomer was confirmed to have a cis-geometry in each case. Recently, the procedure has been further generalized using amino acid esters instead of primary amines as the N-source.

Scheme 16 Solution phase synthesis of thiazolidin-4-ones.

Table 1 Solution Phase Synthesis of Thiazolidin-4-ones

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
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<tr>
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<td>4-Me-C₆H₄</td>
<td>H</td>
<td>58</td>
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Reaction of α- or β-amino acid esters 57, aldehydes 58, and α-mercapto carboxylic acids 54 in refluxing benzene with azeotropic removal of water in the presence of an equimolar amount of tertiary amine gave thiazolidin-4-ones 59 (Scheme 16, Table 1). Under optimized reaction conditions (57:58:54 = 1:2:3) moderate to high yields were achieved. In particular benzaldehyde was efficient in this reaction (entries a, b, and g–j). Furthermore, the use of mercapto acid 54b instead of mercapto acid 54a had no effect on the yield (entry a vs. b), whereas the use of substituted benzaldehydes 58 substantially decreased the yields (entries c, d, and e). When achiral α-amino acid esters 57 were used together with 54a or 54b no diastereoselectivity was observed (entries a and b). However, the use of chiral 57 (entries g, i, and j) gave moderate levels of stere induction (de≤60%). Finally, when β-mercaptopropanoic acid 60 was used, metathiazan-4-ones 62, instead of 59 were obtained (Scheme 17). Steric effects decrease yields in this reaction, as was demonstrated when sterically demanding derivatives of 61, like the valine methyl ester or phenylalanine methyl ester, were used.

Scheme 17 Solution phase synthesis of metathiazan-4-ones.

Although reduction occurred under mild conditions and was usually a fast process, the use of deactivated or ortho-substituted benzaldehydes considerably decreased the reaction rate. Final reaction of secondary amines 65 with 66 in moderate to good yields after cyclization of thiourea intermediate 67.

Scheme 18 Solution-phase synthesis of (thio)-hydantoins.
explored in order to prepare 2-thioxo-4-pyrimidinones 72 (Scheme 19). Initial attempts to carry out the reaction under the same conditions as thiohydantoin-synthesis failed and it was found that heating at 80 °C for two days with excess triethylamine was required to induce cyclization.

**Scheme 19**  Solution-phase synthesis of 2-thioxo-4-pyrimidinones.

Hydantoins are a structurally diverse class of heterocycles with a wide range of interesting properties. Hanessian et al. have developed a novel MCR to prepare 5-alkoxyhydantoins. They reacted N-protected \( \alpha \)-amino acid esters 73 with isocyanates 66a and exposed the resulting intermediate 74 to a primary alcohol 75 and a strong base (Scheme 20). Following this procedure, a library of fifty 5-alkoxyhydantoins 76 was prepared in yields between 70–90%.

**Scheme 20**  Solution-phase synthesis of 5-alkoxyhydantoins.

**MCRs Involving Multiple Anion Capture**

1,3-Dianions are popular intermediates in many synthetic transformations. When the 1-, and 3-positions are functionalized differently, such dianions have nucleophilic sites of different reactivity. This makes them valuable for MCRs, since different electrophiles can be trapped in a sequential and regioselective manner, leading to complex reaction products that would otherwise be difficult to prepare. Langer et al. recently managed to synthesize medium-sized lactones and heterospirocyclic isobenzofuranones by multiple anion capture reactions of 1,3-dianions (Scheme 21). The dianion 78 of 1,1-diphenylacetone 77 was generated and reacted with one equivalent of 79 to give regioselectively dianionic species 80. Subsequently, 80 was reacted with a variety of dicarboxylic acid dichlorides. Medium-sized lactones 84 and 85 were obtained with the aliphatic 81 and 82, whereas furanones 86 were formed when 83 was used. Similar observations were made when the dianion 88 of 2-methylbenzimidazole 87 was generated and reacted with one equivalent of benzophenone 79 to give dianionic intermediate 89 (Scheme 22). Reaction of 89 with oxalyl chloride 81 proceeded as expected and gave oxazine 91 after loss of carbon monoxide, whereas reaction with phthalic dichloride 83 gave heterospirocyclic product 93 in addition to expected reaction product 92. Formation of 93 was unexpected and may result from reaction of dianionic intermediates with isophtalic dichloride 94 (Scheme 23). It has been reported that 94 could be formed in situ by LiCl-catalysed rearrangement of phthalic dichloride 83. Alternatively initial formation of cyclic phthalate 95 and subsequent base-mediated transformation into isomeric heterospirocyclic compounds may also represent a possible mechanism.

**Scheme 21**  Dilactones and heterospirocyclic isobenzofuranones from 1,1-diphenylacetone.
MCRs Involving Boronic Acid Derivatives

A synthetic method for allylamines developed by Petasis et al., 50–53 which is based on the participation of vinyl boronic acids in Mannich-type reactions, has been extended to the preparation of heterocycles. 54 Thus, morpholine derivatives 101 were obtained in modest yields by simply mixing glyoxals 96, α-amino alcohols 97, and organoboronic acids 99 in ethanol at room temperature for one day (Scheme 24 and Table 2).

Although conceptually related to the classical Mannich reaction, the boronic acid Mannich reaction is mechanistically different. The key step concerns nucleophilic attack on organoboronic acid 99, which activates R4 for intramolecular nucleophilic attack to the iminium ion 100, leading to the formation of a novel carbon-carbon bond. As exemplified by Table 2 a wide range of starting materials was tolerated under optimized reaction conditions and the reaction led to diastereomeric mixtures of a variety of differently substituted 2-hydroxymorpholines 101. Diastereomeric ratios appeared to depend on the nature of R1–R5 as might be expected for a thermodynamically controlled reaction.
Microwave Accelerated MCRs

Thermal instability of starting materials limits the optimization of reaction rates by increasing the temperature and forces such reactions to be carried out at moderate or low temperatures. Instead of conventional heating organic reactions may be accelerated by using microwaves, which involves selective absorption of microwave energy by polar molecules. Such a procedure allows a wide range of reactions to be carried out in short times and with high conversions and selectivity.

A ‘green’ dimension was recently given to this type of chemistry by accomplishing microwave reactions on solid support, under solvent-free conditions. This avoids problems associated with the use of excess chemicals and the waste disposal of harmful solvents. Microwaves have frequently been applied to the preparation of heterocyclic compounds. For example, Quiroga et al. recently realized the microwave-assisted synthesis of both, pyrazolopyridines and pyrido[2,3-d]pyrimidines, under solvent-free conditions (Scheme 25). These compounds are useful intermediates for the preparation of biologically active nitrogen-containing heterocycles.

Simple microwave irradiation of a mixture of equimolar amounts of starting materials and either for 20 minutes at 600 W, provided clean reaction products in yields of 70–75%. In comparison, prolonged refluxing of equimolar amounts of starting materials in ethanol gave desired reaction products in poor yields (21–25%). With shorter irradiation times hydrated intermediates were obtained (Figure 2).

The reaction is believed to proceed via Knoevenagel condensation of and . The resulting benzylidenbenzoylacetonitrile is then attacked at the -position by the unsubstituted endocyclic carbon atom to give Michael-adduct. Cyclization followed by final loss of water yields pyrido[2,3-d]pyrimidines. Although not shown here, pyrazolopyridines are formed in a similar way. The possibility of varying the structural nature of the starting materials has not yet been thoroughly studied and libraries of only limited dimensions have been prepared to date.

