C-Vinylpyrroles as Pyrrole Building Blocks

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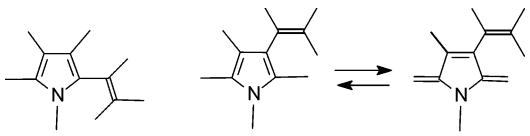
1. Introduction

C-Vinylpyrroles, having the **A**, **B** structural element, have been extensively studied as building blocks for the synthesis of various representatives of the pyrrole family, especially condensed heterocycles genetically related to pyrrole.[1] They are also of interest as vinyl monomers,[2] although this aspect remains so far less developed.



A **B**

N-Vinylpyrroles, which became readily available thanks to the discovery and development of a simple method for their synthesis from ketoximes and acetylene in a MOH−DMSO system (M = Li, Na, K) (the Trofimov reaction),[3] have been systematically studied for three decades as intermediates for new functionalized pyrrole family compounds, biologically active species, and monomers. The results of these investigations have been summarized in a number of monographs and reviews.[1c,3,4] At the same time, systematization of information concerning *C*-vinylpyrroles is lacking compared to the increasingly high amount of new publications in this area, although the need for timely generalizations seems obvious.

2-Vinylpyrrole structure **A** is found in molecules of many vital natural compounds (porphyrins, chlorophylls, vitamin B_{12}, prodigiosins, etc.). 3-Vinylpyrrole structural elements **B** compose molecules of chlorophylls *a*, *b*, *c*, and *d* (which play a key role in photosynthesis processes, i.e., photocatalytic transformation of the solar energy) and haemoglobin (the compound responsible for oxygen transport in mammal organisms).

C-Vinylpyrroles bearing functional groups on the double bond (or those without them) are highly reactive starting compounds for the targeted synthesis of conjugated and fused heterocycles similar to natural pyrrole assemblies.

Over the past few years, functionalized *C*-vinylpyrroles started attracting attention as molecular optical switches, in particular, as ultrafast ones, for design of photo- and electroconducting materials and micro- and nanodevices[5] and also as ligands for new photocatalysts and biologically active complexes.[6]

Therefore, growing interest in the development of synthetic methods for the preparation of *C*-vinylpyrroles and understanding their reactivity seems quite obvious and explicable.

Since the publication of the latest monographs[1a−c] related to various aspects of structure, synthesis, and reactivity of *C*-vinylpyrroles, a large amount of new data has appeared, and this information ought to be systematized, analyzed, and generalized. Recently,[7] the latest advances in the synthesis of *C*-vinylpyrroles were reviewed, but their reactions were not included.

This review covers the reactivity of *C*-vinylpyrroles and their application as building blocks (pyrrole moiety carriers) in the synthesis of more complex pyrrole compounds. It deals mainly with publications of the last 10 years, not including the review papers mentioned above. Presently, all growing attention is paid to the assembling of porphyrine structures

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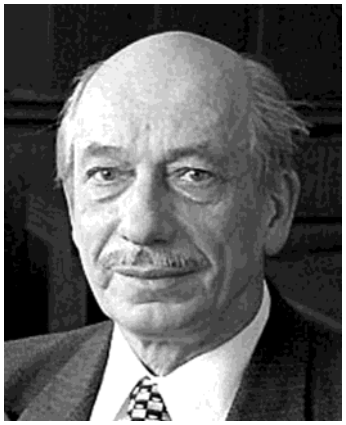

Boris A. Trofimov was born in Tchita, Russia, in 1938. He received his Diploma in 1961, his Ph.D. degree in 1964, and his Doctor of Chemistry in 1970. He became a Professor in 1974 and in 1990 a Corresponding Member of the Academy of Sciences (USSR), of which he became a Full Member (Academician) in 2000. He is currently Director of the A. E. Favorsky Irkutsk Institute of Chemistry, Head of the Laboratory of Unsaturated Heteroatomic Compounds. Dr. Trofimov is a member of the Editorial Board of the *Russian Journal of Organic Chemistry, Journal of Sulfur Chemistry,* and *Arkivoc.* He was awarded the Butlerov Prize of Russian Academy of Science in 1997 and the Medal and Diploma of a Mendeleev Reader (St. Petersburg) in 2003. He is the author of over 850 articles, 49 reviews, and 15 monographs. His current scientific interests are focused on organic synthesis based on acetylene and its derivatives; organic chemistry of sulfur, selenium, tellurium, and phosphorus; organosulfur polymers; functional poly(ethylene glycol) derivatives; chemistry and physical chemistry of vinyl and allenyl ethers, -sulfides, -selenides, -tellurides, -phosphines, -phosphine oxides, and -azoles; addition reactions to multiple bonds; super bases as catalysts and reagents.

Luybov N. Sobenina was born in Gusinoozersk, Russia, in 1950. She received her Ph.D. degree in 1983 at Irkutsk State University, under the supervision of Professor Boris A. Trofimov, and her Doctor of Chemistry in 2003 from Irkutsk Institute of Chemistry. The subject of her D.Sc. dissertation was the synthesis and reactivity of *C*-vinylpyrroles. She is an author of 5 reviews and more than 160 major papers. Her current research interests include study of the chemistry of acetylene and nitrogen- and sulfur-containing heterocyclic compounds, vinylation of ketoximes, pyrroles with acetylenes and other electrophiles in the superbasic systems, novel commercially feasible syntheses of valuable intermediates, polyfunctional monomers, and photosensitive and biologically active compounds.

(chlorophylls, bilirubins, corins, chlorins, vitamin B_{12} fragments) from *C*-vinylpyrroles.[8] However, this topic, being the subject of many publications, is very specific and thus deserves a special review. Also, beyond this review scope are numerous works related to polymeric *C*-vinylpyrroles (for examples, see ref 9).

The most reactive site in the *C*-vinylpyrrole molecules is the outer double bond, which governs their

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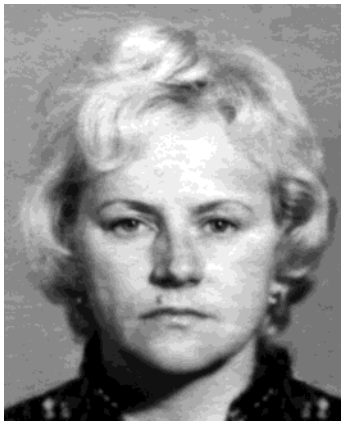


Al'bina I. Mikhaleva was born in Irkutsk, Russia, in 1941. She received her Ph.D. degree in 1970, under the supervision of Professor Boris A. Trofimov, and her Doctor of Chemistry in 1977 at Irkutsk State University. In 1986 she became a Head of Research Group and Professor in 2000. She has published over 250 papers, 12 reviews, and 2 monographs and supervised 6 Ph.D. students. Her current research interests include the chemistry of acetylene and heterocyclic compounds, pyrrole synthesis from ketoximes and acetylene under superbasic conditions, novel commercially feasible syntheses of valuable intermediates, polyfunctional monomers, sulfur-containing cathode materials for lithium batteries, conducting, redox and photosensitive polymers, surfactants, cross-linking agents, biologically active compounds, and medicinal and agricultural chemicals.

chemical transformations. Consequently, this review covers reactions with participation of the vinyl group (including those involving the pyrrole ring) and its functional substituents.

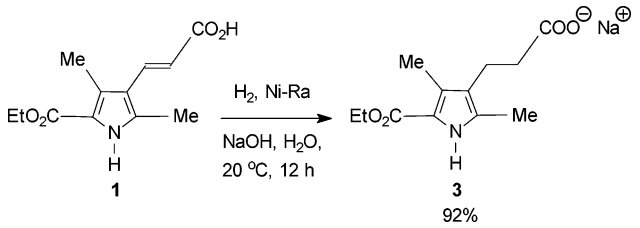
2. Addition Reactions to the Vinyl Group

2.1. Reduction

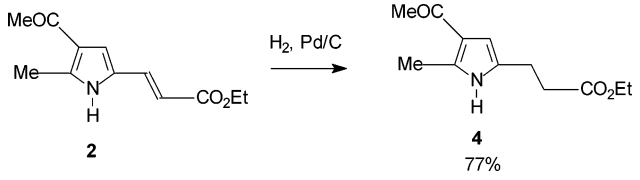
The selective catalytic hydrogenation of the vinyl group in derivatives of 3-(2- and 3-pyrrolyl)acrylic acids **1** (Scheme 1)[10] and **2** (Scheme 2),[11] under mild conditions, gives pyrroles **3** and **4**. Pyrrole **3** is an intermediate in the full synthesis of chlorophyll developed by Woodward.[10]

The double bond in 1,1-bis(pyrrolyl)ethene **5** can be selectively reduced by catalytic hydrogenation in

Scheme 1

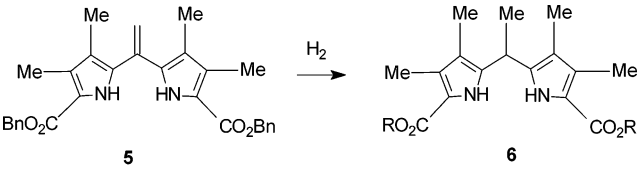


Scheme 2



the presence of Adams catalyst (PtO_2, THF, 20 °C, 5 days) to form dibenzyl 2,3,5,7,8-pentamethyldipyrrolylmethane-1,9-dicarboxylate (**6**, R = Bn) in 72% yield.[12] The hydrogenation with palladium on activated charcoal (THF, 20 °C, 3.5 h) is accompanied by dibenzylation and affords the corresponding 2,3,5,7,8-pentamethyldipyrrolylmethane-1,9-dicarboxylic acid (**6**, R = H) (Scheme 3).[12]

Scheme 3



R = H, Bn

Catalytic hydrogenation (H_2, Pd/C) of dipyrrolylethene **7**, followed by saponification of the reduction product, with KOH, in methanol results in dipyrrolyltetracarboxylic acid **8**, which can be reacted with bromomethylenepyrrolinone **9** to give a bilirubin analogue, homorubin **10** (Scheme 4).[13]

Sodium borohydride selectively reduces the double bond of the nitrovinyl group in vinylpyrroles **11** (Scheme 5)[10] and **12** (Scheme 6)[14] to afford nitroethylpyrroles **13** and **14**. Pyrrole **13** represents a building block in Woodward's full chlorophyll synthesis.[10]

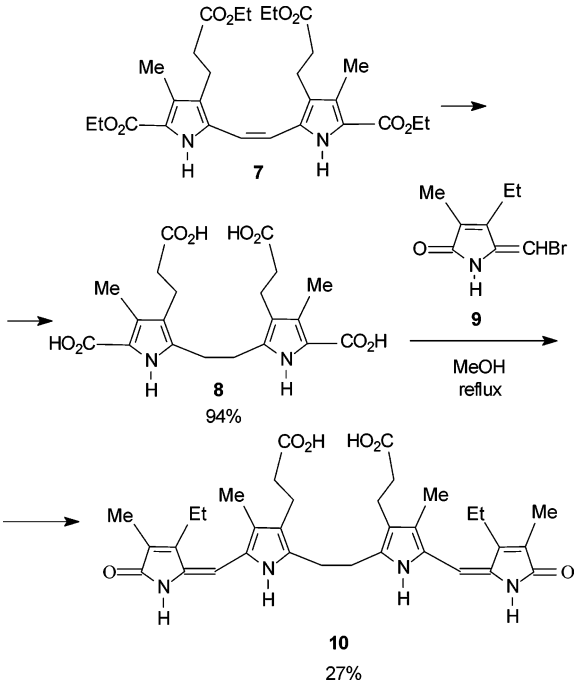
Michael addition of pyrrole **14** to mesityl oxide results in the nitrohexanone **15**. Successive treatment of the latter, first with NaOMe in THF and then with a buffer solution of $TiCl_3$ (pH 6), yields vinylpyrrole **16**, an important intermediate (Western Half) in the synthesis of chlorin (Scheme 7).[14]

The carbene chromium complex **17** containing the ethenylpyrrole system undergoes reduction with $NaBH_4$ to form a 4:1 mixture of the *Z*-isomer of vinyl ether **18** and *E*-isomer of 3-(2-*N*-methylpyrrolyl)-2-propenal (**19**) (Scheme 8).[15]

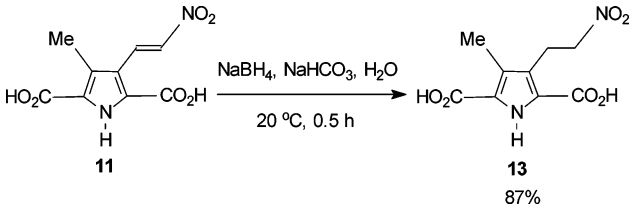
The reaction involves initial addition of the hydride ion to the carbene carbon atom followed by 1,3-migration of the $Cr(CO)_5$ fragment.[15]

Catalytic reduction of functionalized 3-vinylpyrroles **20** (Scheme 9)[16] and **21** (Scheme 10)[17] with sodium borohydride selectively gives pyrroles **22** and **23**, leaving the functional groups on the double bonds intact.

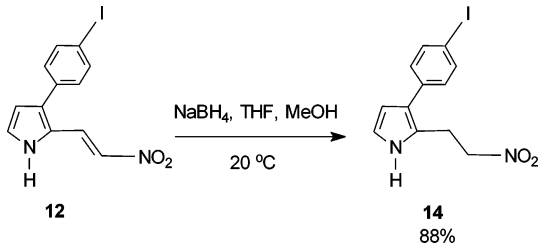
Scheme 4



Scheme 5



Scheme 6



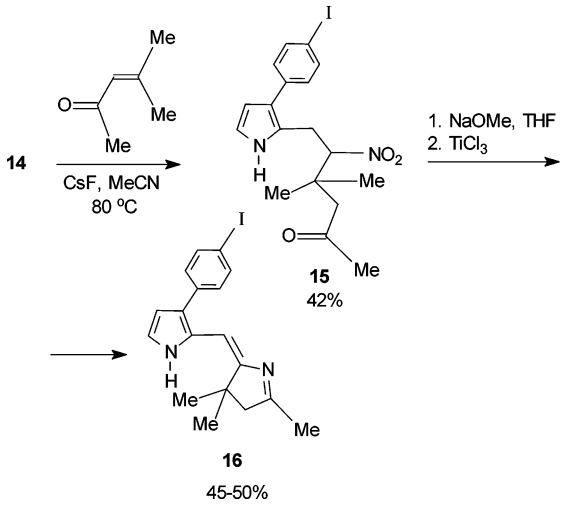
Microbiological reduction of 2-vinylpyrrole **24** under the action of baker's yeast in water results in 1-methyl-2-(2-methyl-2-nitroethyl)pyrrole (**25**) (Scheme 11).[18]

Pyrroloindole **26** can be generated via reductive cyclization of 1-methyl-2-(2-nitro-1-phenylvinyl)pyrrole (**27**) (Scheme 12).[19a,b]

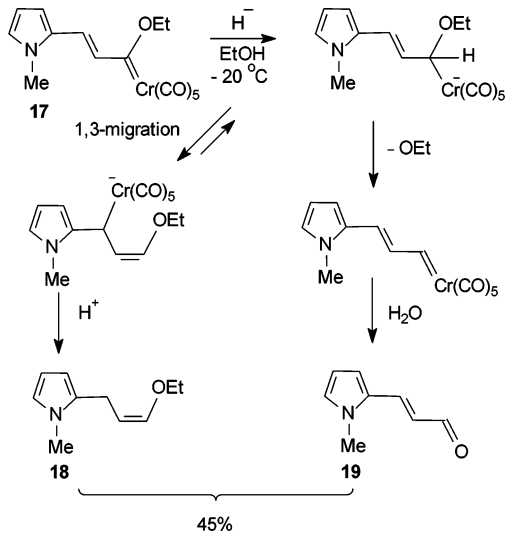
2.2. Photodimerization of 1-Aryl-2-pyrrolylethenes

Regiospecific dimerization of *E*-1-aryl-2-pyrrolylethenes **28a**,**b** occurs photochemically to give pyrroles **29a**,**b**. Under these conditions, pyrrole **28c** transforms mainly to the *Z*-isomer and trace amounts of the tetracyclic product **30c** are also formed (Scheme 13).[20,21] The authors believe that the formation of dimeric products **29a**,**b** occurs via photoinduced electron transfer followed by proton transfer and radical combination.[21]

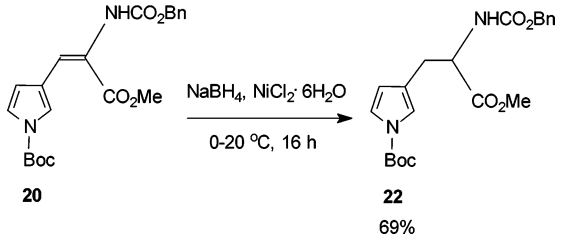
Scheme 7



Scheme 8



Scheme 9



[a] Boc−*tert*-butoxycarbonyl.

