Utilisation of 1,3-Dicarbonyl Derivatives in Multicomponent Reactions

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Although isocyanide-based multicomponent reactions (MCRs), introduced in 1921 by Passerini, largely predominate nowadays in the construction of widely diverse heterocycles, one of the first substrate classes involved in a MCR was that of 1,3-dicarbonyl derivatives, with Hantzsch's dihydropyridine synthesis appearing as early as 1882. The aim of this microreview is to present an overview of the great synthetic potential of MCRs involving the specific reactivity of easily accessible 1,3-dicarbonyl derivatives and to stress their more recent utilisation for the development of new and useful methodologies valuable for the selective construction of highly functionalised small organic molecules of high synthetic and biological value. After a short general introduction, we present chronologically the different methodologies developed on the bases of the reactivity of 1,3-dicarbonyl systems towards many other substrates involved in a variety of synthetic pathways, including Knoevenagel condensations, Michael and Mannich reactions, cyclodehydrations, electrocyclisations, cycloadditions and metal-promoted transformations.

1. Introduction

Although not a very new problem, both economic and ecological pressures, coupled with the concomitant emergence of high-throughput screening, are playing increasingly significant roles in the development of modern synthetic organic chemistry.[1] Selectivity, atom economy,[2−4] time saving, environmental friendliness, cost effectiveness and the reconciliation of molecular complexity with experimental simplicity are some of the pieces of the puzzle needing to be assembled by modern academic and industrial synthetic chemists to reach the maximum of efficiency.[5] All these constraints have resulted in tremendous development of new concepts and new methodologies able to produce valuable elaborated compounds.[6−8] In this context, utilisation of multicomponent reactions (MCRs) involving domino processes,[9−11] with at least three different simple substrates[12,13] reacting in a well defined manner to form a single compound, has emerged as a powerful strategy.[14] This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis and are particularly well adapted for combinatorial chemistry.[15] Since the first MCR, reported in 1850 by Strecker,[16] this well known concept,[17] also widely represented in nature, has been extensively used in both liquid-phase[14] and solid-phase[18] chemistry for the rapid assembly of complex heterocyclic structures of importance for pharmaceutical development.[19]

Although isocyanide-based MCRs,[20−24] introduced in 1921 by Passerini,[25,26] generally predominate nowadays for the construction of widely diverse heterocycles,[27] one of the first substrate classes involved in a MCR was that of 1,3-dicarbonyl derivatives, with Hantzsch's dihydropyridine synthesis[28] appearing as early as 1882. The aim of this microreview is to present an overview of the high synthetic potential of MCRs involving the specific reactivity of easily accessible 1,3-dicarbonyl derivatives[29] and to stress their more recent utilisation for the development of new useful methodologies valuable for the selective construction of highly functionalised small organic molecules of high synthetic and biological value. This presentation focuses only on MCRs involving at least three different substrates, with no discussion being made of transformations dealing with the utilisation of a twofold excess of 1,3-dicarbonyls with another substrate.[30−35]

2. Hantzsch's Heterocyclic Syntheses

2.1. 1,4-Dihydropyridine and Pyridine Syntheses

1,3-Dicarbonyl derivatives constitute important synthetic intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a large variety of synthetic transformations.[29] Their versatility and effectiveness as potential multicomponent substrates were first discovered and utilised by Arthur Hantzsch in 1882,[28] with the one-pot, four-component

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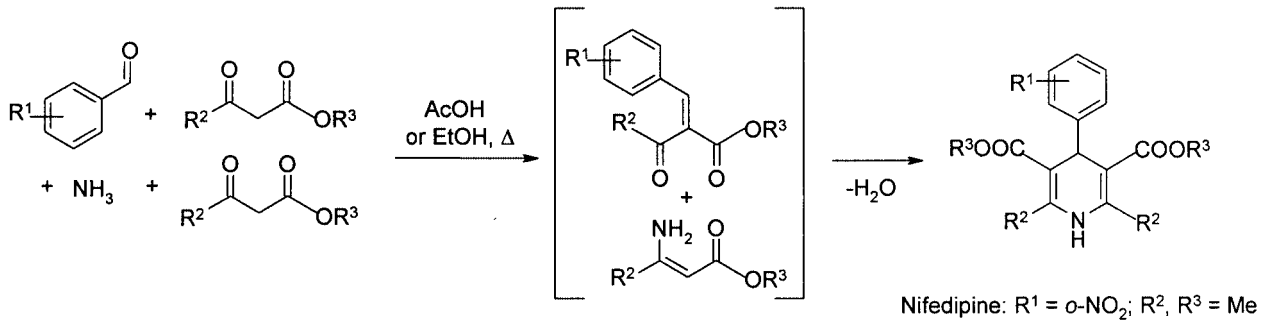
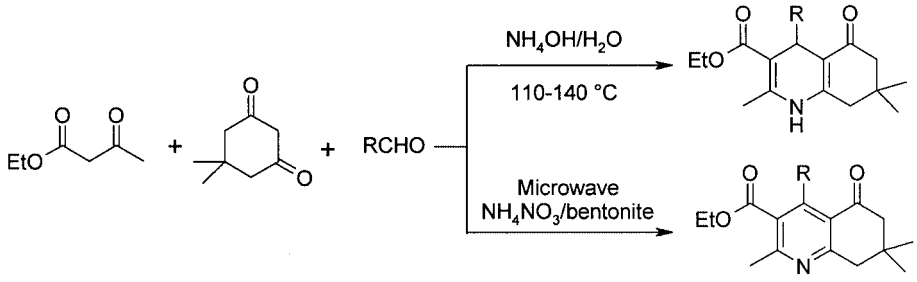


Scheme 1

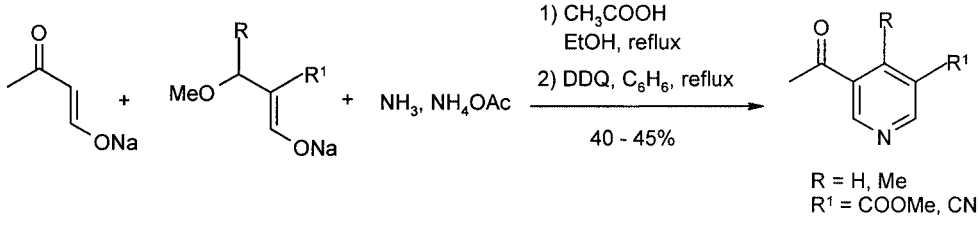
synthesis of symmetrically substituted 1,4-dihydropyridines. Two molecules of an acetoacetic ester were initially involved in this unprecedented transformation, one reacting with an aromatic aldehyde in a Knovenaegel condensation and the other one with ammonia to form an enamine-type intermediate, followed by a cyclodehydration to afford the heterocycle. Thanks to the simplicity of the method and the availability of starting materials, this procedure was widely applied in the search for new heterocyclic derivatives presenting new pharmacological properties.[36] Nifedipine, for example, was prepared at Bayer AG in 1977 as a new, highly active calcium antagonist with important antihypertensive activity (Scheme 1).[37−40]

The standard Hantzsch procedure does not need the intervention of any additive or reagent, and the reaction was originally conducted either in acetic acid or at reflux in alcohol for rather long periods, resulting in low or modest yields of condensation products. The great biological importance of the 1,4-dihydropyridine nucleus has over the years prompted the development of new improved methodologies, including solid-phase synthesis[41,42] and activation with a catalyst such as molecular sieves and pyridine,[41] or more recently Lewis acids[43] and iodo(trimethyl)silane.[44] Replacement of ammonia by ammonium acetate allowed the efficient synthesis of Hantzsch's compounds under mild and solvent-free conditions.[45] Alternatively, microwave irradiation[46−48] represents an important improvement in the transformation and has also been applied for the direct synthesis of pyridines[49] by concomitant in situ aromatisation of the 1,4-dihydropyridine intermediates[50−52] in the presence of ammonium nitrate supported on bentonite clay.[53] Not only traditional β-keto esters, but also, for example, malonaldehyde[40,54] and, more interestingly, cyclic 1,3-diketones can participate in this MCR, allowing four-component Hantzsch syntheses of unsymmetrically substituted 1,4-dihydropyridines or pyridines with good selectivity depending on the reaction conditions (Scheme 2).[46,53]

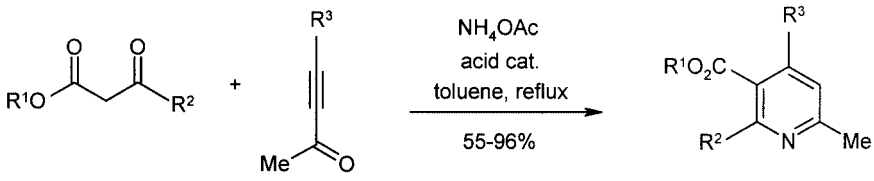
Also of interest is the one-pot formation of simple 3,5-disubstituted 1,4-dihydropyridines, which upon oxidation gave the pyridines involved in the total synthesis of the alkaloid iosalamarine.[55] The key transformation consisted of



Scheme 2



Scheme 3



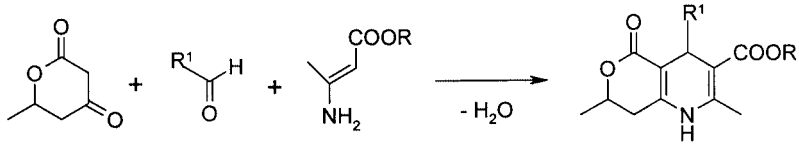
Scheme 4

a cyclocondensation of the sodium salts of functionalised malonoacetaldehydes[54] in the presence of ammonium acetate, followed by DDQ oxidation (Scheme 3).

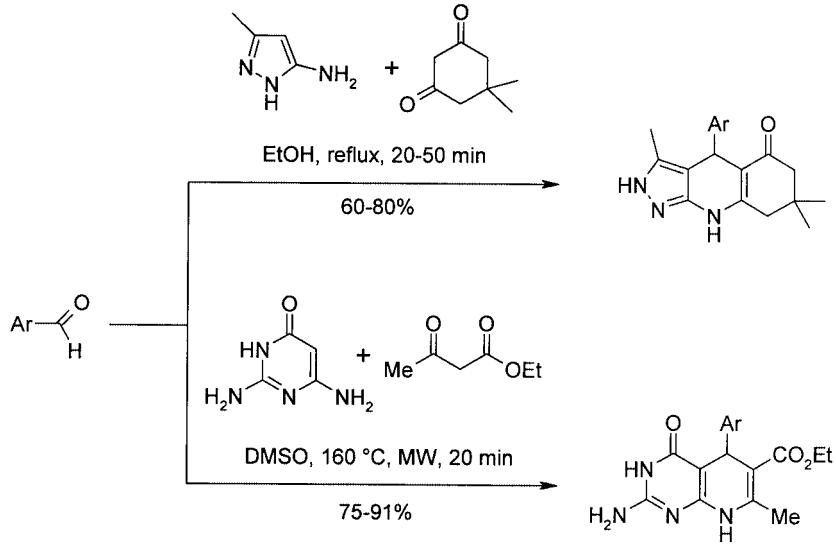
More recently, it was reported that alkynones could also be used as substrates, allowing direct access to polysubstituted pyridines (Scheme 4).[56] This tandem addition-elimination-Michael addition-cyclodehydration process would be related to the indirect Hantzsch pyridine synthesis, but with the advantage of total control over regiochemistry and access to the target heterocycle in the correct oxidation state without addition of any oxidant.

Another possibility for efficient formation of unsymmetrical dihydropyridines is to perform the condensation with aldehydes with use of a 1,3-dicarbonyl derivative in the presence of a preformed enamino ester intermediate.[37] For example, utilisation of a β-ketolactone and simple acyclic primary amino esters in condensations with aldehydes gave the corresponding fused heterocycles in high yields (Scheme 5).

