# ADVANCES AND CHALLENGES IN THE SYNTHESIS OF PYRROLE SYSTEMS OF A LIMITED ACCESS

DOI: http://dx.medra.org/10.17374/targets.2018.21.54

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***Abstract***. *This chapter focuses on the advances and challenges in the synthesis of selected hardly accessible pyrrole systems. The review is divided into three main sections namely the synthesis of 3H-pyrroles, 1-[2-aryl(hetaryl)vinyl]pyrroles (pyrrole analogs of stilbenes) and di- and oligopyrroles separated by heteroaromatic systems.*

**Contents**



## 1. Introduction

The present review summarizes advances and challenges in the synthesis of three classes of hardly accessible pyrrole systems, namely 3*H*-pyrroles, 1-[2-aryl(hetaryl)vinyl]pyrroles (pyrrole analogs of stilbenes) and di- and oligopyrroles separated by heteroaromatic systems. The modern approaches to the synthesis of similar pyrrole systems are quite specific. Therefore, in our opinion, systematization of the known data attempted in the review seems to be rational and convenient for use.

## 2. Synthesis of 3*H*-pyrroles

So far 3*H*-pyrroles remain hardly accessibly and poorly understood class of nonaromatic pyrroles. The key advances in this field of research are summarized in two outdated reviews[1,2] devoted mainly to physical and theoretical aspects of 2*H*- and 3*H*-pyrroles chemistry. The reviews basically covers the data on the best studied 2*H*-pyrroles, whereas information on 3*H*-pyrroles is sporadic and is used, as a rule, for comparison purpose.

Thermodynamic instability of 3*H*-pyrroles as compared to their 2*H*-, and especially, aromatic 1*H*-isomers,[1,3] on one hand, accounts for their scantily explored chemistry owing to the additional difficulties arising in the course of synthesis. The available data on efficient antimicrobial[4,5] and antitumor[6] agents derived from 3*H*-pyrrole derivatives are outcome of accidental rather than systematic investigations in the field of medicinal chemistry. On the other hand, thermodynamic instability of 3*H*-pyrroles enhances their reactivity and, hence, they possess implicitly rich chemistry as compounds, which are essentially prone to various rearrangements, addition and cycloaddition reactions.[1,2]

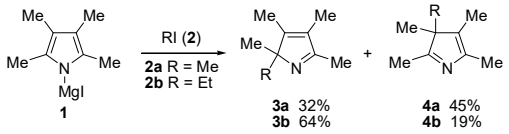
Despite the obvious interest in these molecules and their indisputable prospects to organic chemistry as active intermediates having unique reactivity, a general method for their synthesis is still lacking. In the

present review, we have tried to survey the main known approaches to the synthesis of 3*H*-pyrroles. A huge number of transition tetrahedral intermediates of the electrophilic substitution reactions involving 1*H*-pyrroles, compounds with exocyclic double bonds, and various fused systems have been intentionally excluded from consideration.

### 2.1. Modification of 1*H*-pyrroles

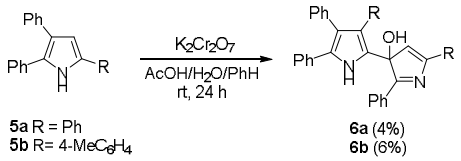
One of the pioneering methods for the synthesis of 3*H*-pyrroles comprises modification of 1*H*-pyrroles. However, the works published in the end of the 19th century,[7,8] provided no reliable evidences whether the obtained compounds are 2*H*- or 3*H*-isomers due to the lack of effective methods of structural assignment. Besides, in the majority of early works, the products were isolated by extraction from the acidified aqueous solutions, sometimes upon boiling. Now 3*H*-pyrroles are known to be unstable in the presence of acids and undergo rearrangement to 2*H*-pyrroles[9,10] or hydrolyzed to 1,4-diketones.[10,11]

It has been shown for the first time[12] that the reaction of pyrrole magnesium iodide **1** with methyl (**2a**) or ethyl iodide (**2b**) affords a mixture of isomeric 2*H*-(**3a,b**) and 3*H*-pyrroles **4a,b** (Scheme 1).



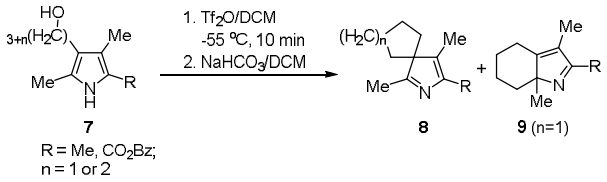

**Scheme 1**

Oxidation of trisubstituted pyrroles **5** under the action of potassium dichromate in the acidic medium gives multicomponent mixtures, from which various isopyrroles, including 3-hydroxy-3*H*-pyrroles **6**, have been isolated (Scheme 2).[13]




**Scheme 2**

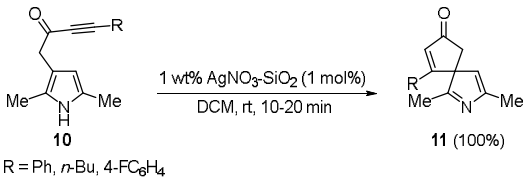
Treatment of 3-(ω-hydroxyalkyl)pyrrole **7** with trifluoromethanesulfonic acid anhydride at the lowered temperatures delivers the corresponding spirocyclic 3*H*-pyrroles **8** (Scheme 3).[14] In some cases, the side fused 2*H*-pyrroles **9** are formed. However, yields of the products and physical-chemical constants of the compounds are not given in this work.




**Scheme 3**

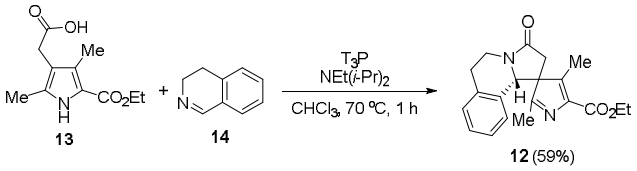
Recently, it has been shown[15] that silica-supported silver nitrate ($AgNO_3$-$SiO_2$) is a highly active catalyst in the dearomatizing spirocyclization of alkyne-tethered aromatics and heteroaromatics including pyrrole derivatives **10** (Scheme 4). In the presence of such catalysts, yields of the corresponding spiro-fused 3*H*-pyrroles **11** become quantitative, while unsupported $AgNO_3$ gives the desired compounds only in 20-

89% yields. It is assumed that efficacy of silica-supported silver nitrate catalysis stems from a synergistic relationship between the silica support and Ag-nanoparticles formed during their preparation.




**Scheme 4**

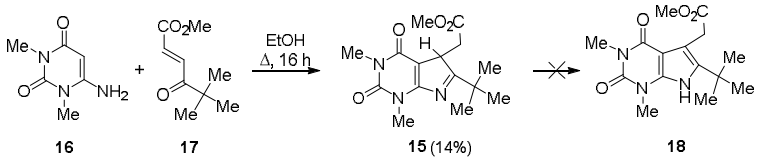
Spirocyclic 3*H*-pyrrole **12** has been synthesized from 3-pyrrolylacetic acid **13** and imine **14** in the presence of propylphosphonic anhydride ($T_3P$) and NEt(*i*-Pr)$_2$ *via* intermediate *N*-acyliminium salts in 59% yield (Scheme 5).[16]




**Scheme 5**

**2.2. From carbonyl compounds**

A stable, unsubstituted in the position 3 of the pyrrole ring, 3*H*-pyrrole **15** has been obtained by the reaction of aminouracil **16** with unsaturated ketoester **17** (Scheme 6).[17] The authors believe that the isomerization to 1*H*-pyrrole **18** is unfavorable owing to steric interactions between the *tert*-butyl and carboxymethyl groups.



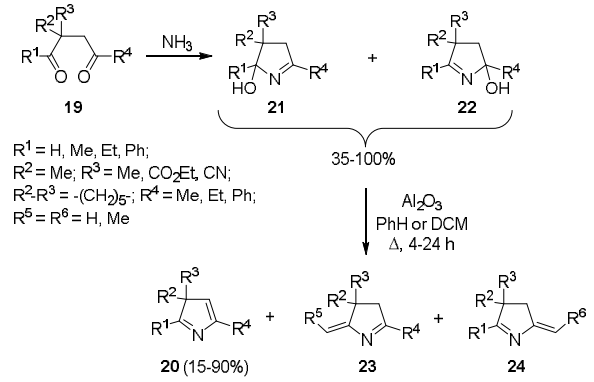

**Scheme 6**

The Paal-Knorr reaction, an interaction of 1,4-diketones with ammonium or primary amines, is a classical method for the synthesis of 1*H*-pyrroles. This approach has been adapted for the preparation of 3*H*-pyrroles using 2,2-disubstituted 1,4-diketones **19** and ammonium as the substrates. Consequently, a number of 3*H*-pyrroles **20** with diverse substituents in the position 3 including ester and nitrile groups (Scheme 7) have been obtained.[10,11,18] The reaction proceeds *via* formation of isomeric hydroxypyrrolines **21** and **22** (isolated as individual compounds) and their further dehydration to the target 3*H*-pyrroles **20**. When at least one hydrogen atom is present in the α-position of $R^1$ or $R^4$ substituents, the side pyrrolines **23** or **24** with exocyclic double bonds are also formed.