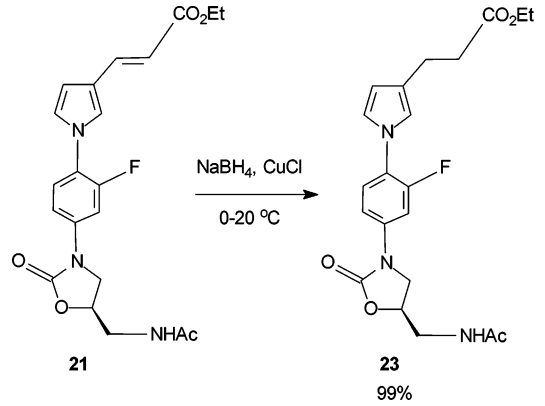
Irradiation of a degassed benzene solution of 2,2′-(1,2-phenylenedivinylene)dipyrrole (**31a**) (10^{-3} M) followed by evaporation of the solvent gives a dark residue, from which a mixture of dimeric stereoisomers **32a** may be isolated in 40% yield (after chromatographic purification). Trace amounts of a minor product **33a** are also formed (Scheme 14).[21]

Under the same conditions, 1,1′-dimethyl-2,2′-(1,2-phenylenedivinylene)dipyrrole (**31b**) undergoes *E,Z*-isomerization only.[21]

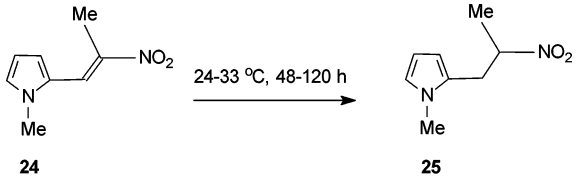
2.3. Nucleophilic Addition

Pyrrole-2-aldehyde **34**, a convenient building block for assembling acetylene−cumulene porphyrinoids,

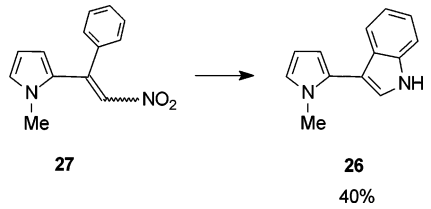
Scheme 10[a]



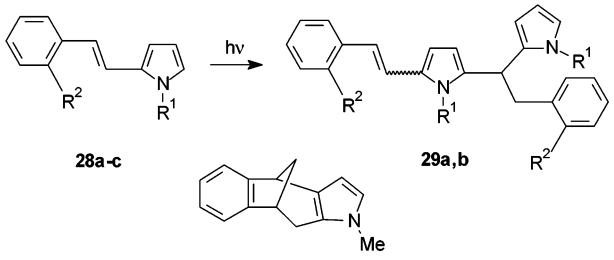
Scheme 11



Scheme 12



Scheme 13



R^1 = H, R^2 = -CH=CH_2 (**a**); R^1 = H, R^2 = Me (**b**); R^1 = Me, R^2 = -CH=CH_2 (**c**)

can be prepared by boiling 2-vinylpyrrole **35** in aqueous methanol in the presence of NaOH (Scheme 15).[22]

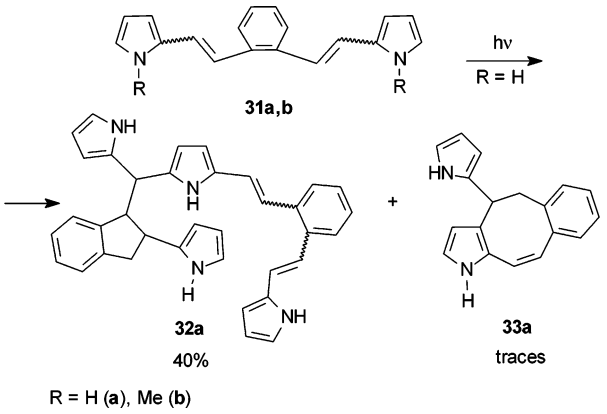
Reaction of aldehyde **34** with acetylene leads to dipyrrolylethyne **36,** which can further be dimerized to the porphyrinoid **37** (Scheme 16).[22]

Treatment of 3-vinylpyrrole **38** with concentrated aqueous NaOH results in analogous vinyl group transformation to the carbonyl group accompanied by hydrolysis of the ester moieties and formation of 3-formyl-2,5-pyrroledicarboxylic acid **39** (Scheme 17).[10]

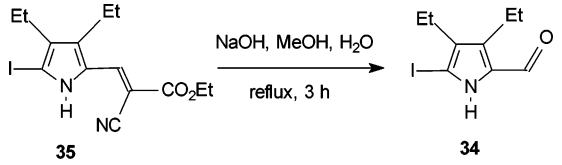
Refluxing vinylpyrrole **40** in aqueous NaOH or in a water−ethanol KOH solution affords pyrrole-2,5-dicarbaldehydes **41**, intermediates for the synthesis of porphyrin **42** (Scheme 18).[23]

The interaction of 3-bromo-5-(2-cyano-2-methoxycarbonylvinyl)pyrrole (**43**) with dimethylacetal in the presence of BF_3·Et_2O yields bis[3-bromo-5-(2-cyano-

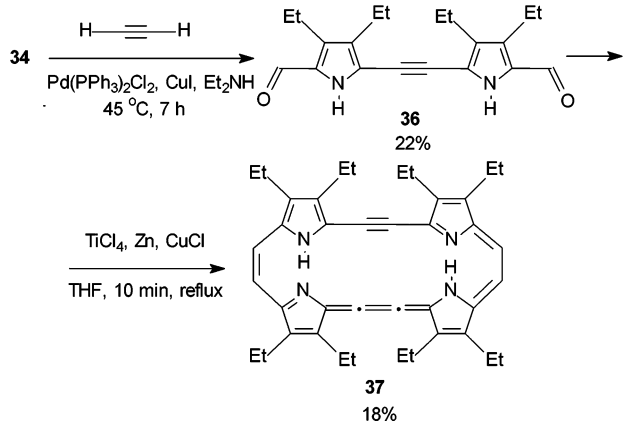
Scheme 14



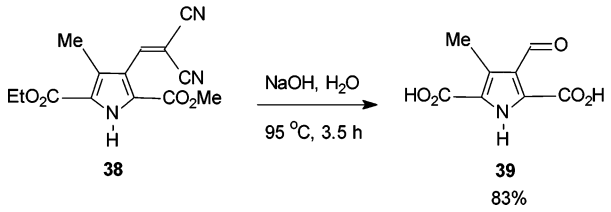
Scheme 15



Scheme 16



Scheme 17

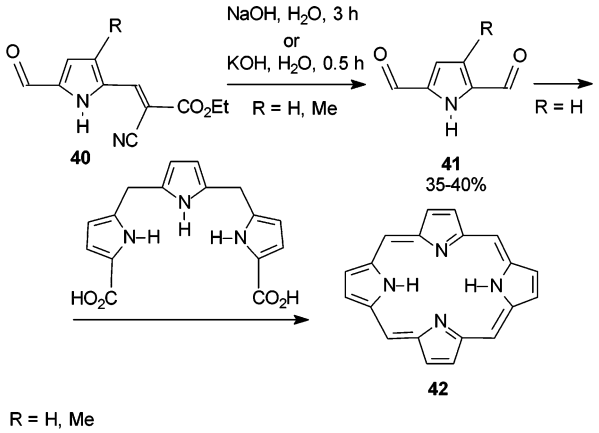


2-methoxycarbonylvinyl)pyrrol-2-yl]methane (**44**). Treatment of **44** with aqueous KOH gives dipyrrole **45** (Scheme 19).[24]

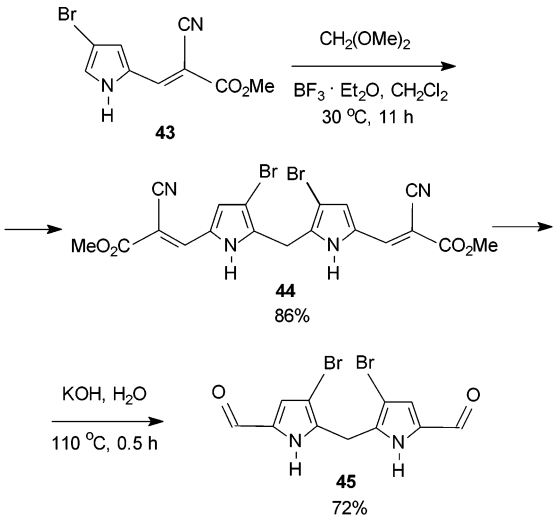
Addition of nitromethane to nitrovinylpyrrole **46** in the presence of potassium acetate and methylamine hydrochloride results in a Michael-mode adduct, 2-(1,3-dinitro-2-propyl)-3-(4-iodophenyl)pyrrole (**47**) (Scheme 20).[14]

Hetarylacrylates can be aminohydroxylated, allowing biologically interesting taxol side chain analogues. However, pyrrole derivatives **48a**−**d** proved to be problematic substrates for asymmetric aminohydroxylation with $(DHQ)_2PHAL$ via transferring the easily deprotecting *N*-benzyloxycarbonyl group. Only the benzyl-protected derivative **48d** gave rise to the

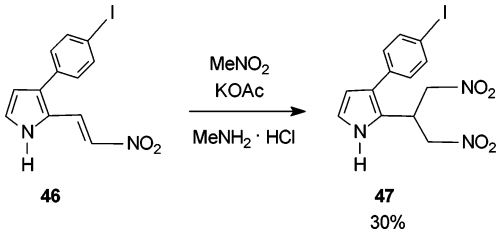
Scheme 18



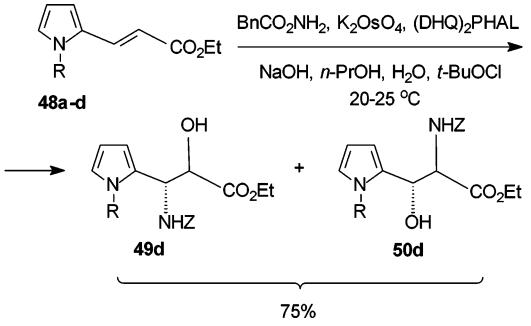
Scheme 19



Scheme 20



Scheme 21

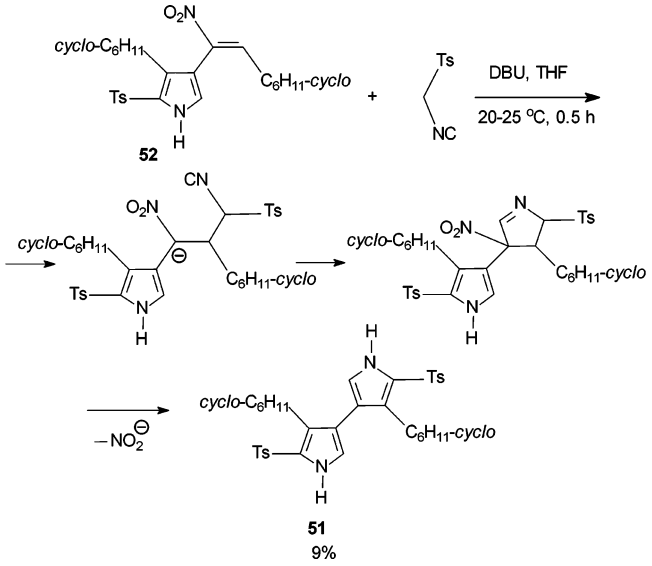


asymmetric aminohydroxylation product, albeit with low regioselectivity (**49d**:**50d**) = 2.1:1) (Scheme 21). The pyrroles **49d** and **50d** were too unstable to determine the enantiomeric ratio of the products.[25]

The base-catalyzed [1,5-diazabicyclo[5.4.0]undec-7-ene (DBU) or BuLi] addition of alkyl isocyanides to more electrophilic double bonds can be utilized for the synthesis of different heterocycles, including pyrroles.[26] Employment of *C*-vinylpyrroles in this reaction allows dipyrroles to be prepared.

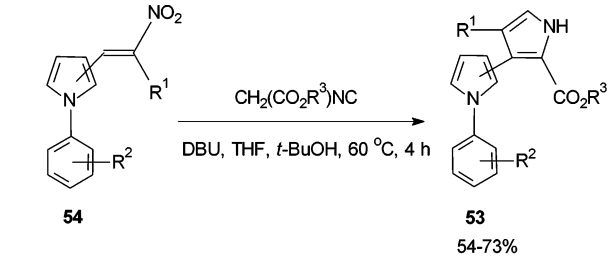
For example, 3,3′-dipyrrole **51** may be obtained from 3-nitrovinylpyrrole **52** and tosylmethyl isocyanide through addition, cyclization, and elimination steps (Scheme 22).[27]

Scheme 22



2- and 3-Pyrrolecarboxylates **53** were synthesized from 2-[28] or 3-[29] (2-nitro-1-alkenyl)-1-arylpyrroles **54** and alkoxycarbonylmethyl isocyanides (2 equiv) first ionized with DBU at room temperature (0.5 h) in a mixture of THF and *tert*-butyl alcohol (Scheme 23).[28,29]

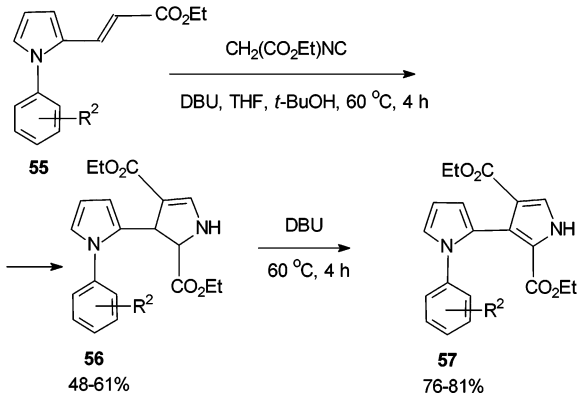
Scheme 23



R^1 = H, Me, Et; R^2 = H, 4-MeO, 2-NO_2, 4-Cl; R^3 = Me, Et

Under analogous conditions, 3-(2-pyrrolyl)acrylates **55** with ethoxycarbonylmethyl isocyanide give pyrrolines **56** in 48−61% yield, which transform to pyrroles **57** on subsequent treatment with 2 equiv of DBU (THF, *t*-BuOH, 60 °C, 4 h). This reaction may be stopped at a pyrroline intermediate stage, since the pyrrolines **56** are stable enough to be isolated. Heating the 3-(2-pyrrolyl)acrylates **55** with ethoxycarbonylmethyl isocyanide (2 equiv) for 8 h in the presence of a 4-fold excess of base affords pyrroles **57** in better yields (76−81%) (Scheme 24).[28] The role of DBU, according to the authors opinion, consists of proton-extracting from pyrrolines **56**, probably followed by hydride-ion transfer, although the final step is not specified.

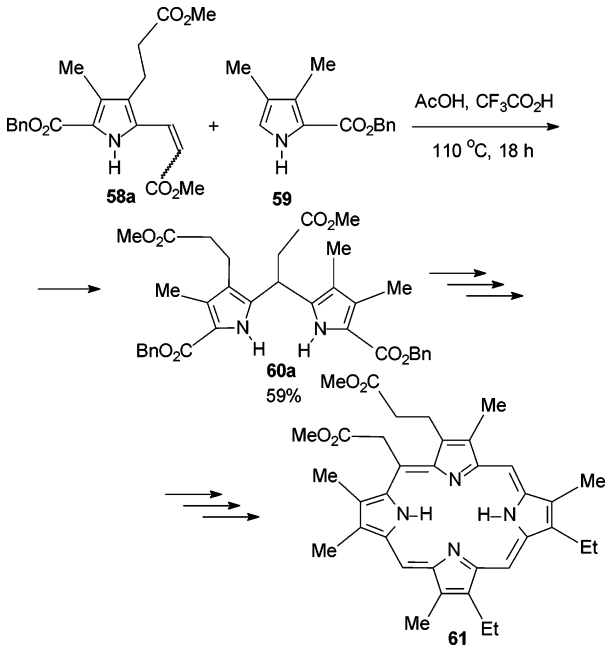
Scheme 24



2.4. Electrophilic Addition

The reaction of pyrroles **58a** and **59** in glacial acetic acid with 15 mol equiv of trifluoroacetic acid affords the unsymmetrical dipyrrolylmethane **60a**, an intermediate for the synthesis of porphyrin in which the *meso* acetic side chain is retained intact **61** (Scheme 25).[8a]

Scheme 25



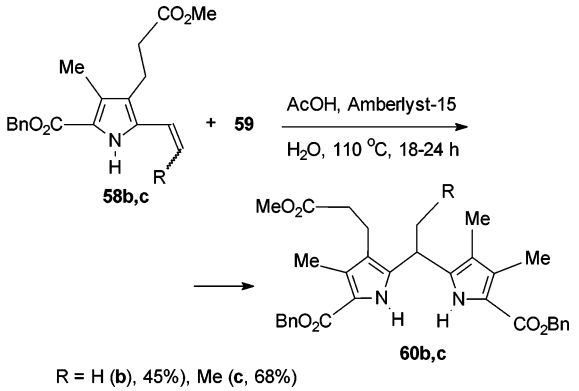
The addition of pyrrole **59** to the nonactivated vinyl group of pyrroles **58b**,**c** occurs in the presence of Amberlyst 15 in its acid form and catalytic amounts of water (Scheme 26).[8a]

2.5. Hydroformylation

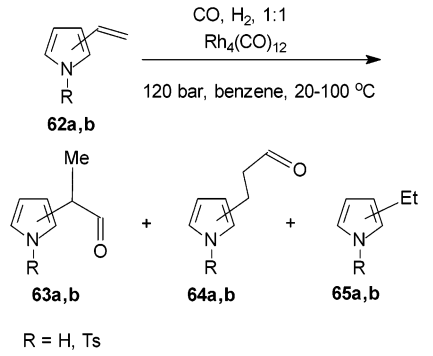
The rhodium-catalyzed hydroformylation of 2- and 3-vinylpyrroles (**62a** and **62b**; 40 °C) give isomeric aldehydes **63a**,**b** and **64a**,**b** in a 94:6 ratio (Scheme 27).[30,31]

At room temperature the process shows high α-regioselectivity (**63a**,**b**:**64a**,**b** ratio = 95:5). At higher temperatures the regioselectivity decreases (at 100

Scheme 26



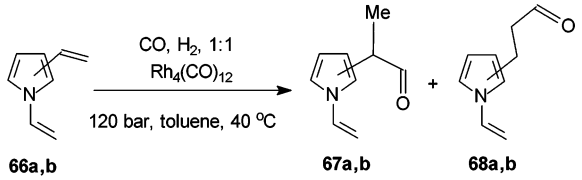
Scheme 27



°C the **63a**,**b**:**64a**,**b** ratio is 87:13 and 83:17). For 1-tosyl-2-vinylpyrrole (**62a**, R = Ts), this effect is much higher than for the corresponding 1*H*-pyrroles (at 100 °C the **63a**:**64a** ratio is 64:36). In all cases, along with aldehydes **63a**,**b** and **64a**,**b**, small amounts (2−4%) of 2- and 3-ethylpyrroles **65a**,**b**, the products of the double bond hydrogenation, are also formed.[31]

Under analogous conditions, 1,2- and 1,3-divinylpyrroles (**66a** and **66b**) are hydroformylated at 40 °C selectively at *C*-vinyl groups to form the corresponding (1-vinylpyrrolyl)propanals **67a**,**b** and **68a**,**b** with high chemo- (over 98%) and α-regioselectivity (**67a**:**68a** = 93:7; **67b**:**68b** = 98:2) (Scheme 28).[32]

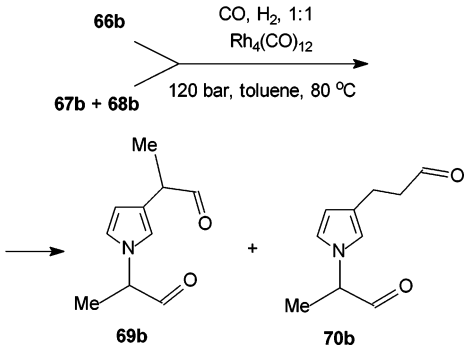
Scheme 28



At 80 °C (other conditions and the formylating system are the same as above) the mixture of aldehydes **67b** and **68b** transforms to a mixture of dialdehydes **69b** and **70b** (**69b**:**70b** ratio is 92:8), that is, the *N*-vinyl group is also hydroformylated (Scheme 29). Direct hydroformylation of 1,3-divinylpyrrole **66b**, at 80 °C, led to an identical result: dialdehydes **69b** and **70b** were obtained in an 86:14 ratio.[32]

In contrast, hydroformylation experiments carried out at 80 °C on **66a** gave the dialdehydes **69a** and **70a** in a very low yield, and the formation of various unidentified byproducts occurred.

