Synthesis and applications of bipyrazole systems

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Abstract
This review focuses on the synthetic methodologies towards ten main classes of bipyrazole systems (according to the type of connection between them): 1,1'-, 1,3'-, 1,4'-, 1,5'-, 3,3'-, 3,4'-, 3,5'-, 4,4'-, 4,5'- and 5,5'-junctions. The research and industrial applications of these bipyrazoles are reported as well.

Keywords: Pyrazoles, bipyrazoles, synthesis, cycloaddition, heterocycles

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1. Introduction

Three main types of connections between two pyrazole moieties can be considered; *N,N*-, *C,N*-, and *C,C*-linked bipyrazoles. According to numbering there are pertinent ten systems of bipyrazole which differ in the position of the bond between the two pyrazole rings as shown in Figure 1.

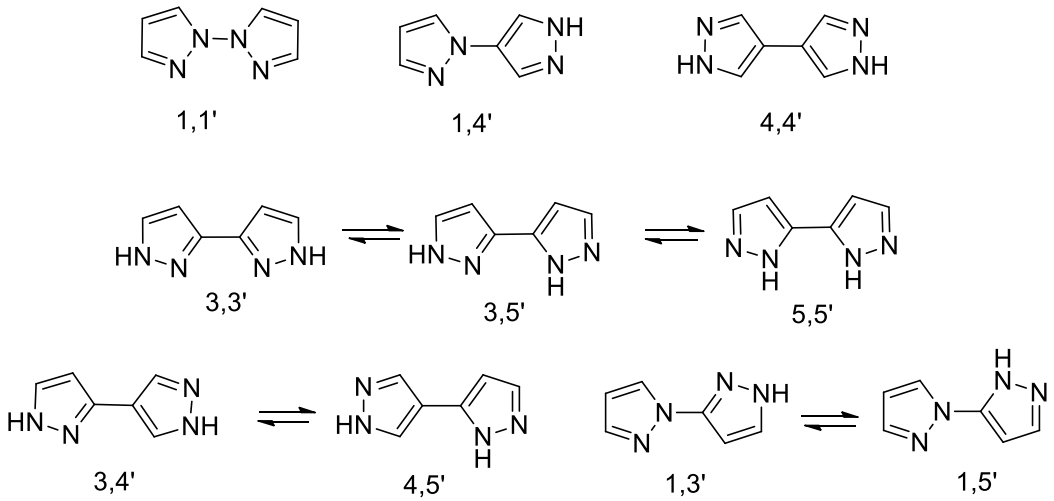


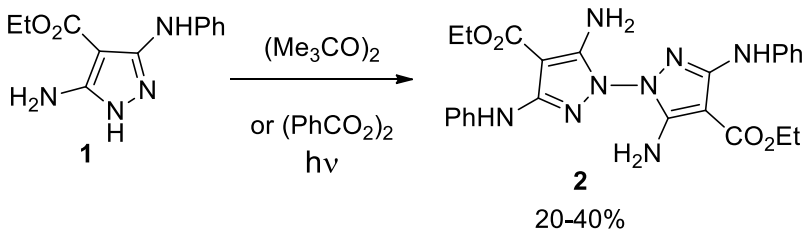
Figure 1

The *NH*-forms of all of these compounds represented in Figure 1, except the 1,1'-, 1,4'- and 4,4'-forms, are subject to annular tautomerism.[1,2] Bipyrazoles were synthesized for the first time in 1893.[3] Since then many publications about bipyrazole derivatives have been reported in the literature.[4] Such compounds are very interesting class of heterocycles that have remarkable pharmacological activities. For example, they were reported to possess potential antitumor,[5] anti-inflamatory,[6-8] antimicrobial,[9] cytotoxic,[10,11] antiallergic,[12] cardiovascular[13] and diuretic[14] activities. Bipyrazoles were also found to be useful as insecticides,[15] herbicides,[16] fungicides,[17-19] in the photographic and paint industry,[20-22] and in the synthesis of heat resistant polymers.[23] Furthermore, bipyrazole derivatives were used as agents for preventing or treating various diseases induced by active oxygen,[24] and as agents for free radical scavenging.[25] In the current review article, the bipyrazole systems are classified according to the type of linkage between the two rings and a survey on the synthesis and applications of all those bipyrazole systems is presented covering all publications till 2011.

2. Synthesis and Reactions of Bipyrazoles

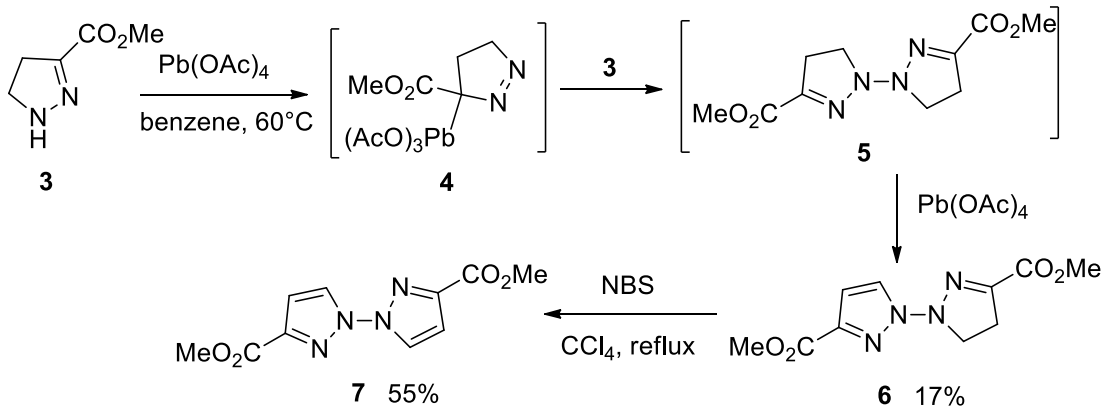
2.1. 1,1'-Bipyrazoles

Photolysis of ethyl 5-amino-3-(phenylamino)pyrazole-4-carboxylate **1**, which is a very good antioxidant, with *tert*-butyl peroxide or with dibenzoyl peroxide under mild reaction conditions resulted in radical dimerization of the pyrazole **1** and led to the formation of the 1,1'-bipyrazole derivative **2** in 40 and 20% yields, respectively (Scheme 1).[26]