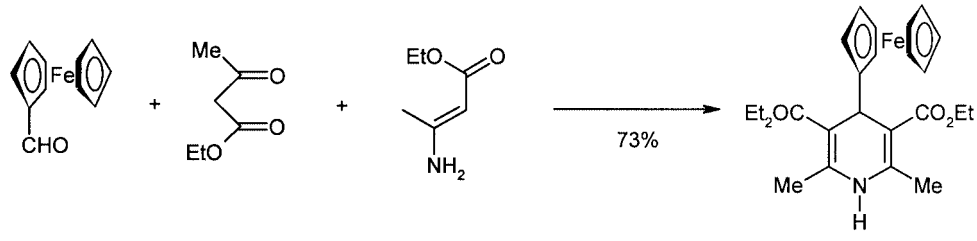
This approach has recently been exploited for the syntheses of (pyrazolo)quinolinones[57] and deazadihydropterins.[43] In the first case, dimedone reacted with 5-amino-3-



Scheme 5



Scheme 6



Scheme 7

methyl-1*H*-pyrazole as an enamine equivalent under thermal conditions, while acyclic β-keto esters or β-keto amides were condensed with 2,6-diaminopyrimidinone in the presence of aryl aldehydes in the presence of microwave activation and Lewis acids (Scheme 6).

More recently, the Hantzsch reaction involving preformed enamino ester intermediates has been applied in the field of the synthesis of ferrocene-containing heterocycles.[58] Thus, a condensation between ferrocenecarboxaldehyde, ethyl acetoacetate and ethyl β-aminocrotonate gave the expected dihydropyridine in 73% yield (Scheme 7).

Since a stereogenic centre is formed during a Hantzsch-style MCR, diastereoselective transformations, starting either with chiral enamino derivatives[37,59,60] or with chiral β-keto esters, have been studied.[61−63] An interesting example involves the four-component condensation between a mandelic keto ester derivative, 3,4-(methylenedioxy)benzaldehyde and 1,3-cyclohexanedione in the presence of ammonia, resulting in high asymmetric induction to give the expected dihydropyridine in up to 98% diastereomeric excess[61] (Scheme 8).

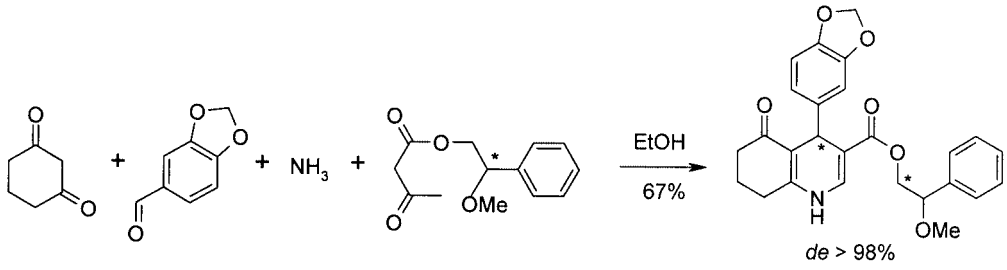
A variation of the Hantzsch reaction for the synthesis of 4*H*-pyran analogues of 1,4-dihydropyridines has been proposed at Bayer AG.[37] 1,3-Cyclohexanedione was condensed with an aldehyde and a nitrile bearing an activated methylene group in the presence of a catalytic amount of piperidine (Scheme 9).

2.2. Pyrrole Syntheses

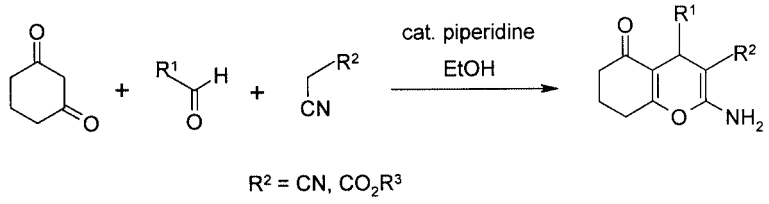
Another contribution by Hantzsch in the field of MCRs concerns the synthesis of pyrroles from a β-keto ester or β-keto amide, a primary amine and an α-halogenated carbonyl compound[64,65] and is also amenable to solid-support conditions.[66] It is assumed that initially formed enamino esters are *C*-alkylated, followed by a dehydrative cyclocondensation to afford highly substituted pyrroles (Scheme 10).

Since these pioneering results, the technique has been intensely exploited and has recently been reviewed.[67] An important variation, with the utilisation of nitroolefins in the condensation with ketones and primary amines, was reported by Meyer in 1981.[68] This has recently been optimised and generalised to monocyclic and fused-bicyclic pyrroles through the use of molten ammonium salts as a medium for the reaction[69] (Scheme 11).

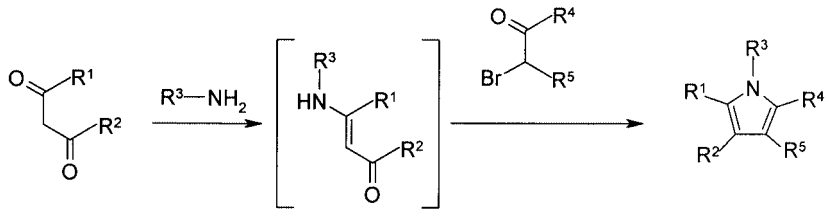
Also of interest is the unprecedented samarium(III)-catalysed three-component coupling reaction of aldehydes, amines and nitroalkanes,[70] which can be performed either on the surface of silica gel or under microwave irradiation conditions.[71] The reaction pathway possibly involves an aldol-type condensation of the imine intermediate followed by a Michael addition and an intramolecular cyclisation, successively with concomitant elimination of H_2O and HNO (Scheme 12).[70,72]



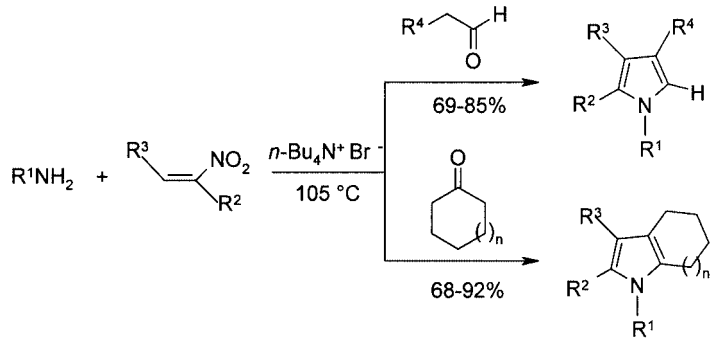
Scheme 8



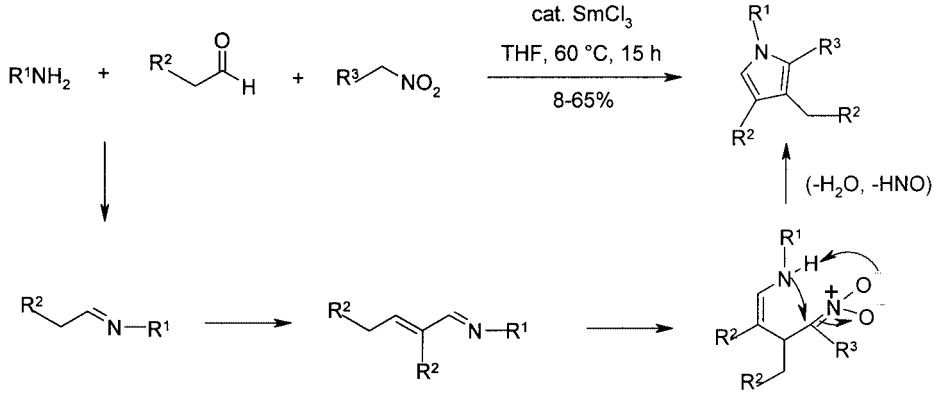
Scheme 9



Scheme 10



Scheme 11



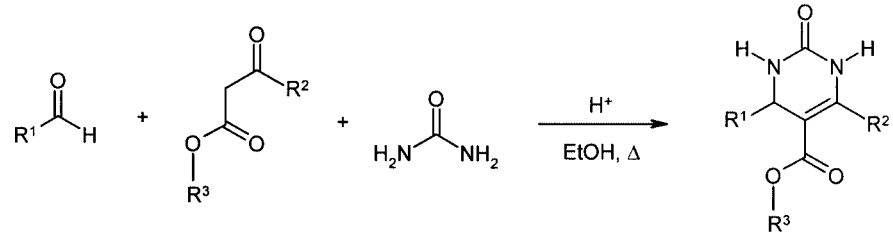
Scheme 12

3. Biginelli Dihydropyrimidine Syntheses

3.1. The Biginelli Condensation

In 1893, shortly after Hantzsch's discovery, Biginelli published a related transformation with urea as the amine component, allowing the facile preparation of multiply functionalised dihydropyrimidines.[73] Typically, the reaction involves the combination of aldehydes and β-keto esters with urea, in protic solvents and under strongly acidic conditions, to produce dihydropyrimidinones with ester moieties in the 5-position of the heterocycle (Scheme 13).

Although the synthetic potential of this particular condensation remained unexplored until the beginning of the



Scheme 13

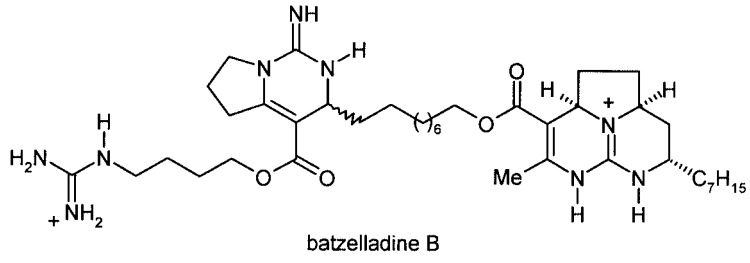


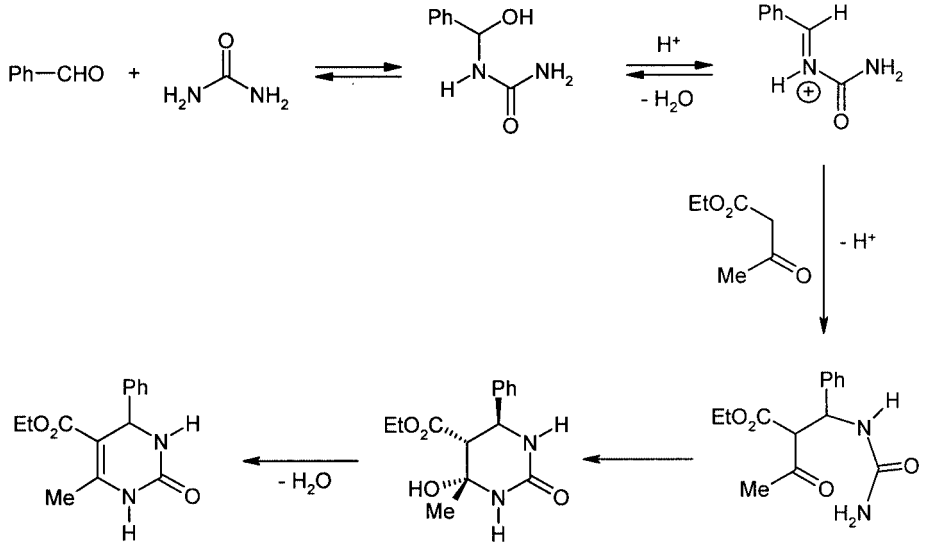
Figure 1. Example of a marine alkalaide from the batzelladine family

1980s, it is now recognised as a powerful heterocyclic synthesis with many important applications and has been the subject of two reviews.[74,75] The increasing interest in dihydropyrimidine scaffolds (DHPMs), known as "Biginelli compounds", is mainly due to their therapeutic and pharmacological properties.[76] They have been found to exhibit a wide spectrum of biological effects including antiviral, antitumour, antibacterial and anti-inflammatory activities. Furthermore, appropriately functionalised DHPMs have emerged as potent calcium channel blockers, antihypertensive agents, α_{1a}-adrenergic antagonists and neuropeptide Y (NPY) antagonists. More recently, several marine alkaloids containing the dihydropyrimidone-5-carboxylate core and possessing interesting biological activities have been isolated,[77] among them the batzelladine alkaloids A and B (Figure 1), which were found to be potent HIV gp-120-CD4 inhibitors.[78]