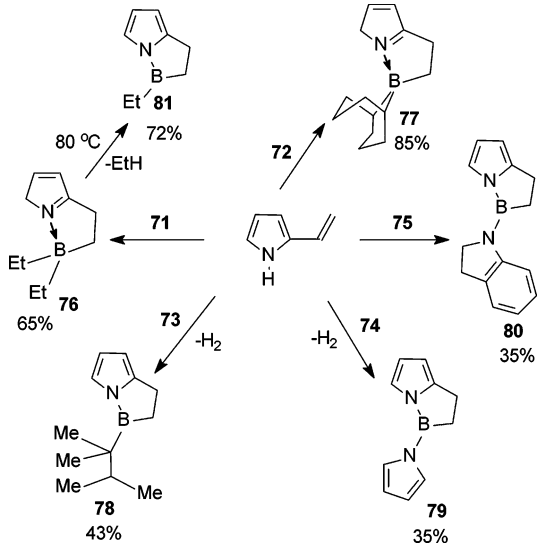
Scheme 29



2.6. Hydroboration

Hydroboration of 2-vinylpyrrole with various hydroborating agents ($Et_2BH_2BEt_2$ (**71**), 9-borabicyclo[3.3.1]nonane (**72**), $Me_2CHCMe_2(H)BH_2B(H)Me_2CHCMe_2$ (**73**), Az-BH_2·THF [Az = pyrrole (**74**), indole (**75**)] (THF, −78−25 °C)) yields pyrroleboranes **76**−**80** (Scheme 30).[33] Smooth reaction of 2-vinylpyrrole with diboranes **71** and **72** affords adducts **76** and **77** bearing nonaromatic 2*H*-pyrrole structural elements stabilized by the N→B coordinating bonds. It is believed that adducts **76** and **77** are formed as a result of the stereoselective hydroboration and 1,2-hydrogen shift.

Scheme 30

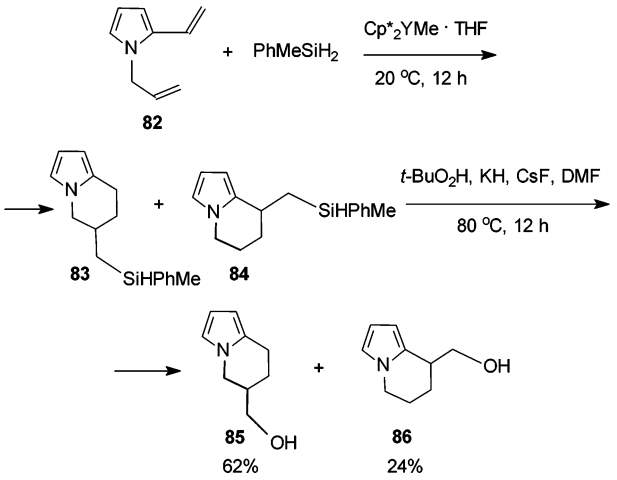


Abstraction of an ethane molecule from compound **76** at 80 °C gives bicyclic pyrroleborane **81**. At the same time, only decomposition occurs on heating adduct **77** at temperatures higher than 160 °C. Hydroboration of 2-vinylpyrrole with boranes **73** and **74** followed by elimination of hydrogen yields pyrroleboranes **78** and **79**. In the reaction of pyrrole with indolylborane **75**, evolving hydrogen adds to the reactive C(2)−C(3) double bond, thus giving borane **80** (Scheme 30).[33]

2.7. Hydrosilylation

1-Allyl-2-vinylpyrrole (**82**) readily adds methylphenylsilane in the presence of the yttrium catalyst, Cp*$_2$YMe·THF (Cp* = η^5-C_5Me_5) (Scheme 31). After

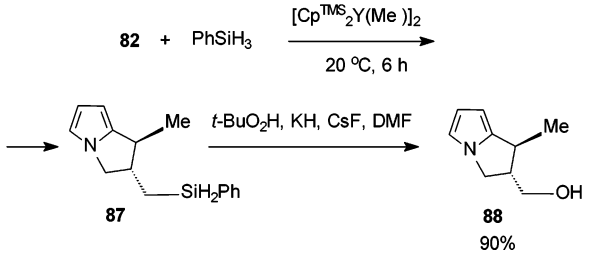
Scheme 31



oxidation, adducts **83** and **84** give a mixture of cyclohexanepyrroles **85** and **86**.[34]

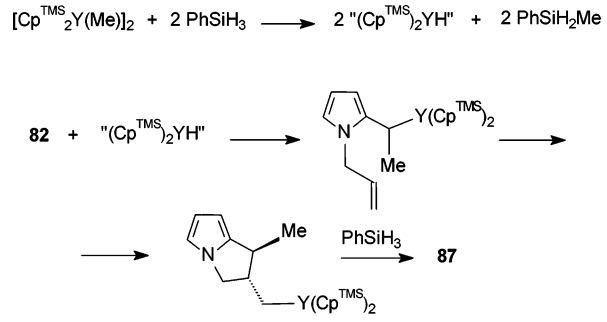
Vinylpyrrole **82** and phenylsilane, in the presence of 8−10% of $[Cp^{TMS}_2Y(Me)]_2$ (Cp = η^5-C_5H_5, TMS = trimethylsilyl), stereoselectively form, in quantitative yield, 1-methyl-2-[(1-phenylsilyl)methyl]-2,3-dihydro-1*H*-pyrrolizine (**87**), which after oxidation gives alcohol **88** (Scheme 32).[34]

Scheme 32



The reaction is believed[34] to start from the addition of catalyst, reduced by silane, to the vinyl group (methyl group thus migrates to silane to form methylphenylsilane), followed by cyclization and silylation (Scheme 33).

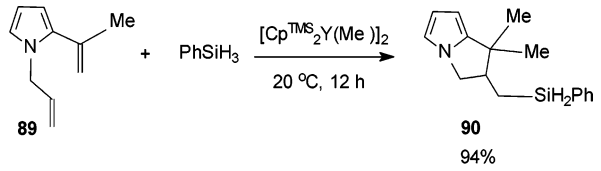
Scheme 33



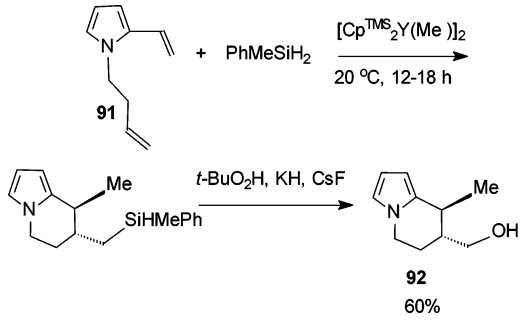
The isopropenyl substituent in 1-allyl-2-isopropenylpyrrole (**89**) reacts preferentially with the less sterically encumbered allyl group. As a result, pyrrolizine **90** is selectively formed (Scheme 34).[34]

Cyclization−silylation of 1-(3-butenyl)-2-vinylpyrrole (**91**) in the presence of $[Cp^{TMS}_2Y(Me)]_2$ followed by oxidation gives (8-methyl-5,6,7,8-tetrahydroindolizin-7-yl)methanol (**92**) (Scheme 35).[34]

Scheme 34



Scheme 35

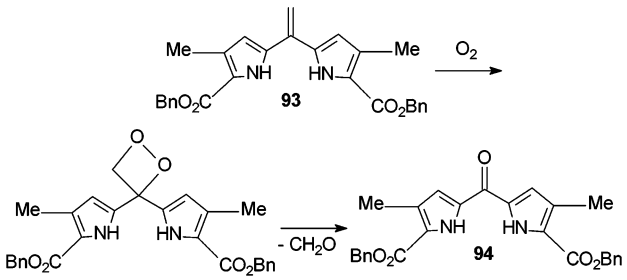


Comparison of the catalytic activity of Cp*$_2$YMe·THF and $[Cp^{TMS}_2Y(Me)]_2$ in the hydrosilylation of 1*H*-2-vinyl- and 1*H*-2-isopropenylpyrroles showed that the reaction catalyzed by the sterically open $[Cp^{TMS}_2Y(Me)]_2$ was several hundred times faster.[35]

2.8. Oxidation of the Vinyl Group

Recrystallization of 1,1-dipyrrolylethene **93** from an ethyl acetate/cyclohexane mixture is accomplished by photooxidation to form the dipyrrolyl ketone **94** (Scheme 36).[12]

Scheme 36



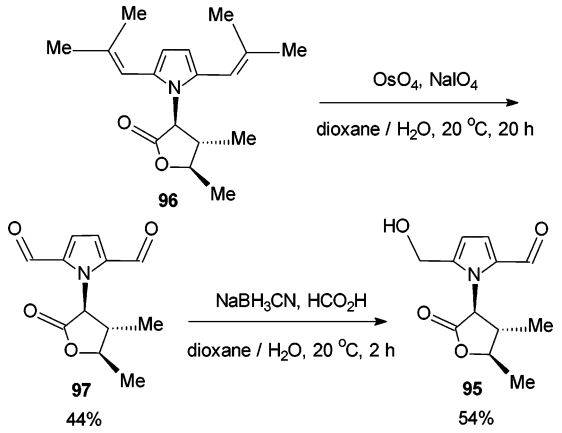
The total synthesis of funebral **95**, a sterically crowded, rotationally restricted pyrrole alkaloid, was achieved by oxidation of the divinylpyrrole **96** with a mixture of osmium tetraoxide and sodium metaperiodate, followed by treatment of the dialdehyde **97** with sodium cyanoborohydride (Scheme 37).[36]

Using a mixture of osmium tetraoxide and HIO_4 as a oxidizing agent, the yield of **97** was increased to 86%.[37]

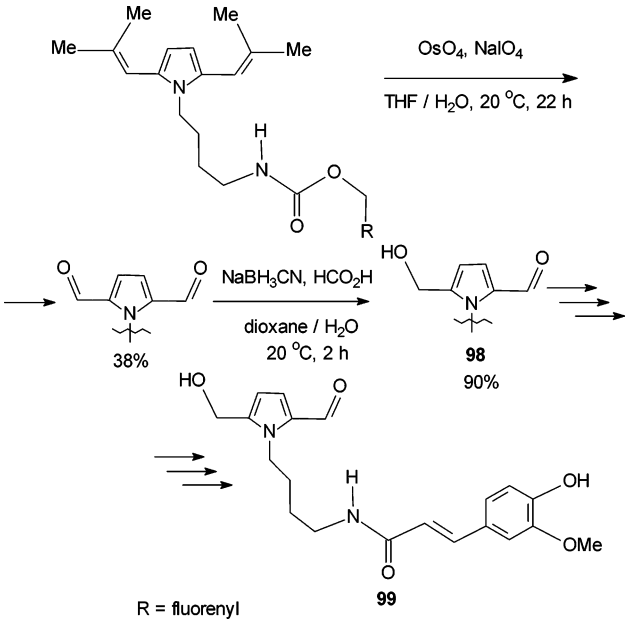
The same procedure was employed for the preparation of 1-(*N*-fluorenyl-methoxycarbonylamino)butyl-2-formyl-5-hydroxymethylpyrrole (**98**), an intermediate in the synthesis of magnolamide alkaloid **99** (Scheme 38).[38]

The key stage in the synthesis of distamycin antibiotic nitro analogue **100** is represented by the oxidation of dipyrrolylethene **101** to dipyrrolyldiketone **102** by potassium permanganate in acetic anhydride (Scheme 39).[39]

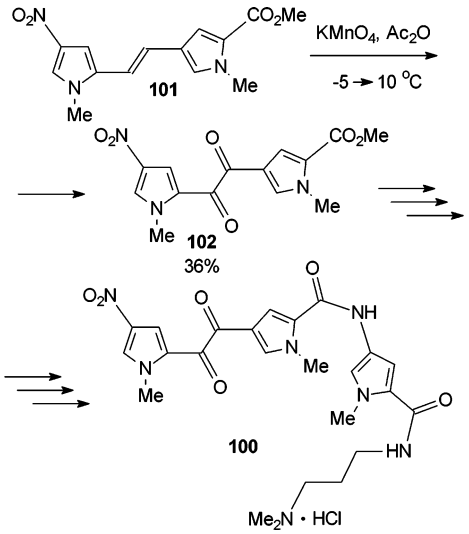
Scheme 37



Scheme 38

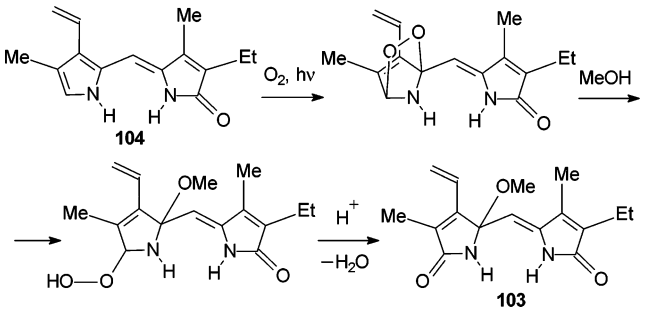


Scheme 39



A novel pyrromethenone derivative, rollipyrrole **103,** can be generated by auto-oxidation of the 2,3-divinylpyrrole **104** followed by nucleophilic attack by methanol. It should be noted that in this case the oxidation does not affect the intact vinyl groups (Scheme 40).[40]

Scheme 40

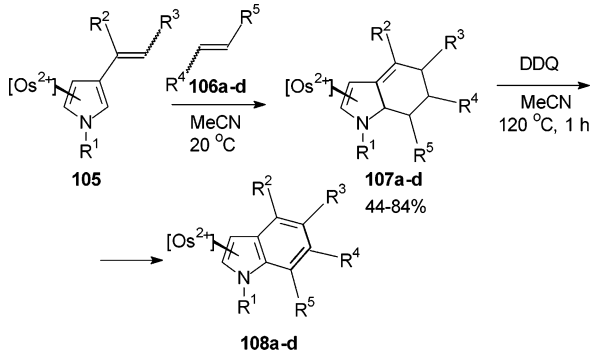


3. Cycloaddition Reactions

3.1. [4+2]-Cycloaddition

The 3-vinylpyrrole osmium complexes **105** (the diene) readily undergo Diels−Alder cycloaddition with electron-deficient olefins **106a**−**d** (the dienophile) to form 5,6,7,7*a*-tetrahydroindole complexes **107**.[41,42] The dienophiles studied were *N*-phenylmaleimide **106a**,[41,42] 4-cyclopentene-1,3-dione **106b**,[42] methacrylate **106c**,[42] and dimethyl fumarate **106d**.[42] Dimethyl acetylenedicarboxylate (DMAD) in the same reaction conditions gives the corresponding dihydroindole derivative.[42] The reaction rate depends on electronic and steric factors. Thus, phenyl-substituted vinylpyrrole complex reacts with 1 equiv of dimethyl fumarate **106d** in 1 h. With methacrylate **106c** the reaction is significantly slower and to obtain a satisfactory yield (76%) of cycloadduct **107c** the authors employed a Lewis acid ($BF_3 \cdot Et_2O$) or a large excess of dienophile. Vinylpyrrole **105** deactivated by an electron-withdrawing group (R^3 = Ac) reacts fast enough only with the most electrophilic dienophiles, such as maleimide **106a**. The treatment of tetrahydroindole complexes **107a**−**d** with 2 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetonitrile followed by heating affords the corresponding indoles **108a**−**d**. DDQ plays a dual role in the reaction: it separates the pyrrole ligand and the metal and oxidizes tetrahydroindole to the indole **108** (Scheme 41).

Scheme 41

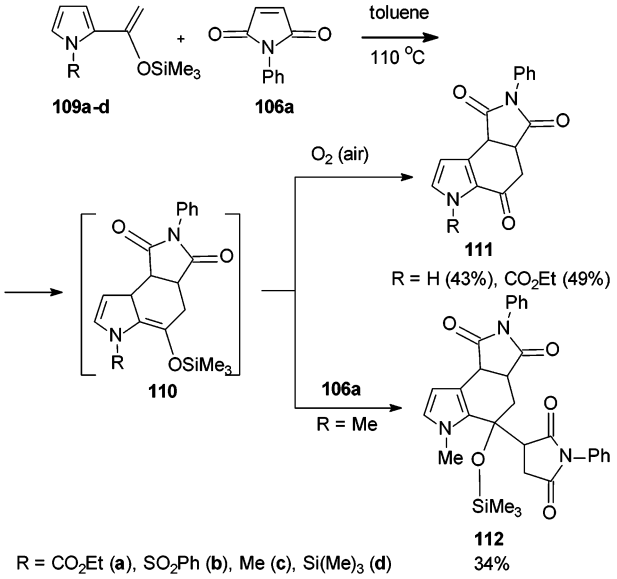


R^1 = H, Me, Ar; R^2 = H, Me, Et, OMe, Ph; R^3 = H, Me, Ac, CO_2Me;
R^4 - R^5 = -C(O)N(Ph)C(O)- (**a**); -C(O)CH_2C(O)- (**b**);
R^4 = H, R^5 = CO_2Me (**c**); R^4 = CO_2Me, R^5 = CO_2Me (**d**)
$[Os^{2+}] = [Os^{II}(NH_3)_5]^{2+}$

[4+2]-Cycloaddition of *N*-phenylmaleimide (**106a**) to pyrrole **109a** (17 h) affords, after exposing the adduct **110** to air, 7-oxo-4,5,6,7-tetrahydroindole **111**.