3 Acid-Catalyzed MCRs

Brønsted and Lewis acid-catalyzed processes play an important role in MCR-based syntheses of heterocyclic compounds. Although classical protocols frequently use strong Brønsted acids or equimolar amounts of reactive Lewis acids, mild and easily manageable catalysts have been developed in the course of time. Rare earth metal triflates are particularly effective Lewis acids and have successfully been used in MCR procedures to prepare a wide range of heterocyclic compounds under mild conditions. The role of these and other acid catalysts in the synthesis of various classes of N- and O-containing heterocycles will be discussed.

MCRs Involving Classical Acids

For some MCRs, the use of classical catalysts such as sulfuric acid, hydrochloric acid, titanium(IV) chloride or borontrifluoride etherate can be attractive because of the

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Table 2 Synthesis of 2-Hydroxymorpholines

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* A mixture of four diastereomers was obtained.

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Figure 2 Intermediates in the formation of pyrido[2,3-d]-pyrimidines.

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Scheme 25 Microwave-assisted synthesis of pyrazolopyridines and pyrido[2,3-d]pyrimidines.

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Table 2 Synthesis of 2-Hydroxymorpholines 101

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Figure 2 Intermediates in the formation of pyrido[2,3-d]-pyrimidines.
ease of reaction work-up. This is exemplified by a multi-component procedure to prepare dihydrophenyl triazines 113, which was originally developed in 1956 by Modest. A combinatorial library of 113 was set up by refluxing a mixture of substituted anilines 110, ketones 111 and cyanoguanidine 112, with an excess of concentrated hydrochloric acid (Scheme 26). In spite of the harsh reaction conditions, the desired reaction products were obtained in fair yields. Isolation and purification was rather straightforward since the hydrochloride-salts of 113 readily precipitated from the reaction mixture. In this way a library of 64 differently substituted dihydrophenyl triazines 113 was generated successfully.

Selective Lewis acid-induced formation of trans-1,2-benzo-oxadecalines 117 was realized by sequential addition of two different aldehydes to α-phenethyl-β-borylallylsilane 114 (Scheme 27). The reaction probably begins with allylation of aldehyde 5 with 114. Subsequent addition of a second aldehyde 58 to the reaction mixture leads to the formation of cationic intermediates 115. From here a cascade of cyclization reactions, in which Prins-type cyclization is followed by intramolecular Friedel–Crafts reaction, results in the formation of products 117 in reasonably good yields. Equimolar amounts of reactive Lewis acids were required to complete the reaction. Initial attempts to carry out the reaction in the presence of equimolar amounts of TMSOTf resulted in the formation of reaction products 117 incorporating two equivalents of aldehyde 5. The procedure was successfully adapted to incorporate two different aldehydes by using TiCl4 instead of TMSOTf.

The experimental results suggest that the boryl group is mainly responsible for the observed trans-diastereoselectivity. When allylsilanes other than α-phenethyl-β-borylallylsilane 114 were used, poor or no diastereoselectivity was observed.99

MCRs Involving Lanthanide Triflates

Although occasionally more reactive Lewis acids can be favorable catalysts for MCR-based syntheses of heterocyclic compounds, the mild lanthanide triflates are usually superior as will become clear in this section. Classical Lewis acids such as Ti-, B-, or Al-reagents are used to activate polar functionalities to nucleophilic attack. However, the majority of such activators immediately react with water to decompose or deactivate. Furthermore, strong or even irreversible coordination to O- and N-containing functionalities frequently requires the use of more than stoichiometric amounts of Lewis acid, which is undesirable for both, economical and environmental reasons. Finally, the reactive nature of most classical Lewis acids prevents them from being used as activators of acid-sensitive compounds. In contrast, rare earth metal triflates have been shown to be particularly effective Lewis acids, which could be used catalytically and were not susceptible to hydrolysis. Interestingly, these triflates were easily recovered from the aqueous phase and could be re-used several times without significant loss of activity. Lanthanide triflates as well as scandium triflate efficiently catalyze many fundamental carbon-carbon bond-forming processes, and were even successfully used in asymmetric Diels–Alder reactions. More recently, rare earth metal triflates were shown to be able to catalytically activate aldmines towards nucleophilic attack in Mannich-type reactions. Accordingly, rare earth metal triflates have been used to catalyze the multi-component synthesis of N-containing heterocycles.

Aziridines are useful heterocyclic compounds and have been used as building-blocks for the synthesis of amino acids, amino alcohols, and amino thiols. Although several procedures for the preparation of aziridines have been developed, carbene transfer to the C=N double bond of imines is one of the most efficient methods. However, when imines derived from aliphatic aldehydes were used, carbene transfer was unsatisfactory and reaction products were obtained in low yields. In their efforts to deal with this limitation, Kobayashi et al. studied the reaction of diazo-ester 119 with N-benzylidene derivative 118 in the presence of 10 mol% of a rare earth metal triflate. When the reaction was carried out in acetonitrile in the presence of Sc(OTf)3, disappointingly, considerable amounts of insertion products 121 and 122 were formed in addition to desired aziridine 120 (Scheme 28).
In hexane in the presence of Yb(OTf)$_3$, the yield of 120 was improved. Further optimization of carbene transfer by using imines derived from 2 and 123 and by addition of a drying agent resulted in various mainly cis-aziridines 124 in good yields (Scheme 29 and Table 3).

### Scheme 29

Yb(OTf)$_3$ catalysed MCR for aziridine synthesis.

Interestingly, common aliphatic aldehydes reacted smoothly under these conditions to afford the corresponding aziridines in high yields and good diastereoselectivities (Table 3, entries c–f).

### Table 3 Optimisation of Yb(OTf)$_3$ Catalyzed MCR for Aziridine Synthesis 124

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>cis:trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>83</td>
<td>95:5</td>
</tr>
<tr>
<td>b</td>
<td>Bz</td>
<td>85</td>
<td>94:6</td>
</tr>
<tr>
<td>c</td>
<td>c-Hex</td>
<td>82</td>
<td>93:7</td>
</tr>
<tr>
<td>d</td>
<td>i-Pr</td>
<td>82</td>
<td>91:9</td>
</tr>
<tr>
<td>e</td>
<td>i-Bu</td>
<td>86</td>
<td>70:30</td>
</tr>
<tr>
<td>f</td>
<td>n-Bu</td>
<td>60</td>
<td>85:15</td>
</tr>
</tbody>
</table>

Because of their implication in many antimicrobial agents, β-lactams are important synthetic targets and accordingly many methods for the synthesis of these four-membered heterocycles have been developed. Few of them rely on the efficiency and flexibility of MCRs. Rare earth metal triflate-catalysed Mannich-type reactions were also used by Kobayashi et al. to construct the β-lactam heterocyclic core. The required precursors 130 were readily obtained by reacting aldehydes 5, benzoylhydrazines 128, and silyl enolates 129 in the presence of Drierite and 5 mol% of either Yb(OTf)$_3$ or Sc(OTf)$_3$ (Scheme 31). In contrast to the method above (Scheme 30), the resulting linear esters 130 had to be cyclized separately. Thus, subjecting β-N'-benzoylhydrazino esters 130 to kinetic ring closure conditions gave the corresponding β-lactams 131 in good yields. However, when 130 were subjected to thermodynamic ring closure conditions, pyrazolinones 132 were obtained. Interestingly, β-lactams 131 were readily transformed into isomeric five-membered pyrazolidinones 133 under thermodynamic reaction conditions.

