



**Recent advances in the synthesis of pyrroles by  
multicomponent reactions**

Journal:	<i>Chemical Society Reviews</i>
Manuscript ID:	CS-REV-01-2013-060015.R1
Article Type:	Review Article
Date Submitted by the Author:	06-Mar-2014
Complete List of Authors:	Estévez, Verónica; Universidad Complutense, Química Orgánica y Farmacéutica Villacampa, Mercedes; Universidad Complutense, Química Orgánica y Farmacéutica Menendez, J. Carlos; Universidad Complutense, Química Orgánica y Farmacéutica

## ARTICLE

## Recent advances in the synthesis of pyrroles by multicomponent reactions

Cite this: DOI: 10.1039/x0xx00000x

Verónica Estévez,<sup>a</sup> Mercedes Villacampa<sup>a</sup> and J. Carlos Menéndez<sup>a,\*</sup>Received 00th January 2012,  
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Pyrrole is one of the most important one-ring heterocycles. The ready availability of suitably substituted and functionalized pyrrole derivatives is essential for the progress of many branches of science, including biology and material science. Access to this key heterocycle by multicomponent routes is particularly attractive in terms of synthetic efficiency, and also from the environmental point of view. We update here our previous review on this topic by describing the progress made in this area in the period between mid-2009 to the end of 2013.

## 1. Introduction

Pyrrole is one of the most relevant simple heterocycles because of its presence in a large number of natural and unnatural compounds with important properties, both in pharmacology and in materials science.

The best-known natural pyrroles are the heme derivatives and chlorophyll, which contain four pyrrole groups joined by methyne bridges. Besides these widespread compounds, pyrrole structural fragments are particularly common in natural products of a marine origin (Figure 1). Among them, the lamellarins,<sup>1</sup> isolated from marine invertebrates, exhibit antitumor and anti-HIV activities. Most of these alkaloids are normally derived from a unique tetracyclic ring system that comprises a pyrrole fragment, but a few of them, like lamellarin R, are derivatives of pyrrole itself. Halitulins are another cytotoxic spongian natural product, isolated from *Haliforclona tulearensis*.<sup>2</sup> The pyrrole-imidazole family of alkaloids comprises hundreds of natural products that have been isolated exclusively from marine sponges, where they act as the major fish feeding deterrent agent. The simplest member of this group, which was also the first one to be isolated, is oroidin, which is considered to be the biogenetic precursor of all the others. The architectural complexity of many of these alkaloids such as, for instance, sceptrin, has rendered them popular synthetic targets.<sup>3</sup> The marinopyrroles<sup>4</sup> are another important class of marine alkaloids, exemplified by the recently isolated marinopyrroles A and B. These compounds have attracted much attention because of their high activity against methicillin-resistant bacteria, an important property bearing in mind the increasing problems associated with antibiotic resistance. In this connection, some hybrid structures containing the core of bromopyrrole marine alkaloids and aroylhydrazone moieties have recently shown good activities against methicillin-resistant *Staphylococcus aureus*.<sup>5</sup> Finally, the pseudillins are a family of highly halogenated marine alkaloids that have been recently shown to be allosteric inhibitors of the third enzyme in the non-mevalonate

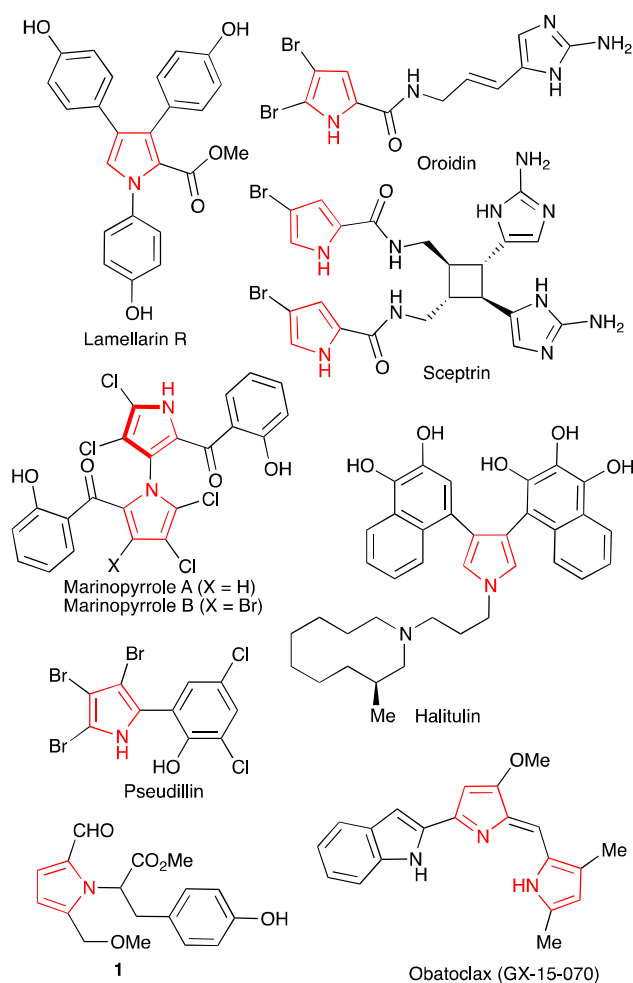


Figure 1. Some representative alkaloids containing isolated pyrrole rings and a related anticancer drug

pathway for isoprenoid biosynthesis, which is absent in mammals and is therefore an attractive target for the development of herbicides and chemotherapeutic agents.<sup>6</sup>

Pyrrole alkaloids have also been isolated from non-marine organisms, and as a first example we will mention compound **1** from the fruits of *Lycium chinense*, a traditional tonic medicine.<sup>7</sup> The prodiginines, exemplified by the well-known *Serratia* pigment prodigiosin, are a family of red-coloured, tripyrrolic alkaloids isolated from bacteria that display many biological activities. These compounds are receiving much attention in recent years as antibacterial,<sup>8</sup> immunosuppressive and anticancer<sup>9</sup> agents, and in particular obatoclax (GX-15-070), a prodiginine analogue, triggers cell death via autophagy and is under phase II clinical studies for the treatment of several tumours.<sup>10</sup>

Besides the natural products and their analogues, unnatural pyrroles show interesting bioactivities, and indeed a considerable number of pyrrole-derived drugs exist. Some representative examples are shown in Figure 2, including the non-steroidal anti-inflammatory agents tolmetin and zomepirac and the anthelmintic pyrvinium. Sunitinib is another commercially available pyrrole-derived drug, which is used as for the oral treatment of renal cancer and acts as a multi-targeted receptor tyrosine kinase inhibitor. Finally, atorvastatin, an inhibitor of HMG-CoA reductase, is very widely used as a cholesterol-lowering agent, being the top selling branded pharmaceutical in history (Figure 2).

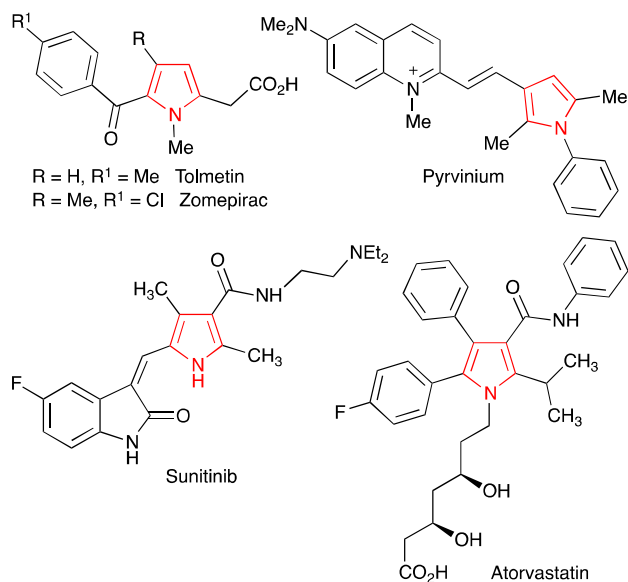


Figure 2. Some pyrrole-derived drugs

The development of methods for the fast and experimentally simple preparation of compounds with biological interest is crucial for the discovery of new bioactive substances. Synthetic efficiency, which can be viewed as one of the topmost requirements of contemporary synthesis, can be approached from several angles, but it is closely related to the concept of step economy, *i.e.*, to the development of methods that significantly reduce the number of synthetic operations required to prepare a particular target molecule. In this connection, reactions that generate several bonds in a single operation (multiple bond-forming transformations, MBFTs) are gaining increasing importance in all fields of organic synthesis,<sup>11,12</sup> and in particular in the preparation of heterocycles.<sup>13</sup> Among them,

multicomponent reactions (MCRs) have undergone an explosive growth in recent years.<sup>14</sup> MCRs can be defined as processes in which three or more reactants are introduced simultaneously or sequentially and become covalently bonded to form a single product that retains significant fragments of all starting materials. They have many advantages over more conventional methodologies, which can be summarized as follows:

- MCRs are endowed with an exceptional synthetic efficiency because of their ability to generate several bonds in a single operation. They are therefore exceedingly attractive as the foundation to improved synthetic routes to natural and unnatural organic compounds.<sup>15</sup>
- They avoid the need for isolation and purification of reaction intermediates and therefore lead to a greatly diminished generation of waste from these operations. It is worth remembering at this point that discarded solvents and chromatographic stationary phases constitute the bulk of the residues arising from synthetic activities, both in academic and industrial settings. Therefore, the development of new MCR-based methodologies can be regarded as one of the most important aspects of green chemistry.
- They are modular and convergent in nature, and this makes them particularly suitable for the generation of libraries of compounds in the discovery of new drugs and agrochemicals.<sup>16</sup>
- They are amenable to automation, potentially leading to savings of time in routine operations and thereby liberating workers for more creative aspects of the synthetic endeavour.

While there is much review literature on the synthesis of pyrroles by conventional protocols,<sup>17</sup> the use of multicomponent reactions in the synthesis of pyrroles has hardly been touched in the review literature. The present article is devoted to a discussion of this topic, covering mainly the literature published in the September 2009–December 2013 period. It is meant as an update of a previous review by the same authors in this journal,<sup>18</sup> and for a complete overview of the topic the interested reader is advised to peruse both articles.

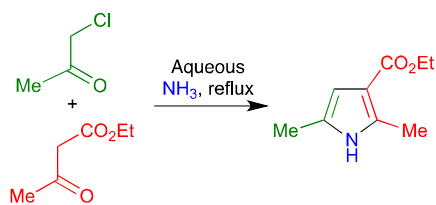
## 2. Multicomponent pyrrole syntheses starting from active methylene substrates: $\beta$ -dicarbonyl compounds and nitriles

### 2.1. The Hantzsch pyrrole synthesis

Hantzsch published in 1890 a brief note reporting that the reaction between “an equimolecular mixture of chloroacetone and acetoacetic ester under reflux in concentrated aqueous ammonia” afforded a new compound, which he correctly identified as a pyrrole derivative (Scheme 1).<sup>19</sup> The development of the so-called Hantzsch pyrrole synthesis has lagged far behind that of other classical name reactions, and until very recent developments it was far from being a general synthesis of polysubstituted pyrroles.

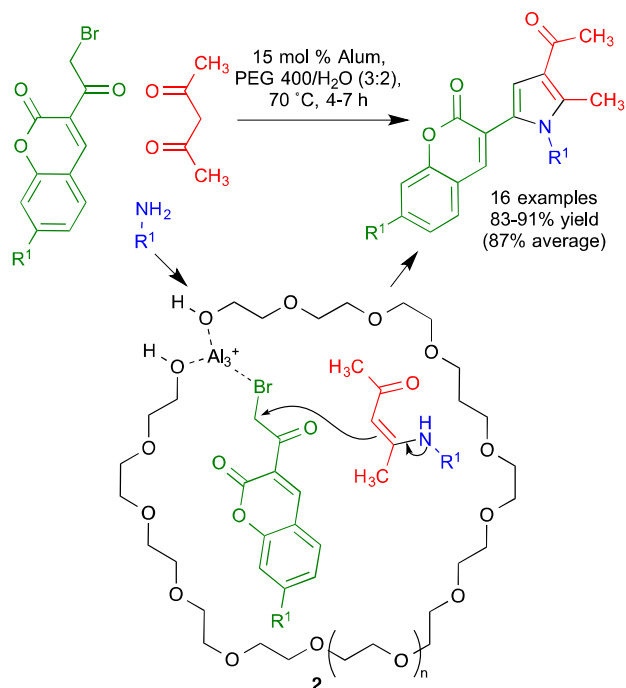


Arthur Rudolf Hantzsch



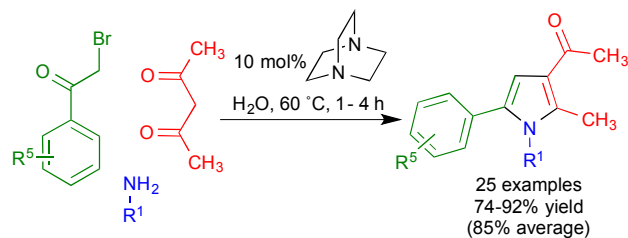
Scheme 1. The first multicomponent pyrrole synthesis, reported by Hantzsch

A three-component Hantzsch synthesis of pyrroles from primary amines, 2,4-pentanedione and 3-(bromoacetyl)-coumarin derivatives has been reported by Das (Scheme 2).<sup>20</sup> The pyrrole derivatives thus obtained were designed to contain a coumarin moiety, which was considered of interest in view of its pharmacological importance. The reaction was catalyzed by Alum ( $\text{Al}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ ), an eco-friendly catalyst that requires an aqueous reaction medium. In this case, the reaction was carried out in a mixture of water and polyethyleneglycol, which provides a micellar environment for the reaction to take place (structure 2).  $\text{Al}^{3+}$  was identified as the active Lewis acidic species that promoted both the enaminone formation and the polarization of the C-Br bond needed to facilitate the first step of the Hantzsch reaction.



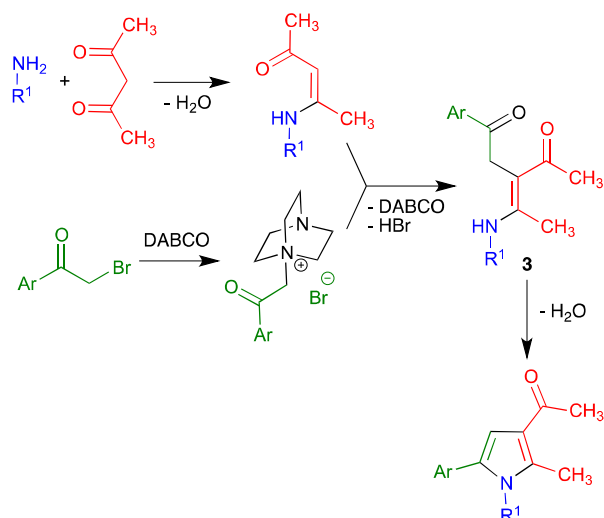
Scheme 2. Alum-promoted Hantzsch pyrrole synthesis in polyethyleneglycol-water reported by Das

A base-catalyzed variation of the Hantzsch pyrrole synthesis has been described by Meshram and coworkers using the organic base 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst and water as the reaction medium.<sup>21</sup> This method lacked generality since it was restricted to a single diketone substrate and substitutions were limited to the positions 1 and 5, from variations in the primary amine and phenacyl bromide components, respectively (Scheme 3).



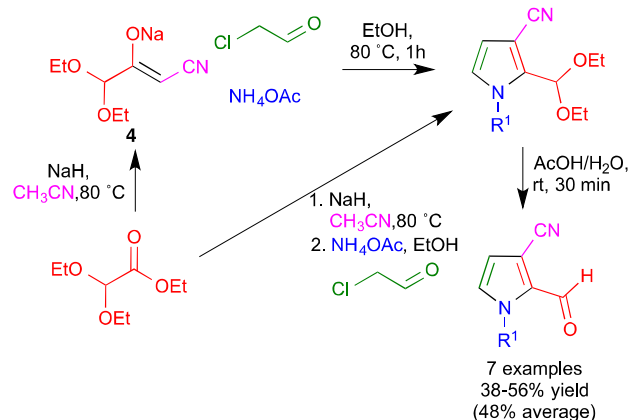
Scheme 3. Base-promoted Hantzsch pyrrole synthesis in water described by Meshram

The authors proposed the DABCO-catalyzed mechanism shown in Scheme 4. First, an enaminone is formed by reaction between the primary amine and pentane-2,4-dione. This intermediate reacts with the quaternary salt formed from DABCO and the phenacyl bromide, leading to intermediate **3** and liberating the basic catalyst. Finally, the cyclodehydration of **3** affords the observed product.



Scheme 4. Mechanism proposed for the DABCO-catalyzed Hantzsch pyrrole synthesis

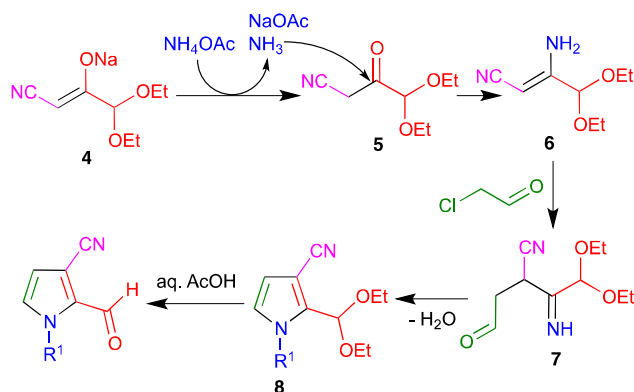
The Hantzsch synthesis has been adapted to the preparation of specific classes of pyrroles difficult to reach by alternative methods. Thus, as shown in Scheme 5, Moss and Nowak



Scheme 5. Adaptation of the Hantzsch pyrrole synthesis to the preparation of 2-formylpyrroles

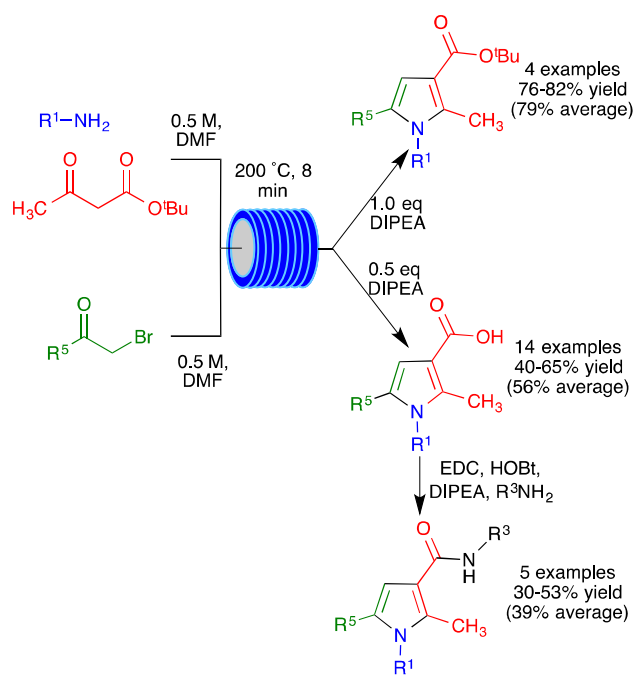
described the synthesis of pyrroles bearing carbonyl substituents at the C-2 and C-3 positions by reaction among the sodium enolate of 4,4-diethoxy-3-oxobutanenitrile **4**, ammonium acetate and chloroacetaldehyde.<sup>22</sup> The masked aldehyde is uncovered by the addition *in situ* of acetic acid/water. It was also possible to carry out the reaction in a four-component protocol starting from acetonitrile and ethyl 2,2-diethoxyacetate in a one-pot protocol.