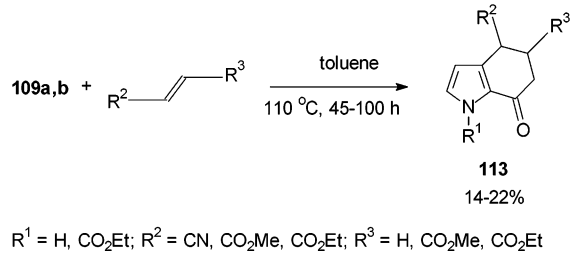
Under analogous conditions (27 h), pyrrole **109b** gives the desulfonated cycloadduct **111** (R = H).[43] Unlike the electron-withdrawing substituents, the methyl group in vinylpyrrole **109c** favors a different route for the rearomatization process: first, a prototropic shift with recovery of the aromatic pyrrole system in the primary adduct **110** occurs and then the subsequent 1,2-addition to the second maleimide **106a** molecule gives the diadduct **112**. The pyrrole **109d** [(R = $Si(Me)_3$] does not react under these conditions at all, apparently due to the steric hindrance (Scheme 42).[43]

Scheme 42



Under the same conditions (45 h), with diethyl fumarate pyrrole **109a** forms the cycloadduct **113** ($R^1 = R^2 = R^3 = CO_2Et$) in 14% yield. Pyrrole **109b** reacts with dimethyl fumarate (48 h) and acrylonitrile (100 h) to give adducts **113** (R^1 = H) in relatively low yield (17% and 22%, respectively) (Scheme 43).[43]

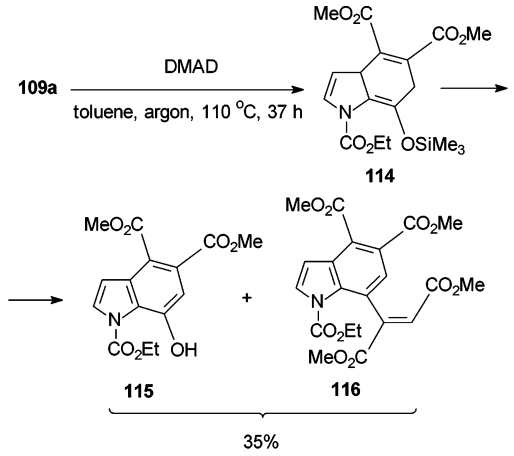
Scheme 43



A noteworthy feature of the reaction with acrylonitrile is represented by its regioselectivity: the CN group is oriented to be located in position 4 of **113**.[43]

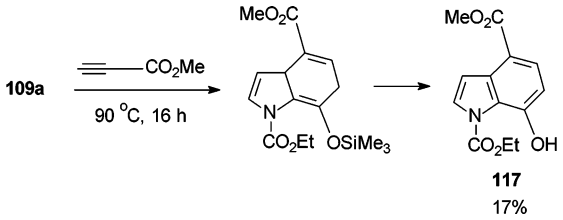
Interaction of pyrrole **109a** with DMAD affords (after exposing adduct **114** to air) 7-hydroxyindole-1,4,5-tricarboxylate **115** and the bis-adduct 7-vinylindole **116** in nearly equal amounts (46:54).[44] Compound **116** is formed as a result of the 1,2-addition of the primary cycloadduct **114** to the second DMAD molecule followed by elimination of trimethylsilanol. When the reaction is performed without solvent under an oxygen atmosphere, indole **115** is mainly formed (**115**:**116** = 72:28) (Scheme 44).

Scheme 44



An analogous reaction with methyl propiolate regiospecifically gives 7-hydroxyindole-1,4-dicarboxylate **117** (Scheme 45).[44]

Scheme 45



The Diels−Alder reactions of sulfur-substituted 3-vinylpyrrole **118**, generated in situ by alkylation of 3-thioacetylpyrrole **119**, with dienophiles were investigated by Murase et al.[45] The cycloaddition reactions were carried out in a sealed glass tube at 100 °C in THF or MeCN under a nitrogen atmosphere. The reaction products of vinylpyrrole **118** with dimethyl maleate, dimethyl fumarate, methyl acrylate, acrylonitrile, acrolein, 1,4-naphthoquinone, maleic anhydride, and *N*-methylmaleimide were transformed to the corresponding indoles **120**−**126** by treatment with DDQ (Schemes 46 and 47).[45]

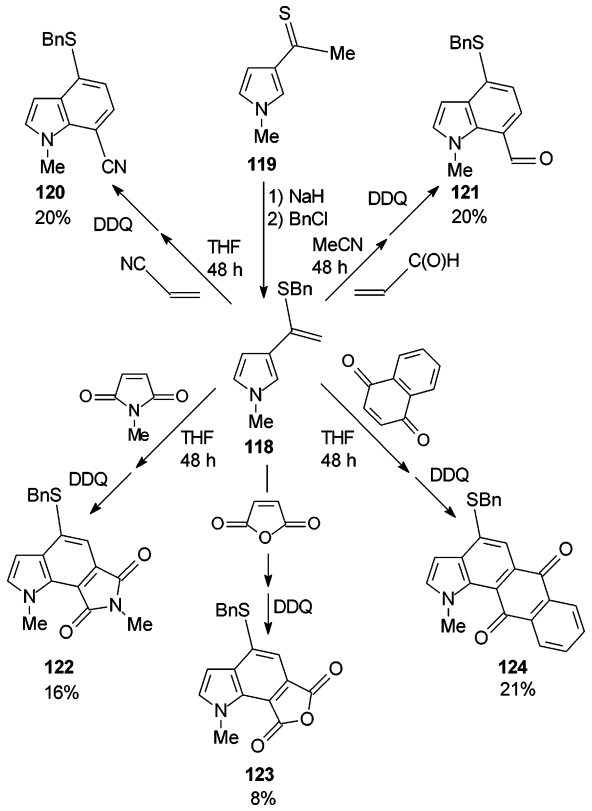
The indoles **125** and **126** were obtained also by reacting vinylpyrrole **118** with methyl propiolate and DMAD (Scheme 47).[45]

Indole **127**, a key intermediate in the synthesis of the substituted chuangxinmycin **128** (an antibiotic alkaloid), was obtained by Diels−Alder reaction of 3-vinylpyrrole **129**, generated in situ from 3-thioacetylpyrrole and methyl bromoacetate in the presence of a large excess of propylene oxide, with DMAD (Scheme 48).[46]

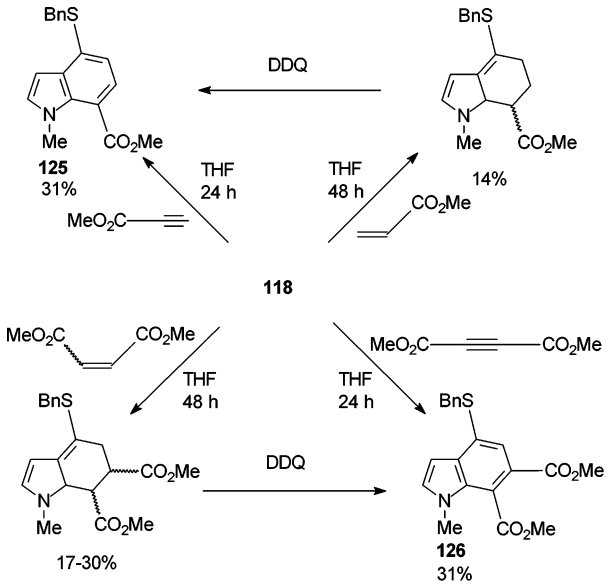
Indoles **130**, intermediates in the synthesis of substituted chuangxinmycins **131**, were synthesized by reacting pyrrole **129** with either *N*-methylmaleimide (with following treatment with DDQ) or 3,4-dibromo-*N*-methyl(benzyl)maleimides (with subsequent in situ oxidation) (Scheme 49).[46]

1-Phenylsulfonyl-2-vinyl-1*H*-pyrrolo[2,3-*b*]pyridine (**132**), a representative of condensed 2-vinylpyrroles, reacts with naphthoquinone (1.5 equiv) in a sealed tube to give a mixture of cycloadducts **133** and **134** (Scheme 50).[47] Since 4,5,6,7-tetrahydroazain-

Scheme 46



Scheme 47

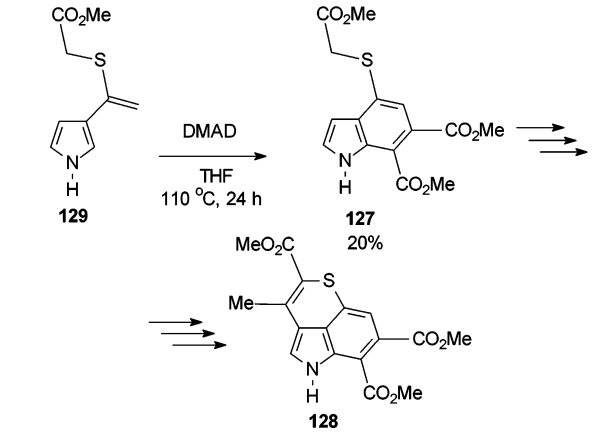


doles, actually pyrroles, are now available[48] and may be readily converted to the corresponding indoles, these reactions may be considered as related to pyrrole chemistry.

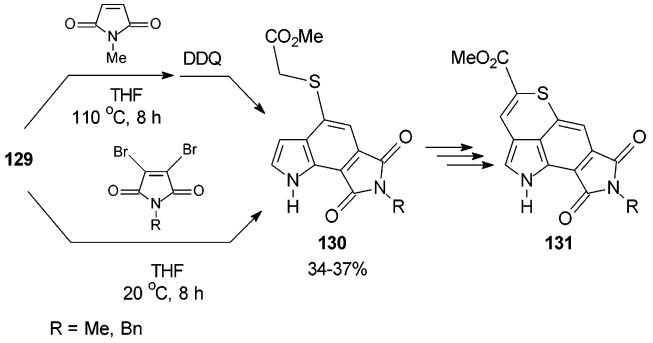
Under similar conditions, 2-vinylpyrrolo[2,3-*b*]-pyridine **132** with DMAD (1.5 equiv) afforded compound **135**, an unexpected derivative **136,** and trace amounts of aromatized derivative from **135**. Attempts to carry out the cycloaddition reaction under atmospheric pressure gave solely **135** in 30% yield (Scheme 51).[47]

The structural assignment for pyrido[2,3-*b*]indole **136** was based on 1D, 2D NOESY and HETCOR data

Scheme 48

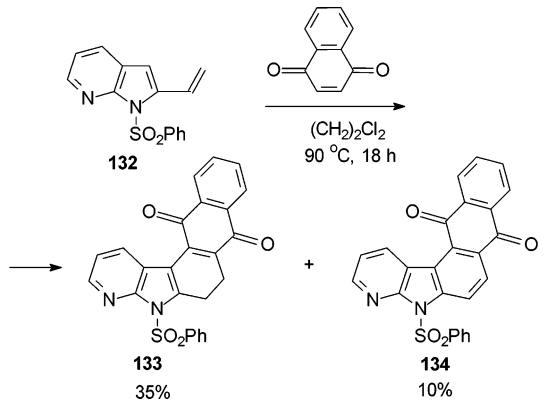


Scheme 49

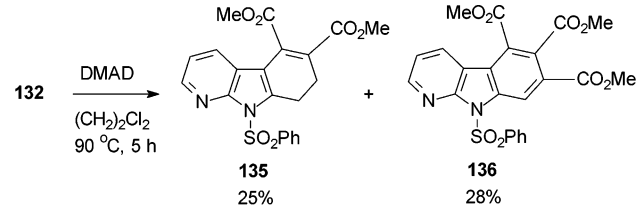


R = Me, Bn

Scheme 50



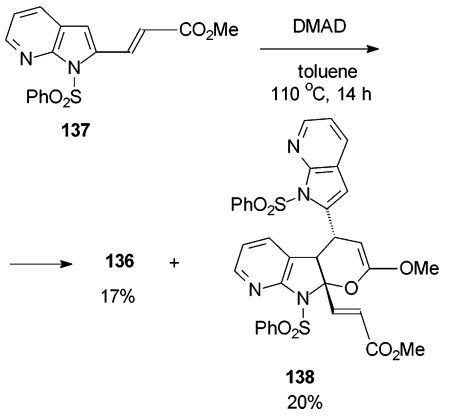
Scheme 51



and through the preparation of this compound by an alternative synthetic route from compound **137** (Scheme 52).

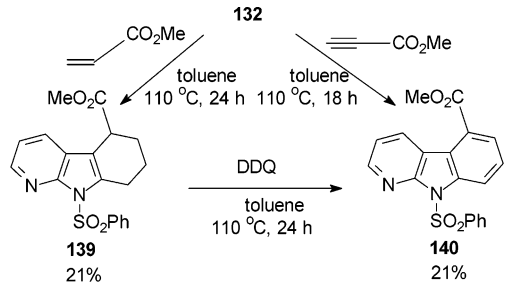
The cycloaddition of vinylpyrrolo[2,3-*b*]pyridine **137** to DMAD (5 equiv) led to compound **136** in low yield due to the decreased reactivity of the diene (22% of the starting material was recovered) and the formation of cyclodimer **138,** resulting from an intermolecular hetero-Diels−Alder reaction of **137** with itself (Scheme 52).[47]

Scheme 52



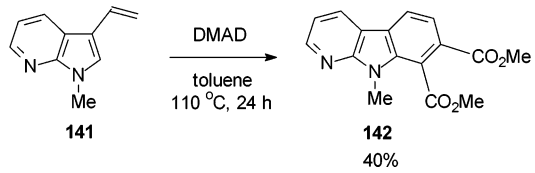
The authors also investigated the regioselectivity of the Diels−Alder reaction with 2-vinylpyrrolo[2,3-*b*]pyridine **132**. The cycloaddition of **132** with methyl acrylate (2 equiv) was performed in a sealed tube, in toluene, to exclusively afford the tetrahydro derivative **139**. The relative position of the ester group on the ring system was unambiguously confirmed by 2D NOESY experiments and by the synthesis of the aromatized compound **140** according to a standard methodology (DDQ, toluene). Reaction of **132** with methyl propiolate (4 equiv) in toluene also gave only **140** (Scheme 53).[47]

Scheme 53



Similarly, 3-vinylpyrrolo[2,3-*b*]pyridine **141** was treated with DMAD (1.2 equiv) to give dimethyl 9-methyl-9*H*-pyrido[2,3-*b*]indole-7,8-dicarboxylate (**142**) (Scheme 54).[47]

Scheme 54

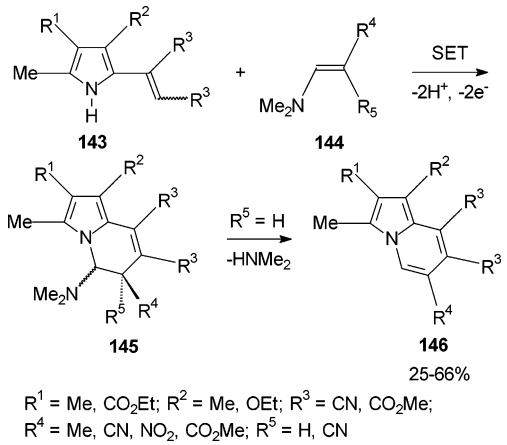


Compounds **135** and **142,** having a pyrido[2,3-*b*]-indole moiety, were also used as starting materials for the synthesis of potential cytotoxic agents via introduction of a dialkylamino group often encountered in anticancer drugs.[47]

The electrochemically induced radical cation hetero-[4+2]-cycloaddition reaction between acceptor-substituted 2-vinylpyrroles **143** and *β*-acceptor-substituted enamines **144** opens up an efficient route to highly substituted dihydroindolizines **145**.[49] It has been shown that for an efficient radical−cation-induced reaction, the oxidation potentials of the diene and dienophile should not differ by much more than 500 mV. Thus, a hetero-[4+2]-cycloaddition reaction occurs between two compounds of nearly identical HOMO energies by a redox umpolung of either the diene or dienophile to the corresponding radical cation. In all cases, the desired indolizines, which have a higher oxidation state than the reactants, were formed under complete regiocontrol in yields of 25−66%. No dimers of the diene or dienophile were observed.