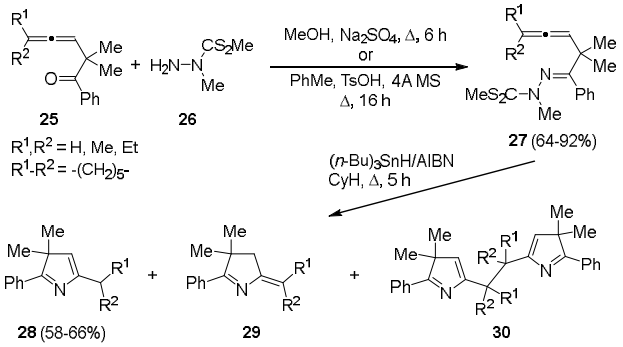
Despite attractiveness of this method, its preparative value decreases because of difficulties with synthesis of the starting 1,4-diketones **19** and formation of the side pyrrolines **23** and **24**, which are often inseparable from the target pyrroles **20**.

The reaction of β-allenylketones **25** with hydrazine **26** furnishes the corresponding hydrazones **27**, undergo radical intramolecular cyclization in the presence of (*n*-Bu)$_3$SnH/AIBN system to produce a mixture of products of **28**-**30** (Scheme 8).[19] In spite of the fact that various ketones tolerate the process and the content of 3*H*-pyrroles in the reaction mixtures reaches 70%, only three products **28** have been obtained as

individual compound that is caused by high reactivity of 3*H*-pyrroles and their transformations in the course of isolation on chromatographic column.

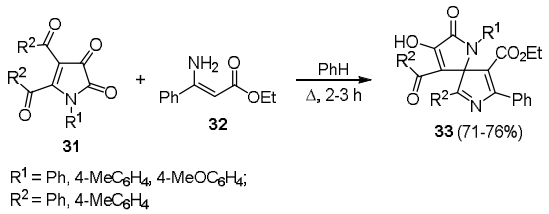



**Scheme 7**




**Scheme 8**

Refluxing the equimolar mixture of 4,5-diaroyl-2,3-dihydro-1*H*-pyrrole-2,3-diones **31** with enamine **32** in benzene gives rise to spirocyclic 3*H*-pyrroles **33** (Scheme 9).[20,21]

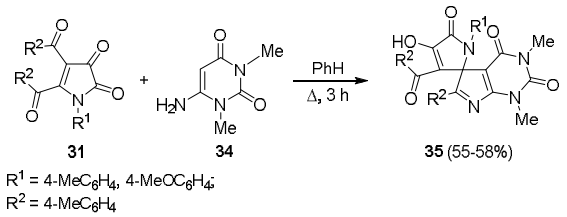



**Scheme 9**

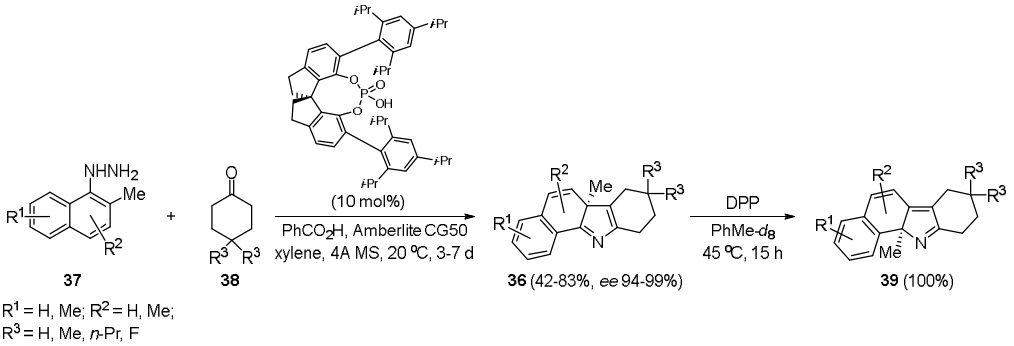
When cyclic enamine **34** is employed under similar conditions, the fused spiro-3*H*-pyrroles **35** are formed in good yields (Scheme 10).[22]

Divergent Brønsted acid-catalyzed asymmetric synthesis of 3*H*-pyrroles **36** by applying a dearomatizing Fischer indolization has been described.[23] Using α-naphtyl hydrazines **37** and cyclohexanones **38** as a starting materials and SPINOL-derived phosphoric acid as a catalyst, tetracyclic 3*H*-pyrroles **36** are obtained in 42-83% yields and 94-99% *ee* (Scheme 11). Upon addition of diphenyl phosphate to the reaction

mixture, all 3*H*-pyrroles **36** are quantitatively converted *via* [1,5]-alkyl shift into the corresponding 2*H*-pyrroles **39**, one of which seems to be a potent nontoxic inhibitor of the Hedgehog signaling pathway by binding to the Smoothened protein.



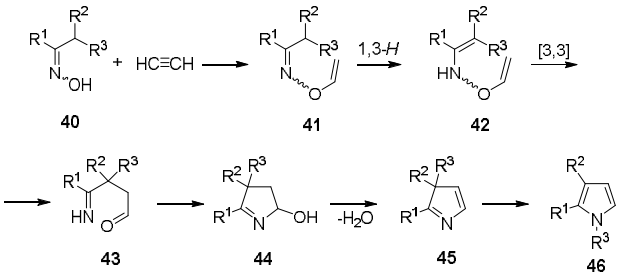

**Scheme 10**




**Scheme 11**

**2.3. From oximes**

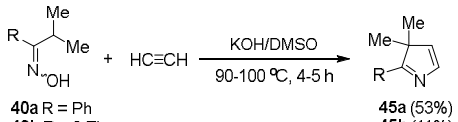
Ketoximes **40**, bearing two or three C-H bonds in the α-position to the oxime function, are known[24] to react with acetylene in the presence of the superbasic system MOH/DMSO (M is alkaline metal) to afford 1*H*-pyrroles. The tandem sequence includes (Scheme 12) the following steps: prototropic shift in *O*-vinyl ketoximes **41**, adducts of ketoximes **40** with acetylene; [3,3]-sigmatropic rearrangements of *N,O*-dialkenylhydroxylamines **42**; cyclization of iminoaldehydes **43**; dehydration of 5-hydroxypyrrolines **44** and aromatization of 3*H*-pyrroles **45** to form 1*H*-pyrroles **46**.




**Scheme 12**

In the case of ketoximes containing only one C-H bond in the α-position to the oxime function (**40**, $R^2$ and $R^3 \neq H$), the above sequence should stop at a stage of formation of the 3,3-disubstituted 3*H*-pyrroles **45**, since their further aromatization is impossible without cleavage of the C-C bond. The possibility of 3*H*-pyrroles **45** formation has been shown for the first time on the example of the reaction between isopropyl

phenyl(2-thienyl) ketoximes **40** and acetylene in the KOH/DMSO system (Scheme 13).[25,26] It is mentioned that the reaction is followed by resinification of the reaction mixture. However, the attempts to optimize yields of the target compounds have met with no success.

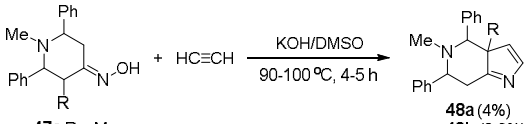



**40a** R = Ph
**40b** R = 2-Th

**45a** (53%)
**45b** (11%)

**Scheme 13**

The reaction of 4-piperidinone oximes **47** with acetylene under similar conditions leads to the fused 3*H*-pyrroles **48** in low yields (Scheme 14).[27]

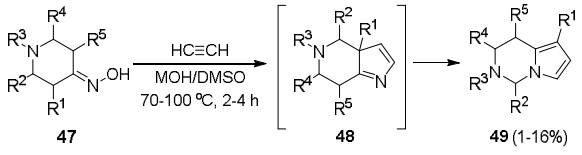



**47a** R = Me
**47b** R = Ph

**48a** (4%)
**48b** (0.3%)

**Scheme 14**

Later, the authors have expanded the scope of oximes **47** and found that under the conditions of the main reaction, 3*H*-pyrroles **48** rearrange to 1*H*-pyrroles **49** (1-16% yields, Scheme 15).[28,29]



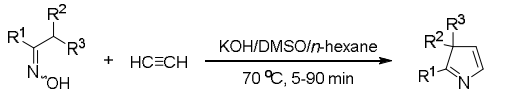

**47** **48** **49** (1-16%)

M = K, Rb;
$R^1$ = Me, Ph; $R^2$ = H, Ph;
$R^3$,$R^5$ = H, Me; $R^4$ = H, Me, Ph

**Scheme 15**

The reaction of ketoximes **40**, bearing only one C-H bond in the α-position to the oxime function, with acetylene in the superbasic systems have been thoroughly studied in a number of recent works.[3,30-36]

For example, the reaction of ketoximes **40** with acetylene under pressure in multiphase superbasic system KOH/DMSO/*n*-hexane delivers the corresponding 3*H*-pyrroles **45** in 8-32% yields (Scheme 16).[3,30]




**40** **45** (8-32%)

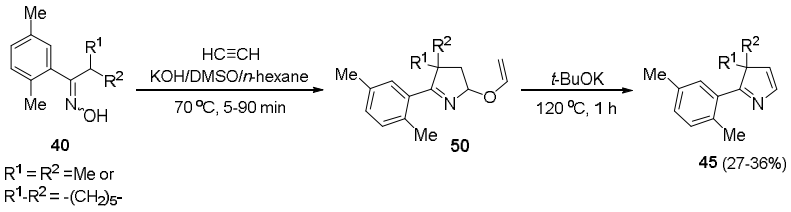
$R^1$ = Ph, 4-Me$C_6H_4$, 2,5-$Me_2C_6H_3$, 2-Th, 2-Fur;
$R^2$ = $R^3$ = Me or $R^2$-$R^3$ = -$(CH_2)_5$-

