Multicomponent reactions for the synthesis of pyrroles

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Multicomponent reactions are one of the most interesting concepts in modern synthetic chemistry and, as shown in this critical review, they provide an attractive entry into pyrrole derivatives, which are very important heterocycles from many points of view including medicinal and pharmaceutical chemistry and materials science (97 references).

1. Introduction

To set the rest of the article in context, we will make in this section some general remarks about multicomponent reactions and the importance of pyrrole.

1.1 Multicomponent reactions

Present-day requirements for new synthetic methods go far beyond the traditional ones of chemo-, regio- and stereo-selectivity, and can be summarized as follows:

1. Use of simple and readily available starting materials.
2. Experimental simplicity.
3. Possibility of automation.
4. Favourable economic factors, including the cost of raw materials, human resources and energy.

For this reason, the creation of molecular diversity and complexity from simple and readily available substrates is one of the major current challenges of organic synthesis, and hence the development of processes that allow the creation of several bonds in a single operation has become one of its more attractive goals.

Multicomponent reactions (MCRs)1–5 can be defined as convergent chemical processes where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials. Therefore, they lead to the connection of three or more starting materials in a single synthetic operation with high atom economy and bond-forming efficiency, thereby increasing molecular diversity and complexity in a fast and often experimentally simple fashion.6,7 For this reason, multicomponent reactions are particularly well suited for diversity-oriented synthesis,8–10 and the exploratory power arising from their conciseness makes them also very powerful for library synthesis aimed at carrying out structure–activity relationship (SAR) studies of drug-like compounds, which are an essential part of the research performed in pharmaceutical and agrochemical companies.11,12 For all these reasons, the development of new multicomponent reactions is rapidly becoming one of...
the frontiers of organic synthesis. While a large part of the work developed in this field is focused on reactions using isonitriles as one of the starting materials and leading to peptide-like structures, recent years have witnessed a steady growth in the development of MCRs that lead directly to heterocycles, the most important single class of compounds in the development of bioactive substances.

1.2 Importance of pyrrole

Pyrrole is one of the most important simple heterocycles, which is found in a broad range of natural products and drug molecules, and is also of growing relevance in materials science. It was first isolated in 1857 from the products of bone pyrolysis, and identified as biologically relevant when it was recognized as a structural fragment of heme and chlorophyll. The current importance of pyrrole can be summarized in the points that are detailed below.

(a) The pyrrole nucleus is widespread in nature, and, as previously mentioned, is the key structural fragment of heme and chlorophyll, two pigments essential for life. Some representative examples of pyrrole-containing secondary metabolites are summarized in Fig. 1. They include some antibacterial 3-halopyrroles such as pentabromopseudodiline and pioluteorine, both isolated from bacterial sources. Pyrrole moieties are particularly prominent in marine natural products, including dimeric structures such as nakamuric acid and the axially chiral marinopyrroles, which showed good activity against metacillin-resistant Staphylococcus aureus strains. We will finally mention the storniamide family, isolated from a variety of marine organisms (mollusks, ascidians, sponges) and containing 3,4-diarylpyrrole fragments. A number of O-methylated analogues of storniamide A have shown potent activity as inhibitors of the multidrug resistance (MDR) phenomenon, which can be considered as the main obstacle to successful anticancer chemotherapy. For this reason, there is much current interest in the development of new MDR modulators.

(b) One interesting property of natural and unnatural products containing polypyrrole structural fragments is that they are often involved in coordination and molecular recognition phenomena. Besides the classical example of the tetrapyrole nucleus of the porphyrins and hemoglobin, we will also mention the case of the bacterial red pigment prodigiosin, synthesized by bacteria belonging to the Serratia genus, and which has antibiotic properties. This compound has been shown to behave as a transporter of chloride anions and protons across phospholipid membranes thanks to the association of its protonated form with chloride anion, leading to a lipophilic species (Scheme 1). The torsional flexibility associated with polypyrrole systems linked by peptide bonds is also key to molecular recognition phenomena involved in the interaction with DNA of the prototype minor groove natural binders netropsin and distamycin and related drugs.

(c) Besides the above mentioned natural products, pyrrole substructures are present in a large number of bioactive compounds including HIV fusion inhibitors and antitubercular compounds, among many others. As examples of pyrrole derived drugs, we will mention the non-steroidal antiinflammatory compound tolmethin, the anticancer drug candidate tallimustine (related to the previously mentioned natural product distamycin) and the cholesterol-lowering agent atorvastatin, one of the top-selling drugs worldwide (Fig. 2).

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J. Carlos Menéndez was born in Madrid and obtained degrees in Pharmacy and Chemistry, followed by a PhD in Pharmacy from UCM. After a postdoctoral stay at the group of Professor Steven Ley at Imperial College, he returned as a Profesor Titular to the Organic and Medicinal Chemistry Department at UCM, where he has pursued his career ever since. His research interests deal mostly with synthetic work related to the development of new antitumour drugs and ligands of prion protein. Other projects pursued in his group place emphasis on the development of new synthetic methodology, including work on CAN as a catalyst for synthesis and on new domino and multicomponent reactions for the preparation of biologically relevant compounds.
Pyrrole derivatives are versatile synthetic intermediates, and can be transformed into many other heterocyclic systems. As an example, we will mention the transformation of a type of fused pyrroles into chiral indolizidines.