### Table 4 Three-Component Synthesis of β-Lactams 127

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Yield (%)</th>
<th>trans: cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>Ph</td>
<td>82</td>
<td>90:10</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>Ph-CH=CH</td>
<td>69</td>
<td>60:40</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>2-Thienyl</td>
<td>54</td>
<td>87:13</td>
</tr>
<tr>
<td>d</td>
<td>Me</td>
<td>i-Hex</td>
<td>90</td>
<td>40:60</td>
</tr>
<tr>
<td>e</td>
<td>Et</td>
<td>Ph</td>
<td>78</td>
<td>95:5</td>
</tr>
<tr>
<td>f</td>
<td>OMe</td>
<td>Ph</td>
<td>59</td>
<td>69:31</td>
</tr>
</tbody>
</table>

Rare earth metal triflate-catalysed Mannich-type reactions were also used by Kobayashi et al. to construct the β-lactam heterocyclic core. The required precursors 130 were readily obtained by reacting aldehydes 5, benzoylhydrazines 128, and silyl enolates 129 in the presence of Drierite and 5 mol% of either Yb(OTf)$_3$ or Sc(OTf)$_3$ (Scheme 31). In contrast to the method above (Scheme 30), the resulting linear esters 130 had to be cyclized separately. Thus, subjecting β-N'-benzoylhydrazino esters 130 to kinetic ring closure conditions gave the corresponding β-lactams 131 in good yields. However, when 130 were subjected to thermodynamic ring closure conditions, pyrazolinones 132 were obtained. Interestingly, β-lactams 131 were readily transformed into isomeric five-membered pyrazolidinones 133 under thermodynamic reaction conditions.
While exploring Sc(OTf)$_3$-catalyzed allylation of in situ generated benzoylhydrazones in aqueous media, Kobayashi et al. discovered a facile method to produce oxazolidinones 138 (Scheme 32). Reacting benzoylhydrazines 134, tetraallyltin 135 and chloroacetaldehyde 136, in the presence of 5 mol% of Sc(OTf)$_3$, afforded 137, which was easily cyclized in the same pot into the corresponding oxazolidinones 138.

The preparative scope of rare earth metal triflates can be further extended to the synthesis of six-membered heterocyclic compounds.\textsuperscript{82,83} \(\delta\)-Lactams are six-membered N-containing heterocycles and are common structural motifs in a variety of natural products. Their synthesis was recently addressed in an efficient MCR based on sequential Lewis acid-catalyzed Michael-addition/imino aldol reaction (Scheme 33 and Table 5).\textsuperscript{84} The reaction starts with Michael-addition of silyl ketene thioacetals 139 to \(\alpha,\beta\)-unsaturated thioesters 140 in the presence of 5 mol% of both SbCl$_5$ and Sn(OTf)$_2$.\textsuperscript{85} Subsequent addition of amines 142, aldehydes 143, and 2.5 mol% of Sc(OTf)$_3$ to the reaction mixture allowed completion of the process. Reaction products were usually obtained in excellent yields as
mixtures of δ-lactams 144a and linear compounds 145 (Table 5). Both were obtained as single stereoisomers. Linear 145 was efficiently separated from cyclic 144a and could be quantitatively cyclized upon treatment with mercuric trifluoroacetate, leading to diastereomeric δ-lactams 144b.

**Table 5** MCR of Silyl Ketene Thioacetals, α,β-Unsaturated Thioesters, Amines, and Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>R&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Yield (%)</th>
<th>144a:144b</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>90</td>
<td>18:82</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>Me</td>
<td>Ph</td>
<td>4-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>90</td>
<td>20:80</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Me</td>
<td>2-Furyl</td>
<td>Ph</td>
<td>91</td>
<td>14:86</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>81</td>
<td>20:80</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>4-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>92</td>
<td>13:87</td>
</tr>
</tbody>
</table>

Pyroles are aromatic N-containing five-membered heterocycles, which are encountered as a constitutive factor of porphyrin and bile pigment in various natural products. Based on a previous report on Sm-catalyzed synthesis of α,β-unsaturated imines,66 Ishii et al. recently described the preparation of substituted alklypyrroles. The Sm-catalyzed three-component reaction of a number of aldehydes, amines, and nitroalkanes was carried out under mild conditions (Scheme 35),87 but the desired pyrroles 148, 151, and 153 were obtained in only moderate yields. When primary aldehydes 150 were used, two equivalents of aldehyde were incorporated into the reaction product 151 and the reaction has to be carried out in the presence of a Sm-catalyst. When α,β-unsaturated carbonyl compounds 147 and 152 were reacted, one equivalent of carbonyl compound is incorporated into reaction products 148 and 153 and the reactions also proceed in the absence of a catalyst. These observations are easily accounted for by the reaction mechanism.

**Scheme 35** Three-component synthesis of substituted alklypyrroles.

When 147 or 152 and primary amine 31 were used as starting materials, α,β-unsaturated imines 154 were obtained immediately after condensation (Scheme 36) and desired reaction products 148 and 153 could be formed in the absence of a catalyst. On the other hand, when 150 and 31 were used, primary imines 155 were obtained after condensation and its’ α,β-unsaturated analogues 156 were only accessible after incorporation of a second equivalent of aldehyde. Although initial condensation can occur in the absence of a catalyst, the subsequent carbon-carbon bond-forming process requires the presence of 5 mol% of SmCl<sub>3</sub> (Scheme 36). This Sm-catalyzed three-component coupling can be used to synthesize tetrahydro(iso)indoles 151a and 151b (Figure 3) by choosing n-butylamine (R<sup>3</sup> = n-Bu), nitroethane (R<sup>4</sup> = Me), and either 1-acetyl-1-cyclohexene 150a, or 2-butylidenecyclohexanone 150b as starting materials, respectively.88
MW Accelerated MCRs on Catalytically Active Supports

Microwave irradiation of mixtures of reagents absorbed onto the surface of an insoluble inorganic support under solvent-free conditions are conceptually efficient and environmentally benign processes. The inorganic supports used include silica, alumina, celite, graphite, and mesoporous inorganic solids, such as montmorillonite K-10 clay and are usually cheap commercially available, and easily manageable bulk-chemicals. Both silica and montmorillonite K-10 clay are believed to owe their catalytic activity to the presence of numerous acidic sites and have been successfully used in the microwave-accelerated multi-component synthesis of a number of heterocyclic compounds. Experimental procedures are reported to be extremely simple and involve initial absorption of the reagents on the solid support, subsequent irradiation in a domestic microwave oven, and final elution of the reaction mixture gave the desired reaction products in satisfactory yields after strikingly short reaction times. Solid supports were usually recovered and could be reused without significant loss of activity.

The multi-component synthesis of pyrroles discussed in the previous section, was recently revisited by Ranu et al. In an attempt to improve the efficiency of the reaction, they developed an identical, but microwave-assisted synthesis on the surface of either silica or alumina. A wide range of structurally different \( \alpha,\beta \)-unsaturated aldehydes and ketones \( \text{147 and 152} \) were successfully coupled under mild conditions with primary amines \( \text{31} \) and nitroalkanes \( \text{149} \) to produce the corresponding pyrroles \( \text{148 and 153} \) in satisfactory yields, which were usually better than those reported by Ishii et al. (Scheme 35). Also, time-efficiency was considerably improved and reactions had generally gone to completion within 10 minutes. Similar observations were made when aldehydes \( \text{157} \), primary amines \( \text{31} \), and \( \alpha,\beta \)-unsaturated nitroalkanes \( \text{158} \) were reacted (Scheme 37). Reaction products \( \text{159} \) were obtained in good yields and reactions were usually complete within 15 minutes. Although a number of aldehydes \( \text{157} \) and primary amines \( \text{31} \) were successfully used as starting materials, the use of \( \alpha,\beta \)-unsaturated nitroalkanes \( \text{158} \) with a free \( \alpha \)-position was troublesome and led to the formation of by-products. Similar observations were made when non-cyclic ketones instead of \( \text{157} \) were used as starting materials. On the other hand, cyclic ketones were successfully coupled with a number of primary amines \( \text{31} \) and \( \text{158} \), which resulted in various fused pyrroles in good yields. In conclusion, its time-efficiency, broad preparative scope, and good chemical yields make the approach developed by Ranu et al. a valuable tool for the preparation of a wide range of substituted pyrroles.