**Scheme 16**

Later,[31] the much safer and feasible method using acetylene under atmospheric pressure in a KOH/DMSO system (90 °C, 4 h) has been elaborated to give 3*H*-pyrroles **45** in 16-38% yields. It should be noted that the isolated yields of 3*H*-pyrroles **45** are about twice as less compared with the content of the target pyrroles in the crude product. The reason is high reactivity of 3*H*-pyrrole **45** which leads to significant

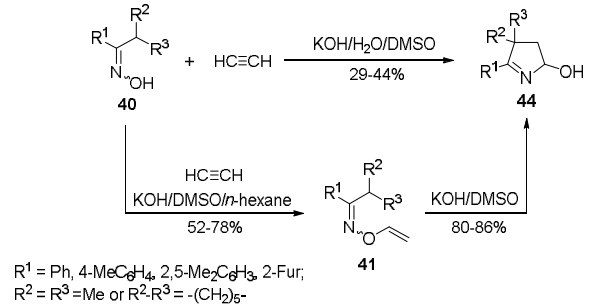
loss (about 40%) due to their both partial hydration upon chromatographic isolation to 5-hydroxypyrrolines **44**[3] and further transformations on chromatography column, *e.g.* silica-catalyzed addition of unreacted ketoximes **40** to the double bond of 3*H*-pyrroles **45**.[31]

It has been shown that in the case of 2,5-dimethylphenyl substituted ketoximes **40** the reaction stops at the formation of *O*-vinylhydroxypyrrolines **50** which prove to be new intermediates of 3*H*-pyrrole synthesis (Scheme 17).[3]

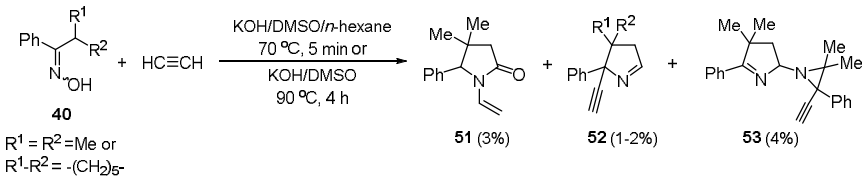



**Scheme 17**

To evaluate the advantages and peculiarities of 3*H*-pyrrole synthesis *via* the reaction between ketoximes **40** and acetylene, further variation of the process conditions (especially basicity of KOH/DMSO system) has been performed. As a result, the clue reaction intermediates, *O*-vinylketoximes **41**[32] and 5-hydroxypyrrolines **44**[32,33] have been chemoselectively synthesized (Scheme 18). Also new minor reaction pathways such as formation of 1-vinylpyrrolidone **51**,[34] ethynylpyrrolines **52**[35] and (ethynylaziranyl)pyrroline **53**[36] which could decrease yields of the target 3*H*-pyrroles **45** were found (Scheme 19).

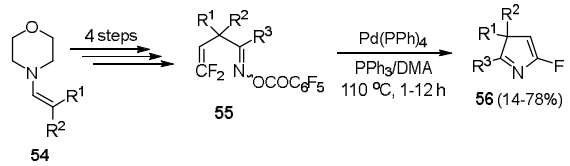



**Scheme 18**




**Scheme 19**

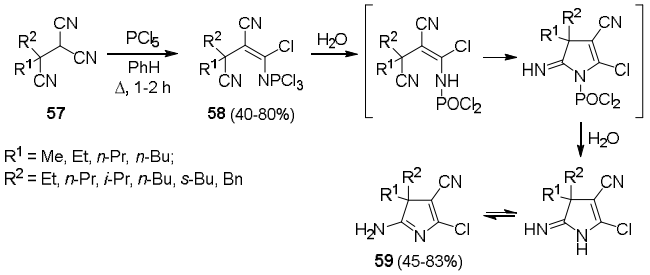
Cyclization of 3,3-difluoroallylketone *O*-pentafluorobenzoyloximes **54** (prepared from the corresponding enamines **55** *via* 4 preparative stages, Scheme 20)[37] leads to 5-fluoro-3*H*-pyrroles **56**. It is mentioned that the presence of difluoromethylene group is a mandatory condition for successful implementation of the reaction.




**Scheme 20**

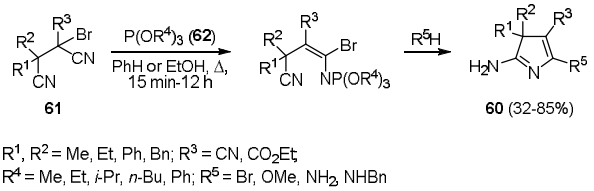
**2.4. From nitriles**

Among convenient reagents for implementation of this approach are dinitriles of various structures. The reaction of 1,1,2-tricyanoalkanes **57** with phosphorus pentachloride gives trichlorophosphazo-1-chloro-3,3-dialkyl-2,3-dicyanopropylenes **58** in 40-80% yields.[38] Hydrolysis of the obtained compounds with the subsequent treatment with alkali is accompanied by cyclization and formation of 2-amino-3*H*-pyrroles **59** (Scheme 21).



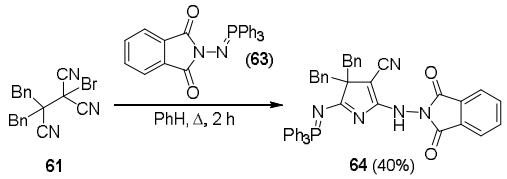

**Scheme 21**

At the same time, structurally close aminopyrrolenines **60** have been synthesized by the reaction of 1-bromo-1,2-dinitriles **61** bearing electron-withdrawing groups with more easy-to-handle trialkylphosphites **62** in up to 85% isolated yields (Scheme 22).[39-42]



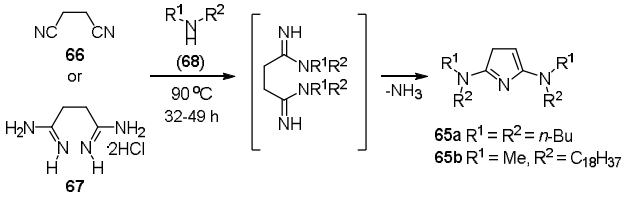

**Scheme 22**

When alkylphosphites **62** are replaced by *N*-phthalimidyl iminophosphorane (**63**), the reaction proceeds similarly to furnish the corresponding pyrrolenyliminophosphorane **64** in 40% yield (Scheme 23).[43]



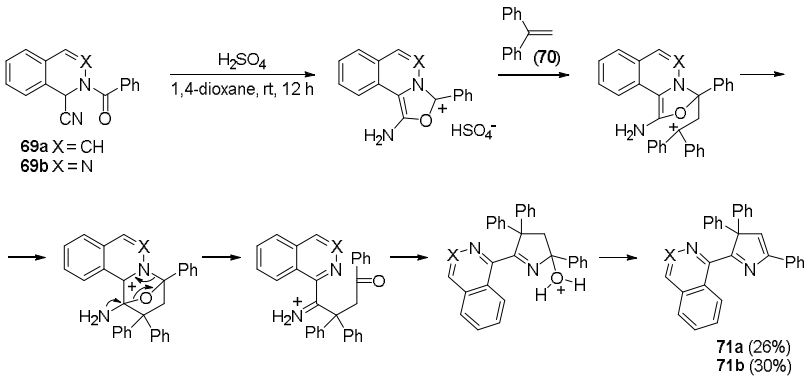

**Scheme 23**

Rare unsubstituted in the position 3 of the pyrrole ring 3*H*-pyrroles **65** are obtained by the reaction of succinonitrile (**66**) or succinic acid amidine hydrochloride (**67**) with secondary amines **68** (Scheme 24), yields and spectral characteristics of the target compounds being not given.[44]



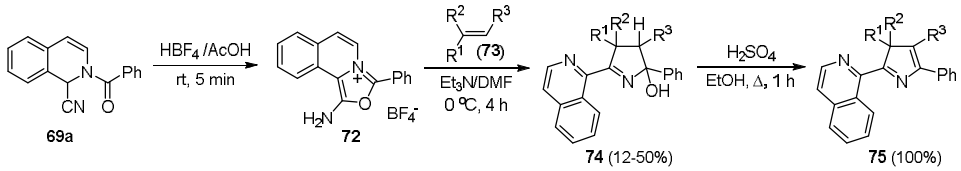

**Scheme 24**

The acid-catalyzed reaction of Reissert compound **69a** with 1,1-diphenylethylene (**70**) leading to 3,3,5-triphenyl-3*H*-pyrrole **71a**, has been thoroughly studied.[45] The experiments with isotope labeled reagents have allowed the reaction mechanism to be rationalized (Scheme 25). Under similar conditions, the corresponding 3*H*-pyrrole **71b** is synthesized from phthalizinyl analog of compound **69a**.[46]




**Scheme 25**

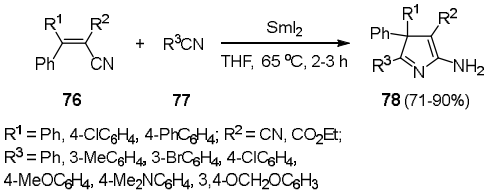
Later, it has been shown that the reaction of salt **72**, obtained from Reissert compound **69a**, with alkenes **73** proceeds as the concerted process like Diels-Alder reaction (Scheme 26).[47] In this case, hydroxypyrrolines **74** have been isolated, which in the presence of sulfuric acid quantitatively transform into pentasubstituted 3*H*-pyrroles **75**.