Pyrrole derivatives are particularly important in materials science (Fig. 3). This is a very extensive field, which cannot be adequately summarized in the context of this Introduction. Among the many possible examples, we will mention the existence of semiconducting materials derived from hexa(N-pyrrolyl)benzene, glucose sensors based on polypyrrole-latex materials and polypyrrole materials for the detection and discrimination of volatile organic compounds. Derivatives of the 4,4-difluoro-4-boradipyrrin system (BODIPY) have a strong absorption in the UV and emit very intense fluorescence. These compounds have many applications as chemosensors, for laser manufacture, image diagnosis, etc.

In this context, the present critical review aims to provide an in-depth account of the use of multicomponent reactions for the synthesis of pyrroles. While a considerable amount of review literature on classical pyrrole synthesis exists, to our knowledge there are only two articles related to the present contribution. One of them deals specifically with MCRs leading to furans and pyrroles that use acetylenes as starting materials, and the other is a 2004 “Highlight” in Angewandte Chemie, International Edition that essentially summarizes the content of four papers. In the present article we have placed particular emphasis on discussing the developments of the subject from 2000 to the end of 2009, although we occasionally mention earlier work when relevant.

2. Multicomponent pyrrole syntheses based on condensation reactions of 1,3-dicarbonyl compounds

2.1 The three-component Hantzsch pyrrole synthesis

The Hantzsch pyrrole synthesis, in its traditional form, is based on the reaction between a β-enaminone and an α-haloketone (Scheme 2).

In spite of its named reaction status, the Hantzsch synthesis has received little attention in the literature. Thus, a study by Roomi and MacDonald published in 1970 concluded that only nine pyrrole derivatives had been prepared by this method in the 80 years elapsed since the initial Hantzsch publication. While the original Hantzsch method was restricted to the use of ethyl β-aminocrotonate, Roomi and MacDonald extended its scope to include R² substituents.
other than methyl and also the case of $R^3 = H$. The yields for these reactions were normally below 50%, and this problem has also been found by more recent authors using the Hantzsch pyrrole synthesis. In any case, neither the original Hantzsch nor the Roomi and MacDonald conditions can be considered multicomponent, and only a few true three-component related pyrrole syntheses have been described, restricted to the case $R^3 = H$ and using either a $\alpha$-chloroaldehydes or ethyl 1,2-dibromoacetate to generate the $\beta$-enaminone in situ.

In 1998, Jung and coworkers described a three-component Hantzsch pyrrole synthesis on an acetoacetylated Rink resin as a solid support. The reaction between this material and primary amines presumably afforded the corresponding $\beta$-enaminones, which were then treated with $\alpha$-halocarbonyl compounds, followed by hydrolytic liberation of the reaction products from the solid support (Scheme 3). This protocol afforded pyrroles with excellent purities, but unfortunately the authors did not describe the yields obtained.

Another modification of the Hantzsch synthesis is based on the use of $\beta$-cyclodextrin as a supramolecular catalyst. This method lacked generality, as it was restricted to the reaction between phenacyl bromide, acetylacetone and ammonium acetate or a variety of amines, most of which were aromatic and a few were benzylic. When these starting materials and $\beta$-cyclodextrin were heated in water at 60–70 °C, the corresponding 1,5-diarylpyrroles were obtained in good to excellent yields (Scheme 4).

### 2.2 Pyrrole syntheses combining enamine formation and aldol reactions

The coupling of the aldol addition of a $\beta$-enaminone with a cyclocondensation step may also be used as the basis for a pyrrole multicomponent synthesis. As shown in Scheme 5, the simplest example of this strategy consists of the three-component reaction among $\beta$-dicarbonyl compounds, arylglyoxals and ammonium acetate in water, which affords 4-hydroxy-5-arylpyrroles in variable yields. In most cases, $\beta$-ketoesters were employed as the dicarbonyl component, although a few examples used $\beta$-diketones. However, the reaction failed for the case of compounds containing phenylketone structural fragments.

The mechanism suggested by the authors is summarized in Scheme 6, and involves an initial aldol addition to give a 1,4-dicarbonyl intermediate, followed by a Paal–Knorr-type cyclization and double dehydration. The fact that the final pyrroles precipitate from the aqueous reaction medium probably helps to direct other possible equilibria towards the desired products.

A related protocol, using a low-valent titanium derivative as catalyst, was developed more or less simultaneously and found to be complementary to the previous one in that it works best for diaryl-1,3-diketones. In this method, dibenzoylmethane derivatives, aldehydes and amines (mostly aromatic, in both...
cases) were mixed in the presence of titanium tetrachloride and samarium powder in THF to give 1,2,3,5-tetrasubstituted pyrroles (Scheme 7). The use of non-symmetric dicarbonyl starting materials led to the isolation of mixtures of regioisomers in variable ratios. 46

2.3 Pyrrole syntheses combining enamine formation and Michael additions

A solvent- and catalyst-free synthesis of pentasubstituted, functionalized pyrrole systems has been developed recently, based on the three-component reaction between primary amines, alkyl acetoacetates and fumaryl chloride. The pyrrole derivatives thus obtained contain a 5-chloro substituent, together with carboxylic ester and carboxymethyl functional groups (Scheme 8).47

The proposed mechanism is initiated by the formation of β-enaminone 2, followed by its Michael addition onto a molecule of fumaryl chloride to afford 3. The intramolecular attack of the enamine nitrogen onto the acyl chloride function leading to the generation of the five-membered ring did not follow the expected pathway with elimination of HCl, but instead involved the loss of a molecule of water with retention of the chlorine substituent (Scheme 9).