The dihydroindolizines **145** thus formed eliminate a dimethylamine molecule to give indolizines **146**. In some cases the aromatization rate is slow and dihydroindolizines **145** may be isolated and characterized. For instance, complete aromatization of the cycloadduct **145** (R^3 = CO_2Me, R^4 = CN) requires several weeks (Scheme 55). If the α-methyl-substituted enam-

Scheme 55



ine **144** (R^4 = CN, R^5 = Me) is used, then aromatization of the cycloadducts **145** is impossible.[49]

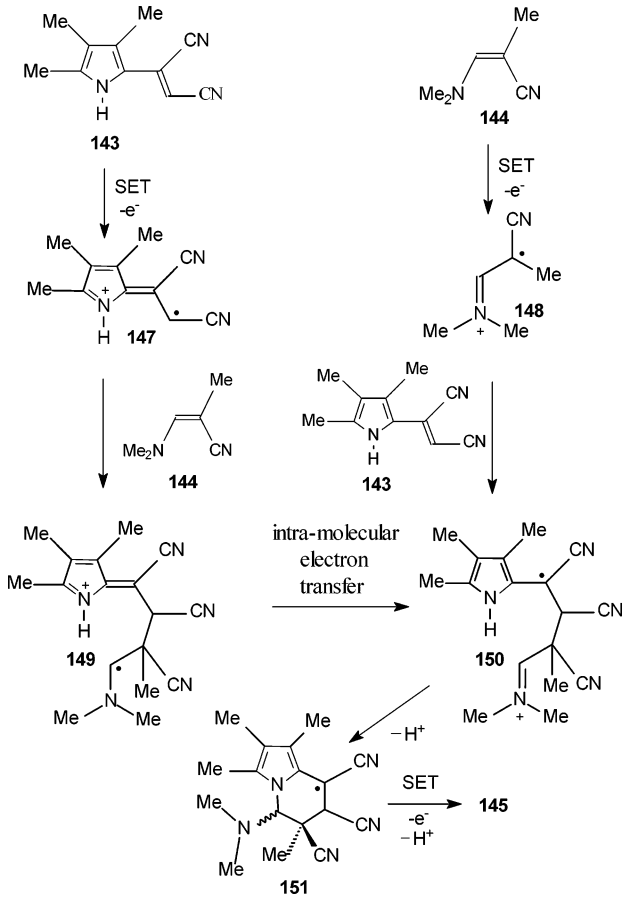
The mechanistic rationalization of these reactions using ab initio calculations (UHF/3-21G$^+$) indicated the formation of a radical cation stabilized as an iminium ion **147** from a 2-vinylpyrrole **143** in a single electron-transfer (SET) process (Scheme 56).[49]

Reasonably, because the oxidation potentials of enamines **144** are lower than those of the 2-vinylpyrroles, initial formation of the radical cations **148** is also considered by the authors. On the basis of numerous mechanistic data of radical cation [4+2]-cycloaddition,[50] the authors[49] discuss two reaction pathways starting with the attack of the electrophilic radical cation of either diene **147** or dienophile **148** at the nucleophilic site of the respective reactant to give the distonic radical cations **149** and **150**. The former is supposed to transform through an intramolecular electron transfer to the thermodynamically favored radical cation **150**. Thus, both pathways lead to the same intermediate **150**, which further cyclizes to radical **151**.

The reaction is terminated by single electron oxidation and deprotonation, leading to the cycloadducts **145** as the only products (Scheme 56).[49]

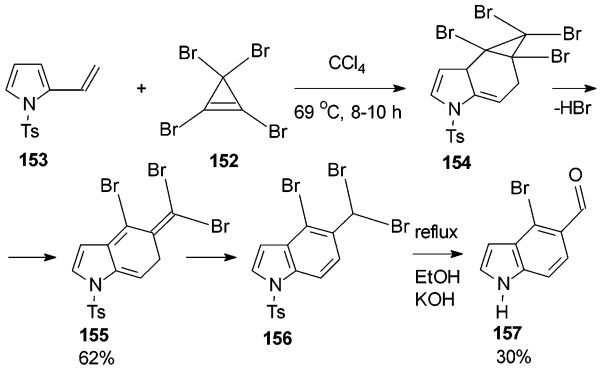
Addition of tetrabromocyclopropene (**152**) to 1-tosyl-2-vinylpyrrole (**153**) proceeds via rearrangement and elimination of HBr from the intermediate **154** to afford dibromovinylidenedihydroindole **155**. Prototropic aromatization of the latter results in indole

Scheme 56



156, which can be transformed to the corresponding carbaldehyde **157** on reflux in ethanol in the presence of KOH (Scheme 57).[51]

Scheme 57

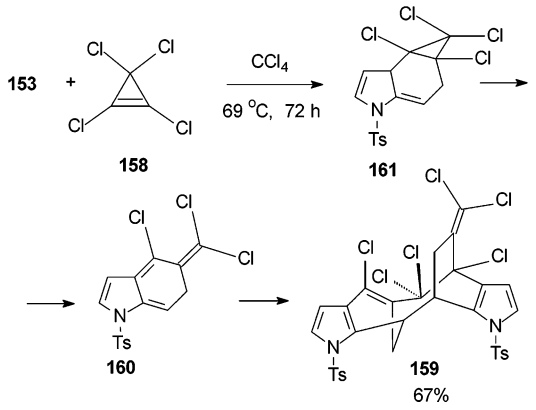


Under analogous reaction conditions, pyrrole **153** reacts with tetrachlorocyclopropene (**158**) to form dipyrrole **159**, a product of the formal [6+4]-cyclodimerization of dichlorovinylidenedihydroindole **160** (Scheme 58).[52]

Because it was impossible to assign the exact atom disposition in compound **159** from spectral data, its crystal structure analysis was carried out, which indicated that it was a 10-membered doubly bridged ring system annelated with two pyrrole cycles as depicted in Scheme 58.[52]

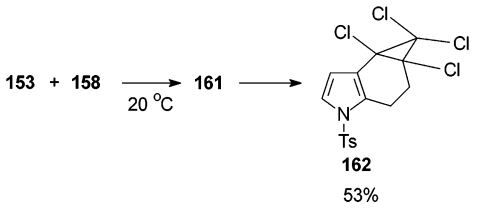
At room temperature, the pyrrole **153** with tetrachlorocyclopropene (**158**) gives [4+2]-cycloadduct **161**.

Scheme 58



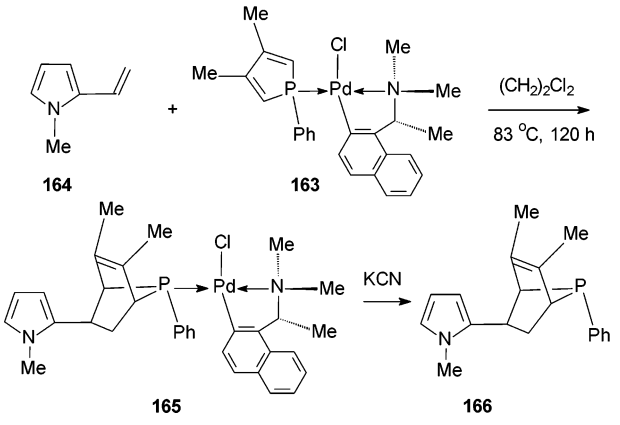
The latter undergoes 1,3-hydrogen shift to furnish the pyrrole **162** (Scheme 59).[52]

Scheme 59



Coordinated 1-phenyl-3,4-dimethylphosphole in a chiral complex, chloro((*S*)-1-(1-dimethylamino)ethyl)-naphthyl-C^2,N)(1-phenyl-3,4-dimethylphosphole-*P*)-palladium **163**, behaves as an activated cyclic diene in the intermolecular Diels−Alder reaction with 1-methyl-2-vinylpyrrole (**164**) to give a pair of diastereomeric *P*-chiral *endo*-cycloadducts **165** (Scheme 60).[53] The diastereomeric palladium complexes may

Scheme 60

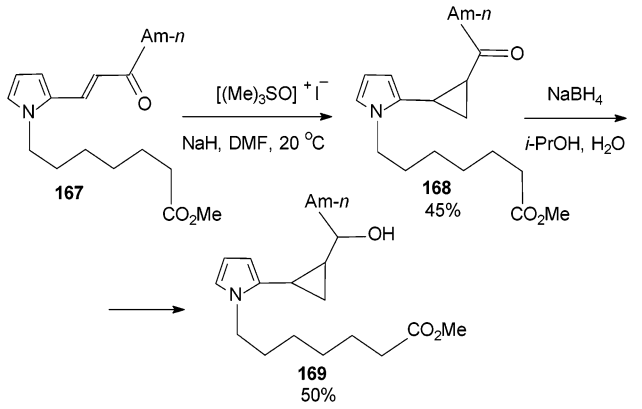


be separated by fractional crystallization, and the enantiomerically pure phosphanobornene ligand **166** may be isolated individually from the complexes by treatment with potassium cyanide. Interestingly, the [4+2]-cycloaddition reaction does not occur under similar conditions when the chloro ligand in the phosphole complex **163** is replaced with a perchlorato ligand. The Diels−Alder reaction is not observed between 1-phenyl-3,4-dimethylphosphole and 1-methyl-2-vinylpyrrole in the absence of the chiral reaction promoter (Scheme 60).[53]

3.2. Other Cycloaddition Reactions

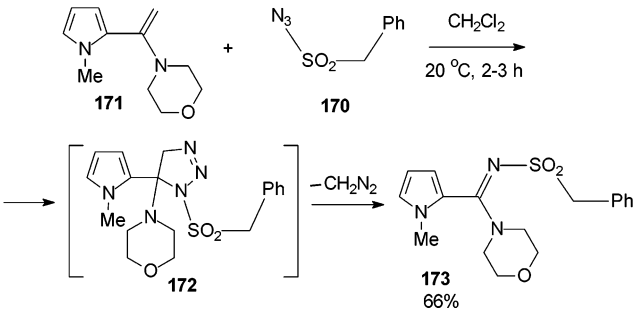
Corey cyclopropanation of 2-vinylpyrrole **167** by trimethyloxosulfonium iodide, at room temperature, affords 2-(1,2-methylene-3-oxooctyl)-*N*-(6-methoxycarbonylhexyl)pyrrole (**168**). Reduction of the latter with sodium borohydride suspension in aqueous 2-propanol gives the corresponding alcohol **169**, an analogue of prostaglandin (Scheme 61).[54]

Scheme 61



The cycloaddition of azide **170** to 2-vinylpyrrole **171** proceeds via the unstable intermediate **172**, which readily eliminates diazomethane to give amidine **173** (Scheme 62).[55]

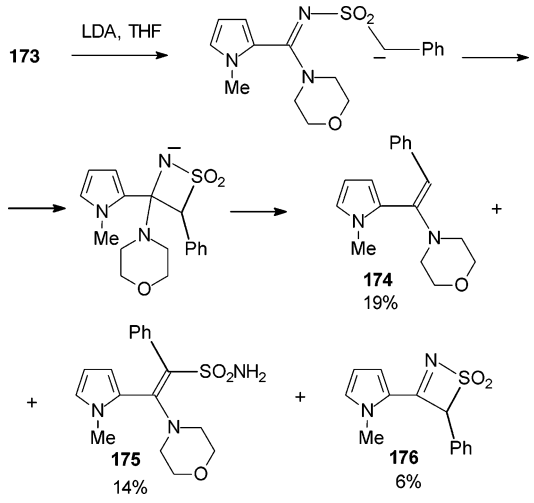
Scheme 62



The amidine **173**, when treated with bases [sodium hydride, potassium *tert*-butylate, DBU, and lithium diisopropylamide (LDA)], forms a carbanion capable of intramolecular addition to the C=N bond. The use of LDA in THF at low temperature proved to be the most suitable: under these conditions amidine **173** transformed to a mixture of products, from which enamines **174** and **175** along with thiazete-*S*,*S*-dioxide **176** were isolated by the column chromatography (Scheme 63).[55]

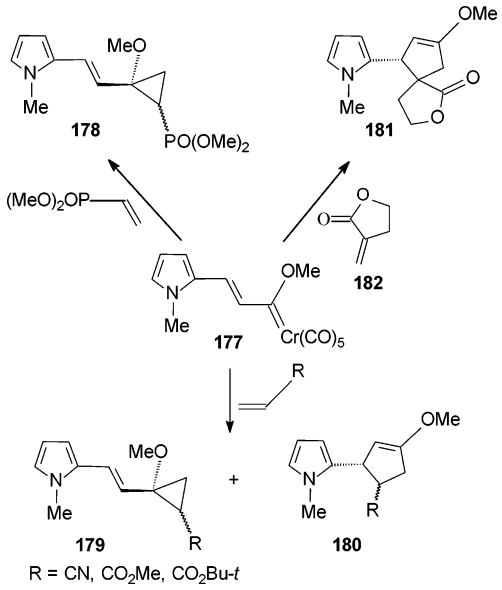
Vinylpyrrole functionalized by vinylcarbenium Fisher complex **177** adds regio- and stereoselectively electron-deficient alkenes to afford, depending on the reaction conditions and alkene structure, either pyrrolylvinylcyclopropanes **178**, **179** (formal [2+1]-cycloaddition), or isomeric pyrrolylcyclopentenes **180** and **181** (formal [3+2]-cycloaddition).[56,57] Thus, thermal (80 °C) reactions of the complex **177** with methyl and *tert*-butyl acrylic acid esters (R = CO_2Me, CO_2Bu-*t*) in cyclohexane give exclusively cyclopentenylpyrroles **180** (mixtures of *E*- and *Z*-isomers) in 67% and 80% yield, respectively. However, in polar

Scheme 63



solvents (acetone, acetonitrile), either predominant (90% in acetone) or exclusive (in acetonitrile) formation of vinylcyclopropanes **179** is observed. A much slower reaction of complex **177** with α-methylene-γ-butyrolactone **182** in cyclohexane (80 °C, 48 h) affords the stereoisomers of spiro compound **181** in 36% yield only. The corresponding vinylcyclopropane was isolated in a negligible amount (1%) (Scheme 64).[57]

Scheme 64

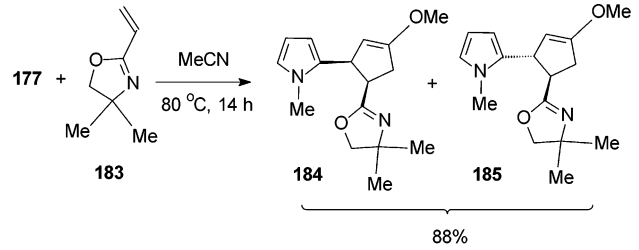


Acrylonitrile (R = CN) and complex **177** in cyclohexane (80 °C, 3.5 h) give vinylcyclopropane **179** (6%) and cyclopentene **180** (51%). Under these conditions, dimethylvinylphosphonate and complex **177** afford solely cyclopropane derivative **178** (82%).[57]

Although the cyclopentenes **180** may be products of a ring opening−ring closure (RORC) reaction of intermediate vinylcyclopropanes **179** rather than those directly formed from complex **177**, the authors, based on several control experiments, consider this unlikely under the reaction conditions employed. They argue[57] that interconversion should proceed via 1,3-zwitterions and therefore is to be favored in more polar solvents, which is not the case.

However, later in a similar reaction the vinylcyclopropane intermediates were isolated and further converted into the corresponding cyclopentenes.[58] Indeed, when an equimolecular mixture of complex **177** and alkenyl oxazoline **183** is heated in acetonitrile, a diastereomeric mixture of cyclopentenes **184** and **185** is formed in high yield, *cis*-**184** being the major stereoisomer (**184**:**185** ratio is over 20:1) (Scheme 65).[58]

Scheme 65



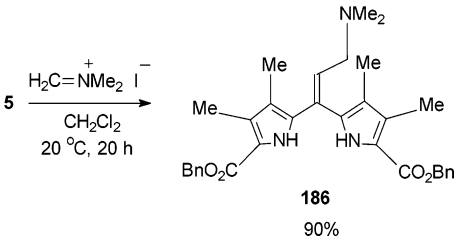
In this case cyclopentannulation is shown to involve a cyclopropanation reaction to form vinylcyclopropanes followed by thermal RORC reaction. Thus, reaction of phenyl-substituted carbene complex with alkene **183** under appropriate reaction conditions (THF, 60 °C, 14 h) led to the cyclopropane intermediates, which were further converted into a mixture of cyclopentenes on heating (MeCN, 80 °C, 12 h).[58]

Interestingly, the stereochemical course of this cyclopentannulation reaction is opposite, and therefore complementary, to that observed in earlier work.[57] The mechanistic arguments, provided by the authors,[57] in favor of a process via a formal [3+2]-cycloaddition rather than via a [2+1]-RORC sequence (see above), imply that the two different reaction pathways, depending on the structure of electron-deficient alkenes, can occur.

4. Substitution of Hydrogen or Functional Groups at the Double Bond

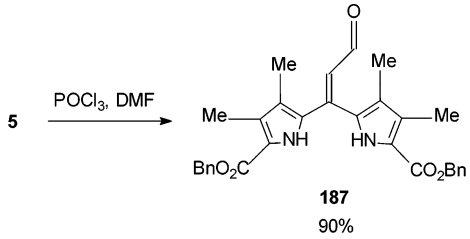
Treatment of 1-bis(2-pyrrolyl)ethene **5** with a large excess of dimethyl(methylene)ammonium iodide (the Echenmoser salt) results in 1,1-bis[5-(benzyloxycarbonyl)-3,4-dimethyl-2-pyrrolyl]-3-dimethylaminopropene (**186**) (Scheme 66).[12,59]

Scheme 66



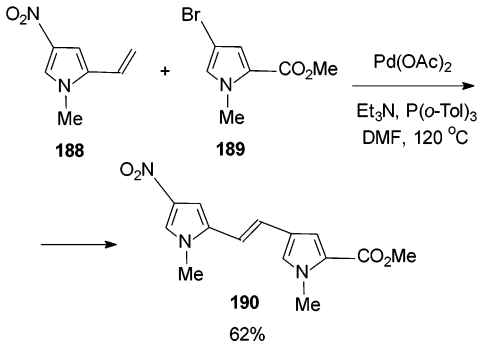
The vinyl group in 1,1-bis(2-pyrrolyl)ethene **5** can be easily formylated by the Vilsmeier reagent. Thus, treatment of **5** with the $POCl_3$−DMF system followed by alkaline hydrolysis affords 3,3-bis[5-(benzyloxycarbonyl)-3,4-dimethyl-2-pyrrolyl]acrolein (**187**) (Scheme 67).[12,59]

Scheme 67



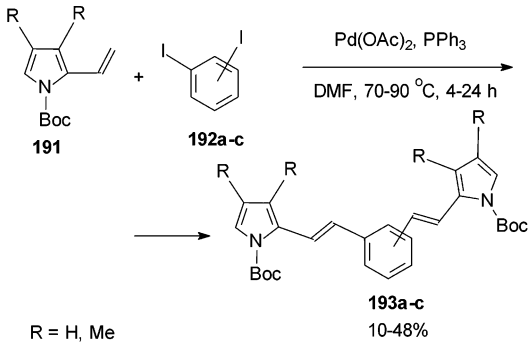
Heck reaction between 1-methyl-2-vinyl-4-nitropyrrole (**188**) and 1-methyl-2-carbomethoxy-4-bromopyrrole (**189**) gives dipyrrolylethene **190** (Scheme 68).[39]

Scheme 68



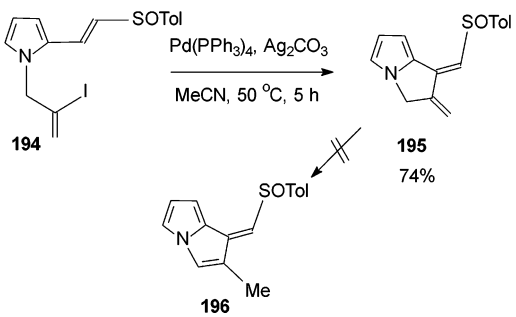
The 2-fold Heck reaction of vinylpyrroles **191** with *m*-, *p*-, and *o*-diiodobenzenes **192a**−**c** in the presence of catalytic amounts of palladium and bases (potassium acetate and tetrapropylammonium bromide, silver acetate, or triethylamine) leads to the linear pyrrole oligomers, divinylbenzene-1,3-bispyrroles **193a**−**c** (Scheme 69).[60]

Scheme 69



The vinylpyrrole **194** in the intramolecular Heck reaction (20 mol % of $Pd[P(Ph_3)]_4$, 2 equiv of Ag_2CO_3) gives the pyrrolizine **195** (Scheme 70).[61] Interestingly,

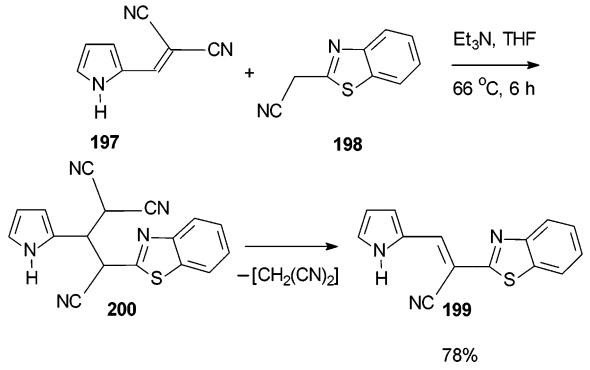
Scheme 70



the prototropic isomerization to pyrrolizine **196** does not occur to any extent, implying the isomer **195** is thermodynamically much more stable (Scheme 70).

