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Recent advances in the synthesis of 2,3-dihydropyrroles

Dong Wang,*a Yu Fan,a Peng Yu,a and Laurent Désaubry*a,b

The 2,3-dihydropyrrole unit is a privileged heterocycle found in many pharmacologically active natural products. Significant recent advances in the synthesis of this heterocycle have led to intense interest in the development of new drug candidates. The aim of this review is to summarize advances accomplished in this stimulating field with an emphasis on recent developments or important seminal contributions.

1. Introduction

2,3-Dihydropyrroles, also called 2-pyrrolines, are structural components of a large number of biologically active natural compounds (Figure 1). For example, isolated from the fungus Aspergillus fumigatus, Spirotryprostatin B (1), inhibits cell cycle progression in mammalian cells.1 Meropenem(SM-7338) (2),3 is a broad-spectrum antibiotic active against Gram-positive and negative bacteria. Recently, in combination with vaborbactam, it was approved by FDA for the treatment of adult patients with complicated urinary tract infections.4 The pyrrolobenzodiazepines Anthramycin (3) and Sibiromycin (4) produced by actinomycetes are potent DNA alkylating agents with impressive antineoplastic activity.5

Many methods have been developed to prepare 2,3-dihydropyrroles, however there can be restrictions according to their substitutions pattern, particularly on the nitrogen. For convenience, these methods have been classified into functional group manipulation of preexisting pyrrolidones or pyrrolidines, and ring closure of acyclic precursors. Finally, several examples of the use of 2,3-dihydropyrroles as intermediates in the total synthesis of natural products will be discussed. This topic has been reviewed by Jubault, Leclerc, and Quirion in 2007, but remarkable progress has been achieved over the last 13 years.6

2. Functional group manipulation with pyrrolidones or pyrrolidines

2.1. Reduction of 2-pyrrolidones and reaction with Grignard or lithiated reagents

Reduction of N-protected 2-pyrrolidones 5 by DIBAL-H, Super-Hydride or NaBH₄ followed by dehydration induced by TFAA in the presence of a base remains a convenient approach to prepare N-protected 2-pyrrolidones non-substituted in positions 2 and 3 (Scheme 1).7

![Scheme 1](image)

**Scheme 1.** Reduction and dehydration of N-protected 2-pyrrolidones.7

2.2. Alkylation reactions

In addition, a number of successful transformations of 2-pyrrolidones into 2,3-dihydropyrroles have been reported by alkylation reactions (Scheme 2).8

![Scheme 2](image)

**Scheme 2.** Selected example of addition of an organometallic reagent to a N-protected 2-pyrrolidone followed by dehydration.8

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Addition of Grignard or lithiated reagents with N-protected 2-pyrrolidones also afford after dehydration substituted 2,3-dihydropyrroles with a new substituent in position 2 (Scheme 2).  

### 3.2. Oxidation of pyrrolidines

2,3-Dihydropyrroles can also be generated by a controlled oxidation of pyrrolidines. For instance, Groves’ team recently developed a desaturation of N-protected pyrrolidines 10 using PIDA (11) and the catalyst Mn(TPFPP)Cl (12) (Scheme 3).

### 3. Cyclization

#### 3.1. 5-Endo-dig cyclization of homopropargylamines

In 1998, Rutjes’ group reported the Pd-catalyzed 5-endo-dig cyclization of protected propargylglycine 14 into dihydropyrrole 15, with an enantioemic excess of 33% (Scheme 4). Further studies from this team showed that the use of xantphos as a ligand allows this reaction to be performed without racemization.

![Scheme 4. 5-Endo-dig cyclization of protected propargylglycine 14.](image)

The same year, Knight’s group disclosed the iodocyclization of homopropargylic sulfonamides 16 to give with excellent yields the iododihydropyrroles 17, which can be readily transformed into pyrroles 18 upon treatment DBU (Scheme 5).

The same group also prepared functionalized 3-hydroxy-2,3-dihydropyrroles starting from the diastereoselective condensation of ynoles 19 and the tin(II) enolate of glycinate 20, to afford the β-hydroxy-α-amino esters 21 with a good diastereoselectivity (ca. 9:1) (Scheme 6). Upon treatment with copper(II), palladium(II) and mercury(II) salts these adducts afforded the hydroxy-dihydropyrroles 22. The best yields were observed with Cu(OAc)₂.