A double enaminone formation-Michael addition sequence can be used as the basis for a 3,3′-bipyrrrole synthesis. Thus, the reaction between β-ketoesters or symmetrical β-diketones, diaroylacetylenes and ammonium acetate in the presence of indium trichloride afforded compounds 4, which turned out to exhibit axial chirality (Scheme 10).48

The mechanism proposed for this transformation starts with coordination of the indium catalyst to one of the ketone carbonyls, followed by the Michael addition of the enol tautomer of the dicarbonyl compound onto the conjugated triple bond of the acetylene substrate to give intermediate 5. This is then tautomerized into compound 6, which contains a 1,4-dicarbonyl fragment and gives pyrrole 7 through a Paal–Knorr condensation. An example of a compound 7 could be isolated by stopping the reaction before completion, and this observation was considered as a proof in favour of the proposed mechanism. A subsequent second Michael addition onto the α,β-unsaturated imine fragment of 7 gives 8, again a 1,4-dicarbonyl compound, and this is followed by a second Paal–Knorr reaction to give the observed products 4 (Scheme 11).
2.4 Pyrrole syntheses combining Michael and aldol reactions

A three-component reaction starting from β-ketoesters or β-diketones, 2-hexenal and sodium nitrite provides access to 1-hydroxypyrrole derivatives. In contrast to other reactions mentioned in this section, in this case the carbonyl function remaining from the β-dicarbonyl starting material is at the C-2 position of the final product rather than at C-3 (Scheme 12). 49

Regarding the mechanism of this transformation, the authors propose that it starts with the nitrosation of the β-dicarbonyl substrate to give the corresponding oxime 9, whose nitrogen atom then adds to the α,β-unsaturated aldehyde in a conjugate fashion. The complete chemoselectivity of this Michael addition in favour of the oxime nitrogen was explained by the stabilization of the hydroxy group by intramolecular hydrogen bonding with the adjacent carbonyl, which would prevent its participation in a similar Michael addition. The five-membered ring would then be generated by an intramolecular aldol condensation, followed by aromatization through a 1,7-hydrogen shift (Scheme 13). 50

2.5 Pyrrole syntheses combining nucleophilic substitution, enamine formation and 5-exo-dig cycloisomerization reactions

A one-pot, three-component reaction between primary amines, β-ketoesters or β-diketones and propargyl alcohols provided an efficient entry into pyrroles, as shown by Gimeno and coworkers. This transformation was carried out in sealed vessels using tetrahydrofuran containing trifluoroacetic acid as the reaction medium and in the presence of the [Ru(η1-2-C₅H₄Me)(CO)(dppf)][SbF₅] system, where dppf is 1,1'-bis(diphenylphosphanyl)ferrocene, and afforded fully substituted derivatives of the pyrrole system in good to excellent yields (Scheme 14). 51 This reaction is related to, but much more general than, a previously published platinum-catalyzed pyrrole synthesis based on a three-component reaction between anilines, ketones and propargyl alcohols. 52

Mechanistically, this transformation was explained by two competitive pathways. In the first one, an acid-promoted propargylation of the β-dicarbonyl substrate affords a γ-ketoalkyne 10, which could be isolated in a separate experiment. Intermediate 10 then reacts with the primary amine to give the propargylated β-enaminone 11, which undergoes a final Ru-catalyzed 5-exo-dig annulation leading to the observed pyrrole final products. Alternatively, intermediate 11 can be reached by propargylation of the β-enaminone 12, arising from the reaction between the starting β-dicarbonyl and primary amine components and which was detected by GC-MS experiments. These proposals are summarized in Scheme 15.
Subsequent work by a different group proved that the synthesis of pyrroles from primary amines, \( \beta \)-dicarbonyl compounds and propargyl alcohols can also be carried out under experimentally simpler conditions in the presence of indium trichloride, using toluene as solvent.\(^5\)

3. Multicomponent synthesis of pyrroles using isonitriles as starting materials

A four-component reaction between acetylenedicarboxylates, succinimide or maleimide and two molecules of an isonitrile in refluxing dichloromethane was found to afford pyrroles in good to excellent yields, albeit in rather long reaction times (Scheme 16).\(^4\) The mechanism proposed for this transformation is summarized in pathway \( b \) of Scheme 17 and assumes an initial addition of the isonitrile to the electron-deficient alkyne to give species 13. Reaction of the latter with a second molecule of isonitrile affords bis-ketenimine 14, as previously reported.\(^5\) Its reaction with the imide component followed by cyclization explains the isolation of the observed pyrroles. The use of sterically hindered isonitriles (e.g. tert-butyl isonitrile) prevented the generation of 14, probably because of steric hindrance. In this case, intermediate 13 deprotonates the imide to give intermediate 15, and this is followed by a Michael addition that leads to the observed products (compounds 16), as shown in Scheme 17, pathway \( a \).

The four-component reaction between alkynes, amines and isonitriles catalyzed by a variety of titanium catalysts affords 4-amino-1-azadienes derived from a formal iminoamination reaction.\(^6\) Replacing these catalysts by the pseudotetrahedral \( \text{Ti(NMe}_2\text{)}_2(\text{IndMe}_2) \) species, generated from 2,3-dimethylindole and \( \text{Ti(NMe}_2\text{)}_4 \), induced the incorporation of a second molecule of isonitrile, leading to the isolation of pyrrole products (Scheme 18). This reaction works well only with anilines not bearing an ortho substituent and tert-butyl isonitrile.\(^7\) Other substrates lead preferentially to acyclic products derived from the previously mentioned three-component process. Internal alkynes require higher reaction
temperatures or/and longer reaction times than their terminal counterparts.