**Scheme 26**

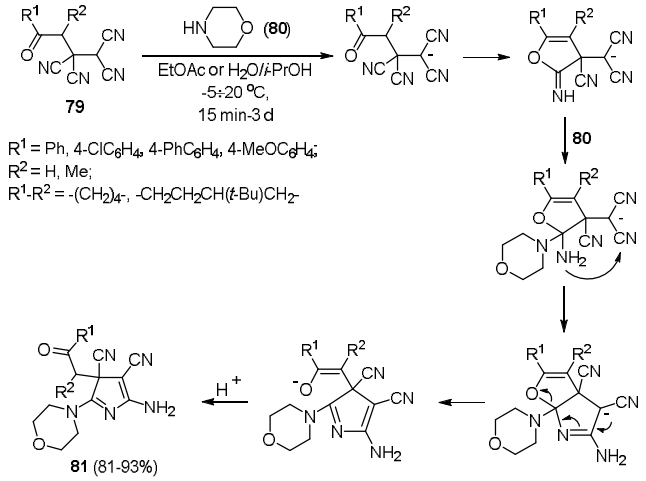
The reaction of 1,1-diaryl-2-cyanoethylenes **76** with arylnitriles **77** in the presence of samarium iodide proceeds under mild conditions to deliver polysubstituted 3*H*-pyrroles **78** in 71-90% yields (Scheme 27).[48] In view of sensitivity of samarium iodide to air oxygen, the authors have tried to generate it *in situ* from

metal samarium and iodine that slows down the reaction (to 10-12 h) and decreases isolated yields of products **78** (to 52-75%).[49]



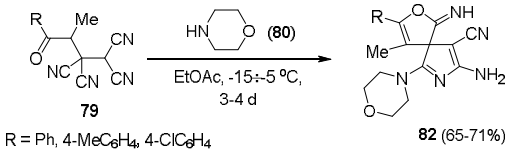

**Scheme 27**

4-Aryl-4-oxobutane-1,1,2,2-tetracarbonitriles **79** react with morpholine (**80**) giving rise to polyfunctionalized 3*H*-pyrroles **81**.[50-52] At the first stage, morpholine (**80**) acts as a base deprotonating the CH acidic center of substrate **79**. Further the salt obtained undergoes a number of the transformations furnishing the target products **81** (Scheme 28).




**Scheme 28**

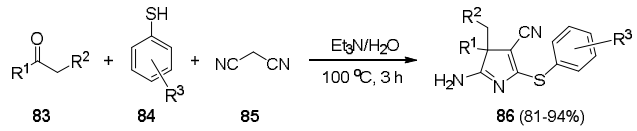
In the case of 3-methyl-1,1,2,2-tetracarbonitriles (**79**, $R^2$ = Me), a sequence of transformations under similar conditions ends up with the assembly of 2-oxa-7-azaspiro[4.4]nona-3,6,8-trien systems **82** (Scheme 29).[53]




**Scheme 29**

Multicomponent reaction between ketones **83**, thiols **84** and malonodinitrile (**85**) in the presence of triethylamine permits pentasubstituted 3*H*-pyrroles **86** to be synthesized in 81-94% yields (Scheme 30).[54] Some of the synthesized 3*H*-pyrroles **86** demonstrate excellent inhibition efficiency for mild steel at 50 mg/L

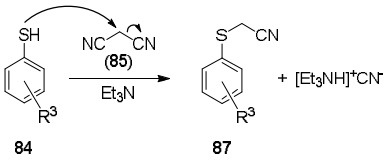
concentration in 1M HCl.[55] Experimental and theoretical methods show that the 3*H*-pyrroles **86** act as anodic type inhibitors by adsorbing on the metal surface.



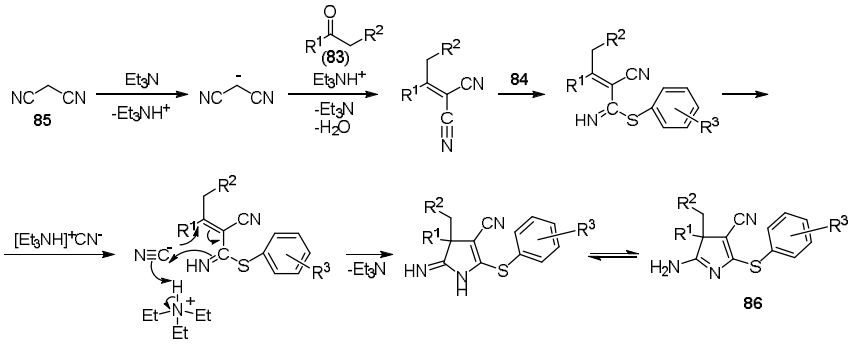

$R^1$ = Me, Et, Bn; $R^2$ = *i*-Pr, Ph, 4-$ClC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 2-Th, 2-Flu; $R_3$ = 4-Me, 4-*i*-Pr, 3-Cl, 4-Cl, 3,4-$C_4H_4$

**Scheme 30**

It has been assumed that the reaction involved generation of the cyanide ion due to nucleophilic attack of malonodinitrile (**85**) by thiols **84** (Scheme 31). The formed arylthioacetonitrile **87** is isolated after careful treatment of the reaction mixture. Further transformations are classical and presented in Scheme 32.



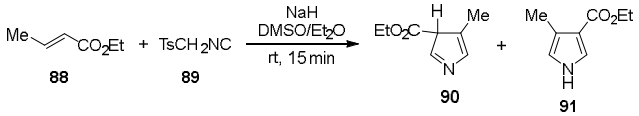

**Scheme 31**




**Scheme 32**

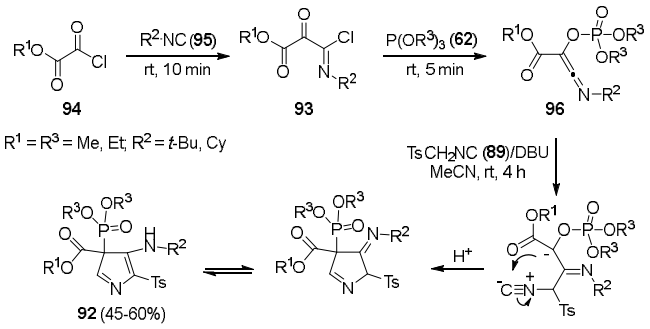
**2.5. From isonitriles**

To synthesize antitumor agent CC-1065, a reaction of ethyl ether of crotonic acid (**88**) with tosylmethylisocyanide (**89**) has been studied. The reaction is shown to give a mixture of two pyrroles **90** and **91** (yields and ratio of the products are not specified, Scheme 33).[56] Under the reaction conditions, 3*H*-pyrrole **90** is completely transformed (16 h) into pyrrole **91**.



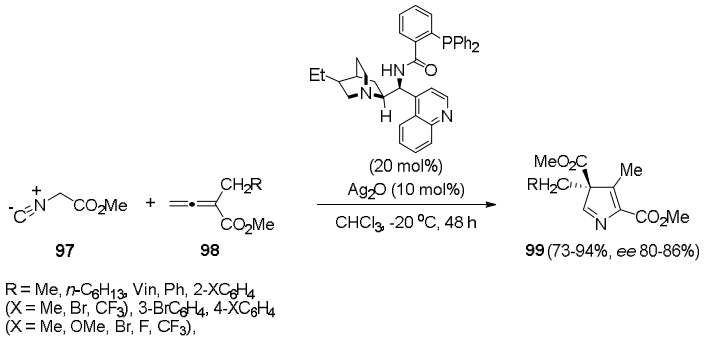

**Scheme 33**

Recently,[57] phosphorus-containing 3*H*-pyrroles **92** (Scheme 34) have been synthesized. The first stage of the process includes the interaction of imidoyl chlorides **93**, formed from acyl chlorides **94** and isonitriles **95**, with trialkylphosphites **62** (Perkow-type reaction). The obtained ketimine intermediates **96** under mild conditions react with deprotonated tosylmethylisocyanide (**89**) to produce pyrroles **92** in 45-60% yields.




**Scheme 34**

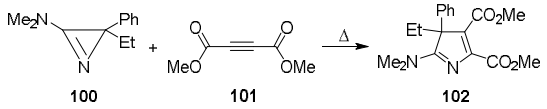
Reaction of methyl isocyanoacetate (**97**) with methylallenoates **98** in the presence of silver oxide and a phosphine ligand represents an example of successful synthesis of 3*H*-pyrroles **99** with a high enantioselectivity (Scheme 35).[58]




**Scheme 35**

**2.6. Miscellaneous methods**

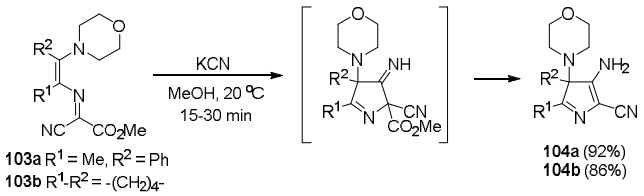
Thermolysis of 2*H*-azirine **100** in the presence of dimethylacetylenedicarboxylate (**101**) is accompanied by formation of 3*H*-pyrrole **102** (Scheme 36), the yield being not given.[59,60]



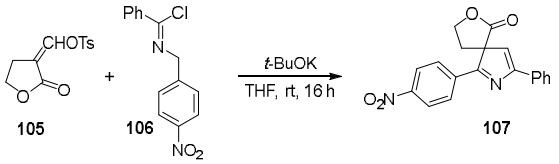

**Scheme 36**

The interaction of 2-aza-1,3-dienes **103** with potassium cyanide under mild conditions followed by decarboxylation leads to the corresponding 3*H*-pyrroles **104** (Scheme 37).[61]

The reaction of tosyloxytulipaline A (**105**) with various nitrile ylides, generated *in situ* from the corresponding imidoyl chlorides **106** has been studied (Scheme 38).[62] In the case of 4-nitrosubstituted imidoyl chloride **106**, the reaction unexpectedly affords spiro-3*H*-pyrrole **107** (the yield is not specified).




