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Synthesis and biological activity of pyrrole, pyrroline and pyrrolidine derivatives with two aryl groups on adjacent positions

Fabio Bellina and Renzo Rossi*

Dipartimento di Chimica e Chimica Industriale, University of Pisa, Via Risorgimento 35, I-56126 Pisa, Italy

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1. Introduction

Five-membered heterocycle derivatives with two aryl groups on adjacent positions include several classes of natural and unnatural compounds that exhibit a variety of biological and biomedical properties.[1–10] Some excellent reviews concerning these properties have been published[11] but, to the best of our knowledge, no review has been devoted so far

Keywords: Pyrroles; Pyrrolines; Pyrrolidines; Synthesis; Bioactivity; Natural products.
Abbreviations: Ac, acetyl; Ar, aryl; Bn, benzyl; Bt, benzotriazol-1-yl; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF, dimethylformamide; DMPA, *N*,*N*-dimethylaminopyridine; DMSO, dimethylsulfoxide; DNA, deoxyribonucleic acid; DOPA, 3,4-dihydroxyphenylalanine; GSK-3β, glycogen synthase-3β; HIV-1, human immunodeficiency virus type 1; HMG-CoA, hydroxymethylglutaryl-coenzyme A; HMPA, hexamethylphosphoric triamide; LHMDS, lithium hexamethyldisilazane; LTB_4, leukotriene-B_4; MDR, multidrug resistance; Me, methyl; NBS, *N*-bromosuccinimide; PKC, protein kinase C; SEM, 2-(trimethylsilyl)ethoxymethyl; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TIPS, triisopropylsilyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TOSMIC, tosylmethyl isocyanide; Ts, *p*-toluenesulfonyl.
* Corresponding author. Tel.: +39 050 2219214; fax: +39 050 2219260; e-mail: rossi@dcci.unipi.it

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to exhaustively summarizing and commenting on the procedures used for the synthesis of single classes of these diaryl-substituted heterocycles.

This review has the aim of covering the literature up to the end of September 2005 on the use of classical or improved methods and the design and development of new procedures for preparing pyrrole, pyrroline and pyrrolidine derivatives with two aryl groups on adjacent positions. It also aims to critically complete the picture of the studies summarized in several available reviews on the synthesis of substituted pyrroles[12] and to summarize several data concerning the biological properties of these vicinal diaryl-substituted heterocycles. In fact, these substances include unnatural compounds and a wide variety of substances isolated from natural sources (e.g., lamellarins,[1] lukianols,[13] ningalins,[14] storniamides,[15] arcyriarubins,[16] polycitones[17–19] and polycitrins[17]) that exhibit remarkable biological properties such as hypolipidemic,[20,21] antimicrobial,[22,23] anti-inflammatory[24] and antitumour activity[25,26] and are able to inhibit retroviral reverse transcriptases [i.e., human immunodeficiency virus type 1 (HIV-1)],[27] cellular DNA polymerases[27] and protein kinases.[28–31] Furthermore, some of these compounds are useful intermediates in the synthesis of biologically important naturally occurring alkaloids[32–47] and unnatural heterocycle derivatives.[48]

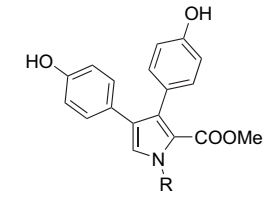
The topics that are covered in the review include (i) the description of the structures and properties of biologically active natural and unnatural pyrrole derivatives with two aryl groups on adjacent positions; (ii) a critical summary of the methods reported in the literature for the synthesis of 1,2-, 2,3- and 3,4-diaryl-1*H*-pyrroles, 1,2,3- (1,4,5-), 1,2,5-, 1,3,4-, 2,3,4- (3,4,5-) and 2,3,5-triaryl-1*H*-pyrroles, 1,2,3,5- and 2,3,4,5-tetraaryl-1*H*-pyrroles, 1,2,3,4,5-pentaaryl-1*H*-pyrroles and 2,3,3-triaryl-3*H*-pyrroles; (iii) a survey of the literature data on the biological properties and the methods used to prepare 1-, 2- and 3-pyrrolines, pyrrolin-2-ones, 2,3-dihydropyrrole-2,3-diones, pyrrolidines, 2-pyrrolidinones, 3-hydroxy-3-pyrrolin-2-ones and pyrrolidine-2,4-diones with two aryl groups on adjacent positions; (iv) a description of the structures and biological properties of naturally occurring symmetrical and unsymmetrical 2,3-diarylmaleimides (3,4-diaryl-pyrrolidine-2,5-diones); and (v) a critical summary of the methods designed and developed for preparing symmetrical and unsymmetrical 2,3-diarylmaleimides and 2,3-diarylsuccinimides (3,4-diarylpyrrolidine-2,5-diones).

This review does not cover the biological properties and the methods used to prepare vicinal diaryl-substituted nitrogen five-membered heterocycles fused with other rings such as indoles, indolizines, indolo[2,3-*a*]carbazoles, [1]pyrano[3,4-*b*]-pyrroles, 5,6-dihydropyrrolo[2,1-*a*]isoquinolines and pyrrolo[2,1-*a*]isoquinolines with two aryl groups on adjacent positions. These topics will, however, occasionally be tackled.

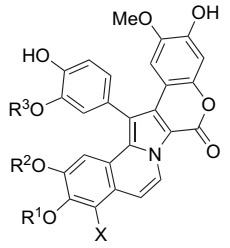
2. Pyrrole derivatives with two aryl groups on adjacent positions

2.1. Biologically active natural and unnatural pyrrole derivatives with two aryl groups on adjacent positions

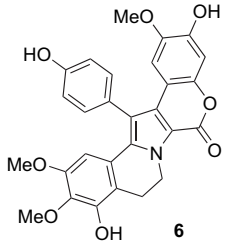
Pyrrole derivatives with two aryl groups on adjacent positions include important classes of marine natural products, some of which display remarkable biological and pharmacological properties. Thus, lamellarins O (**1**),[1,49] P (**2**),[1,49] Q (**3**)[1,50] and R (**4**)[1] are 3,4-diarylpyrrole-2-carboxylic acid esters, which belong to a large group of DOPA-[1-amino-3-(3′,4′-dihydroxyphenyl)propionic acid]-derived pyrrole alkaloids first isolated from the prosobranch mollusc *Lamellaria* sp.[12,51] and later obtained from the ascidian *Didemnum* sp.,[1,52–57] the Australian sponge *Dendrilla cactus*,[1,49,50] and an unidentified ascidian collected from the Arabian sea.[58]



1 : R = 4-(MeO)$C_6H_4COCH_2$
2 : R = 2-(HO),4-(MeO)$C_6H_3COCH_2$
3 : R = H
4 : R = 4-(HO)C_6H_4



5 : R^1 = X = H; R^2 = R^3 = Me
7 : R^1 = R^2 = R^3 = Me; X = OH
8 : R^1 = R^2 = R^3 = X = H



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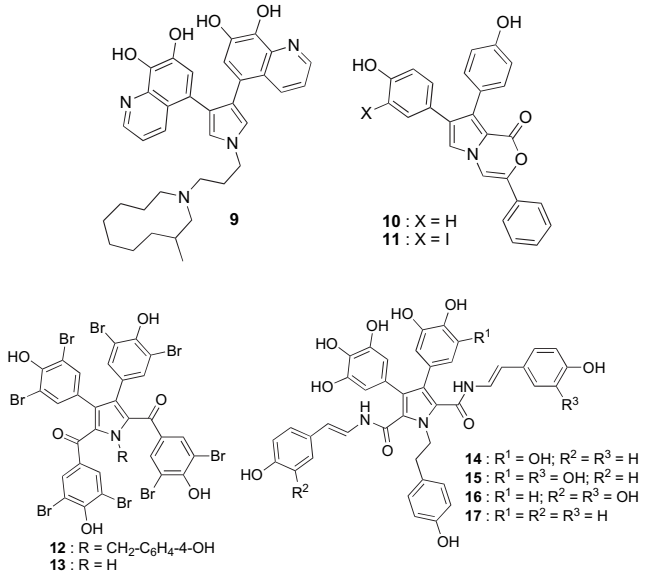
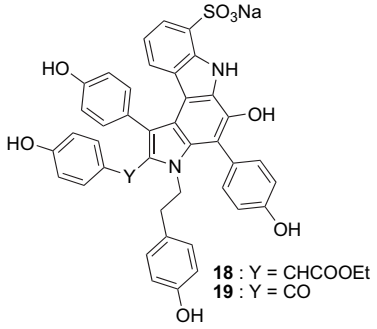
Virtually all of the lamellarins have been found to be cytotoxic to a wide range of cancer cell lines and the most potent of these compounds, i.e., lamellarins D (**5**), K (**6**) and M (**7**), have been shown to exhibit cytotoxicity values in the mid-to-high nanomolar range (38–110 nM).[59] Interestingly, lamellarins are also single-digit micromolar inhibitors of P-glycoprotein (P-gp) responsible for the multidrug resistance (MDR) effect and even at noncytotoxic concentrations they reverse MDR by inhibiting P-gp-mediated drug efflux.[32,59] Lamellarin D (**5**) is also a potent inhibitor of human topoisomerase I[60] and lamellarin H (**8**) is a potent inhibitor of both *Molluscum contagiosum* virus topoisomerase and HIV-1 integrase.[61] On the other hand, lamellarins O (**1**) and P (**2**) demonstrated antibiotic activity[49] and lamellarin D (**5**) caused inhibition of cell division.[51]

Other marine natural products possessing a 3,4-di(hetero)-aryl-substituted pyrrole ring as a common structural subunit include halitulin (**9**), which is a strongly cytotoxic pyrrole alkaloid isolated from the sponge *Haliclona tulearensis*,[26] lukianols A (**10**) and B (**11**), which have been found in an unidentified encrusting tunicate collected in the lagoon of the Palmyra atoll,[13] polycitones A (**12**) and B (**13**),[18] which have been isolated from the Indo-Pacific ascidian *Polycitor* sp.,[17,18] storniamides A (**14**), B (**15**), C (**16**) and D (**17**), which are alkaloids isolated from marine sponges of the genus *Clona*,[15] dictyodendrins A (**18**) and B (**19**), which are the first telomerase inhibitory marine natural products isolated from the Japanese marine sponge *Dictyodendrilla verongiformis*,[62] and ningalins A (**20**) and B (**21**), 3,4-diaryl-pyrrole derivatives bearing a 2-carboxylate group, which

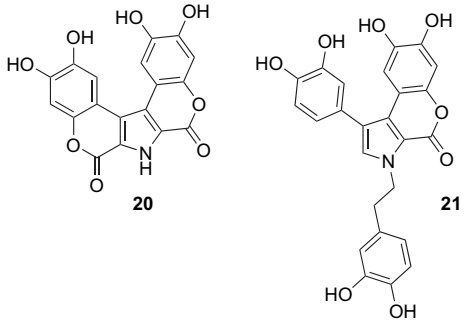
have been isolated from the ascidian of the genus *Didemnum* collected in Western Australia near Ningaloo Reef.[14]



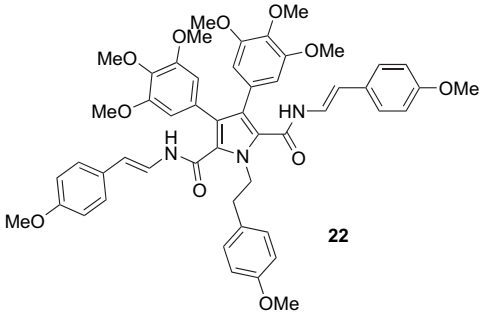
Interestingly, halitulin (**9**), which incorporates the 3,4-bis(7′,8′-dihydroxyquinolin-5′-yl)-1*H*-pyrrole unit as key motif, was found to be cytotoxic against several tumour cell lines (e.g., P-388, A-549, HT-29 and MEL-28) with IC_{50} values in the 12–25 ng/mL range.[26]

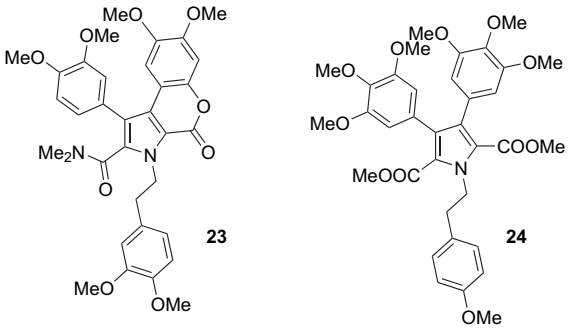


Such properties, coupled with the unique structure of this marine alkaloid, prompted a patent filing[63] claiming 3,4-bis(7′,8′-dihydroxyquinolin-5-yl)-1*H*-pyrroles as antitumour agents. On the other hand, lukianol A (**10**) was shown to exhibit cytotoxic activity against a cell line derived from human epidermatoid carcinoma (KB)[13] and afforded excellent cytotoxicity in the murine L1210 lymphoid leukaemia cell line and some human leukaemia cells with ED_{50} values less than 20 μM, which compared well with the clinical antineoplastic standards.[64] Storniamides A–D (**14**–**17**) showed antibiotic activity against several Gram-positive bacteria[15] and permethyl storniamide A (**22**), which lacks inherent cytotoxic properties, was shown to potently reverse MDR, resensitizing a resistant human colon cancer cell line (HCT 116–VM46) to vinblastine and doxorubicin.[32] Polycitone A (**12**) was found to be a potent inhibitor of retroviral transcriptases and cellular DNA polymerases,[27] while its penta-*O*-methyl derivative was found to inhibit the growth of SV40 transformed fibroblast cells at concentrations of 10 μg mL^{-1}.[17] Ningalin A (**20**), similar to lamellarin O (**1**), was found to lack cytotoxic activity, but proved to effectively reverse MDR.[31] Recently, compound **23**, which is a synthetic analogue of ningalins, was shown to be a potent MDR reversal agent that hypersensitizes P-gp-resistant tumour cell lines to front-line conventional therapeutic agents.[65]



In this regard, it is worth mentioning that some literature data indicate that exhaustive O-methylation of the lateral hydroxyl groups of marine alkaloids consisting of a pyrrole core surrounded by a periphery of polyoxygenated phenyl rings significantly reduces the cytotoxicity of these compounds, but leaves the capacity of MDR reversal virtually unchanged.[32,36,66] Moreover, for the storniamide A core structure **24**, it has been demonstrated that this chemical modification goes hand in hand with a complete loss of the DNA-cleaving capacity of the alkaloid.[66]





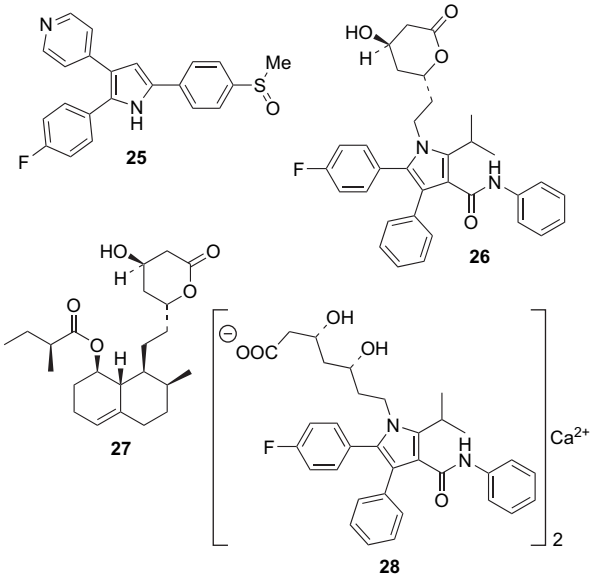
Several synthetic pyrrole derivatives with two (hetero)aryl groups on adjacent positions have also been shown to possess interesting biological and/or biomedical properties. Thus, 3-(4-pyridyl)-2-(4-fluorophenyl)-5-(4-methylsulfinylphenyl)-1*H*-pyrrole (**25**) was reported to be a potent, orally bioactive inhibitor of p38 mitogen-activated protein (MAP) kinase,[67] a family of serine/protein kinases that participate

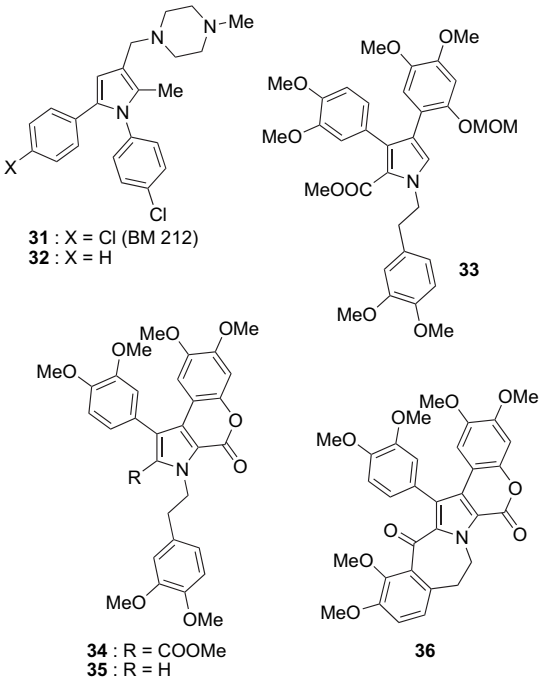
in signal transduction pathways controlling intracellular events, also involved in immunological and inflammatory disorders,[68–71a,72] including rheumatoid arthritis, inflammatory bowel disease, septic shock and osteoporosis, and that have recently been implicated in other disease states including Alzheimer's disease,[71b,c] cancer,[71d,e] asthma[73] and cardiovascular disease.[71f] 4,5-Diaryl-1*H*-pyrrole **26** is a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor fivefold more potent than the fungal metabolite compactin (mevastatin) (**27**) in vitro[74] and atorvastatin (**28**) is another hypolipidemic agent (CI-981)[20,21] currently marketed in the United States as LIPITOR. This last chiral 4,5-diarylpyrrole, in addition to its effect on lipoprotein profile, reduces triglycerides to a greater extent than other HMG-CoA reductase inhibitors.[21]

The pyridyl diaryl-1*H*-pyrrole **29**[75] has been reported to be a glucagon receptor antagonist, i.e., a substance able to block glucose production, and compounds **30a–c**[76] have also demonstrated good sugar-lowering activity. Thus, all these pyrrole derivatives might be used in a therapeutic approach to the treatment of diabetes.[77,78]

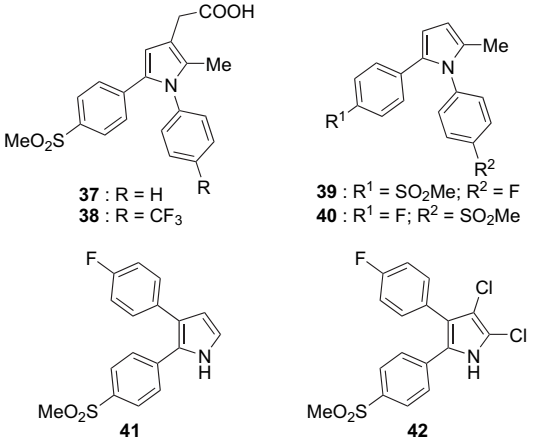
Compounds **31** (BM-212)[22] and **32**[23] have been described as antimicrobial agents. On the other hand, permethyl storniamide A (**22**),[32] and compounds **34**,[32] **33**,[36] **35**[36] and **36**,[36] like lamellarin D (**5**),[79] have been shown to be modulators of P-gp-mediated MDR.

Finally, 1,2-diaryl-1*H*-pyrroles **37**,[80] **38**,[80] **39**[81] and **40**[81] and 2,3-diaryl-1*H*-pyrroles **41**[82,83] and **42**[83] have been identified as cyclooxygenase-2 (COX-2)-selective inhibitors.[84]





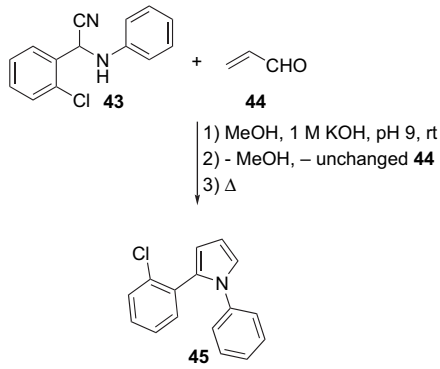
Interestingly, a correlation was found between the energy of the highest-occupied molecular orbital (E_{HOMO}) of anti-inflammatory 1,2-diaryl-1*H*-pyrroles and their COX-2 inhibition.[85] No correlation was, however, observed between E_{HOMO} and the inhibition efficiency of COX-1, the constitutively expressed enzyme, protective to organisms.[85] This result suggests that the inhibition of the two isomeric forms follows different molecular mechanisms.



2.2. Synthesis of pyrrole derivatives with two aryl groups on adjacent positions

2.2.1. Synthesis of 1,2-diaryl-1*H*-pyrroles. Several approaches have been described in the literature to the synthesis of 1,2-diaryl-1*H*-pyrroles. Thus, a low yielding procedure[86] involving the base-catalyzed condensation of a 2-(*N*-arylamino)-2-arylacetonitrile **43** with acrolein (**44**) was used to prepare 2-(2′-chlorophenyl)-1-phenyl-1*H*-pyrrole (**45**) (Scheme 1).[87]

Several other 1,2-diaryl-1*H*-pyrrole derivatives have been cleanly and more conveniently prepared in modest to high

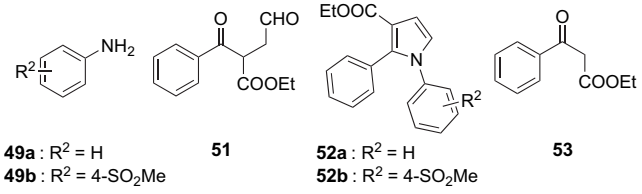


Scheme 1. Synthesis of 1,2-diaryl-1*H*-pyrrole **45**.

yields by Paal–Knorr condensation of 1,4-dicarbonyl compounds with appropriate arylamines.[23,80,81,88–90] The requisite 1,4-dicarbonyl compounds have often been obtained by the Stetter reaction,[91] which typically involves the reaction of aryl aldehydes with α,β-unsaturated ketones under cyanide or thiazolium salt catalysis. This approach was used for the efficient synthesis of a series of 1,2-diaryl-1*H*-pyrroles **50** having an alkyl group at position 5, which have been shown to be potent (IC_{50}=15–100 nM) and selective inhibitors of COX-2 (Scheme 2).[81]

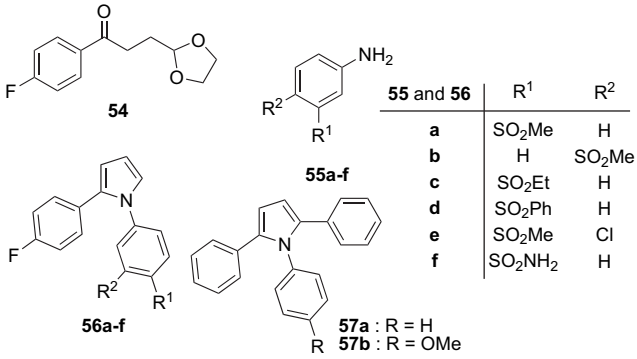
In particular, pyrroles **50** were prepared by condensation of arylamines **49** with 1,4-diketones **48** obtained by Stetter reaction of aryl aldehydes **46** with α,β-unsaturated ketones **47**.

Recently, ethyl 1,2-diaryl-1*H*-pyrrole carboxylates **52a** and **52b** have been analogously prepared by reaction of 3-ethoxycarbonyl-4-oxo-4-phenylbutanal (**51**) with anilines **49a** and **49b**, respectively, in ethanol in the presence of acetic acid.[90] The key synthon **51** was obtained by a three-step procedure starting from β-ketoester **53**.[90]



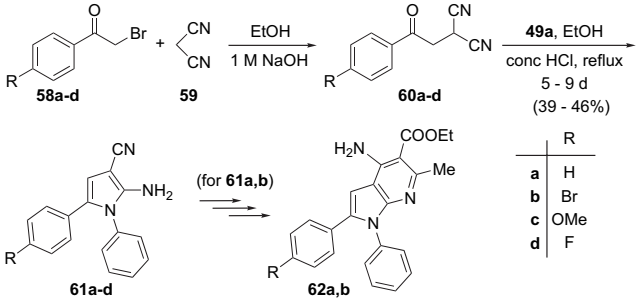
On the other hand, a Paal–Knorr-type reaction of 1,4-ketoacetal **54** with anilines **55a–f** in toluene in the presence of *p*-toluenesulfonic acid was used to synthesize some 1-(4-fluorophenyl)-2-aryl-1*H*-pyrroles **56a–f** in 50–70% yield.[81]

In 2005, the 5-alkyl-1,2-diaryl-1*H*-pyrroles **50a** (R=H) and **50b** (R=OMe) and the 1-aryl-2,5-diphenyl-1*H*-pyrroles **57a**,**b** have been prepared by Banik and co-workers using a modification of the Paal–Knorr reaction in which an arylamine is reacted with a 1,4-diketone in CH_2Cl_2 at room temperature in the presence of 5 mol % bismuth nitrate.[92]

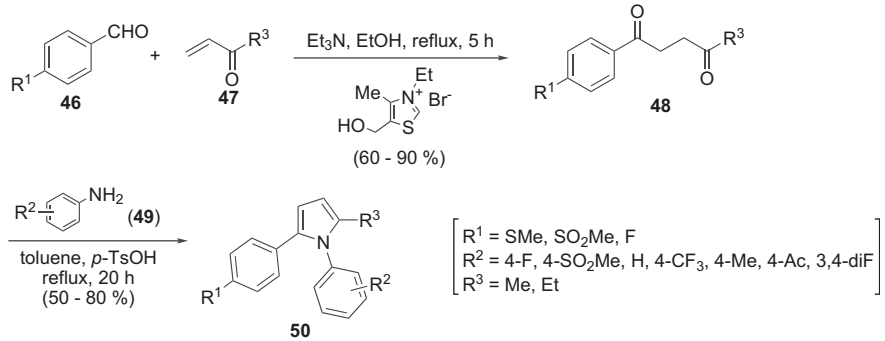


This modification, which requires very mild experimental conditions, has been shown to be much superior to the strong Lewis acid- or other strong acid-mediated syntheses of pyrroles in terms of the yields of the products. Moreover, unlike many other procedures, it does not require an extra energy source, like microwave irradiation or ultrasound.