The mechanism proposed by the authors to explain the isolation of pyrroles involves the initial generation of a titanium imido intermediate 17, which then undergoes a [2+2] cycloaddition onto the starting alkyne to afford an azatitanacyclobutene 18. Incorporation of the first molecule of isonitrile furnishes a five-membered metallacycle 19, which reacts with a further molecule of isonitrile, leading to a six-membered titanacycle 20. Protolytic cleavage of this intermediate by a new molecule of the amine closes the catalytic cycle and releases intermediate 21, which affords the final products by 5-exo-trig intramolecular nucleophilic attack followed by tautomerism (Scheme 19).

A very efficient route to trisubstituted pyrroles bearing an unusual 4-nitro functionality has been developed by the Ley group, which is based on a three-component reaction between nitrostyrenes, toluenesulfonylmethyl isocyanide (TosMIC) and ethyl chloroformate under strongly basic conditions achieved by the addition of BuLi.58 The concentration of the reaction medium was found to play a significant role in the outcome of the reaction, with high concentrations leading to better yields. Purification of the final products also proved challenging, as conventional workup often provided low yields (method A in Scheme 20). The optimal procedure, which led to much improved results, turned out to be one based on the use of a polymer-assisted catch-and-release protocol for workup and purification by addition of a basic polystyrene resin (method B).59,60 These observations are summarized in Scheme 20.

The mechanism for this pyrrole synthesis was proposed to be initiated by the generation of intermediate 22 from base-promoted condensation between TosMIC and ethyl chloroformate followed by deprotonation to give anion 22. Addition of 22 to the starting nitrostyrene affords 23, which yields the observed major product by 5-endo-trig cyclization onto the isonitrile group, followed by a 1,2-hydrogen shift and a final elimination with loss of the tosyl group and tautomerism (pathway a in Scheme 21). In some cases, the reaction led to minor amounts of pyrroles 25, whose formation was explained by an intramolecular attack of the nitroalkane anion onto the ester group, leading to its rearrangement and affording intermediate 26, which then evolves to 25 by the usual route (pathway b). Neither the sequence following cyclization in pathway a nor the one following ester transfer in pathway b seem to be reversible. The mechanism proposed for the isolation of 25 was confirmed by independent preparation of alkene 27, which afforded 25 in excellent yield upon treatment with TosMIC in the presence of BuLi (reaction c).

4. Multicomponent synthesis of pyrroles using nitroalkanes and nitroalkenes as starting materials

The Ranu group developed a four-component coupling of aldehydes, amines and nitroalkanes in the presence of a catalytic amount of samarium trichloride at 60 °C, which afforded tetrasubstituted pyrroles in poor to moderate yields (Scheme 22).61 The scope of this reaction did not include the use of ketones as starting materials.
As shown in Scheme 23, the mechanism proposed for this transformation involves the initial formation of the imine 28 from the starting amine and one molecule of aldehyde. A samarium-catalyzed aldol-type self-condensation of 28 affords the \( \alpha,\beta \)-unsaturated imine 29, which is attacked by the nitroalkane in a conjugate fashion to yield intermediate 30. An intramolecular proton transfer followed by a 5-exo-dig cyclization affords a new intermediate 31, which then evolves to the final aromatic pyrrole following loss of water and HNO.

The sequence of reactions starting from the \( \alpha,\beta \)-unsaturated imine 29 is not catalyzed by the samarium species, as proved by an independent experiment that showed that the uncatalyzed reaction of 29 and nitroalkanes led to pyrroles in yields similar to those of the corresponding samarium-catalyzed experiment.

As shown in Scheme 24, the same group subsequently noticed that a related three-component reaction between amines, \( \alpha,\beta \)-unsaturated aldehydes or ketones and nitroalkanes did not require any catalyst, presumably owing to the enhanced stability of the initial imine due to its conjugation. The use of unsaturated ketones allowed access to compounds bearing a substituent at C-2 and hence to penta-substituted pyrroles. Subsequent work, again by the Ranu group, proved that this transformation could be performed in the solid state by supporting the reactants on silica gel. This transformation was accelerated by microwave irradiation, which also afforded greatly improved yields (Scheme 25). The same reaction was also subsequently studied in ethanol solution under the influence of ultrasound irradiation, which allowed to bring the reaction to completion in reaction times ranging from 20 to 60 min.

The first mention of the synthesis of pyrroles through a three-component reaction between an amine, a ketone and a nitroalkene can be found in a 1981 paper by Meyer, although only two low-yielding examples were described (Scheme 26). Ranu and coworkers showed subsequently that this method for pyrrole synthesis was much improved in terms of yield when the reaction was irradiated with microwaves in the solid state, with all substrates adsorbed onto alumina or in molten tetrabutylammonium bromide as an ionic liquid. In both cases, the reaction was restricted to the synthesis of 2-unsubstituted pyrroles since open-chain ketones did not give the reaction (Scheme 27). However, conditions involving heating in molten tetrabutylammonium bromide gave good results with cyclic ketones as substrates, furnishing tetrahydroindoles as products.
A similar transformation could also be achieved through a sequential procedure using as starting materials amines, nitroalkenes and diketene, a well-known acetoacetylating reagent that presumably generates a \( \beta \)-ketoamide by reaction with one molecule of the starting amine. Therefore, the final pyrrole contains a 3-carboxamide substituent (Scheme 28).