The mechanism proposed to explain this transformation is shown in Scheme 6 and starts with the protonation of enolate **4** by ammonium acetate, generating *in situ* ammonia and the unstable ketonitrile **5**. The formation of enamine **6** occurs next, followed by its alkylation by chloroacetaldehyde to give intermediate **7**. Finally, an intramolecular cyclodehydration leads to pyrrole **8**, whose acetal group is hydrolysed *in situ* to give the final product.



Scheme 6. Mechanism proposed for the 2-formylpyrrole synthesis developed by Moss

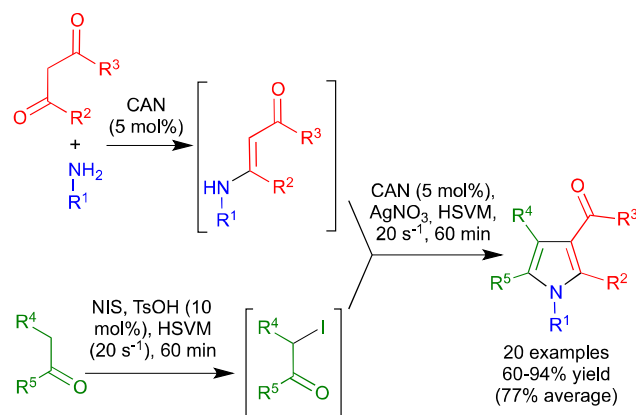
Non-conventional synthetic methodologies have been applied to the improvement of the Hantzsch pyrrole synthesis. Thus, the group of Cosford has described a one-pot continuous flow



Scheme 7. Cosford's flow synthesis of pyrroles based on the Hantzsch reaction

synthesis of pyrrole-3-carboxylic derivatives based on the Hantzsch reaction (Scheme 7).<sup>23</sup> The method involves the continuous flow of *tert*-butyl acetoacetate combined with primary amines and 2-bromoketones, which undergo reaction at 200 °C during 8 min. The HBr generated in the reaction was cleverly used in the flow method to hydrolyse the *t*-butyl ester, providing *in situ* the corresponding carboxylic acid derivatives. Alternatively, the hydrolysis could be avoided in the presence of one equivalent of diisopropyl ethylamine (DIPEA), allowing the isolation of the esters. The coupling of the carboxylic substituent to diverse amines was also described, achieving an efficient preparation of pyrrole-3-carboxamide derivatives, including two cannabinoid receptor subtype 1 (CB1) inverse agonists.

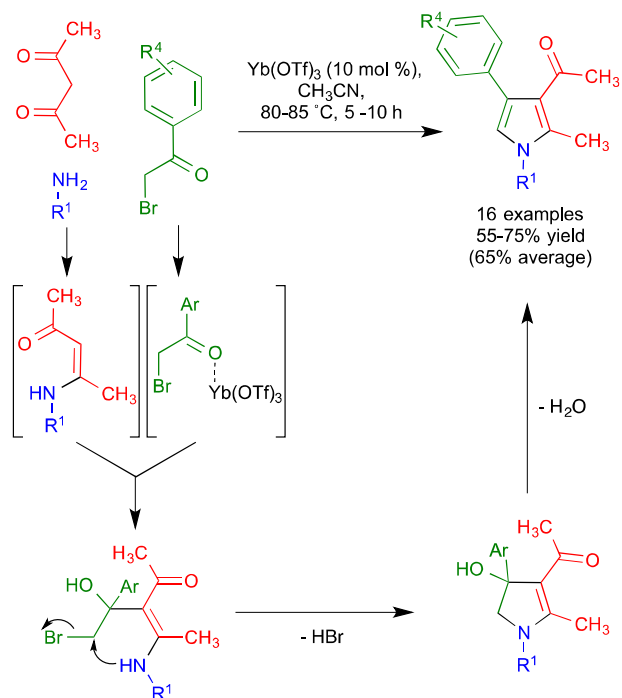
In another non-conventional approach, we have recently disclosed our preliminary results on a mechanochemical synthesis of pyrroles carried out under high-speed vibration milling conditions (HSVM). This sequential process involves the initial  $\alpha$ -iodination of ketones with N-iodosuccinimide in the presence of toluenesulfonic acid, followed by the addition of a mixture of a primary amine and a 1,3-dicarbonyl compound in the presence of Ce(IV) ammonium nitrate (CAN) and silver nitrate. This triggers an *in situ* Hantzsch reaction that furnishes polysubstituted pyrroles and in which the silver salt has the role of trapping the hydroiodic acid liberated in the alkylation step (Scheme 8).<sup>24</sup> This solvent-free methodology can be considered as the most general version of the Hantzsch reaction developed to date in terms of substrate scope, and provided the first example of a multicomponent reaction carried out with the sole input of mechanical energy.



Scheme 8. Generalization of the Hantzsch pyrrole synthesis under mechanochemical (HSVM) conditions developed by the Menéndez group

The reason for employing  $\alpha$ -iodoketones in our reactions instead of the more usual  $\alpha$ -bromo compounds was that the latter gave a mixture of both possible regioisomeric pyrroles. This loss of regioselectivity was attributed to competition of the Lewis acid-activated carbonyl with the halogen halide fragment in the reaction of the  $\alpha$ -haloketone with the  $\beta$ -enaminone. This effect of the presence of Lewis acids found an interesting synthetic application when Pal devised a fully regioselective synthesis of 1,2,3,4-tetrasubstituted pyrroles based on a three-component Hantzsch reaction combining primary amines, 2,4-pentanedione and phenacyl bromides in the presence of ytterbium triflate.<sup>25</sup> A single crystal X-ray diffraction study of one of the products confirmed the unusual 1,2,3,4-substitution pattern of the pyrrole core of the reaction products. As shown in Scheme 9, the reaction starts with the formation of a  $\beta$ -

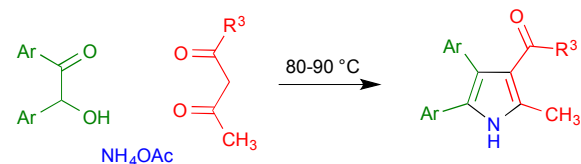
enaminone that reacts with the carbonyl substituent of the Yb(OTf)<sub>3</sub>-activated  $\alpha$ -bromoketone, leading to an intermediate in which the  $\alpha$  position of the enaminone bears a bromine substituent suitably poised for an intramolecular cyclization by nucleophilic displacement of bromide anion. A final dehydration reaction would give the observed pyrrole products. Interestingly, some of these 1,2,3,4 tetrasubstituted pyrroles showed promising activity as phosphodiesterase IV inhibitors.



Scheme 9. Reversed regiochemistry in the ytterbium triflate-catalyzed Hantzsch pyrrole synthesis

## 2.2. Multicomponent synthesis of pyrroles from $\beta$ -dicarbonyl compounds and $\alpha$ -hydroxyketones

Tamaddon and coworkers developed a three-component reaction for the synthesis of 2,3,4,5-tetrasubstituted pyrroles. They studied the reaction among ammonium acetate, 1,3-dicarbonyl compounds and benzoin derivatives in acidic conditions, using as catalysts silica sulfuric acid (SSA)<sup>26</sup> or molybdate sulfuric acid (MSA).<sup>27</sup> Both procedures were carried

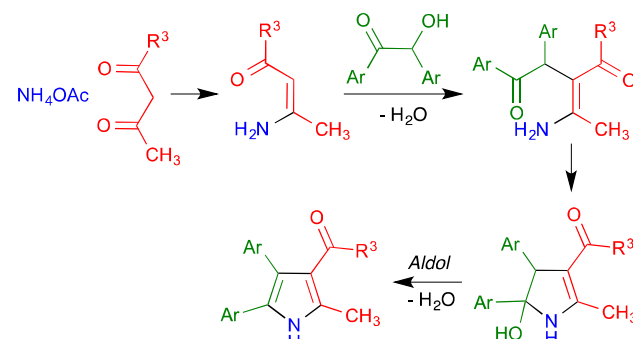


Method	Time	Nr. of examples	Yield		Ref.
			Range	Average	
MSA	24-80 min	9	87-96%	92%	26
SSA	10-60 min	8	87-96%	92%	27
H <sub>2</sub> O-EtOH	3-10 h	15	87-98%	93%	28
Solvent-free	2 h	13	76-98%	86%	29

Scheme 10. Synthesis of 4,5-diarylpyrroles from  $\beta$ -dicarbonyl compounds, arylglyoxals and ammonia

out under solvent-free conditions and the catalyst could be recovered. The same authors later described a three-component reaction in aqueous ethanol without any added catalyst.<sup>28</sup> In the three methodologies, high yields were reported although under catalyst-free conditions the reaction times were longer (Scheme 10). Recently, Bhatt and Trivedi developed the same reaction under solvent- and catalyst-free conditions.<sup>29</sup>

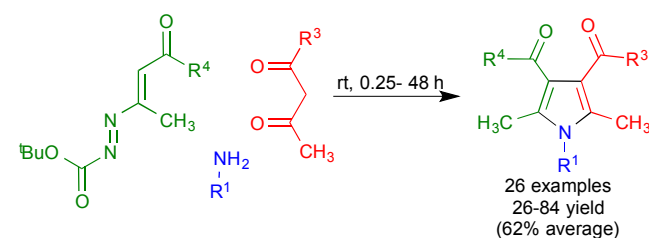
A plausible mechanism that explains these transformations is summarized in Scheme 11. After the initial formation of a  $\beta$ -enaminone from the dicarbonyl compound and ammonia, an acid-catalyzed alkylation by the benzoin starting material takes place, followed by an intramolecular aldol condensation that yields the 4,5-diarylpyrrole after dehydration.



Scheme 11. Plausible mechanism explaining the isolation of pyrroles from amines,  $\beta$ -dicarbonyl compounds and benzoin

## 2.3. Other multicomponent pyrrole syntheses starting from $\beta$ -dicarbonyl compounds

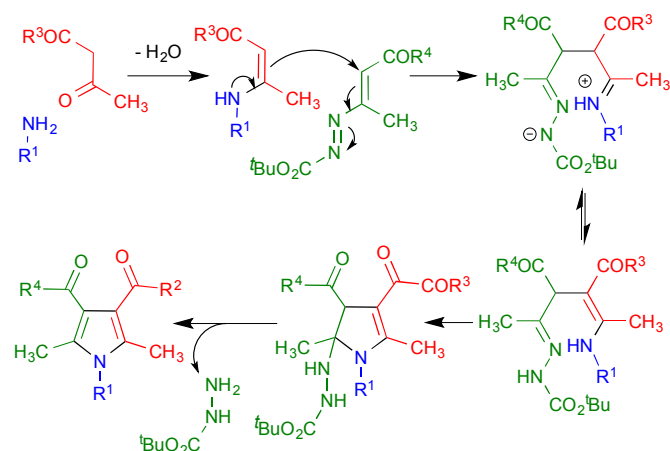
A three-component reaction between primary aliphatic amines, 1,3-dicarbonyl compounds and 1,2-diaza-1,3-dienes (DDs) that leads to fully substituted pyrrole derivatives under solvent- and catalyst-free conditions was reported by Attanasi *et al.* (Scheme 12).<sup>30</sup>



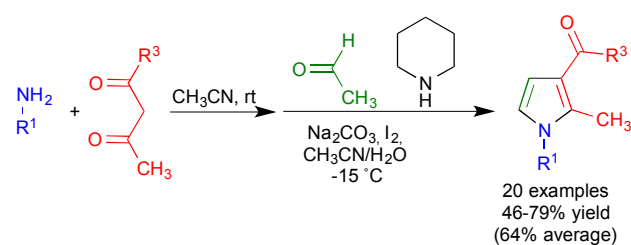
Scheme 12. Attanasi's three-component synthesis of pyrroles from aliphatic amines, 1,3-dicarbonyl compounds and 1,2-diaza-1,3-dienes

A mechanism that explains this transformation starts with the formation of an enaminone by reaction between the primary amine and the 1,3-dicarbonyl compound. Its Michael addition to the carbon end of the 1,2-diazadiene leads to a zwitterionic adduct that tautomerizes to the corresponding enaminone and then undergoes an intramolecular azacyclization followed by aromatization to give the expected pyrrole with concomitant loss of a hydrazine derivative (Scheme 13).

Zeng has described an efficient method for the synthesis of 1,2,3-trisubstituted pyrroles from primary amines, dicarbonyl compounds and acetaldehyde (Scheme 14).<sup>31</sup> This three-component synthesis was developed as a one-pot, two-step reaction involving an iodine-mediated cyclization.

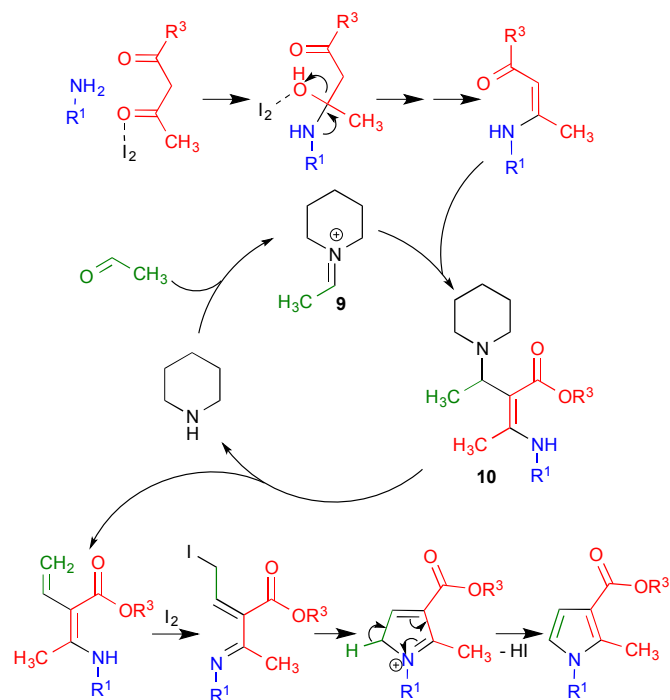


Scheme 13. Mechanism proposed to explain the pyrrole synthesis developed by Attanasi



Scheme 14. Iodocyclization-mediated synthesis of pyrroles developed by Zeng

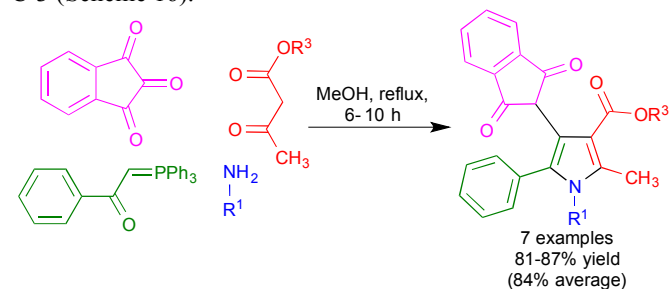
The authors proposed the mechanistic pathway shown in scheme 15 that starts with the iodine-mediated formation of an enaminone from the amine and dicarbonyl components. Simultaneously, acetaldehyde reacts with piperidine forming iminium derivative **9**, which then gives a Knoevenagel condensation with the enaminone, leading to intermediate **10**.



Scheme 15. Mechanism proposed for the iodine-promoted pyrrole synthesis

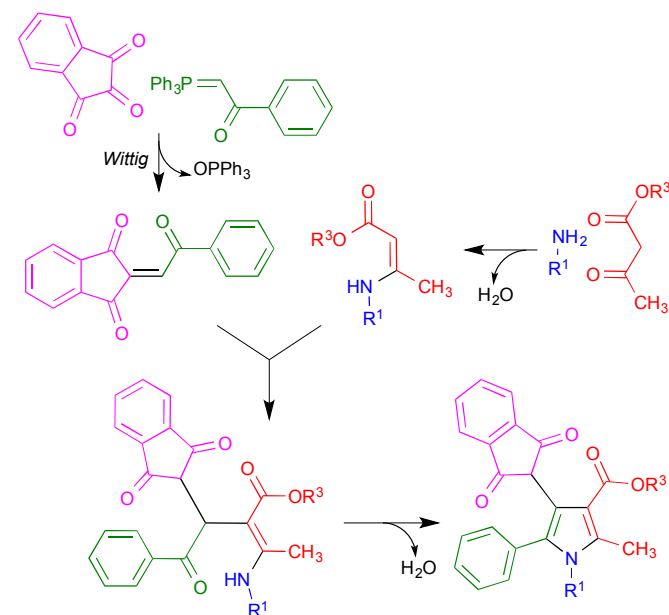
The vinylogous enaminoester resulting from loss of a molecule of piperidine from **10** reacts with iodine selectively at its terminal methylene and then cyclizes *via* an intramolecular nucleophilic displacement. A subsequent aromatization by deprotonation completes the formation of the final pyrrole product.

Recently, a four-component reaction leading to fully substituted pyrroles has been reported from primary amines, ninhydrin and 1-phenyl-2-(1,1,1-triphenyl- $\lambda^5$ -phosphanylidene)-1-ethanone as the key reagent.<sup>32</sup> Seven examples were prepared in very good yield when the reaction mixture was refluxed in methanol for at least six hours. Unfortunately, only two positions can be varied, namely the pyrrole nitrogen and the ester substituent at C-3 (Scheme 16).



Scheme 16. Four-component synthesis of 4-(2-indenyl)pyrroles

A plausible explanation for this transformation is depicted in Scheme 17. First, enaminone formation takes place between the amine and alkyl acetoacetate components, while a Wittig reaction occurs between ninhydrin and the phosphorous ylide. Next, a Michael addition reaction between both intermediates leads to a precursor that undergoes cyclization with loss of a molecule of water to form the final product.

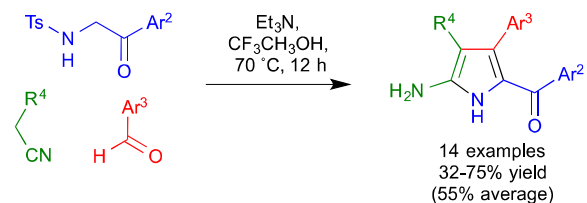


Scheme 17. Wittig-Michael mechanism proposed to explain the formation of indenylpyrroles

A few additional pyrrole syntheses starting from the combination of  $\beta$ -dicarbonyls and other  $\alpha$ -dicarbonyl compounds will be discussed in Section 3.1.

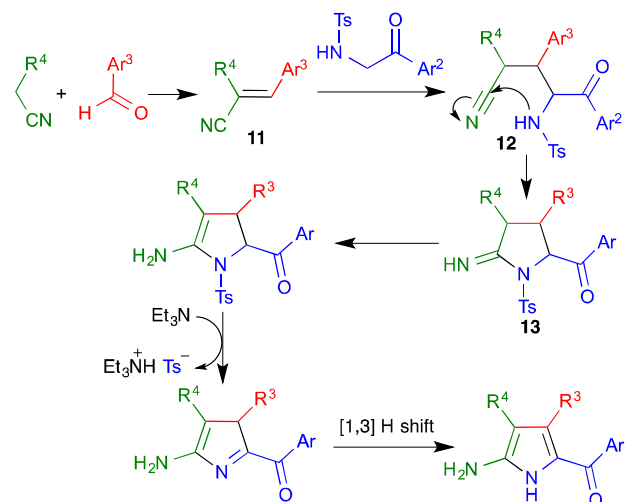
### 2.3. Multicomponent pyrrole syntheses from $\alpha$ -activated nitriles

A very efficient synthesis of derivatives of the 2-amino-5-ketoarylpyrrole scaffold, which were prepared because of their potential pharmaceutical interest, has been developed by Wang and Dömling (Scheme 18).<sup>33</sup> A mixture of *N*-protected  $\alpha$ -amino acetophenones, aromatic aldehydes and malonodinitrile, after 12 hours of reflux in trifluoroethanol, was found to lead to pyrroles as solids that precipitated from the reaction mixture, thus avoiding the need for chromatography.