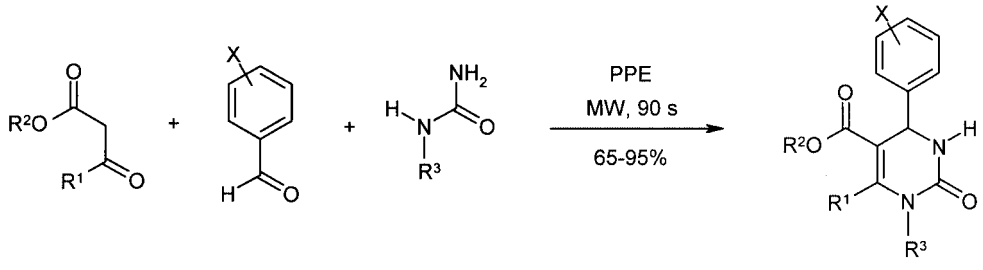
Since the pioneering work of Folkers and Johnson in 1933,[79] the mechanism of the Biginelli reaction has been investigated by several research groups[80] and over the past decades has been the subject of some debate. Recently, on the basis of ^{1}H and ^{13}C NMR experiments, Kappe clearly demonstrated the formation of an *N*-acyliminium ion as the key intermediate, resulting from the acid-catalysed condensation of benzaldehyde and urea. Interception of this iminium ion by ethyl acetoacetate produces open-chain ureide, which subsequently cyclises to the dihydropyrimidine (Scheme 14).[81]

3.2. Variations of the Traditional Biginelli Condensation

The traditional Biginelli one-pot procedure, in its simplest form, is catalysed by mineral acids, typically hydrochloric acid. In spite of its high simplicity, this method suffers from long reaction times and low to moderate yields (20−60%) especially with aliphatic and some substituted aromatic aldehydes. Some other protic acid promoters, such as *p*-toluenesulfonic acid,[82] potassium hydrogen sulfate[83] or reusable silica sulfuric acid,[84] have been used in order to overcome these drawbacks. Moreover, the elucidation of the mechanism has prompted renewed interest in improving the efficiency of this process, and so a large variety of reaction conditions have been investigated, with the aim of increasing the yield by favouring the formation and interception of iminium ion intermediates. In this context, several improved procedures have recently been reported, including the use of various Lewis acids such as BF_3-OEt_2,[85] lithium salts,[86−88] transition metal complexes,[89−95] zinc chloride[96] or cadmium chloride,[97] bismuth[98,99] and indium[100,101] derivatives, or lanthanide compounds.[102−105] Iodotrimethylsilane[106] and trimethylsilyl triflate,[107] and also polyphosphate ester (PPE)[108] or reusable polyaniline-



Scheme 14



Scheme 15

bismoclite complex[109] have also been reported to catalyse the Biginelli condensation.

Significant rate and yield enhancements were also reported for Biginelli reactions carried out under microwave irradiation conditions, either in combination with PPE[110] or not.[111] Under these solvent-free conditions, large amount of products can be obtained in short reaction times, and with at least > 95% purity by a simple aqueous workup procedure (Scheme 15).

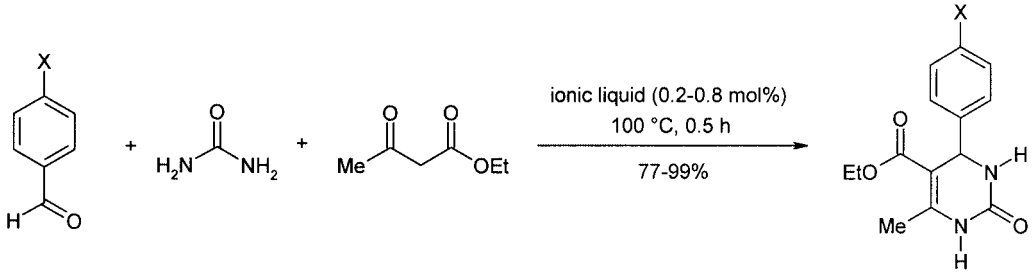
In addition, various solvent-free procedures have been reported to be efficient alternatives to the classical Biginelli condensation. Thus, montmorillonite KSF clay has been used as a solid acid catalyst for this transformation.[112] Furthermore, a combination of KSF clay and microwave irradiation gave a faster and higher-yielding one-pot synthesis of dihydropyrimidinones.[113] These compounds can also be synthesised in high yields in the presence of catalytic amounts of room temperature ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) or hexafluorophosphate ($BMImPF_6$)[114] (Scheme 16).

Finally, it has recently been reported that not only trialkylammonium halides,[115] but also the very inexpensive and easily available ammonium chloride,[116] efficiently catalyse the three-component Biginelli condensation under neutral and solvent-free conditions.

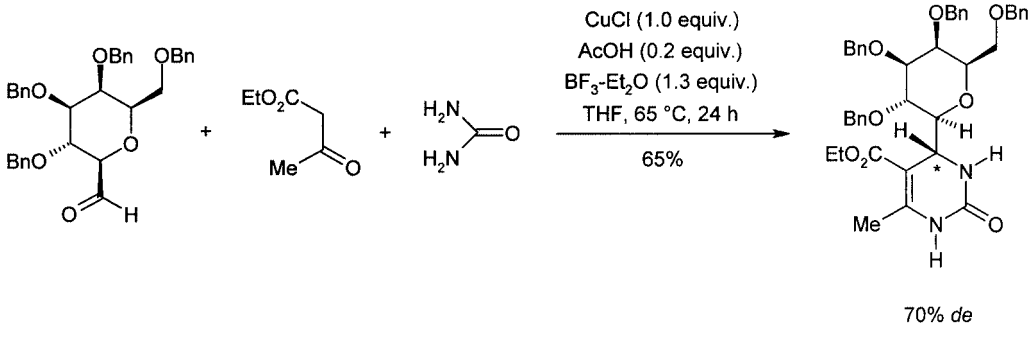
In order to exploit its synthetic potential, the original cyclocondensation has been extended widely to include variations in all three components. Meldrum's acid and barbituric acid derivatives,[117] or benzocyclic ketones and substituted α-keto acids[118] have been used as alternative substrates, for example, while substituted ureas proved able to replace the urea component,[119] affording some novel drug-like dihydropyrimidinone scaffolds in good to excellent yields. The aldehyde component has been widely varied, including not only many aromatic, but also aliphatic and heterocyclic aldehydes. Of these, cyclic hemiaminals furnished high yields of DHPMs when acetonitrile/trifluoroacetic acid was used as a reaction medium.[120] Also of particular interest are reactions in which the aldehyde is derived from a carbohydrate, affording access to *C*-glycosylated dihydropyrimidinones (Scheme 17). Although the Biginelli reaction has mostly been carried out in its achiral version, its noteworthy that in this case a satisfactory asymmetric induction was observed, affording chiral products with given configurations at the C-4 stereocenter of the DMPH ring.[121]

3.3. Adaptations of the Biginelli Condensation to Solid-Support Techniques

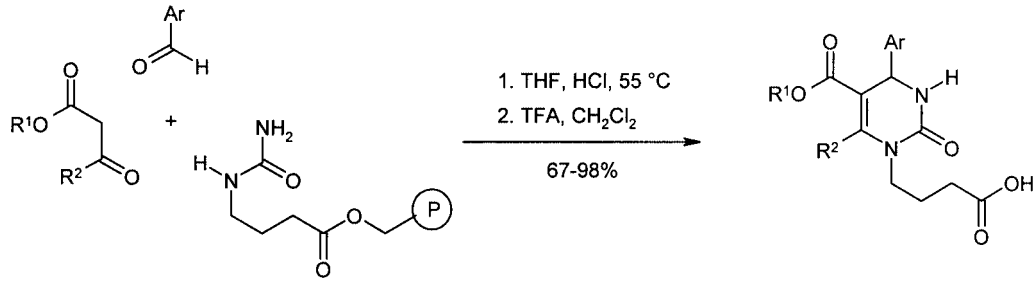
Since a large number of substrates for the Biginelli condensation are commercially available, this simple one-pot multicomponent reaction is particularly useful for the creation of DHPM libraries, and so some combinatorial approaches involving this sequence have been described in the literature. Fréchet and co-workers reported on the generation of a 140-member single-compound DHPM library through the combination of 25 aldehydes, 6 ureas/thioureas, and 7 acetoacetates or acetamides under standard reaction conditions (EtOH/HCl).[122] In 1995, Wipf and Cunningham were the first to report on the adaptation of this reaction to solid-phase techniques.[123] Their approach consisted of the fixation of a γ-aminobutyric acid-derived urea on Wang resin, followed by condensation with excesses of β-keto esters and aldehydes in the presence of a catalytic amount of HCl. Subsequent cleavage of the product by 50% trifluoroacetic acid provided DHPMs in high yields and excellent purities (Scheme 18).



Scheme 16



Scheme 17



Scheme 18

An adaptation of this sequence to fluorous-phase conditions was also published by the same group.[124] Although both of these approaches are efficient for the preparation of DHPM libraries, they invariably afford *N*-1-functionalised products, which are of limited biological interest. Kappe and co-workers therefore developed an alternative approach, in which the acetoacetate building block is linked to the solid support, allowing access to pharmacologically active *N*-1-unsubstituted DHPMs in high overall yields (Scheme 19).[125]

4. MCRs Based on the Mannich Reaction

4.1. The Mannich Reaction

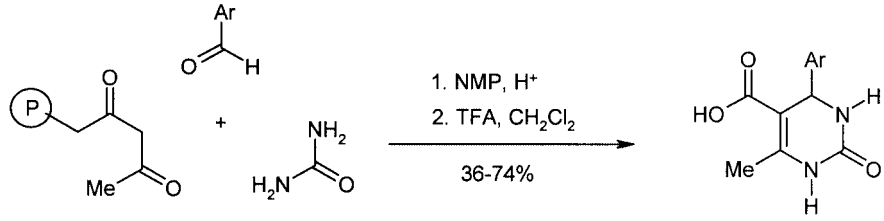
The Mannich sequence[126] is a three-component reaction involving the addition of resonance-stabilised carbon nucleophiles to iminium salts and imines. In its original form, a nonenolisable aldehyde, usually formaldehyde, is condensed with ammonia (or a primary or a secondary amine) and a compound containing an active hydrogen atom (Scheme 20). In the product, known as a "Mannich base", the active hydrogen is replaced by an aminomethyl group.

The Mannich reaction is of great use for the construction of nitrogen-containing molecules, and numerous variants have been published, including the use of aromatic amines,[127] preformed enolate equivalents or preformed iminium salts and imines.[128,129] A direct and highly enantioselective proline-catalysed version of this reaction was also recently reported.[130] Introduction of 1,3-dicarbonyl systems into the reaction in combination with two equivalents of aldehyde allowed domino sequences based on double Mannich condensation (i.e. inter- and intramolecular condensations). This reaction thus offers a wide range of applications in the preparation of azacyclic products, especially bicyclic systems with nitrogen as the bridging atom, resulting in numerous synthesis of natural products, mainly alkaloids. Because of their pioneering work in this field, the synthesis of tropinone by the Robinson−Schöpf methodology is regarded as a classic example.

4.2. The Robinson−Schöpf Reaction and its Variants

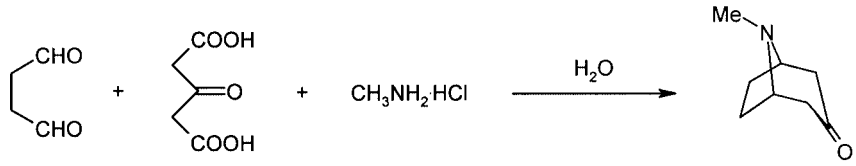
In 1917, Robinson described the synthesis of tropinone through a double Mannich condensation involving succinaldehyde, methylamine and acetone.[131] In 1937, Schöpf improved this reaction by replacing acetone by 1,3-acetonedicarboxylic acid or its diester derivatives.[132,133] It was thus shown that the reaction can be run under biogenetic-like conditions (i.e. the α,-dialdehyde undergoes a decarboxylative double Mannich condensation with methylamine hydrochloride and acetonedicarboxylic acid to furnish the expected azabicyclo[3.2.1]octanone; Scheme 21).