Compounds including imidazole ring systems have numerous pharmaceutical activities and play an important role in many biochemical processes. Both conventional and multi-component procedures for the synthesis of imidazoles have been developed over the past century. In addition to these methods, recently an efficient microwave-assisted four-component synthesis of highly substituted imidazoles has been reported. When aldehydes, primary amines, benzil, and \( \text{NH}_2\text{OAc} \) are mixed with conventional silica or alumina and then irradiated in a domestic microwave oven, reaction products \( \text{162} \) were obtained in good yields (Scheme 38). Time-efficiency was striking and reactions had generally gone to completion within 6 minutes. In spite of its relatively moderate energy, the reaction is useful because of its simple experimental set-up, facile work-up, good chemical yields, and short reaction times.

Brönsted acids were used to catalyze microwave-accelerated multi-component synthesis of substituted isoflav-3-ones \( \text{166} \) (Scheme 39). Irradiating a mixture of cyclic amines \( \text{163} \) and phenyl acetaldehyde \( \text{164} \) led to the formation of the corresponding enamines, which, upon addition of salicylaldehydes \( \text{165} \) and a catalytic amount of \( \text{NH}_2\text{OAc} \) gave \( \text{166} \) in modest yields. In the absence of solvent the reaction was completed within 5 minutes.
Sonogashira coupling was recently successfully incorporated into the multi-component synthesis of several interesting classes of heterocyclic compounds. For example, Chaplin and Flynn developed a fast and flexible route to benzo[b]furans and indoles to prepare various structural analogues of tubulin polymerization inhibitor 167 (Figure 4)."}

"Figure 4 Example of a synthetic tubulin polymerization inhibitor.

Initial transformation of readily available o-iodophenols 168a and terminal acetylenes 169 into their corresponding magnesium chloride salts was followed by Sonogashira coupling (Scheme 40). The resulting o-alkynylphenoxy magnesium chlorides 170a were then, in the same pot, reacted with suitable coupling partners 171 and 2,3-disubstituted benzo[b]furans 172a were obtained in 45–88% yield. Alkenyl bromides, alkenyl iodides and aryl iodides were all effective coupling partners in heteroannulation, as were allyl acetate and propargyl tosylate. When the final coupling was carried out under a CO-atmosphere, carbonylative formation of 172c was observed. It should be noted that the use of styrenyl iodide as coupling partner in heteroannulation led, under CO-conditions, to formation of 173 (Figure 5). This is clearly the result of an alternative coupling pathway. Finally, when o-iodoacetanilides 168b instead of o-iodophenols 168a were used, the procedure appeared to be also suitable for the preparation of indoles 172b, which significantly broadens the scope of this MCR.

"Figure 5 3-Alkylidene-benzo[b]furan-2-one

Müller et al. recently made an interesting and useful contribution to the scope of Sonogashira-type MCRs for the synthesis of several classes of heterocycles. When reacting organic halides 174 with propynols 175, trans-configured propenones 179 instead of the expected Sonogashira coupling products 176 were obtained (Scheme 41)."
It is assumed that the initially formed 176 undergo base-catalyzed isomerization. Selective deprotonation of 176 yields resonance-stabilized anions 177, which are readily transformed into thermodynamically stable allenes 178. Tautomerization then selectively leads to trans-configured propenones 179. Preliminary studies revealed that the use of (hetero)aryl propynols 175 and electron-deficient alkenyl or (hetero)aryl halides 174 is required for isomerization. For example, when reacting iodobenzene (174, R1 = Ph, X = I) with 1-phenyl-prop-2-yn-1-ol (175, R2 = Ph) isomerization did not take place and Sonogashira coupling product was obtained in nearly quantitative yield. The coupling-isomerization sequence allows the mild and stereoselective synthesis of electron deficient propenones 179 that would otherwise be difficult to prepare and as such, it complements the classical aldol condensation.

Müller et al. discovered that propenones 179 smoothly react with appropriate nucleophiles which results in multiply functionalized heterocycles (Scheme 42). Thus, a series of 3,5-diaryl-2-pyrazolines 182 were prepared in a single step by reacting (hetero)aryl halides 180, aryl propynols 175a and N-methylyhydrazine with [Pd(PPh3)2Cl2], and CuI in a boiling mixture of THF and triethylamine. The concept had been shown to work, the three-component synthesis of several other classes of heterocyclic compounds was successfully addressed by simply using nucleophiles other than N-methylyhydrazine. A similar multi-component strategy condenses amidinium salts 183 with propenones 179 to give pyrimidines. In this way, a small library of 2,4,6-tri(hetero)aryl-pyrimidines 184 could be prepared by reacting equimolar amounts of (hetero)aryl-halides 180, 175a, and amidinium salts 183. The reaction proceeded smoothly and the expected reaction products 184 were obtained in yields of 41–70%. Whereas the electron-deficient nature of Ar1 again appeared to be crucial for successful coupling–isomerization, both, Ar2 and Ar3 could be varied to some extent and electron-rich, electron-deficient, and heterocyclic substituents were tolerated. The broad scope of the coupling–isomerization–cyclocondensation sequence was further exemplified by the synthesis of several benzoheteroazepines 186 and tetrasubstituted pyroles 188 as well. Synthesis of the latter requires a slightly modified procedure that reacts (hetero)aryl-aldehydes 13a with propenones 181 in the presence of a thiazolium salt. Intermediate 1,4-diketones 187 were obtained in good yields. Bearing the classical and well-known Paal–Knorr synthesis in mind, it was anticipated that pyroles 188 could be prepared by simply adding excess amounts of primary amines 160 to 1,4-diketones 187. Although structural variation of the starting materials was rather limited, several pyroles 188 were synthesized in moderate yields via this coupling–isomerization–stetter–Paal–Knorr sequence. The coupling–isomerization sequences reported thus far, give facile access to a large number of heterocyclic compounds, albeit reaction times are relatively long. Further studies to explore the preparative scope of these procedures and to extend their potential as viable routes to other interesting heterocyclic systems are currently under way.

MCRs Involving Palladium-Catalyzed Cyclization

In continuation of their studies directed to the Pd-mediated cyclization of alkenes and alkynes, Balme et al. re-
ported a fast and flexible approach to five-membered oxygen-containing heterocycles.\textsuperscript{107} The methodology relies on Pd-mediated heteroannulation and involves the use of readily available starting materials (Scheme 43).

After oxidative addition of aryl halides 195 to the transition metal catalyst (i), the resulting arylpalladium 196 forms a complex with 191 (ii) that have been generated in situ by intermolecular conjugate addition of allyl alcohols 189 to Michael acceptors 190.\textsuperscript{109} Heteroannulative coupling followed by ligand exchange (iii) then transforms π-complexes 192 into intermediates 193. Subsequently, species 193 undergoes reductive elimination (iv) to yield tetrahydrofurans 194. Initial attempts to react 190, 195, and the alkoxides derived from 189 in a one-pot process were not successful and the alkoxides were trapped by π-complexes 192. Various bases and solvents were tested in order to optimize the reaction conditions and the combination of DMSO and KH proved most effective.

Scheme 42  Synthesis of pyrazolines, pyrimidines, benzoheteroazepines, and pyrroles.