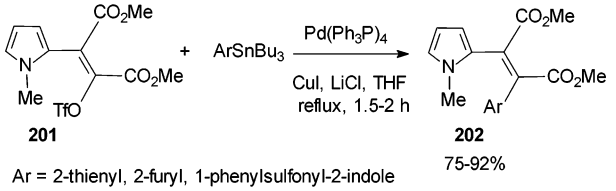
2-(2,2-Dicyanoethenyl)pyrrole (**197**) reacts with cyanomethylbenzothiazole **198** eliminating malononitrile to form 2-benzothiazolo-3-(2-pyrrolyl)acrylonitrile (**199**),[62] seemingly via the intermediate adduct **200** (Scheme 71).

Scheme 71



Combination of triflates **201** with aryltributylstannanes results in isomerically pure vinylpyrroles **202** (Scheme 72).[63]

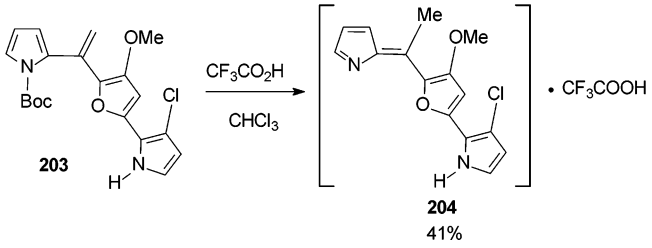
Scheme 72



5. Migration of the Double Bond

Treatment of vinylpyrrole **203** with trifluoroacetic acid in chloroform affords an analogue of Roseophilin antibiotic, 2-methylene-2*H*-pyrrole **204** in salt form (Scheme 73).[64]

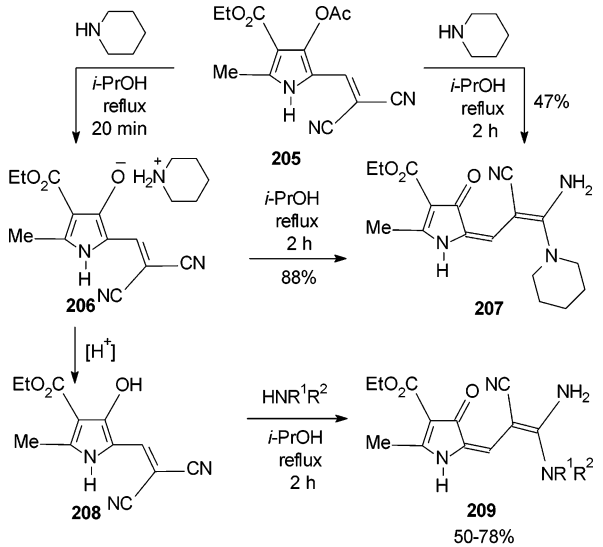
Scheme 73



Brief reflux of 2-vinylpyrrole **205** in 2-propanol with piperidine results in salt **206**, which transforms to pyrrolone **207** on longer reflux. Pyrrolone **207** may be prepared directly from the vinylpyrrole **205** by heating in a 2-propanol solution with piperidine for 2 h (Scheme 74).[65]

Acidification of salt **206** gives 2-methyl-3-ethoxycarbonyl-4-hydroxy-5-(2,2-dicyanovinyl)pyrrole (**208**). Treatment of the latter with amines readily affords pyrrolones **209**.[65]

Scheme 74

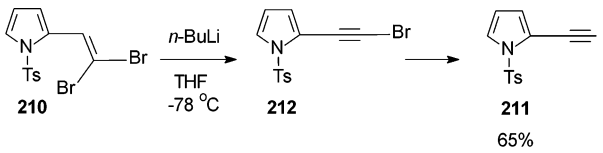


R^1 = H; R^2 = Bn, $CH_2C_6H_4OMe$-4, $CH_2C_6H_3(OMe)_2$-3,4;
R^1 - R^2 = $(CH_2)_2O(CH_2)_2$

6. Elimination Reactions

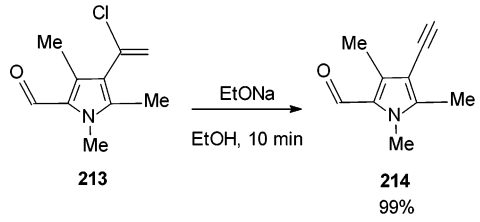
Treatment of 2-(2,2-dibromoethenyl)pyrrole **210** with BuLi gives 2-ethynylpyrrole **211**, probably via the intermediate 2-bromoethynylpyrrole **212** (Scheme 75).[66]

Scheme 75



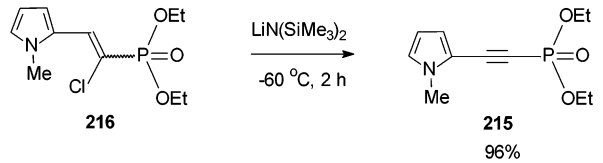
Reaction of 3-(1-chlorovinyl)-1,2,4-trimethylpyrrole-5-carbaldehyde (**213**) with sodium ethoxide affords the corresponding 3-ethynylpyrrole **214** (Scheme 76).[67]

Scheme 76



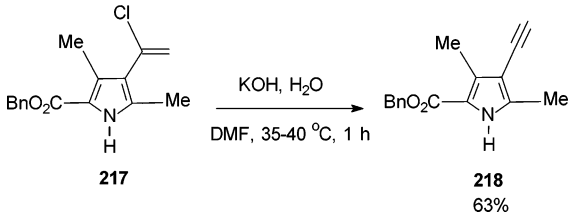
Ethynylpyrrole **215** can be synthesized by dehydrochlorination of the pyrrole **216** bearing an α-chlorovinylphosphonate group with $LiN(SiMe_3)_2$, followed by treatment with a saturated solution of NH_4Cl (Scheme 77).[68]

Scheme 77



Reaction of benzyl 4-(1-chlorovinyl)-3,5-dimethylpyrrole-2-carboxylate (**217**) with aqueous KOH affords benzyl 3,5-dimethyl-4-ethynylpyrrole-2-carboxylate (**218**) (Scheme 78).[69]

Scheme 78



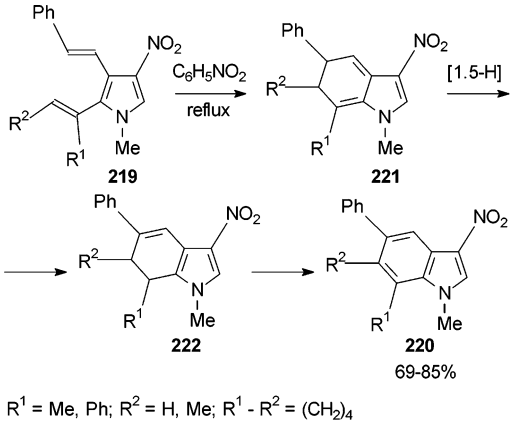
217 **218** 63%

7. Intramolecular Cyclization

7.1. Cyclization of 2,3-Divinylpyrroles

2-Alkenyl-1-methyl-4-nitro-3-(2-phenylethenyl)pyrroles **219** form 3-nitroindoles **220** on reflux in nitrobenzene. The reaction is likely to proceed via the primary electrocyclization products **221** and their 1,5-hydrogen-shifted isomers **222**, which are in situ dehydrogenated by nitrobenzene. *NH*- and *N*-tosyldivinylpyrroles do not cyclize under the conditions studied (Scheme 79).[70]

Scheme 79

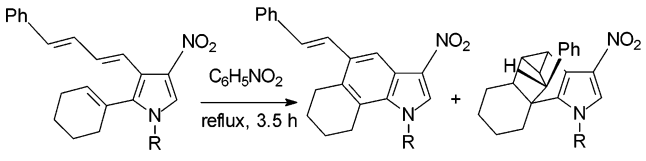


219 **221** **222** **220** 69-85%

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

Electrocyclization of 2-cyclohexenyl-1-methyl-4-nitro-3-(4-phenyl-1,3-butadienyl)pyrrole (**223**) (R = Me) caused by reflux in nitrobenzene affords not only 5-(2-phenylethenyl)nitroindole **224**, but also a product of its intramolecular cyclization **225** having a cage structure (Scheme 80).[70,71]

Scheme 80



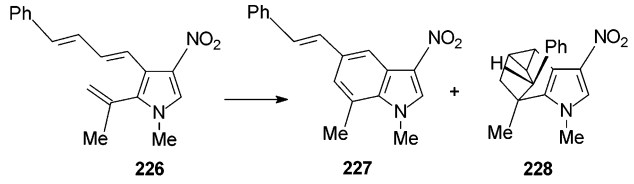
223 **224** **225**

R = H, Me 21% 50%

Replacement of the solvent for triglyme (reflux) gives only cage-structured indoles **225** (for R = Me and H the yields are 75% and 78%, respectively).[70]

Reflux of pyrrole **226** in nitrobenzene furnishes a mixture of indole **227** and cage compound **228** in 68% and 12% yields, respectively, whereas in triglyme, the major product is 3-nitrotetrahydroindole **228**, yields of **227** and **228** being 10% and 70%, respectively (Scheme 81).[70]

Scheme 81



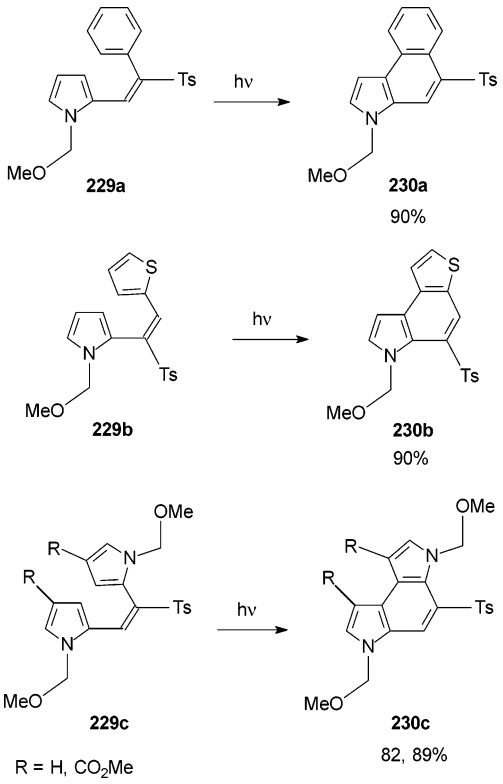
226 **227** **228**

The structures of compounds **225** and **228** were confirmed by X-ray analyses.

7.2. Cyclization of Pyrrole Analogues of Stilbene

UV irradiation of ethanol solutions of 2-{2-[phenyl-(2-thienyl, 2-pyrrolyl)]vinyl}pyrroles **229a**−**c** in the presence of catalytic amounts of iodine affords the corresponding benzo(thieno, pyrrolo)indoles **230a**−**c** in 46−89% yield. Higher yields (82−90%) of benzoindole **230a** were obtained when an equimolar amount of iodine and an excess amount of propylene oxide were used. The tosyl group can be easily removed by magnesium in methanol at room temperature or by sodium dihydronaphthalenidyl at −78 °C (Scheme 82).[72]

Scheme 82



229a **230a** 90%

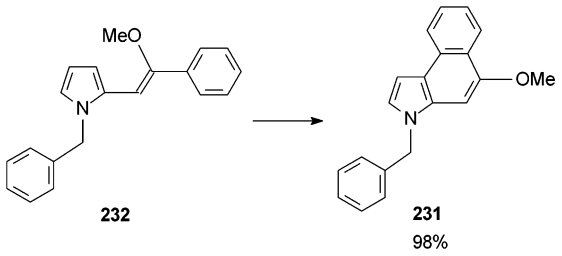
229b **230b** 90%

229c **230c** 82, 89%

R = H, CO_2Me

The benzoindole **231** can be prepared by cyclization of vinylpyrrole **232** on reflux in acetonitrile (30 min) in the presence of 4-nitrobenzoic acid, triethylamine, and palladium on carbon, followed by UV irradiation (Scheme 83).[73]

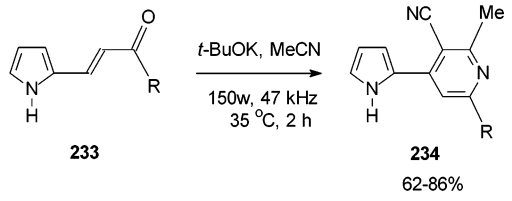
Scheme 83



7.3. Cyclization with Participation of Functional Groups

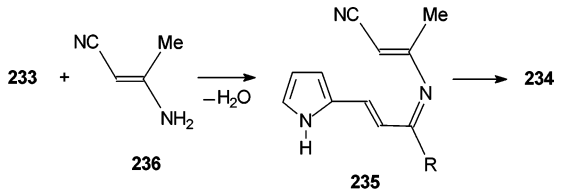
Sonication of a suspension of 2-vinylpyrroles **233** and *t*-BuOK in acetonitrile affords a number of 4-(2-pyrrolyl)-3-cyano-2-methylpyridines **234**, which can be readily transformed to nicotinic acids (Scheme 84).[74]

Scheme 84



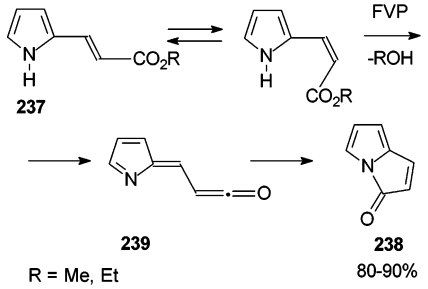
The reaction is likely to involve intramolecular cyclization step of intermediate **235**, formed from the 2-vinylpyrrole **233**, and the product of acetonitrile dimerization, the aminonitrile **236** (Scheme 85).[74]

Scheme 85



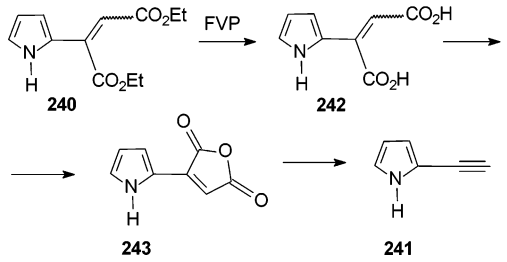
3-(2-Pyrrolyl)propenoate esters **237** undergo concerted elimination of alcohols under flash vacuum pyrolysis (FVP) conditions to give pyrrolizine-3-ones **238**, apparently via electrocyclization of the 2-pyrrolylideneketene intermediate **239** (Scheme 86).[75−81]

Scheme 86



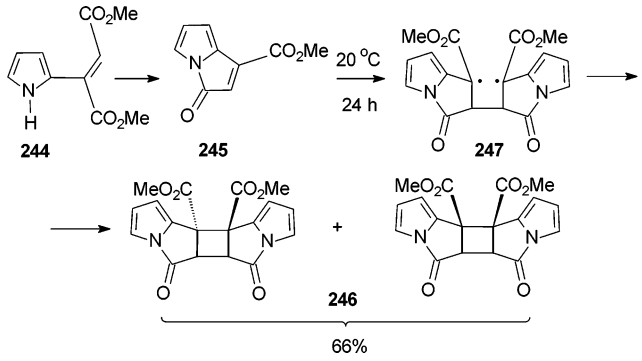
FVP (700−750 °C, 10^{-3} Torr) of 2-(1,2-diethoxycarbonylvinyl)pyrrole (*E*, *Z*) (**240**) affords 2-ethynylpyrrole (**241**) as the major product together with a small amount of pyrrolizin-3-one **238**. Alkyne formation mechanism probably involves *E*−*Z*-isomerization of the alkene (if required), accompanied by elimination of ethylene from one (or both) of the ester functions. The diacid **242** can dehydrate thermally to anhydride **243**, and cleavage of CO and CO_2 from the anhydride gives the observed alkyne **241** (Scheme 87). This mechanism is strongly supported by independent pyrolysis of the maleic acid **242** and of the anhydride **243** (prepared either by dehydration or by mild thermolysis of the diacid **242**), both of which lead to 2-ethynylpyrrole **241** under the same conditions as the diesters **240**. No significant amounts of the parent pyrrolizinone **238** were obtained in either of these reactions, and so it probably formed from **240** by the standard route followed by ester elimination and decarboxylation (Scheme 86).[76]

Scheme 87



Under analogous conditions, the corresponding dimethyl ester **244** gives the unstable 3-oxo-3*H*-pyrrolizine-1-carboxylate (**245**), which further spontaneously dimerizes to afford two isomers of the [2+2]-cycloadduct **246** in a ratio of 2:1. The reaction likely proceeds via the intermediate stabilized diradical **247** (Scheme 88).[76]

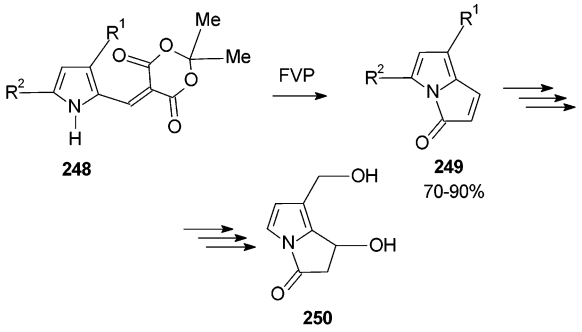
Scheme 88



FVP of vinylpyrroles **248** (600 °C, 10^{-2}−10^{-3} Torr), derivatives of the Meldrum acid, allows one to obtain pyrrolizinones **249** in good yield and purity.[78,81] This process represents one of the most common synthetic pathways to this formally antiaromatic heterocyclic π-system.[81,82] The method gives access to 1-,[78] 5-,[78] 6-,[78] and 7-substituted pyrrolizinones from the corresponding 2-vinylpyrroles (Scheme 89).[75,78,83]

Acetoxymethylpyrrolizinone **249** ($R^1 = CH_2OAc$; $R^2 = H$) obtained by the above procedure was employed as an intermediate in the synthesis of pyrrolizidine alkaloid, 3,8-didehydroheliotridin-5-one **250**.[75,81,83]

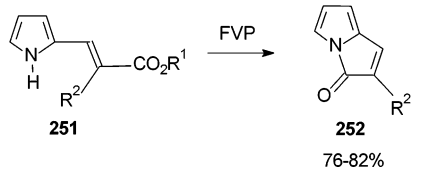
Scheme 89



R^1 = H, Me, MeO, CO_2Me, CH_2OAc, CH_2OH; R_2 = H, Me, Ph, CO_2Et

FVP (550−650 °C, 10^{-2}−10^{-3} Torr) of vinylpyrroles **251** leads to 2-substituted pyrrolizines **252**,[78] which cannot be prepared from Meldrum acid derivatives **248** (Scheme 90).