Later, Paquette and Heimaster studied a variant of this reaction and published an efficient synthesis of tricyclic amino ketones through the introduction of a cyclic 1,3-dialdehyde into the classical sequence.[134] More recently, some studies of the reactivity of tropinone derivatives, prepared by the Robinson−Schöpf methodology, were also reported.[135,136]

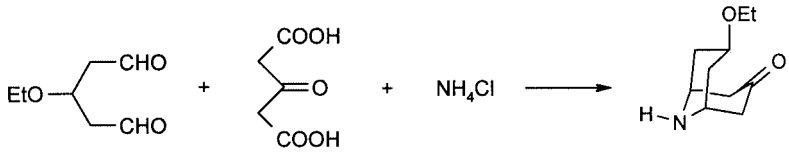


Scheme 19

Scheme 20



Scheme 21



Scheme 22

Similarly, cyclocondensation with functionalised 1,3-dialdehydes such as β-ethoxyglutaraldehyde in the presence of ammonium chloride afforded the corresponding 9-azabicyclo[3.3.1]nonanones in good yields (Scheme 22).[137]

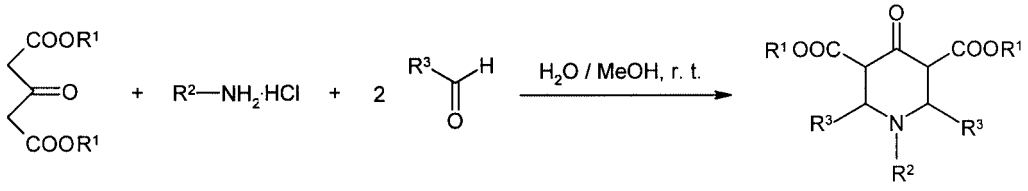
4.3. Other MCRs Based on the Double Mannich Condensation

Numerous other azacycles are accessible through double Mannich condensation. As early as 1934, Mannich described the synthesis of piperidones by condensation of a salt of an aliphatic primary amine, 1,3-dimethyl acetonedicarboxylate and two equivalents of an aliphatic aldehyde in protic solvent and at room temperature.[126] Two years later, he developed the same reaction with formaldehyde (Scheme 23).[138]

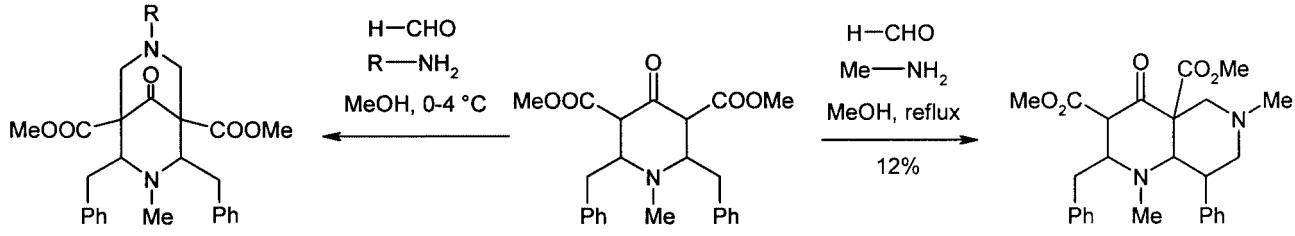
Piperidones can in turn be involved in a double Mannich condensation with formaldehyde and methylamine, allowing efficient access, depending on the reaction conditions, either to diazabicyclo[3.3.1]nonanones,[139] sometimes called bispidines, or to unexpected 1,6-naphthyridine derivatives (Scheme 24).[140]

However, *N*,*N*′-diarylbispidinone derivatives cannot be obtained directly from aromatic amines in this way. To overcome this drawback, Gogoll and co-workers developed a condensation of dimethylacetone dicarboxylate with formaldehyde and trimeric methyleneaniline, in methanol at room temperature, representing a direct synthesis of a bispidine derivative from an aromatic amine (Scheme 25).[141]

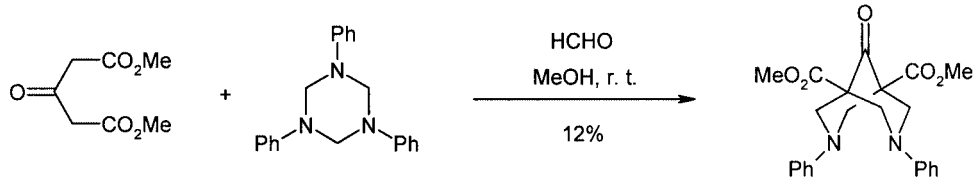
Finally, applications of this sequence to cyclic substrates such as 1,3,5-tricarbonyl[142–144] derivatives, β-keto es-



Scheme 23



Scheme 24



Scheme 25

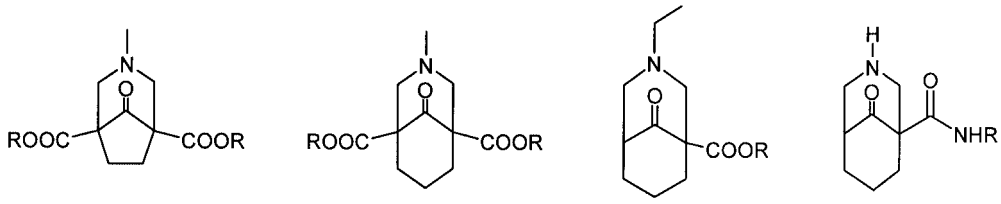


Figure 2. Examples of azabicyclo[3.3.1]nonanones prepared by MCRs

ters[145] or β-keto amides[146] allowed access to azabicyclo[3.2.1]octanones or azabicyclo[3.3.1]nonanones (Figure 2).[147]

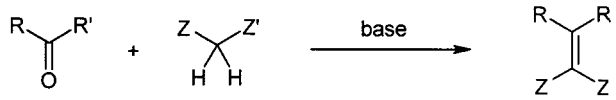
In 1962, Hohenlohe-Oehringen reported a novel three-component synthesis of piperidone by a combination of the Mannich condensation and the Michael addition with use of a γ-unsaturated β-keto ester as starting material.[148] As shown in Scheme 26, mixing of phenylacetaldehyde, ethyl acryloyl acetate and methylamine in absolute ethanol directly gave 2-benzyl-3-ethoxycarbonyl-1-methyl-4-piperidone. This sequence was particularly useful for the synthesis of labelled neuroleptic butyrophenones.[149]

Alternatively, α,β-unsaturated carbonyl compounds can also be used in the Mannich sequence in combination with 1,3-dicarbonyls. Thus, Cravotto and co-workers recently reported that 4-hydrocoumarin reacts with α,β-unsaturated iminium salts derived from enals other than acrolein to give 1,2-addition products.[150] The resulting adducts further evolve through electrocyclisation to afford 2*H*-pyrano[3,2-*c*]coumarins with moderate to good yields (Scheme 27). In addition, α,β-unsaturated iminium salts derived from enones afford substituted 2-hydroxy-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]coumarins by intramolecular cyclisation of the Michael adduct.

5. MCRs Based on the Knoevenagel Reaction

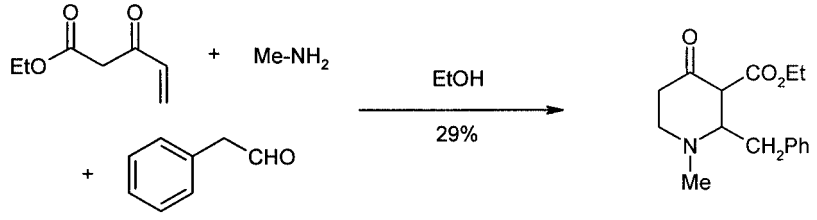
5.1. The Knoevenagel Reaction

The Knoevenagel reaction consists of the condensation of aldehydes and ketones with active methylene compounds in the presence of a weak base (e.g., ammonia, primary, secondary or tertiary amine) to give alkylidene- or benzylidene-dicarbonyls or analogous compounds (Scheme 28).[151]

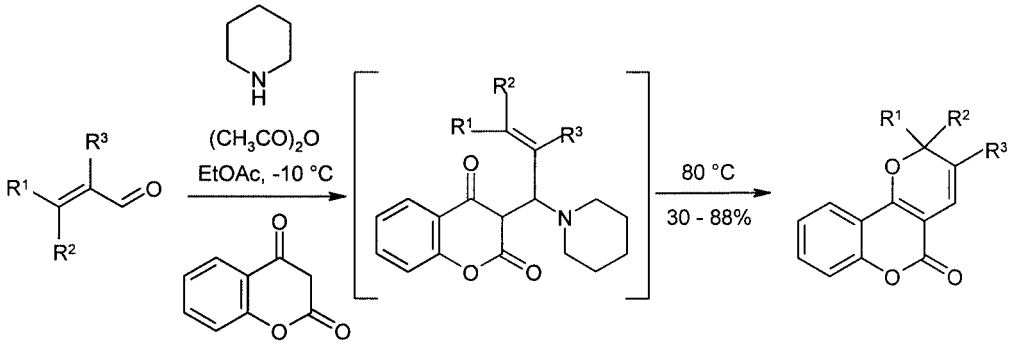


Scheme 28

Although the reaction can be performed with a large variety of compounds possessing activated methylene groups, those bearing two electron-withdrawing substituents are usually employed. Among them, cyclic and acyclic 1,3-dicarbonyl derivatives are particularly common substrates. Thus, not only substances such as malonates, acetoacetates and acetylacetone, but also cyclic compounds such as 1,3-



Scheme 26



Scheme 27

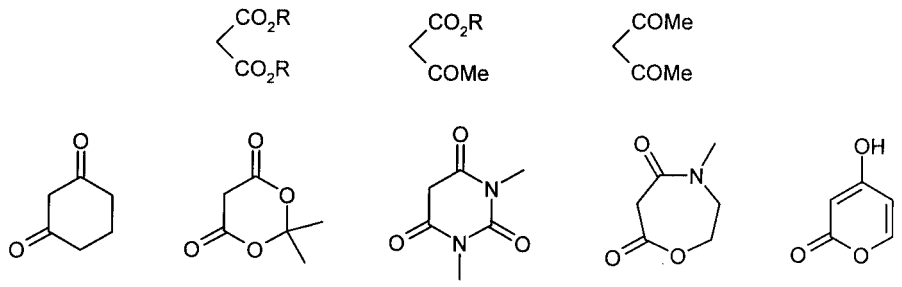


Figure 3. Common cyclic and acyclic substrates for the Knoevenagel reaction

cyclohexanediones, Meldrum's acid, barbituric acids, oxazepanediones and 4-hydroxycoumarins are frequently employed (Figure 3).

Thanks to its mild reaction conditions, its simplicity and the low coast of the substrates, the Knoevenagel reaction is a synthetic method with a broad scope. Moreover, Knoevenagel products are highly reactive compounds because of their low-energy LUMOs, so this sequence has been used in one-pot combination with other classical synthetic reactions, resulting in some very efficient multicomponent sequences. Among them, the domino-Knoevenagel hetero-Diels–Alder reaction, introduced by Tietze, is probably one of the more documented.

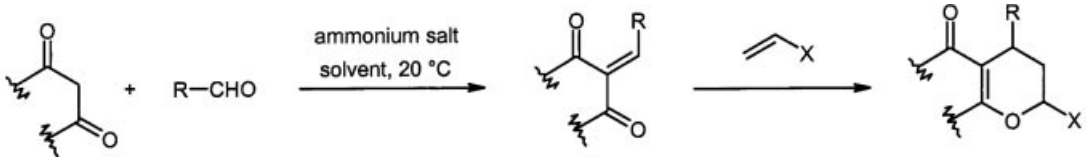
5.2. The Domino-Knoevenagel Hetero-Diels–Alder Reaction

In the domino-Knoevenagel hetero-Diels–Alder reaction,[9,152–154] a highly reactive alkene moiety is first formed in situ through a Knoevenagel condensation between an aldehyde and a cyclic or acyclic 1,3-dicarbonyl compound. In the subsequent step, the resulting 1-oxa-1,3-butadiene can undergo a cycloaddition with a dienophile such as an enol ether or an enamine to afford functionalised dihydropyrans (Scheme 29). In this sequence, ammonium salts are used as mild catalysts at room temperature in a wide range of solvents.