Scheme 43  Palladium-mediated synthesis of tetrahydrofurans.
When a 1 M solution of 2 equivalents of potassium alkoxide in DMSO was slowly added to 1 equivalent of 190, 1.5 equivalents of 195, and 0.05 mol% of preformed Pd(dppe) in DMSO at 50 °C, tetrahydrofurans 194 were obtained in fair yields and 85% de. The trans-diastereomer predominates, most likely due to thermodynamically controlled heteroannulation via a chair-like transition state (Figure 6).

![Figure 6](image)

**Figure 6** Heteroannulation via a chair-like transition state.

Although various aryl halides 195 and Michael acceptors 190 were tolerated under optimized reaction conditions, the reluctance of secondary and tertiary allyl alcohols 189 to participate in the reaction considerably reduced the E_N of the procedure. To deal with this problem, readily available 197 were used instead of their allyl analogues 189 (Scheme 44).[^108]

Initial attempts to react organic halides 196, 197 and Michael acceptors 190 in one pot failed and considerable amounts of 199 were obtained. Formation of 199 could result from a reaction involving a Pd-hydride instead of the organopalladium halides. Competitive formation of 199 was effectively inhibited by changing the solvent and the nature of the Pd-catalyst. Thus, reacting 196, 197 and 190 in a 1:1 mixture of DMSO and THF in the presence of in situ generated [Pd(PPh_3)_2 Cl_2], led to the exclusive formation of the desired 198 in 46–90% yields. The reaction took place at ambient temperature in less than 15 minutes. Furthermore, the choice of propargyl-alcohols (or -amines) 197 was much less confined and a range of derivatives was successfully used as starting materials.[^108b,c]

Interestingly, when 1,3-disubstituted propynols were used, 5-exo-dig-cyclization was accompanied by competitive 6-endo-dig-cyclization.[^108] For example, reaction of iodobenzene 200, 2-butyn-1-ol 201, and the malonic acid dimethyl ester 202, gave as well as the expected 203, dihydropyran 204 (Scheme 45).

**MCRs Involving Cu-Mediated Steps**

Many antimicrobial agents belong to the widely employed class of β-lactam antibiotics contain the heterocyclic structure present in 205. These are conveniently prepared from chiral monocyclic β-lactams 206 by manipulation at N-1 and C-4 followed by ring closure (Scheme 46).

![Scheme 46](image)

**Scheme 46** Most bicyclic β-lactam antibiotics are retrosynthetically derived from monocyclic β-lactams.

Stereoselective methods to synthesize monocyclic β-lactams that involve single-step coupling of three different starting materials are relatively few and usually incorporate only one C–C-bond forming step.[^75] A conceptually different strategy involves the formation of two C–C-bonds by reacting readily available dialkylcuprates 207, chiral Michael acceptors 208 and imines 209 (Scheme 47).[^77] The reaction probably starts with the addition of 207 to Michael acceptors 208 and the resulting enolates subsequently undergo condensation with 209. After final cyclization, azetidin-2-ones 210 are obtained. Both yield and stereocchemical outcome of the reaction, critically depend on the structural nature of 207, chiral auxiliaries X*, and 209.[^77]

![Scheme 47](image)

**Scheme 47** Multicomponent synthesis of tetrahydrofurans.

![Scheme 45](image)

**Scheme 45** Reaction of 2-butyn-1-ol led to the formation of isomeric heterocycles.

---

Synthesis of 3,4-disubstituted azetidin-2-ones.

The best results were obtained when dialkylcuprates 207 were reacted with either 211 or 212, and activated imines (Figure 7). Both efficiently induced asymmetric Michael addition and subsequent stereoselective attack of the intermediate enolates by 209, whereas no reaction occurred when 213 were used. Azetidinones 210 were obtained in good stereoselectivities and ee’s up to 99% were achieved (Scheme 48, Table 6). Diastereoselectivity was dramatically influenced by both the temperature at which imine trapping took place and the electronic nature of the imines 209. Imines 209a bearing electron-withdrawing C-substituents mainly afforded cis-210a, whereas imines 209b bearing electron-withdrawing N-substituents exclusively afforded trans-210b. Both 210a and 210b were obtained in high ee’s. Similar observations were made when dialkylcuprates other than dimethylcuprate were used, which makes this a flexible and enantioselective route to both cis- and trans-configured 210.

In relation to this, Hayes et al. recently developed a diastereoselective Cu(I)-catalyzed MCR to prepare 2-substituted piperidines (Scheme 49). When optically pure aziridines 215 were reacted with 214, metalloenamines 216 were obtained. These were readily alkylated by 1,3-difunctionalized 217. The resulting imines 218 were treated with NaHB(OAc)₃ and diasteriomerically enriched piperidines 219 were obtained after final cyclization. The concept has been used to prepare naturally occurring (S)-coniine 220 (R₁ = n-Pr) in two steps in 40% overall yield and >95% ee.

Figure 7 Chiral Michael acceptors that have been used in the synthesis of azetidin-2-ones.

Scheme 47 Synthesis of 3,4-disubstituted azetidin-2-ones.

Scheme 48 Synthesis of 3,4-disubstituted azetidin-2-one.

Table 6 Synthesis of 3,4-Disubstituted Azetidin-2-one

<table>
<thead>
<tr>
<th>Entry</th>
<th>Michael Acceptor</th>
<th>R¹</th>
<th>R³</th>
<th>R⁴</th>
<th>Imine Trapping Yield (%)</th>
<th>cis/trans</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>211a</td>
<td>Me</td>
<td>CO₂Me</td>
<td>PMP</td>
<td>–78</td>
<td>55</td>
<td>60/40</td>
</tr>
<tr>
<td>b</td>
<td>211a</td>
<td>Me</td>
<td>CO₂Me</td>
<td>PMP</td>
<td>0</td>
<td>50</td>
<td>88/12</td>
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<tr>
<td>c</td>
<td>211b</td>
<td>Me</td>
<td>CO₂Me</td>
<td>PMP</td>
<td>0</td>
<td>57</td>
<td>98/2</td>
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<td>d</td>
<td>212b</td>
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<td>CO₂Me</td>
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<td>62</td>
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<tr>
<td>f</td>
<td>213</td>
<td>Me</td>
<td>CO₂Me</td>
<td>PMP</td>
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<td>–</td>
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</tr>
</tbody>
</table>

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5 MCRs Involving Cycloaddition Reactions

Most of the classical methods to prepare heterocyclic compounds are cyclization reactions and as such, rely on intramolecular interactions between nucleophilic and electrophilic functionalities. However, cycloaddition reactions, which usually rely on intermolecular interactions, have become increasingly popular tools for the preparation of various classes of heterocycles. Cycloadditions are efficient reactions that proceed in excellent regio- and stereo-selectivity and tolerate a wide range of functionalities. Their efficiency and outstanding Eₙ make cycloadditions attractive for incorporation into MCRs. Indeed, both, (Lewis) acid-catalyzed 1,3-dipolar cycloadditions and Diels–Alder (DA) reactions play an important role in the multi-component synthesis of five- and six-membered heterocycles.

MCR/DA-Reactions

Incorporation of DA-reactions into multi-component processes requires initial in situ generation of dienes and subsequent addition of suitable dienophiles or vice versa. In fact, both approaches have been shown to be viable and useful for the preparation of various mono- and polycyclic oxygen- and nitrogen-containing heterocycles. The section below covers MCR/DA-reactions in which ambiphilic N-arylilmines are involved. The next section reveals MCR/DA sequences in which various aza-dienes generated in situ viaaza-Wittig reaction, are crucial. The third section deals with Knoevenagel condensation to generate various oxo-dienes in situ as input for MCR/DA-reactions.