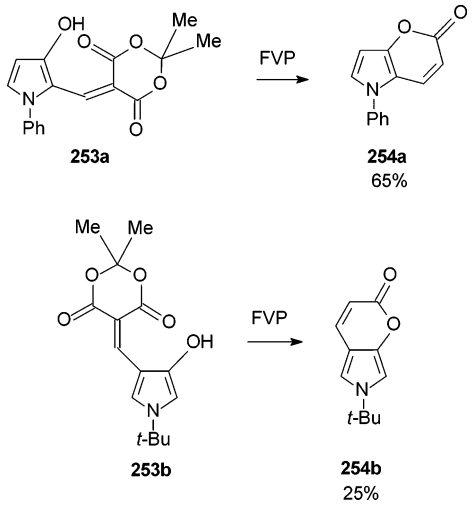
Scheme 90



R^1 = Me, Et; R^2 = Me, CN, COMe, CO_2Me, CO_2Et

Under the FVP conditions (600 °C, 10^{-2}−10^{-3} Torr), 2-vinyl-3-hydroxypyrroles **253a**,**b** transform to pyranopyrroles **254a**,**b** (Scheme 91).[81,84]

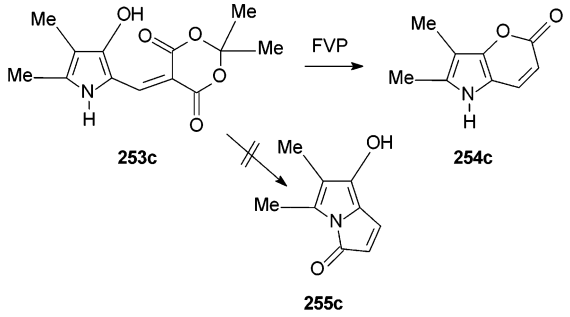
Scheme 91



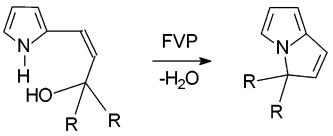
Under analogous reaction conditions, the *N*-unsubstituted 2-vinyl-3-hydroxypyrrole **253c** cyclizes to give pyranopyrrole **254c**. No pyrrolizine **255c**, the product of possible cyclization with participation of the nitrogen atom, was observed (Scheme 92).[81,84]

Gas-phase pyrolysis of 2-(3-hydroxy-1-propenyl)-pyrrole **256a** (650 °C) proceeds in an analogous mode, via elimination of water and electrocyclization, to give pyrrolizine **257a** in high yield. The pyrolysis of tertiary alcohol **256b** at the same temperature results in formation of a number of unidentified side products in the pyrolysate. Satisfactory yield and purity of 3,3-dimethyl-3*H*-pyrrolizine **257b** (64% after distillation) were achieved when the pyrolysis was carried out at 550 °C (Scheme 93).[80]

Scheme 92



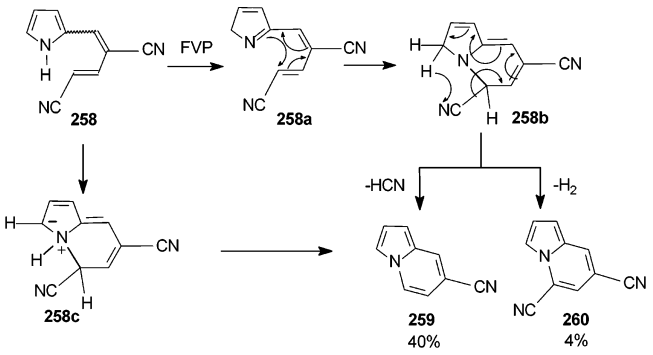
Scheme 93



R = H (**a**), Me (**b**)

Flash vacuum pyrolysis (750 °C, 2−3·10^{-3} Torr) of 4-[(2-pyrrolyl)methylidene]-2-pentenedinitrile (**258**) gives annulated dihydroaromatic 1,3-dicarbonitriles by electrocyclic ring closure. Fully aromatized products, indolizines **259** (as a major product) and **260** (minor product), form by secondary loss of HCN or H_2 (Scheme 102). A mechanism for this cyclization would involve initial equilibration of the pyrrole with 5*H*-pyrrolenine **258a**, which could then cyclize to 3,5-dihydroindolizine **258b**. A variant of this scheme would involve direct cyclization of the pyrrole **258** to dipolar species **258c**, an isomer of **258b** (Scheme 94).[85]

Scheme 94

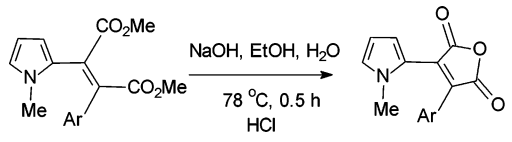


Alkaline hydrolysis of vinylpyrroles **261** with subsequent treatment of the products with an acid (HCl) gives maleic anhydrides **262**, intermediates in the synthesis of indole-containing alkaloids (Scheme 95).[63]

Hydrolysis of the pyrrole **261** (Ar = 1-phenylsulfonyl-2-indolyl, 1-phenylsulfonyl-3-indolyl) results in elimination of the 1-phenylsulfonyl group and formation of the pyrrole **262** (Ar = 2-indolyl, 3-indolyl).[63]

Vinylpyrroles **263**, formed on condensation of pyrrolecarbodithioates **264** with CH-acids **265a**−**d**[86−89] (ethylcyano- and ethylacetoacetates, diethyl- and ethylbenzylmalonates, etc.) often cyclize during the

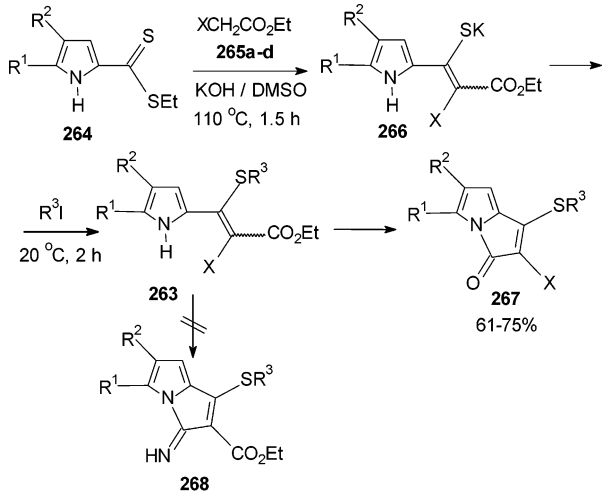
Scheme 95



Ar = 2-thienyl, 2-furyl, 1-phenylsulfonyl-2-indolyl, 1-phenylsulfonyl-3-indolyl, 2-indolyl, 3-indolyl

synthesis. The reaction is effected in the KOH−DMSO system. Alkylation of intermediate thiolates **266** with alkyl halides proceeds in situ at room temperature. When, along with the ethoxycarbonyl group, other functions capable of reacting with NH pyrrole moiety (for instance, cyano group in the pyrrole **263a**) are attached to the double bond, only ethoxycarbonyl takes part in the cyclization (Scheme 96).

Scheme 96



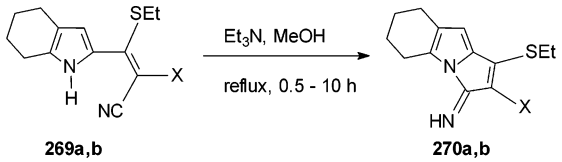
R^1 = *n*-Pr, *n*-Bu, Ph; R^2 = H, Et, *n*-Pr; R^1 - R^2 = $(CH_2)_4$;
R^3 = Et, *n*-Bu, Allyl; X = CN (**a**), COMe (**b**), CO_2Et (**c**), CO_2Bn (**d**)

Condensation of ethyl 4,5,6,7-tetrahydroindole-2-carbodithioate (**264**) [(R^1−R^2 = $(CH_2)_4$] with cyanoacetic ester **265a** gave 3*H*-pyrrolizin-3-one **267** (61% yield) in addition to the expected vinylpyrrole **263a** (29% yield). The product of possible cyclization involving the nitrile group **268** was not detected in reaction mixtures.[86−89]

2-(1-Ethylthio-2,2-dicyanoethenyl)pyrrole **269a** cyclizes quantitatively to 3*H*-3-iminopyrrolizine **270a** on reflux in methanol (0.5 h) in the presence of catalytic amounts of triethylamine.[89] The pyrrole **269b** cyclizes more reluctantly than the pyrrole **269a**. With refluxing the reagents for 10 h, the yield of pyrrole **270b** is just 46%, and this is likely to be due to the reaction reversibility (a substantial part of pyrrole **270b** interconverts to pyrrole **269b** on staying in methanol for 1 month) (Scheme 97).[90]

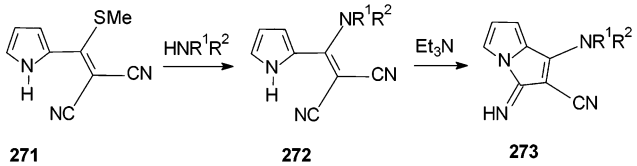
2-(1-Methylthio-2,2-dicyanoethenyl)pyrrole (**271**) is reported[91] to be capable of displacing its SMe group by secondary amines to result in 2-(1-amino-2,2-dicyanoethenyl)pyrroles **272,** which upon heating with Et_3N undergo annelation to the corresponding 1-amino-2-cyano-3-imino-3*H*-pyrrolizines **273** (Scheme 98).

Scheme 97



X = CN (**a**), $CONH_2$ (**b**)

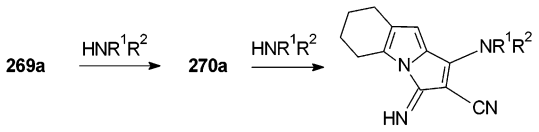
Scheme 98



R^1 = R^2 = Et; R^1 - R^2 = $(CH_2)_5$; $(CH_2)_2O(CH_2)_2$

However, investigation of this reaction on the example of vinylpyrrole **269a** bearing analogous functions on the double bond[92,93] revealed that the cyclization may be the first reaction step, the substitution of the ethylthio group for an amino group taking place later in 1-alkylthio-3-imino-2-cyano-3*H*-pyrrolizine **270a** formed. Such a reaction scheme is supported by the synthesis of aminopyrrolizines **274** by treatment of the ethylthio derivative **270a** with secondary amines (Scheme 99).

Scheme 99



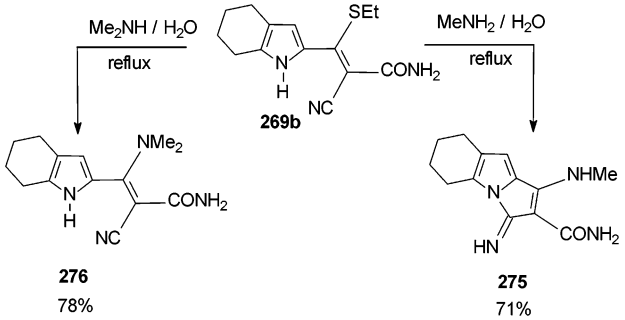
R^1 = R^2 = Et; R^1 - R^2 = $(CH_2)_5$; $(CH_2)_2O(CH_2)_2$

Condensation of the pyrrole **269a** with aqueous dimethylamine to furnish 1-(dimethylamino)-2-cyano-3-imino-3*H*-pyrrolizine **274** (R^1 = R^2 = Me) in 73% yield proceeds analogously (Scheme 99).[90]

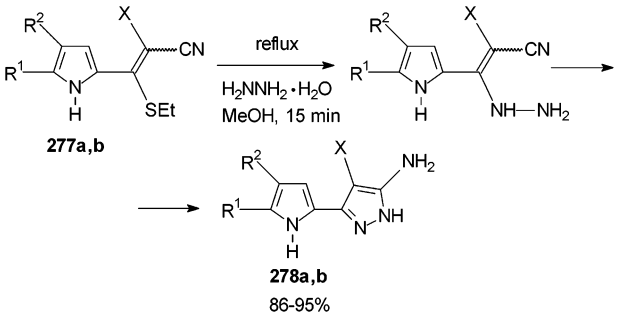
At the same time it should be noted that under these conditions the pyrrole **269b** cyclizes only in the presence of methylamine, giving 3*H*-3-iminopyrrolizine **275**. With dimethylamine, under analogous conditions, exchange of the alkylthio group for an amine residue occurs to form 2-(1-(dimethylamino)-2-cyano-2-carbamoylethenyl)pyrrole **276** (Scheme 100).[90]

2-(1-Alkylthio-2-cyanoethenyl)pyrroles **277a**,**b** with hydrazine hydrate give 3-(2-pyrrolyl)-5-aminopyrazoles **278a**,**b** (Scheme 101).[94−96]

Scheme 100



Scheme 101

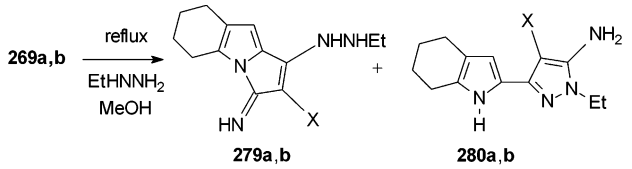


R^1 = *n*-Pr, *n*-Bu, Ph; R^2 = H, Et, *n*-Pr; R^1 - R^2 = $(CH_2)_4$; X = CN (**a**), $CONH_2$ (**b**)

A feature of the reaction is its high chemoselectivity: neither 1-alkylthio-3-imino-2-cyano-3*H*-pyrrolizines **270a**,**b,** which may form on addition of the pyrrole NH group to the nitrile moiety (see above), nor reaction intermediates hydrazinoethenylpyrrole are detected.