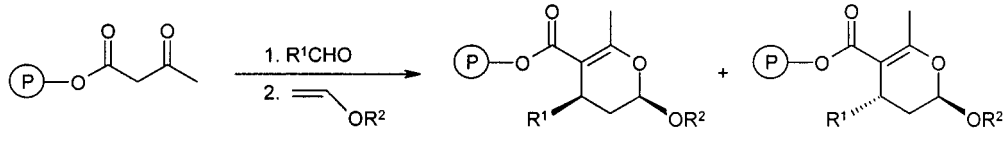
The reaction can be performed as a "two-component reaction", by putting a 1,3-dicarbonyl derivative and an aldehyde containing a dienophile moiety together, or as a "three-component reaction" through the use of a mixture of a 1,3-dicarbonyl derivative, an aldehyde and a dienophile. The cycloaddition in the first reaction is intramolecular, and in the second case intermolecular. Although the "two-component reaction" has been the subject of a large number of publications,[9][153] particularly because of its high level of stereoselectivity, we only focus in this review on its multicomponent version.

For the domino-Knoevenagel hetero-Diels–Alder reaction in its intermolecular three-component version, there are almost no limitations concerning the natures of the aldehyde, the 1,3-dicarbonyl compound and the enol ether. As a catalyst, the neutral ammonium salt ethylenediammonium diacetate (EDDA) or piperidinium acetate are commonly used. The yields are as high as in the "two-component reaction", although the selectivity decreases and mixtures of *cis* and *trans* adducts are obtained. The Knoevenagel condensation and the subsequent cycloaddition usually take place at ambient temperature. They can also be promoted by Lewis acids, allowing the domino sequence to proceed at lower temperatures. Enantiomerically pure products can also be obtained through the use of enantiomerically pure aldehydes[155] or 1,3-dicarbonyl compounds,[156] or in the presence of chiral Lewis acids.[157] For all these reasons, the range of applications of this sequence is very large, especially in the field of natural product synthesis.

Moreover, the domino-Knoevenagel-hetero-Diels–Alder condensation has been adapted to solid phase synthesis by Tietze's group, allowing the generation of combinatorial libraries. Thus, the reaction can be carried out on a modified Merrifield resin to give substituted 3,4-dihydropyrans (Scheme 30).[158] The polymer-bound acetoacetate reacts with different aldehydes to provide the Knoevenagel prod-



Scheme 29



Scheme 30

ucts, which undergo hetero-Diels−Alder reactions with a variety of enol ethers. Cleavage from the solid support is achieved by base-induced transesterification to give the expected substituted methyl 3,4-dihydro-2*H*-pyran-5-carboxylates, in low to moderate overall yields, ranging from 12 to 37%, but with excellent purities of about 90%.

5.3. Variants of the Domino-Knoevenagel Hetero-Diels−Alder Reaction

Some variants of the domino-Knoevenagel hetero-Diels−Alder reaction have been developed, further illustrating the high synthetic potential of this sequence. Here we give two recent examples.

To begin with, the total synthesis of (±)-Preethulia Coumarin was achieved by starting from 4-hydroxy-5-methylcoumarin, with a new type of Lewis acid-catalysed three-component domino-Knoevenagel hetero-Diels−Alder reaction as a key step.[159] The sequence employed α-dicarbonyl compounds as electrophilic carbonyl component to generate chromanediones, and vinyl ethers to trap them (Scheme 31). Optimisation of the sequence resulted in the use of activated molecular sieves, and ytterbium triflate as a catalyst. Under these conditions, a total diastereoselectivity was observed during the cycloaddition step.

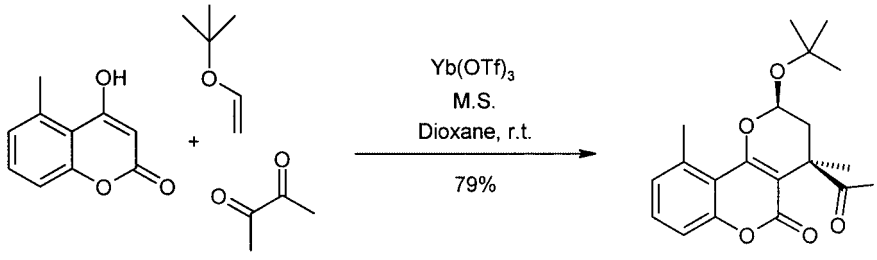
Another modified domino-Knoevenagel hetero-Diels−Alder reaction, involving the use of amino aldehydes as electrophilic carbonyl components, was published at the same time by Tietze and co-workers (Scheme 32).[160] Condensation of a 1,3-dicarbonyl compound with an amino aldehyde and an enol ether, followed by an intramolecular reductive amination, resulted in the formation of betaines, which could be precipitated from the solution in high purity. This sequence illustrated a novel concept in combinatorial chemistry, combining the advantages of reactions in solution with those of solid-phase synthesis.

As a complement to the dienophile character of Knoevenagel adducts, Barbas III and co-workers showed that enamines derived from L-proline and enones act as dienes in a concerted [4+2] cycloaddition with arylidene intermediates derived from 1,3-dicarbonyls. Indeed, they found that L-proline catalysed three-component asymmetric domino-Knoevenagel hetero-Diels−Alder reactions of readily available enones, arylaldehydes and either 1,3-indanediones[161] or Meldrum's acid,[162] affording highly substituted spiro-[cyclohexane-1,2′-indane]-1′,3′,4-triones or spiro[5,5]undecane-1,5,9-triones, respectively. The reaction proceeded in a highly diastereoselective fashion and usually with excellent yields and up to 71% *ee*s (Scheme 33).

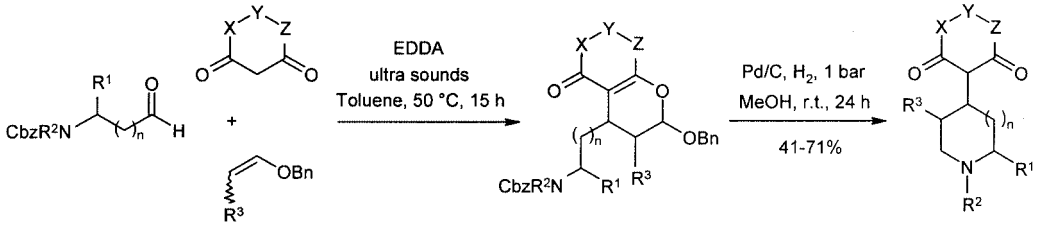
5.4. Combinations of the Knoevenagel Reaction with Michael Addition

So far, we have described synthetic applications in which Knoevenagel products react as heterodienes or dienophiles. Because of their structures, however, they can also be viewed as Michael acceptors, and can react with a variety of nucleophiles. Multicomponent reactions combining Knoevenagel condensation and Michael addition have therefore been developed, and have found interesting applications in organic synthesis.

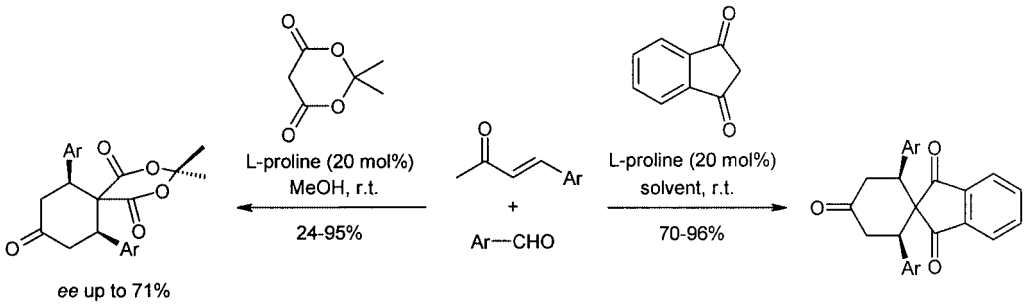
Apart from the 1,3-dicarbonyl itself,[163−166] a variety of nucleophiles have been used in the tandem Knoevenagel condensation/Michael addition. Among them, enamines have been extensively studied. As examples, condensation of indole,[167] or more recently indolin-2-one,[168] with Meldrum's acid and various aldehydes resulted in the one-pot syntheses of ethyl indolylpropionates and of spiro[pyrrolidine-3,3′-indolinones], respectively, in a so-called Yonemitsu condensation. Extending this three-component reaction to 2-substituted indoles, Sati and co-workers recently reported an easy access to functionalised tetrahydrocarbazoles.[169] Finally, a variant of this reaction consisting of the diastereoselective trimolecular condensation of indole, Meldrum's acid and Garner's aldehyde (Scheme 34) was reported



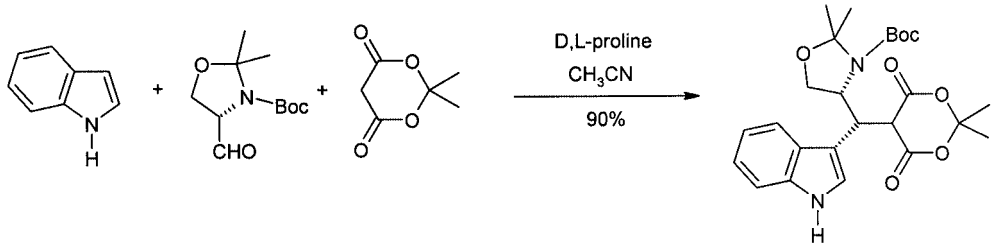
Scheme 31



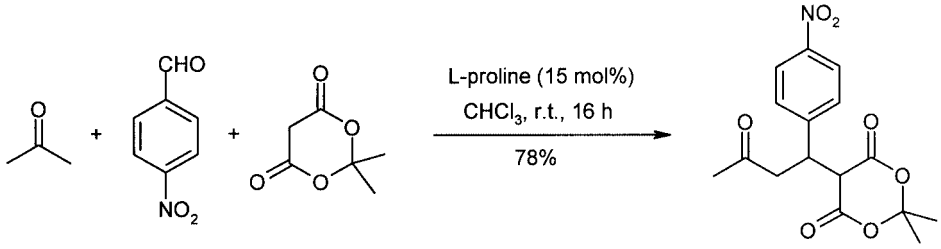
Scheme 32



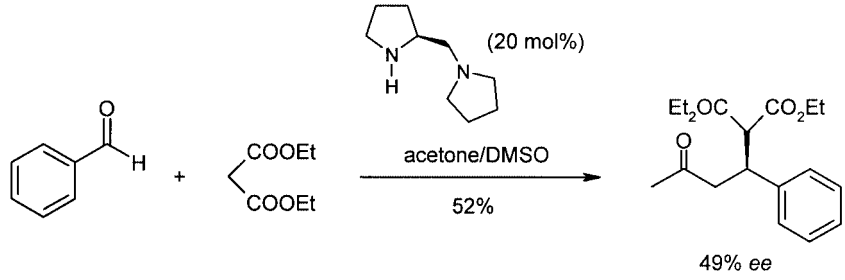
Scheme 33



Scheme 34



Scheme 35



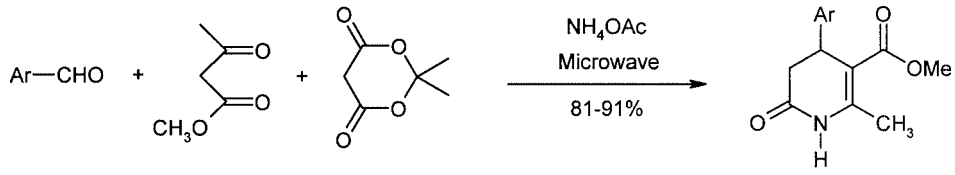
Scheme 36

as a key step in the synthesis of chiral 2′,3′-pyranone(pyrrolidinone)-fused tryptamines.[170]

In 2001, List and Castello reasoned that alkylidene derivatives and enamines should be generatable in situ from ketones, aldehydes and Meldrum's acid by use of a catalytic amount of proline. In this way they developed a novel three-component reaction consisting of a direct catalytic Michael addition of unmodified ketones to α,β-unsaturated carbonyl compounds, avoiding the use of preformed enolate equivalents, but unfortunately without any enantioselectivity (Scheme 35).[171,172]

At the same time, Barbas and co-workers reported an enantioselective version of this reaction using (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine as the catalyst.[173] Thus, Michael adducts with up to 91% *ee*s were obtained by treatment of alkylidene malonates with simple unactivated ketones under mild conditions. In the multicomponent variant of this sequence, one-pot treatment of benzaldehyde with diethyl malonate in an acetone/DMSO mixture, in the presence of 20 mol % of the chiral amine, resulted in the formation of the desired keto ester in 52% yield and with 49% *ee* (Scheme 36).