In 2004, 1,2-diaryl-1*H*-pyrroles **61a–d**, which contain amino and cyano groups, have been synthesized in 39–46% yield by the reaction of the corresponding phenacylmalononitrile derivatives **60a–d** with aniline (**49a**) in absolute ethanol in the presence of catalytic amounts of concd HCl (Scheme 3).[93] Compounds **60a–d** have been prepared by treatment of phenacyl bromides **58a–d** with malononitrile (**59**) in ethanol in the presence of 1 M NaOH.[93,94] The pyrrole derivatives **61a** and **61b** have been used as precursors to two new pyrrolo[2,3-*b*]pyridines **62a** and **62b**, respectively, which are potent inhibitors of tumour necrosis factor.[93]

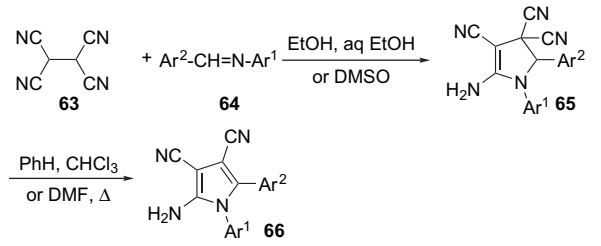


Scheme 3. Synthesis of compounds **61a–d** and **62a**,**b**.



Scheme 2. Synthesis of 5-substituted 1,2-diaryl-1*H*-pyrroles **50**.

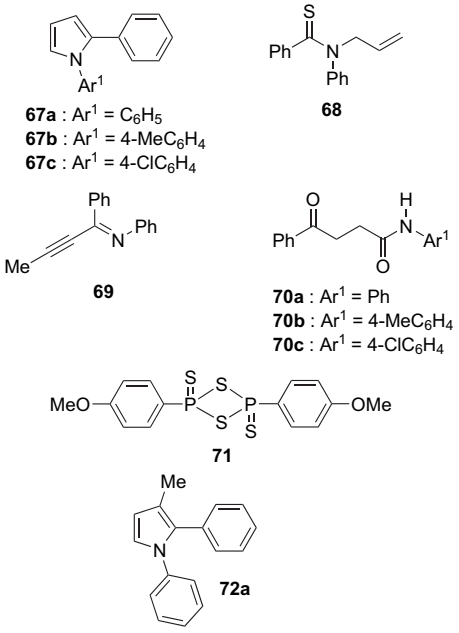
The synthesis of a great number of pyrroles of general formula **66**, which is similar to compounds **61** contain amino and cyano groups, had been previously performed in 88–98% yield by the reaction of tetracyanoethane (**63**) with the Schiff bases **64** in ethanol, aqueous ethanol or DMSO. The reaction produces tricyanodihydropyrroles **65** as intermediates, which lose hydrogen cyanide on heating in benzene, $CHCl_3$ or DMF to give the required pyrroles (Scheme 4).[95,96]



[Ar^1 = Ph, 4-HOC_6H_4, 4-ClC_6H_4, 2-pyridyl; Ar^2 = Ph, 2-HOC_6H_4, 2-furyl]

Scheme 4. Synthesis of compounds **66**.

In 1995, a two-step procedure involving the S-methylation of *N*-allyl-*N*-phenylthiobenzamide (**68**), followed by treatment of the resulting thioamidate salt with LHMDS was developed to prepare 1,2-diphenyl-1*H*-pyrrole (**67a**).[97]

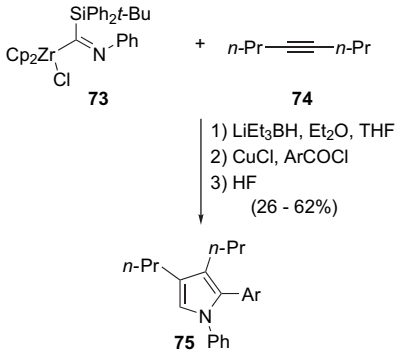


This compound was subsequently prepared in 86% yield by CuI-assisted cycloisomerization of the readily available imine **69**.[98] This procedure, which entirely satisfies the atom economy requisite, was also applied to the preparation of other 1,2-disubstituted and some 1,2,5-trisubstituted 1*H*-pyrroles.[98]

In 1998, Nishio reported that 1,2-diaryl-1*H*-pyrroles **67a–c** could be obtained in modest yields (35–48%) by reaction of the corresponding 4-ketoamides **70a–c** with an equimolar amount of Lawesson's reagent **71** in toluene at reflux temperature under argon.[99]

More recently, 3-methyl-1,2-diphenyl-1*H*-pyrrole (**72a**) and other polysubstituted 1*H*-pyrroles have been prepared in 50–91% yield by hydrogenolysis of the aldol products formed by reaction between α-(*N*-benzyl or *N*-Cbz)amino aldehydes and lithium enolates of various ketones.[100]

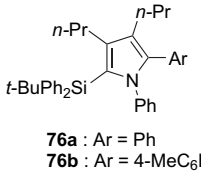
On the other hand, four tetrasubstituted 2-aryl-1-phenyl-1*H*-pyrroles of general formula **75** and some pentasubstituted pyrrole derivatives have been synthesized in low to modest yield via a CuCl-mediated one-pot reaction of acyl halides with the azazirconacyclopentene prepared from the iminosilacyl complex **73** and 4-octyne (**74**) (Scheme 5).[101]



[Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4]

Scheme 5. One-pot synthesis of compounds **75**.

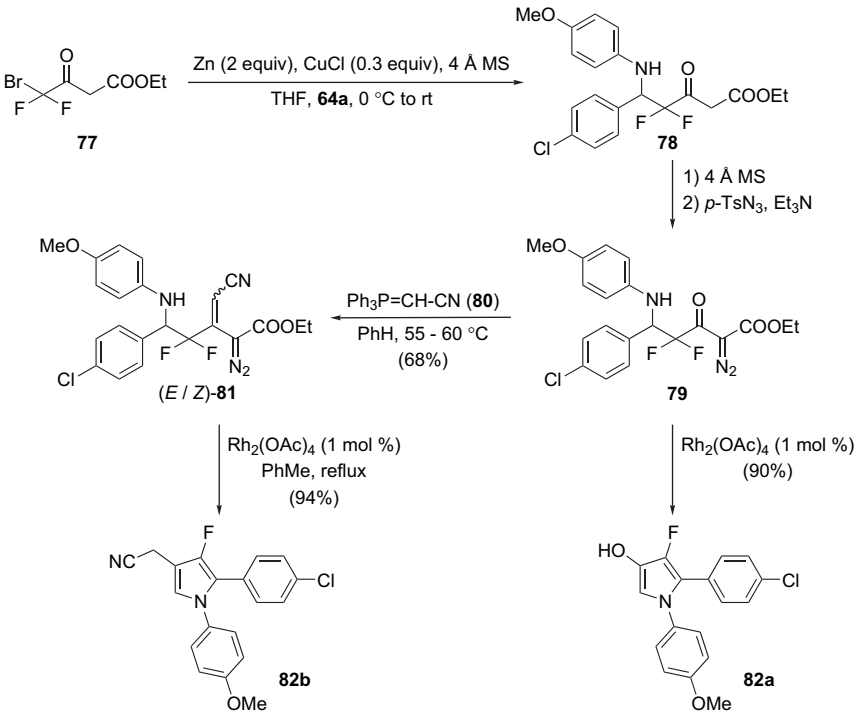
Interestingly, a catalytic amount of CuCl was found to be effective for this reaction.[101] Moreover, it was observed that, when the crude reaction mixture was treated with silica gel instead of HF, compounds **76a** and **76b** could be obtained in 50 and 55% yield, respectively.[101]



76a : Ar = Ph
76b : Ar = 4-MeC_6H_4

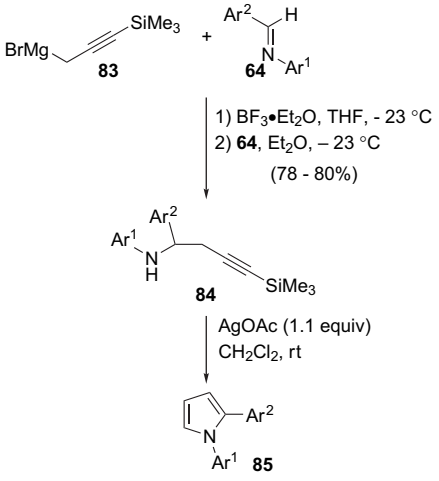
Wang and Zhu prepared the 1,2-diaryl-3-fluoro-1*H*-pyrroles **82a** and **82b** by $Rh_2(OAc)_4$-catalyzed intramolecular NH insertion of α-diazo-β-ketoester **79** and vinyldiazomethane **81**.[102] In particular, compound **82a** was synthesized in 94% yield by intramolecular NH insertion of vinyldiazomethane **79**, obtained, in good yield, by diazo transfer of compound **78** with tosyl azide and triethylamine. Compound **78** was, in turn, obtained from β-ketoester **77** and aldimine **64a** (Ar^1=4-MeC_6H_4; Ar^2=4-ClC_6H_4) (Scheme 6).[102] Compound **82b** was obtained by a Wittig reaction of the α-diazo-β-ketoester **79** with triphenylphosphoranylideneacetonitrile **80** to give the vinyldiazomethane **81** and a subsequent Rh(II)-catalyzed NH insertion (Scheme 6). Other polyfunctionalized 1,2-di(hetero)aryl-1*H*-pyrroles were obtained by similar reaction sequences from **77** and suitably substituted aldimines **64**.[102]

In 2004, Agarwal and Knölker[103] reported a novel procedure for pyrrole annulation via silver(I)-promoted oxidative cyclization of homopropargylamines **84**. This procedure, in which compounds **84** are easily prepared by addition of a propargyl Grignard reagent to the appropriate Schiff bases, has been used for the synthesis in high yields of



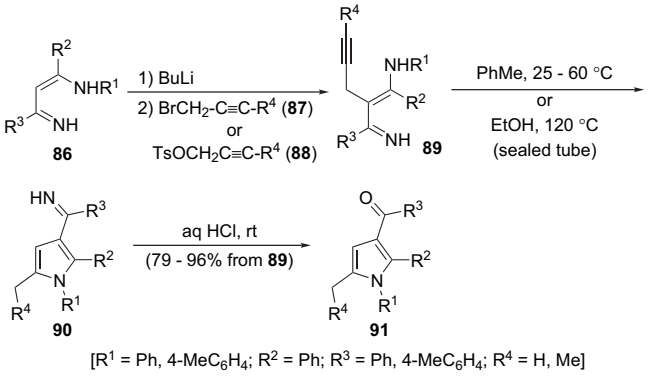
Scheme 6. Synthesis of compounds **82a–b**.

1,2-diarylpyrroles **85** starting from the Grignard reagent **83** and aldimines **64** (Scheme 7).[103]



Scheme 7. Synthesis of 1,2-diaryl-1*H*-pyrroles **85** from compounds **64** and **83**.

Previously, Barluenga and co-workers[104] had developed an efficient approach to 3-functionalized pyrroles **91** via propargylation/cycloamination of propargylazadienes **89** obtained in multigram quantities by metalation of azadienes **86**[105] with *n*-butyllithium, followed by C-alkylation with propargyl bromide **87** (R^4=H) or 2-butynyl *p*-toluenesulfonate (**88**) (R^4=Me) (Scheme 8). Interestingly, the primary cycloamination products **90** could not be isolated in pure form because of their easy hydrolysis when subjected to purification by column chromatography.[104] Their imine function could, however, be acylated or reduced in situ.[104]



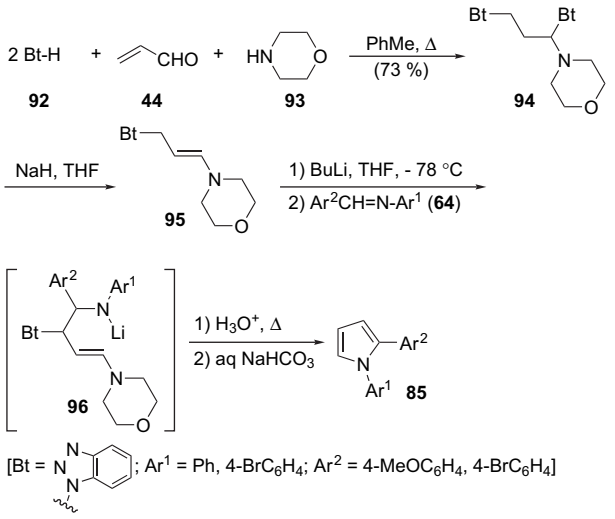
Scheme 8. Synthesis of 1,2-diaryl-1*H*-pyrroles **91**.

Some interesting procedures for the synthesis of a series of 1,2-diaryl-1*H*-pyrroles, which are based on the strong electron-withdrawing ability and nucleofugicity of the benzotriazolyl (Bt) group of benzotriazole derivatives, were developed by Katritzky and co-workers.[106–109] Despite the fact that these procedures are lengthy and do not fulfil the atom economy requisite, they were shown to be quite versatile and allowed the preparation of compounds not easily and conveniently available by other synthetic approaches.

In particular, in 1995, Katritzky and co-workers reported that 1-(3-morpholinoprop-2-enyl)benzotriazole (**95**), which can be prepared in quantity by a two-step procedure involving treatment of acrolein (**44**) with 2 equiv of benzotriazole (**92**) and 1 equiv of morpholine (**92**) and subsequent elimination of one benzotriazole moiety from **94** on treatment with NaH, is a valuable precursor of 1,2-diaryl-1*H*-pyrroles **85**.[106]

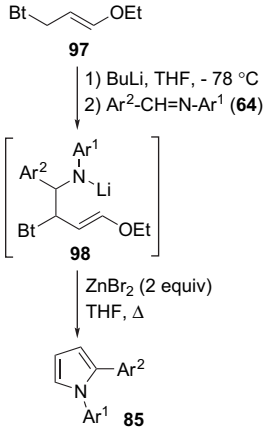
In fact, reaction of **95** with butyllithium, followed by addition of diarylimines **64** and brief heating in the presence of

a catalytic amount of sulfuric acid, provided the required pyrroles in 60–68% total yield via **96** (Scheme 9).[106]



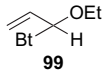
Scheme 9. Synthesis of 1,2-diaryl-1*H*-pyrroles **85** from compounds **44**, **92** and **93**.

In the same year, the same group expanded the synthetic applications of the benzotriazole derivatives and described that 1,2-diaryl-1*H*-pyrroles **85** can also be prepared regioselectively and in satisfactory yields by an approach involving treatment of 3-(benzotriazol-1-yl)-1-ethoxyprop-1-ene (**97**) with butyllithium at −78 °C, followed by addition of diarylimines **64** and heating of the resulting compounds **98** in the presence of $ZnBr_2$ (Scheme 10).[107]



Scheme 10. Synthesis of 1,2-diaryl-1*H*-pyrroles **85** from compounds **64** and **97**.

Compound **97**, which was the C_3 fragment in this [3+2] pyrrole synthesis, was prepared in 95% yield by reaction of 3-(benzotriazol-1-yl)-3-ethoxyprop-1-ene (**99**) with 1 equiv of $ZnBr_2$ in THF at room temperature.[107]

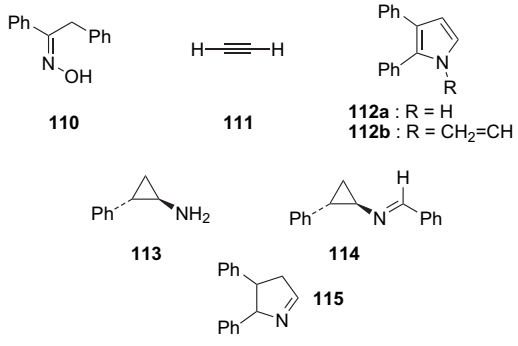


More recently, the synthesis of numerous compounds of general formula **85** and 1,2-diaryl-3-methyl-1*H*-pyrroles **72a**,**b** has been accomplished by a two-step procedure from imines **64** and *N*-allylbenzotriazole (**100**) and 2-(buten-3-yl)benzotriazole (**102**), respectively, via Pd(II)-catalyzed intramolecular oxidative cyclization (Scheme 11).[108] In particular, 1,2-diaryl-1*H*-pyrroles **85a–l** were prepared by oxidative cyclization of compounds **101** obtained by lithiation of **100** followed by treatment with imines **64**. On the other hand, 1,2-diaryl-3-methyl-1*H*-pyrroles **72a**,**b** were synthesized by intramolecular oxidative cyclization of compounds **103** prepared by lithiation of 2-(buten-3-yl)benzotriazole (**102**) and subsequent reaction with aldimines **64**. Interestingly, the yields of compounds **85a–l** were found to depend dramatically on the nature of the substituents in both the aromatic rings of imines **64**. In fact, a halogen in the *para*- or *meta*-position of these rings facilitated significantly the reaction, and the presence of electron-donor substituents, e.g., MeO, caused the opposite effect. On the contrary, the electron-donating or electron-withdrawing properties of a heterocyclic moiety did not have a significant effect on the yield of the resulting pyrrole derivatives.[108]

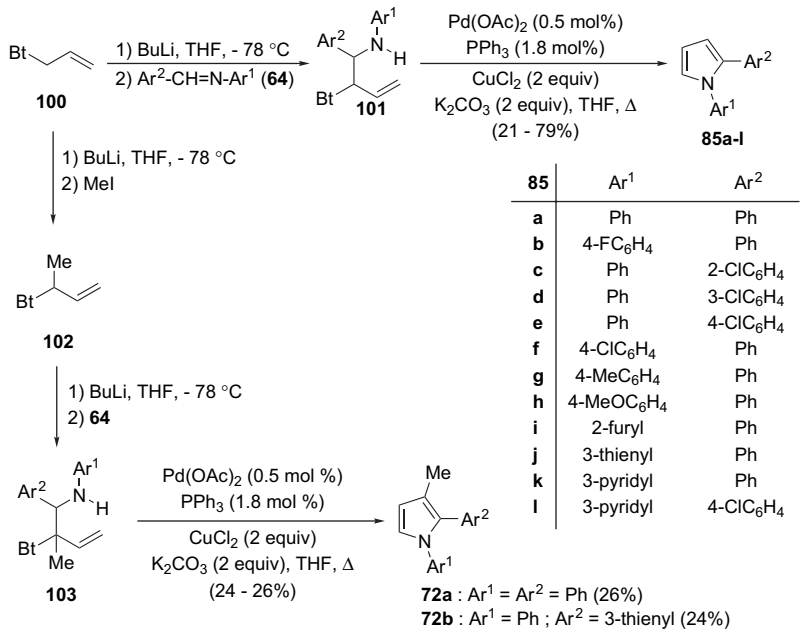
It should be noted that the benzotriazole synthetic methodology had also been previously used for the synthesis of the tetrasubstituted 1,2-diaryl-1*H*-pyrroles **109a** and **109b** from the acetylene dicarboxylates **108** and the 1,3-diaryl-2-(benzotriazol-1-yl)aziridines **106a** and **106b**, respectively, presumably via formation of azomethines **107a**,**b** (Scheme 12).[109]

Compounds **106a**,**b** were obtained in high yield by the reaction of 1-chloromethylbenzotriazole (**104**) with LHMDS in THF/HMPA at −20 °C, followed by treatment with imines **105**.[109]

2.2.2. Synthesis of 2,3-(4,5-)diaryl-1*H*-pyrroles. In 1978, 2,3-diphenyl-1*H*-pyrrole (**112a**) was prepared in 78% yield by the Trofimov reaction between oxime **110** and acetylene (**111**) under atmospheric pressure at 100 °C in DMSO in the presence of KOH.[110–112] When the initial pressure of **111** was 10–14 atm, however, the reaction furnished 2,3-diphenyl-1-vinyl-1*H*-pyrrole (**112b**) in 73% yield.[110,111]

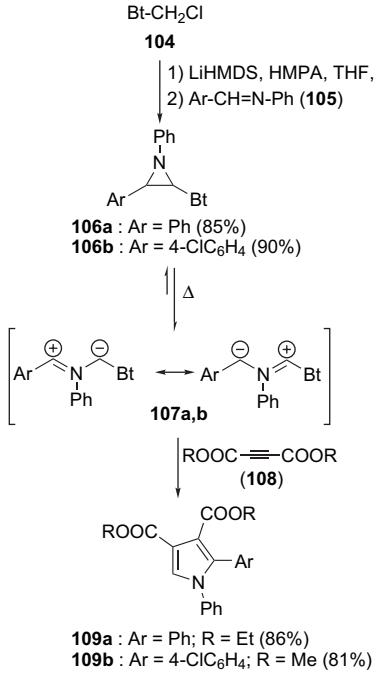


More recently, **112a** has been synthesized in 65% overall yield via photochemical rearrangement of *N*-cyclopropylimine **114**, followed by oxidation during the workup of the resulting crude 1-pyrroline **115**.[112] Imine **114** was obtained by reaction of commercially available *trans*-2-phenylcyclopropylamine (**113**) with benzaldehyde in refluxing toluene with occasional addition of molecular sieves.[112]

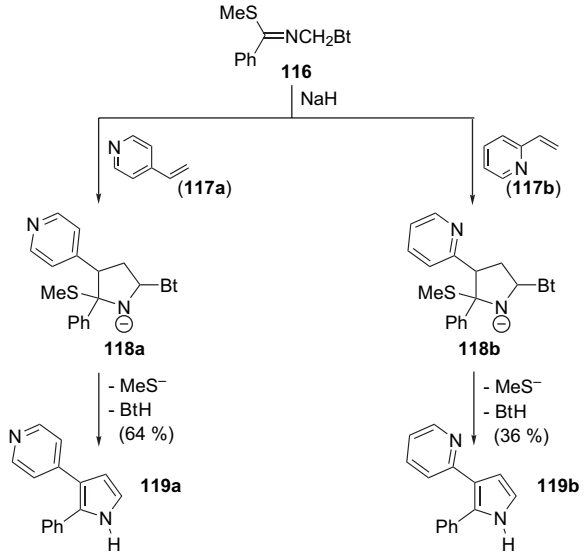


85	Ar^1	Ar^2
a	Ph	Ph
b	4-FC_6H_4	Ph
c	Ph	2-ClC_6H_4
d	Ph	3-ClC_6H_4
e	Ph	4-ClC_6H_4
f	4-ClC_6H_4	Ph
g	4-MeC_6H_4	Ph
h	4-$MeOC_6H_4$	Ph
i	2-furyl	Ph
j	3-thienyl	Ph
k	3-pyridyl	Ph
l	3-pyridyl	4-ClC_6H_4

Scheme 11. Synthesis of 1,2-diaryl-1*H*-pyrroles **85** and 1,2-diaryl-3-methyl-1*H*-pyrroles **72** from *N*-allylbenzotriazole **100**.



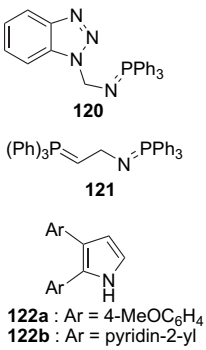
Scheme 12. Synthesis of compounds **109a** and **109b**.



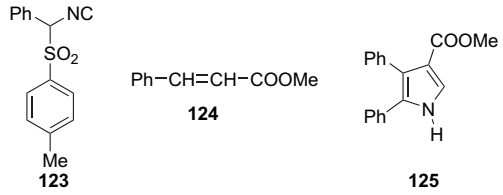
Scheme 13. Synthesis of compounds **119a** and **119b**.