A single example of a three-component pyrrole synthesis from a primary amine and two molecules of a nitroalkene in the presence of samarium triisopropoxide has been described (Scheme 29). This reaction was developed as a three-component variant of a previously known synthesis of pyrroles from imines and nitroalkenes. The mechanism proposed to explain this transformation starts with the formation of imine 32 from the amine and a molecule of nitroalkene, with nitromethane acting as a leaving group. Samarium triisopropoxide, which in this case behaves as a base, activates this imine to form the enamine complex 33. The reaction of 33 with a second molecule of the nitroalkene gives adduct 34, which cyclizes to a pyrrole derivative that evolves to the final product and a new samarium species that evolves by loss of water and HNO, with concomitant activation of a new molecule of imine 32 that thus becomes 33 and is able to enter the catalytic cycle (Scheme 30).

5. Multicomponent pyrrole syntheses based on the generation and subsequent reactions of 1,4-dicarbonyl compounds

The transformations described in this section can be considered as variations of the classical Paal–Knorr pyrrole synthesis where the 1,4-dicarbonyl compound is generated \textit{in situ}. Unavoidably, there is some overlap with previous sections and for instance the reactions summarized in Schemes 5, 6, 10 and 11, which also involve 1,4-dicarbonyl intermediates, might also have been included here.

5.1 Pyrrole synthesis through a four-component process based on a Sonogashira/isomerization/Stetter/Paal–Knorr domino sequence

The Müller group discovered a synthesis of chalcones from propargyl alcohols and electron-poor bromoarenes through a
Sonogashira cross-coupling/base-promoted isomerization sequence, which was considered to have some advantages over the traditional aldol-based protocols. On this basis, they subsequently developed a sophisticated one-pot method for pyrrole synthesis involving a sequential procedure that starts by generation of a chalcone using the above mentioned Sonogashira/isomerization, followed by the in situ preparation of a 1,4-dicarbonyl compound via the Stetter reaction and a final Paal–Knorr pyrrole synthesis (Scheme 31). The pyrrole derivatives thus obtained, which show aryl substituents on at least two positions, exhibited a strong blue fluorescence.71

The mechanistic course of this reaction sequence is shown in Scheme 32, and starts with the Sonogashira coupling of the propargyl alcohol and the aryl bromide, which requires that the latter bears a sufficiently electron-withdrawing substituent and results in the formation of 35. Deprotonation of the propargyl C–H bond by triethylamine yields a resonance-stabilized propargyl-allenyl anion that is protonated to give hydroxyallene 36, which then tautomerizes to chalcone 37. This compound enters the catalytic cycle of a Stetter reaction. Thus, the thiazolium catalyst is deprotonated by triethylamine to the C-nucleophilic dipolar species 38, which can also be viewed as an N-heterocyclic carbene and traps the aldehyde component to furnish 39 after a hydrogen-shift step. This intermediate, whose polarity is inverted with regard to that of the aldehyde, reacts with 37 leading to intermediate 40 and then to 1,4-diketone 41, which finally yields the observed pyrrole products by reaction with the amine component through the classical Paal–Knorr mechanism.

A closely related reaction that allows the preparation of highly complex phenyl- and heterocycle-substituted pyrroles was developed by the group of Jing, following the same strategy but starting from pre-synthesized α,β-unsaturated ketones and using DBU as base. Thiazolium-catalyzed Stetter reaction of the latter with aldehydes generates 1,4-diketone intermediates, and the sequential addition of primary amines leads to the desired pyrrole products (Scheme 33).72

5.2 Three-component pyrrole synthesis based on a sila-Stetter/Paal–Knorr sequence

Another variant of the previous sequence, reported by the Scheidt group, is based on the combination of sila-Stetter and Paal–Knorr reactions.73,74 In this case, the starting materials employed were chalcones and acylsilanes instead of aldehydes, and the first reaction requires the addition of p-toluenesulfonic acid and 4 Å molecular sieves in order to facilitate the Paal–Knorr reaction (Scheme 34).
The mechanism proposed for the sila-Stetter reaction is depicted in Scheme 35, and involves the addition of the acylsilane to the nucleophile \( \text{42} \), generated by deprotonation of the thiazole catalyst. Intermediate \( \text{43} \) thus obtained undergoes a 1,2-silyl group shift from carbon to oxygen, known as a Brook rearrangement leading to \( \text{44} \), which is desilylated by the alcohol additive to yield \( \text{45} \). From that point, the reaction follows the usual Stetter mechanism and affords 1,4-diketone \( \text{46} \), the direct precursor to the pyrrole final products. Intermediate \( \text{44} \), obtained independently, was shown to afford 1,4-dicarbonyl compounds upon reaction with a chalcone, which can be considered as proof for the proposed mechanism.

6. Pyrrole syntheses based on 1,3-dipolar cycloadditions

1,3-Dipolar cycloadditions are one of the most useful approaches to five-membered heterocycles. One of the most versatile substrates employed as masked 1,3-dipoles are 1,3-oxazolium-5-oxides, commonly known as Münchnones, which contain a mesionic ring that can react with a wide variety of double and triple-bond dipolarophiles. They are effective for the synthesis of pyrrole via a one-pot, three-component procedure.