Scheme 18. Dömling's three-component synthesis of 2-acylpyrroles

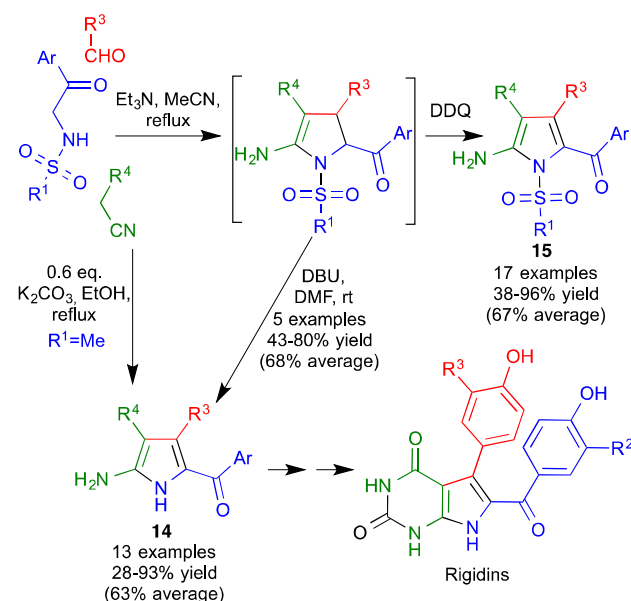
The mechanism proposed to explain this transformation starts with a Knoevenagel condensation between the most acidic component, namely the cyanomethylene derivative, and the aldehyde leading to the  $\alpha,\beta$ -unsaturated nitrile **11**. The sulfonamide next gives a Michael-type addition, acting as a C-nucleophile, forming intermediate **12**, which cyclizes and tautomerizes to pyrrolidine **13**. Finally, the elimination of one molecule of toluenesulfonic acid followed by a [1,3] hydrogen shift leads to aromatization and affords the expected 2-aminopyrrole derivatives (Scheme 19).



Scheme 19. Mechanism proposed to explain the 2-acylpyrrole synthesis

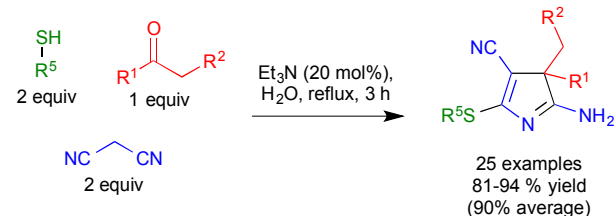
A variation of this reaction was investigated by the group of Magedov.<sup>34</sup> In this method, the combination of aldehydes, *N*-(substituted sulfonamido) acetophenones and activated methylene compounds leads to polysubstituted pyrroles that are oxidized *in situ* to 2-aminopyrrole derivatives. In the case of *N*-unsubstituted pyrroles **14**, DBU in DMF was used to promote the dehydrosulfinylation of the 2-pyrrolines. On the other hand, pentasubstituted pyrroles **15** were accessible *via* a one-pot procedure that required the addition of triethylamine followed by DDQ for the oxidation step (Scheme 20). In subsequent studies, the use of 0.6 equiv of  $K_2CO_3$  in refluxing ethanol was identified as the method of choice to

access pyrroles **14** when tosyl was the leaving group. These conditions were used to prepare 2-aminopyrrole-3-carbamide precursors that allowed a very concise (four-step) synthesis of the rigidin alkaloids.



Scheme 20. Synthesis of tetra- and pentasubstituted aminopyrroles reported by Magedov and used as a key step in the synthesis of the rigidins

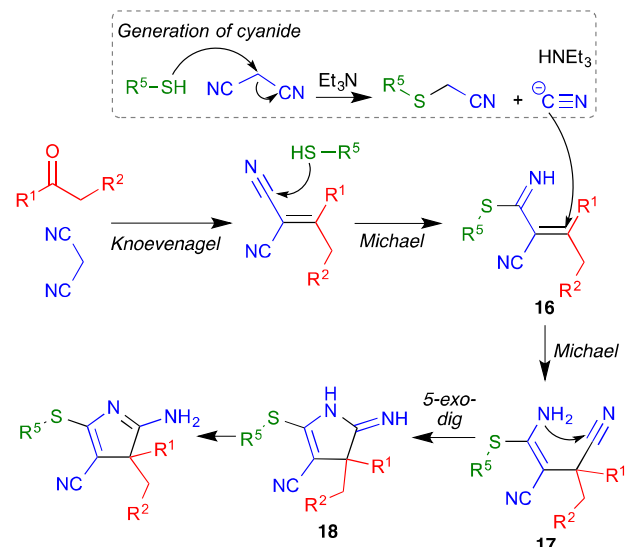
Recently, Mukhopadhyay and coworkers disclosed a novel multicomponent strategy that affords 3*H*-pyrroles from ketones, thiols and malononitrile (Scheme 21).<sup>35</sup> The reaction, which was catalyzed by triethylamine in water, required the use of two equivalents of malononitrile and the corresponding thiols. This approach elegantly exploits the dual role of nitriles, which are able to act both as nucleophiles and electrophiles.



Scheme 21. Mukhopadhyay's synthesis of 3*H*-pyrroles

The postulated mechanism (Scheme 22) starts with a base-promoted Knoevenagel condensation between the ketone and one molecule of malononitrile. The Michael substrate thus formed then experiences a nucleophilic attack by the corresponding thiol, leading to intermediate **16**. Next, a second Michael addition of a cyanide anion takes place to give an enaminonitrile **17** that, after a 5-*exo-dig* cyclization, affords an iminopyrroline **18** that tautomerizes to the final product. The *in situ* formation of the required cyanide anion is easily explained by the nucleophilic attack of one molecule of the thiol to another of malononitrile.



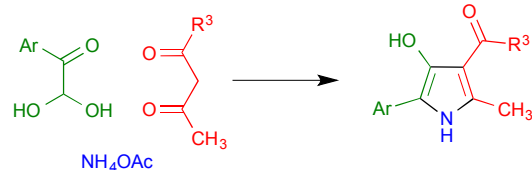


Scheme 22. Mechanistic explanation of the synthesis of 3H-pyrroles

### 3. Multicomponent synthesis of pyrroles starting from $\alpha$ -dicarbonyl compounds or their precursors

#### 3.1. Pyrroles from the combination of $\alpha$ - and $\beta$ -dicarbonyl compounds

The three-component reaction starting from ammonium acetate, 1,3-dicarbonyl compounds and arylglyoxal hydrates under solvent-free conditions led to 4-hydroxypyrroles.<sup>29</sup> Independently and almost simultaneously, a fast, ultrasound-assisted version of the same transformation was also developed.<sup>36</sup> The latter protocol involved the use of water as the reaction medium and its main advantage was the short reaction times required (Scheme 23).

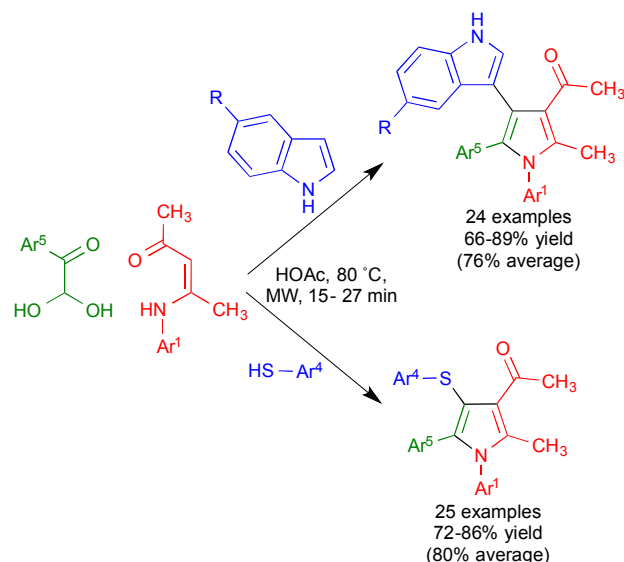


Conditions	Nr. of examples	Yield		Ref.
		Range	Average	
Solvent-free, 50 °C, 120 min	3	83-92%	87%	29
Ultrasound, water, 3-5 min	11	50-95%	85%	37

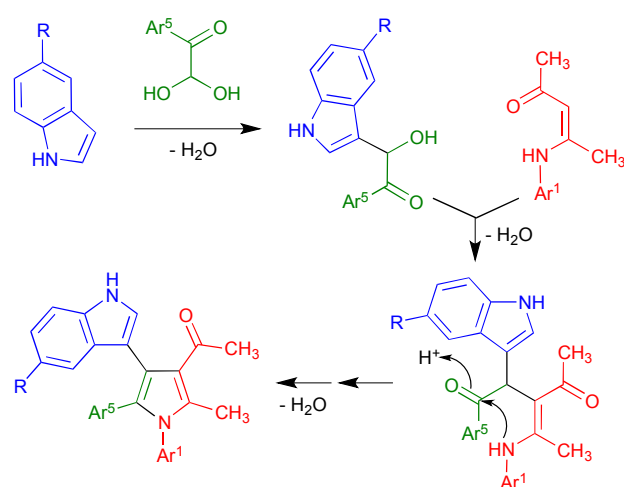
Scheme 23. Solvent-free and ultrasound-assisted synthesis of 4-hydroxypyrroles

Tu and coworkers developed a related three-component pyrrole synthesis that allows the incorporation of nucleophilic moieties to the pyrrole C-4 position.<sup>37</sup> This method is based on the microwave-promoted reaction between indoles or benzenethiols with  $\beta$ -enaminones and arylglyoxal monohydrates in the presence of acetic acid (Scheme 24).

The mechanism proposed for the indolation-initiated reaction is shown in Scheme 25. It starts with the nucleophilic attack of indole to the protonated arylglyoxal monohydrate with displacement of a molecule of water, followed by a similar nucleophilic displacement of water by the enaminone. Finally, a cyclodehydration step leads to the final product.



Scheme 24. Indolation and thiolation-based three-component pyrrole synthesis developed by Tu

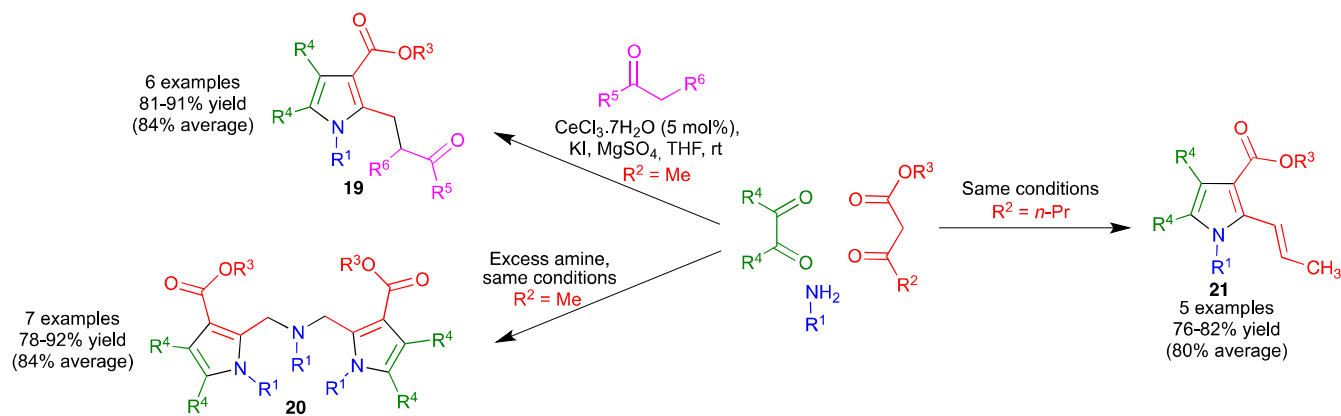


Scheme 25. Mechanism proposed for the indolation-initiated pyrrole synthesis

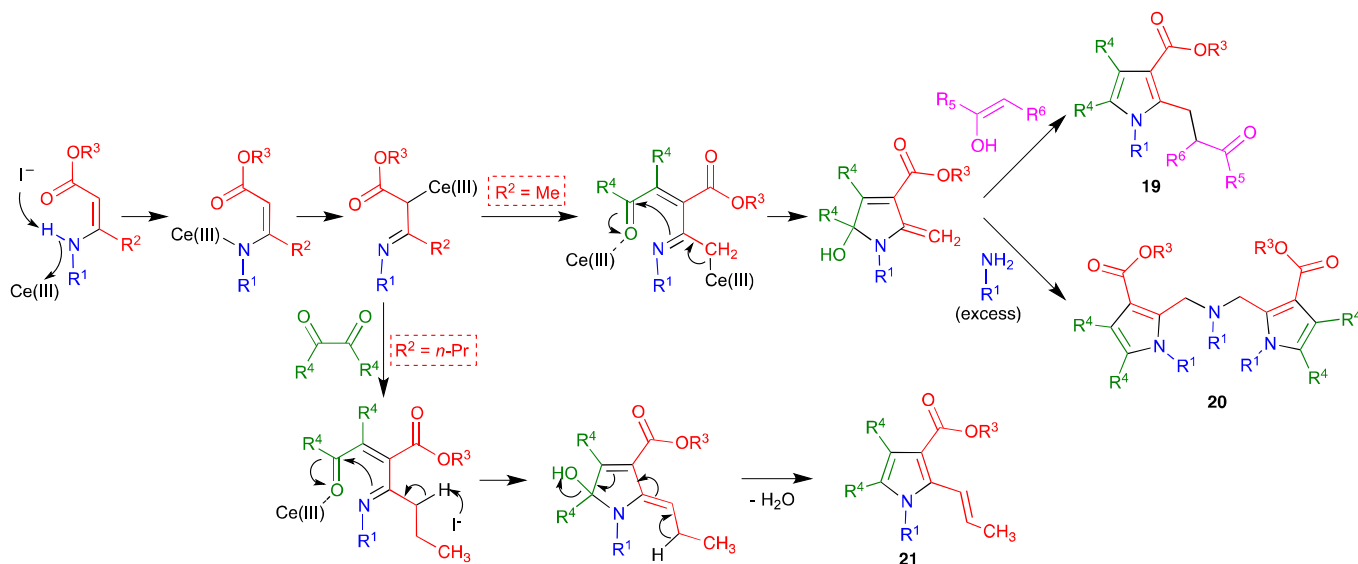
A  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ -catalyzed multicomponent synthesis of pentasubstituted pyrroles, allowing the simultaneous introduction of side-chain functions, was reported by Maiti (Scheme 26).<sup>38</sup> When primary amines,  $\beta$ -ketoester derivatives and 1,2-diketones are combined with a second ketone in a four-component reaction, the final pyrrole **19** contains a carbonyl group at the C-2 position. Highly aryl-substituted bis-aminomethylpyrroles **20** were also prepared *via* a pseudo seven-component reaction among 1,2-diketones,  $\beta$ -ketoesters and an excess of the primary amines. On the other hand, the reaction among primary amines, 1,2-diketones and ethyl 3-oxohexanoate leads to pentasubstituted pyrroles **21** bearing a C-2 olefinic side-chain.

Although the exact mechanism for these transformations is unknown, the authors proposed the pathway shown in Scheme 27. The reaction starts with the usual generation of an enaminone from the 1,3-dicarbonyl compound and the primary amine, followed by a N-H insertion of Ce(III), assisted by KI deprotonation. This allows the activation of the vinylic  $\text{sp}^2$  C-H bond of the enaminone, promoting its nucleophilic attack to

## ARTICLE



Scheme 26. Multicomponent syntheses of pyrroles reported by Maiti, catalysed by the Ce(III)-KI system

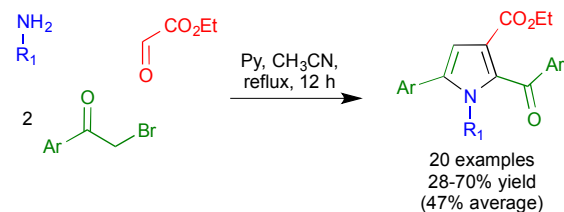


Scheme 27. Mechanism proposed for the Ce(III)/KI-catalyzed multicomponent pyrrole synthesis

1,2-diketone. Ce(III) then promotes the final cyclization, which is followed by the simultaneous elimination of water and incorporation of the corresponding ketone or amine by allylic nucleophilic displacement of water with concomitant aromatization to afford pyrroles **19**. On the other hand, by using an excess of the amine component it is possible to drive the reaction towards the formation of compounds **21** via a double allylic nucleophilic displacement reaction. In the substrates for which  $R^2 = Et$ , an elimination reaction in the side chain occurs, installing a double bond with complete *trans*-selectivity and leading to compounds **20**.

### 3.2. Other multicomponent routes to pyrroles from $\alpha$ -dicarbonyl compounds or their precursors

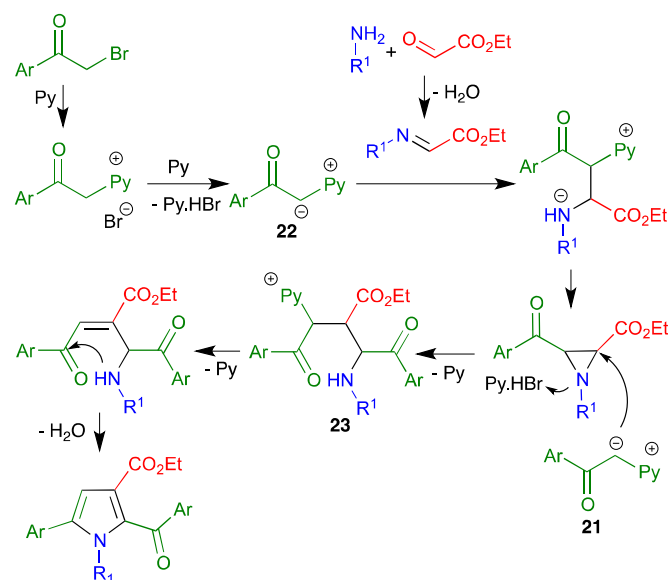
A straightforward route to 1,2,3,5-tetrasubstituted pyrroles has been developed by Wang and coworkers (Scheme 28), and is based on a four-component reaction in refluxing acetonitrile among primary amines, ethyl glyoxylate and two equivalents of



Scheme 28. Four-component synthesis of 2-acylpyrroles described by Wang

2-bromoacetophenones in the presence of pyridine as a basic catalyst.<sup>39</sup> This transformation involves the creation of four bonds by the assembly of [2 + 1 + 1 + 1] atom fragments. Additionally, the authors described a concise synthesis of benzo[*g*]indole derivatives as an evidence of the synthetic utility of these pyrrole derivatives.

The mechanism proposed for this process is depicted in Scheme 29 and starts with the reaction between phenacyl bromide and pyridine forming a pyridium ylide **22** after deprotonation. An imine is simultaneously generated *in situ* from the primary amine and ethyl glyoxylate, and then it undergoes nucleophilic attack from ylide **22**, followed by an intramolecular nucleophilic substitution to generate an aziridinium, which is protonated to the corresponding aziridinium bromide by the HBr liberated in the first step. Opening of the aziridinium ring by a second molecule of **22** furnishes intermediate **23** that then loses a molecule of pyridine by an elimination reaction that generates an unsaturated system. An intramolecular cyclodehydration reaction then completes the formation of the final pyrrole product.



Scheme 29. Mechanistic explanation of the four-component synthesis of 2-acylpyrroles

A modification of this pyrrole synthesis was reported by Pal and coworkers, who reported that the optimal conditions involve the use of DMF-pyridine at 50 °C.<sup>40</sup> Pyrrole derivative **24**, obtained by this method, was the starting material employed to prepare a library of new potential inhibitors of

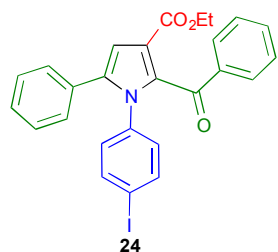
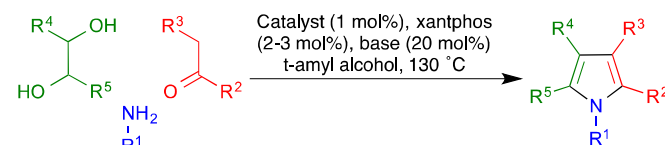


Figure 3. Structure of a precursor to phosphodiesterase 4 inhibitors prepared by a four-component multicomponent reaction

phosphodiesterase 4 (PDE4) *via* Pd-catalyzed cross-coupling reactions.