2-Phenyl-3-(pyridin-4-yl)-1*H*-pyrrole (**119a**) and 2-phenyl-3-(pyridin-2-yl)-1*H*-pyrrole (**119b**) had been previously synthesized in 64 and 36% yield, respectively, by [3+2] cycloaddition reactions of *S*-methyl *N*-(benzotriazol-1-ylmethyl)thioimidate (**116**) with the vinylpyridines **117a** and **117b**, followed by spontaneous elimination of benzotriazole and the thioalkoxy group (Scheme 13).[113]

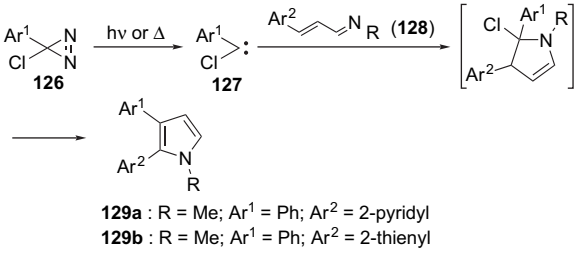
On the other hand, 1,2-diphenyl-1*H*-pyrrole (**112a**), 2,3-bis(4-methoxyphenyl)-1*H*-pyrrole (**122a**) and 2,3-di(2-pyridin-2-yl)-1*H*-pyrrole (**122b**) were conveniently prepared in 67, 75 and 58% yield, respectively, by a Wittig/aza-Wittig reaction of the required 1,2-diketones with 1-aza-1,3-bis(triphenylphosphoranylidene)propane (**121**). This compound was synthesized in situ by treatment of 1-{[(triphenylphosphoranylidene)amino]methyl}-benzotriazole (**120**) with methylidenetriphenylphosphorane, followed by reaction with butyllithium.[114a,b]



The synthesis of disubstituted 2,3-diaryl-1*H*-pyrroles different from **112a**, **119a**,**b** and **122a**,**b** has not been explored. On the contrary, since 1972, the development of efficient and/or simple protocols for the preparation of trisubstituted 2,3-diaryl-1*H*-pyrroles has received great attention. Specifically, 2,3-diphenyl-4-(methoxycarbonyl)-1*H*-pyrrole (**125**) was synthesized in 23% yield by an elegant approach based on van Leusen's chemistry, which involves treatment of α-tosylbenzyl isocyanide (**123**)[115] with the α,β-unsaturated ester **124** in Et_2O/DMSO in the presence of 1.2 equiv of NaH.[116]



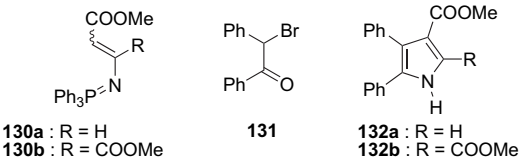
On the other hand, some 1,2,3-trisubstituted-1*H*-pyrroles that included 1-methyl- and 1-benzyl-2,3-diaryl-1*H*-pyrrole were synthesized in satisfactory yields by a method involving the reaction of arylchlorocarbenes with 1-azabuta-1,3-dienes.[117,118] In particular, arylchlorocarbenes **127**, generated by photolysis or thermolysis of arylchlorodiazirines **126**, were reacted with 1-azabuta-1,3-dienes **128** to give pyrroles **129** via, presumably, the dihydropyrrole derivatives (Scheme 14).[117] 3,4-Diaryl-1*H*-pyrroles **129** were prepared in 40–65% total yield via thermolysis of **126** and in 30–50% total yield via photolysis of these three-membered heterocycles.[117]



Scheme 14. Synthesis of compounds **129**.

The 2-aryl-3-heteroaryl-1-methyl-1*H*-pyrroles **129a**,**b** were, however, obtained only in 14–15% yield by flash photolysis of the corresponding heteroarylchlorodiazirines in the presence of the required 1-azabuta-1,3-dienes.[118]

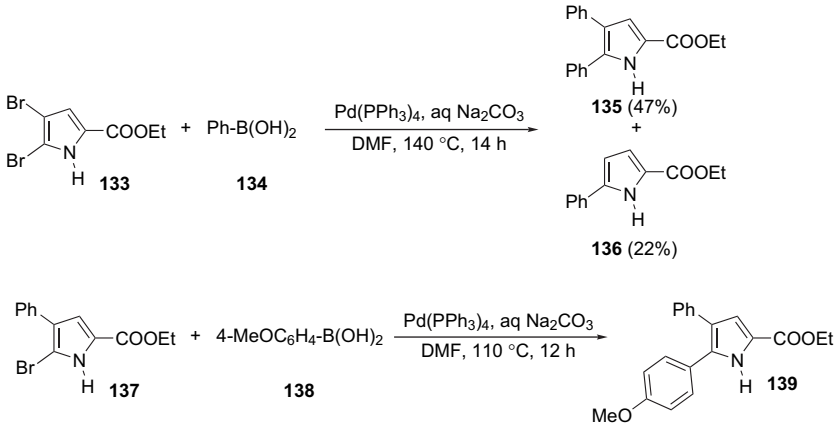
In 2002, the trisubstituted 2,3-diaryl-1*H*-pyrrole **132a** and the tetrasubstituted 2,3-diaryl-1*H*-pyrrole **132b** were synthesized in 43 and 57%, respectively, by reaction of *N*-vinylic phosphazenes **130a** and **130b** with α-bromoketone **131** in toluene at 110 °C in the presence of Et_3N.[119] This procedure was also used for the synthesis of three disubstituted 1*H*-pyrroles in satisfactory yields.[119]



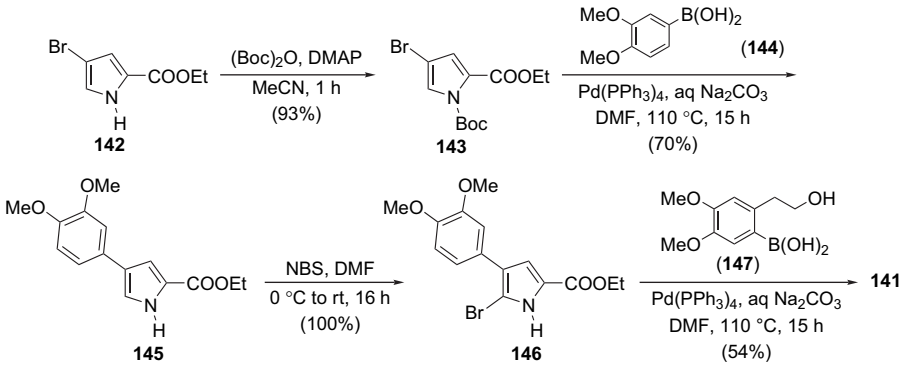
Sometimes, Pd-catalyzed cross-coupling reactions involving organometallic compounds and halopyrroles have also been used to access 2,3- (4,5-)diaryl-1*H*-pyrrole derivatives. Thus, Pd-catalyzed Suzuki-type reactions have been used for the synthesis of the trisubstituted 4,5-diaryl-1*H*-pyrroles **135** and **139** from dibromopyrrole **133** and bromopyrrole **137**, respectively (Scheme 15).[120] Interestingly, the cross-coupling reaction between **133** and phenylboronic acid (**134**) provided **135** along with a significant amount of the monoarylated pyrrole **136**.[120] This last compound most likely derived from a Suzuki-type reaction involving 2-bromo-5-ethoxycarbonyl-1*H*-pyrrole formed by selective dehalogenation of **133** during the Pd-catalyzed cross-coupling reaction.

On the other hand, the Pd-catalyzed reaction between **137** and arylboronic acid **138** furnished cleanly the diaryl-1*H*-pyrrole derivative **139** in 74% yield.

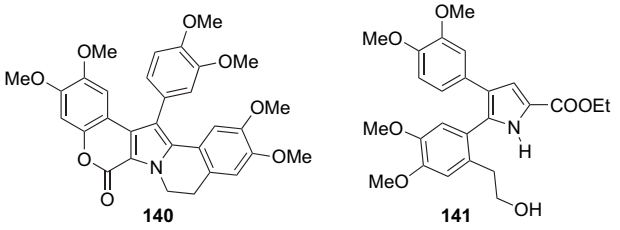
In 2004, a 4,5-diaryl-1*H*-pyrrole 2-carboxylic acid ethyl ester **141** was prepared via regioselective halogenation/Pd-catalyzed cross-coupling reactions in the course of a study concerning the total synthesis of lamellarin G trimethyl ether (**140**) (Scheme 16).[121]



Scheme 15. Synthesis of compounds **135**, **136** and **139**.



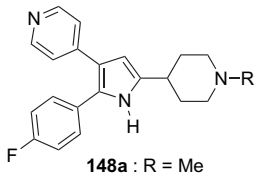
Scheme 16. Synthesis of compound **141**.



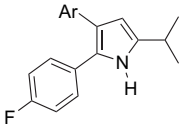
Specifically, the bromopyrrole ester **142**, prepared in three steps from pyrrole,[121] was protected as the corresponding *tert*-butyl carbamate to give **143** in 93% yield. It was necessary to perform this reaction prior to a Pd-catalyzed Suzuki-type reaction, since it had been previously found that the nitrogen of **142** must be protected to avoid extensive dehalogenation during the cross-coupling reaction.[121] In fact, the Suzuki-type reaction of **143** with 2–3 equiv of boronic acid **144** proceeded cleanly to give **145** in 70% yield. Treatment of this compound with an equimolar amount of *N*-bromosuccinimide led cleanly to the 5-bromo derivative **146**, which was finally coupled with boronic acid **147** under standard Suzuki-coupling conditions to give **141** in 54% yield (Scheme 16).[121]

Several 2-aryl-3-(4-pyridyl)-5-(*N*-substituted)piperidyl-1*H*-pyrroles have been synthesized by reaction of the corresponding 1,4-dicarbonyl compounds with ammonium acetate in acetic acid at 110 °C.[122] More recently, these trisubstituted pyrrole derivatives have been evaluated as inhibitors of *Eimeria tenella* cGMP-dependent protein kinase and in vivo anticoccial assays and, among these substances, compounds **148a** and **148b** have been shown to be the most potent and have demonstrated a broad spectrum of activity.[123]

Previously, in the context of a study concerning the development of novel potent inhibitors of HMG-CoA reductase, a Paal–Knorr condensation had been used to prepare the trisubstituted pyrroles **149a–c**, free of the corresponding regioisomers.[124,125]

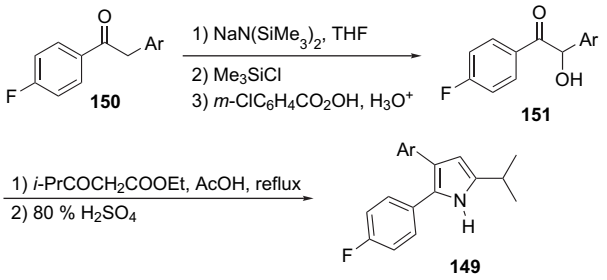


148a : R = Me
148b : R = Et



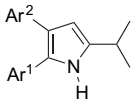
149a : Ar = 4-pyridyl
149b : Ar = 2-pyridyl
149c : Ar = 4-pyridyl-*N*-oxide
149d : Ar = 4-FC_6H_4

Some compounds of general formula **149** were alternatively obtained by hydroxylation of 4-fluorophenyl ketones **150**, followed by cyclocondensation of the resulting benzoins **151** with ethyl isobutyrylacetate in the presence of ammonium acetate in refluxing acetic acid (Scheme 17).[125] Compound **149d** was so prepared in % yield from **151a** (Ar=4-F–C_6H_4).



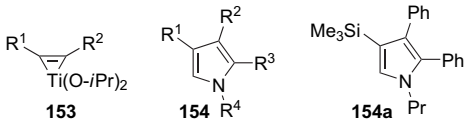
Scheme 17. Synthesis of compounds **149**.

When unsymmetrical benzoins were, however, used, both 5- and 4-(fluorophenyl)-1*H*-pyrroles **152a** and **152b** were formed in an approximate ratio of 9:1.[125]

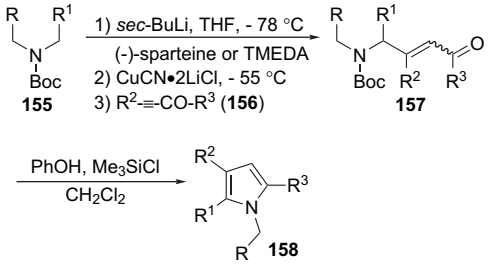


152a : Ar^1 = 4-FC_6H_4; Ar^2 = 4-pyridyl, 2-pyridyl, 4-pyridyl-*N*-oxide
152b : Ar^1 = 4-pyridyl, 2-pyridyl, 4-pyridyl-*N*-oxide; Ar^2 = 4-FC_6H_4

To the best of our knowledge, only four methods have been reported in the literature for the synthesis of tetrasubstituted 2,3-diaryl-1*H*-pyrroles.[119,126–128] The first method, which was used for the preparation of **132b**, has been previously discussed. The second method was developed in 1996 by Sato and co-workers[126] in the context of the one-pot synthesis of substituted pyrroles **154**, which included the tetrasubstituted 2,3-diaryl-1*H*-pyrrole **154a**. This convenient method allowed the preparation of the required compounds in good-to-excellent yields from the titanium–acetylene complexes **153**.[126]

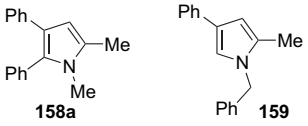


The third method was subsequently designed and developed by Dieter and Yu, who synthesized some polysubstituted pyrroles **158** by conjugate addition of *N*-protected α-aminoalkylcuprates derived from amines **155** to alkynyl ketones **156**, followed by amine deprotection and cyclization of the resulting adducts **157** (Scheme 18).[127]



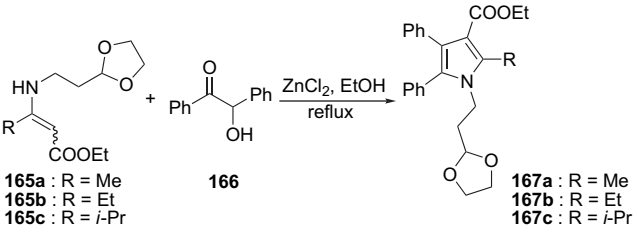
Scheme 18. Synthesis of polysubstituted pyrroles **158**.

This protocol, which exhibits a broad scope, was also used to prepare in 50% yield a mixture of the tetrasubstituted pyrrole **158a** and the trisubstituted pyrrole **159** in which **158a** was the major component.[127]

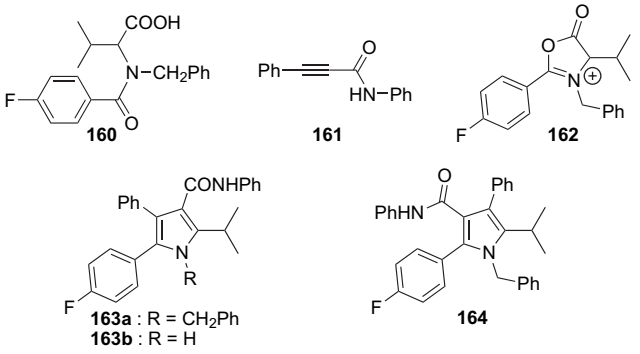


In 2004, Pandey and Rao developed the fourth method for the synthesis of tetrasubstituted 2,3-diaryl-1*H*-pyrroles.[128] These authors prepared efficiently and economically compound **163b**, which was used as a key intermediate for the synthesis of the HMG-CoA reductase inhibitor atorvastatin (**28**).[128] A key step of this method was the 1,3-dipolar cycloaddition reaction of mesoionic münchnone (1,3-oxazolium-5-olate) **162**, derived from cyclodehydration of **160**, with *N*-1,3-diphenyl-2-propynamide (**161**). This reaction furnished in 80% yield a mixture of the regioisomers **163a** and **164** in a 1:1 ratio, which were easily separated by crystallization. Regioisomerically pure **163a** could be easily debenzylated using sodium in liquid ammonia in the presence of *t*-BuOH at −78 °C to give **163b** in 83% yield.[128]

On the contrary, the development of methods useful for the synthesis of pentasubstituted 2,3-(4,5-)diaryl-1*H*-pyrroles has received little attention. In 1991, two of these compounds containing an ester group at position 4, i.e., **167a** and **167b**, were synthesized in 75 and 36% yield, respectively, by $ZnCl_2$-catalyzed condensation of benzoin (**166**) with enamines **165a** and **165b** (Scheme 19).[129]

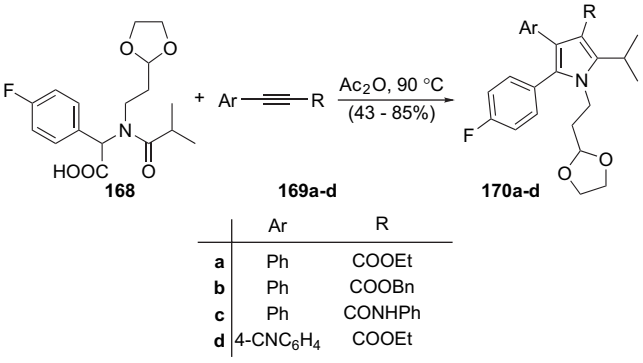


Scheme 19. Synthesis of pentasubstituted pyrroles **167a–c**.



These last compounds were prepared from (2-aminoethyl)-1,3-dioxolane[130] and the requisite β-ketoesters. The procedure used to prepare **167a** and **167b**, however, proved to be ineffective for the synthesis of the more sterically hindered pyrrole **167c**, which was obtained from **165c** in 4% yield (Scheme 19).[129]

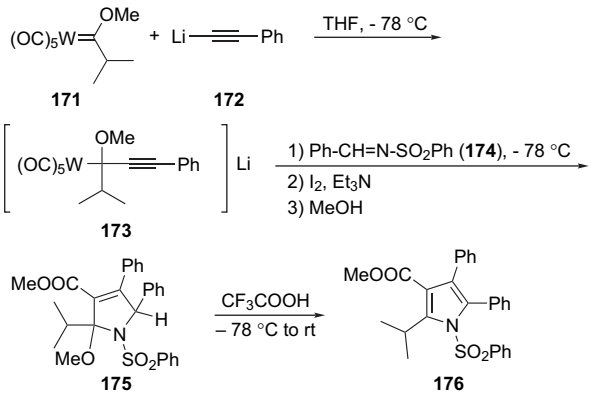
Four additional pentasubstituted 2,3-diaryl-1*H*-pyrroles containing an ester or an amide group at position 4, i.e., compounds **170a–d**, were regioselectively synthesized by [3+2] cycloaddition of the readily available amidoacid **168** with acetylenes **169a–d** (Scheme 20).[129] Compounds **167a–c** and **170a–d** were then elaborated at their position 1 to give derivatives able to inhibit the enzyme HMG-CoA reductase.[129]



	Ar	R
a	Ph	COOEt
b	Ph	COOBn
c	Ph	CONHPh
d	4-CNC_6H_4	COOEt

Scheme 20. Synthesis of pentasubstituted pyrroles **170a–d**.

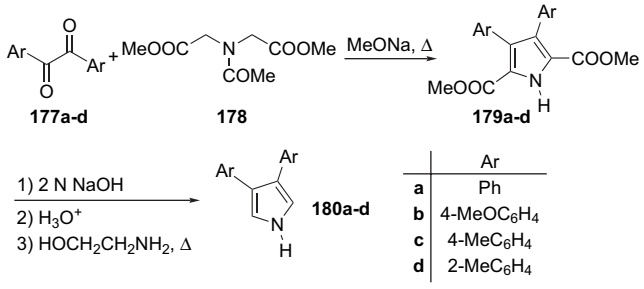
More recently, the pentasubstituted 2,3-diaryl-1*H*-pyrrole **176** has been prepared in 70% yield using a highly efficient method for the synthesis of fully substituted five-membered heterocycles from tungsten carbene complexes.[131] Specifically, complex **171** was first reacted with 1-lithium-1-alkyne **172** at −78 °C and the resulting compound **173** was then treated with sulfonylimine **174**. The iodine oxidation of the resulting crude reaction product gave dihydropyrrole **175**, which was then treated with trifluoroacetic acid to produce pyrrole **176** (Scheme 21).[131]



Scheme 21. Synthesis of compound **176**.

2.2.3. Synthesis of 3,4-diaryl-1*H*-pyrroles. 3,4-Diaryl-1*H*-pyrrole moieties appear frequently in naturally occurring compounds, such as lamellarins,[12] lukianols,[13] ningalins,[14] storniamides[15] and their congeners, that elicit important biological responses. The biological activities of 3,4-diaryl-1*H*-pyrrole derivatives have made them popular synthetic targets and numerous methods for the synthesis of these heterocycle derivatives have been developed.

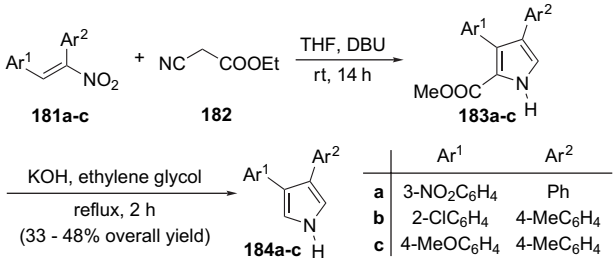
Several years ago, compounds **180a–d** were prepared in 45, 57, 41 and 2.5% overall yield by reaction of dimethyl *N*-acetyliminodiacetate (**178**) with benzyls **177a–d** in the presence of sodium methoxide, followed by hydrolysis and decarboxylation of the resulting pyrrole dicarboxylic acid esters **179a–d** (Scheme 22).[132a] Notable is that two 2,5-diamidopyrroles synthesized from diester **179a** have recently been shown to function as effective receptors for oxoanions.[132b]



Scheme 22. Synthesis of 3,4-diaryl-1*H*-pyrroles **180a–d**.

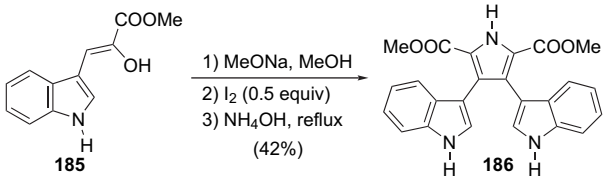
Compound **180a** was also subsequently prepared by the reaction of β-nitrostyrene (**181a**) with aqueous $TiCl_3$.[133,134] Although THF was used as the solvent in the original literature, in 1988 it was reported that replacement of THF with dioxane increases the yield of **180a** from 25 to 50%.[134] This modified procedure was used to prepare several other 3,4-diaryl-1*H*-pyrroles in 19–50% yield from the corresponding β-nitrostyrenes.

3,4-Diaryl-1*H*-pyrroles **184a–c** were prepared in low to modest yields from the α-nitrostyrenes **181a–c** and ethyl isocyanoacetate (**182**) by the Barton–Zard pyrrole synthesis and treatment of the resulting pyrrole carboxylic methyl esters **183a–c** with KOH in refluxing ethylene glycol (Scheme 23).[134–136]



Scheme 23. Synthesis of unsymmetrical 3,4-diaryl-1*H*-pyrroles **184a–c**.

The synthesis of lycogalic acid A dimethyl ester (**186**), also named lycogarubin C, which is a metabolite isolated from the fruit bodies of the myxomycete *Lycogala epidendrum*,[137] was accomplished by a one-pot reaction involving the oxidative coupling of two molecules of methyl 3-(indol-3-yl)-pyruvate (**185**) and the Paal–Knorr condensation of the resulting crude 1,4-diketone with ammonium hydroxide (Scheme 24).[138]

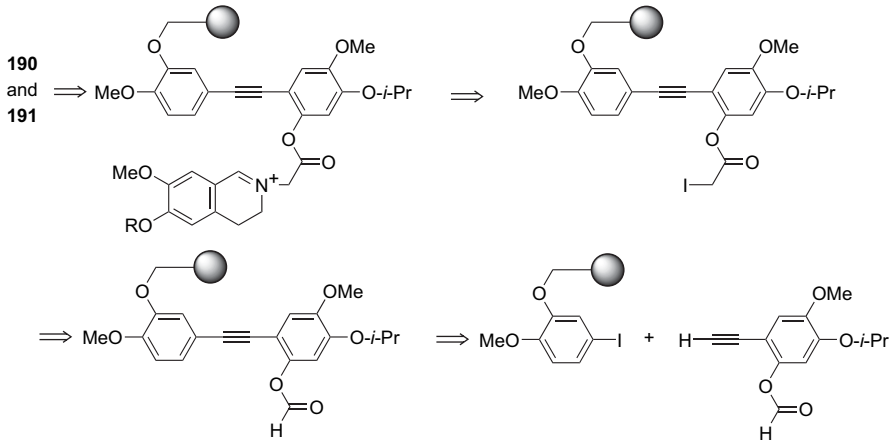


Scheme 24. Synthesis of lycogalic acid A dimethyl ester (**186**).