MCR/DA-Reactions Using Ambiphilic N-Arylimines

As discussed, imines are key intermediates in a number of MCRs leading to various classes of heterocyclic compounds. Addition of electron-accepting substituents, and electrophilic functionalities, imines are valuable aza-dienophiles and, if properly substituted, can serve as aza-dienes as well. Both can be used as starting materials in DA-reactions to prepare a variety of N-containing six-membered heterocycles. Imines derived from primary anilines are of particular interest because of their ambiphilic nature. When reacted with electron-rich dienes, they act like normal dienophiles 221a (Figure 8). However, when reacted with electron-rich dienophiles, they act like dienes with inverse electron demand, 221b. Both types of reaction lead to distinct types of heterocyclic compounds and will be discussed in the remainder of this section.

When reacted with suitable dienes, N-arylilmines 221a act like dienophiles and can be used to prepare pyridines. Thus, combination of in situ generated 221a from commercially available aldehydes 5 and anilines 222 with Danishefsky’s diene 223 provides an efficient and flexible route to a variety of pyridines 224 (Scheme 50). Although various aldehydes 5 and anilines 222 were successfully used as starting materials, the use of dienes other than 223 was troublesome and led to complicated reaction mixtures. This unfortunately reduces the Eₙ of the reaction.

Several sets of reaction conditions were reported favorable and gave desired reaction products 224 in a time- and atom-efficient manner. Table 7 compares reaction conditions, -times, and yields as reported by Kobayashi, 112 Frost, 113 and Akiyama. 114 Kobayashi et al. reacted aldehydes 5, anilines 222 and Danishefsky’s diene 223 in the presence of 10 mol% of either Sc(OTf)₃ or Yb(OTf)₃. The desired pyridines 224 could be obtained at room temperature and in good yields. 112 The catalytic use of Sc(OTf)₃ gave slightly better results than application of the corresponding lanthanide catalysts (entries a and b). Although atom-efficient processes, reactions needed 20 hours to go to completion. Time-efficiency was considerably improved by using other catalysts. 113,114 Addition of 0.5 mol% of In(OTf)₃ to the reaction mixture afforded 224 in less than 30 minutes and at room temperature (entries c, i, j, k, and m). 113 Various aromatic aldehydes and amines were successfully used as starting materials which considerably broadens the scope. In order to develop an environmentally benign procedure, Akiyama et al. carried out the reaction in water or aqueous media in the presence of 10

Scheme 49  Synthesis of 2-substituted piperidines (X* = chiral auxiliary).

Scheme 50  Three-component synthesis of pyridines.

Figure 8  N-Arylimines can act like both dienophiles and dienes.
mol% of a Brønsted acid.\textsuperscript{114a,b} Reaction products \textsuperscript{224} were rapidly formed in good yields and optimization studies revealed \textsuperscript{HBF_4} to be the most efficient catalyst. Interestingly, various non-aromatic aldehydes could be successfully used as starting materials as well (entries r, s, t and u). In addition, only very recently it was shown that pyridines \textsuperscript{224} can also efficiently be formed without a catalyst in methanol at room temperature.\textsuperscript{114c}

On the other hand, imines \textsuperscript{221b} may react as dienes with suitably substituted dienophiles \textsuperscript{225}, which have been used for the multi-component synthesis of a variety of tetrahydroquinolines (Scheme 51). This MCR/DA-reaction proceeded smoothly and mostly gave the expected tetrahydroquinolines \textsuperscript{226} under mild conditions, in fair yields and good de. Various classes of electron-rich dienophiles \textsuperscript{225} have been used for this purpose as will be discussed below.

When activated imines derived from \textsuperscript{221b}, \(\alpha\)-branched enolisable aldehydes \textsuperscript{227}, and nucleophiles were reacted in the presence of \textsuperscript{Yb(OTf)_3}, heterocycles \textsuperscript{231} were obtained (Scheme 52).\textsuperscript{115} At room temperature in dichloromethane and in the presence of 10 mol\% of catalyst a yield of up to 97\% of \textsuperscript{231} could be isolated. The reaction proceeds upon Lewis acid-catalysed tautomerization of \textsuperscript{227} into enols \textsuperscript{228}, which act as dienophiles and readily undergo cycloaddition to form cationic intermediates \textsuperscript{229}. Subsequent loss of water and final nucleophilic attack restores aromaticity and leads to tetrahydroquinolines \textsuperscript{231}.

\begin{center}
\begin{table}
\centering
\caption{Comparison of Kobayashi,\textsuperscript{112} Frost,\textsuperscript{113} and Akiyama’s\textsuperscript{114} Reaction Conditions}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Entry & \(R^1\) & \(R^2\) & Catalyst & Solvent & Reaction time (h) & Yield (\%) & Ref. \\
\hline
a & Ph & H & \textsuperscript{Yb(OTf)_3} & MeCN & 20 & 80 & \textsuperscript{112} \\
b & Ph & H & \textsuperscript{Sc(OTf)_3} & MeCN & 20 & 83 & \textsuperscript{112} \\
c & Ph & H & \textsuperscript{In(OTf)_3} & MeCN & 0.5 & 51 & \textsuperscript{113} \\
d & Ph & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O–MeOH} & 0.5 & 95 & \textsuperscript{114} \\
e\textsuperscript{*} & Ph & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O} & 1 & 88 & \textsuperscript{114} \\
f & Ph & \textsuperscript{p-OMe} & \textsuperscript{Yb(OTf)_3} & MeCN & 20 & 83 & \textsuperscript{112} \\
g & Ph & \textsuperscript{p-OMe} & \textsuperscript{HBF_4} & \textsuperscript{H_2O–MeOH} & 0.5 & 88 & \textsuperscript{114} \\
h & Bz & \textsuperscript{p-OMe} & \textsuperscript{Yb(OTf)_3} & MeCN & 20 & 76 & \textsuperscript{112} \\
i & \textsuperscript{2-F-C_6H_4} & H & \textsuperscript{In(OTf)_3} & MeCN & 0.5 & 84 & \textsuperscript{113} \\
j & \textsuperscript{2-Pyridyl} & H & \textsuperscript{In(OTf)_3} & MeCN & 0.5 & 95 & \textsuperscript{113} \\
k & \textsuperscript{2-Furyl} & H & \textsuperscript{In(OTf)_3} & MeCN & 0.5 & 61 & \textsuperscript{113} \\
l & \textsuperscript{2-Furyl} & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O–MeOH} & 0.5 & 58 & \textsuperscript{114} \\
m & \textsuperscript{2-Thienyl} & H & \textsuperscript{In(OTf)_3} & MeCN & 0.5 & ...\textsuperscript{b} & \textsuperscript{113} \\
n & \textsuperscript{4-Me-C_6H_4} & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O–MeOH} & 0.5 & 79 & \textsuperscript{114} \\
o\textsuperscript{*} & \textsuperscript{4-Me-C_6H_4} & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O} & 1 & 86 & \textsuperscript{114} \\
p & \textsuperscript{c-Hex} & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O–MeOH} & 0.5 & 80 & \textsuperscript{114} \\
r\textsuperscript{*} & \textsuperscript{c-Hex} & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O} & 1 & 75 & \textsuperscript{114} \\
s & \textsuperscript{PhCH_2CH_2} & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O–MeOH} & 0.5 & 75 & \textsuperscript{114} \\
t & \textsuperscript{i-Pr} & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O–MeOH} & 0.5 & 77 & \textsuperscript{114} \\
u\textsuperscript{*} & \textsuperscript{PhCH=CH} & H & \textsuperscript{HBF_4} & \textsuperscript{H_2O} & 1 & 86 & \textsuperscript{114} \\
\hline
\end{tabular}
\end{table}
\end{center}

\textsuperscript{a} A surfactant was added to the reaction mixture
\textsuperscript{b} No reaction observed.
Various imines, aldehydes and nucleophiles were tested. Successful nucleophiles included alcohols, thiols, and primary amines. Reasonable diastereoselectivities were generally observed and the diastereomer formed depended on the nucleophiles used. Successful aldehydes required the presence of -substituents. The use of linear aldehydes, aldehydes bearing -substituents, and carbonyl compounds other than aldehydes was not successful. Enantiomerically pure 2-benzyloxypropanal (227; R₃ = Me; R₄ = OPh) gave optically active reaction products 231. The reaction can be extended to a four-component synthesis via in situ generation of the activated imines. Although the activated imines and enols are suggested to react in a concerted manner, discussion still goes on. A number of experimental observations support a stepwise mechanism through highly polar transition states. While reacting anilines, aldehydes, and electron-rich dienophiles to prepare tetrahydroquinolines (Scheme 53), Kobayashi et al. collected evidence in favour of the stepwise mechanism.