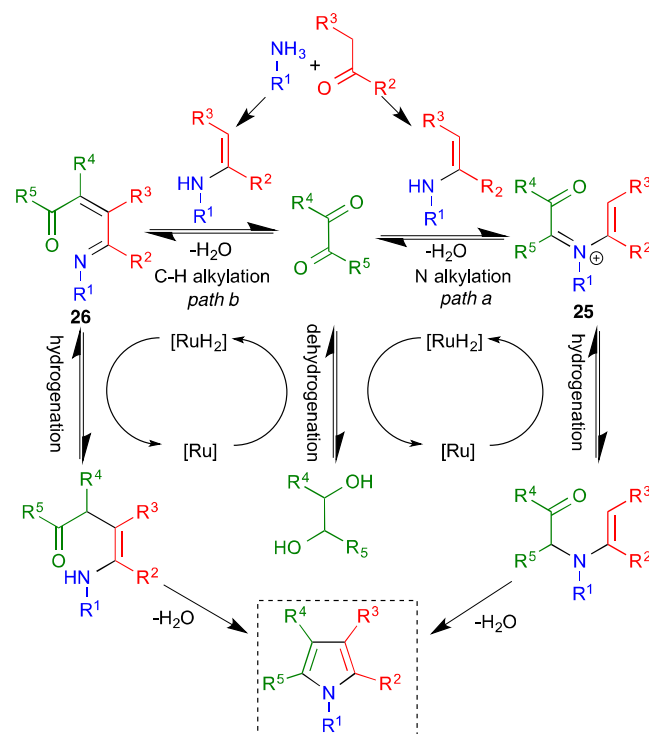
Recently, the group of Beller has reported the three-component combination of ketones, amines and diols in the presence of ruthenium catalytic systems as a highly regioselective route to polysubstituted pyrroles, with water as the only side product. They studied two different combinations of ruthenium catalyst and base,<sup>41,42</sup> both of which showed similar efficiencies in terms of yields, as shown in Scheme 30. When non-symmetrical diols were used, very high or complete regioselectivities were achieved, whereby the C-H alkylation occurs at the more reactive, sterically less hindered position of the diol.



Catalyst	Base	Time	Number of examples	Yield	
				Range	Average
[RuCl <sub>2</sub> (p-cymene)] <sub>2</sub>	tBuOK	16 h	40	30-92 %	70 %
Ru <sub>3</sub> (CO) <sub>12</sub>	K <sub>2</sub> CO <sub>3</sub>	18 h	36	30-90%	67 %

Scheme 30. Three-component ruthenium-promoted pyrrole synthesis reported by Beller

The mechanism proposed by the authors to explain this reaction (Scheme 31) is based on the “hydrogen autotransfer” concept, a tool developed for the amination and alkylation of alcohols. The first step of the pathway is the Ru-catalyzed dehydrogenation of the starting diol to generate the corresponding  $\alpha$ -diketone. Next, a condensation with the



Scheme 31. Mechanism proposed for the Ru-promoted pyrrole synthesis, involving hydrogen autotransfer processes

enaminone nitrogen (path a) or with the activated methylene of the enaminone (path b) gives iminium **25** or 1-azadiene **26**, respectively. Finally, the hydrogenation of both intermediates releases the corresponding precursors for the intramolecular cyclization that yields the desired pyrrole. This hydrogenation is effected by the hydrogenated Ru catalyst resulting from the initial transformation of the starting diol into a diketone.

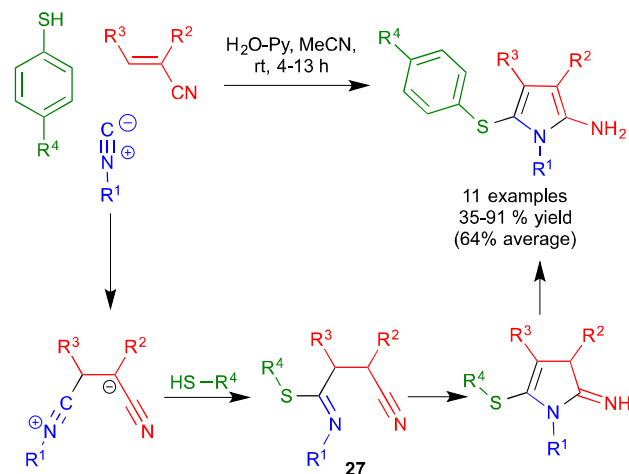
Some additional MCR processes leading to pyrroles from  $\alpha$ -dicarbonyl compounds and that involve the use of activated alkynes as a second starting material will be discussed in Section 6.

#### 4. Multicomponent pyrrole syntheses using isonitriles as the source of the heterocyclic nitrogen

Isonitriles are very important starting materials in multicomponent chemistry due to their unique modes of reactivity, leading some authors to coin the term "Isonitrile-based multicomponent reactions" (IMCRs).<sup>43</sup> Obviously, this reflects in their widespread use in the development of new multicomponent reactions for the synthesis of pyrroles, and we will discuss below recent progress made in this area.

The Mironov group described the preparation of 2-amino-5-arylthiopyrroles starting from isocyanides, thiophenols and *gem*-diactivated olefins under basic conditions.<sup>44</sup> If the olefin contained an alkyl group as  $R^3$ , a decrease in the reaction time and an increase of yields were observed. It was also found that the use of aliphatic thiols was not successful.

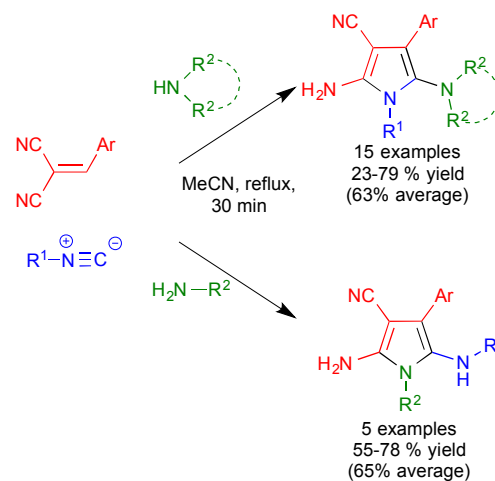
The mechanism proposed for this transformation starts with the reaction between the isocyanide and the olefin, leading to the formation of a zwitterionic intermediate, which undergoes a nucleophilic attack by the thiophenol to furnish intermediate **27**, containing thioimidate and nitrile functional groups. Its 5-*exo-dig* cyclization yields a 2-iminopyrroline that finally tautomerizes to the isolated product. Depending of the choice of isocyanide, the last step may not take place due to steric hindrance, and in this case the product isolated from the reaction is the corresponding thioimidate **27** (Scheme 32).



Scheme 32. Three-component synthesis of 2-amino-5-arylthiopyrroles starting from isocyanides, thiophenols and *gem*-diactivated olefins

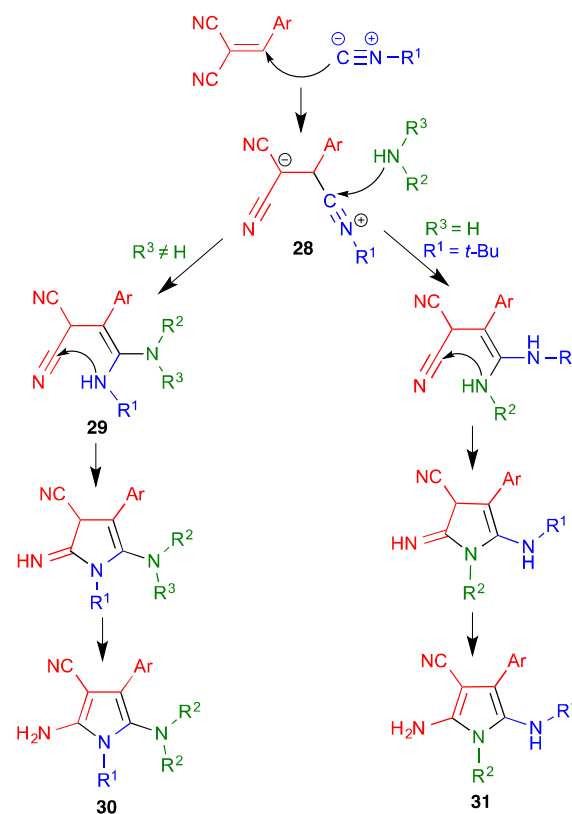
A three-component reaction among isocyanides, *gem*-diactivated olefins and primary or secondary amines was found to provide a chemoselective access to 2,5-diaminopyrrole derivatives (Scheme 33).<sup>45</sup> The reaction allowed the presence of both electron-donating and electron-withdrawing groups in the

aromatic ring. However, a few substrates failed to give the reaction, including ethyl isocynoacetate on the isocyanide side, hindered or scarcely reactive secondary amines and aliphatic aldehydes.



Scheme 33. Three-component synthesis of 2,5-diaminopyrroles from isocyanides, *gem*-diactivated olefins and primary or secondary amines

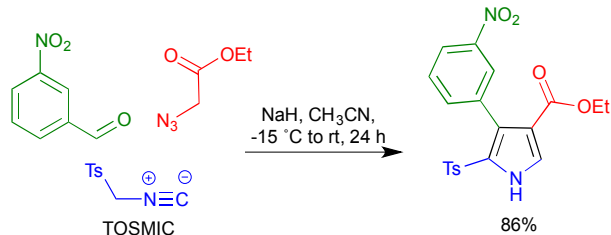
From the mechanistic point of view (Scheme 34), the reaction was proposed to start with the nucleophilic addition of isocyanide to the *gem*-diactivated olefin. The resulting zwitterionic intermediate **28** undergoes a nucleophilic attack by the corresponding amine. If the latter is secondary, the nitrogen from the isocyanide group participates in the cyclization step to



Scheme 34. Mechanism that accounts for the formation of 2,5-diaminopyrroles from isocyanides, *gem*-diactivated olefins and amines

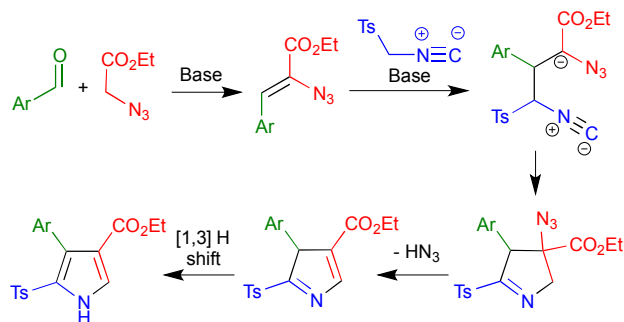
form intermediate **29** and then pyrrole **30**. On the other hand, the use of a primary amine entails its subsequent attack to the cyano group, affording pyrroles **31** bearing at nitrogen the substituent corresponding to the amine. In order to ensure the regioselectivity of this reaction, an isocyanide bearing a bulky substituent ( $R^1 = t\text{-Bu}$ ) is employed.

Yu and coworkers reported a facile two-component synthesis of 2,3,4 trisubstituted pyrroles from tosylmethyl isocyanide (TOSMIC) and vinyl azides, previously obtained from aldehydes and  $\alpha$ -azidoesters, under mild conditions. They also reported a single example of a one-pot, three-component version of the same reaction where the requisite vinylazide was prepared *in situ* from *m*-nitrobenzaldehyde and ethyl 2-azidoacetate component (Scheme 35).<sup>46</sup>



Scheme 35. Single example of a three-component reaction among *m*-nitrobenzaldehyde, ethyl 2-azidoacetate and TOSMIC

In this sequential process, a mixture of *m*-nitrobenzaldehyde and ethyl 2-azidoacetate was first stirred for 2 hours at  $-15\text{ }^\circ\text{C}$  using NaH as a base, whereby a Knoevenagel condensation took place. Next, TOSMIC was added onto the Knoevenagel product and the reaction mixture was stirred at room temperature for 24 hours. Under these conditions, a Michael addition took place followed by intramolecular cyclization *via* nucleophilic substitution with loss of the  $\text{N}_3^-$  anion as a leaving group. The final aromatic pyrrole product is generated through an [1,3]-intramolecular proton shift (Scheme 36).



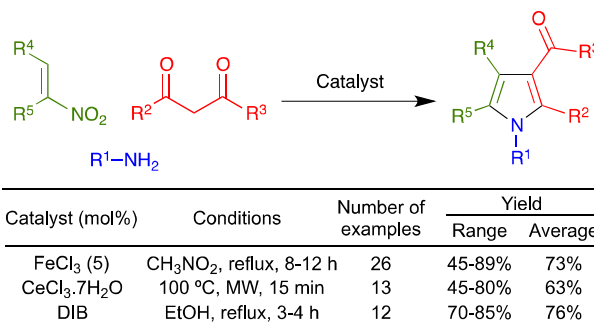
Scheme 36. Mechanism proposed to explain the isolation of a 5-tosylpyrrole derivative from a three-component reaction

## 5. Multicomponent synthesis of pyrroles from nitroalkanes and nitroalkenes

### 5.1. Multicomponent pyrrole syntheses involving Michael additions to nitroolefins

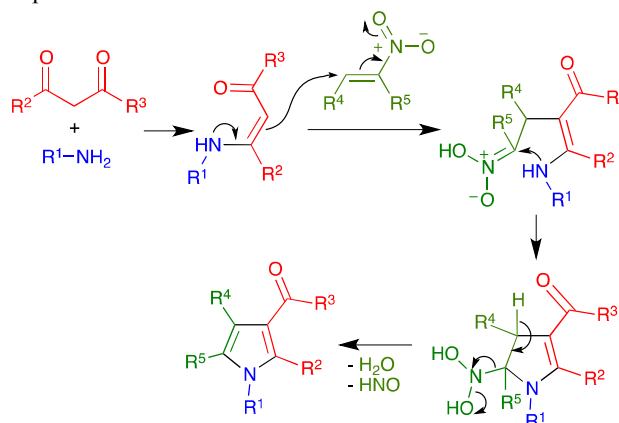
Polisubstituted pyrroles can be synthesized by one-pot coupling of nitroalkenes, amines and 1,3-dicarbonyl compounds *via* a Grob-Camenish type reaction (Scheme 37). Different catalysts have been used to improve the outcome of this reaction, with

Lewis acids catalyzed-reactions being highly dependent on the nature of the solvent and the reaction temperature. Nitromethane and  $100\text{ }^\circ\text{C}$  showed to be the most effective conditions for the reactions catalysed by Fe(III) chloride.<sup>47</sup> On the other hand, the use of microwave irradiation afforded similar yields in shorter times, in reactions performed in the presence of cerium trichloride.<sup>48</sup> Similarly, the Telvekar group has described a simple and efficient three-component synthesis of tetrasubstituted pyrroles from acetylacetone, amines and nitrostyrenes using (diacetoxyiodo)benzene (DIB) as catalyst and ethanol as solvent.<sup>49</sup>



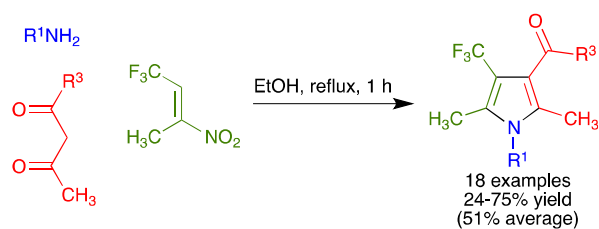
Scheme 37. Three-component synthesis of pyrroles from nitroalkenes, amines and 1,3-dicarbonyl compounds

A common mechanism can be proposed for these transformations and involves the *in situ* initial formation of a  $\beta$ -enaminone, followed by its Michael addition to the nitroolefin and cyclization followed by aromatization by loss of hyponitrous acid (Scheme 38). Thus, the nitro group acts both as a stabilizer of the intermediate anion in the initial Michael addition and as a good leaving group in the final aromatization step.



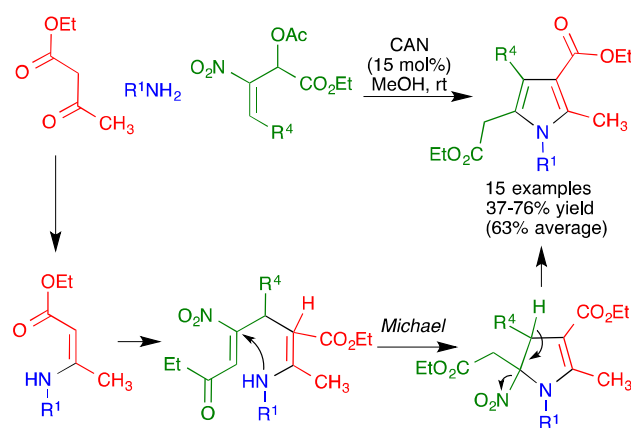
Scheme 38. Mechanism proposed for the pyrrole synthesis from nitroalkenes, amines and 1,3-dicarbonyl compounds

Substituted  $\beta$ -(trifluoromethyl)pyrroles were similarly synthesized in good yields by the three-component reaction of 1,1,1-trifluoro-3-nitrobut-2-ene with 1,3-dicarbonyl compounds and ammonia or primary aliphatic amines in refluxing ethanol. In this case, no catalyst was required (Scheme 39).<sup>50</sup>



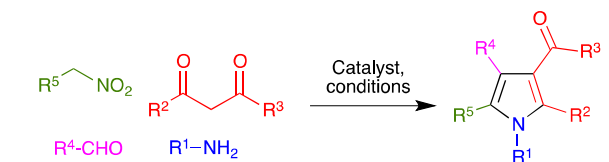
Scheme 39. Three-component synthesis of 4-trifluoromethylpyrroles

Chen developed a similar multicomponent reaction from amines, ethyl acetoacetate and nitroallylic acetates, catalyzed by ceric ammonium nitrate (CAN), for the synthesis of N-protected pyrrole diethyl 2,4-dicarboxylate derivatives. The proposed mechanism involves an allylic displacement reaction between the  $\beta$ -enaminone and the nitroalkene, followed by a 5-*exo-trig* cyclization *via* a Michael addition and a final aromatization (Scheme 40).<sup>51</sup>



Scheme 40. Three-component synthesis of pyrroles from amines, ethyl acetoacetate and nitroallylic acetates developed by Chen

Four-component versions of this reaction have been widely investigated (Scheme 41) by reacting together nitroalkanes, aldehydes, 1,3-dicarbonyl compounds and primary amines in the presence of different catalysts, including  $\text{FeCl}_3$ ,<sup>52</sup>  $\text{I}_2$ ,<sup>53</sup>



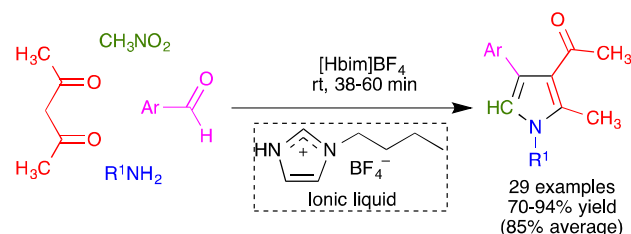
Catalyst (mol%)	Conditions	Number of examples	Yield	
			Range	Average
$\text{FeCl}_3$ (10)	Reflux, 5-16 h	36	38-85%	59%
$\text{I}_2$	90-95 °C, 6-8 h	16	60-85%	75%
$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (10)	Reflux, 6-12 h	23	52-78%	69%
STA (10)	Reflux, 4-6 h	24	60-88%	81%
Montmorillonite clay K10 or KSF	60 °C, 5-8 h	17	68-88%	85%
Nano CuO (10)	100-105 °C, 12 h	13	65-81%	73%
GAAS (50 wt%)	100 °C, 3-48 h	39	48-93%	83%

Scheme 41. Four-component synthesis of pyrroles from nitroalkanes, aldehydes, 1,3-dicarbonyl compounds and primary amines

nickel chloride hexahydrate,<sup>54</sup> silica gel-supported tungstic acid (STA),<sup>55</sup> montmorillonite clay,<sup>56</sup> CuO nanoparticles<sup>57</sup> and gluconic acid aqueous solution (GAAS).<sup>58</sup>

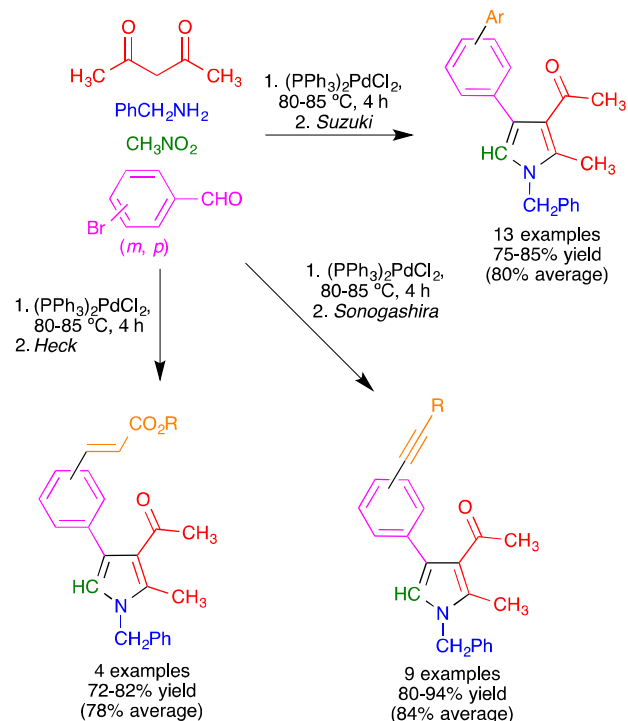
A common mechanism can be proposed for all these syntheses. Following a Henry condensation of the nitroalkane with the aldehyde, the reaction then proceeds along the mechanistic pathway summarized in Scheme 38.