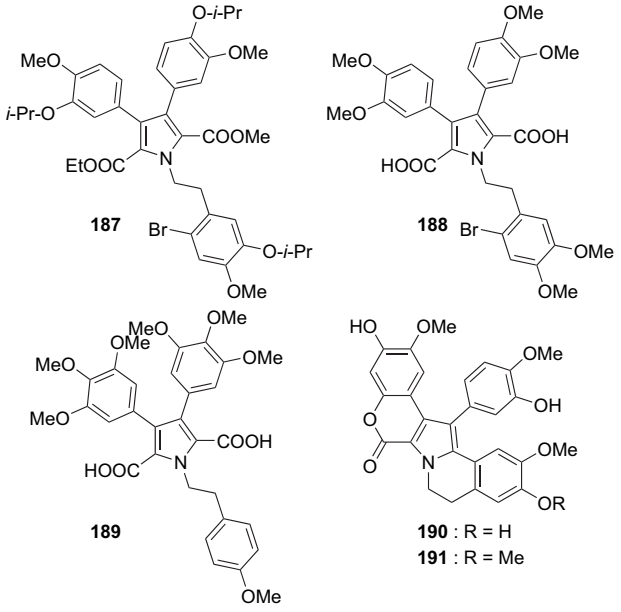
The first total synthesis of ningalin A (**20**),[139] a biomimetic synthesis of some 3,4-diaryl-1-pyrrole-2,5-dicarboxylic acids[140] and the preparation of compounds **187**,[35] **188**[141] and **189**[142] were analogously performed by oxidative dimerization of the required arylpyruvic acids, followed by condensation of the resulting 1,4-dicarbonyl compounds with the suitable 2-arylethylamines. The pyrrole derivatives **187**, **188** and **189**, prepared in 53, 62 and 56% yield, respectively, were then used as precursors to lamellarin L (**190**),[35] lamellarin G trimethyl ether (**140**)[141] and storniamide A nonamethyl ether (**22**),[142] respectively.

More recently, pentacyclic lamellarins L (**190**) and U (**191**) have been synthesized in the solid phase on the basis of a retrosynthetic analysis (Scheme 25) in which an intramolecular [3+2] cycloaddition of a 3,4-dihydroisoquinolinium salt over a triple C–C bond was a key step.[143,144]

In 2002, Smith and co-workers[145] performed an efficient one-pot synthesis of symmetrical and unsymmetrical 3,4-diaryl-1*H*-pyrroles of general formula **180** and **184**, which consisted of the reaction between symmetrical and unsymmetrical (*E*)-1,2-diarylethenes **192** and **193**, respectively, with a molar excess of tosylmethyl isocyanide (TOSMIC) (**194**)[146] in DMSO at 25–80 °C in the presence of 2 equiv of *t*-BuONa.

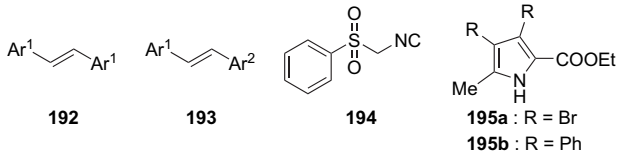


Scheme 25. Retrosynthetic analysis for the preparation of compounds **190** and **191**.



The protocol was particularly efficient (yields >65%) when electron-poor aryl groups were present in the alkene.[145]

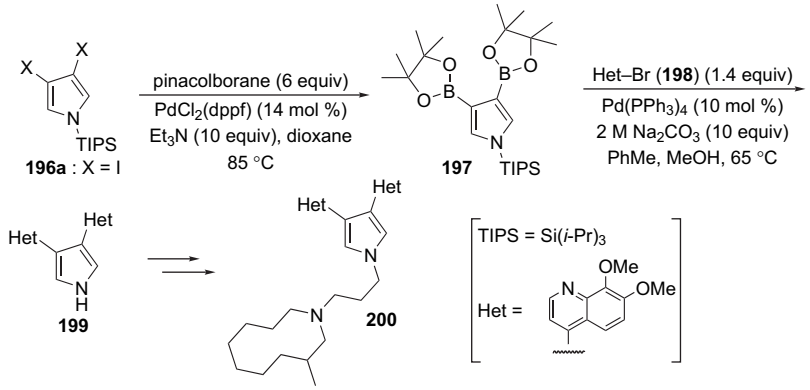
In recent years, 3,4-diaryl-1*H*-pyrroles, which include precursors to natural products and their congeners, have also been frequently prepared by Pd-catalyzed cross-coupling reactions of 3,4-(pseudo)halo-1*H*-pyrroles. Thus, ethyl 3,4-diphenyl-5-methyl-1*H*-pyrrole-2-carboxylate (**195b**) was synthesized in 95% yield by the reaction of dibromopyrrole **195a** with phenylboronic acid in DMF in the presence of aqueous Na_2CO_3 and 3.5 mol % $Pd(PPh_3)_4$.[147]



Similarly, compound **199**, which was employed as a precursor to the tetra-*O*-methyl ether derivative **200** of the strongly cytotoxic marine alkaloid halitulin (**9**), was prepared by a Suzuki reaction of the bromoquinoline derivative **198** with the organoboron derivative **197**, obtained by treatment of 3,4-diiodopyrrole (**196a**) with pinacolborane in the presence of a catalytic quantity of $PdCl_2$(dppf) (Scheme 26).[148]

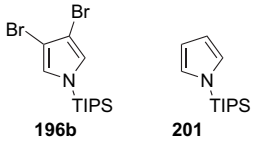
In 2003, Steglich and co-workers[149] used a very similar reaction sequence in a total synthesis of halitulin (**9**). Moreover, Alvarez and co-workers[144f] very recently performed a total synthesis of lamellarin D (**5**) in which the two aryl groups of this marine alkaloid were introduced on the pyrrole ring by a sequential and regioselective bromination/Suzuki cross-coupling procedure.

A methodology involving Stille- and Suzuki-type reactions has been used in the key steps of convergent syntheses of



Scheme 26. Synthesis of compounds **199** and **200** via Pd-catalyzed reactions.

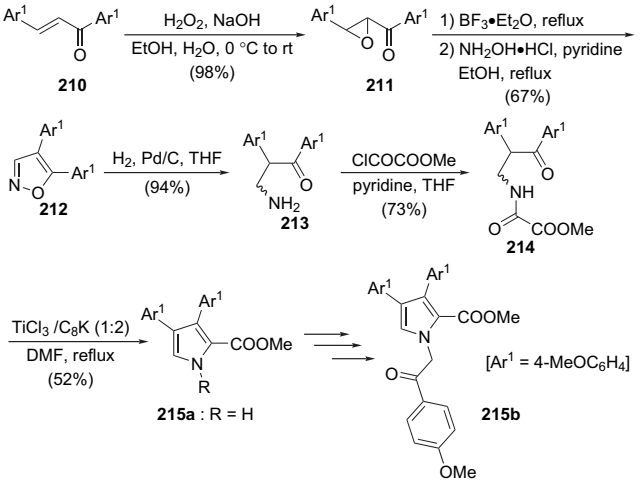
the marine natural products lamellarin O (**1**), lamellarin Q (**3**) and lukianol A (**10**).[150] The pivotal dibromopyrrole **196b** required for these syntheses was prepared from 1-triisopropylsilyl-1*H*-pyrrole (**201**) using procedures developed by Muchowski and co-workers.[151]



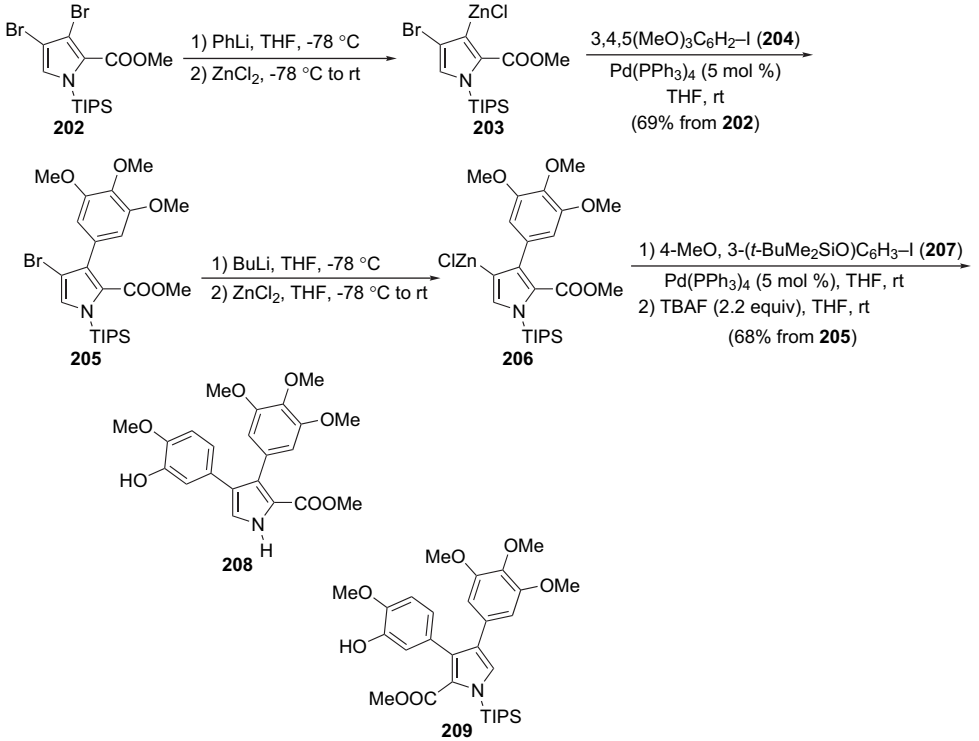
A different strategy was used to prepare the unsymmetrical 3,4-diaryl-1*H*-pyrroles **208** and **209**, which are configurationally stable structural hybrids of the powerful antimitotic agents combretastatin A-4[152] and colchicine.[153] In fact, the Stille- and Suzuki-type reactions used to prepare the naturally occurring compounds **1**, **3** and **10** proved to be unsuitable for providing access to unsymmetrical 3,4-diaryl-1*H*-pyrroles.[150] Thus, dibromopyrrole **202** was regioselectively converted into the organozinc derivative **203**, which underwent a Negishi cross-coupling reaction with aryl iodide **204** to give the monoarylated bromopyrrole **205**. This last compound was then subjected to halogen/metal exchange followed by transmetalation and the resulting organozinc derivative **206** was cross coupled with iodide **207** to give the target pyrrole **208** after desilylation.[150] The unsymmetrical 3,4-diaryl-1*H*-pyrrole **209** was next prepared from **202** via a similar reaction sequence (Scheme 27).[150]

In 2004, Marfil, Albericio and Álvarez used Pd-catalyzed Negishi- and Suzuki-type reactions for a solid-phase synthesis of lamellarins O (**1**) and Q (**3**) in which a 4-iodophenoxy resin and compound **203** were key reagents.[154]

Compound **215a**, used by Banwell and co-workers as an intermediate in the synthesis of lukianol A (**10**),[151] was employed by Fürstner in the first total synthesis of **10** and lamellarin *O*-dimethyl ether (**215b**).[155] In this synthesis, chalcone **210** was employed as the starting material, isoxazole **212** was used a surrogate of the labile keto–enamine **213** and the pyrrole ring of the required alkaloids was regio- and chemoselectively formed by a Ti-mediated oxo–amide coupling reaction of keto–enamide **214** bearing three different carbonyl groups (Scheme 28).[155] Isoxazole **212** was prepared by the reaction of hydroxylamine with the crude 1,3-keto-aldehyde obtained by the BF_3-mediated rearrangement of (*E*)-2,3-epoxy-1,3-bis(4-methoxyphenyl)propanone (**211**).

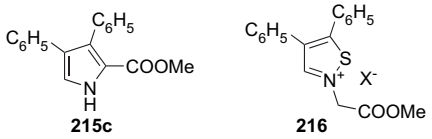


Scheme 28. Synthesis of compounds **215a** and **215b**.

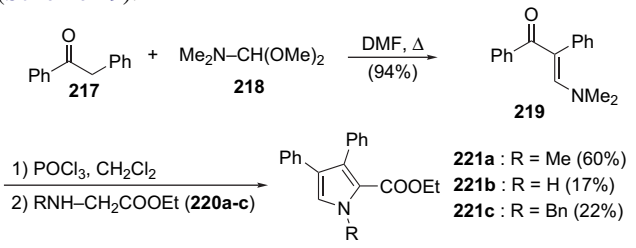


Scheme 27. Synthesis of the unsymmetrical 3,4-disubstituted-1*H*-pyrrole derivatives **208** and **209**.

Compound **215c**, which is an analogue of **215a**, had been previously synthesized in 87% yield by ring transformation of a thiazolium salt **216**.[156]



In 1998, the 3,4-diphenyl-1*H*-pyrrole derivatives **221a–c** were prepared by treatment of 3-dimethylamino-1,2-diphenyl-prop-2-enone (**219**) with $POCl_3$ in CH_2Cl_2, followed by condensation of the resulting chloropropeniminium salt with glycinates **220a–c** in DMF in the presence of NaH (Scheme 29).[157]



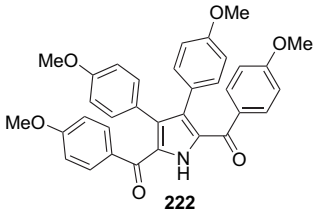
Scheme 29. Synthesis of compounds **221a–c**.

Compound **219** was readily obtained by the reaction of ketone **217** with *N*,*N*-dimethylformamide dimethylacetal (**218**) in refluxing DMF.[157]

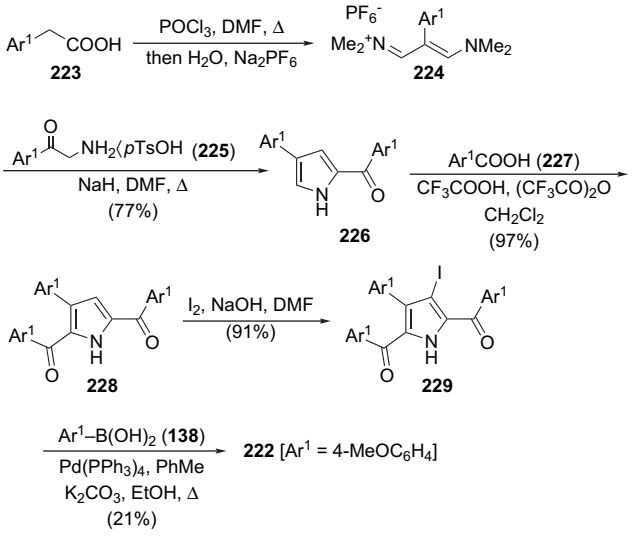
The synthetic methodology used for the synthesis of **221a–c** was subsequently employed to prepare the Fürstner intermediate **215a**[158] and ningalin B (**21**).[159]

In 2002, the Steglich group performed the total synthesis of the marine alkaloid polycitones A (**12**) and B (**13**) employing an elegant approach that included the synthesis of compound **222** by a Paal–Knorr reaction of the appropriate 1,4-diketone with ammonia.[160]

Very recently, compound **222** has been prepared from the vinamidinium salt **224** using two different approaches.[161] In the first of these, **224**, prepared from arylacetic acid **223**, was reacted with aminoketone **225** under base-mediated conditions to give **226** in 77% yield (Scheme 30). This pyrrole derivative was then acylated with carboxylic acid **227** and compound **228**, obtained in 97% yield, was converted in high yield into the iodo derivative **229**.

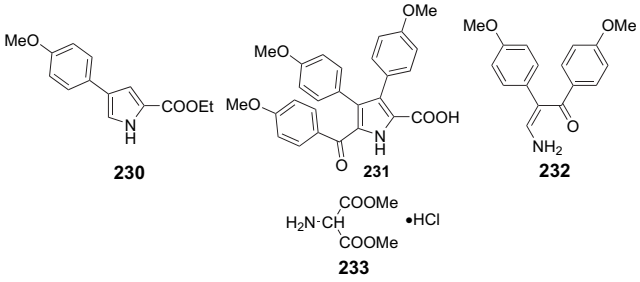


This compound was then subjected to standard Suzuki cross-coupling conditions with arylboronic acid **138** to furnish the Steglich synthon **222** in 21% yield (Scheme 30).[161] Nevertheless, when the Pd-catalyzed reaction of **229** with **138** was performed under microwave irradiation, compound **222** was obtained in 64% yield.[161]

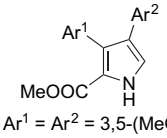


Scheme 30. Synthesis of compound **222** from arylacetic acid **223**.

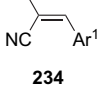
The second method for the synthesis of **222** was based on the conversion of **224** into 2-carbethoxy-4-(4-methoxyphenyl)-1*H*-pyrrole (**230**) and the subsequent preparation of the tetrasubstituted pyrrole **231** by the application of a series of reactions analogous to those reported in Scheme 30 for the preparation of **222** from **226**.[160] This method furnished **222** in 33% total yield from **224**.



In 2001, the procedure, pioneered by the Gupton group to prepare the Fürstner intermediate **215a** utilizing a vinylogous iminium salt derivative prepared from the vinylogous amide **232**,[158] was modified by Kim and co-workers who synthesized **215a** through a cyclocondensation reaction of **232** with dimethyl aminomalonate hydrochloride (**233**) in acetic acid.[162] This modified procedure was also employed to prepare 2-carbomethoxy-3,4-diaryl-1*H*-pyrroles **183d** and **183e** from the corresponding α-aryl ketones in 47 and 39% overall yield, respectively.[162] More recently, a large variety of unsymmetrical 3,4-diaryl-1*H*-pyrroles of general formula **183** have been regioselectively prepared in 51–60% yield, regardless of the electron-withdrawing or electron-releasing substituents in each aromatic ring, by [2+3] cycloaddition of ethyl isocyanoacetate (**182**) to α,β-unsaturated nitriles **234** in the presence of *t*-BuOH.[163]



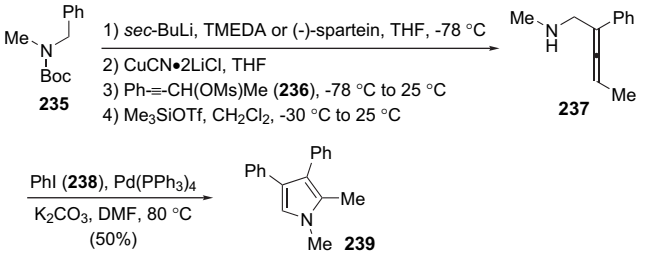
183d : $Ar^1 = Ar^2 = 3,5\text{-}(MeO)_2C_6H_3$
183e : $Ar^1 = 3,5\text{-}(MeO)_2C_6H_3$; $Ar^2 = 4\text{-}MeOC_6H_4$



234

This methodology, which represents a valuable complement to other procedures for the regioselective synthesis of unsymmetrical 3,4-diaryl-1*H*-pyrroles,[131,150,162] was employed to prepare **215a**, which is a key intermediate for the synthesis of the marine natural products lukianol A (**10**), lamellarin O (**1**) and lamellarin Q (**3**), and to perform a high yield total synthesis of ningalin B (**21**).[163]

Several procedures have also been devised for the synthesis of tetrasubstituted 3,4-diaryl-1*H*-pyrroles. In 2001, the pyrrole derivative **239** was synthesized in 50% yield by a Pd-catalyzed reaction of iodobenzene (**238**) with aminoallene **237**, which was available via reaction of the α-(*N*-carbamoyl)alkylcuprate, derived from the *N*-protected amine **235**, with the propargyl mesylate **236** (Scheme 31).[165]



Scheme 31. Synthesis of compound **239**.

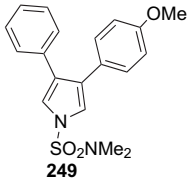
Presumably, formation of **239** involved initial formation of the corresponding 3-pyrroline, followed by Pd-promoted dehydrogenation.[164]

In 1999, permethyl storniamide A (**22**) and the marine natural products ningalin A (**20**), lamellarin O (**1**) and lukianol A (**10**) were synthesized using a concise approach[32] in which the 3,4-diaryl-1*H*-pyrrole derivatives **243a–c**, employed as precursors to these substances, were obtained by a heteroaromatic azadiene Diels–Alder reaction of compounds **240** with tetrazine **241**,[165,166] followed by a reductive ring-contraction reaction of the resulting 1,2-diazines **242a–c** (Scheme 32).

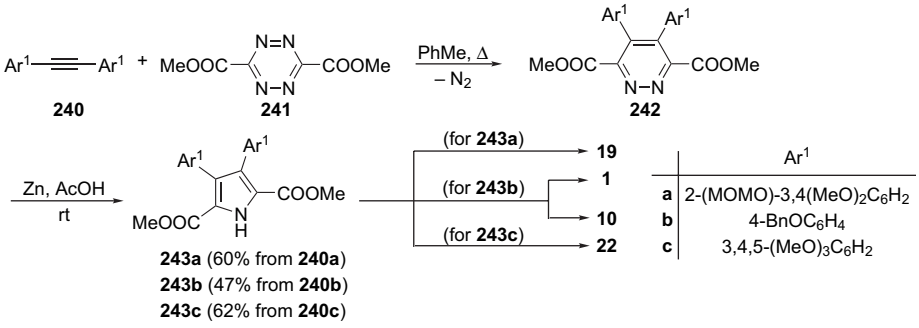
A similar strategy has recently been used by the Boger group for a concise and effective total synthesis of ningalins B (**21**)[36] and D.[167]

In 2000, the synthesis of the tetrasubstituted pyrrole derivative **248** was achieved in high yield starting from *N*,*N*-dimethyl-2-methoxycarbonyl-3,4-bis(trimethylsilyl)-1*H*-pyrrole-1-sulfonamide (**244**) through stepwise and repeated iodination and Pd-catalyzed Suzuki-type reactions (Scheme 33).[168] Iodopyrroles **245** and **247**, which were used as intermediates in this synthesis, were prepared by *ipso*-iodination of compounds **244** and **246**, respectively. Interestingly, the preferred position for iodination of **244** proved to be the 4-position. Compound **248** was then used in a formal total synthesis of lukianol A (**10**).[168]

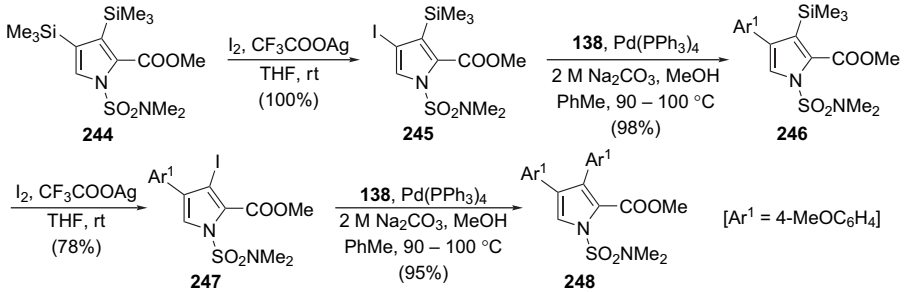
In the same year, a similar protocol was used to prepare the unsymmetrical 3,4-diaryl-1*H*-pyrrole derivative **249**.[169]



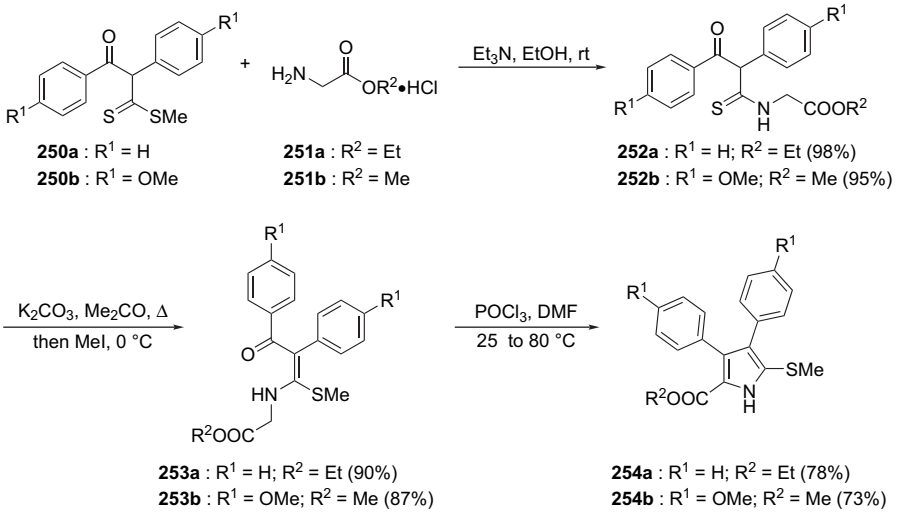
Finally, very recently, it has been reported that treatment of the dithiocarboxylates **250a**,**b** with alkyl glycinates **251a**,**b** followed by alkylation of the resulting β-oxothioamides



Scheme 32. Synthesis of compounds **1**, **10**, **19** and **22** via a heteroaromatic azadiene Diels–Alder reaction.



Scheme 33. Synthesis of compound **248**.

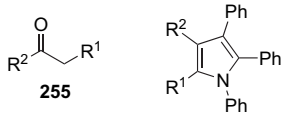


Scheme 34. Synthesis of compounds **254a** and **254b**.