6.1 Methods based on the use of Münchnones and their analogues as 1,3-dipoles

Arndtsen and Dhawan reported a pyrrole synthesis based on the preparation of Münchnones in one step by a palladium-catalyzed coupling between imines, acid chlorides and carbon monoxide, and then the corresponding pyrroles by the addition of alkynes (Scheme 36). The mechanism proposed to explain this reaction starts with the generation of the \( N \)-acyliminium salt \( \text{47} \), and continues with its oxidative addition to \( \text{Pd}(0) \) to give \( \text{48} \). In the next step, coordination of CO generates the palladium complex \( \text{49} \) followed by migratory insertion leading to \( \text{50} \). Next, the base promotes elimination of chloride as a salt to give ketene \( \text{51} \) that is in equilibrium with Münchnone \( \text{52} \). Finally, the 1,3-dipolar cycloaddition between this Münchnone and the starting alkyne takes place, to form a cycloadduct \( \text{53} \) that releases a molecule of \( \text{CO}_2 \) and leads to the desired pyrrole. After a study of ligand (L) influence, the authors observed that the more favorable scenario involves a donor ligand, the best one being \( \text{P(}o\text{-tolyl)}_3 \) due to its high reactivity during catalyst generation and its capability of promoting the catalytic cycle in the presence of alkynes (Scheme 37).

Similarly, Merlic and coworkers developed an entry to Münchnones via an acylamino chromium carbene complex followed by a 1,3-dipolar cycloaddition with acetylenedicarboxylates that yields pyrroles. Although this was not the procedure normally employed, this reaction could be carried out as a one-pot, three-component procedure.
Its mechanism (Scheme 39) begins with the acylation of the starting aminocarbene chromium complex with benzoyl chloride to give an acylaminocarbene complex. Insertion of carbon monoxide can be achieved in a direct, non-photochemical fashion to give a ketene complex. This step is unusual in that CO insertion in heteroatom-substituted chromium complexes is generally considered a photochemical process. The ketene cyclizes to a metal-free Münchnone, which could be isolated if desired, with the demetalation step being probably facilitated by the presence of CO. The 1,3-dipolar cycloaddition to the alkyne is followed by loss of a molecule of carbon dioxide, yielding the final pyrrole.

More recently, the Arndtsen group developed a 1,3-dipolar cycloaddition where the carbonyl group of the Münchnone was replaced with a Ph₃P unit. This phosphorus-based 1,3-dipolar substrate can be generated by the one-pot reaction of phosphines, imines and acid chlorides and undergoes a cycloaddition leading to pyroles under mild conditions, and this process was compatible with a diverse range of imine and acid chloride substrates. It was found that the yields improved when the addition of the isocyanide, and then the base, was carried out sequentially (Scheme 42). In these reactions, the in situ generated N-acyliminium salt is attacked by isocyanide to give 62, which then cyclizes to 63. Subsequent addition of base leads to the amino analogue of Münchnone 64, which undergoes a 1,3-dipolar cycloaddition with the alkyne to form the corresponding cycloadduct, followed by elimination of a molecule of isocyanate to give the desired pyrrole (Scheme 43).

A multicomponent process that combines imines with dibromodifluoromethane and alkynes leads to 2-fluoropyrrole derivatives (Scheme 44). The 1,3-dipole involved in the cycloaddition is a difluorocarbene, generated in situ from dibromodifluoromethane using different protocols. The best results were obtained with active lead, prepared by reduction of the starting imine and acyl chloride complex with BuLi, THF, -78 to 0 °C, 45 min. Insertion of carbon monoxide can be achieved in a direct, non-photochemical fashion to give a ketene complex. This step is unusual in that CO insertion in heteroatom-substituted chromium complexes is generally considered a photochemical process. The ketene cyclizes to a metal-free Münchnone, which could be isolated if desired, with the demetalation step being probably facilitated by the presence of CO. The 1,3-dipolar cycloaddition to the alkyne is followed by loss of a molecule of carbon dioxide, yielding the final pyrrole.

### 6.2 Methods using 1,3-dipoles different from Münchnones

A multicomponent process that combines imines with dibromodifluoromethane and alkynes leads to 2-fluoropyrrole derivatives (Scheme 44). The 1,3-dipole involved in the cycloaddition is a difluorocarbene, generated in situ from dibromodifluoromethane using different protocols. The best results were obtained with active lead, prepared by reduction of the starting imine and acyl chloride complex with BuLi, THF, -78 to 0 °C, 45 min. Insertion of carbon monoxide can be achieved in a direct, non-photochemical fashion to give a ketene complex. This step is unusual in that CO insertion in heteroatom-substituted chromium complexes is generally considered a photochemical process. The ketene cyclizes to a metal-free Münchnone, which could be isolated if desired, with the demetalation step being probably facilitated by the presence of CO. The 1,3-dipolar cycloaddition to the alkyne is followed by loss of a molecule of carbon dioxide, yielding the final pyrrole.
of aqueous lead acetate with sodium borohydride, instead of the more usual powdered lead or zinc dust. The reaction conditions are compatible with a variety of functional groups on the imines, although the structures of the alkyne dipolarophiles are restricted to compounds bearing electron-withdrawing groups. This one-pot synthesis occurs in four steps. First, difluorocarbene is generated by reduction of dibromodifluoromethane with active lead in presence of tetrabutylammonium bromide. Then, the carbene is attacked by the nitrogen lone pair of the imine to form the intermediate azomethine ylide (Scheme 45), which participates in a 1,3-dipolar cycloaddition with the activated alkynes to give a 2,2-difluoro-3-pyrroline. The last step is the dehydrofluorination of the latter compound to give the desired 2-fluoropyrrole (Scheme 45).