The group of Meshram has recently described a “catalyst-free” four-component synthesis of pyrroles using a reusable ionic liquid as reaction medium. Coupling of 1,3-pentanedione, amines, nitromethane and aromatic aldehydes in the presence of 1-n-butylimidazolium tetrafluoroborate ( $[\text{Hbim}][\text{BF}_4]$ ) afforded tetrasubstituted pyrroles in good to excellent yields and in short reaction times (Scheme 42). A variety of aromatic aldehydes and amines can be used, including alkynylamines. The authors reported that only traces of the desired pyrroles were obtained when the reaction was carried out in neat conditions and therefore, it has to be assumed that the ionic liquid used as solvent has catalytic activity. The solvent can be reused up to three cycles without any appreciable loss of activity.<sup>59</sup> The mechanism proposed for this transformation is similar to the one described in Scheme 40 and involves the formation of a  $\beta$ -enaminone by condensation of acetylacetone with the primary amine and a  $\beta$ -nitrostyrene by condensation of nitromethane with aldehyde, followed by cyclocondensation between both intermediates.



Scheme 42. Four-component synthesis of pyrroles in an ionic liquid

The four-component reaction among nitroalkanes, aldehydes, 1,3-dicarbonyl compounds and primary amines can also be carried out in the presence of  $(\text{PPh}_3)_2\text{PdCl}_2$ . This discovery allowed telescoping the multicomponent pyrrole synthesis with several Pd-catalyzed cross-couplings, including Heck, Suzuki and Sonogashira reactions (Scheme 43). Some of the compounds thus obtained showed activity as phosphodiesterase 4 inhibitors.<sup>60</sup>



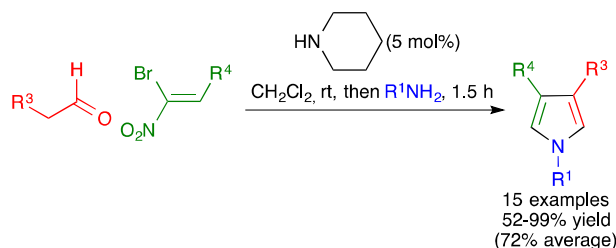
Suzuki:  $\text{ArB(OH)}_2$ , 1,4-dioxane/ $\text{H}_2\text{O}$  (4:1), 80-85 °C, 3.5 h

Heck:  $\text{CH}_2=\text{CHCO}_2\text{R}$ , DMF,  $\text{Et}_3\text{N}$ , 80-85 °C, 5-6 h

Sonogashira:  $\equiv\text{C-R}$ , CuI,  $\text{Et}_3\text{N}$ , DMF,  $\text{Et}_3\text{N}$ , 80-85 °C, 4-6 h

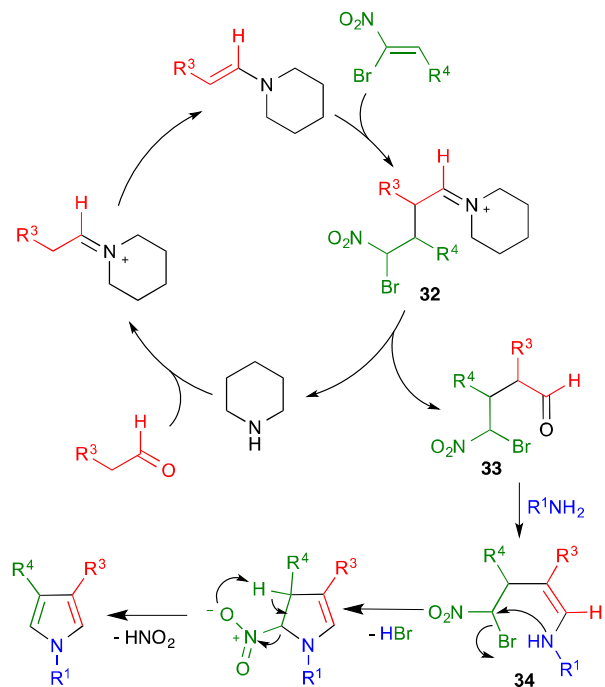
Scheme 43. Combination of a 4CR pyrrole synthesis with Pd-catalyzed cross-coupling reactions in a one-pot transformation

In a different approach, Alemán has reported a sequential three-component reaction that affords 1,3,4-trisubstituted pyrroles starting from aldehydes,  $\alpha$ -bromonitroolefins and primary amines in the presence of piperidine as a basic catalyst (Scheme 44).<sup>61</sup>



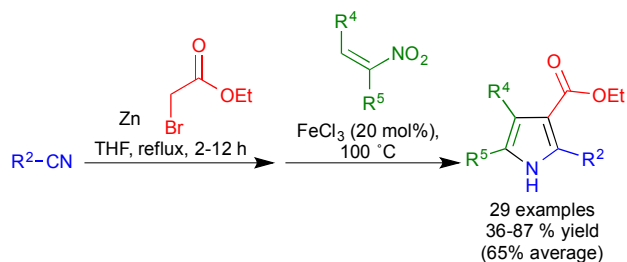
Scheme 44. Three-component synthesis of 1,3,4-trisubstituted pyrroles developed by Alemán

The mechanism proposed to explain this transformation starts with the formation of an enamine from the aldehyde and piperidine, which is followed by its Michael addition to the bromonitroolefin to furnish intermediate **32**. Its hydrolysis yields the recovered catalyst and  $\gamma$ -bromo- $\gamma$ -nitroaldehyde **33**, which then alkylates the primary amine to give **34**. Its final cyclization, with loss of a molecule of  $\text{HNO}_2$ , yields the final products (Scheme 45).



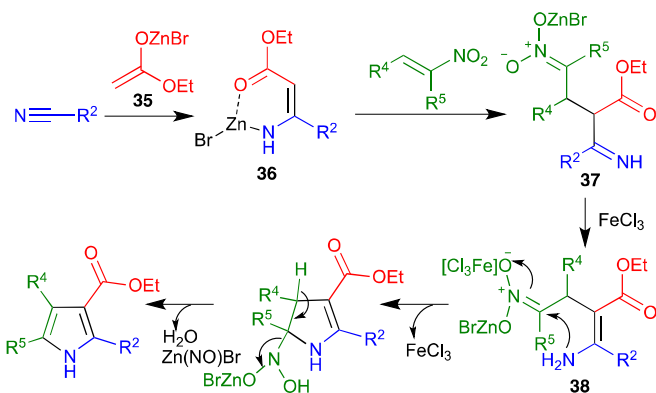
Scheme 45. Mechanism proposed to explain the isolation of pyrroles from aldehydes,  $\alpha$ -bromonitroolefins and primary amines

N-unsubstituted pyrroles were prepared in a one-pot protocol via an alternative preparation of the enaminone precursor.<sup>62</sup> Thus, a refluxing mixture of nitriles and ethyl 2-bromoacetate in the presence of zinc leads to the formation of a Blaise reaction intermediate, and this is followed by the addition of nitroolefins and iron trichloride to achieve the desired pyrroles (Scheme 46).



Scheme 46. Three-component synthesis of pyrroles from nitriles, ethyl 2-bromoacetate and nitroolefins

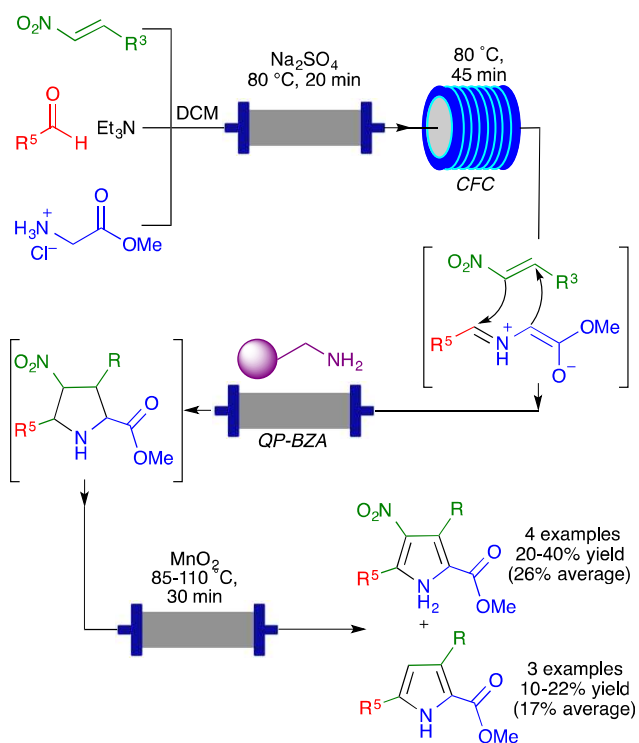
A possible mechanism that explains this transformation starts with the nucleophilic addition of an *in situ* generated Reformatsky reagent **35** to the nitrile leading to Blaise reaction intermediate **36**. Next, a Michael-type addition of **36** to nitroolefin takes place to form intermediate **37**. Subsequently the tautomerization and coordination with  $\text{FeCl}_3$  give intermediate **38** that undergoes an intramolecular cyclization, followed by an elimination to afford the expected pyrrole (Scheme 47).



Scheme 47. Mechanistic explanation of the three-component reaction synthesis via a Blaise reaction intermediate

## 5.2. Multicomponent pyrrole syntheses involving 1,3-dipolar cycloadditions to nitroolefins

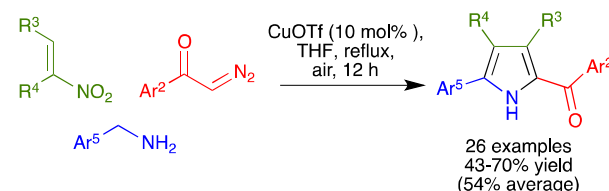
Ley has reported the use of 1,3-dipolar cycloaddition reactions of azomethine ylides with nitroalkenes to give 3-nitropyrrolidines by application of flow chemistry (Scheme 48). Thus, acetonitrile solutions of  $\beta$ -nitrostyrene derivatives, aldehydes and glycine methyl ester hydrochloride were passed through a glass column containing anhydrous sodium or magnesium sulphate at 50–80 °C to achieve imine formation. The reaction mixture was then directed to a convection flow coil (CFC) heated at 80–100 °C, where the dipolar cycloaddition took place. Inline workup by passing the reaction mixture through a column containing a benzylamine scavenger (QP-BZA) afforded the pyrrolidines in yields above 70% and



Scheme 48. Flow synthesis of 4-nitropyrroles and their desnitro derivatives developed by Ley

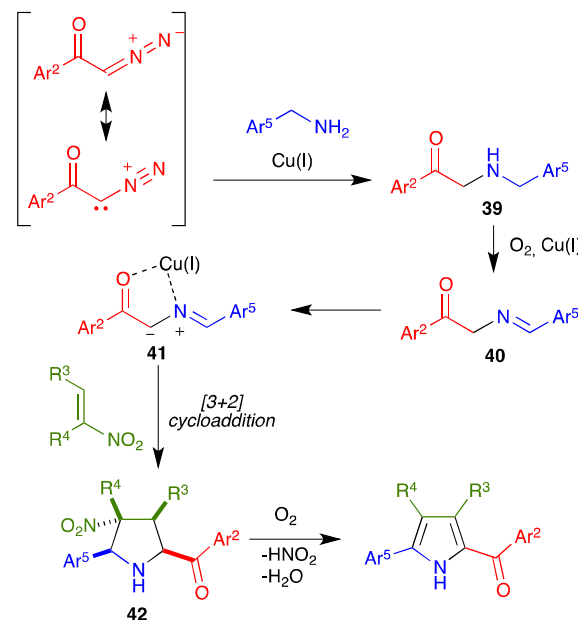
as mixtures of diastereomers. A further inline oxidation reaction that transformed these compounds into fully aromatic pyrroles was also developed by running the reaction mixture through a column of manganese dioxide. Two different types of pyrrole products were obtained and identified as 4-nitropyrroles and their desnitro derivatives, arising from formal elimination of nitrous acid rather than hydrogen in the final aromatization process.<sup>63</sup>

The copper-catalyzed three-component reaction of  $\alpha$ -diazoketones, nitroalkenes, and amines under aerobic conditions was found to afford polysubstituted pyrroles, as shown in Scheme 49.<sup>64</sup>



Scheme 49. Three-component, copper-catalyzed synthesis of pyrroles from  $\alpha$ -diazoketones, nitroalkenes, and amines

The authors proposed a tentative mechanism to explain this transformation, which is summarized in Scheme 50. In the presence of the copper catalyst, an  $\alpha$ -ketocarbene arising from the diazoketone is trapped by benzylamine to form a secondary amine **39** through N–H insertion. Its copper-catalyzed oxidative dehydrogenation forms imine **40**, which then generates azomethine ylide **41**, the first component necessary for the cycloaddition. Intermediate **41** is trapped by the starting nitroalkene to give the *exo* pyrrolidine **42** via a copper-catalyzed [3 + 2] cycloaddition. The final pyrrole products arise from the thermal extrusion of nitrous acid and concomitant dehydrogenative aromatization. The intermediacy of pyrrolidines **42** was proved by their isolation, and their structure was unambiguously confirmed by X-ray diffraction.



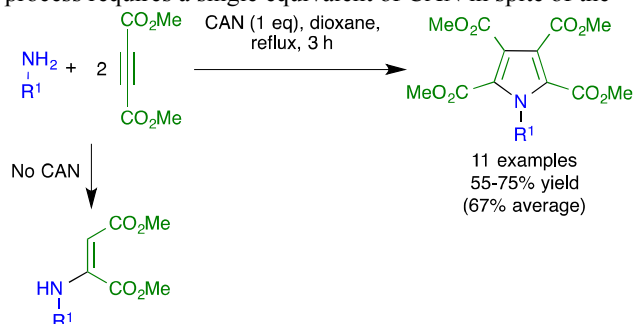
Scheme 50. Mechanism that explains the isolation of pyrroles from  $\alpha$ -diazoketones, nitroalkenes, and amines



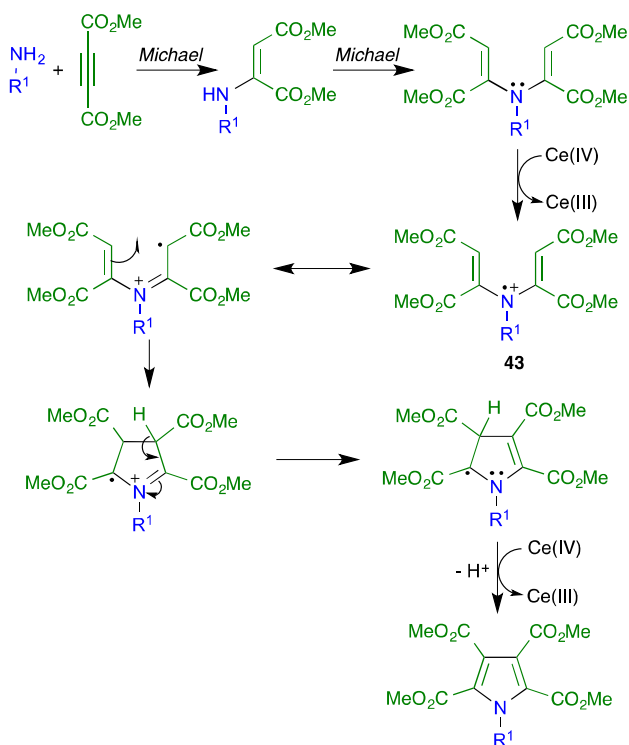
## 6. Multicomponent pyrrole syntheses from alkynes

The pseudo three-component reaction between one equivalent of alkylamines and two equivalents of dimethyl acetylenedicarboxylate (DMAD)<sup>65</sup> in the presence of Ce(IV) ammonium nitrate (CAN) was reported by Madabhushi to afford pyrrole-2,3,4,5-tetracarboxylates in good yields, even for very hindered amines (*e.g.* adamantylamine gave 73% yield).<sup>66</sup> In the absence of CAN, the only product observed was the 1:1 adduct of the amine to DMAD (Scheme 51). Almost simultaneously, Wu disclosed a very similar transformation promoted by copper acetate in an oxygen atmosphere.<sup>67</sup>

The mechanism of this reaction (Scheme 52) was proposed to be initiated by a double Michael addition, which may presumably be catalysed by CAN, acting as a Lewis acid.<sup>68</sup> The resulting adduct undergoes an intramolecular cyclization *via* a CAN-promoted one-electron oxidation to give radical cation **43**, which is finally transformed into the final product by means of a second one-electron oxidation. Intriguingly, the whole process requires a single equivalent of CAN in spite of the

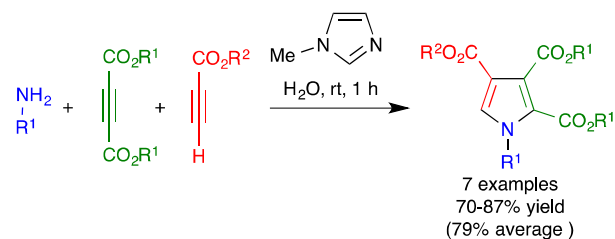


Scheme 51. CAN-promoted pseudo-three component reaction of pyrrole-2,3,4,5-tetracarboxylates reported by Madabhushi



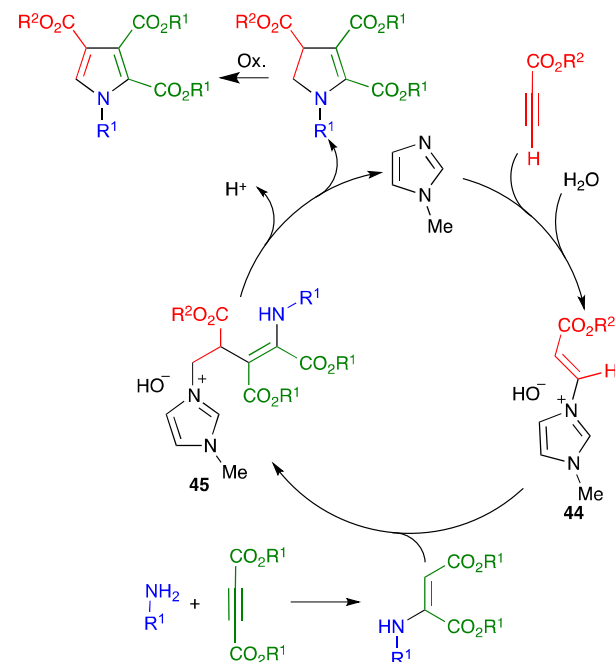
Scheme 52. Mechanism proposed for the pyrrole-2,3,4,5-tetracarboxylate synthesis

existence of two oxidation steps, which suggests that Ce(III) must be partially recycled to Ce(IV) by oxygen from the air. Slightly earlier, Sayyed-Alangi had described a related organocatalyzed reaction that allows the use of two differently activated acetylenes. Thus, the reaction between primary amines, propiolates and acetylenedicarboxylates in the presence of *N*-methylimidazole in water afforded non-symmetrical pyrrole-2,3,4-tricarboxylate derivatives in good yields (Scheme 53).<sup>69</sup>



Scheme 53. Sayyed-Alangi's three-component synthesis of pyrrole-2,3,4-tricarboxylates

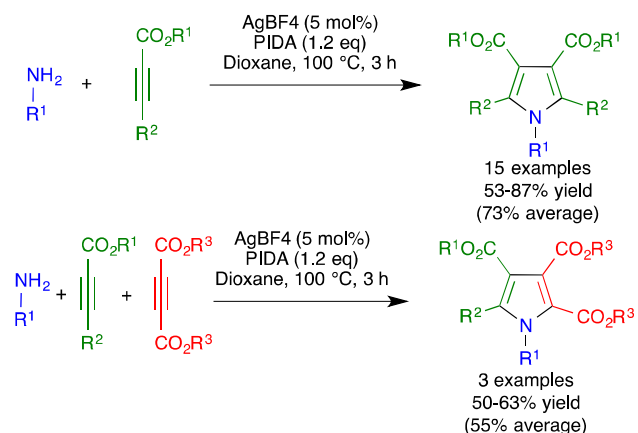
The mechanism proposed for this reaction starts with the Michael addition of the imidazole catalyst to the more reactive alkyne, *i.e.* the propiolate derivative, to give enaminone **44**. A second enaminone, arising from the primary amine and the acetylenedicarboxylate, leads to intermediate **45** that cyclizes to a dihydropyrrole derivative by an intramolecular nucleophilic displacement. A final dehydrogenation reaction, presumably by oxygen in the air, leads to the final product (Scheme 54).