252a,**b** gives ketene *N*,*S*-acetals **253a**,**b**, which are able to undergo smooth cyclization to afford the tetrasubstituted 3,4-diaryl-1*H*-pyrroles **254a**,**b** in good yields under Vilsmeier–Haack conditions (Scheme 34).[170]

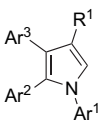
Compound **254b**, prepared in this way, has then been converted into the Fürstner intermediate **215a** by reductive removal of the alkylsulfamyl group using Raney Ni.[170]

2.2.4. Synthesis of 1,2,3- (1,4,5-), 1,2,4-, 1,2,5-, 1,3,4-, 2,3,4- (3,4,5-) and 2,3,5-triaryl-1*H*-pyrroles, 1,2,3,5- and 2,3,4,5-tetraaryl-1*H*-pyrroles, 1,2,3,4,5-pentaaryl-1*H*-pyrroles and 2,3,3-triaryl-3*H*-pyrroles. 1,2,3-Triphenyl-1*H*-pyrroles of general formula **256** have been synthesized in 20–70% yield by condensation of aniline (**49a**), benzoin (**166**) and carbonyl compounds **255**.[171] Methyl 1,2,3-triphenyl-4-carboxylate (**257a**) had been previously prepared in 70% yield by condensation of desylaniline (**258**) and methyl propiolate (**259**) in the presence of sodium acetate.[172]

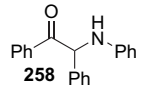


255

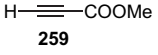
256 : R^1 = H, Me, Ph
R^2 = H, Me, Ph



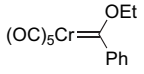
257a : $Ar^1 = Ar^2 = Ar^3$ = Ph; R^1 = COOMe
257b : $Ar^1 = Ar^2 = Ar^3$ = Ph; R^1 = H
257c : Ar^1 = 4-$MeOC_6H_4$; $Ar^2 = Ar^3$ = Ph; R^1 = H
257d : $Ar^1 = Ar^2$ = Ph; Ar^3 = 2-MeC_6H_4; R^1 = H
257e : $Ar^1 = Ar^2$ = Ph; Ar^3 = 3-MeC_6H_4; R^1 = H
257f : $Ar^1 = Ar^2$ = Ph; Ar^3 = 4-MeC_6H_4; R^1 = H
257g : $Ar^1 = Ar^2$ = Ph; Ar^3 = 4-ClC_6H_4; R^1 = H



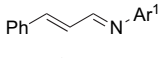
258



259



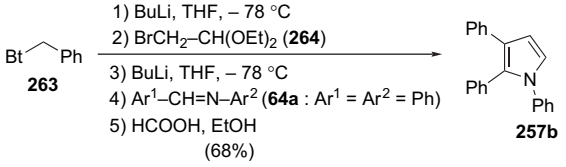
260



261 : Ar^1 = Ph
262 : Ar^1 = 4-$MeOC_6H_4$

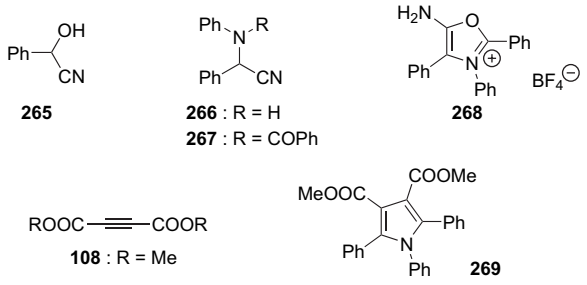
Danks and Velo-Rego have reported that thermolysis of the chromium carbene complex **260** with 1-azadienes **261** and **262** provides 1,2,3-triphenyl-1*H*-pyrrole (**257b**) and the 1,2,3-triaryl-1*H*-pyrrole **257c** in 50 and 60% yield, respectively.[173] Compound **257b** could also be obtained by hydrolysis of **257a**, followed by decarboxylation in quinoline with a copper chromite catalyst.[172]

Moreover, this pyrrole derivative **257b** could be efficiently synthesized by sequential lithiation and alkylation of 1-benzylbenzotriazole (**263**) with 2-bromoacetaldehyde diethylacetal (**264**) and *N*-benzylideneaniline (**64**, Ar^1=Ar^2=Ph), followed by treatment with formic acid in ethanol (Scheme 35).[174] This last versatile procedure was also used to prepare compounds **257d**–**g** in good yields.[174]



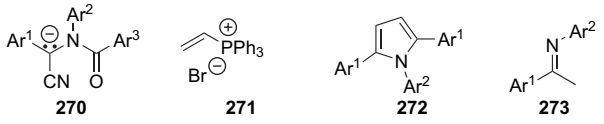
Scheme 35. Synthesis of 1,2,3-triphenyl-1*H*-pyrrole (**257b**) from 1-benzylbenzotriazole (**263**).

To the best of our knowledge, no data have been reported in the literature on the synthesis of 1,2,4-triaryl-1*H*-pyrroles. On the contrary, although 1,2,5-triaryl-1*H*-pyrrole derivatives do not include substances with significant biological activities, great attention has been given in the literature to the design and development of efficient procedures for the synthesis of this class of heterocycles.[175–181] In 1980, dimethyl 1,2,5-triphenyl-1*H*-pyrrole-3,4-dicarboxylate (**269**) was prepared in 80% yield by treatment of dimethyl acetylenedicarboxylate (**108**, R=Me) with 5-imino-2,3,4-triphenyl-1,3-oxazolinium tetrafluoroborate (**268**) at 110 °C for 12 h.[175] This last compound was readily available by the reaction of cyanohydrin **265** with aniline (**49a**), followed by acylation of the resulting aminonitrile **266** with benzoyl chloride and reaction of the open-chain analogue **267** of the resulting Reissert analogues with fluoroboric acid in glacial acetic acid.[175]

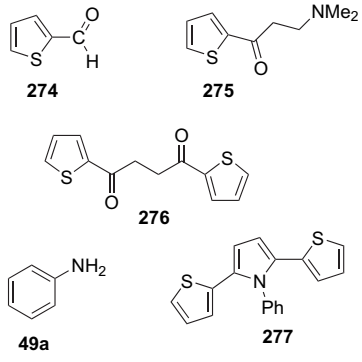


Subsequently, Cooney and McEwen prepared several 1,2,5-triaryl-1*H*-pyrroles of general formula **272** in 65–100% yield by addition of the conjugate bases **270** of open-chain analogues of Reissert analogues to vinyltriphenylphosphonium bromide (**271**).[176]

In 1999, pyrroles **272** were prepared by a simple and convenient one-pot process, which favourably compares with the method of Cooney and McEwen,[176] and consists of the reaction of CH_2Cl_2 solutions of ketimines **273** with 2 equiv of Et_3N and 2 equiv of $TiCl_4$ at 0–25 °C.[178] The compounds **272** were obtained in 63–90% yield.

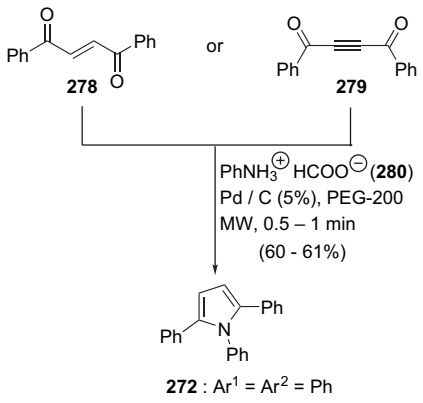


On the other hand, the Paal–Knorr condensation of aniline (**49a**) with 1,4-diketone **276** in the presence of acetic acid under azeotropic conditions was used to synthesize 1-phenyl-2,5-di(2-thienyl)-1*H*-pyrrole (**277**).[177] Compound **276** was obtained by a Stetter reaction of 2-thiophenecarbaldehyde (**274**) with the Mannich base **275**.[177]



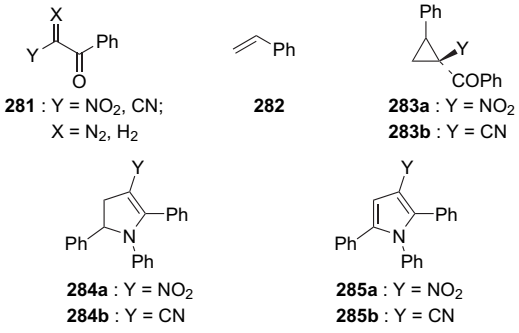
Recently, 1,2,5-triphenyl-1*H*-pyrrole (**272a**) has been conveniently prepared by a microwave-mediated one-pot reaction of ene–dione **278** or yne–dione 2**79** with anilinium formate (**280**) and Pd/C in PEG-200 (Scheme 36).[179] This interesting procedure, which conveniently combines a reduction reaction with an amination–cyclization step, was also used to prepare several other polyaryl-1*H*-pyrrole derivatives.[179]

More recently, tetrasubstituted 1,2,5-triaryl-1*H*-pyrroles **285a**,**b** have been synthesized by oxidation of the corresponding 2-pyrrolines **284a**,**b** with DDQ in refluxing toluene.[180] These pyrrolines were obtained in high yields by

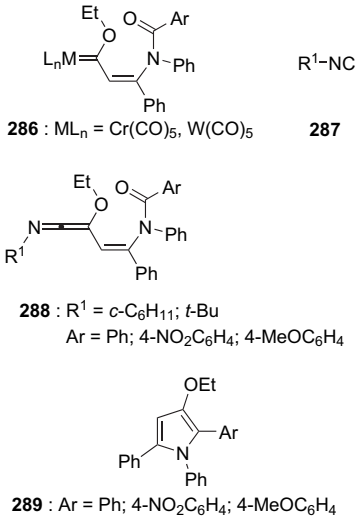


Scheme 36. Synthesis of pyrrole **272a** from compounds **278** or **279**.

a two-step sequence involving a Rh(II)-catalyzed cyclopropanation reaction of styrene (**282**) either with α-nitro- or α-cyano-α-diazoketones **281** or in situ-generated phenyliodonium ylides derived from compounds **281** (X=H_2), followed by reaction of the obtained 1-nitro- or 1-cyano-1-cyclopropyl ketones **283a**,**b** with aniline.[180]



Tetrasubstituted 2-aryl-4-ethoxy-1,5-diphenyl-1*H*-pyrroles **289** had previously been synthesized in excellent yields by thermolysis of (*Z*)-[2-(acylamino)ethenyl]ketene imines **288**, prepared in 63–95% yield by reaction of the carbene complexes **286** with 2 equiv of aryl isocyanides **287**.[181]

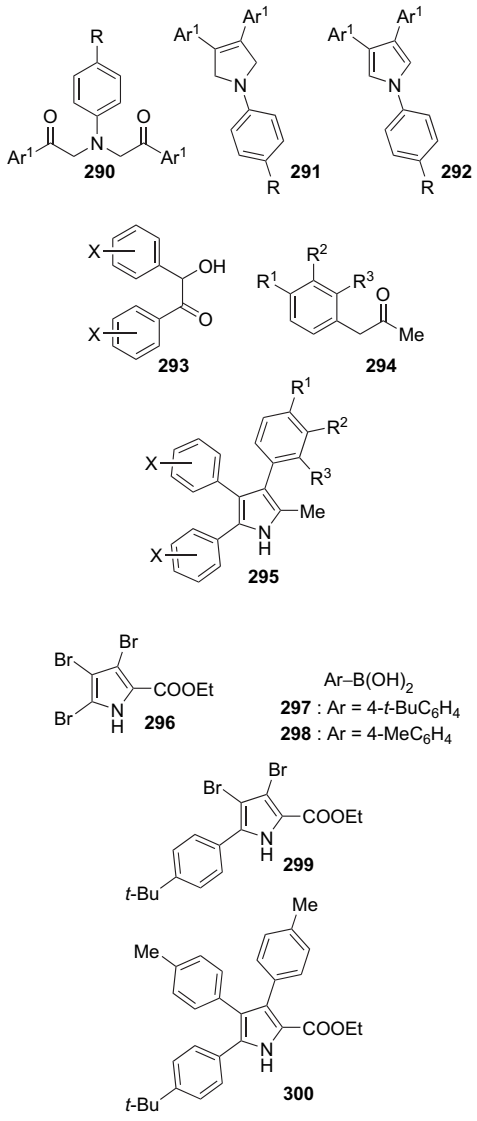


Despite the numerous known syntheses of substituted pyrroles, it is surprising that only one protocol has been

described so far for the synthesis of 1,3,4-triaryl-1*H*-pyrroles.[182] Specifically, some symmetrical pyrroles of general formula **292** have been synthesized in 65–89% yield by irradiation with a high-pressure Hg lamp of CH_2Cl_2 solutions of the corresponding 1,3,4-triaryl-2,5-dihydropyrroles **291**, prepared efficiently by McMurry coupling of dicarbonyl compounds **290** with $TiCl_4$/Zn.[182]

On the other hand, a classical method involving the reaction of a benzoin **293** with a benzyl methyl ketone **294** and anhydrous ammonium acetate in refluxing acetic acid has been used to prepare various 2-methyl-3,4,5-triaryl-1*H*-pyrroles **295**.[76] It should be noted that three of the heterocycles prepared showed a significant inhibition of post-prandial hyperglycemia in normal rats post-sucrose loaded.[76]

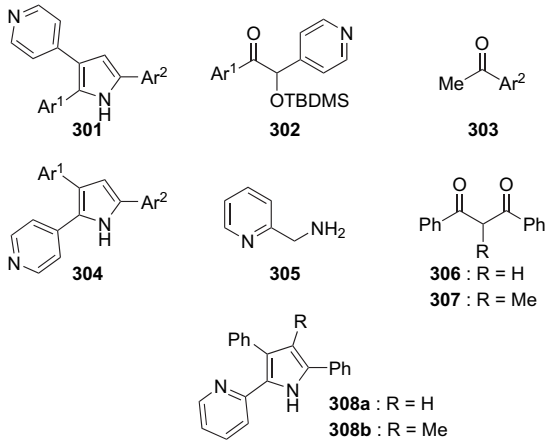
Very recently, the 3,4,5-triaryl-1*H*-pyrrole derivative **300** has been synthesized in 58.8% yield by a regioselective Pd-catalyzed Suzuki cross-coupling reaction of the tribromopyrrole derivative **296** with 1.2 equiv of arylboronic acid **297** and a subsequent cross-coupling at positions C-3 and C-4 of the resulting 5-aryl-3,4-dibromopyrrole carboxylate **299** with 4 equiv of boronic acid **298**.[183]



Recently, much attention has been directed to the preparation of 2,3,5-triaryl-1*H*-pyrroles.[67,75,184–190] Thus, de Laszlo and co-workers have utilized a Paal–Knorr condensation of 1,4-dicarbonyl compounds with ammonium acetate in refluxing acetic acid for the preparation of several 3-(4-pyridyl)-2,5-diaryl-1*H*-pyrroles **301** that include compound **25**, which is a potent orally bioactive inhibitor of p38 kinase.[67]

On the other hand, several 2-(4-pyridyl)-3,5-diaryl-1*H*-pyrroles **304**, which include a potent selective antagonist of glucagon, have been prepared in low yields in a one-pot reaction involving condensation of a silyl acyloin **302** with acetophenones (**303**) or, alternatively, in satisfactory yields via a Paal–Knorr condensation of 1,4-dicarbonyl compounds with ammonium acetate.[75]

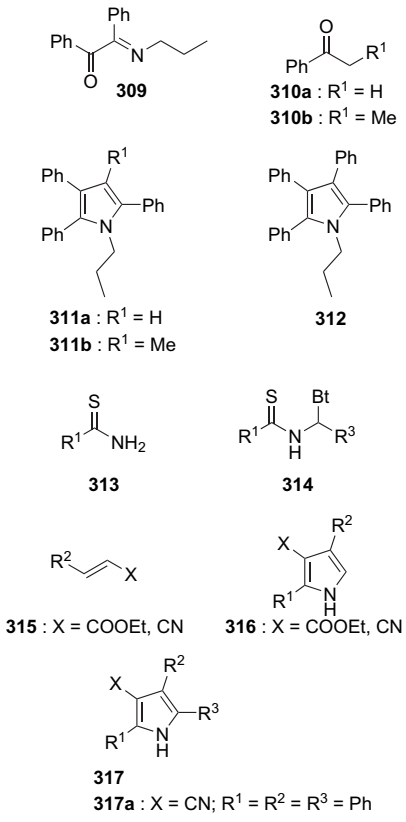
3,5-Diphenyl-2-(2-pyridyl)-1*H*-pyrroles **308a** and **308b** have been synthesized by McNeill and co-workers in 69 and 52% yield, respectively, by condensation of amine **305** with 1,3-diones **306** and **307** in xylenes at 170 °C in the presence of 0.1 equiv of *p*-toluenesulfonic acid and molecular sieves.[184]



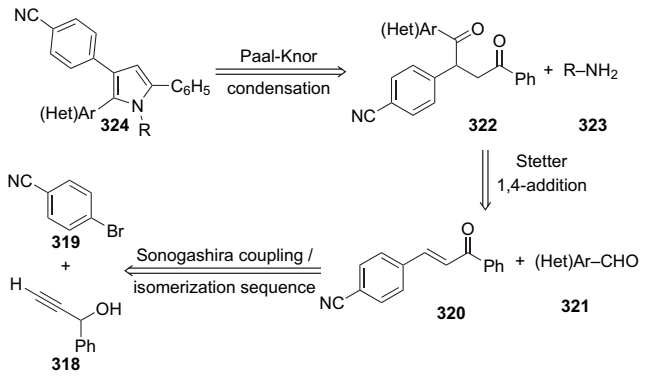
In 2001, the 2,3,5-triphenyl-1*H*-pyrroles **311a** and **311b** were prepared in good yields by the samarium(II) iodide-mediated reaction of α-iminoketone **309** with a molar excess of ketones **310a** and **310b**, respectively.[185] Moreover, similar samarium(II) iodide-mediated reactions were used to prepare efficiently some 2,3-diaryl-1*H*-pyrroles and the pentasubstituted pyrrole **312**.[185]

The year before, in continuation of their concentrated and fruitful activity on the synthetic applications of benzotriazole reagents,[106–110,113,114,174] Katritzky and co-workers had reported that a variety of tri- and tetrasubstituted 1*H*-pyrroles of general formula **316** and **317**, respectively, which include the 2,3,5-triphenyl-1*H*-pyrrole derivative **317a**, could be synthesized in moderate to good yields by a one-pot procedure involving the conversion of a thioamide **313** into the benzotriazole derivative **314**, followed by treatment with *t*-BuOH in THF and subsequent reaction with an activated olefin **315** in the presence of an additional 3 equiv of *t*-BuOH.[186]

In 2001, a variety of 2,3,5-triaryl-1*H*-pyrroles of general formula **324** were prepared in good yields by the Müller

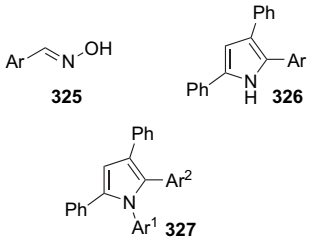


group[187] using a very interesting and convenient one-pot, three-step, four-component process.[191] This process, which used the electron-poor aryl halide **319**, the propargyl alcohol **318**, a (hetero)aryl aldehyde **321** and a primary amine **323** as starting materials, involved a Sonogashira coupling–isomerization–Stetter reaction–Paal–Knorr condensation sequence. Scheme 37 illustrates the retrosynthetic concept of this four-component synthesis.

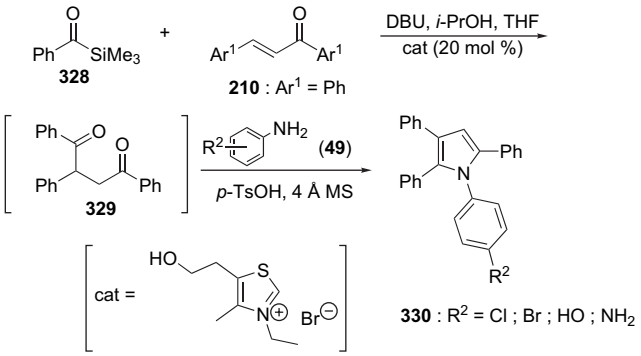


Scheme 37. Retrosynthetic analysis for the preparation of compound **324**.

More recently, some 2-aryl-3,5-diphenyl-1*H*-pyrroles **326** have been concisely and efficiently prepared by a coupling reaction of 1,3-diketone **306** with oximes **325**, which was promoted by low valent titanium prepared from $TiCl_4$ and Zn powder in anhydrous THF.[189] Some 1,2-diaryl-3,5-diphenyl-1*H*-pyrroles **327** have been similarly synthesized in good yields from **306** and imines **64**.[189]



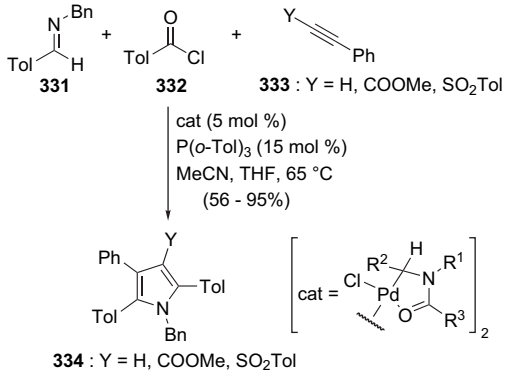
Recently, Bharadwaj and Scheidt have disclosed a novel three-component approach to the synthesis of 1-alkyl-2,3,5-triphenyl-1*H*-pyrroles and 1-aryl-2,3,5-triphenyl-1*H*-pyrroles **330**, which is based on the combination of a new variant of the Stetter reaction with a Paal–Knorr condensation (Scheme 38).[188]



Scheme 38. Synthesis of compounds **330**.

The procedure involves a thiazolium-catalyzed reaction of acylsilane **328** with the α,β-unsaturated ketone **210** (Ar^1=Ph) in the presence of DBU, which is followed by treatment in situ of the resulting 1,4-dicarbonyl compound **329** with an arylamine **49** in the presence of *p*-toluenesulfonic acid and molecular sieves.

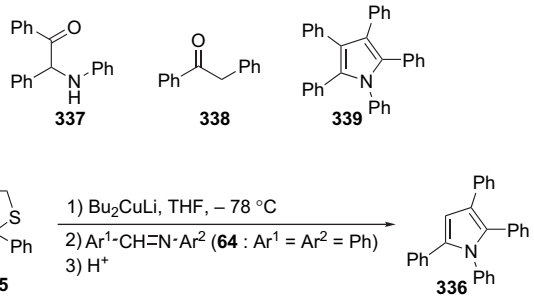
On the other hand, Dhawan and Arndtsen have recently assembled the pyrrole ring of 2,3,5-triaryl-1*H*-pyrrole derivatives **334** by Pd-catalyzed multicomponent coupling of imine **331**, acyl chloride **332** and alkynes **333** (Scheme 39).[190,191] This process has been used to prepare a pyrrole derivative that is a member of a class of multicyclic pyrroles[190] which are of utility as potential therapeutics and retinoic acid regulators.[192]



Scheme 39. Pd-catalyzed synthesis of compounds **334**.

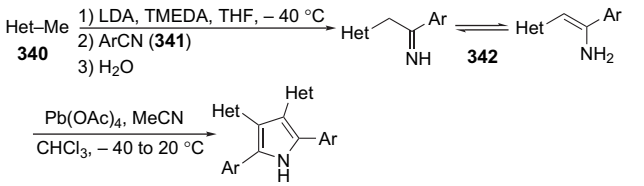
A modification of the Paal–Knorr reaction involving the use of iodine as the catalyst has recently been employed to synthesize 1,2,3,5-tetraphenyl-1*H*-pyrrole (**336**).[193a]

This compound had previously been prepared in 73% yield by a one-pot annulation reaction involving treatment of the propargylic dithioacetal **335** with 0.6 equiv of Bu_2CuLi in THF at −78 °C followed by reaction with imine **64a** (Scheme 40).[193b] Compound **336** had also been synthesized in 70% yield by condensation of aniline (**49a**) with benzoin (**166**) under catalysis by traces of formic acid and treatment of the resulting 2-anilino-2-phenylacetophenone (**337**) with acetophenone (**303**; Ar^2=Ph).[171] On the other hand, reaction of **337** with ketone **338** under acidic catalysis furnished 1,2,3,4,5-pentaphenyl-1*H*-pyrrole (**339**) in 20% yield.[171]



Scheme 40. Synthesis of compound **336** from dithioacetal **335**.