![Scheme 5. Iodocyclisation of homopropargylic sulfonamides 16 and base-catalyzed elimination of sulfinate.](image)

![Scheme 6. Synthesis of ynoates 21 and conversion into hydroxy-dihydropyrroles 22.](image)
Hou group performed a similar reaction with cyclic substrates to furnish dihydropyrroles cyclopentane- and cyclohexane-fused 2,3-dihydropyroles 24 and 26 using respectively PdCl$_2$ or AuCl as catalyst under microwave conditions (Scheme 7). Gold has been found to catalyze also the 5-endo-dig cyclization of homopropargyl sulfonamides 27 in presence of triethylamine and 2,6-dibromopyridine (Scheme 8). In absence of these additives, the formation of a dimer 29 was observed. Gold(III) oxide also catalyzes the cyclization of α-amino-ynones 30 into pyrrolin-4-ones 31 in high yields with a moderate to total stereocontrol (Scheme 9).

Recently, an enantioselective homopropargylamines 34 has been devised using an allenyl boronic acid pinacol ester (33) in presence of silver fluoride and the chiral ligand Walphos-1 (Scheme 10). Interestingly, Hill and co-workers found that TBAF can catalyze the 5-endo-dig cyclization of N-tosyl homopropargylamines in absence of transition metal to generate a 2,3-dihydropyrrole or a pyrrole according whether the alkyne is terminal or disubstituted (Scheme 11).

### Scheme 7. Intramolecular cyclization catalyzed by PdCl$_2$ or AuCl to generate 2,3-dihydropyrroles 24 and 26.

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\text{Scheme 7. Intramolecular cyclization catalyzed by PdCl}_2\text{ or AuCl to generate 2,3-dihydropyrroles 24 and 26.}\]

\[
\text{Scheme 8. Gold-catalyzed cyclization of homopropargyl sulfonamides 27.}\]

\[
\text{Scheme 9. Gold-catalyzed cyclization of α-amino-ynones into pyrrolin-4-ones 30.}\]

\[
\text{Scheme 10. Enantioselective silver-catalyzed propargylation of N-tosylimine 32 and cyclization into 2,3-dihydropyrrole 35.}\]

\[
\text{Scheme 11. TBAF-catalyzed cyclization of homopropargyl sulfonamides.}\]

### 3.2. Cascade reactions

#### 3.2.1. Cascade Michael addition/annulation

Domino reactions, which enable the one-pot sequential formation of several chemical bonds, represent an extremely efficient process for rapid synthesis of complex molecules. Thus, He’s group developed a catalytic $[4 + 1]$ cyclization of α,β-unsaturated imines with allylic carbonates to diastereoselectively prepare trisubstituted N-tosyl dihydropyroles in high yields via phosphorus ylide intermediates (Scheme 12). Similarly to many of the previous synthesis, this method gives access to 2,3-
2,3-dihydropyrroles protected by a tosyl, which cannot be deprotected without generating a pyrrole.

Lattanzi group reported synthesis of unprotected 2,3-dihydropyrroles that relies on a sequential one-pot DABCO-catalyzed Michael addition/deprotection/cyclization/tautomerization approach starting from readily accessible glycine imine esters and Knoevenagel reagent. This efficient method provides dihydropyrroles in good yield and high diastereoselectivity. In contrast with the previous method, it also has the advantage to avoid the requirement to protect the imine with a tosyl that cannot be easily removed subsequently.

3.2.2. Cascade metallo-ene/Suzuki coupling reaction

Liu group developed an original tandem metallo-ene/Suzuki coupling reaction between allenamides and boronic acids catalyzed by palladium (Scheme 14). Unfortunately the preparation of the substrates is not straightforward, which limits the interest of this reaction.

3.2.3. Cascade [2+2] cycloaddition/rearrangement

Vedejs’ group reported the controlled reduction of oxazolium salts to afford the nucleophilic dehydro-oxazolines that can undergo a [2+2] cycloaddition with dimethyl acetylenedicarboxylate (DMAD) to give the cyclobutenes. These unstable intermediates spontaneously afford 2,3-disubstituted dihydropyrroles, probably through intermediate.

3.3. Carboamination of alkynes with aziridines

Wender’s group was the first to report in 2009 the use of Lewis and Brønsted acids to catalyze the condensation of N-tosylaziridines with alkynes to afford polysubstituted dihydropyrroles in a regiospecific manner under mild reaction conditions.
Zhang group developed a similar cycloaddition of vinylaziridines with alkynes through a different mechanism catalyzed by [Rh(NBD)_2]BF_4 with broad substrate scope and high stereoselectivity under mild reaction conditions (Scheme 17). Subsequently, the same group developed an iridium-catalyzed domino-ring-opening cyclization of vinylaziridines with β-ketocarbonyls (Scheme 18).

Ghorai group developed a domino ring-opening condensation of substituted N-sulfonyl aziridines with malononitrile to provide corresponding dihydropyroles in good yields and with a high stereoselectivity (Scheme 19). Importantly, the adducts protected by a nosyl could easily be removed in good yield to provide N-unsubstituted dihydropyroles.