Scheme 54. Mechanism proposed to explain the synthesis of pyrrole-2,3,4-tricarboxylates

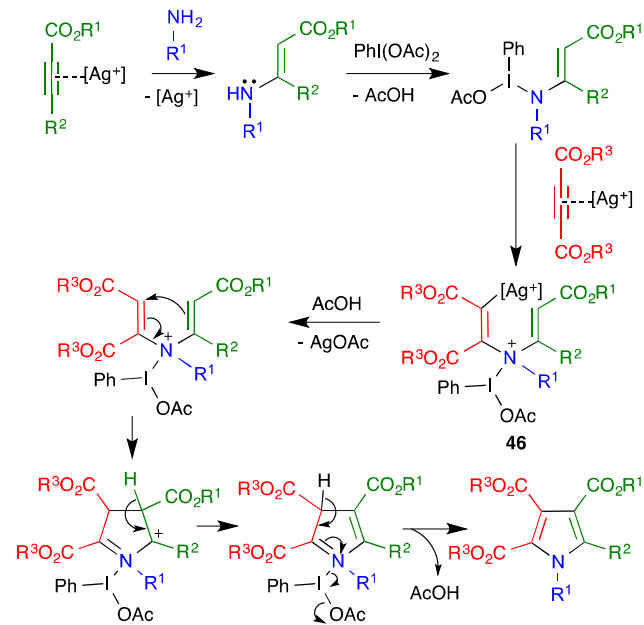
A more general solution to the problem of the preparation of symmetrical and non-symmetrical pyrroles from primary amines and activated alkynes comes from work by Jiang.<sup>70</sup> In this approach, silver tetrafluoroborate was employed as a Lewis acid catalyst and phenyliodonium diacetate (PIDA) as an oxidant. The reaction was quite general in terms of the amine substituent, which could be aliphatic or aromatic. Interestingly,

the Jiang method offers the possibility to obtain, in some cases, reasonable yields of products arising from the use of crossed alkynoates (Scheme 55).



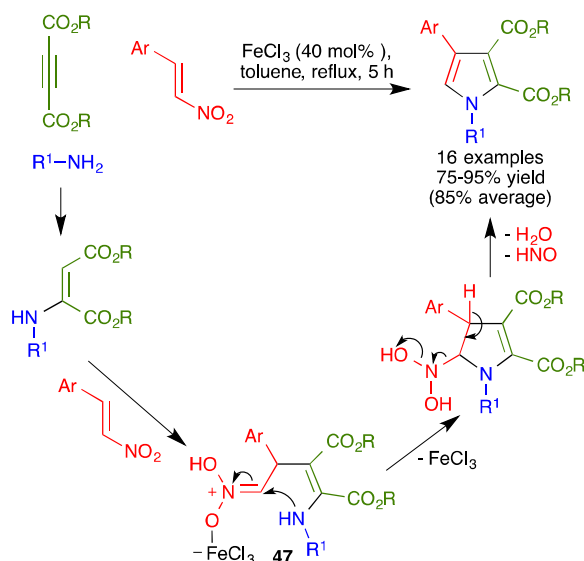
Scheme 55. Three-component synthesis of pyrroles from amines and alkynoates reported by Jiang

The mechanistic rationale proposed for this transformation is summarized in Scheme 56. Activation of the triple bond of the alkyne by Ag(I) promotes the addition of the amine, leading to a  $\beta$ -enaminone that then reacts with the iodonium reagent and then with the second activated alkyne to give a nitrenium species **46**. Its electrocyclic ring closure leads to a carbocation that evolves by deprotonation and then by loss of iodobenzene and a molecule of acetic acid.



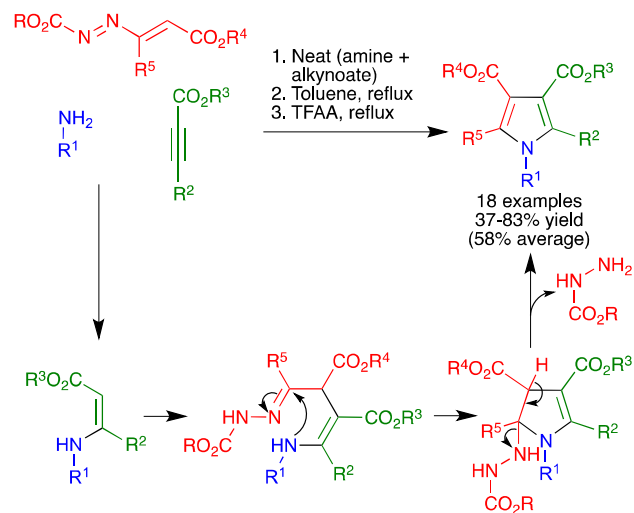
Scheme 56. Mechanism proposed to explain the synthesis of pyrroles in the presence of silver tetrafluoroborate and PIDA

Balalaie reported that the three-component reaction of primary amines, dialkyl acetylenedicarboxylates and  $\beta$ -nitrostyrene derivatives in the presence of Fe(III) chloride afforded 1,2,3,4-tetrasubstituted pyrroles in high yields, as shown in Scheme 57.<sup>71</sup> This transformation may proceed by a Michael-Michael sequence leading to intermediate **47** followed by cyclization with concomitant loss of water and hyponitrous acid.



Scheme 57. Fe(III)-catalyzed synthesis of pyrroles from primary amines, dialkyl acetylenedicarboxylates and  $\beta$ -nitrostyrene

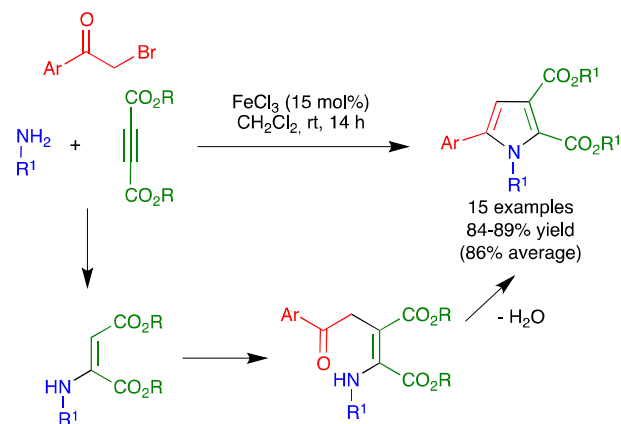
Another enaminone-initiated multicomponent protocol involving two Michael additions that affords polysubstituted pyrroles in good to excellent yields was developed by Attanasi and is based upon the reaction between primary aliphatic amines, alkynoates and 1,2-diaza-1,3-dienes. The mechanism of this transformation involves the initial formation of a  $\beta$ -enaminone by the Michael reaction between the amine and the alkynoate, its Michael addition to the diazadiene compound and an intramolecular ring closure *via* an addition-elimination process (Scheme 58).<sup>72</sup> This reaction is closely related to the one summarized in Scheme 13.



Scheme 58. Three-component synthesis of pyrroles from primary aliphatic amines, alkynoates and 1,2-diaza-1,3-dienes

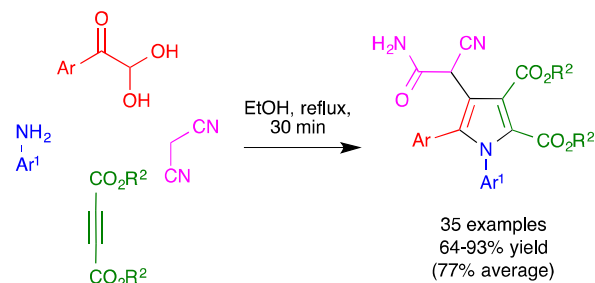
Das has described the preparation of polysubstituted pyrroles by a three-component reaction between primary amines, alkyl dialkynoates, and phenacyl bromides in the presence of iron(III) chloride as a Lewis acid catalyst. This transformation, which is closely related to the Hantzsch pyrrole synthesis, proceeds *via* an initial Michael addition of the amine to the

activated alkyne, followed by the  $S_N$  displacement of the halide and a final cyclodehydration (Scheme 59).<sup>73</sup> Other groups have published variations of this reaction, including the use of polyethyleneglycol as solvent under catalyst-free conditions,<sup>74</sup> the use of  $\beta$ -cyclodextrin as catalyst in aqueous medium<sup>75</sup> and reactions in ionic liquids.<sup>76</sup>



Scheme 59. Hantzsch-like three-component synthesis of pyrroles from primary amines, dialkyl alkynoates and phenacyl bromides

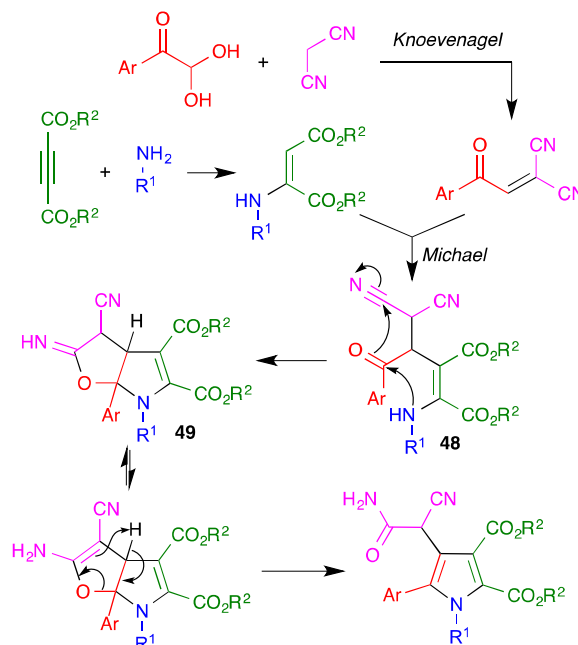
A recent catalyst-free synthesis of polysubstituted pyrroles involves refluxing in ethanol an arylglyoxal monohydrate, an aniline, a dialkyl alkynedioate and malononitrile (Scheme 60).<sup>77</sup> It is interesting to note that a very similar combination of reagents, using 1,2-diketones and in the presence of triethylamine, affords spiro dihydropyridines instead of pyrroles.<sup>78</sup>



Scheme 60. Synthesis of pyrroles from arylglyoxal monohydrates, anilines, dialkyl alkynedioates and malononitrile

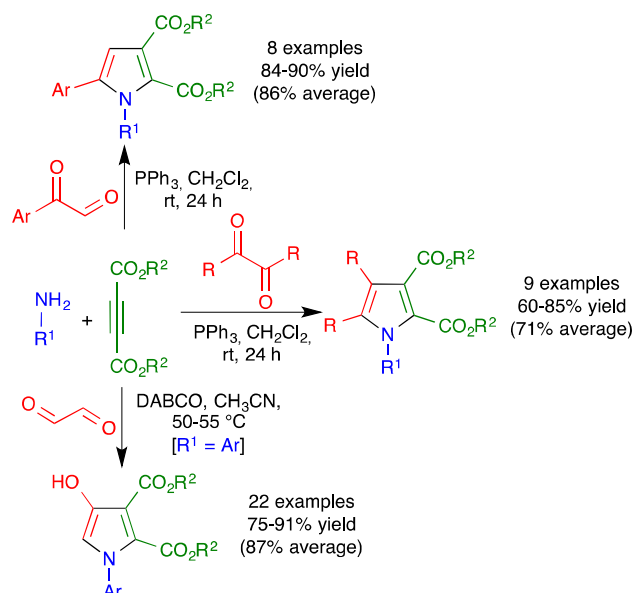
This transformation was explained by the complex mechanism summarized in Scheme 61. A Knoevenagel reaction takes place between the arylglyoxal and malononitrile while a  $\beta$ -enamine is initially formed by reaction between the amine and the activated alkyne. The Michael reaction between both intermediates thus generated affords **48**, which is transformed into the furo[2,3-*b*]pyrrole derivative **49** by a double cyclization. Its imine-enamine tautomerism, followed by aromatization with concomitant opening of the furan ring, furnishes the final product.

The Anaraki-Ardakani group found triphenylphosphine to promote the three-component reaction between primary amines, arylglyoxals and alkynedioates to give pyrroles.<sup>79</sup> The same group later extended this chemistry to the preparation of pyrroles bearing specific  $R^1$  heterocyclic substituents, such as 2-(benzo)thiazolyl<sup>80</sup> and 2-pyridyl.<sup>81</sup> The same method was also



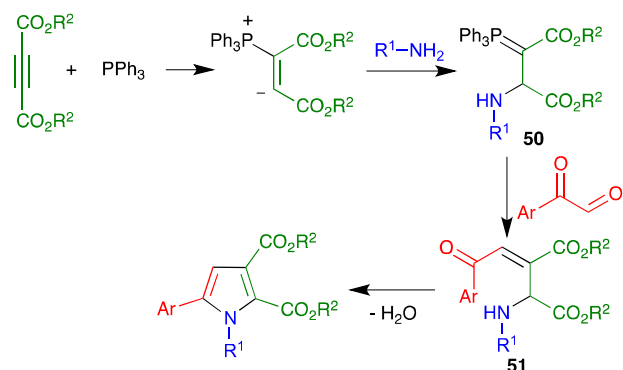
Scheme 61. Mechanism that accounts for the formation of pyrroles from arylglyoxal monohydrates, anilines, dialkyl alkynedioates and malononitrile

found to be applicable to  $\alpha$ -diketone substrates, leading to a route to 4,5-dialkyl- or 4,5-diarylpyrroles.<sup>82</sup> Glyoxal itself was also employed as one of the components of a reaction starting from aromatic amines and activated alkynes in the presence of DABCO that afforded 4-hydroxypyrroles (Scheme 62).<sup>83,84</sup>



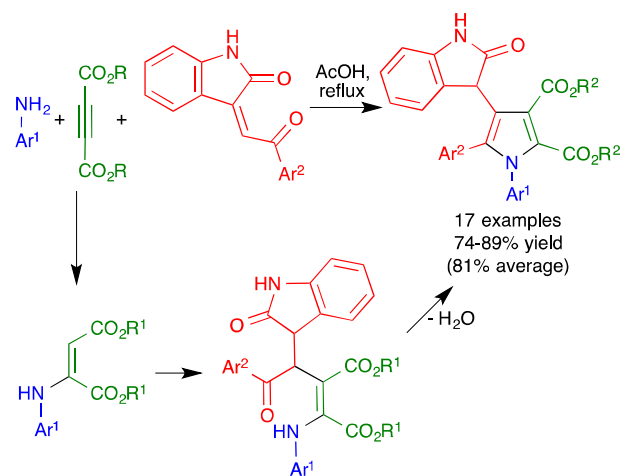
Scheme 62. Three-component synthesis of pyrroles from primary amines, dialkyl alkynedioates and glyoxals or  $\alpha$ -diketones

On the basis of literature precedent, these transformations were proposed to be initiated by the generation of a 2-aminophosphorane **50** from the reaction of the phosphine, the alkynedioate and the amine. A Wittig reaction with the glyoxal derivative would lead to intermediate **51**, and a final cyclodehydration would explain the isolation of the final products (Scheme 63).