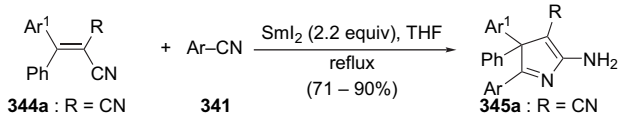
In 1999, symmetrical 2,3,4,5-tetraaryl-1*H*-pyrroles **343**, which include compounds able to prevent Fe^{2+}-induced lipid peroxidation on microsomes, were synthesized in moderate to high yields from the methylheteroarenes **340** and aromatic nitriles **341** according to a two-step reaction sequence in which the second step involved treatment of imine–enamines **342** with $Pb(OAc)_4$ (Scheme 41).[194]



343 : Het = 2-pyrazinyl, 2-pyridyl, 4-pyridyl;
Ar = Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$
2-pyridyl, 4-pyridyl, 2-furyl, 2-thienyl

Scheme 41. Two-step synthesis of compounds **343**.

Finally, several 2,3,3-triaryl-3*H*-pyrroles **345a**,**b** have recently been prepared in good-to-excellent yields by samarium(II) iodide-mediated reductive cyclization of 1,1-diaryl-2,2-dicyanoethylenes **344a**,**b** with aromatic nitriles **341** under neutral and mild conditions (Scheme 42).[195]



344a : R = CN
344b : R = COOEt

345a : R = CN
345b : R = COOEt

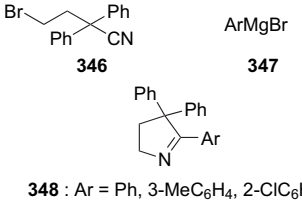
Scheme 42. SmI_2-mediated synthesis of compounds **345a**,**b**.

3. Synthesis of 1-, 2- and 3-pyrrolines with two aryl groups on adjacent positions

Three isomeric groups are possible for the dihydro derivatives of pyrrole: 1-pyrrolines (3,4-dihydro-2*H*-pyrroles), 2-pyrrolines (2,3-dihydro-1*H*-pyrroles) and 3-pyrrolines (2,5-dihydro-1*H*-pyrroles). All of these compounds have been used as intermediates in the synthesis of biologically and/or medically active compounds,[196] but, among these three groups of heterocycles, the 1-pyrrolines are the most interesting. In fact, the latter moieties are present in important biologically active compounds such as hemes,[197] chlorophylls[197] and alkaloids.[198] Moreover, 1-pyrrolines have been used as templates for new drugs.[199] Thus, several methods have been developed for the synthesis of these heterocycles from acyclic, alicyclic or heterocyclic compounds.[200] Nevertheless, the preparation of vicinal diaryl-substituted derivatives of 1-, 2- or 3-pyrrolines has received little attention so far. Here, we summarize the literature data on this subject.

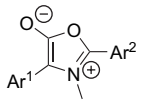
Several years ago, Demoen and Janssen reported that some 2-aryl-3,3-diphenyl-1-pyrrolines **348** can be prepared in satisfactory yields by the reaction of γ-bromonitrile **346** with aryl Grignard reagents **347** in a boiling mixture of Et_2O and xylene.[201]

In 1993, Pal and co-workers synthesized 2,3-diaryl-1-pyrrolines **115** and **352** in high yields by a two-step sequence[202] in which the first step involved alkylation of ketones **349a** and **349b**, respectively, via formation of their zinc enolates prior to a Michael reaction with nitroethylene (**350**). In the second step, the nitroketones **351a** and **351b** were reacted with a catalytic amount of Raney Ni in ethanol at 50 psi H_2, which resulted in the formation of the required 1-pyrrolines.[202]

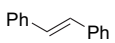


As mentioned in Section 2.2.2, compound **115** has also been prepared from *trans*-2-phenylcyclopropylamine (**113**) via photochemical rearrangement of the corresponding *N*-cyclopropylimine **114**.[112]

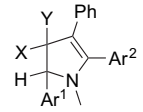
On the other hand, some 2-pyrrolines with two aryl groups on adjacent positions have been synthesized by 1,3-dipolar cycloaddition of münchnones with alkenes.[203,204] Thus, the tetraphenyl-2-pyrroline **355a** was prepared from münchnone **353a** and *trans*-2-stilbene (**354**)[203] and pyrroline **355b** was regioselectively synthesized from münchnone **353b** and alkene **356a**.[204] Compound **355c** was similarly obtained from **353c** and **356b**.[204]



353a : $Ar^1 = Ar^2 = Ph$
353b : $Ar^1 = Ph$; $Ar^2 = 4\text{-}MeOC_6H_4$
353c : $Ar^1 = Ph$; $Ar^2 = 4\text{-}NO_2C_6H_4$



354

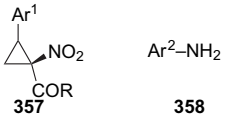


355a : $Ar^1 = Ar^2 = X = Ph$; $Y = H$
355b : $Ar^1 = Ph$; $Ar^2 = 4\text{-}MeOC_6H_4$; $X = CN$; $Y = COOMe$
355c : $Ar^1 = Ph$; $Ar^2 = 4\text{-}NO_2C_6H_4$; $X = Y = CN$

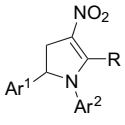
356a : X = CN; Y = COOMe
356b : X = Y = CN

As mentioned in Section 2.2.4, 2-pyrrolines **284a** and **284b** could be obtained by treatment of aniline with the activated cyclopropanes **283a** and **283b**, respectively.[180] A number of 1,5-diaryl-2-pyrrolines **359** were similarly prepared in high yields from the 1-nitrocyclopropyl derivatives **357** and aromatic primary amines **358**.[180]

In Section 2.2.4, it was also reported that some symmetrical 1,3,4-triaryl-3-pyrrolines can be efficiently prepared by McMurry coupling of *N*,*N*-(diarylmethyl)arylamines with $TiCl_4/Zn$.[182]



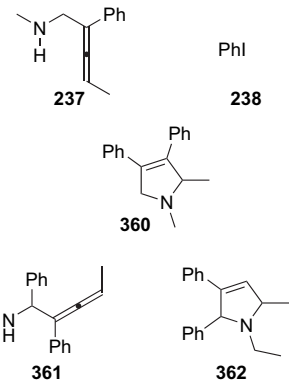
357 **358**



359

Some interesting methods for the synthesis of aryl-substituted 3-pyrrolines are based on the use of aminoallenes. Thus, 3-aryl-3-pyrrolines have been synthesized by a Pd-catalyzed cyclization reaction of α-aminoallenes with aryl iodides in DMF in the presence of K_2CO_3 and Bu_4NCl.[164] This useful reaction has been used to prepare 3-pyrroline **360** from α-aminoallene **237** and iodobenzene (**238**) in 55% yield.[164]

Moreover, a diastereomeric mixture of the 2,3-diphenyl-3-pyrroline **362** has recently been obtained in 88% yield by



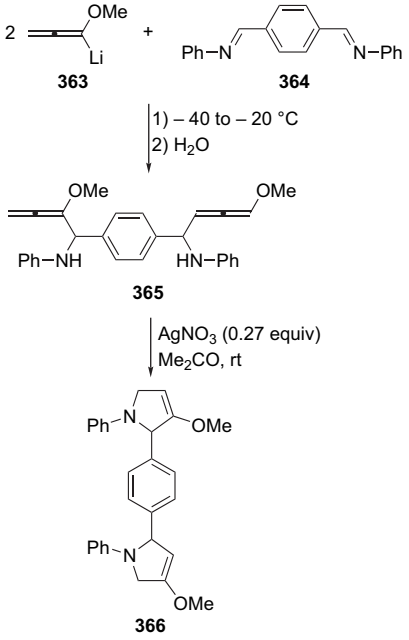
237 **238**

360

361 **362**

an $AgNO_3$-catalyzed reaction of aminoallene **361** in acetone at room temperature.[205] This cyclization reaction could also be performed in dioxane at 100 °C in the presence of 1.5 equiv of Et_3N and 1 mol % $Ru_3(CO)_{12}$ but **362** was obtained only in 56% yield.[205]

Finally, the 3-pyrroline derivative **366** has been synthesized in 94% yield by the reaction of lithiated methoxyallene **363** with diimine **364**, followed by an $AgNO_3$-catalyzed cyclization of the resulting allenyl amine **365** (Scheme 43).[206]



363 **364**

365

366

Scheme 43. Synthesis of compound **366**.

4. Synthesis of 3-pyrrolin-2-ones and 2,3-dihydro-1*H*-pyrrole-2,3-diones with two aryl groups on adjacent positions

3-Pyrrolin-2-ones (1,5-dihydro-2*H*-pyrrol-2-ones) are important structural units of the structurally related indolocarbazole

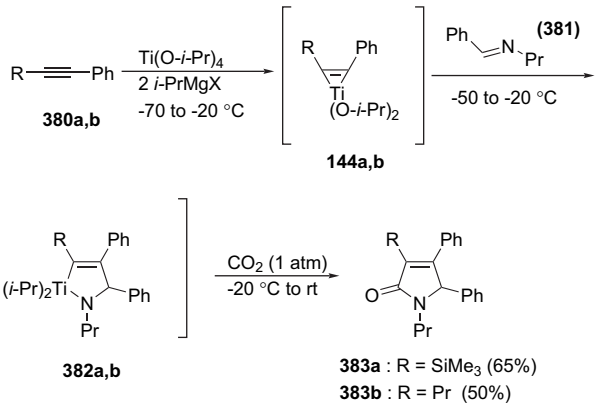
alkaloids (+)-staurosporine (**367**)[207] and (+)-K252a (**368**),[208] which are strong kinase inhibitors widely used as molecular tools.

On the other hand, 3,4-diaryl- and 1,3,4-triaryl-3-pyrrolin-2-ones, **369a**,**b** and **370**, have been shown to be a prospective new type of COX-2 selective inhibitors.[209,210] Moreover, the α,β-unsaturated γ-butyrolactam moiety can be utilized as a Michael acceptor for a variety of nucleophiles.[211] Therefore, the synthesis of 3-pyrrolin-2-ones is currently receiving considerable attention[212] and several interesting methods have been reported to prepare 3- and 4-pyrrolin-2-ones with two aryl groups on adjacent positions.[213–225] One of the methods developed for the synthesis of 3-pyrrolin-2-ones is based on a formal [2+3] cycloaddition reaction of diphenylcyclopropenone (**371**)[226] with imines[213] or diimines.[214,215] In fact, some years ago, it was found that the reaction of **371** with acyclic enaminones **372a**,**b** and aminoester **373** in refluxing toluene leads to the formation of the 5-functionalized 3,4-diphenyl-3-pyrrolin-2-ones **374a–c** in good yields.[213]

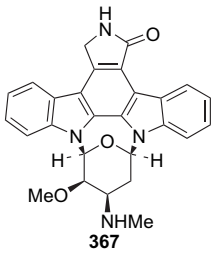
The cyclic enaminone **375**, however, proved to be much less reactive towards **371** than compounds **372** and **373** and the 2:1 product **376** was the principal cycloadduct.[213,226]

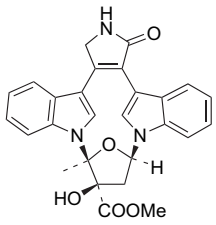
1-Aryl-5-(*N*-aryl)iminomethyl-2,3-diphenyl-2-pyrrolin-4-ones **378** have been reported to be the major products of the reaction of **371** with 1,4-diaryl-1,4-diazabutadienes **377** in refluxing toluene.[214] Nevertheless, it has recently been established that the structure of these compounds corresponds to the tautomers **379** in the *E*-configuration, which are more stable than compounds **378** having extended conjugation and hydrogen bonding.[215]

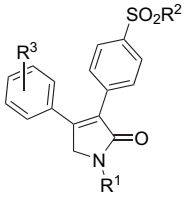
4,5-Diphenyl-3-pyrrolin-2-ones **383a**,**b** have been prepared in good yields by a one-pot procedure that involved the reaction of alkynes **380a**,**b** with Ti(O-*i*-Pr)$_4$, imine **381** and carbon dioxide at atmospheric pressure (Scheme 44).[216] This method, in which an azatitanacyclopentene complex **382a**,**b** is obtained as an intermediate, has also been used to synthesize regioselectively other substituted 3-pyrrolin-2-ones.[216]

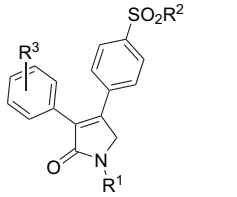


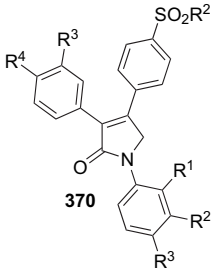
Scheme 44. Synthesis of compounds **383a**,**b**.

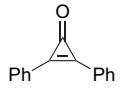

367

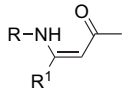

368

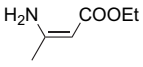

369a : R^1 = Me, Pr, *c*-C_3H_5, R^2 = Me, NH_2, R^3 = H, 3-Cl, 3-F, 3-Br, 4-F, 4-Cl, 4-Br, 4-Me

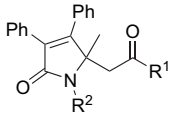

369b : R^1 = Me, Pr, *c*-C_3H_5, R^2 = Me, NH_2, R^3 = H, 3-Cl, 3-F, 3-Br, 4-F, 4-Cl, 4-Br, 4-Me

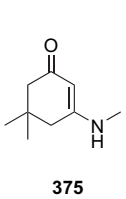

370


371


372a : R = H; R^1 = Me
372b : R = R^1 = Me


373


374a : R^1 = Me; R^2 = H
374b : R^1 = R^2 = Me
374c : R^1 = OEt; R^2 = H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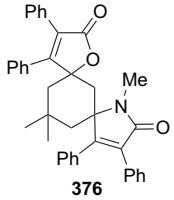
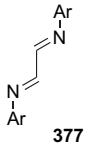

376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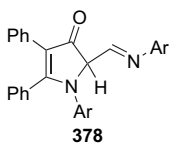
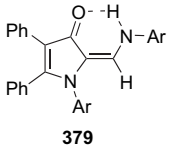
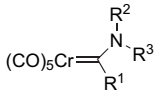
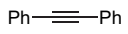

378


379

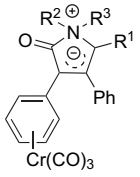
In 1995, Rudler and co-workers demonstrated that the *N*-ylide complexes **385**, obtained upon diphenylacetylene (**380b**) insertion into the carbene complexes **384a**,**b**, are able to react with cyclopentadiene in refluxing benzene to give 3,4-diphenyl-3-pyrrolin-2-ones **386a**,**b** in 65–71% yield.[217]



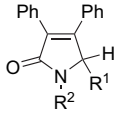
384a : $R^1 = R^2 = R^3 = Me$
384b : $R^1 = Ph$; $R^2 = R^3 = Me$



380b



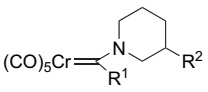
385



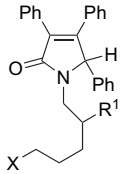
386a : $R^1 = R^2 = Me$
386b : $R^1 = Ph$; $R^2 = Me$

More recently, these authors have reported that aminocarbene complexes **387a–c** are able to react with **380b**, X–H species (X=PhS, PhSe) and, finally, with pyridine to give 3,4,5-triphenyl-3-pyrrolin-2-ones **388a–c** via *N*-ylide complexes of general formula **385**.[218]

A series of 1,5-diaryl-3-arylamino-3-carboxymethyl-3-pyrrolin-2-ones **390** had been previously obtained by the reaction of α-ketoglutaric acid (**389**) with Schiff bases **64**.[219] Compounds **390a–e** were then converted into 1,5-diaryl-3-hydroxy-4-carboxymethyl-3-pyrrolin-2-ones **391a–e** by hydrolysis with hydrochloric acid.[219]



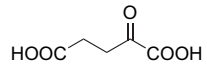
387a : $R^1 = Ph$; $R^2 = H$
387b : $R^1 = Me$; $R^2 = H$
387c : $R^1 = Ph$; $R^2 = Me$



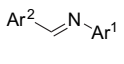
388a : $R^1 = H$; X = PhS
388b : $R^1 = Me$; X = PhS
388c : $R^1 = H$; X = PhSe

3,4-Diheteroaryl-3-pyrrolin-2-one **394**, which was a key intermediate in a stereocontrolled synthesis of the indolocarbazole (+)-K252a (**368**), was synthesized in 92% yield by DBU-catalyzed cyclization of compound **393** in the presence of molecular sieves.[39] This last substance could be obtained in 93% yield by regioselective oxidation of amide **392** with 2 equiv of DDQ in aqueous THF.[39]

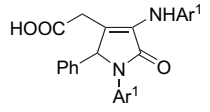
Miller and co-workers[220] prepared the solid phase pyrrolinone **398a** and other 3-carboxy-3-pyrrolin-2-ones by using a protocol in which the polymer-bound malonamides **395** were oxidized to the corresponding ketones **396** by treatment with $CrO_2(O\text{-}t\text{-}Bu)_2$ and these last compounds were cyclized in the presence of LDA or LHMDS to afford the carboxypyrrolinones **397**. Trifluoroacetic acid treatment then released the required compounds **398** in 43–80% overall yield.



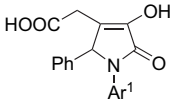
389



64

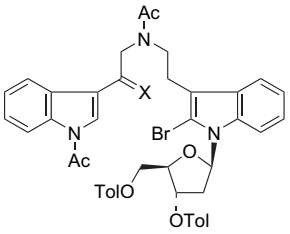


390a-e

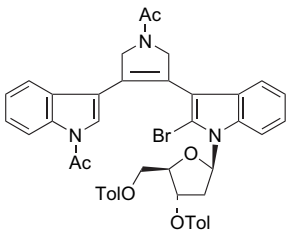


391a-e

	Ar^1
a	4-IC_6H_4
b	Ph
c	4-$NO_2C_6H_4$
d	4-ClC_6H_4
e	2,4-$(MeO)_2C_6H_3$



392 : X = H_2
393 : X = O



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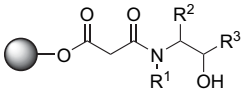

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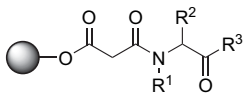

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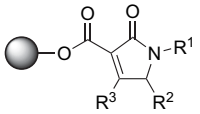
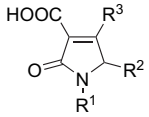
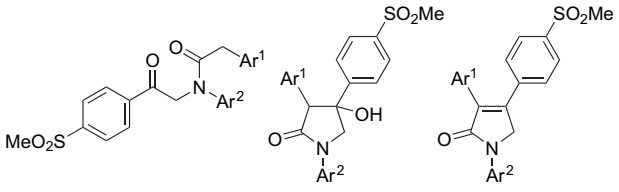


397



398
398a : $R^1 = CH_2CH(Et)_2$; $R^2 = R^3 = Ph$

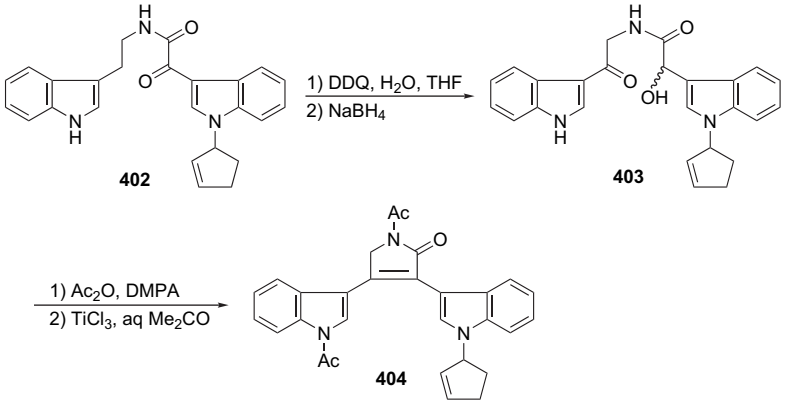


399 **400** **401**

In 2000, several 1,3,4-triaryl-3-pyrrolin-2-ones **401**, which included some novel selective COX-2-inhibitors, were synthesized by a high-yielding aldol-type cyclization of amides **399** with DBU in acetonitrile at 0 °C, followed by dehydration of the resulting lactam alcohols **400** with *p*-toluenesulfonic acid in refluxing benzene.[210]

In 2002, Trost and co-workers elaborated regioselectively the readily available glyoxamide **402** to the corresponding 1-acetyl-3,4-(1-indol-3-yl)-3-pyrrolin-2-one derivative **404** via **403** (Scheme 45)[221] according to a strategy already used in the literature for the synthesis of the staurosporine aglycon.[227]

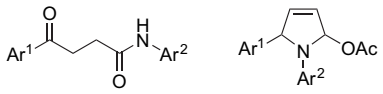
More recently, mixtures of 1,2-diaryl-3- and -4-pyrrolin-2-ones **407a**,**b** and **408a**,**b** have unexpectedly been obtained by the reaction of 3-aroylpropionamides **405a**,**b** with a large excess of refluxing acetyl chloride, followed by alkaline hydrolysis of compounds **406a**,**b**.[222] The pure



402 403 404

Scheme 45. Synthesis of compound **404**.

3-pyrrolin-2-ones **407a**,**b** could be, however, obtained in high yield by recrystallization of the pyrroline mixtures.[222]

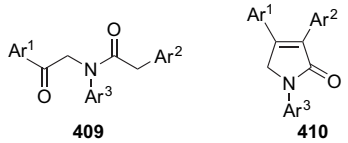


405a,b **406a,b**

407a,b **408a,b**

	Ar^1	Ar^2
a	Ph	Ph
b	4-MeC_6H_4	Ph

On the other hand, Pal and co-workers have found that cyclization of *N*-aryl-*N*,*N*-di(2-oxo-2-arylethyl)amines **409** by treatment with 1.5 equiv of K_2CO_3 in aqueous ethanol in the presence of atmospheric oxygen at 75 °C for 3 h provides 1,3,4-triaryl-3-pyrrolin-2-ones **410** in good-to-excellent yields.[223]

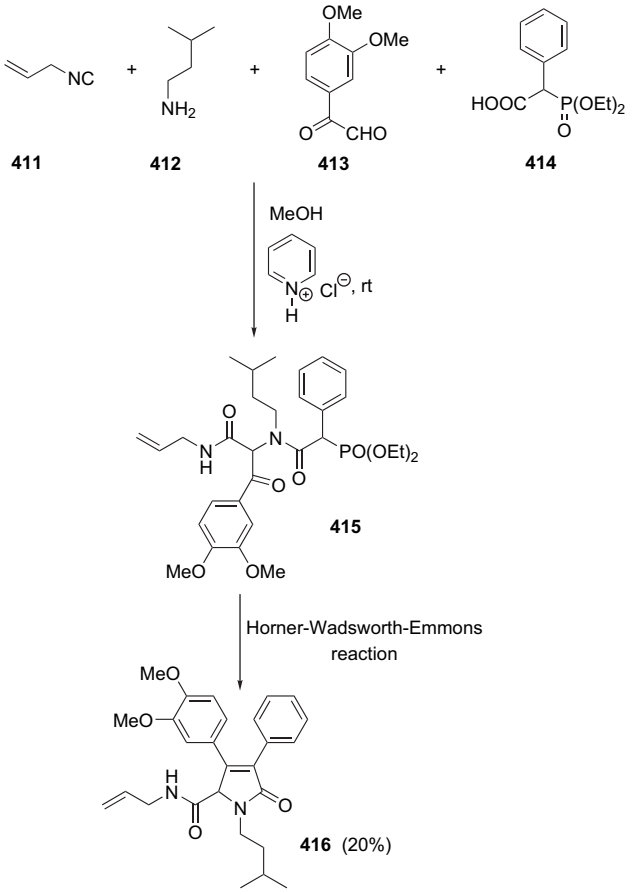


409 **410**

A convergent assembly of 3,4-diaryl-3-pyrrolin-2-ones **416** has recently been performed by combining a Ugi four-component reaction of isocyanide **411**,[228] amine **412**, α-ketoaldehyde **413** and phosphonic acid diethyl ester **414** to give **415**, with a subsequent Horner–Wadsworth–Emmons ring-closing reaction (Scheme 46).[224] This strategy also allowed the preparation of several other 3-pyrrolin-2-one derivatives in low to high yields.[224]

Recently, the synthesis of 2,3-dihydro-1*H*-pyrrole-2,3-diones with two aryl groups on adjacent positions has also received attention.[229–231]

Thus, a series of 1-aryl-4-cyano-5-phenyl-1*H*-pyrrole-2,3-diones **422** and 1-aryl-4-methoxycarbonyl-5-phenyl-1*H*-

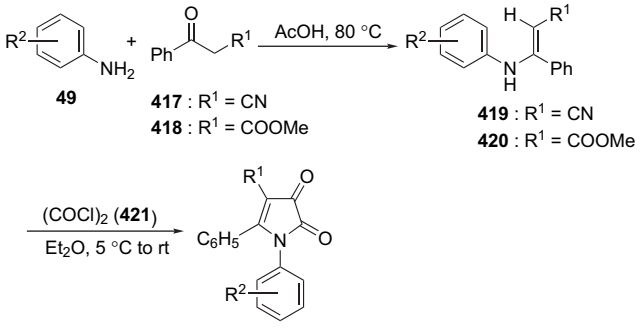


411 **412** **413** **414** **415** **416** (20%)

Scheme 46. Synthesis of compound **416** via a four-component reaction.