**Scheme 37**

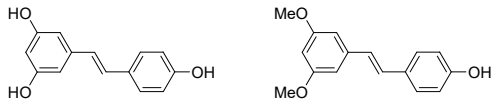



**Scheme 38**

Thus, despite thermodynamic instability of 3*H*-pyrroles, several successful attempts of their synthesis have been made. However, it should be noted that the majority of methods require hardly accessibly starting reagents and catalysts and leads to highly functionalized products that often does not allow constructing 3*H*-pyrrole scaffold with tailor-made arrangement and nature of the substituents. One of the most general and straightforward approaches to the synthesis of 3*H*-pyrroles with application of inexpensive starting reagents and catalysts is the reaction of acetylene with ketoximes bearing only one C-H bond in the α-position to the oxime function.[3,30,31]

**3. Synthesis of pyrrole analogues of stilbenes**

*N*-Styrylpyrroles, heterocyclic analogs of stilbenes, which are extensively used in various spheres of human activity, are of particular interest as the pyrrole functional derivatives. For example, resveratrol possesses potent anti-inflammatory and antioxidant action, prevents the aggregation of thrombocytes and growth of different cancer cells.[63-65] It is also found that resveratrol increases the lifespan of the lowest organisms by 70%,[66,67] and pterostilbene has a beneficial effect on concentration of glucose in blood.[68]




An important property of the stilbene derivatives is the fast and reversible *E/Z*-isomerization. For this reason, these compounds can be considered as "smart" molecules, which could find application in devices for record and storage of information,[69] and as photo-activated molecular muscles.[70] The substituted stilbenes, possessing attributes of fluorescent labels and sensors, gain new advantages (owing to their photochromic properties), in particular, in various dynamic processes involving biological membranes and surface layers.[71]

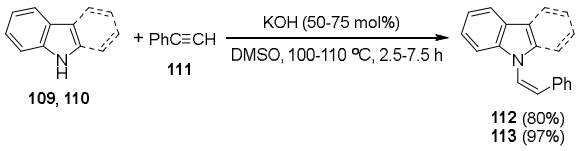
Another promising direction in this field is the investigation of nonlinear-optical properties of heterocyclic analogs of stilbene,[72,73] since electron-rich heterocycles (furans, thiophenes, pyrroles) have lower delocalization energy as compared to benzene, and hence should be more efficient charge carriers than benzene.

A wide variety of methods for the synthesis of 1-[2-aryl(hetaryl)vinyl]pyrroles, covered in this part of the review, once again confirms research interest in this class of compounds.

**3.1. Nucleophilic addition to het(aryl)acetylenes**

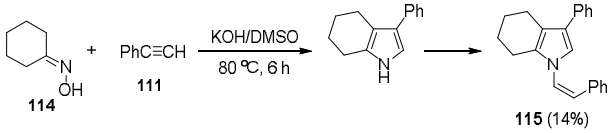
The reaction of nucleophilic addition to unsubstituted acetylene is most widespread route for introduction of the vinyl group to nitrogen atom in various heterocycles.[24] However, the use of pressure still seriously limits the employment of this synthetic approach in technological processes since there are hard constrains for application of the acetylene in industry. Considerable advances in the solution of this problem have been achieved with the development and systematic usage of the superbasic media in acetylene chemistry.[24] *N*-Vinylpyrrole derivatives have been synthesized (in up to 97% yields) for the first time by addition of pyrroles to acetylene in the KOH/DMSO system.[74] At the same time, until now applicability of this approach to the synthesis of *N*-arylvinyl derivative of pyrroles has been shown only on the example of the reactions of pyrrole (**108**), indole (**109**) and carbazole (**110**) with phenylacetylene (**111**).

For instance, it is disclosed that the reaction of indole (**109**) and carbazole (**110**) with phenylacetylene (**111**) in the superbasic system KOH/DMSO furnishes *Z*-isomers of 1-(2-phenylvinyl)indole (**112**) and 9-(2-phenylvinyl)carbazole (**113**) (Scheme 39).[75]



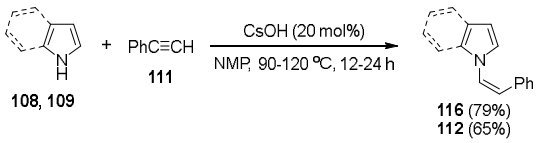

**Scheme 39**

(Z)-[1-(2-Phenylvinyl)]-3-phenyl-4,5,6,7-tetrahydroindole (**115**) has been synthesized in 14% yield by the Trofimov reaction from cyclohexanone oxime (**114**) and pnenylacetylene (**111**) (Scheme 40).[76] Taking into account conversion of the starting ketoxime **114** (34%), the product yield is 42%.



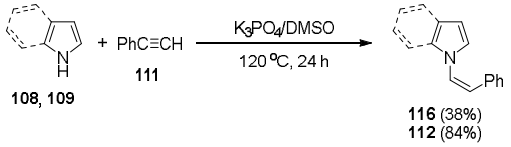

**Scheme 40**

Pyrrole (**108**) and indole (**109**) stereoselectively add to phenylacetylene (**111**) in the presence of cesium hydroxide (Scheme 41).[77] In case of 1-(2-phenylvinyl)pyrrole (**116**), *Z*-stereoselectivity reaches 100%, and for 1-(2-phenylvinyl)indole (**112**) stereoselectivity is 92%.




**Scheme 41**

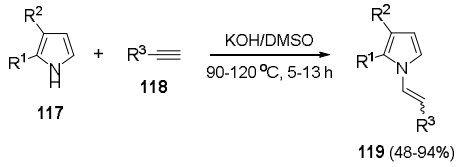
It has been shown later that potassium phosphate as the base can be used (Scheme 42),[78] which, apparently, is exposed to hydrolysis forming insignificant amounts of potassium hydroxide.




**Scheme 42**

However, a generality and applicability of this approach to the synthesis of various pyrrole and indole analogs of stilbenes remain disputable for a long time. Recently, these issues have been successfully addressed in a number of works.[79-82]

Addition of 2- and 2,3-substituted pyrroles **117** to arylacetylenes **118** in the KOH/DMSO system to afford *N*-styrylpyrroles **119** in 48-94% yields has been realized (Scheme 43).[79]



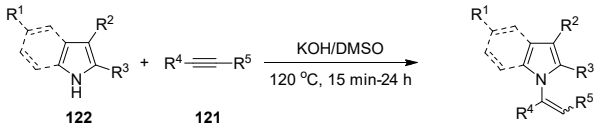

**117** **118** **119** (48-94%)

$R^1$ = H, Me, Ph, 2-Th, 2-Py, $R^2$ = H; $R^1$-$R^2$ = -$(CH_2)_4$-;
$R^3$ = Ph, 4-Me$C_6H_4$, 2,5-$Me_2C_6H_3$, 4-Ph$C_6H_4$, 3-F$C_6H_4$, 2-Py

**Scheme 43**

As shown by special experiments and quantum-chemical calculations, the addition stereochemistry is controlled kinetically on the initial stages of the reaction and thermodynamically in the end of the process depending on the reactants structure and the reaction conditions that allows individual *E*- or *Z*-stereoisomers of the adducts to be isolated. Preliminary spectroscopic and photophysical studies have revealed that *N*-styrylpyrroles as a heterocyclic analogs of stilbene are characterized by similar intensities and locations of the long-wave absorption and fluorescence bands. The substitution of the benzene cycle in the stilbene molecule by the pyrrole ring or two benzene cycles by the pyrrole and pyridine moieties affects mainly the fluorescence quantum yield values, which are significantly lower than those for stilbene.[79]

The system KOH/DMSO permits to synthesize adducts **120** in up to 99% yields, using acetylenes **121** (both terminal and internal) and NH-heterocycles **122** as the starting reagents (Scheme 44).[80-82]

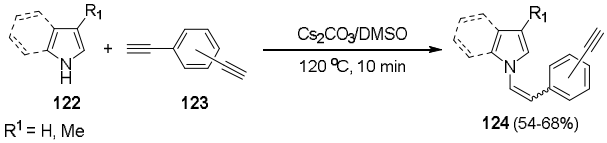



**122** **121** **120** (40-99%)

$R^1$ = H, Br, OMe, 4-$MeOC_6H_4$;
$R^2$ = H, Me, $CH_2CH_2NH_2$; $R^3$ = H, Me;
$R^4$ = H, AlkAr, 3-$MeOC_6H_4$;
$R^5$ = AlkAr, 3-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 3-Th

**Scheme 44**

With diethynylbenzenes **123** and cesium carbonate as a catalyst, monoadducts **124** are selectively formed (Scheme 45).[81]




**122** **123** **124** (54-68%)

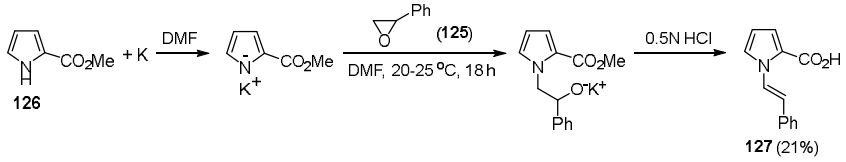
$R^1$ = H, Me

**Scheme 45**

### 3.2. Syntheses from oxiranes

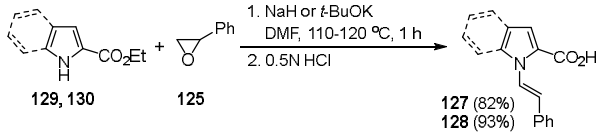
1-(2-Arylvinyl)pyrroles have been prepared by the reaction of 2-phenyloxirane (**125**) and ethers of pyrrole-2-carboxylic acids. So, the interaction of potassium metal with methyl ether pyrrole-2-carboxylic acid (**126**) in DMF delivers pyrrole anion, which is introduced into the reaction with oxirane **125** (Scheme

46).[83] Further treatment of the reaction mixture with hydrochloric acid gives rise to *E*-isomer of 1-(2-phenylvinyl)pyrrole-2-carboxylic acid (**127**). The irradiation of benzene solution of *E*-isomer **127** (350 nm, 6 h) leads to its isomerization to the *Z*-isomer (by 80%).