Scheme 63. Mechanistic explanation of the triphenylphosphine-promoted synthesis of pyrroles from primary amines, dialkyl alkyndioates and arylglyoxals

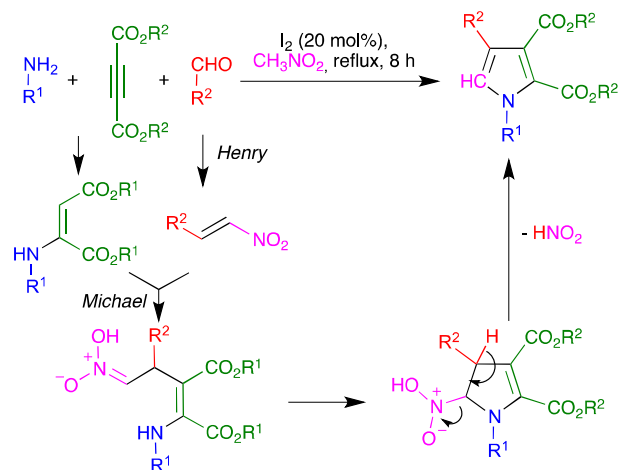
$\alpha,\beta$ -Unsaturated carbonyl compounds can also serve as the electrophilic component of reactions leading to pyrroles. Thus, treatment of anilines with alkyndioates and 3-phenacylidene-2-oxindoles in refluxing acetic acid afforded fully substituted pyrrole derivatives bearing an oxindole substituent at C-4. The reaction was proposed to proceed *via* the usual initial formation of an enaminone from the amine and the activated alkyne, followed by a Michael addition to the unsaturated carbonyl component and a final cyclodehydration (Scheme 64).<sup>85</sup>



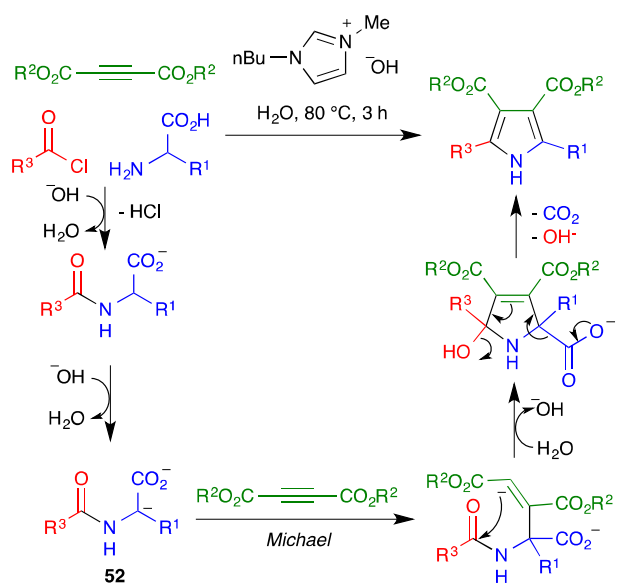
Scheme 64. Three-component synthesis of 4-(3-indolyl)pyrroles from anilines, dialkyl alkyndioates and 3-phenacylidene-2-oxindoles

A similar enaminone-Michael sequence can be the basis for a four-component process if the Michael acceptor is generated *in situ*. For instance, the molecular iodine-catalyzed four-component reaction between primary amines, activated alkynes, aldehydes and nitromethane, which also serves as the reaction medium, affords tetrasubstituted pyrroles (Scheme 65).<sup>86</sup>

The three-component reaction of  $\alpha$ -amino acids, alkyl alkyndioates and acyl chlorides, using an aqueous basic ionic liquid, namely buthyl methylimidazolium hydroxide, (bmim[OH]) as the reaction medium, affords tetrasubstituted pyrroles.<sup>87</sup> This transformation was assumed to take place by an initial acylation of the amino acid by the acyl chloride followed by subsequent deprotonation to give dianion **52**. This nucleophilic species gives a Michael addition to the activated alkyne and the resulting carbanion provides a pyrrole derivative via cyclodehydration, which is accompanied by decarboxylation (Scheme 66).

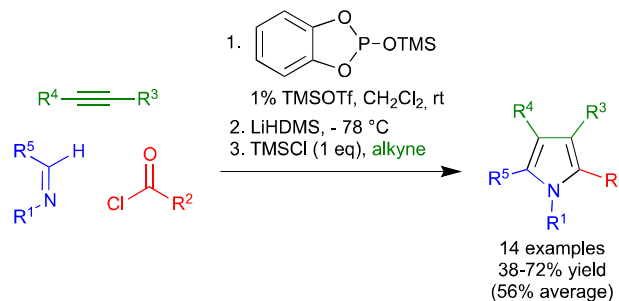


Scheme 65. Iodine-promoted synthesis of pyrroles from primary amines, dialkyl alkyndioates, aldehydes and nitromethane



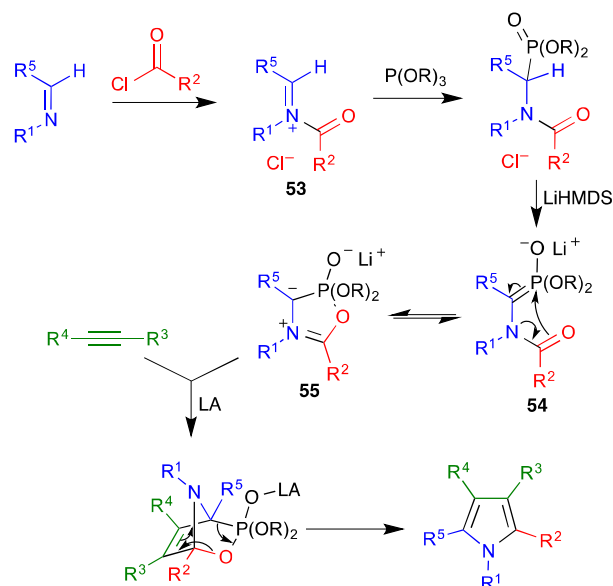
Scheme 66. Three-component synthesis of pyrroles from  $\alpha$ -amino acids, alkyl alkyndioates and acyl chlorides in an ionic liquid

In a refinement of their previous work on the synthesis of pyrroles by 1,3-dipolar cycloadditions of phosphorus-based 1,3-dipolar substrates,<sup>88</sup> the Arndtsen group has reported the preparation of pyrroles by reaction between imines, alkynes and acyl halides in the presence of phosphites (Scheme 67).<sup>89</sup>



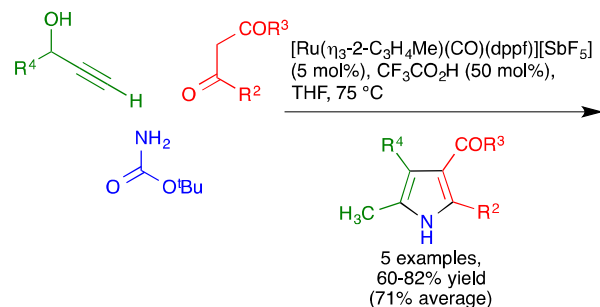
Scheme 67. Arndtsen's synthesis of pyrroles from imines, alkynes and acyl halides in the presence of phosphites

This transformation proceeds *via* the combination of a Lewis acid-catalyzed Arbusov reaction with an alkyne 1,3-dipolar cycloaddition. Thus, the initial reaction between the imine and acyl halide components provides intermediate **53**, which is transformed into the amido-substituted Horner-Wadsworth-Emmons reagent **54** by reaction with the phosphite followed by deprotonation. Its cyclization yields the Münchnone-like 1,3-dipole **55**, which finally furnishes the final product by a 1,3-dipole cycloaddition-retro [4+2] cycloaddition sequence (Scheme 68).



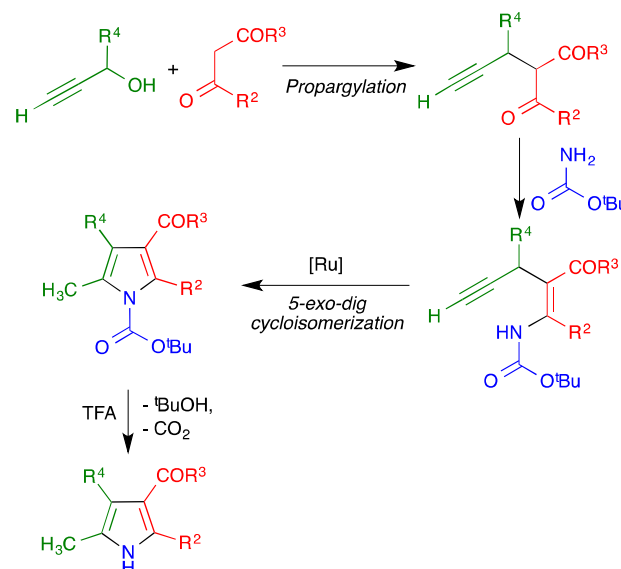
Scheme 68. Mechanism proposed to explain the phosphite-promoted three-component assembly of imines, alkynes and acyl halides

Cadierno and Gimeno have described a three-component pyrrole synthesis by reaction between *tert*-butyl carbamate, propargyl alcohols and  $\beta$ -dicarbonyl compounds in the presence of the 16-electron allyl-ruthenium(II) complex  $[\text{Ru}(\eta^3\text{-C}_3\text{H}_4\text{Me})(\text{CO})(\text{dppf})][\text{SbF}_6]$ , where dppf is 1,1'-bis(diphenylphosphanyl)ferrocene (Scheme 69).<sup>90</sup> This reaction is an extension of previous work by the same group based on the use of primary amines which was very slow when using ammonia and was therefore not amenable to the preparation of N-unsubstituted pyrroles.<sup>91</sup> The use of *tert*-butyl carbamate as the source of the pyrrole nitrogen atom was inspired in previous work by Zhan, who achieved a similar transformation using indium trichloride as the catalyst.<sup>92</sup> Iodine was subsequently found to be a suitable catalyst for the reaction.<sup>93</sup>



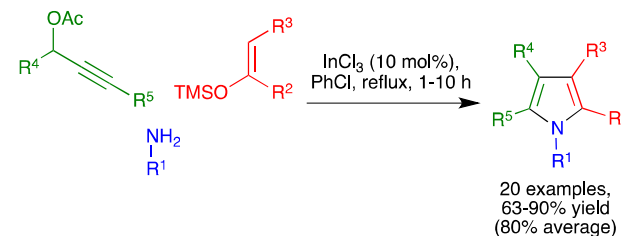
Scheme 69. Synthesis of pyrroles from *tert*-butyl carbamate, propargyl alcohols and  $\beta$ -dicarbonyl compounds reported by Cadierno and Gimeno

The mechanism of this reaction was proposed to involve an initial acid-promoted propargylation of the dicarbonyl compound by the alcohol, followed by condensation with the carbamate to give a  $\beta$ -enaminone, a ruthenium-catalyzed 5-*exo-dig* annulation and the final hydrolysis of the carbamate function, which is accompanied by decarboxylation and affords the final product (Scheme 70).



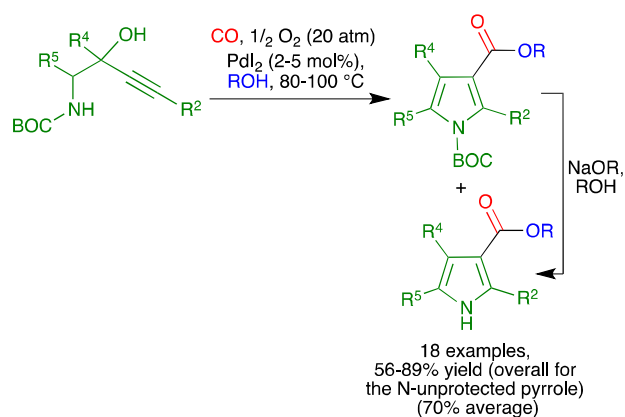
Scheme 70. Mechanism of the reaction among *tert*-butyl carbamate, propargyl alcohols and  $\beta$ -dicarbonyl compounds

The active carbonyl compound in the previous reaction can be replaced by other C-nucleophiles. Thus, the reaction between primary amines, propargylic acetates and silyl enol ethers catalyzed by indium trichloride<sup>94</sup> or zinc(II) chloride<sup>95</sup> affords pyrroles in good to excellent yields (Scheme 71).



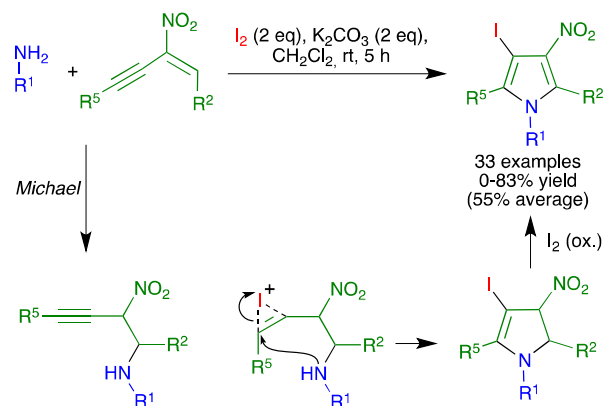
Scheme 71. Synthesis of pyrroles from primary amines, propargylic acetates and silyl enol ethers

Gabriele has described an intramolecular version of the propargylic alcohol-based pyrrole synthesis, featuring a Pd-catalyzed oxidative heterocyclization-alkoxycarbonylation domino process. The reactions were carried out in alcohols as solvents under 20 atm of a carbon monoxide-air mixture (Scheme 72).<sup>96</sup>



Scheme 72. Synthesis of pyrroles based on a Pd-catalyzed oxidative heterocyclization-alkoxycarbonylation domino process

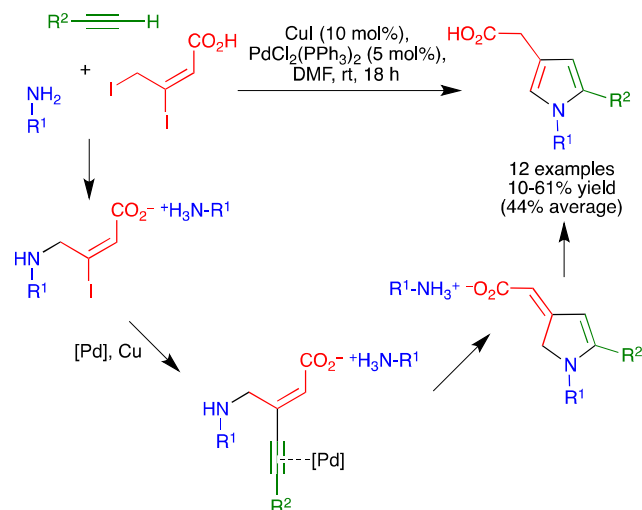
In a somewhat related procedure, Punniyamurthy has reported that the reaction between 2-nitro-1,3-enynes and primary amines in the presence of iodine affords pentasubstituted pyrroles. This reaction is presumed to start by an aza-Michael reaction of the amine to the electron-deficient 1,3-enyne system, followed by activation of the triple bond by its reaction with iodine, cyclization of the resulting iodonium species and a final iodine-mediated dehydrogenative aromatization step (Scheme 73).<sup>97</sup>



Scheme 73. Synthesis of pyrroles from 2-nitro-1,3-enynes and primary amines in the presence of iodine

Duchêne and Parrain have investigated the synthesis of pyrroles from 3,4-diiodo-2-alkenoic acids, primary amines and terminal alkynes in the presence of a palladium catalyst. The reaction was proposed to start by an initial amine allylation *via* nucleophilic displacement of iodide, followed by a Sonogashira cross-coupling reaction and a 5-*endo-dig* cyclization by Pd-catalyzed intramolecular hydroamination that gives an exocyclic double bond that finally rearranges to afford aromatic pyrroles (Scheme 74).<sup>98</sup>

In a somewhat related transition metal-catalyzed process, the silver-promoted reaction between secondary amines, alkynes and imidazole-4-carbaldehyde in the presence of a small amount of water afforded derivatives of the pyrrole-2-carbaldehyde system in moderate to good yields (Scheme 75) rather than the expected product from the simple coupling of the starting materials.<sup>99</sup>

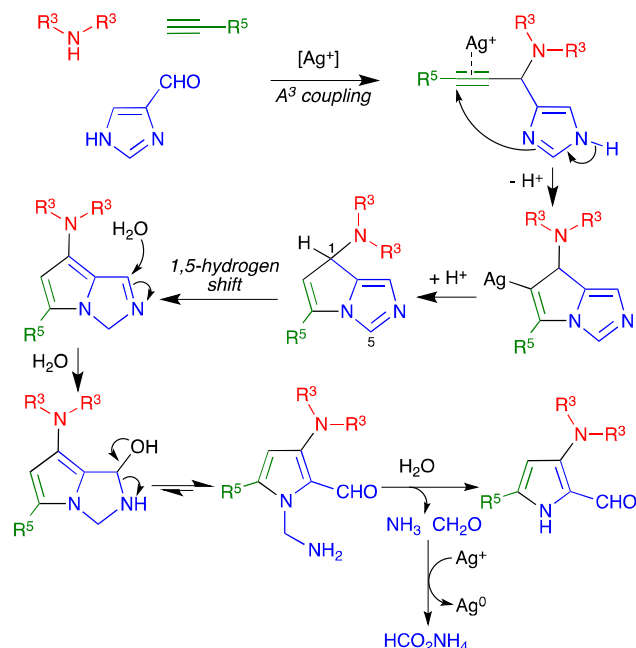


Scheme 74. Pd-catalyzed synthesis of pyrroles from 3,4-diiodo-2-alkenoic acids, primary amines and terminal alkynes developed by Duchêne and Parrain



Scheme 75. Silver-promoted, three-component synthesis of pyrroles from secondary amines, alkynes and imidazole-4-carbaldehyde

The mechanism of this complex transformation (Scheme 76) was proposed to start by the  $\text{Ag}^+$ -catalyzed three-component reaction of the aldehyde, alkyne and amine, which is normally known as the  $\text{A}^3$ -coupling.<sup>100</sup> This would followed by a silver-

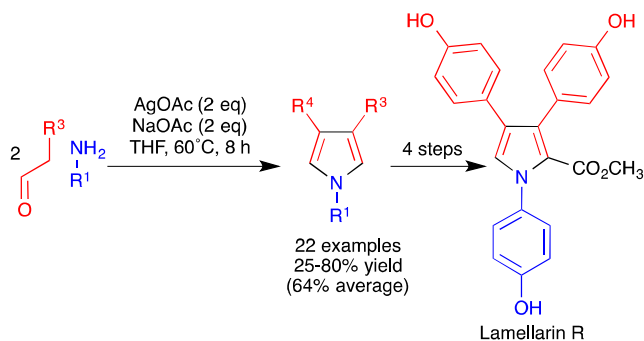


Scheme 76. Mechanism proposed to explain the formation of pyrroles from secondary amines, alkynes and imidazole-4-carbaldehyde

promoted *5-endo-dig* cyclization, and then by silver-proton exchange reaction. A subsequent [1,5] sigmatropic hydrogen shift would destroy the aromaticity of the imidazole ring and set the stage for its fragmentation, which was proposed to take place by imine hydrolysis followed by loss of the aminomethyl side chain to afford the final pyrrole derivative, together with formaldehyde and ammonia. In the presence of the silver salts, the classical Tollens reaction takes place, consuming the formaldehyde and thereby forcing the equilibria towards the final products. Indeed, the formation of the silver mirror characteristic of this reaction was observed in some of the examples.

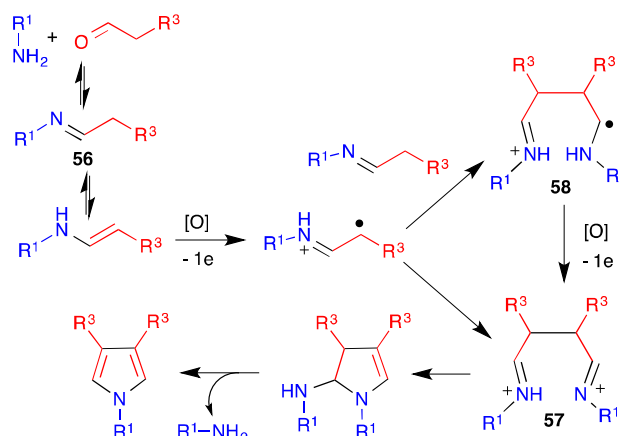
## 7. Miscellaneous multicomponent pyrrole syntheses

A one-pot synthesis of 1,3,4-trisubstituted or 3,4-disubstituted pyrroles was developed by Jia and coworkers, starting from aldehydes and amines (Scheme 77).<sup>101</sup> This reaction, which is reminiscent of the Piltoty-Robinson synthesis, required the presence of silver acetate to promote the oxidative homodimerization that takes place and the addition of sodium acetate to buffer the acid formed during the reaction. The preparation of unsymmetrical pyrroles, from different aldehydes, turned out to be non-selective. The same group has exploited this reaction to construct the pyrrole core of some marine alkaloids such as lamellarin R, which was prepared in four steps.<sup>102</sup>



Scheme 77. Pseudo three-component synthesis that gives 1,3,4-trisubstituted pyrroles from aldehydes and primary amines

The mechanism for this pseudo three-component pyrrole synthesis was proposed to be initiated by the reaction of the amine with one molecule of the aldehyde to give imine **56**, which equilibrates to the corresponding enamine. Silver acetate induces a one-electron oxidation of the enamine, forming an  $\alpha$ -radical cation. This radical can undergo self-coupling, giving diimine **57**, or alternatively it can react with another molecule of enamine resulting in a radical cation **58** that leads to **57** after a second oxidation from silver acetate. Finally, the cyclization of **57** produces the final pyrrole and releases one molecule of the starting amine (Scheme 78).