Another example of the use of enamines as nucleophiles in the tandem Knoevenagel condensation/Michael addition involving a four-component reaction was recently reported. 4-Aryl-substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydro-



Scheme 37

pyridones were prepared in one-pot condensations from Meldrum's acid, methyl acetoacetate and the appropriate benzaldehyde in the presence of ammonium acetate as the ammonia under microwave irradiation conditions in the absence of solvent (Scheme 37).[174]

In this example, resembling the Hantzsch dihydropyrimidine synthesis, the reaction consists of several successive steps with prior formation of two intermediates: the compound resulting from Knoevenagel condensation between Meldrum's acid and benzaldehyde and the enamino ester produced from acetoacetate and ammonia. The key step of the overall reaction is the Michael-type addition of the enamino ester to the Knoevenagel product, followed by decarboxylative cleavage of the Meldrum's acid nucleus. A similar reaction with dimedone and utilisation of ionic liquids as catalysts under solvent-free conditions, affording polyhydroquinoline derivatives in high yields, was developed very recently.[175]

More simply, Iqbal and co-workers have described a novel one-pot, four-component synthesis of β-acetamido ketones through a cobalt-catalysed coupling of aldehydes in acetonitrile, with the nucleophile role played by 1,3-diketones or β-keto esters (Scheme 38).[176] Heating of a mixture of enolisable ketone, aldehyde and acetyl chloride in acetonitrile for 8−12 h in the presence of a catalytic quantity of dry cobalt(II) chloride, followed by basic aqueous workup, allowed a series of β-acetamido ketones to be prepared in moderate to good yields.

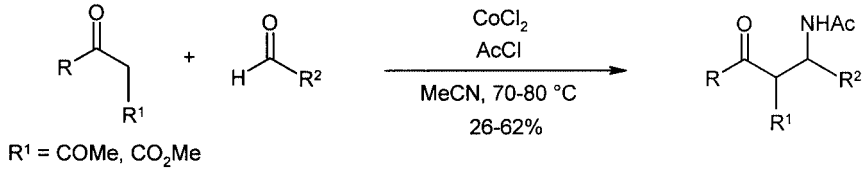
The versatility of this multiple component condensation was demonstrated by the preparation of a library.[177] However, the transformation is influenced by the presence of molecular oxygen, which causes the formation of α,β-unsaturated carbonyl compounds (Knoevenagel products) along with the expected β-acetamido ketones. Formation of these by-products could be suppressed by working under nitrogen atmosphere.[178] More recently, a development of this reaction by a combinatorial approach resulting in a general synthesis of β-amino acid derivatives through the application of a polymer-supported cobalt-catalysed three-component coupling procedure was reported.[179] Iqbal and co-workers also recently showed that the reaction could be conducted at room temperature over 5 days, which constitutes a distinct improvement over the previous method in terms of enhanced yields and easy workup procedure.[180]

Finally, it has also been reported that phenol derivatives can be used as nucleophiles in the tandem Knoevenagel condensation/Michael addition. In this way, the methylene derivatives resulting from the reactions between aldehydes and Meldrum's acid have been intercepted with phloroglucinol, offering a convenient route to certain dihydrocoumarins (Scheme 39).[181]

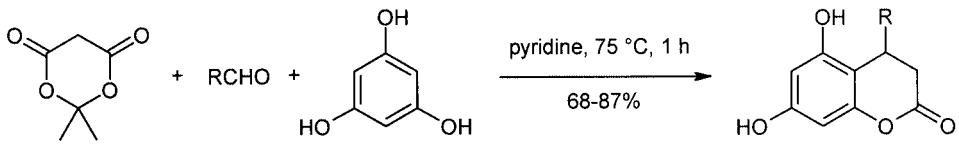
6. MCRs Based on Michael Addition

As illustrated in the preceding paragraphs, MCRs involving 1,3-dicarbonyl compounds and based on Mannich or Knoevenagel condensations are numerous and well documented in the literature. In contrast, only a few examples of MCRs involving such substrates and based on the Michael addition as starting point have been reported so far.

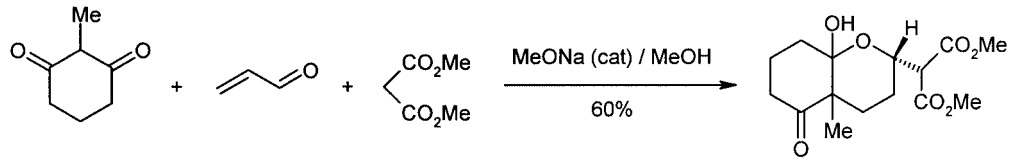
To begin with, in 1979 Eschenmoser and co-workers described a fragmentational approach to macrolides, starting from substrates accessible through a spectacular three-component condensation of acrolein, 2-methyl-1,3-cyclohexanedione and dimethyl malonate (Scheme 40).[182] The Michael addition of 2-methyl-1,3-cyclohexanedione to acrolein in methanol was catalysed by sodium methoxide, and the resulting adduct was condensed with dimethyl malonate in a



Scheme 38



Scheme 39



Scheme 40

one-pot reaction. A crystalline bicyclic keto hemiacetal diester was produced in 60% yield as a single diastereomer containing three stereogenic centres, in which the stereochemistry of the ring junction has not yet been clearly elucidated.

After these pioneering results, MCRs initiated by Michael additions remained unexplored for over 20 years. As part of our continuing efforts directed towards the development of new domino transformations initiated by Michael additions,[11,18,184] three years ago[185] we developed the first multicomponent domino reaction between 1,3-dicarbonyl derivatives, α,β-unsaturated aldehydes or ketones, and primary amines, providing a one-pot route to polyheterocyclic compounds of biological and pharmaceutical interest. Products are generally obtained with good purity simply by heating a mixture of the three components at reflux in toluene in the presence of 4-Å molecular sieves, followed by simple filtration through a short pad of celite.

The structures of the products obtained through this sequence strongly depend on the nature of the amine. Therefore, by using ω-functionalised primary amines, we were able to prepare fused polyheterocyclic or spiro-type polyheterocyclic compounds bearing aminal functions (Scheme 41).

As illustrated in Figure 4, a large variety of polyheterocycles have been synthesised, starting from functionalised primary amines including aliphatic α,ω-diamines, amino-alcohols, amino-thiols or aromatic diamines. Various substrates such as (ethoxycarbonyl)piperidone, cyclic β-keto esters or 1,3-diketones can be used in this sequence.

When *o*-hydroxyaniline was used as primary amine, a spiro-type tetracyclic compound was obtained (Figure 5). In the particular case of the use of an aminodiol, the one-pot sequence resulted in the formation of up to three new cycles, five novel bonds and up to six stereogenic centres.

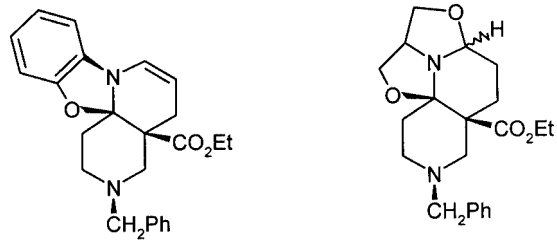
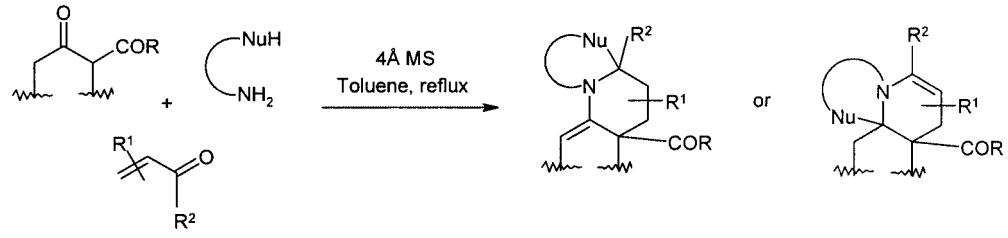


Figure 5. Spiro-type tetracyclic compounds obtained by a michael addition based MCR

Alternatively, the introduction of various unfunctionalised primary amines into this three-component domino reaction resulted in the formation of other families of polyheterocycles. The reaction between commercially avail-



Scheme 41

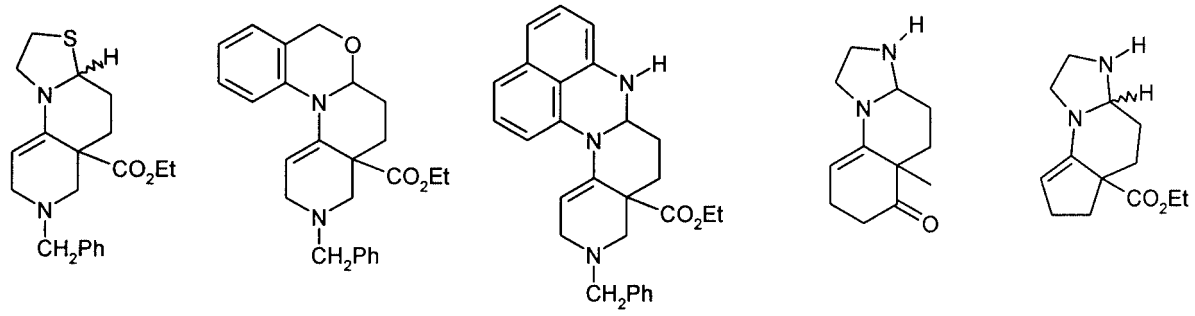
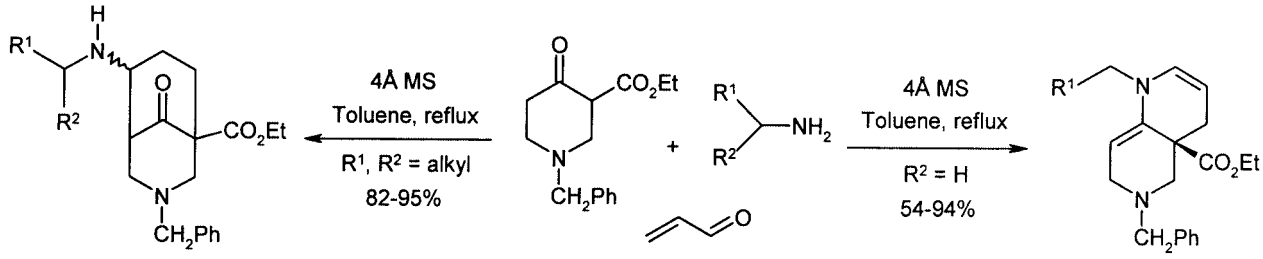


Figure 4. Large variety of polyheterocycles obtained by a Michael addition based MCR



Scheme 42

able (ethoxycarbonyl)piperidone, acrolein and a primary amine in toluene at reflux and in the presence of 4-Å molecular sieves therefore resulted in the formation either of 1,6-hydronaphthyridines or of amino azabicyclo[3.3.1]nonanones, depending on the substitution of the amines (Scheme 42).[186]