Reaction of pyrroles **269a**,**b** with ethylhydrazine proceeds more reluctantly: even after 10 h of refluxing in methanol, their conversion does not exceed 80%.[95] The predominant pathway of the reaction of ethylhydrazine with the pyrrole **269a** is the intramolecular cyclization into 1-ethylthio-3-imino-2-cyano-3*H*-pyrrolizine **270a** with the following substitution of 1-ethylthio group for ethylhydrazine moiety. The final outcome of this reaction is a 3:1 mixture of pyrrolizine **279a** and pyrazole **280a** in 48% overall yield. On the contrary, in the case of pyrrole **269b**, the reaction gives pyrazole **280b** mainly, the ratio of pyrrolizine **279b**:pyrazole **280b** being 1:2.5 (Scheme 102).[95]

Scheme 102

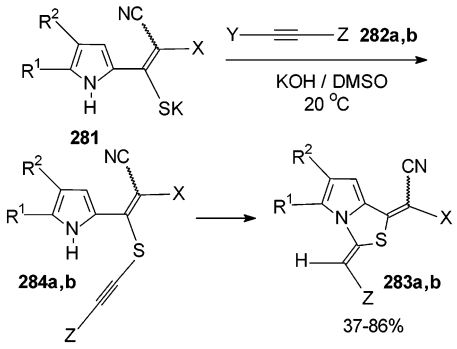


X = CN (**a**), $CONH_2$ (**b**)

Reaction of vinylthiolates **281**, which are formed in situ from pyrrole-2-carbodithioates **264** and methylenoactive nitriles, with 2-benzoyl-1-bromo- and 2-chloro-1-ethylthioacetylenes **282a**,**b** in the KOH−DMSO system affords functionalized pyrrolothiazoles **283a**,**b** (Scheme 103).[97−100]

Vinylthiolates **281** and bromobenzoylacetylene **282a** stereoselectively form *Z*-isomers of pyrrolothiazoles **283a**. The observed stereospecificity is likely caused by steric hindrances which do not allow formation of the *E*-isomer. With ethylthiochloroacetylene **282b**, vinylthiolates **281** react to give mainly *E*-isomers, but the latter transform almost completely to the less spatially hindered *Z*-isomers during isolation and purification stages (recrystallization from DMSO or eluation from aluminum oxide). The same transformation is observed on stirring a mixture of the above isomers in ether in the presence of HCl. All steps of the synthesis of pyrrolothiazoles **283a**,**b** are performed in a single reactor without isolation of intermediate products.[97−100]

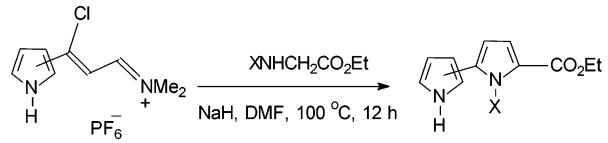
Scheme 103



R^1 = Me, *n*-Pr, *n*-Bu; R^2 = Me, Et, *n*-Pr;
X = CN, $CONH_2$; Y = Br, Z = COPh (**a**), Y = Cl, Z = SEt (**b**)

2- and 3-Vinylpyrroles **285a** react with *NH*- and *N*-methylglycinate to afford dipyrroles **286** with the 2,5-substituted pyrrole ring (Scheme 104).[101]

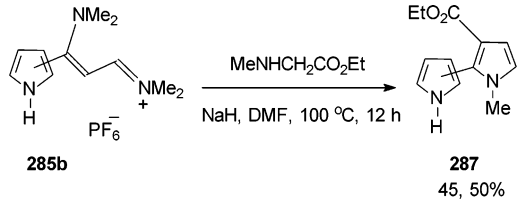
Scheme 104



X = H, Me

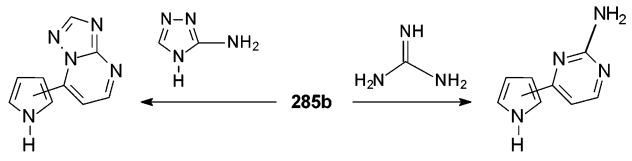
When the chlorine atom in salt **285a** is replaced by a dimethylamino group (the salt **285b**), dipyrroles with a 2,3-disubstituted ring **287** are formed (Scheme 105).[101]

Scheme 105



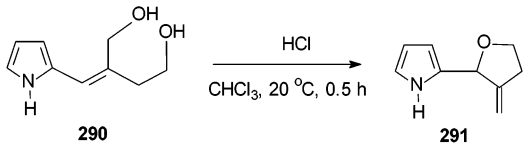
Under the same conditions, cyclization of salt **285b** with 3-aminotriazole affords selectively 7-(2- and 3-pyrrolyl)triazolo[1,5-*a*]pyrimidines **288**. 2- and 3-Pyrrolylpyrimidines **289** are formed in the reaction of salt **285b** with guanidine (Scheme 106).[101]

Scheme 106



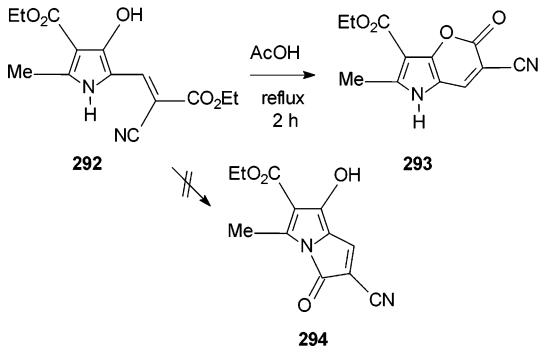
Treatment of the diol **290** with hydrochloric acid (a 10% aqueous solution) leads to cyclization and dehydration of the former into methylenetetrahydrofuranylpyrrole **291**.[102] It is remarkable that the starting and final pyrroles (which have no strong electron-withdrawing substituents) are unusually stable toward HCl (Scheme 107).

Scheme 107



On boiling in acetic acid, 2-vinylpyrrole **292** cyclizes into pyrano[3,2-*b*]pyrrole **293** in high yield (Scheme 108).[103]

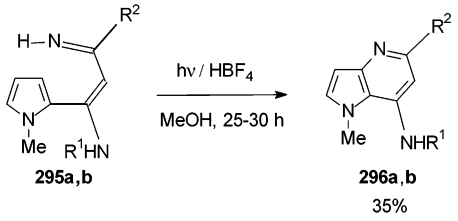
Scheme 108



A product of possible cyclization with participation of the N−H bond, 3*H*-pyrrolizine-3-one **294** was not fixed.[103]

UV irradiation of 2-pyrrolylvinylimines **295a**,**b** in an acidic medium (54% HBF_4 ether solution, Hg lamp, 125W, 25−30 h) in anhydrous MeOH gives 1-methyl-7-(R^1-amino-5-R^2-pyrrolo[3,2-*b*]pyridines) **296a**,**b** (Scheme 109).[104]

Scheme 109



R^1 = Ph, R^2 = 4-MeC_6H_4 (**a**); R^1 = Bn, R^2 = Ph (**b**)

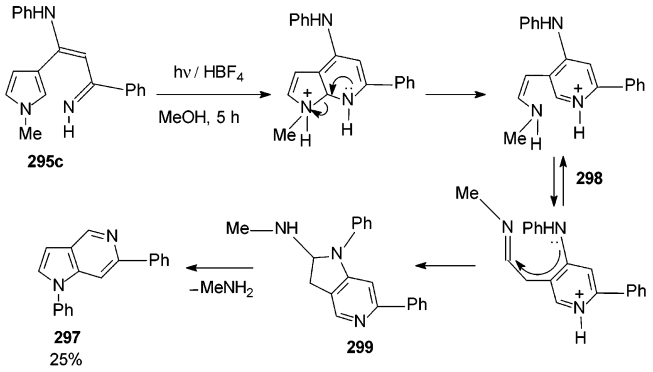
Unexpectedly, under analogous conditions, 3-pyrrolylvinyl imine **295c** cyclizes into 1,6-diphenylpyrrolo[3,2-*c*]pyridine **297** (Scheme 110).[104]

Seemingly, the RORC mechanism involves a pyrrole ring-opening step to form intermediate **298**. Subsequent attack of the phenylamino group to the imine double bond results in cyclization into the pyrrolinopyridine **299**, which, after elimination of methylamine, aromatizes into **297** (Scheme 110).[104]

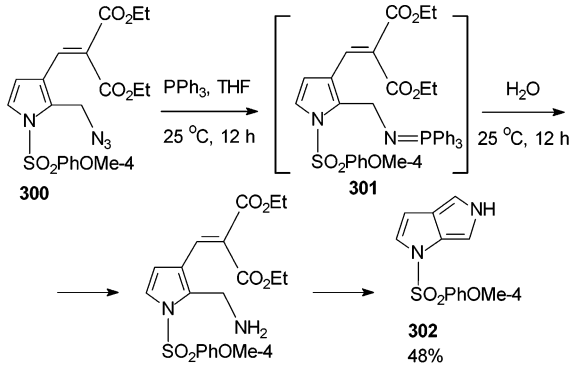
Treatment of vinylpyrrole **300** bearing an azide function with triphenylphosphine, followed by hydrolysis of the intermediate **301**, gives the pyrrolo[3,4-*b*]pyrrole **302** (Scheme 111).[105]

The cyclization is likely to proceed via 2-aminomethylpyrrole-3-carbaldehyde **303**, whose aldehyde group is formed as a result of elimination of malonic acid following the reverse Knoevenagel reaction (Scheme 112).

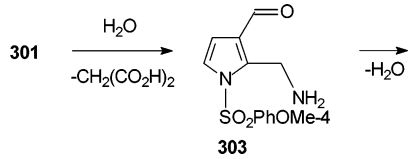
Scheme 110



Scheme 111



Scheme 112



Attempting to remove the protecting (4-methoxyphenylsulfonyl) group led to decomposition of the product.[105]

Reaction of bromide **304** with benzylamine results in pyrrolo[3,4-*b*]pyrrole **305**, which transforms to cycloadduct **306** on treatment with DMAD. Oxidation of compound **306** with *m*-chloroperbenzoic acid followed by thermolysis gives indole **307** via *N*-oxide **308** (Scheme 113).[105]

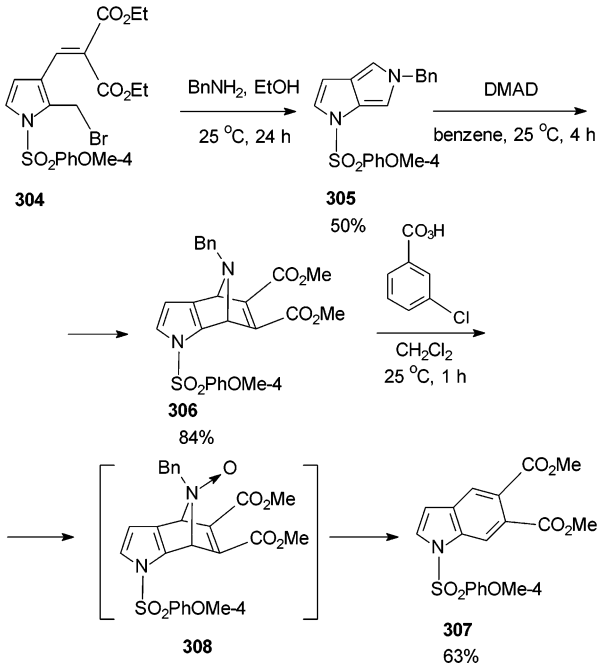
Dipyrrolo[3,4-*b*:3′,4′-*d*]pyrrole **309** was obtained from 3,4-divinyl-2,5-di(bromomethylene)pyrrole (**310**) by treatment of the latter with a 25% solution of ammonia in ethanol (Scheme 114).[105]

In this case, the cyclization may also be preceded by the retro-Knoevenagel reaction with recovery of aldehyde functions and simultaneous substitution of the bromine atom for an amino group (i.e., via intermediates such as **311** and **312**) (Scheme 115).[105]

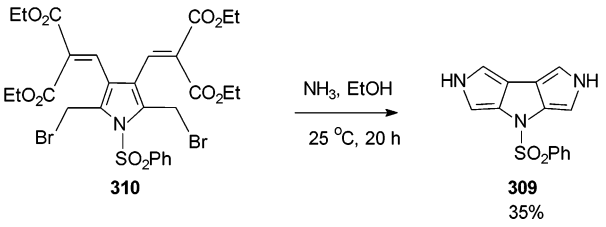
Simultaneous annelation of two pyridine rings to the pyrrole ring was effected using the aza-Wittig electrocyclic cyclization of 2,5-di(2-azido-2-ethoxycarbonylvinyl)pyrrole **313** (Scheme 116).[106]

On interaction with triphenylphosphine, azido groups readily transform into iminophosphorane functions. Divinylpyrrole **314** thus obtained may be cyclized with 2 equiv of ketenes or isocyanates in a

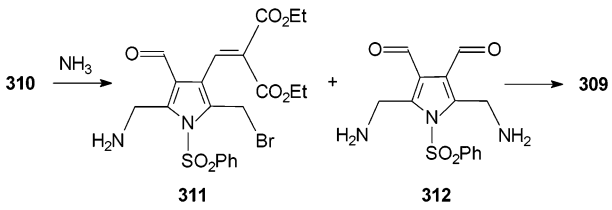
Scheme 113



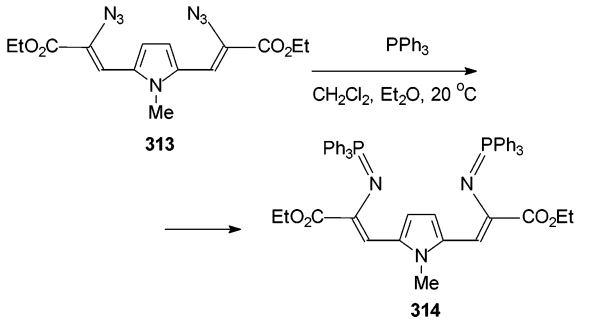
Scheme 114



Scheme 115



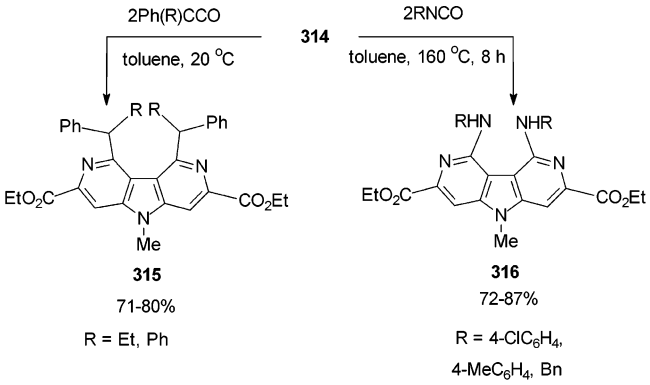
Scheme 116



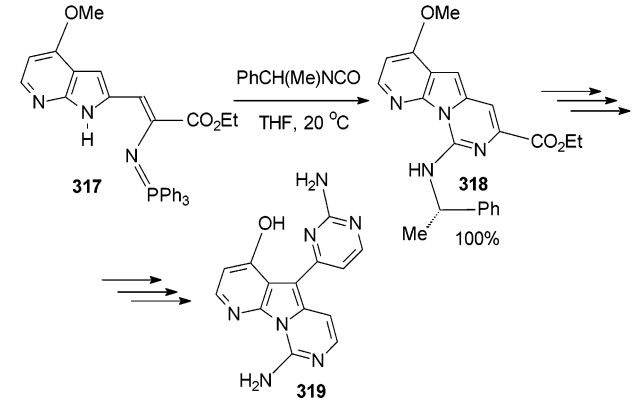
sealed ampoule to afford pyridoazoindoles **315** and **316** (Scheme 117).[106]

The aza-Wittig reaction of the vinylpyrrole **317** bearing an iminophosphorane function with α-methylbenzylisocyanate furnishes tricyclic pyridopyrrolopyridine **318**, an intermediate in the synthesis of variolin B alkaloid **319**, in almost quantitative yield (Scheme 118).[107]

Scheme 117

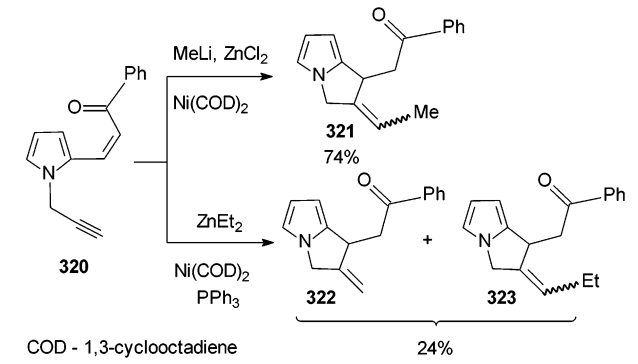


Scheme 118



The pyrrole **320** cyclizes into the pyrrolizine **321** in the presence of a complex catalytic system, [(MeLi–$ZnCl_2$, 1.5:1; 5–10 mol % of $Ni(COD)_2$]. Reductive cyclization ($ZnEt_2$, 5–10 mol % of $Ni(COD)_2$, 20 mol % of PPh_3) of the pyrrole **320** is less efficient: a 1:3 mixture of pyrroles **322** and **323** is formed (Scheme 119).[108]

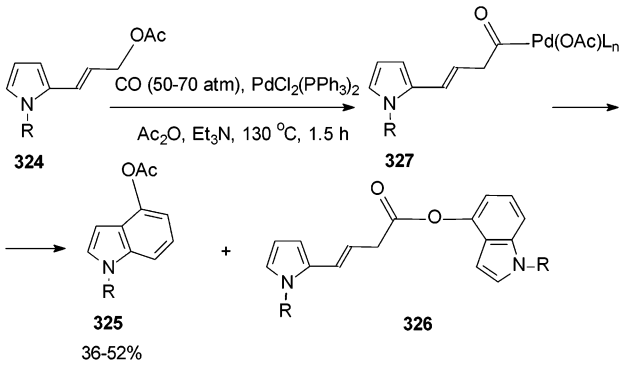
Scheme 119



Carbonylation of 2-(3-acetoxy-1-propenyl)pyrroles **324** results in 4-acetoxyindoles **325**. When R = CH_2OMe, along with the indole **325**, the dimer **326** is also isolated, which, seemingly, is formed as a result of reaction of intermediate **327** with a molecule of 4-acetoxyindole **325** (Scheme 120).[109] The formation of **326** is suppressed either by performing the reaction at a higher temperature (170 °C) or by using a large excess of Ac_2O and Et_3N.

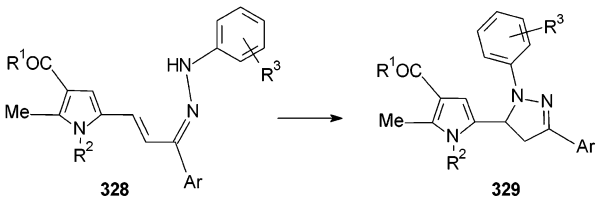
Cyclization of vinylpyrroles with hydrazone function **328** gives pyrazolines **329**, which may then be oxidized to the corresponding pyrazoles (Scheme 121).[110]

Scheme 120



R = CH_2OMe, CH_2OBn; L = CO, PPh_3; n = 1, 2

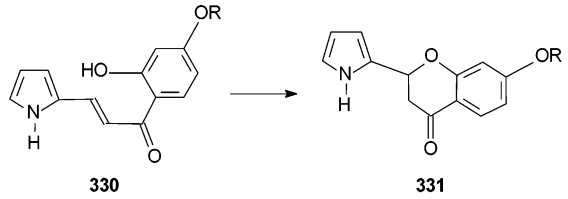
Scheme 121



R^1 = Ph, OEt; R^2 = H, Me; Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-HOC_6H_4, 4-$NH_2C_6H_4$, 4-$NO_2C_6H_4$; R^3 = H, 4-NO_2

The intramolecular nucleophilic addition of the hydroxyl group to the activated double bond in functionalized vinylpyrroles **330** is a route to benzopyranones **331** (Scheme 122).[111]

Scheme 122



R = EtO_2CCH_2, $HO(CH_2)_2$

8. Conclusions

The information presented in this review clearly illustrates the substantial advances achieved over the past decade in the field of the chemistry of *C*-vinylpyrroles, especially those with functional groups. Owing to their rich and broad synthetic capabilities, especially high affinity to cycloaddition reactions and intramolecular cyclizations with participation of functional groups on the double bond, these compounds have been and are being extensively used in organic synthesis as convenient building blocks for the construction of complex pyrrole systems.

9. Acknowledgment

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