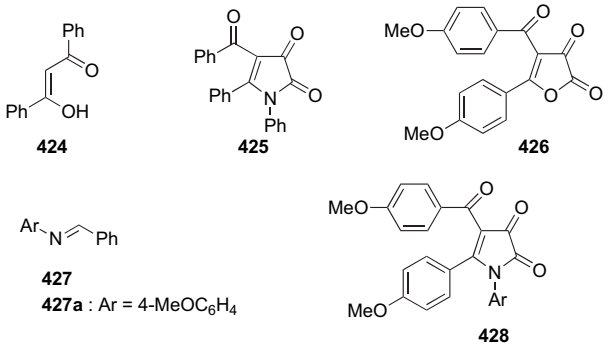
pyrrole-2,3-diones **423** have been synthesized in 75–94% yield by the reaction of oxalyl chloride (**421**) with 3-phenyl-3-arylaminopropenenitriles **419** and ethyl 3-phenyl-3-arylaminoprop-2-enoates **420**, respectively. These last compounds were available from arylamines **49** and benzoylacetonitrile (**417**) and methyl benzoylacetate (**418**), respectively (Scheme 47).[229]

On the other hand, 4-benzoyl-1,5-diphenyl-2,3-dihydro-1*H*-pyrrole-2,3-dione (**425**) has been prepared by reaction of the imine of dibenzoylmethane (**424**) with aniline and oxalyl chloride.[230]



49
417 : R1 = CN
418 : R1 = COOMe
419 : R1 = CN
420 : R1 = COOMe
422 : R1 = CN; R2 = H, 3-F, 4-F, 3,4-F2, 2,3,4-F3
423 : R1 = COOMe; R2 = H, 3-F, 4-F, 3,4-F2, 2,3,4-F3

Scheme 47. Synthesis of compounds **422** and **423**.



424 425 426
427
427a : Ar = 4-MeOC6H4
428

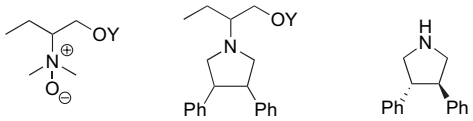
Finally, other red-coloured 4-aroyl-1,5-diaryl-2,3-dihydro-1*H*-pyrrole-2,3-diones **428** have been obtained by treatment of the 4-aroyl-5-aryl-2,3-dihydro-1*H*-furan-2,3-dione **426** with Schiff bases **427** at 60–70 °C.[231]

5. Synthesis of pyrrolidines, 2-pyrrolidinones, 3-hydroxy-3-pyrrolin-2-ones and pyrrolidine-2,4-diones with two aryl groups on adjacent positions

Substituted pyrrolidines and pyrrolidinone derivatives are widespread structural features of natural and designed biologically active molecules.[232] In addition, these heterocycles can be used for pharmaceutical purposes[233] and ligands of transition metal catalysts.[234] Consequently, the efficient preparation of these heterocycles has received significant attention.

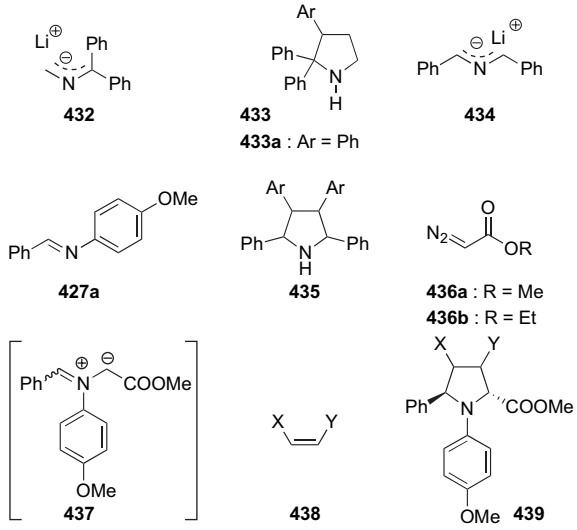
The numerous methods for the synthesis of 2-pyrrolidinones (γ-lactam) derivatives include intramolecular acylation of γ-amino-functionalized carboxylic acids or esters,[235] one-carbon ring expansion of β-lactams,[236] intramolecular C–H insertion reactions[237] and Pd-catalyzed intramolecular allylations.[238]

Several strategies have also been developed for the synthesis of pyrrolidines,[239–250] some of which have been used to prepare vicinal diaryl-substituted pyrrolidine derivatives. Thus, compounds **430a** and **430b** have been synthesized in 34 and 70% yield, respectively, by [3+2] cycloaddition of stilbene (**354**) with the non-stabilized azomethine ylides generated by the reaction of β-aminoalcohol *N*-oxides **429a** and **429b** with LDA at 0 °C.[249] Pyrrolidines **430a** and **430b** could then be converted into 3,4-diphenyl-*trans*-pyrrolidine (**431**) in high yield.[249]



429a : Y = H
429b : Y = *t*-Bu
430a : Y = H
430b : Y = *t*-Bu
431

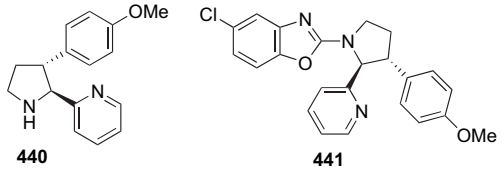
On the other hand, it has been found that the [3+2] cycloaddition reaction of the 2-azaallyllithium **432** with styrene (**282**) provides 2,2,3-triphenylpyrrolidine (**433a**) in 85% yield.[251] Other [3+2] cycloaddition reactions involving the 2-azaallyllithium derivatives **432** and **434** have been usefully employed to prepare other 2,2-diphenyl-3-arylpyrrolidines **433**[240] and some 3,4-diaryl-2,5-diphenylpyrrolidines **435**,[252] respectively.



432
433
433a : Ar = Ph
434
427a
435
436a : R = Me
436b : R = Et
437
438
439

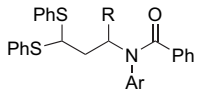
The cycloaddition reaction of dipolarophiles **438** with azomethine ylide **437**, generated by the ruthenium porphyrin-catalyzed reaction of α-diazoester **436a** with imine **427a**, has recently been used for the synthesis of 1-(4-methoxyphenyl)-2-phenylpyrrolidine derivatives **439** in satisfactory yields.[253] It has also been reported that the Cu(I)-catalyzed combination of α-diazoester **436b** and an imine generates a transient azomethine ylide,[254] which is able to undergo diastereoselective cycloaddition with various activated dipolarophiles to afford in a convergent manner highly substituted pyrrolidines which include 1,2-diphenyl derivatives.[254]

An azaallyl cycloaddition strategy has also been used to prepare compound **440**, which is a key intermediate for the synthesis of the LTB_4 inhibitor BIRZ-227 (**441**).[255]

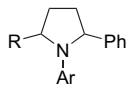


440
441

On the other hand, 1,2-diarylpyrrolidines **443a–d** have been obtained by treatment of *N*-[3,3-bis(phenylthio)propyl]anilides **442a–d** with the titanium(II) species $Cp_2Ti[P(OEt)_3]_2$.[256]



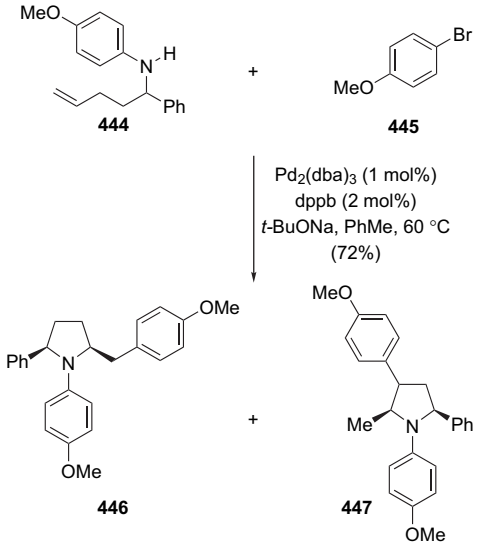
442a-d



443a-d

	R	Ar
a	H	Ph
b	H	2,5-$Me_2C_6H_3$
c	H	4-$MeOC_6H_4$
d	Me	Ph

Recently, a 10:1 mixture of the 1,2-diarylpyrrolidine **446** and the 1,2,4-triarylpyrrolidine **447** have been obtained in 72% yield by a Pd-catalyzed reaction of the *N*-arylamine **444** with the bromo derivative **445** (Scheme 48).[257]

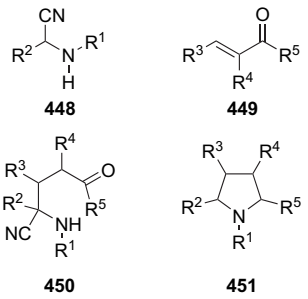


Scheme 48. Pd-catalyzed synthesis of a mixture of compounds **446** and **447**.

Similar Pd-catalyzed tandem *N*-arylation–carboamination reactions of γ-(*N*-arylamino)alkenes with aryl bromides have allowed access to a variety of *N*-arylpyrrolidines with good levels of diastereoselectivity and satisfactory yields.[257,258] Unfortunately, in most cases, the reactions furnished mixtures of regioisomers.

Very recently, polysubstituted pyrrolidines **451** that include some 1,2-diaryl derivatives have been obtained by α-deprotonation of α-aminonitriles **448** and 1,4-addition of the resulting stabilized carbanions to α,β-unsaturated carbonyl compounds **449** and reductive cyclization of the resulting δ-keto-α-aminonitriles **450**.[259] On the other hand, some 1,2-diaryl- and 1,2,5-triarylpyrrolidines **454**, in which the major diastereomer bears a cis relationship between the substituents at the 2- and 5-positions, have been synthesized in high yields by the reaction of aldimines, generated in situ from anilines **49** and aromatic aldehydes **452**, with 1,1-cyclopropanediesters **453** in the presence of a catalytic amount of $Yb(OTf)_3$.[260]

Worthy of mention also is a new catalytic procedure for the synthesis of 1,2-diphenylpyrrolidine (**443a**) via C^3_{sp}–H bond direct arylation of *N*-phenylpyrrolidine (**455**) with iodobenzene in *t*-BuOH at 150 °C for 18 h in the presence of 1.2 equiv of Cs_2CO_3 and 5 mol % of $Ru(H_2)_2(H)_2(PCy_3)_2$.[261] Compound **443a** has been found to be the major product

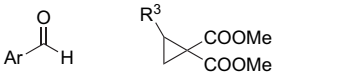


448 **449**

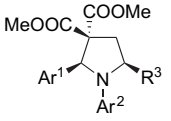
450 **451**

of this reaction which, however, also produces significant amounts of pyrrolidines **456** and **457**.[261]

Attention has also been turned in the literature to the development of efficient and convenient methods for the synthesis of 2-pyrrolidinones with two aryl groups on adjacent positions.[233a,262–268]

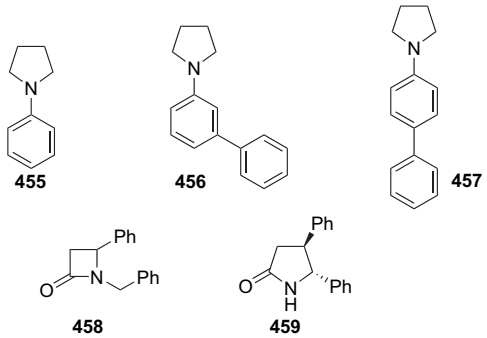


452 **453** : R^3 = H, alkenyl, aryl



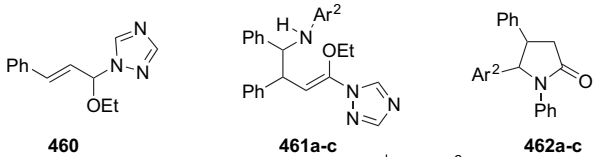
454 : R^3 = H, alkenyl, aryl

Thus, racemic *trans*-4,5-diphenyl-2-pyrrolidinone (**459**) has been obtained in 93% yield by LDA-induced ring enlargement of azetidinone **458**[262] and 1,4-diphenyl-5-aryl-2-pyrrolidinones **462a–c** have been prepared in high yields by deprotonation of the 1,2,4-triazole derivative **460** with 2 equiv of butyllithium followed by reaction with aldimines **64** (Ar^1=Ph) and acidic treatment of the resulting compounds **461a–c**.[263] Recently, racemic **459** has been resolved via the preparation of diastereomers with *N*-phthalyl-L-alanine chloride or D-alanine chloride and the absolute configuration of one of its enantiomers has been determined by X-ray crystallographic analysis.[267]



455 **456** **457**

458 **459**

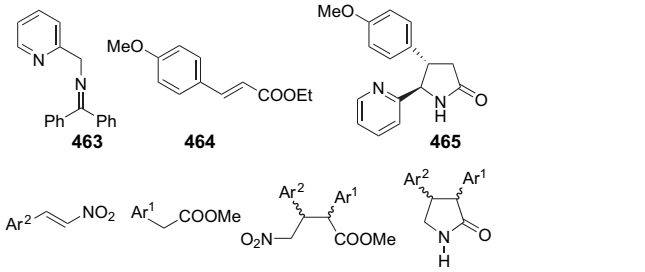


460 **461a-c** **462a-c**

	Ar^2
a	Ph
b	4-ClC_6H_4
c	4-MeC_6H_4

The racemic *trans*-4,5-diaryl-2-pyrrolidinone **465**, used as a key intermediate in the synthesis of the leukotriene-B_4 inhibitor BIRZ-227, has been synthesized on a multigram scale in 52% yield by a one-pot procedure in which the Schiff base **463** was reacted with ethyl 4-methoxycinnamate (**464**) in the presence of 0.5 equiv of aqueous 50% NaOH and 5 mol % $BnEt_3NCl$ and the resulting adduct was hydrolyzed in acidic conditions and then neutralized.[233a,264]

Stereoisomeric mixtures of several 3,4-diaryl-2-pyrrolidinones **469**, which include compound **469a**, have been synthesized by a Michael reaction of the nitroethene derivatives **466** with the esters **467**.[263]

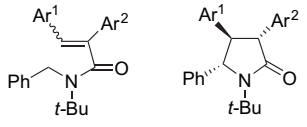


463 **464** **465** **466** **467** **468** **469**

469a : $Ar^1 = Ar^2$ = 3-indolyl

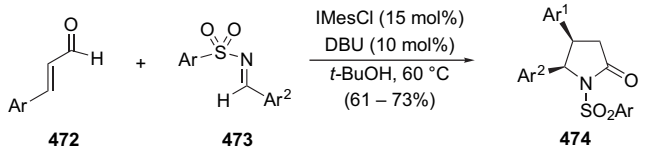
Hydrogenation over Raney Ni of the resulting methyl 4-nitrobutanoates **468** and subsequent lactonization in refluxing toluene in the presence of a small amount of NaH provided the required compounds **469** in low to moderate yields, which were then processed to give staurosporine derivatives.[265] It should be noted that compounds of the basic structure **469a** are known to be biologically active, but often the reported activity is low, probably because mixtures of diastereomers were synthesized and tested.[269] Nevertheless, these mixtures are part of patent claims.[270]

Recently, 3,4-diaryl-5-phenyl-2-pyrrolidinones **471** have been prepared in low to modest yields by the 5-*endo*-*trig*-cyclization reaction of the lithium derivatives obtained by treatment of the substituted acrylamides **470** with LDA in THF at 0 °C.[266]



470 **471**

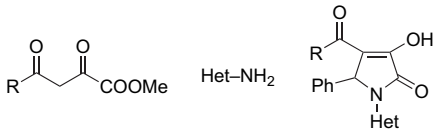
More recently, a variety of *cis*-1-arylsulfonyl-4,5-diaryl-2-pyrrolidinones **474** have been obtained in good yields and modes-to-good diastereomeric purities by annulation of the enals **472** and electrophilic imines **473** in *t*-BuOH at 60 °C in the presence of 15 mol % 1,3-bis(2,4,6-trimethylphenyl)-2-chloroimidazolium chloride (ImesCl) and 10 mol % DBU (Scheme 49).[269]



472 **473** **474**

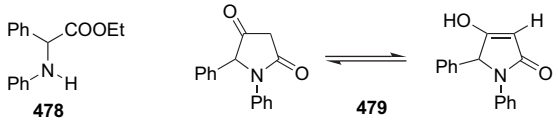
Scheme 49. Synthesis of compounds **474**.

Some data are also available from the literature on the synthesis of 3-hydroxy-3-pyrrolin-2-ones (pyrrolidine-2,3-diones) and pyrrolidin-2,4-diones (4-hydroxy-3-pyrrolin-2-ones) with two aryl groups on adjacent positions. Thus, some 4-acyl-5-phenyl-1-(2-heteroaryl)-3-hydroxy-3-pyrrolin-2-ones **477** have been prepared in high yield by brief heating of mixtures of equimolar amounts of α-ketoesters **475**, benzaldehyde and a heteroarylamine **476** in glacial acetic acid.[271,272] Interestingly, some of these heterocyclic derivatives have been shown to have moderate antimicrobial activity.[272]

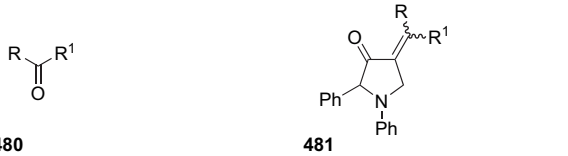


475 **476** **477**

On the other hand, 1,5-diphenylpyrrolidin-2,4-dione (**479**) has been prepared by refluxing ethyl 2-(phenylamino)phenylacetate (**478**) with acetyl chloride and treatment of the resulting *N*-acetyl derivative with Na in toluene at 120–130 °C followed by acidification at 0 °C.[273]



478 **479**



480

480a : R = 3,4-$Cl_2C_6H_3$; R^1 = H

480b : R = 4-ClC_6H_4 ; R^1 = Me

481

481a : R = 3,4-$Cl_2C_6H_4$; R^1 = H

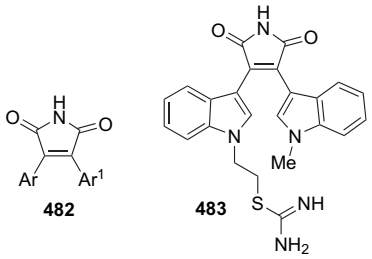
481b : R = 4-ClC_6H_4 ; R^1= Me

It is also worthy of mention that compounds **481a** and **481b**, obtained by condensation of **479** with the carbonyl compounds **480a** and **480b**, respectively, in an acidic medium under reflux, displayed activity against *Staphylococcus aureus* strains.[274]

6. 2,3-Diarylmaleimides (3,4-diaryl-3-pyrroline-2,5-diones) and 2,3-diarylsuccinimides (3,4-diarylpyrrolidine-2,5-diones)

6.1. Biologically active natural and unnatural 2,3-diarylmaleimides

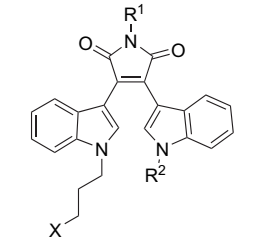
Natural and unnatural 2,3-diarylmaleimides **482** represent a class of compounds, which exhibit diverse biological activities. One of these interesting heterocycles is Ro-31-8220 (**483**), which is a synthetic analogue of naturally occurring (+)-staurosporine (**367**), an alkaloid isolated from the bacterium *Streptomyces staurosporeus*.[207] In fact, **483** is able to induce apoptosis independent of its ability to inhibit protein kinase C (PKC),[28] a family of serine–threonine specific kinases thought to be an essential element in the signal transduction of a variety of hormones, cytokines and growth factors[275] and which is implicated in a wide range of physiological processes including growth differentiation.[276]



482 **483**

The bis-indolylmaleimide GF-109203X (**484a**) like **367** is a potent PKC inhibitor,[29,277] which displays high selectivity as compared to five different protein kinases. Moreover, it is able to inhibit the necrotic cell death induced by oxidative stress in a variety of primary-cultured cells.[29]

Compounds **484b–d** are also PKC inhibitors.[278–280] and **484d**, which is orally adsorbed in rats, may represent an attractive lead in the development of even more potent inhibitors.[279]



484a : $R^1 = R^2 = H$; $X = NMe_2$
484b : $R^1 = R^2 = H$; X =
484c : $R^1 = R^2 = H$; $X = NH_2$
484d : $R^1 = H$; $R^2 = Me$; $X = NH_2$
484e : $R^1 = R^2 = Me$; $X = NH_2$
484f : $R^1 = Me$; $R^2 = H$; $X = NH_2$

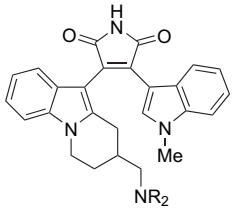
On the other hand, the maleimides **484b** and **484c** are also able to inhibit PDK1, a key kinase from the insulin signalling pathway,[29] and **484e** has been shown to be a potent inhibitor of H_2O_2-induced necrotic death of human leukaemia HL60 cells.[280]

Ro-31-8425 (**485**) and the corresponding *N*,*N*′-dimethyl derivative **486** are two conformationally restricted PKC inhibitors.[281,282] Compound **485** can also inhibit superoxide generation in human neutrophils activated by both receptor and post-receptor stimuli and **486** can antagonize phorbol ester-induced paw edema in mice.[282]

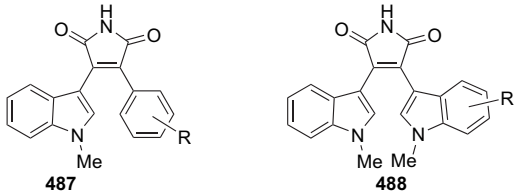
Some 2-phenyl-3-indolylmaleimides **487** have also been shown to be PKC inhibitors, but their activity proved to be lower than that of the 2,3-bis-indolylmaleimides **488**.[283]

The novel indolylindazolylmaleimides **489a** and **489b** have recently been identified as low-nanomolar inhibitors of PKC-β,[30] which is an enzyme induced in response to hyperglycemia in cardiac, aortic, renal and retinal tissues.

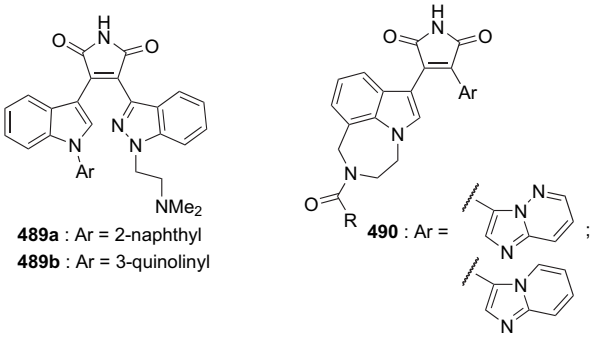
Interestingly, these substances have demonstrated excellent selectivity over other PKC isozymes and glycogen synthase-3β (GSK-3β),[30] a serine–threonine protein kinase involved in signalling from the insulin receptor.[284] On the other hand, **487a** and some 3-aryl-[1,7-aza-annulated-indol-3-yl]maleimides **490** have been reported as potent GSK-3 inhibitors.[285–287]



485 : R = H
486 : R = Me



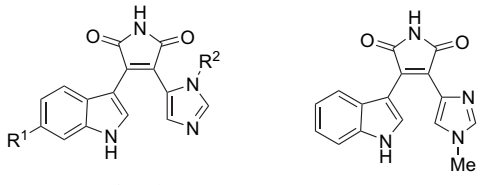
487 **488**
487a : $R = 2,4\text{-}Cl_2$



489a : Ar = 2-naphthyl
489b : Ar = 3-quinolinyl
490 : Ar =

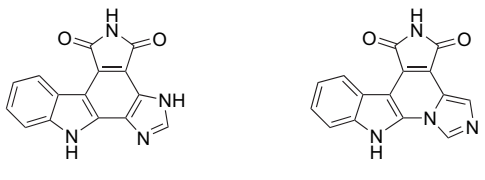
Moreover, some compounds **490**, which show a high degree of selectivity against both serine–threonine and tyrosine kinases, have been shown to be highly efficacious oral agents for reduction of blood glucose in the ZDF rat model of non-insulin dependent diabetes mellitus.[287]

The 2,3-diarylmaleimide moiety is also present in a number of naturally occurring compounds, some of which are endowed with relevant biological activities. Thus didemnimides A (**491a**), B (**491b**), C (**491c**) and D (**491d**) are



491a : $R^1 = R^2 = H$
491b : $R^1 = Br$; $R^2 = H$
491c : $R^1 = H$; $R^2 = Br$
491d : $R^1 = Br$; $R^2 = Me$

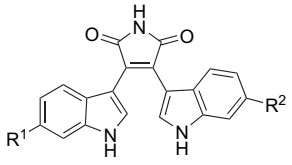
492



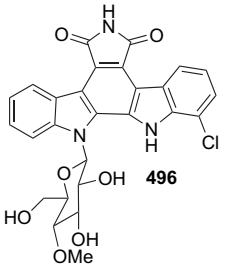
493 **494**

members of a class of indole–maleimide–imidazole tricyclic compounds isolated from the Caribbean mangrove ascidian *Didemnum conchyliatum* that are predator deterrents.[288] Compounds **491a** and **491b** have also been found together with didemnimide E (**492**) in the crude extracts of the ascidian *Didemnum granulatum* collected in Brazil.[289] Interestingly, these extracts showed activity in a screen for G2 cell cycle checkpoint inhibitors and this activity was demonstrated to be due to granulatimide (**493**) and isogranulatimide (**494**) present in the extracts.[289]

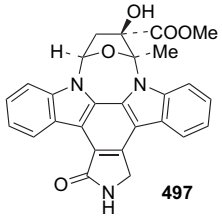
Arcyriarubins A (**495a**), B (**495b**) and C (**495c**), which represent the simplest members of natural bis-indolylmaleimides,[290] are a family of pigments produced by slime moulds (*Myxomycetes*). These substances are structurally related to the aglycon of (+)-staurosporine (**367**),[207] the potent antitumour agent rebeccamycin (**496**) isolated from *Nocardia aerocoligenes*,[291] SF-2370 (**497**)[292] and other biologically active metabolites from *Streptomycetes*.