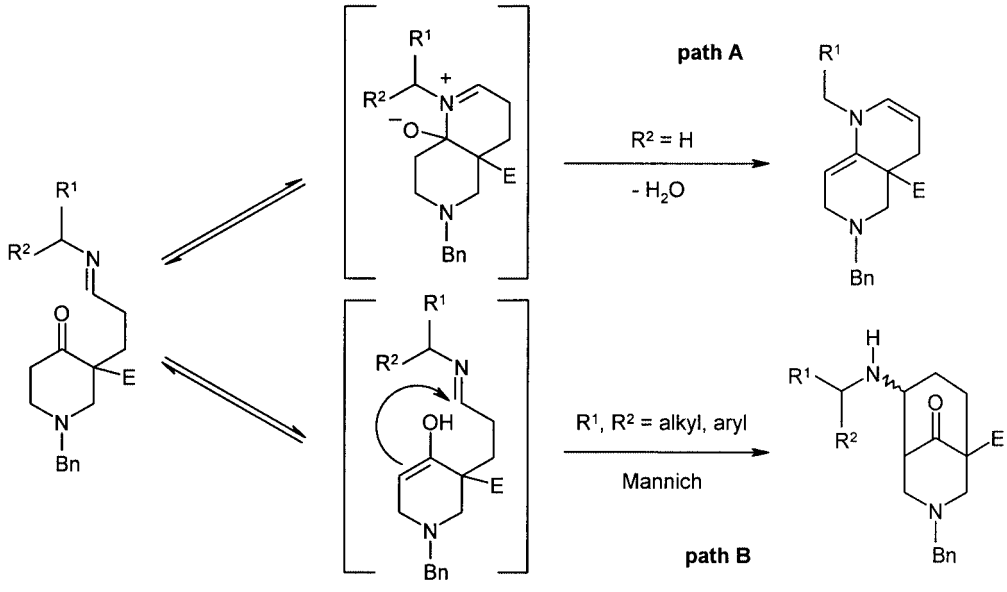
From a mechanistic point of view, we have shown[185,187] that the first step of the reaction consists of a molecular sieves-initiated Michael addition of the β-keto ester to acrolein to give the corresponding adduct, which reacts chemoselectively with the primary amine to form an aldimine. Then, depending on the substitution of the amine,[188] subsequent reversible nucleophilic addition of the aldimine to the ketone, providing an iminium intermediate, may be observed. In the case of unfunctionalised primary amines, when R^2 is H, dehydration occurs on the iminium, giving access to the 1,6-hydronaphthyridines (Scheme 43, path A). Alternatively, when R^1 and R^2 are alkyl or aryl groups, steric interactions disfavour the formation of the iminium, and the intramolecular Mannich reaction then takes place to afford the amino azabicyclo[3.3.1]nonanones (Scheme 43, path B).

In the case of nucleophilic functionalised amines, the two possible iminium intermediates can be trapped by the nucleophilic function, resulting in the formation of fused or spiro-type polyheterocycles bearing aminal functions (Scheme 44).

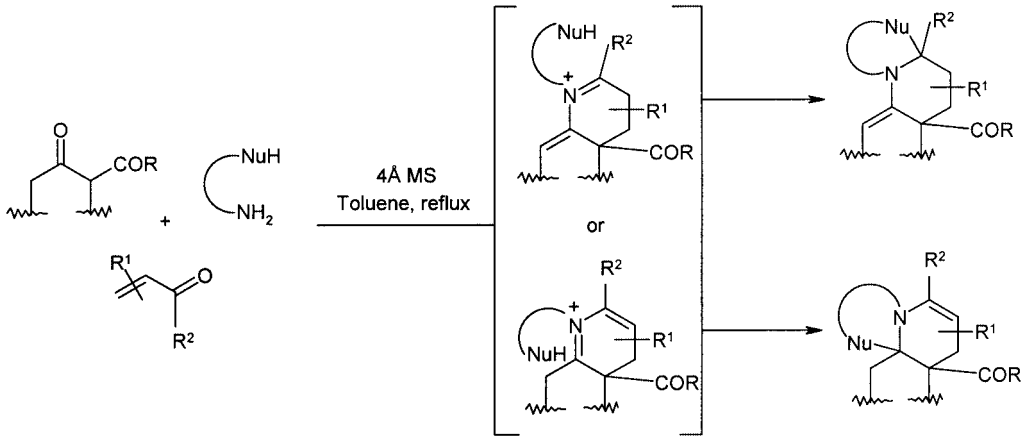
At the same time, some other developments of Michael addition-initiated MCRs were reported in the literature. In 2002, for example, a series of substituted 5-oxo-octahydroquinoline derivatives was prepared in high yields from dimedone and 1,3-diaryl-2-propen-1-one in DMF at 80 °C in the presence of ammonium acetate (Scheme 45).[189] After the Michael addition, the resulting 1,5-dicarbonyl adduct was cyclodehydrated with ammonium acetate as ammonia source.

Finally, since Michael additions between 1,3-dicarbonyl compounds and α,β-unsaturated aldehydes or ketones may be viewed as C-alkylations of the corresponding enolates, we envisaged replacement of the α,β-unsaturated acceptor by an alkyl halide. In this context, we recently described a new multicomponent transformation involving 1,3-dicarbonyls, aldehydes and allylic, propargylic or benzylic halides, providing a regio-, chemo- and stereoselective one-pot route to α,γ-difunctionalised α-keto esters and amides of high synthetic value (Scheme 46).[190]

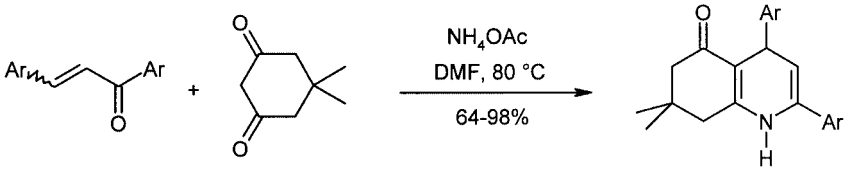
The overall sequence takes place under mild conditions, probably through a reversible α-aldolisation, and constitutes a convenient approach for the facile one-pot construction of elaborated cycloalkanones containing quaternary



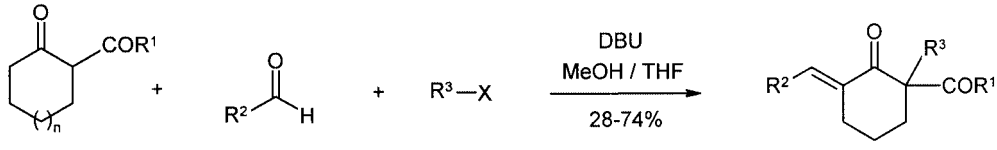
Scheme 43



Scheme 44



Scheme 45



Scheme 46

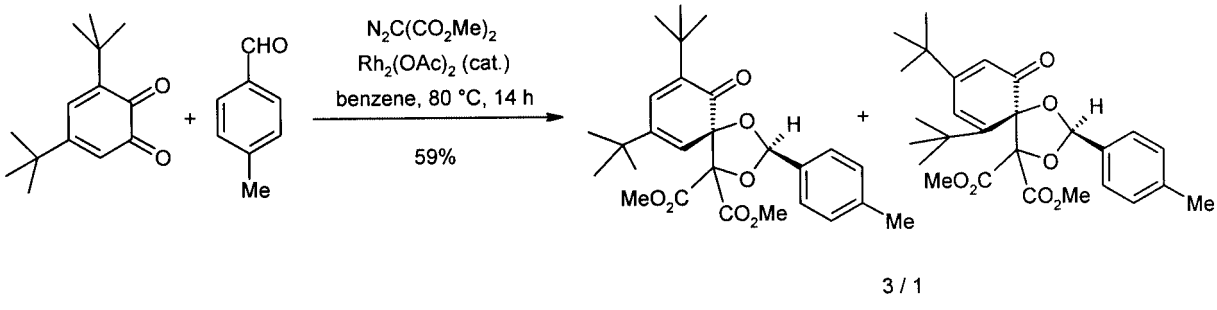
centres, valuable for further synthetic transformations by ring-closing metathesis to give azaspiro systems found in bioactive natural products.

7. Miscellaneous

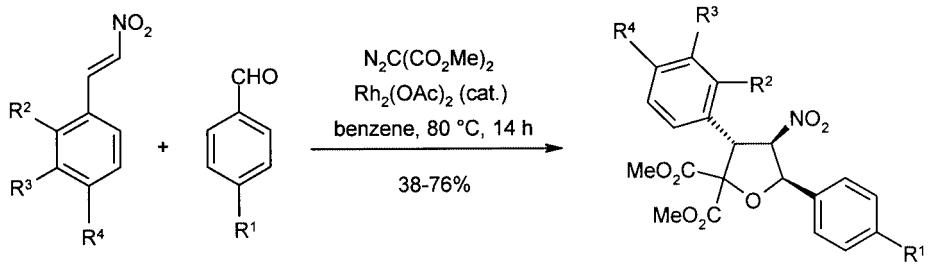
Other MCRs involving 1,3-dicarbonyls or their synthetic equivalents have received more and more attention in the last few years. Some of the more recent examples in this field are reported in the following sections.

7.1. Metal-Catalysed MCRs Involving 1,3-Dicarbonyl Derivatives

In 2003, Nair and co-workers published the synthesis of novel spiro-dioxolanes through a facile three-component, rhodium-catalysed reaction of bis(methoxycarbonyl)carbene, aldehydes and *o*-quinones.[191] Rh^{II}-catalysed decomposition of dimethyl diazomalonate in the presence of *p*-tolualdehyde and 3,5-di-*tert*-butyl-1,2-benzoquinone, for example, afforded a 3:1 regioisomeric mixture of dioxolanes (Scheme 47).



Scheme 47



Scheme 48

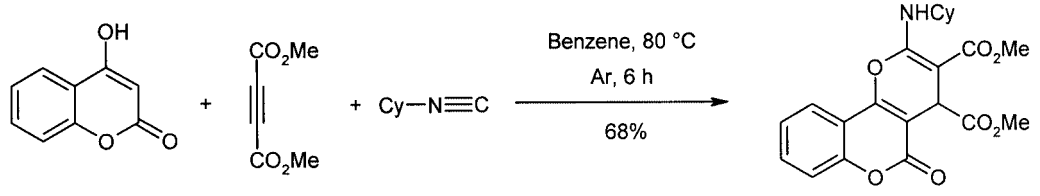
This multicomponent reaction probably involves the formation of a carbonyl ylide through the reaction between a carbene and the aldehyde and its trapping by the quinone carbonyl. The reaction was found to be general with respect to a variety of aromatic aldehydes and 1,2-benzoquinone. This sequence has more recently been developed with β-nitrostyrenes, providing highly substituted tetrahydrofuran derivatives (Scheme 48).[192]

7.2. MCRs Involving 1,3-Dicarbonyls in Combination with Isocyanide Derivatives

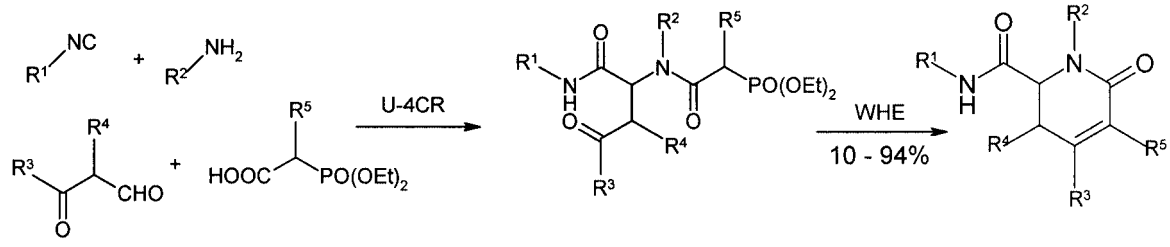
In 2002, Nair and co-workers reported a novel approach to pyran-annulated heterocyclic systems, through an efficient multicomponent reaction involving the interception of the zwitterionic intermediates formed between dimethyl acetylenedicarboxylate and isocyanides with some active methylene compounds.[193] As an illustration, treatment of 4-hydroxycoumarin with dimethyl acetylenedicarboxylate and a stoichiometric amount of cyclohexyl cyanide at reflux in benzene afforded the corresponding product in 68% yield (Scheme 49).

In a very recent publication, Dömling and co-workers demonstrated that isocyanides, primary amines, β-keto aldehydes and phosphonoacetic acids react smoothly at ambient temperature in methanol to afford the corresponding Ugi products (Scheme 50).[194] A subsequent Wittig ring-closing reaction, in its Horner/Wadsworth/Emmons variant, afforded highly substituted pyridones in low to excellent yields.