The rhodium-catalyzed multicomponent reaction of aryl imines, diazoacetonitrile and acetylenedicarboxylates as the dipolarophile partner provides ready access to 1,2-diarylpyrroles (Scheme 46). The mechanism proposed for this reaction starts with the combination of the rhodium acetate and diazoacetonitrile, affording the corresponding metalcarbenoid. Addition of the latter to the starting imine leads to the formation of the azomethine ylide intermediate (66), although the authors did not discard an alternative mechanism via an aziridine intermediate. The 1,3-dipolar cycloaddition of (66) with the activated alkyne affords a pyrroline adduct that undergoes elimination of hydrogen cyanide to form the aromatic pyrrole (Scheme 47). Among the transition metal salts studied, the best results were provided by rhodium acetate in just 1 mol% catalyst loading.

Another case where the formation of NH-azomethine ylide as an intermediate is the key step in a pyrrole synthesis can be found in a sequential multicomponent process that uses as starting materials an aldehyde derivative, aminoesters and acetylenic dipolarophiles for the preparation of 3,4,5-trisubstituted pyrrole derivatives (Scheme 48). In many cases, the use of pyridinium p-toluenesulfonate (PPTS) as an additive was required for the reaction to achieve completion. A plausible mechanism that explains this transformation starts with the formation of an imine between the heterocyclic aldehyde and the aminoester. This initial imine undergoes a 1,2-shift of the acidic hydrogen to produce the NH-azomethine ylide (67), which is stabilized by intramolecular hydrogen bonding. The cycloaddition reaction between this 1,3-dipole and the starting alkyne furnishes compound (68) with complete regioselectivity in favour of the pyrroline derivative bearing the ester group at the C-3 position. This intermediate is cleaved under the acidic reaction conditions to give fragments (69) and (70). The 2H-pyrrole initial products (71) are transformed into the finally observed 1H-pyrroles by aromatization through a 1,5-ester rearrangement followed by tautomerism (Scheme 49).

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**Scheme 42** Isonitrile-mediated three-component synthesis of pyrroles.

**Scheme 43** Mechanism of the pyrrole synthesis based on 1,3-dipolar cycloadditions of amino analogues of Münchnones.

**Scheme 44** Three-component synthesis of 2-fluoropyrroles from dibromodifluoromethane, imines and alkynes.

**Scheme 45** Mechanism of a pyrrole synthesis based on 1,3-dipolar cycloadditions of fluorinated azomethine ylides.

**Scheme 46** Rhodium-catalyzed synthesis of pyrroles from imines, diazo compounds and activated alkynes.
A three-component reaction between isonitriles, tosylimines and acetylenedicarboxylates was found to provide a very efficient access to 2-aminopyrroles, again having a 1,3-dipolar cycloaddition reaction of an azomethine ylide as the key step (Scheme 50).84

7. Miscellaneous multicomponent pyrrole syntheses using alkynes as starting materials

We will describe here some reactions that have in common the use of alkynes as starting materials and that have not been covered in previous sections.

7.1 Methods based on nucleophilic additions onto carbonyl and imino groups

The reaction of alkynes, aldehydes and amines in the presence of ytterbium triflate afforded 1,3-oxazines 72. The reaction can be stopped at this stage, and compounds 72 thus isolated were shown to slowly rearrange to pyrroles. As depicted in Scheme 51, it was subsequently proved that by carrying out the whole process under solvent-free conditions in the presence of triethylamine, with the reagents supported on silica gel and under microwave irradiation, pyrroles were obtained directly from the acyclic starting materials.85 Overall, this transformation generates two C–C and two C–N bonds and comprises up to nine individual reaction steps. The mechanism proposed to explain it involves two coupled domino processes. An initial three-component domino reaction between the aldehyde and two molecules of alkyne affords the enol-protected propargyl alcohol 73, which then reacts with the amine to give 1,3-oxazolidine 72. Its skeletal rearrangement starts by ring opening and isomerization to 74. A hydrogen shift then takes place to afford an enamine, which then undergoes the final cyclization. This hydrogen shift was proved by the fact that the reaction starting from acetaldehyde-d4 furnished a pyrrole derivative with deuterium at the methyl position, but not at the ring (Scheme 52).
The reaction between an alkynylsilane, an imine and an aldehyde in the presence of a catalytic amount of a phosphazene base (tBu-P₄) afforded the corresponding pyrrole (Scheme 53). However, in most cases this reaction was performed in a two-component fashion, starting from imines and isolated propargyl silyl ethers. The mechanism proposed to explain this transformation involves the initial formation of a propargyl silyl ether 75, followed by a base-promoted generation of allene anion 76 which then adds to the starting imine. The final pyrrole product is formed following a 5-endo-trig cyclization and elimination of a molecule of trimethylsilyl alcohol (Scheme 54).

As shown in Scheme 55, another multicomponent sequence that leads to pyrrole products involves the reaction between phenylacetylene, imines derived from ethyl glyoxylate and dialkylzinc derivatives. Mechanistically, this reaction was proposed to be initiated by the addition of a molecule of the dialkylzinc reagent to the starting imine to give a N-Zn-aminoester intermediate, followed by reaction of a molecule of the C₁-zinc-derivative of the starting terminal alkyne to the ester group, with elimination of R₂ZnOEt, addition of a second molecule of the same alkynylzinc reagent, cyclization and a final elimination step (Scheme 56).