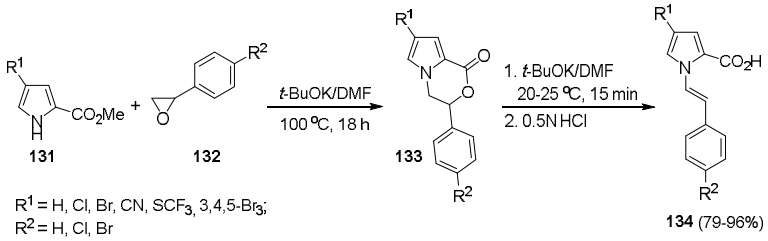

**Scheme 46**

Implementation of the above reaction in DMF using NaH or *t*-BuOK affords *N*-styrylpyrrole **127** and *N*-styrylindole **128** from the corresponding ethers **129** and **130** (Scheme 47).[84] Besides, this reaction has been successfully extended over a series of heterocycles (pyrazole, benzimidazole, pyrrolidone).




**Scheme 47**

The *E*-isomers of *N*-styrylpyrroles **134** are prepared from ethers 4-substituted pyrrole-2-carboxylic acids **131** and aryloxiranes **132** (*via* lactones **133**) in the system *t*-BuOK/DMF (Scheme 48).[85]

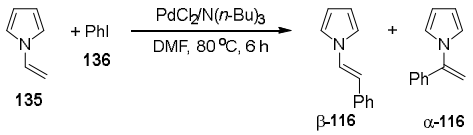



**Scheme 48**

The photoisomerization of *E*-isomers **134** (Hg lamp, ethanol, rt, 5 h) leads to the *Z*-isomers **134** (in 78-96% yields), precursors of substituted 11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepines, which are prospective drugs.[85]

### 3.3. Syntheses involving transition-metal complexes

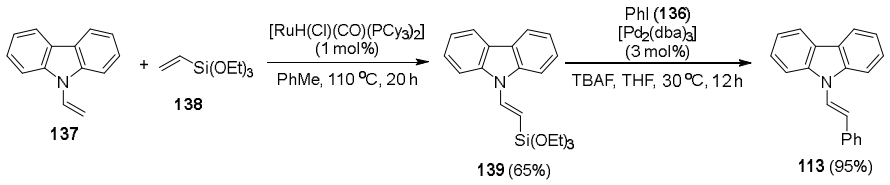
1-(Arylvinyl)pyrroles have been synthesized from *N*-vinylpyrrole (**135**) and its substituted analogs and iodobenzene (**136**) by the Heck reaction (Scheme 49).[86-88] In the case of substituted pyrroles, regioselective formation of α-adducts occurs. A good yield of β-adduct **116** (α/β ratio = 30/70, a total yield of both regioisomers is 95%) is achieved only when unsubstituted *N*-vinylpyrrole (**135**) is employed in the reaction.




**Scheme 49**

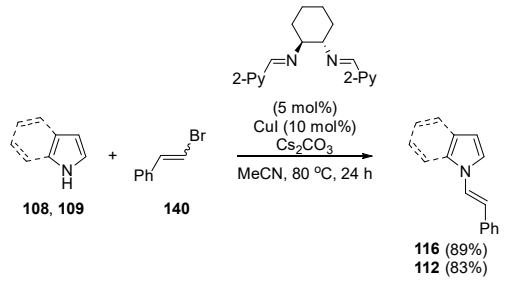
Though stereoselectivity of the reaction has not been studied, the $^1$H NMR data (signals of olefin protons), given in the work, allow drawing a conclusion on the *E*-configuration of *N*-styrylpyrrole (β-**116**).

The cross-coupling of *N*-vinylcarbazole (**137**) and (triethoxy)vinylsilane (**138**) in the presence of a ruthenium complex affords (*E*)-9-[2-(triethoxysilyl)vinyl]carbazole (**139**). The latter in the Hiyama reaction with iodobenzene (**136**) in the presence of the palladium catalyst gives (*E*)-[9-(2-phenylvinyl)]carbazole (**113**) (Scheme 50).[89]




**Scheme 50**

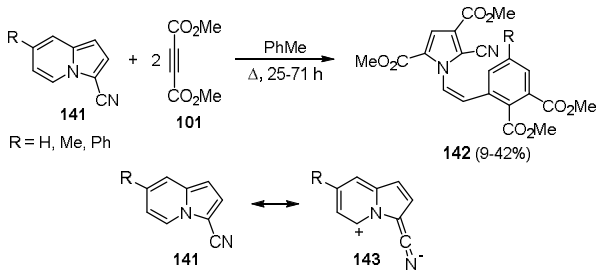
The interaction of pyrrole (**108**) and indole (**109**) with a mixture of the *E,Z*-isomers of styrylbromide (**140**, *E/Z* = 9/1) in the presence of copper (I) iodide and a tetradentate ligand furnishes the *E*-isomers of 1-(2-phenylvinyl)pyrrole (**116**) and 1-(2-phenylvinyl)indole (**112**) (Scheme 51).[90] Under the reaction conditions, side elimination reaction of *Z*-styrylbromide to phenylacetylene takes place.




**Scheme 51**

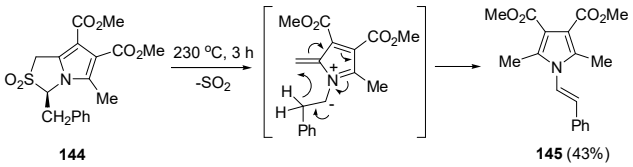
### 3.4. Miscellaneous methods

Also, other more "exotic" syntheses of *N*-stryrylpyrroles are known. It has been shown[91] that the boiling of 3-cyanoindolizines **141** with acetylenedicarboxylic acid dimethyl ether (**101**) in toluene results in the formation of substituted 1-(2-arylvinyl)pyrroles **142** (Scheme 52). It is assumed that the reaction proceeds as Diels-Alder process, in which 3-cyanoindolizines **141** act as 1,5-dipoles **143**.



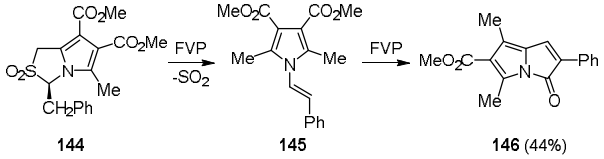

**Scheme 52**

Thermolysis of azafulvene **144**, leading to 1-(2-phenylvinyl)pyrrole **145** in 43% yield has been described (Scheme 53).[92,93]



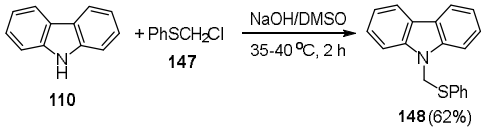

**Scheme 53**

The flash-vacuum pyrolysis (FVP) of compound **144** also gives rise to pyrrole **145**, which further is transformed into 5-oxo-5*H*-pyrrolizine **146** in 44% yield (Scheme 54). FVP comprises the heating of a sample up to 700 °C under pressure $1.5 \cdot 10^{-2}$ mm Hg.



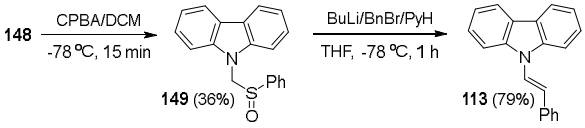

**Scheme 54**

Synthesis of *N*-(2-phenylvinyl)carbazole (**113**) has been carried out in several steps using organometallic compounds.[94] Carbazole (**110**), employed as a starting reagent, is subjected to the reaction with phenyl(chloromethyl)sulfide (**147**) in the presence of 50% aqueous solution of NaOH in DMSO to deliver 9-[(phenylthio)methyl]carbazole (**148**) (Scheme 55).




**Scheme 55**

The target product, *N*-styrylcarbazole (**113**), can be synthesized from sulfide **148** by three different ways. The treatment of sulfide **148** with *m*-chloroperbenzoic acid in dichloromethane gives the corresponding sulfone **149** (Scheme 56), which consecutively reacts with butyl lithium, benzyl bromide and pyridine to produce (*E*)-[9-(2-phenylvinyl)]carbazole (**113**).