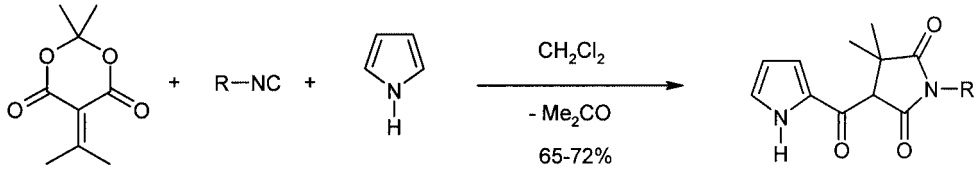
Contemporaneously, Yavari and Habibi reported a three-component synthesis of pyrrolidine-2,5-diones involving a 1,3-diester derivative as substrate.[195] 5-isopropylidene-substituted Meldrum's acid smoothly underwent reaction with alkyl isocyanides in the presence of pyrrole or indole to give the corresponding products in good yields (Scheme 51).



Scheme 49



Scheme 50



Scheme 51

7.3. MCRs Involving Cyanomalonate Derivatives

In the last few years, cyanomalonate derivatives − which can be regarded as 1,3-dicarbonyl equivalents − have gained considerable attention as useful substrates in multicomponent reactions. Most of these sequences are initiated by Knoevenagel condensations between cyanoacetates, cyano ketones or malononitrile and carbonyl compounds. We give some recent examples of these one-pot procedures below.

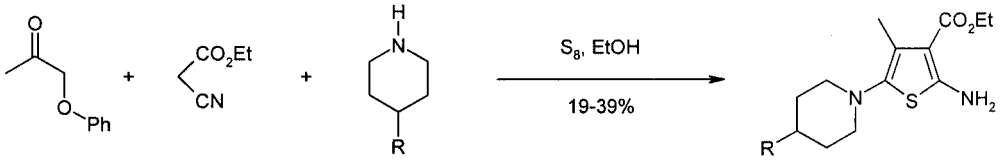
In 1965, Gewald reported a three-component condensation of a β-keto ester, a cyanoacetate and elemental sulfur in the presence of an organic base to yield a thiophene nucleus.[196] This reaction remained unexploited until 1999, when McKibben and Castelhano published an improvement of the reaction conditions for semi-automated synthesis to provide tetrasusbstituted thiophenes.[197] Following this work, Pinto et al. described the four-component preparation of 5-aminothiophenes through an extension of Gewald's reaction (Scheme 52).[198] Condensations of ethyl cyanoacetate, phenoxyacetone, elemental sulfur and various cyclic secondary amines, for example, provided the corresponding 5-aminothiphenes in moderate yields.

In the case of α-cyano ketones, Quiroga and co-workers described a simple and efficient synthesis of pyrazolopyridines, which are interesting biological targets, through three-component reactions involving aminopyrazoles, benzoylacetonitrile and various aromatic aldehydes (Scheme 53).[199,200] More recently, by replacing aminopyrazoles by aminopyrimidines, they succeeded in the development of a regioselective, facile and practical method for the preparation of novel pyrimidinones.[201] The synthesis was conducted with the aid of microwave irradiation under solvent-free conditions, providing the corresponding products in good yields.

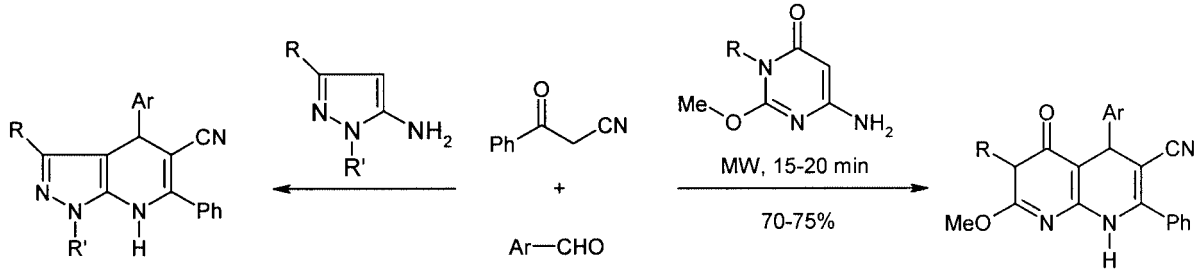
Malononitrile has also been widely exploited; to begin with, Ballini and co-workers in 2001 reported a three-component process for the synthesis of 2-amino-2-chromenes simply by heating a mixture of an aldehyde, malononitrile and a phenol at reflux in water in the presence of a catalytic amount of cetyl(trimethyl)ammonium chloride (Scheme 54).[202] More recently it was shown that tetrabutylammonium bromide[203] or basic alumina[204] could also act as catalysts for this transformation.

The key step in this one-pot sequence involves the *ortho*-*C*-alkylation of the phenol with the electrophilic C=C double bond of the Knoevenagel adduct resulting from the condensation of malononitrile with the aldehyde. A subsequent nucleophilic addition of the phenolic OH group to the CN moiety produces the final 2-amino-2-chromene (Scheme 55).

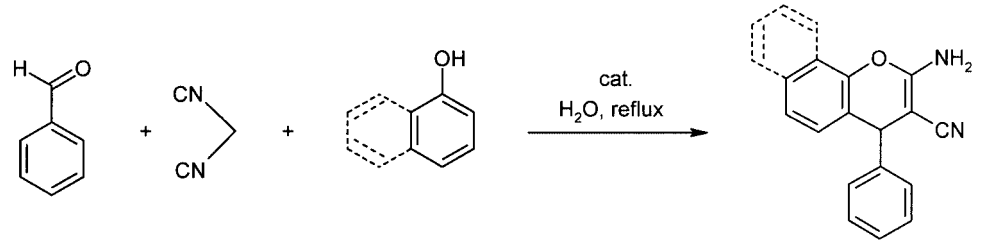
Some other nucleophiles have been introduced in this one-pot sequence, providing simple access to various polyheterocycles (Scheme 56). As one example, microwave-assisted use of barbituric acids under solvent-free conditions



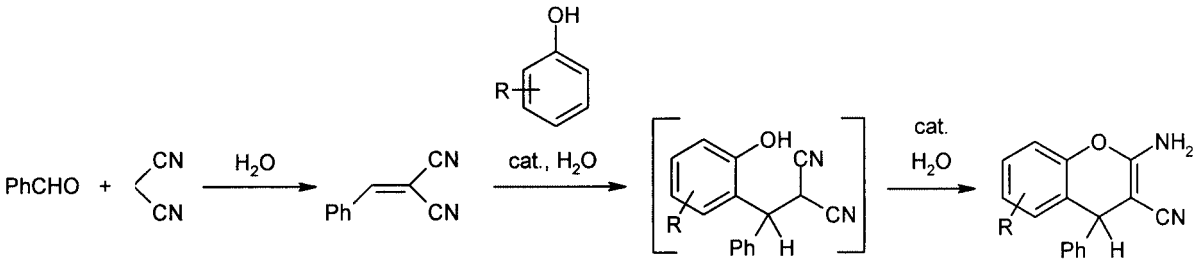
Scheme 52



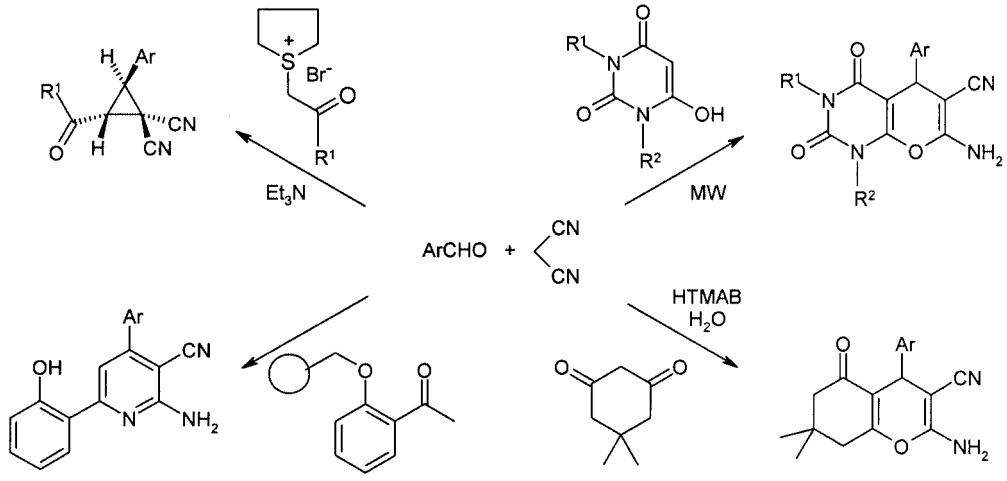
Scheme 53



Scheme 54



Scheme 55



Scheme 56

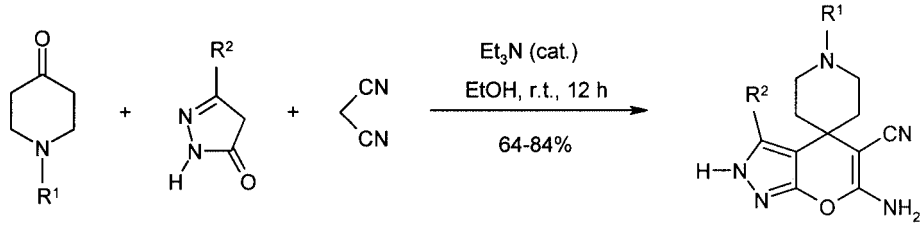
gave pyrano[2,3-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines in excellent yields.[205,206] A clean synthesis of tetrahydrobenzo[*b*]pyran derivatives, with dimedone as nucleophile and hexadecyl(trimethyl)ammonium bromide as catalyst in aqueous media, has also been reported.[207] This transformation was adaptable to solid-phase conditions, as illustrated by the efficient synthesis of 3-cyano-6-(2-hydroxyphenyl)pyridines through condensation of hydroxyacetophenone immobilised on Wang resin with malonitrile and various aldehydes.[208] Finally, the three-component reaction of sulfonium salts, malonitrile and aldehydes in ionic liquid, in the presence of Et_3N, provided a convenient synthesis of substituted 1,1-dicyanocyclopropanes.[209]

In 2002, Evans and co-workers reported a three-component condensation of substituted piperidin-4-one, pyrazol-5-ones and malononitrile in the presence of a catalytic amount of Et_3N, giving highly substituted spiro-pyrazolopyrans in good yields (Scheme 57).[210,211] On replacement of the chemical base by an electrogenerated base, the authors showed that the sequence became more regioselective and the yields ca.12−15% greater than those of the reaction catalysed by chemical bases.

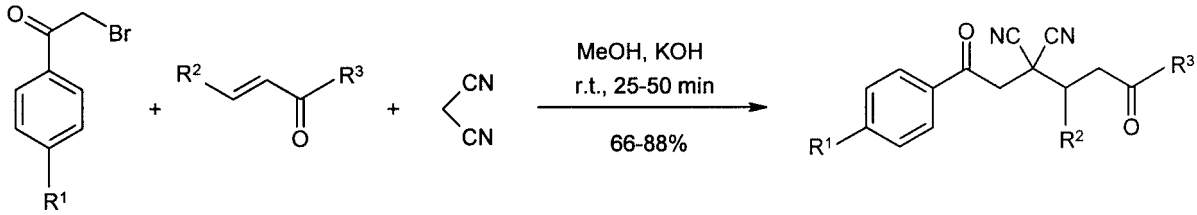
Finally, Boruah and co-workers have recently described the first preparation of 1,6-diketones from α-bromo ketones in a three-component Michael-initiated transformation.[212] Treatment of 2-bromo ketones with malononitrile and α,β-unsaturated keto compounds in the presence of methanolic potassium hydroxide resulted in a facile synthesis of 1,6-diketones (Scheme 58).

8. Conclusion

This critical selection of diverse MCRs developed over more than a century clearly shows that simple 1,3-dicarbonyl derivatives still constitute versatile substrates in organic chemistry and can be accommodated in many diverse synthetic pathways. The high synthetic potential of these very easily accessible reagents has found numerous appli-



Scheme 57



Scheme 58

cations, especially for the synthesis of complex heterocyclic structures found in important natural and unnatural compounds. Future development of new synthetic transformations making use of the high reactivity of 1,3-dicarbonyls towards many other substrates should enlarge the scope of this field, allowing the facile and selective construction of highly functionalised small organic molecules of high synthetic and biological value.

We are currently engaged in efforts to develop new MCRs with 1,3-dicarbonyl systems, especially transformations involving Michael additions and Knoevenagel reactions.[213−215]

Acknowledgments

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