7.2 Methods based on nucleophilic additions onto nitrile groups

Coupling of an acetylene, two α-alkoxynitriles and a titanium reagent generated from titanium tetraisopropoxide and isopropylmagnesium chloride affords pyrrole-2-carbaldehydes (Scheme 57). The mechanism involves the titanium-promoted...
initial reaction between the alkyne and the first nitrile, leading to the formation of an azatitanacyclopentadiene intermediate 77, which can trap in situ another nitrile molecule to give diazatitanacycloheptatriene 78, the precursor to the tetrasubstituted pyrrole final products (Scheme 58).88

In a related procedure, the zircocene-mediated reaction between bis(arylalkynyl)silanes and nitriles was found to yield pyrroles in moderate yields (Scheme 59).89

### 7.3 Methods based on Michael additions

The reaction between triphenylphosphine, dimethyl acetylenedicarboxylate and amines was known to lead to β-aminophosphoranes.90 On this basis, a new synthesis of N-phenylpyrroles was developed, based on the treatment of aniline, acetylenedicarboxylates and arylglyoxals in the presence of triphenylphosphine (Scheme 60).91 A plausible mechanism for the triphenylphosphine-mediated pyrrole synthesis starts with an initial Michael addition of the phosphine onto the conjugated triple bond that affords the dipolar intermediate 79, which then undergoes a proton exchange with the amine followed by a second Michael addition having as nucleophile the anion derived from the latter to give the β-aminophosphorane 80. A domino sequence comprising a chemoselective Wittig reaction and a final cyclocondensation affords the observed pyrrole product (Scheme 61). A similar transformation starting from ammonium acetate, dialkyl acetylenedicarboxylates and 2,3-butanedione afforded N-unsubstituted pyrroles (Scheme 62).92

Another three-component pyrrole synthesis that includes a Michael addition onto a dialkyl acetylenedicarboxylate is summarized in Scheme 63, which uses acyl chlorides and α-amino acids as the two additional components and was performed in an aqueous solution containing 1-butyl-3-methylimidazolium hydroxide ([bmim]OH), an ionic liquid.93 Mechanistically, this transformation was assumed to start by acylation of the amino acid, followed by decarboxylation to give an anion 81 that adds onto the acetylenic ester. This leads to another anion 82 that undergoes an intramolecular addition onto the amide carbonyl and a final elimination of a molecule of water to furnish the final product (Scheme 64).

![Scheme 57](image-url) Ti-promoted three-component pyrrole synthesis from alkynes and nitriles.

### 7.4 Methods based on palladium-catalyzed cross-coupling reactions

The reaction between acyl chlorides, N-Boc protected propargylamines and sodium iodide in the presence of copper iodide and a catalytic amount of PdCl2(PPh3)2 afforded 2-substituted N-Boc-4-iodopyrroles through a coupling/addition/cyclocondensation sequence having the N-acylated compound 83 as an intermediate. It was subsequently found that these 4-iodopyrroles, upon addition of a further molecule of alkyne, underwent an in situ Sonogashira coupling to yield 2-substituted-4-alkynyl-N-Boc pyrroles (Scheme 65).94

In Scheme 66 another example is summarized of a palladium-catalyzed multicomponent pyrrole synthesis, in which carbon dioxide was found to promote the intramolecular Pd-catalyzed oxidative carbonylation reaction of 2-en-4-ynilamines, providing a new route to pyrrole-2-acetic...
esters. This reaction was proposed to take place through the mechanism summarized in Scheme 67. The alkoxy carbonylation process involves reduction of PdI2 to Pd(0) and two molecules of HI. Pd(0) is subsequently back-transformed into the active species PdI2 by I2 generated from HI and oxygen. The amine that serves as the substrate for this reaction is sufficiently basic to trap HI and can therefore inhibit the reoxidation of Pd(0).

While this problem can often be solved by running the reaction in the presence of a large excess of oxygen, which favours the oxidation of HI to I2, this approach could not be employed in the present case owing to the low stability of pyrroles to oxidation. The authors found that carbon dioxide provided an efficient method for freeing HI by reversibly binding to the amino group, generating a carbamate that, after serving its purpose as a protecting group, underwent decarboxylation during the final cyclization process.

The use of double oxidative carboxylation reactions allowed the synthesis of pyrrole-3,4-diacetic ester derivatives. In this case, the use of CO2 as a temporary protection was not necessary because the starting material was an amide derived from dipropargylamine. The initial experiments afforded compounds 84,96 but it was later found that they could be isomerized in situ to the corresponding pyrroles by using dimethylacetamide (DMA) as cosolvent (Scheme 68).

Conclusions

Pyrrole derivatives have great relevance in many fields of chemistry, and we hope to have shown that multicomponent reactions are an excellent, multipurpose approach to their synthesis. Besides the development of new reactions or improved conditions for the classical ones, future
developments in this field will probably involve the application of multicomponent-based strategies to target-oriented synthesis. We hope that this review will serve to stimulate research in this fascinating and very useful area of organic synthesis.

Notes and references

7 For a symposium in print on MCRs, see: Tetrahedron Symposium in Print, ed. I. Marek, 2005, vol. 67, p. 11299.
50 Our interpretation of the last steps of this mechanism is slightly different from that of the original authors (see the previous reference).