3.4. Multicomponent reactions
Multicomponent reactions are one-pot reactions that use several reagents to generate a single product containing most of the reagent atoms. As such, they are extremely valuable in medicinal chemistry to generate complex molecules in only one step.

3.4.1. Rhodium catalyzed three component synthesis
An interesting three component reaction to prepare N-sulfonyl 2,3-dihydropyroles was reported by Murakami and co-workers (Scheme 20). Condensation of a terminal alkyne with a N-sulfonyl-azide to provide a 1,2,3-triazole generates in situ an α-imino rhodium carbene complex, which reacts with an α,β-unsaturated aldehyde to produce a trans-2,3-disubstituted dihydropyrole.
3.4.2. Phosphonite mediated three component reaction

Another three component reaction, based on the phosphonite \( \text{PhP}[2\text{-catechyl}] \) \( (84) \) induced coupling of alkene-tethered imines \( 83 \) with acid chlorides, has been reported by Arndtsen and co-workers.\(^\text{35}\) This reaction involves phosphorus-containing 1,3-dipoles \( 85 \) that undergo an intramolecular 1,3-dipolar cycloaddition with high stereo- and regioselectivity to generate the intermediate \( 86 \). Then loss of phosphine oxide and deprotonation of the iminium provides the 2,3-dihydropyrroles \( 87 \).

![Scheme 21. Coupling of alkene-tethered imines 83 and acid chlorides.\(^\text{31}\)](image-url)

3.4.3. Multicomponent reaction using \( \alpha \)-ketoamides

In 1887 Oskar Döbner reported that the condensation of an aniline \( (88) \) with an aromatic aldehyde \( (89) \) and pyruvic acid \( (90) \) generates a quinoline \( (91) \) (Scheme 22).\(^\text{36, 37}\) More than 130 years later, the replacement of pyruvic acid \( (90) \) with a pyruvic amide \( (93) \) was found to lead to the stereoselective formation of a polysubstituted 2,3-dihydropyrrole \( (101) \) instead of the expected quinolines.\(^\text{38}\) The mechanism of this reaction was proposed to involve the condensation of enone \( 94 \) with imine \( 95 \) to produce intermediate \( 96 \) that reacts with aldehyde \( 89 \), leading to 3-oxazine \( 98 \). Successive dehydration and deprotonation then generate the azomethine ylide \( 100 \) that undergoes an intramolecular 1,5-dipolar cycloaddition to afford the 2,3-dihydropyrrole \( 101 \). This reaction does not require a \( N \)-protection by a tosyl difficult to remove and generates five new bonds (~90% average yield per bond formation) in one step. It was applied to the synthesis of potent \( \alpha \)-glucosidase inhibitors.\(^\text{39}\) Thereafter the scope of this reaction was extended by adding \( \beta \)-nitroalkene \( 102 \) and \( 108 \) or \( \beta \)-pivaloxy-nitroalkane \( 113 \) to generate 2,3-dihydro-4-nitropyroles functionalized in every position (Scheme 23).\(^\text{39}\)

![Scheme 22. Döbner reaction and formation of dihydropyrroles 101 with pyruvic amides.\(^\text{38}\)](image-url)

![Scheme 23. Multicomponent synthesis of 2,3-dihydro-4-nitropyroles.\(^\text{39}\)](image-url)
3.5. Miscellaneous

3.5.1. Condensation of hypervalent alkynyliodonium salts with aliphatic amines

Feldman group discovered that the condensation of tosylamide anions \(115\) with alkynyliodonium triflates \(116\) generates alkylidene carbenes \(118\) that undergo a C-H insertion to afford 2,3-dihydropyrroles \(119\) (Scheme 24).\(^{40}\) This reaction occurs with lower yields when the amine is substituted by a protecting group other than a tosyl. Another limitations of this reaction is the instability of the adduct in acidic medium, which requires silica gel to be pretreated with \(\text{Et}_3\text{N}\) before to be used for flash chromatography purification.

![Scheme 24. Synthesis of 2,3-dihydropyrroles by condensation of lithiated sulfonamides with alkynyliodonium triflates.](image)

3.5.2. Iodine-promoted synthesis of polysubstituted 2,3-dihydropyrroles

Gao’s group developed a convenient synthesis of polysubstituted trans-2,3-dihydropyrroles \(124\) from chalcones \(120\) and \(\beta\)-enaminocarbonyls \(121\) via an iodine promoted Michael addition followed by an iodination and an annulation step (Scheme 25).\(^{41}\) Subsequently Wang’s group performed this reaction in absence of solvent and generated the \(\beta\)-enaminocarbonyls in situ by condensation of amines with alkyne esters (Scheme 26).\(^{42}\)

![Scheme 25. Iodine-promoted synthesis of dihydropyrroles \(124\) from chalcones \(120\) and \(\beta\)-enaminocarbonyls \(121\).](image)