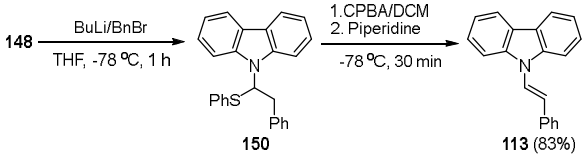



**Scheme 56**

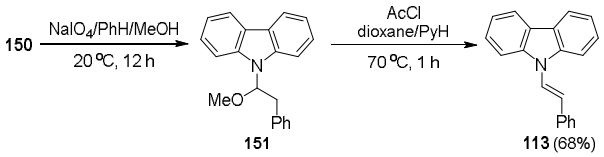
The reaction of sulfide **148** with butyl lithium and benzyl bromide leads to the formation of compound **150**, from which styrylcarbazole (**113**) has been obtained by two protocols.[94] The first protocol involves the treatment of **150** with *m*-CPBA in dichloromethane followed by the addition of dry piperidine (Scheme 57).

The second protocol includes the interaction of **150**, dissolved in a benzene-methanol mixture, with sodium periodate. The isolated product **151** is dissolved in a pyridine-dioxane mixture, and the solution obtained is mixed with acetyl chloride to prepare *N*-styrylcarbazole **113** (Scheme 58).[94]

Thus, nucleophilic addition of NH-heterocycles to aryl(hetaryl)acetylenes in the presence of superbasic systems still remains the only general and most effective method for the synthesis of pyrrole analogues of stilbenes.




**Scheme 57**




**Scheme 58**

**4. Synthesis of di- and oligopyrroles separated by conjugated heterocyclic systems**

Over the last decade, along with development of monopyrrole derivatives chemistry, the research endeavors are invested in search for new synthetic approaches to the assembly of di- and oligopyrrole ensembles separated by the conjugated units, in particular, by heterocyclic systems.

These compounds generate a special interest since they are prospective precursors for preparation of fluorescent sensors,[95-98] and convenient monomers for the synthesis of polyconjugated polypyrroles used for design of lasers, light-emitting diodes (LED) and unipolar transistors (FET).[99,100] The monomers consisting of the heterocyclic ring coupled with two π-donor heterocycles (furan, thiophene, pyrrole) have lower oxidation potentials and give more ordered polymers with a higher electroconductivity in the dopped form in comparison with the asymmetrical monoanalogues owing to less pronounced undesirable processes of β-coupling, cross-linking and reoxidations occurring in the course of polymerization.[101]

Due to the rapid development (over the last two decades) of methods for the synthesis of di- and oligopyrroles separated by heterocyclic spacers, the present review covers only to the most recent and indicative approaches in this field.

For example, porphyrine-like oligopyrroles **154** and **155** have been prepared from the derivatives of dipyrrole **152** and terpyrrole **153** by the oxidative coupling procedure (Scheme 59).[102] It has been noted that compounds **154** and **155** could be reduced to tetrapyrrole **156** and hexapyrrole **157**, but the oxidized forms are more stable upon storage.

From oligocyclic oligoacetals **158** and **159** (prepared by the reaction of furans with donor-acceptor cyclopropanes) and amines **160,** 3,3'-terpyrrole **161** (Scheme 60) and 3,3'-tetrapyrrole **162** (Scheme 61) have been synthesized.[103] Further authors intend to apply this methodology to the synthesis of pyrrolo[3,2-*e*]indoles, close structural analogs of the anticancer drug, duocarmycin.

1,3-Dipolar cycloaddition of 1,2-di(phenylsulfonyl)ethylene (**163**) to azomethines, obtained from dipyrrole-2-carboxaldehydes **164** and glycine methyl ether hydrochloride (**165**), followed by elimination under the action of DBU, affords terpyrroles **166** in 61-69% yields (Scheme 62).[104,105]

Tetrapyrrole **167** and pentapyrrole **168** are prepared analogously from the corresponding dialdehydes in 39 and 16% yields, respectively (Scheme 63).[104,105]

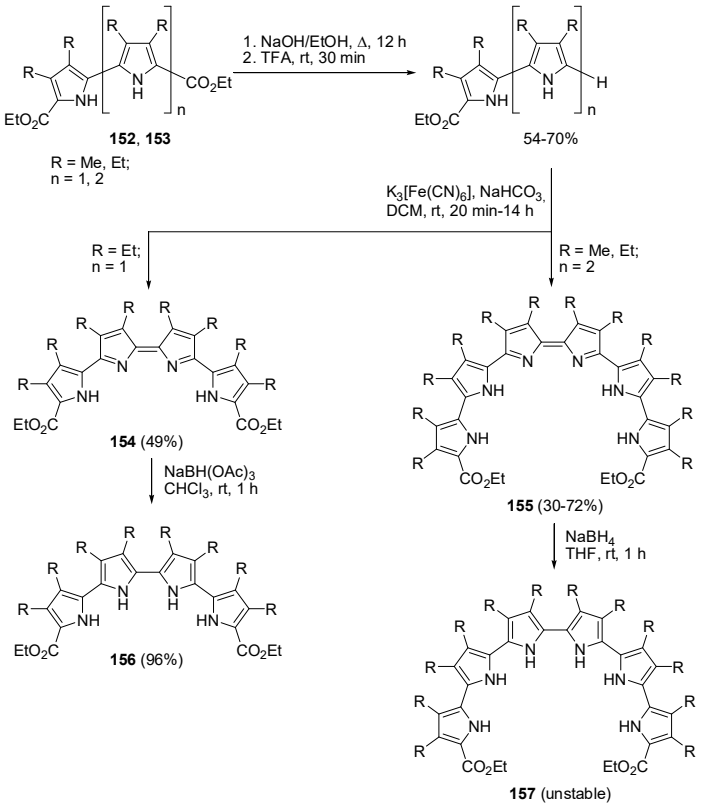
Dipyrroles **169,** separated by thiophene spacer, have been synthesized by Paal-Knorr reaction from tetraketones **170** (Scheme 64).[106] The latter are prepared from dimethyl ether of thiophene-2,5-dicarboxylic acid (**171**) without isolation of the intermediate diketones **172**.

Pentamers **173** (Scheme 65) and hexamers **174** (Scheme 66) with the alternating pyrrole and thiophene cycles have also been obtained by Paal-Knorr method in good isolated yields.[107] The oligomers **173** and **174** are promising *p*-type semiconductors which can be used for design of field-effect transistors (FET).

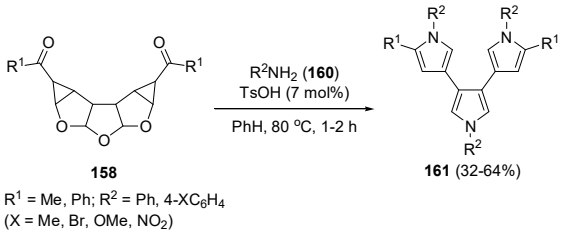
An original reaction of tetrachlorosubstituted BODIPY **179** with pyrroles **180** followed by removing of the $BF_2$ group gives 2,2'-oligopyrroles **181** (Scheme 67).[108]

Polymers for organic electrochromic devices have been synthesized from the diimine monomers **182** produced by condensation of diaminocarbazoles **183** with pyrrole-2-carboxaldehyde (**184**) (Scheme 68).[109] It

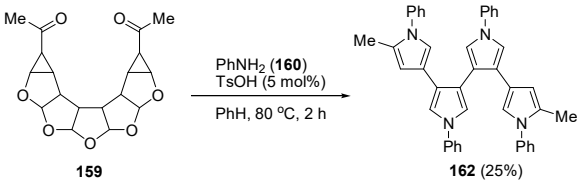
should be noted that the starting diaminocarbazoles **183** are obtained from carbazole **110** in three preparative stages, *N*-alkylation, nitration and reduction of the nitro groups.