Scheme 78. Mechanistic pathways that explain the silver-promoted synthesis of pyrroles from imines and aldehydes

## Conclusions

Pyrrole synthesis continues to be a very active field, and the use of multicomponent approaches to its preparation will continue to be an important endeavour in the future. We conclude this review by hoping that it will stimulate researchers to develop new and creative synthetic access routes to this heterocyclic system, which will be instrumental in the advancement of many branches of chemistry.

## Acknowledgements

Work from our group cited in this review was supported by grants CTQ2009-12320/BQU and CTQ2012-33272-BQU from MICINN and MINECO, respectively. We also gratefully acknowledge Comunidad Autónoma de Madrid for a predoctoral contract to VEC.

## Notes and references

<sup>a</sup> Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid.

- For a review, see: T. Fukuda, F. Ishibashi and M. Iwao, *Heterocycles*, 2011, **83**, 491.
- Y. Kashman, G. Koren-Goldshlager, M. D. García-Grávalos and M. Schleyer, *Tetrahedron Lett.*, 1999, **40**, 997.
- For a review, see: B. Forte, B. Malgesini, C. Piutti, F. Quartieri, A. Scolaro and G. Papeo, *Mar. Drugs*, 2009, **7**, 705.
- For a review, see: D. L. J. Clive and P. Cheng, *Tetrahedron*, 2013, **69**, 5067.
- R. A. Rane, N. U. Sahu, C. P. Shah and N. K. Shah, *J. Enzym. Inhib. Med. Chem.*, 2013, doi:10.3109/14756366.2013.793183.
- A. Kunfermann, M. Witschel, B. Illarionov, R. Martin, M. Rottmann, H. W. Höffken, M. Seet, W. Eisenreich, H.-J. Knölker, M. Fischer, A. Bacher, M. Groll and F. Diederich, *Angew. Chem. Int. Ed.*, 2014, **53**, 2235.
- U. J. Youn, Y.-S. Kil, J.-W. Nam, Y. J. Lee, J. Kim, D. Lee, J.-H. Lee and E.-K. Seo, *Helv. Chim. Acta*, 2013, **96**, 1482.
- N. R. Williamson, H. T. Simonsen, R. A. Ahmed, G. Goldet, H. Slater, L. Woodley, F. J. Leeper and G. P. Salmond, *Mol. Microbiol.*, 2005, **56**, 971.

- 9 For a review, see: N. R. Williamson, P. C. Fineran, T. Gristwood, S. R. Chawrai, F. J. Leeper and G. P. C. Salmond, *Future Microbiol.*, 2007, **2**, 605.
- 10 F. Basit, S. Cristofanon and S. Fulda, *Cell Death Differ.*, 2013, **29**, 1161.
- 11 Y. Coquerel, T. Boddaert, M. Pisset, D. Mailhol and J. Rodriguez, in: B. Pignataro (Ed.), *Ideas in Chemistry and Molecular Sciences: Advances in Synthetic Chemistry*, Wiley-VCH: Weinheim, 2010, Chap. 9, pp. 187 – 202.
- 12 D. Bonne, T. Constantieux, Y. Coquerel and J. Rodriguez, *Chem. Eur. J.*, 2013, **19**, 2218.
- 13 For a special issue on this topic, see: J. C. Menéndez (Ed.) *Multibond forming reactions. A new frontier in the synthesis of heterocycles*, *Curr. Org. Chem.*, 2013, **17**, issue 18 (pp-1919-2064).
- 14 Representative general reviews of multicomponent reactions: (a) A. Dömling, *Chem. Rev.*, 2006, **106**, 17. (b) M. M. Sánchez-Duque, C. Allais, N. Isambert, T. Constantieux and J. Rodriguez, *Top. Heterocycl. Chem.*, 2010, **23**, 227. (c) B. Jiang, T. Rajale, W. Wever, S.-J. Tu, and G. Li, *Chem. Asian J.*, 2010, **5**, 2318. (d) H. Eckert, *Molecules*, 2012, **17**, 1074. (e) M. J. Climent, A. Corma and S. Iborra, *RSC Adv.*, 2012, **2**, 16. (f) C. de Graaff, E. Ruijter and R. V. A. Orru, *Chem. Soc. Rev.*, 2012, **41**, 3969. (g) G. van der Heijden, E. Ruijter and R. V. A. Orru, *Synlett*, 2013, **24**, 666.
- 15 Representative reviews on the use of multicomponent reactions in natural product synthesis: (a) A. Ulaczyk-Lesanko and D. G. Hall, *Curr. Opin. Chem. Biol.*, 2005, **9**, 266. (b) B. B. Touré and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439. (c) S. Perreault and T. Rovis, *Chem. Soc. Rev.*, 2009, **38**, 3149.
- 16 Representative reviews on the use of multicomponent reactions in the discovery of bioactive compounds: (a) C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51. (b) J. E. Biggs-Houck, A. Younai and J. T. Shaw, *Curr. Opin. Chem. Biol.*, 2010, **14**, 371. (c) A. Dömling, W. Wang, and K. Wang, *Chem. Rev.*, 2012, **112**, 3083.
- 17 For selected reviews, see: (a) V. F. Ferreira, M. C. B. V. de Souza, A. C. Cunha, L. O. R. Pereira and M. L. G. Ferreira, *Org. Prep. Proced. Int.*, 2001, **33**, 411. (b) S. D. Joshi, U. A. More, V. H. Kulkarni and T. M. Aminabhavi, *Curr. Org. Chem.*, 2013, **17**, 2279. (c) A. V. Gulevich, A. S. Dudnik, N. Chernyak, and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084.
- 18 V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.*, 2010, **39**, 4402.
- 19 A. Hantzsch, *Chem. Ber.*, 1890, **23**, 1474.
- 20 G. Pal, S. Paul and A. R. Das, *Synthesis*, 2013, **45**, 1191.
- 21 H. M. Meshram, V. M. Bangade, B. C. Reddy, G. S. Kumar and P. B. Thakur, *Int. J. Org. Chem.*, 2012, **2**, 159.
- 22 T. A. Moss and T. Nowak, *Tetrahedron Lett.*, 2012, **53**, 3056.
- 23 A. Herath and N. D. P. Cosford, *Org. Lett.*, 2010, **12**, 5182.
- 24 V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Commun.*, 2013, **49**, 591.
- 25 G. R. Reddy, T. R. Reddy, S. C. Joseph, K. S. Reddy, C. L. T. Meda, A. Kandale, D. Rambabu, G. R. Krishna, C. M. Reddy, K. V. L. Parsa, K. S. Kumar and M. Pal, *RSC Adv.*, 2012, **2**, 9142.
- 26 F. Tamaddon and M. Farahi, *Synlett*, 2012, **23**, 1379.
- 27 F. Tamaddon, M. Farahi and B. Karami, *J. Mol. Catal.*, 2012, **356**, 85.
- 28 F. Tamaddon and M. Farahi, *Synlett*, 2013, **24**, 1791.
- 29 S. I. Bhat and D. R. Trivedi, *Tetrahedron Lett.*, 2013, **54**, 5577.
- 30 O. A. Attanasi, G. Favi, F. Mantellini, G. Moscatelli and S. Santeusano, *J. Org. Chem.*, 2011, **76**, 2860.
- 31 P. Xu, K. Huang, Z. Liu, M. Zhou and W. Zeng, *Tetrahedron Lett.*, 2013, **54**, 2929.
- 32 A. Alizadeh and J. Mokhtari, *C. R. Chimie*, 2013, **16**, 103.
- 33 K. Wang and A. Dömling, *Chem. Biol. Drug. Des.*, 2010, **75**, 277.
- 34 L. V. Frolova, N. M. Evdokimov, K. Hayden, I. Malik, S. Rogelj, A. Kornienko and I. V. Magedov, *Org. Lett.*, 2011, **13**, 1118.
- 35 P. Das, S. Ray and C. Mukhopadhyay, *Org. Lett.*, 2013, **15**, 5622.
- 36 B. Eftekhari-Sis and S. Vahdati-Khajeh, *Curr. Chem. Lett.*, 2013, **2**, 85.
- 37 J. Liu, Q. Li, B. Jiang and S. Tu, *RSC Adv.*, 2013, **3**, 5056.
- 38 D. Dhara, K. S. Gayen, S. Khamarui, P. Pandit, S. Ghosh and D. K. Maiti, *J. Org. Chem.*, 2012, **77**, 10441.
- 39 X. Lin, Z. Mao, X. Dai, P. Lu and Y. Wang, *Chem. Commun.*, 2011, **47**, 6620.
- 40 T. B. Kumar, C. Sumanth, S. Vaishaly, M. S. Rao, K. B. C. Sekhar, C. L. T. Meda, A. Kandale, D. Rambabu, G. R. Krishna, C. M. Reddy, K. S. Kumar, K. V. L. Parsa and M. Pal, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5639.
- 41 M. Zhang, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2013, **52**, 597.
- 42 M. Zhang, X. Fang, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2013, **135**, 11384.
- 43 For selected reviews of IMCRs, see: (a) A. Dömling, *Chem. Rev.*, 2006, **106**, 17. (b) S. S. van Berkel, B. G. M. Bögels, M. A. Wijdeven, B. Westermann and F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, 2012, 3543.
- 44 A. N. Kolontsova, M. N. Ivantsova, M. I. Tokareva and M. A. Mironov, *Mol. Divers.*, 2010, **14**, 543.
- 45 X. Wang, X. Xu, S. Wang, W. Zhou and S. Ji, *Org. Lett.*, 2013, **15**, 4246.
- 46 W. Chen, J. Shao, Z. Li, M. A. Giulianotti and Y. Yu, *Can. J. Chem.*, 2012, **90**, 214.
- 47 S. Sarkar, K. Bera, S. Maiti, S. Biswas and U. Jana, *Synth. Commun.*, 2013, **43**, 1563.
- 48 C. C. Silveira, S. R. Mendes, G. M. Martins, S. C. Schlösser and T. S. Kaufman, *Tetrahedron*, 2013, **69**, 9076.
- 49 N. C. Jadhav, P. B. Jagadhane, H. V. Patile and V. N. Telvekar, *Tetrahedron Lett.*, 2013, **54**, 3019.
- 50 V. Y. Korotaev, A. Y. Barkov, I. V. Kotovich and V. Y. Sosnovskikh, *J. Fluorine Chem.*, 2012, **138**, 42.
- 51 D. R. Magar, Y.-J. Ke and K. Chen, *Asian J. Org. Chem.*, 2013, **2**, 330.
- 52 S. Maiti, S. Biswas and U. Jana, *J. Org. Chem.*, 2010, **75**, 1674.
- 53 G. R. Reddy, T. R. Reddy, S. C. Joseph, K. S. Reddy and M. Pal, *RSC Adv.*, 2012, **2**, 3387.
- 54 A. T. Khan, M. Lal, P. R. Bagdi, R. S. Basha and P. Saravanan, *Tetrahedron Lett.*, 2012, **53**, 4145.
- 55 A. B. Atar and Y. T. Jeong, *Tetrahedron Lett.*, 2013, **54**, 5624.
- 56 J. B. Bharate, R. Sharma, S. Aravinda, V. K. Gupta, B. Singh, S. B. Bharate and A. Vishwakarma, *RSC Adv.*, 2013, **3**, 21736.
- 57 H. Saedian, M. Abdoli and R. Salimi, *C. R. Chim.*, 2013, **16**, 1063.



- 58 B.-L. Li, P.-H. Li, X.-N. Fang, C.-X. Li, J.-L. Sun and L.-P. Mo, *Tetrahedron*, 2013, **69**, 7011.
- 59 H. M. Meshram, B. M. Babu, G. S. Kumar, P. B. Thakur and V. M. Bangade, *Tetrahedron Lett.*, 2013, **54**, 2296.
- 60 G. R. Reddy, T. R. Reddy, S. C. Joseph, K. S. Reddy, L. S. Reddy, P. M. Kumar, G. R. Krishna, C. M. Reddy, D. Rambabu, R. Kapavarapu, C. Lakshmi, T. Meda, K. K. Priya, K. V. L. Parsa and M. Pal, *Chem. Commun.*, 2011, **47**, 7779.
- 61 C. Martín-Santos, C. Jarava-Barrera, A. Parra, F. Esteban, C. Navarro-Ranninger and J. Alemán, *ChemCatChem*, 2012, **4**, 976.
- 62 M. Zhao, H. Liang, Z. Ren and Z. Guan, *Adv. Synth. Catal.*, 2013, **355**, 221.
- 63 M. Baumann, I. R. Baxendale, A. Kirschning, S. V. Ley and J. Wegner, *Heterocycles*, 2011, **82**, 1297.
- 64 D. Hong, Y. Zhu, Y. Li, X. Lin, P. Lu and Y. Wang, *Org. Lett.*, 2011, **13**, 4668.
- 65 For a review of the synthetic applications of DMAD, see: C. G. Neochoritis, T. Zarganes-Tzitzikas and J. Stephanidou-Stephanatou, *Synthesis*, 2014, **46**, 537.
- 66 S. Madabushi, V. S. Vangipuram, K. K. R. Mallu, R. Jillella, S. Kurva and S. R. Pamulaparathi, *Tetrahedron Lett.*, 2013, **54**, 6737.
- 67 L. Zhang, X. Wang, S. Li and J. Wu, *Tetrahedron*, 2013, **69**, 3805.
- 68 For a review of the synthetic use of CAN as a catalyst, see: V. Sridharan and J. C. Menéndez, *Chem. Rev.*, 2010, **110**, 3805–3849.
- 69 S. Z. Sayyed-Alangi, Z. Hossaini and F. Rostami-Charati, *Chin. Chem. Lett.*, 2012, **23**, 1119.
- 70 W. Liu, H. Jiang and L. Huang, *Org. Lett.*, 2010, **12**, 312–315.
- 71 E. Ghabraie, S. Balalaie, M. Bararjanian, H. Reza Bijanzadeh and F. Rominger *Tetrahedron*, 2011, **67**, 5415.
- 72 O. A. Attanasi, G. Favi, F. Mantellini, G. Moscatelli, and S. Santeusano, *Adv. Synth. Catal.*, 2011, **353**, 1519.
- 73 B. Das, G. C. Reddy, P. Balasubramanyam and B. Veeranjanyulu, *Synthesis*, 2010, 1625.
- 74 L. Nagarapu, R. Mallepalli, L. Yeramanchi and R. Bantu, *Tetrahedron Lett.*, 2011, **52**, 3401–
- 75 K. Ramesh, K. Karnakar, G. Satish and Y. V. D. Nageswar, *Chin. Chem. Lett.*, 2012, **23**, 1331.
- 76 I. R. Siddiqui, D. Kumar and S. Shamin, *J. Heterocycl. Chem.*, 2013, **50**, E111.
- 77 X. Feng, Q. Wang, W. Lin, G.-L. Dou, Z.-B. Huang and D.-Q. Shi, *Org. Lett.*, 2013, **15**, 2545.
- 78 S. E. Kiruthika, N. V. Lakshmi, B. R. Banu and P. T. Perumal, *Tetrahedron Lett.*, 2011, **52**, 6508.
- 79 M. Anary-Abbasinejad, K. Charkhati and H. Anaraki-Ardakani, *Synlett*, 2009, 1115.
- 80 M. Anary-Abbasinejad, H. Dehghanpour-Farashah, H. Anaraki-Ardakani and N. Shams, *Synth. Commun.*, 2012, **42**, 1877.
- 81 H. Anaraki-Ardakani, M. Noei, M. Karbalei-Harofteh and S. Zomorodbaksh, *E-J. Chem.*, 2012, **9**, 2239.
- 82 J. Azizian, J. Hosseini, M. Mohammadi and F. Sheikhoeslami, *Synth. Commun.*, 2010, **40**, 3472.
- 83 K. Ramesh, S. Naryana, M. K. Karnakar and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2011, **52**, 3937.
- 84 R. Eligeti, K. Baireddy and R. Saini, *Chin. Chem. Lett.*, 2013, **24**, 134.
- 85 Y. Han, Y. Sun, J. Sun and C.-G. Yan, *Tetrahedron*, 2012, **68**, 8256.
- 86 B. Das, N. Bhunia and M. Lingaiah, *Synthesis*, 2011, 3471.
- 87 I. Yavari and E. Kowasari, *Mol. Divers.*, 2009, **13**, 519.
- 88 D. J. St Cyr and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2007, **129**, 12366.
- 89 M. S. T. Morin, D. J. St-Cyr and B. A. Arndtsen, *Org. Lett.*, 2010, **12**, 4916.
- 90 V. Cadierno, J. Gimeno and N. Nebra, *J. Heterocycl. Chem.*, 2010, **47**, 233.
- 91 V. Cadierno, J. Gimeno and N. Nebra, *Chem. Eur. J.*, 2007, **13**, 9973.
- 92 X.-T. Liu, L. Huang, F.-J. Zheng and Z.-P. Zhan, *Adv. Synth. Catal.*, 2008, **350**, 2778.
- 93 N. Bhunia and B. Das, *Synlett*, 2013, **24**, 1045.
- 94 M. Lin, L. Hao, R. Ma and Z.-P. Zhan, *Synlett*, 2010, 2345.
- 95 X.-T. Liu, M. Lin, L. Chen and Z.-P. Zhan, *Org. Biomol. Chem.*, 2010, **8**, 3064.
- 96 B. Gabriele, L. Veltri, R. Mancuso, G. Salerno, S. Maggi and B. M. Aresta, *J. Org. Chem.*, 2012, **77**, 4005.
- 97 G. Bharathiraja, S. Sakthivel, M. Sengoden and T. Punniyamirthy, *Org. Lett.*, 2013, **15**, 4996.
- 98 S. Lamandé-Langle, M. Abarbri, J. Thibonnet, A. Duchêne and J.-L. Parrain, *Chem. Commun.*, 2010, **46**, 5157.
- 99 J. Zeng, Y. Bai, S. Cai, J. Ma and S.-W. Liu, *Chem. Commun.*, 2011, **47**, 12855.
- 100 V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.*, 2012, **41**, 3790.
- 101 Q. Li, A. Fan, Z. Lu, Y. Cui, W. Lin and Y. Jia, *Org. Lett.*, 2010, **12**, 4066.
- 102 Q. Li, J. Jiang, A. Fan, Z. Lu, Y. Cui and Y. Jia, *Org. Lett.*, 2011, **13**, 312.

Verónica Estévez was born in Madrid, and studied Pharmacy at Universidad Complutense, Madrid (UCM). She joined the Department of Organic and Medicinal Chemistry, School of Pharmacy, UCM, and received her PhD in 2013. Her thesis work, supervised by Drs Villacampa and Menéndez, was focused on new multicomponent reactions for the synthesis of pyrroles and their application to the preparation of bioactive compounds. She is currently working as a postdoctoral researcher in the group of Professor R. Orru at VU University (Amsterdam) in the European Lead Factory (ELF) project, a novel European platform for innovative drug discovery.

Mercedes Villacampa was born in Madrid. She studied Pharmacy and Optics at UCM. For her Ph. D. thesis, she worked on the synthesis of natural product-based serotonin analogues. After postdoctoral studies with Professor Nicholas Bodor (University of Florida, Gainesville), she obtained a position of Profesor Titular at the Organic and Medicinal Chemistry Department, UCM. She has also done postdoctoral work at the laboratory of Professor Kendall N. Houk (University of California at Los Angeles, UCLA). Her research interests include computational chemistry and the development of new synthetic methodologies, including multicomponent reactions, for their application to the preparation of bioactive heterocycles.

José Carlos Menéndez was born in Madrid and obtained degrees in Pharmacy and Chemistry, followed by a Ph. D. 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 are focused on the development of new multiple bond forming transformations for the preparation of biologically relevant compounds. His group also pursues medicinal chemistry projects in the areas of chemotherapy (cancer, tuberculosis, neglected tropical diseases) and neuroprotection.



1334x761mm (72 x 72 DPI)