![Scheme 26. Mechanosynthesis of trans-2,3-dihydropyrroles \(129\) from amines, alkyne esters, and chalcones.](image)

3.5.3. Intramolecular Pd(II)-catalyzed annulation

In line with the former approach, Loh’s group reported a palladium-catalyzed 5-endo-trig cyclization of \(N\)-tosyl homoallylamines in presence of chloranil as oxidant (Scheme 27).\(^{43}\)

![Scheme 27. Palladium-catalyzed cyclization of \(N\)-sulfonyl homoallylamines.](image)

3.5.4. [2+3] annulation of allenylstannanes with \(\alpha\)-imino esters

Takahiko and coworkers described the copper-catalyzed enantioselective [2+3] annulation of allenylstannane \(133\) with \(\alpha\)-imino ester \(134\) followed by a Stille reaction to afford \(N\)-tosyl-dihydropyrroles (Scheme 28).\(^{44}\)

![Scheme 28. Condensation of allenylstanniane \(133\) and \(\alpha\)-imino ester \(134\) followed by a Stille reaction.](image)
3.5.5. Organocatalytic synthesis of chiral N-formyl-2,3-dihydropyrroles
A convenient asymmetric tandem Michael addition/cyclization between formylaminomalonates 139 and aromatic dicyanoolefins 140 catalyzed by the novel chiral thiourea 141 furnishes N-formyl-2,3-dihydropyrroles 142 with high yields and good enantioselectivities in only one step (Scheme 29).45

![Scheme 29. Organocatalytic synthesis of chiral N-formyl-2,3-dihydropyrroles 142.45](image)

4. 2,3-Dihydropyrroles as intermediates in the total synthesis of natural products
2,3-Dihydropyrroles have been used as critical intermediates in the synthesis of natural products. For instance, deprotonation of ketone 143 and alkylation with sulfonate 144 stereospecifically afforded the dihydropyrole 145, which underwent Strecker-like reaction with TMSCN generating 146, en route toward the total synthesis of Stephacidin B described by Myers’ group (Scheme 30).46

![Scheme 30. Use of 2,3-dihydropyrole 145 as an intermediate in Myers’ enantioselective total synthesis of Stephacidin B.46](image)

The approach of Martin and co-workers to fashion the scaffold of the complex manzamine alkaloids relies on the readily accessible chiral dihydropyrrole 149 that was converted in one step to the key tricyclic intermediate 151 through a tandem Stille/Diels-Alder reaction (Scheme 31).47

![Scheme 31. Synthesis of the tricyclic core of Ircinol A (152) by Martin and co-workers.47](image)

The Melodinus alkaloid (±)-Meloscine 155 has been prepared in 2011 by the groups of Curran and Mukai using in both cases a dihydropyrole (153 or 156) to assemble the core structure of this complex alkaloid exploiting an elegant radical-initiated cyclization and an intramolecular Pauson-Khand reaction (Scheme 32).48,49

Knölker and colleagues developed a silver(I)-catalyzed 5-endo-dig cyclization of homopropargylamines 159 into 2,3-dihydropyrole 160 that was applied to the synthesis of the natural myosin ATPase inhibitor pentabromopseudilin (161), a polyhalogenated pyrrole synthesized by Pseudomonas bromoutilis and Chromobacteria (Scheme 33).50

![Scheme 32. Curran and Mukai’s syntheses of the tetracyclic skeleton (±)-Meloscine (155).48,49](image)
Millingtonine A (167) is a glycosidal alkaloid extracted from the Asian medicinal plant Millingtonia hortensis. Baxendale and coworkers’ approach to assemble the core of this complex heterocycle began with the isomerization of the protected 1,2-dihydropyrrole 162 into 2,3-dihydropyrrole 163 with Wilkinson’s catalyst (Scheme 34).\textsuperscript{51} Engagement of this protected enamine into a Ueno-Stork cyclization with the allylic alcohol 164 furnished the key intermediate 165 that was converted in few steps to millingtonine A (167).

5. Conclusion

From the endo-dig cyclization of homopropargylamines to the cascade or multicomponent reactions, methods to prepare these heterocycles span the breadth of functional groups, and classical and modern reactions. Even if some of them suffer from the necessity to use a tosyl, which is difficult to deprotect, the synthetic studies towards 2,3-dihydropyrroles has been rich in intellectual excitement and has already been applied to several natural products and bioactive compounds. While we tried our very best to be comprehensive, it is possible that we have inadvertently missed some important reports, for which we express our regret here in advance.

Last but not least, we hope that this review will be useful for the design and synthesis of functionally active molecules, especially for biological applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The acknowledgements come at the end of an article after the conclusions and before the notes and references.

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