The alkenes 232 that were tested provided interesting mechanistic information. Common electron-rich alkenes like vinyl ethers, vinyl sulfides, styrene derivatives, and enamines, gave the expected 233 in good yields. However, when p-anisidine 125, benzaldehyde 234, and 2-methoxypropene 235 were reacted, β-amino ketone 236 and its dimethylacetal 237 were obtained instead of the expected tetrahydroquinoline 238 (Scheme 54).

Formation of Mannich-type reaction products 236 and 237 was explained by stepwise addition of 235 to in situ generated 239 (Scheme 55). Instead of undergoing cyclization towards 238, intermediate 240 was trapped by water or methanol to afford 236 and 237 respectively. When N-arylamine 239 and 235 were reacted with 10 mol% of Yb(OTf)₃ in the absence of water, tetrahydroquinoline 238 was obtained in 83% yield. Similar results were obtained by Baudelle et al., who also extended the array of successful dienophiles to ethoxyacetylene, 2,3-dihydrofuran, and 3,4-dihydro-2H-pyran.

Cyclic alkenes 243 form an interesting class of dienophiles for the synthesis of a variety of polycyclic, fused tetrahydroquinolines 244 (Scheme 56). Both, carbonyl and heterocyclic alkenes 243 proved to be suitable dienophiles. Cycloaddition to various in situ generated N-arylimes of type 221b derived from aromatic aldehydes 5 (R = Ar) went smoothly in the presence of a catalyst, but yields and de’s were strongly dependent on solvent and catalyst. When the reaction was carried out in the presence of either a soluble, or a polymer-supported rare earth metal triflate catalyst, cis-fused tetrahydroquin-
olines 244 were obtained in high yields and excellent diastereoselectivities. Successful dienophiles included cyclopentadiene, indene, and 2,3-dihydrofuran.

An equally efficient, though cleaner, safer, and environmentally more benign procedure was developed by Sar-tori et al. 119 By carrying out the reaction in water and using natural clays to catalyze cycloaddition of cyclopentadiene to 221b, cis-configured heterocyclic products 244 were obtained stereoselectively in nearly quantitative yields.

When O-containing alkenes 243 (e.g. 3,4-dihydro-2H-pyran) were reacted with 222 and 5 in the presence of TFA, cis-configured 244 could be obtained. 118 The relatively poor diastereoselectivities of the latter reactions were improved when either electron-rich aromatic aldehydes 5, or electron-rich anilines 222 were used as starting materials. However, yields of 244 decreased significantly. The N-containing alkenes 243 were also observed to smoothly react with a number of in situ generated N-arylimines of type 221b. 120

Inspired by the intriguing structures of martinelline 245 and its carboxylic acid derivative 246, Batey et al. took advantage of the ability of nitrogen-containing heterocyclic alkenes to undergo cycloaddition. They developed an efficient procedure to gain rapid access to the tricyclic core (Figure 9). 120,121

Initial attempts to react anilines 222, aromatic aldehydes 5, and N-protected 2-pyrrole 247 in MeCN in the presence of catalytic amounts of Dy(OTf)3 were only moderately successful (Figure 10). 120 Although expected reaction products 248 were obtained in fair to good yields, diastereoselectivities were usually poor. Better de’s were observed when the reaction was carried out in aqueous media, which however dramatically decreased the yield.

The scope was considerably improved when N-protected 2-pyrrole 247 was replaced by a synthetic equivalent 249 (Figure 10). 121a After initial Lewis acid-promoted loss of R3OH a smooth DA-reaction with 221b, gave trans-configured 250 in good yields and reasonable de’s and the total synthesis of martinelline could be completed. 121b

MCR/DA-Reactions Using Aza-dienes

While exploring the synthetic potential of iminophosphoranes derived from heterocyclic β-enamino esters and uracils, Wamhof et al. reported a novel three-component reaction for the synthesis of a variety of biologically relevant ring-fused heterocycles (Scheme 57). 122,123 Reaction of the uracil derivative 251, isocyanates 252, and pyridines 253 afforded highly coloured heteropolycyclic uracils 254 in yields of 6–59%. 122 Reactions were usually carried out in the absence of a solvent, but required excess amounts of 251 and 252.

Various commercially available pyridines 253 (except those carrying strongly basic or a-substituents) as well as aromatic and aliphatic isocyanates 252 were successfully used as starting materials. The vast majority of reaction products 254 were very stable, almost completely unreactive, and of rather limited solubility in common organic solvents.
solvents. Experimental observations suggested initial aza-Wittig reaction of 251 and isocyanates 252, the resulting aza-dienes 255 were assumed to undergo a formal cycloaddition to give 257 (Scheme 58). Desired reaction products 254 were then obtained after final oxidation of 257. In order to further explore the preparative scope of the reaction, pyridines 253 were replaced by isoquinoline and phthalazine. Both reacted as expected, although reaction conditions had to be carefully controlled in order to promote final oxidation. Replacement of 251 by other heterocyclic iminophosphoranes, like phosphoranylidene pyrazole derivatives, was also successful and led to expected reaction products.

MCR/DA-Reactions Involving Knoevenagel Condensation

Pyranocoumarins are widespread naturally occurring compounds and form an important class of commercial anticoagulants. As was noticed by Tietze such heterocycles can be obtained by in situ generation of O-containing dienes and their subsequent cycloaddition to suitably functionalized dienophiles. Further elaboration and application of this concept to the synthesis of a library of pyranocoumarins was recently reported by Cravotto et al.

Thus, reacting 4-hydroxycoumarin 258, benzaldehyde 234 and various electron-rich alkenes 259 in the presence of a catalytic amount of ethylenediammonium diacetate (EDADA) gave a variety of differently functionalized pyranocoumarins 260 (Scheme 59). The reaction is mechanistically straightforward and involves base-catalyzed Knoevenagel condensation of 258 and 234, followed by cycloaddition of the resulting oxo-diene with 259. Various vinyl ethers and enamines proved successful dienophiles and gave preferentially trans-configured 260 in reasonable yields and de’s. The library was further extended by using 2-methoxypropene 235 as a dienophile and by varying the aldehyde component.

Commercial 2,3-butanedione 262 proved a successfull starting material in this MCR as well. However, initial attempts to react 261, 262, and 263 under the above conditions failed. Subsequent optimization studies revealed that the reaction was best carried out in dry dioxane in the presence of molecular sieves and catalytic amounts of Yb(OTf)3, which allowed pyranocoumarin 264 to be obtained in good yield (Scheme 60). With building block 264 in hands, further synthetic studies were undertaken and an efficient total synthesis of natural preethulia coumarin 265 was realised in five additional steps.