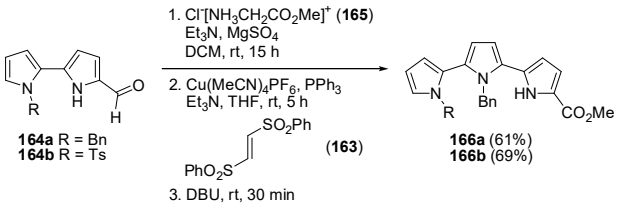

**Scheme 59**



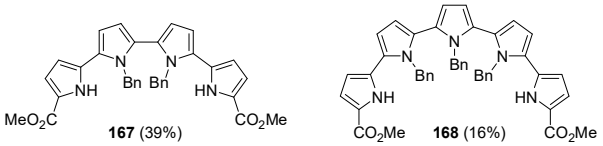

**Scheme 60**



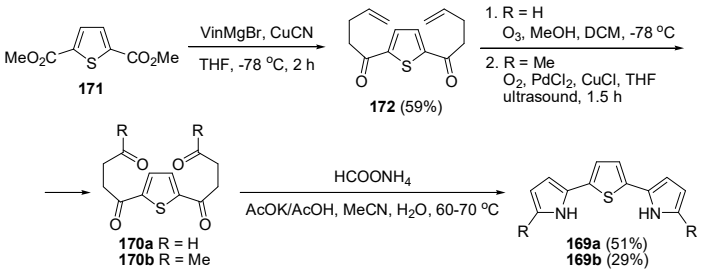

**Scheme 61**



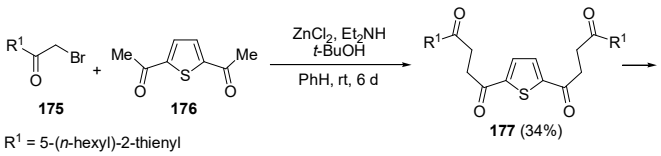

**Scheme 62**

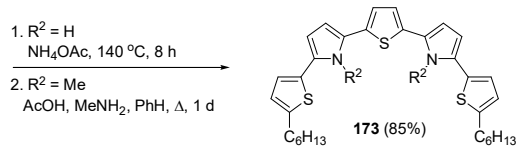



**Scheme 63**

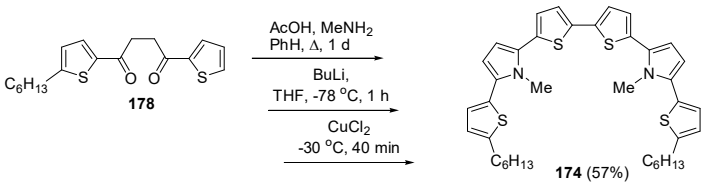



**Scheme 64**

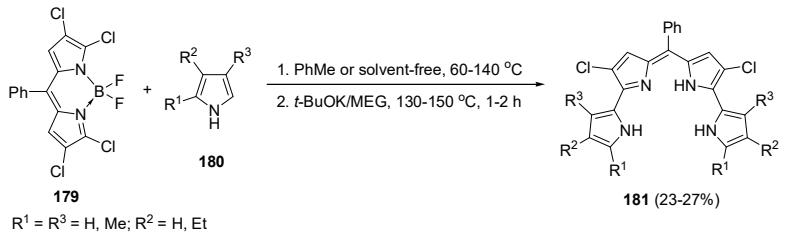


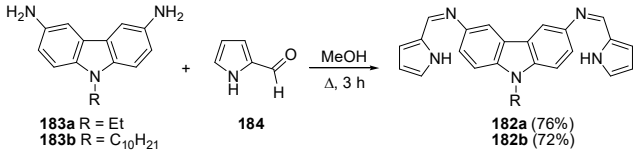

**Scheme 65**




**Scheme 66**



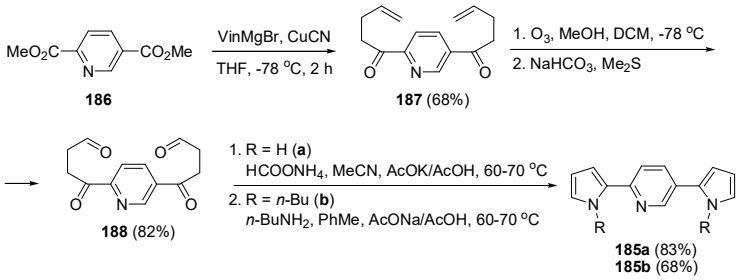

**Scheme 67**




**Scheme 68**

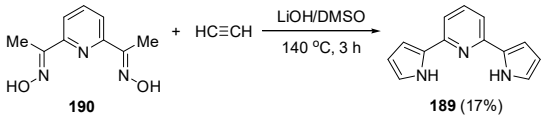
Dipyrroles, separated by the pyridine spacer, owing to the presence of the pyridine nitrogen atom can possess such properties as susceptibility to the pH media and chelating ability towards the metal cations. Nevertheless, synthesis of such compounds still faces some difficulties.

For instance, 2,5-dipyrrolylpyridines **185** have been obtained by Paal-Knorr method from diether pyridine-2,5-dicarboxylic acid **186** in 38-46% total yields (Scheme 69).[106]




**Scheme 69**

The one-step method for the synthesis of dipyrroles **189** comprises the reaction of dioxime **190** with acetylene in the system LiOH/DMSO (Scheme 70).[110] Despite a low yield of the target product, a facile methodology, availability of the reagents and easy scalability of the approach makes it attractive for further development.

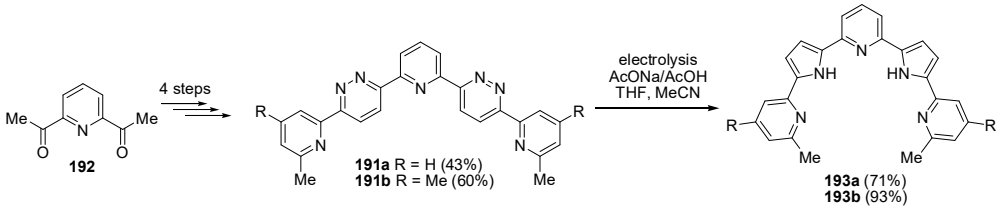



**Scheme 70**

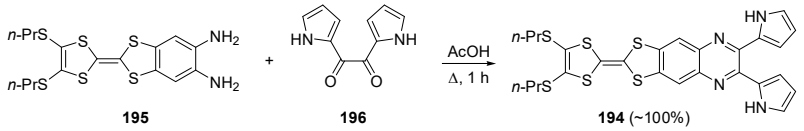
Electrochemical reduction of dipyridazine precursors **191**, obtained from 2,5-diacetylpyridine (**192**) leads to pentamers **193** (Scheme 71).[111] Authors also have managed to prepare copper complexes of pentamers **193**, which formation is accompanied by violation of the ligands planarity.

The dipyrroles separated by quinoxaline fragments attract the particular attention of the research community owing to their ability to act as highly sensitive sensors relative to various anions.[95] A general

method for the synthesis of such compounds involves the interaction of vicinal diamines with 1,2-diketones giving rise tetrathiafulvalene derivative **194** (Scheme 72).[112]

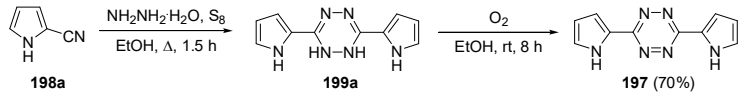



**Scheme 71**



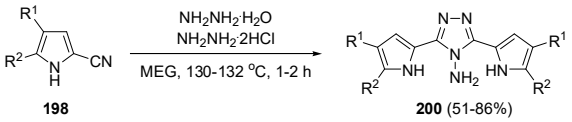

**Scheme 72**

Tetrazines show a high affinity to electron (*i.e.* they are easily reduced) and low-lying π*-orbitals (n-π*-transition is in the visible spectral region) that allows considering them as basic molecules for optics and electrochemistry. Dipyrrole **197**, containing tetrazine spacer, has been prepared[113] from pyrrole-2-carbonitrile (**198a**) and hydrazine *via* oxidation of the intermediate dihydrotetrazine **199** by air oxygen (Scheme 73).




**Scheme 73**

Noteworthy that the reaction of substituted pyrrole-2-carbonitriles **198** with hydrazine hydrate in the inert atmosphere in the presence of the acidic catalyst (hydrazine dihydrochloride) ends up with the formation of dipyrroles **200**, separated by 4-amino-1,2,4-triazole spacer, in 51-86% yields (Scheme 74).[114]



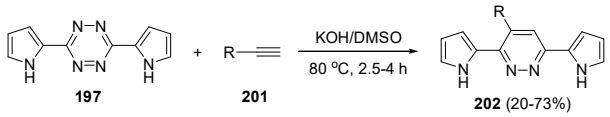

$R^1$ = H, $R^2$ = H, Me, Ph, 2-Th;
$R^1$-$R^2$ = -$(CH_2)_4$-

**Scheme 74**

The [4+2] cycloaddition of acetylenes **201** to 3,6-di(pyrrol-2-yl)-1,2,4,5-tetrazine (**197**) in the presence of the KOH/DMSO system to afford dipyrrolylpyridazines **202** in 20-73% yields has been elaborated (Scheme 75).[115] The reaction represents the first example of a base-catalyzed hetero-Diels-Alder reaction with inverse electron demand. Although the role of superbase in this transformation is not fully clear, the proposed mechanisms[115] (involving formation of carbanionic adduct of tetrazine with hydroxide ion or initial deprotonation of acetylenes with base) are sound reasonable and have experimental and theoretical rationales.

Thus, despite the fact that di- and oligopyrroles separated by heteroaromatic spacers are very prospective building blocks for design of new materials with unique properties, convenient and easily

scalable methods for their synthesis from available reagents and catalysts are still absent. Obviously, search for such synthetic procedures and development of absolutely different from the classical approaches to dipyrrole ensembles is a challenge for organic chemist for the coming years.




R = H, Ph, 4-$MeC_6H_4$, 4-$PhC_6H_4$, 4-$BrC_6H_4$, 3-$FC_6H_4$, 3-$MeOC_6H_4$

**Scheme 75**

**List of abbreviations**

| | |
|---|---|
| Ac | acetyl |
| AIBN | 2,2'-azobis(2-methylpropionitrile) |
| Bn | benzyl |
| Bz | benzoyl |
| CPBA | *meta*-chloroperoxybenzoic acid |
| Cy | cyclohexyl |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCM | dichloromethane |
| DMA | *N*,*N*-dimethylacetamide |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DPP | diphenyl phosphate |
| *ee* | enantiomeric excess |
| Flu | fluorenyl |
| Fur | furyl |
| FVP | flash vacuum pyrolysis |
| MEG | monoethylene glycol |
| MS | molecular sieves |
| NMP | *N*-methyl-2-pyrrolidone |
| Py | pyridyl |
| rt | room temperature |
| SPINOL | 1,1'-spirobiindane-7,7'-diol. |
| $T_3P$ | propylphosphonic anhydride |
| TBAF | tetra-*n*-butylammonium fluoride |
| Tf | triflyl, trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| Th | thienyl |
| THF | tetrahydrofuran |
| Ts | tosyl, toluenesulfonyl |
| Vin | vinyl |

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