495a : $R^1 = R^2 = H$
495b : $R^1 = OH$; $R^2 = H$
495c : $R^1 = R^2 = OH$

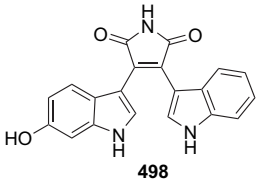


496

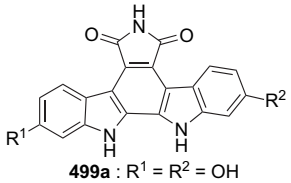


497

Recently, arcyriarubin C (**495c**) has been isolated together with dihydroarcyriarubin C (**498**) and arcyriaflavin C (**499a**) from the fruit bodies of *Arcyria ferruginea*.[293] Moreover, arcyriaflavin C, which has been found to exhibit a cell cycle inhibition effect at G1 and G2/M stage at 10 and 100 ng/mL, respectively, has been isolated from *Tubifera cassaparyi*, together with arcyriaflavin B (**499b**).[293]

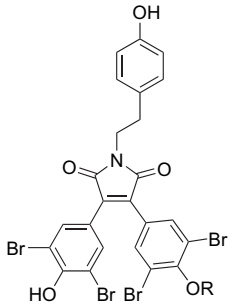


498



499a : $R^1 = R^2 = OH$
499b : $R^1 = OH$; $R^2 = H$

Arcyriaflavins are also the main pigments of *Arcyria denudata*.[291b,294] Some of their derivatives have shown antimicrobial activity against *Bacillus cereus*,[25] antitumour activity against P388 leukaemia cells,[25] and have been demonstrated to be able to inhibit tyrosine and serine kinases.[25,295,296] On the other hand, some *N*-glucosyl derivatives of arcyriarubin A have demonstrated potent antiproliferative activities.[297]



500a : R = H
500b : R = Me

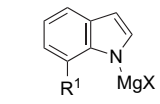
Finally, two 2,3-maleimides, polycitrin A (**500a**) and polycitrin B (**500b**), have been isolated from the ascidian *Polycitor* sp., together with polycitone A (**12**).[17] This last compound was shown to be a potent inhibitor of the HIV-1 RT DNA polymerase activity, but polycitrin A exhibited a significantly lower activity.[27]

6.2. Synthesis of symmetrical and unsymmetrical 2,3-diarylmaleimides and 2,3-diarylsuccinimides

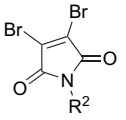
The bis-indolylmaleimides are valuable intermediates in the synthesis of the aglycones of indolocarbazole alkaloids such as staurosporine and rebeccamycin. Thus several methods have been developed for the preparation of these heterocycle derivatives.

A convenient synthesis of symmetrical and unsymmetrical bis-indolylmaleimides involves the reaction of indolyl Grignard reagents with dihalomaleimides. This method was investigated in 1980 by Steglich and co-workers who prepared compound **503a** in 60% yield by reaction of indolylmagnesium iodide (**501a**) with *N*-methyl-2,3-dibromomaleimide (**502a**) in benzene at 25 °C in the presence of a small amount of HMPA.[16] The method was then used by Kaneko,[298] the Weinreb group[299] and Xie and Lown[300] for the synthesis of **503b** from **501b** and **502b** and of **503c** from **501c** and **502c**.

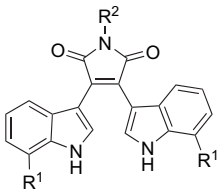
A few years later, Steglich reported that the outcome of the reaction between **501c** and **502a** is strongly dependent on the solvent and that, in toluene, the reaction gives the bis-indolyl



501a : $R^1 = H$; X = I
501b : $R^1 = Cl$; X = I
501c : $R^1 = H$; X = Br



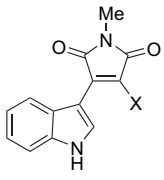
502a : $R^2 = Me$
502b : $R^2 = CH_2OBn$
502c : $R^2 = Bn$



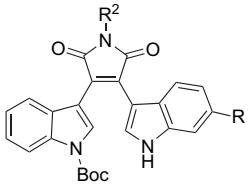
503a : $R^1 = H$; $R^2 = Me$
503b : $R^1 = Cl$; $R^2 = CH_2OBn$
503c : $R^1 = H$; $R^2 = Bn$

compound **503a** in 70% yield, whereas, in THF, the monosubstitution product **504a** is obtained in 74% yield.[301] This last compound, after protection of the indole NH group with a Boc residue, was coupled with **502a** in refluxing THF to give the unsymmetrical substituted bis-indolylmaleimide **505a** in 85% yield.[301] A similar procedure was then followed to prepare **505b**, which was used as a precursor to arcyriarubin B (**495b**).[301]

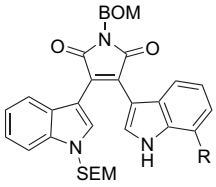
Subsequently, the Danishefsky group employed a similar protocol to prepare compound **506a**, which was used as a key intermediate in a total synthesis of rebeccamycin (**496**),[302] and the unsymmetrical bis-indolylmaleimide **506b**, which was employed as an intermediate in the first total synthesis of naturally occurring (+)-staurosporine (**367**) and its enantiomer.[40]



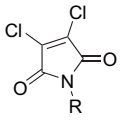
504a : X = Br
504b : X = Cl



505a : R = H
505b : R = THPO



506a : R = Cl
506b : R = H
(SEM = $Me_3SiCH_2CH_2$-O-CH_2)

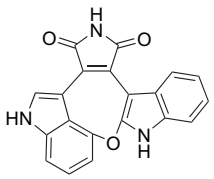


507a : R = Me
507b : R = H
507c : R = Bn

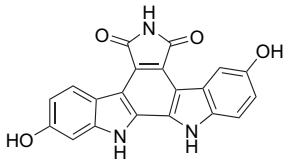
In 1995, Faul and co-workers reported that even 2,3-dichloro-*N*-methylmaleimide (**507a**) can be converted into the bis-indolylmaleimide **503a** by a coupling reaction with 2.2 equiv of the Grignard reagent **501c** in THF and toluene.[303] They also found that the formation of **503a** was reduced and the amount of compound **504b** increased as the ratio of THF to toluene increased and observed that the formation of **503a** became favoured when the solvent was changed from THF to Et_2O.[303] Moreover, they developed a direct method to prepare arcyriarubin A (**495a**) in 72% yield, which involved treatment of 2,3-dichloromaleimide (**507b**) with 5 equiv of **501c** in a 5:1:1 mixture of toluene, Et_2O and THF, respectively, at 90 °C for 24 h.[303]

Bis-indolylmaleimides, prepared as mentioned above or by analogous protocols from 2,3-dibromo-*N*-methylmaleimide (**502a**) or *N*-benzyl-2,3-dichloromaleimide (**507c**) and indolylmagnesium halides or indolyllithium, have been employed in practical syntheses of natural products which include arcyroxin A (**508**),[41] arcyriaflavins A (**499a**), B (**499b**) and D (**509**),[42] the dechlororebeccamycin aglycon[304] and macrocyclic bis-indolylmaleimides in which the indole nitrogens are linked with a tether.[305]

On the other hand, the bis-(7-azaindolyl)maleimide **512a** has recently been prepared according to a strategy that involves a monocoupling reaction of **502a** with 2 equiv of



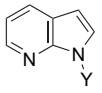
508



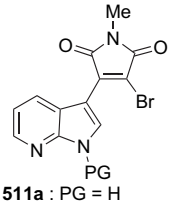
509

the 7-azaindolic Grignard reagent **510b** in toluene and CH_2Cl_2, protection of the NH indolic group of the resulting 3-(7-azaindolyl)-2-bromo-*N*-methylmaleimide (**511a**) and a coupling reaction of the resulting compound **511b** with 2 equiv of the lithium derivative prepared by treatment of 7-azaindole (**510a**) with a molar excess of LHMDS.[305] Compound **512a** was then converted easily into **512b** by reaction with 2 equiv of TBAF in refluxing methanol.[305]

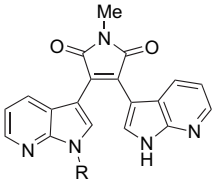
A similar efficient protocol based on the use of 2,3-dibromo-*N*-methylmaleimide (**502a**) has been employed to prepare a series of 3-[1-methyl-2,5-dioxo-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrol-3-yl]indole-1-carboxylic acid *tert*-butyl esters **513**.[306] Compounds **512** and **513** have then been used to prepare substances containing an indolocarbazole framework, which could be useful for the preparation of glycosylated derivatives susceptible to target topoisomerase I and/or certain protein kinases.[306]



510a : Y = H
510b : Y = MgBr

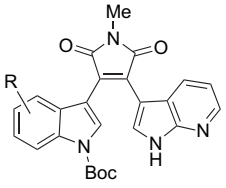


511a : PG = H
511b : PG = $PhSO_2$



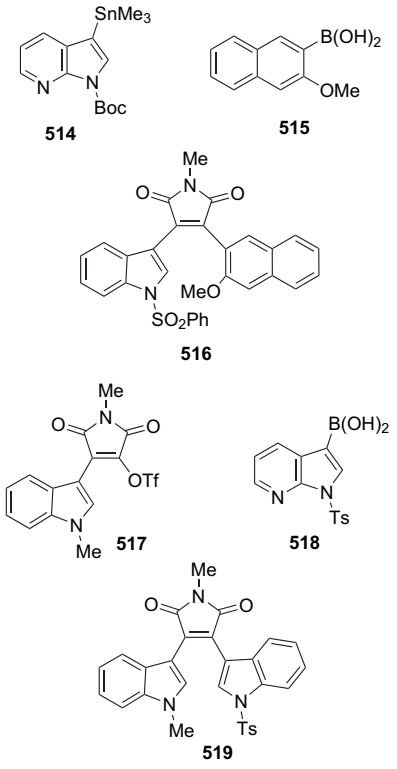
512a : R = $PhSO_2$
512b : R = H

More recently, 1-methyl-3,4-bis(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrrole-2,5-dione (**512b**) has been synthesized in 41% yield by a Stille reaction of **507a** with 3 equiv of 3-trimethylstannylpyrrolo[2,3-*b*]pyridine-1-carboxylic acid *tert*-butyl ester **514** in toluene at 95 °C in the presence of 4.7 equiv of LiCl and 4.7 mol % $PdCl_2(PPh_3)_2$.[307] On the other hand, the unsymmetrical 2,3-disubstituted maleimide **516** has been prepared in 80% yield by a Suzuki reaction of **511b** with 3-methoxynaphthalene-2-boronic acid (**515**) in dioxane and water at 100 °C in the presence of 2 equiv of K_2CO_3, 10 mol % $Pd(OAc)_2$ and 20 mol % PPh_3.[308]

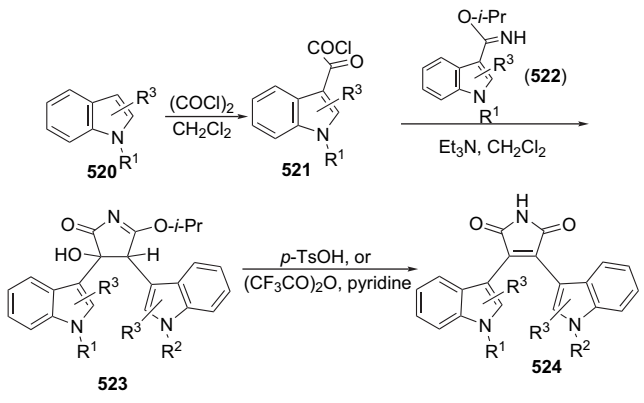


513 : R = H; 9-OBn; 10-OBn; 11-$OCHPh_2$

Very recently, Suzuki-type reactions between 2,3-diiodomaleimides and various organoboron derivatives have been used as key steps in the synthesis of substituted bis(fur-2-yl)-, bis(fur-3-yl)- and bis(thien-2-yl)maleimides with potential antidiabetic properties.[309] A Suzuki reaction had previously been employed to prepare the unsymmetrical 2,3-(3-indolyl)maleimide **519** from the triflate **517** and the boronic acid **518** in 55% yield.[310] This reaction was performed in dioxane at 15–25 °C in the presence of 3 equiv of CsF, 3 equiv of CsBr and a catalytic amount of $Pd_2(dba)_3 \cdot CHCl_3$.



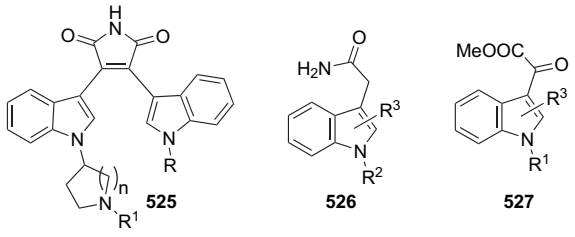
In 1993, Hill and co-workers synthesized symmetrical and unsymmetrical bis-indolylmaleimides **524** by a mild and flexible method that involved the conversion of indoles **520** into indolyl-3-glyoxylyl chlorides **521** and the reaction of these compounds with appropriately substituted indolyl-3-acetimidates **522** in the presence of a molar excess of Et_3N, followed by hydrolysis of the resulting hydroxypyrroline derivatives **523** (Scheme 50).[311]



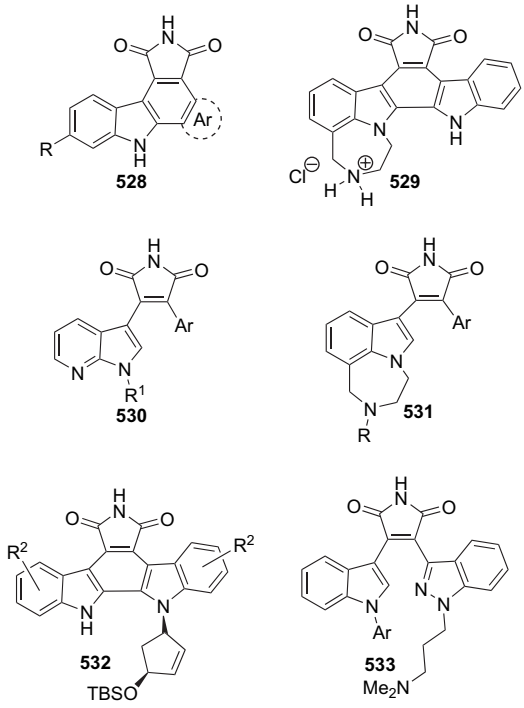
Scheme 50. Synthesis of compounds **524**.

More recently, a similar method has been employed to prepare in low yields a new class of *N*-(azacycloalkyl)bis-indolylmaleimides **525**, which are able to produce selective inhibition of PKCβ.[312]

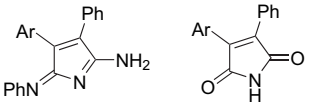
Previously, symmetrical and unsymmetrical bis-indolylmaleimides **524** have alternatively been synthesized by the reaction of readily available indole-3-acetamides **526** with methyl indolyl-3-glyoxylates **527** in THF in the presence of *t*-BuOH.[313]

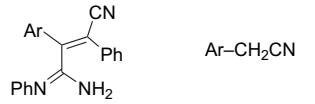


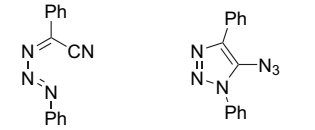
This protocol, which provides the required compounds in 84–100% yield, has subsequently been applied extensively for the preparation of substances that include natural products such as didemnimides A (**491a**) and B (**491b**),[314] rebeccamycin (**496**),[43] congeners of isogranulatimide,[45] arylpyrrolo[3,4-*c*]carbazoles and indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **528**, which are selective G1 blockers of the cell cycle,[315] *N*-(azacycloalkyl)bis-indolylmaleimides **525**, which are selective inhibitors of PKCβ,[316] indolocarbazole **529**, which was shown to be a potent kinase inhibitor,[317] acyclic 3-(7-azaindolyl)-4-(hetero)arylmaleimides **530**, which include potent and selective inhibitors of GSK-3β,[318] 3-(hetero)aryl-4-[1,7-aza-annulatedindol-3-yl]maleimides **531**, some of which exhibit potent GSK-3 inhibitory activity,[286,287] unsymmetrical indolopyrrolocarbazoles mono-*N*-substituted with a pentacycle, (**532**),[319] and novel indolylindazolylmaleimides **533**, which include potent inhibitors of PKC-β.[30]



On the other hand, some 2-aryl-3-phenylmaleimides **535** have been prepared by acid-catalyzed hydrolysis of the diarylmaleimidine derivatives **534**, which were easily obtained by isomerization of α-aryl-β-cyano-*N*-phenylcinnamidines **536** by warm alcoholic alkali.[320] The latter compounds could be synthesized in 22–68% yield by a base-catalyzed reaction of arylacetonitriles **537** with 3-(α-cyanobenzylidene)-1-phenyl-1,2,3-triazene (**538**), the product of thermolysis of 5-azido-1,4-diphenyl-1,2,3-triazole (**539**).[320]

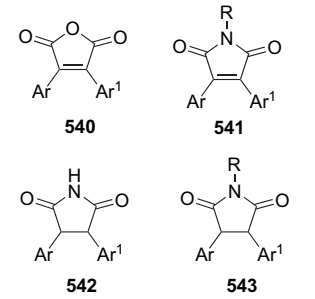




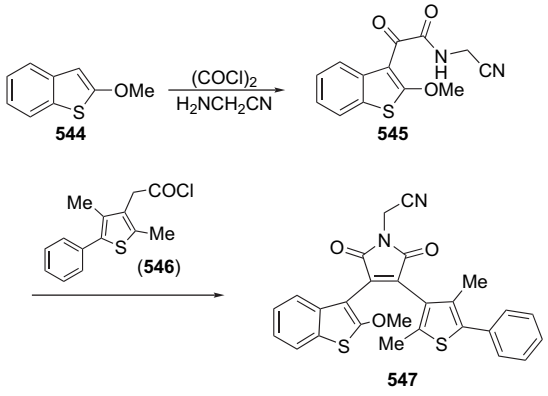


2,3-Diarylmaleimides **482** have occasionally been prepared from the corresponding maleic anhydrides by the standard method of heating at high temperature in the presence of ammonia or an ammonia source[321] or by a procedure also applicable to maleimides containing a sensitive functionality such as an ester or a nitrile group,[322] which involves treatment with a mixture of methanol and hexamethyldisilazane (HMDS) at room temperature.[323] On the other hand, at least in principle, the procedure used to synthesize some *N*-alkyl- and *N*-aryl-succinimides (pyrrolidine-2,5-diones) and -maleimides by a Lewis acid-promoted reaction of HMDS and primary amines with succinic anhydrides and maleic anydrides,[324] respectively, in refluxing benzene[325] might also be employed for preparing *N*-substituted 2,3-diarylsuccinimides **543** and *N*-substituted 2,3-diarylmaleimides **541**.

Established protocols to prepare the latter compounds require heating of maleic anhydrides **540** with primary amines in phenol and Hünig base,[324] in ethanol[141] or DMF[326] or the N-alkylation of the potassium salts of 2,3-diarylmaleimides **482**.[327] Alternatively, maleimides **482** and **541** have been obtained by oxidation of the corresponding 2,3-diarylsuccinimides **542** and **543**, respectively, with 1 equiv of DDQ in CH_2Cl_2 or benzene at room temperature.[44,33]

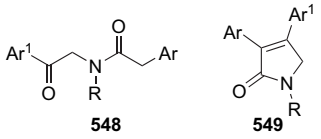


In 1998, the unsymmetrical *N*-cyanomethyl-2,3-diheteroarylmaleimide **547** was synthesized by treatment of 2-methoxythiophene (**544**) with oxalyl chloride and aminoacetonitrile and reaction of the resulting compound **545** with the carboxylic acid chloride **546** (Scheme 51).[328]



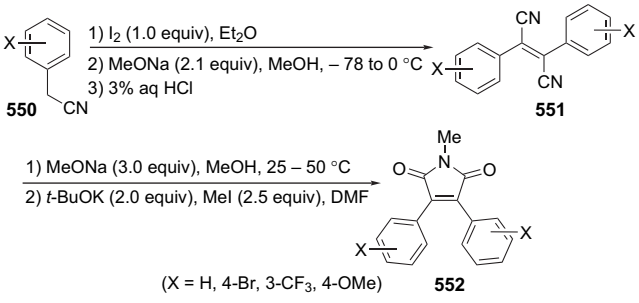
Scheme 51. Synthesis of compound **547**.

More recently, a variety of symmetrical and unsymmetrical *N*-substituted 2,3-diarylmaleimides have been prepared in 59–71% yield by intramolecular ring closure of phenacyl amides **548** with DBU in acetonitrile under an oxygen atmosphere.[224]



Interestingly, this procedure furnished 3,4-diarylpyrrolidin-2-ones **549** in good-to-excellent yields when K_2CO_3 was used in place of DBU.[328]

Finally, in 2004, *N*-methyl-2,3-diarylmaleimides **552** have been conveniently prepared from arylacetonitriles **550** through the diaryl-substituted fumaronitriles **551** by a two-step effective method illustrated in Scheme 52.[329]



Scheme 52. Synthesis of compounds **552**.

7. Conclusions and perspectives

The vicinal diaryl-substituted pyrrole, pyrroline and pyrrolidine derivatives include natural and unnatural compounds with notable biological and pharmacological properties.

These classes of heterocyclic derivatives have stimulated great interest from synthetic and medicinal chemists. We believe that this interest will be secured for some time yet, owing to the continued attention being paid to these and similar heterocycle derivatives in medicinal chemistry and drug development and the progresses in synthetic methodology obtained in recent years. With regard to this last aspect, it is worth mentioning the considerable recent interest, particularly in terms of synthetic and atom efficiency, in the development and application of selective methods to form C–C bonds via C–H activation of (hetero)arenes, in which only one component of the transition metal-catalyzed reaction needs to possess a reactive functional group.[330]

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Biographical sketch

Renzo Rossi was born in Pisa (Italy) and graduated in Chemistry with first-class honours at the University of Pisa in 1960 defending a thesis performed under the guidance of Professor Piero Pino. In 1969, he became Assistant Professor and in 1971 he earned the *libera docenza* in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full Professor of Organic Chemistry at the University of Calabria. In 1982, he joined the University of Pisa again where he has held the Chair of Chemistry of Naturally Occurring Compounds. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. At the beginning of his career, he was interested in stereochemistry, the study of the chemistry and bioactivity of insect pheromones and the synthesis of insecticidal unsaturated carboxyamides, acetylenic and thiophenic phototoxins, structural analogues of naturally occurring fungicidal compounds of agrochemical interest and natural products useful for controlling insects and fungi which are devasting pests of historical and cultural papery and wooden materials. His current research interests include the total synthesis of naturally occurring compounds of biological and/or pharmacological interest, the study of transition metal-catalyzed carbon–carbon and carbon–heteroatom bond forming reactions and their applications for the synthesis of pharmacologically active compounds, and the design and development of new, efficient and selective methods for the synthesis of vicinal diaryl-substituted heterocycles that include potential antineoplastic derivatives. He is a fellow of the Royal Society of Chemistry and the Società Chimica Italiana.

Fabio Bellina was born in Catania (Italy) in 1964. He studied Chemistry at the University of Pisa and received his Laurea Degree in 1990 under the supervision of Professor R. Rossi. After his national service (1991–1992) in 1992 he joined the University of Pisa as an Organic Chemistry Researcher at the Dipartimento di Chimica e Chimica Industriale, working under the supervision of Professor R. Rossi. In October 2003, he was appointed by the Faculty of Science of the University of Pisa as an Associate Professor of Organic Chemistry. Most of his research has been devoted to the study of transition metal-catalyzed reactions and their application to the selective synthesis of bioactive natural and synthetic heterocyclic compounds, and particularly of substances which are cytotoxic against human tumour cell lines.