Scheme 58 Mechanism for the formation of heteropolycyclic uracils.

Scheme 59 Three-component synthesis of pyranocoumarins.

Scheme 60 Synthesis of (±)-preethulia coumarin.
MCR/1,3-Dipolar Cycloaddition Reactions

The above MCR/DA-procedures include a formal [4+2] cycloaddition, which gives fast access to a wide range of six-membered O- and N-heterocycles. Analogously, MCRs including [3+2] cycloadditions are highly efficient processes for the preparation of a variety of five-membered heterocycles. Most MCR/[3+2] cycloadditions rely on in situ generation of 1,3-dipolar reagents from easily accessible starting materials, which subsequently undergo cycloaddition upon addition of suitable dipolarophiles to the reaction mixture.126–128

MCR/1,3-Dipolar Cycloaddition with Nitrones

Nitrones are known to easily undergo [3+2] cycloaddition to activated alkenes, which gives fast access to a wide range of isoxazolidines. Transformation of such processes into versatile three-component procedures has been realized by in situ generation of nitrones from commercially available starting materials.129 Hydroxylamines 266, activated alkenes 267, and aldehydes 5 react in an efficient one-pot three-component coupling to form isoxazolidines 268 (Scheme 61). After in situ formation of nitrones, diastereoselective [3+2] cycloaddition to activated alkenes 267 went smoothly and endo-adducts 268 were obtained in excellent yields. Reactions were best carried out in toluene in the presence of 20 mol% of catalyst and molecular sieves. The mild reaction conditions were tolerant to a wide range of starting materials like aromatic, aliphatic and heterocyclic aldehydes, but also methyl vinyl ketone, N-phenylmaleimide and several oxazolidinones were found to be good substrates.129

![Scheme 61 Multi-component synthesis of isoxazolidines.](image)

Multiple cycloaddition reactions employing both, bidentate and bidentate dipolarophiles, are potentially interesting tools for the construction of complex molecular frameworks. This concept was applied to a novel strategy for the synthesis of isoxazoline- and isoxazolidine-based macrocycles.130 One of two strategies concerned the use of bifunctional dipolarophiles and two equivalents of in situ generated nitrene, which resulted in the formation of C-linked bisoxazolidines 273 (Scheme 62).

![Scheme 62 Multi-component synthesis of C-linked bisoxazolidines.](image)

Thus, reacting two equivalents of each cyclopentanone oxime 270 and phenyl vinyl sulfone 269 and one equivalent of N,N'-methylenebisacrylamide 272 in refluxing toluene afforded the desired reaction product 273 in 63% yield.130

Alternatively, reaction of in situ generated dipole and two equivalents of a properly chosen dipolarophile resulted in the formation of N-linked bisoxazolines 277 (Scheme 63). Thus, reacting two equivalents of each 270 and dimethyl acetylene dicarboxylate 274, and one equivalent of divinyl sulfone 275 in refluxing toluene afforded the desired reaction product 277 in 51% yield.130

![Scheme 63 Multi-component synthesis of N-linked bisoxazolines.](image)
Some heterocyclic systems can serve as interesting precursors for the synthesis of highly functionalized linear compounds that are difficult to prepare otherwise. The heterocyclic systems concerned were easily accessible via highly efficient multi-component procedures, which all relied on [3+2] cycloaddition of properly chosen dipolarophiles to in situ generated nitrones. In one case, in situ generation of nitrones was achieved by base-promoted condensation of \(\alpha\)-activated aldehydes and activated nitroalkanes (Scheme 64). The nitrone intermediates were used as an anchor to link olefinic residues to, after which spontaneous intramolecular [3+2] cycloaddition took place to afford heterocycles. Subsequent unfolding gave access to a number of interesting linear amino-polyhydroxylated structures, such as, which were isolated as the equivalent lactone. The assembly of was carried out by stirring, and imidazole in acetonitrile at ambient temperature. Polycycles were obtained in satisfactory yields as mixtures of two diastereomers, which results from the initial (racemic) condensation step of and . In another case, a one-pot tandem [4+2]/[3+2] cycloaddition of electron-poor nitroalkenes, ethyl vinyl ether, and dipolarophiles, gave diastereomeric mixtures of bicyclic heterocycles (Scheme 65). Aldehydes were then obtained after selective opening of the six-membered ring.

MCR/1,3-Dipolar Cycloaddition with Azomethine Ylides

Azomethine ylides are valuable reaction partners in [3+2] cycloadditions because they give access to pyrroles and reduced pyrroles. Transformation of such processes into versatile three-component procedures was realized by in
available starting materials, such as 1,2-dicarbonyl compounds and \( \alpha \)-amino acids.\textsuperscript{134–136} For example, chalcones \textbf{293} were expected to capture dipolar intermediates \textbf{294} resulting from isatins \textbf{295} and \( \alpha \)-amino acids \textbf{296} (Scheme \textbf{66}).\textsuperscript{134} Indeed, when \textbf{293}, \textbf{295}, and \textbf{296}, were reacted in aqueous methanol, acetonitrile, or dioxane, spiro-pyrrolidines \textbf{297} were obtained in good yields and high purities. The reaction was observed to proceed in a highly regio- and stereocontrolled fashion. The relative stereochemistry was believed to result from \textit{exo}-addition of \textbf{293} to thermodynamically favored \textit{anti}-ylides \textbf{294}. The high purity and good yields made the procedure a suitable tool for the synthesis of a compound library of >25000 differently substituted pyrrolidines \textbf{297}.

6 Conclusion and Outlook

Nitrogen-, oxygen-, and sulfur-containing heterocycles are common structural elements in many natural products and pharmacologically active substances. Accordingly, development of efficient methods for the synthesis of (combinatorial libraries of) heterocyclic compounds has been challenging organic chemists for over a century. In the course of time, MCRs have proved a convenient tool for the construction of many classes of heterocyclic compounds.

Initial attempts were mainly focused on the development of procedures in which one of the starting materials was immobilized on a suitable resin. Current interest however tends to move away from solid-phase procedures and increasingly focuses on the emerging area of solution-phase procedures. Accordingly, many groups all over the world have reported on solution-phase multi-component methodology for the synthesis of heterocyclic compounds.

In this review, the methods that have been published so far are categorized which provides some insight into the logic of multi-component chemistry in general. Many interesting examples have been put forward and it has become evident that many classes of mono- and polycyclic heterocycles are now accessible by means of flexible and highly efficient solution-phase multi-component procedures. The methods currently available are conveniently classified according to the conditions under which they are carried out. Non- and acid-catalyzed procedures represent the vast major class of MCRs. On the other hand, transition metal-catalysis is becoming increasingly popular.

As has been emphasized, MCRs are a well-appreciated tool for the generation of moderate to large libraries of related heterocyclic compounds that are to be screened for pharmacological activity or as ligands for novel transition metal catalysts. Furthermore, solution-phase MCRs have occasionally been used to optimize existing or to develop efficient novel routes to complex target compounds and as such, play an increasingly important role in total synthesis. However, despite the achievements made so far, the concept of solution-phase multi-component chemistry for the efficient synthesis of heterocyclic compounds has not reached its full potential. The multi-component synthesis of many classes of heterocycles is still to be addressed. Existing procedures sometimes lack flexibility and will have to be optimized in order to avoid restrictions on the choice of starting materials. The obstacle to be overcome most urgently, however is the fact that the vast majority of solution-phase MCRs occur in a non-stereoselective manner and reaction-products are mostly obtained as racemates. Thus, future developments in multi-component chemistry will focus on cheap, efficient, and stereoselective procedures.

References

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Synthesis 2003, No. 10, 1471–1499 © Thieme Stuttgart · New York