Scheme 1

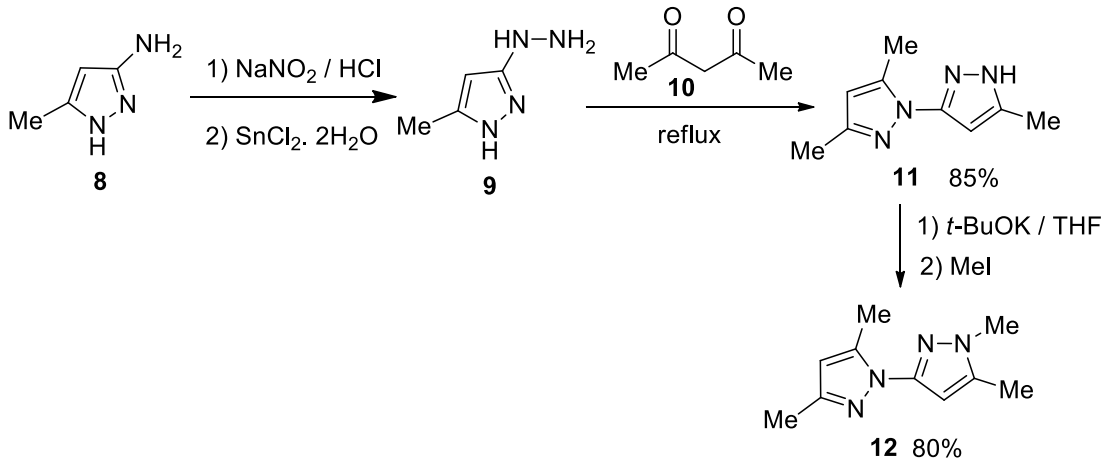
Treatment of 3-methoxycarbonyl-2-pyrazoline **3** with 1.1 equivalent of lead tetraacetate in benzene at 60 °C gave the pyrazoline intermediate **4** which underwent further attack on **3** to give the 1,1'-bipyrazole derivative **6** in 17% yield. The oxidation of **6** with *N*-bromosuccinimide (NBS) in refluxing carbon tetrachloride in the presence of few drops of dry pyridine gave the symmetrical 3,3'-dimethoxycarbonyl-1,1'-bipyrazole **7** in 55% yield (Scheme 2).[27]



Scheme 2

2.2. 1,3'-Bipyrazoles

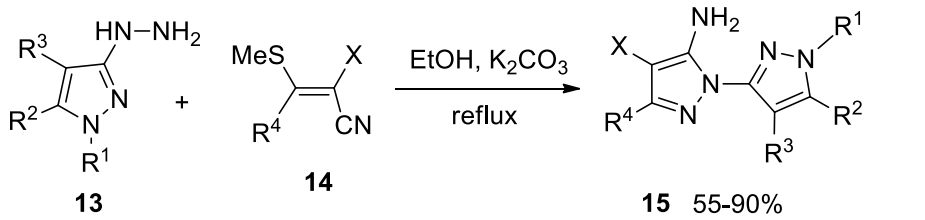
Diazotization of 3-amino-5-methylpyrazole **8** in HCl followed by reduction with tin chloride gave 3-hydrazino-5-methyl-1*H*-pyrazole **9**. Cyclocondensation reaction of **9** with acetylacetone **10** afforded 3,5,5'-trimethyl-1'*H*-1,3'-bipyrazole **11** in high yield. The methylation of **11** in the presence of *t*-BuOK led to the formation of 1',3,5,5'-tetramethyl-1'H-1,3'-bipyrazole **12** in high yield (Scheme 3).[28-30]



Scheme 3

The 1,3'-bipyrazole derivatives **15** were prepared in good yields by cyclocondensation of the acrylonitrile derivatives **14** with 3-pyrazolylhydrazines **13** in the presence of potassium

carbonate in refluxing ethanol (Scheme 4).[16,31]

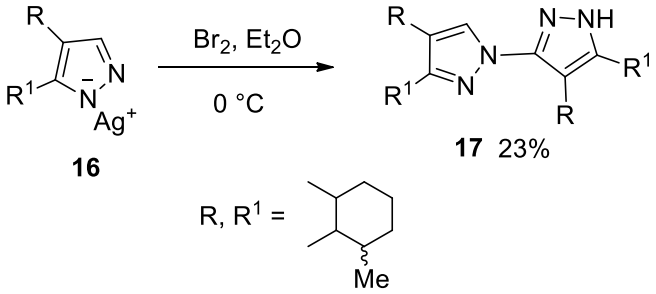


R^1 = H, Me, Et; R^2 = H, Me, OMe, SMe, CF_3; R^3 = H, Cl, Br, CN, CO_2Et

R^4 = H, Me, SMe, CF_3, Ph; X = H, CN, CO_2Et,

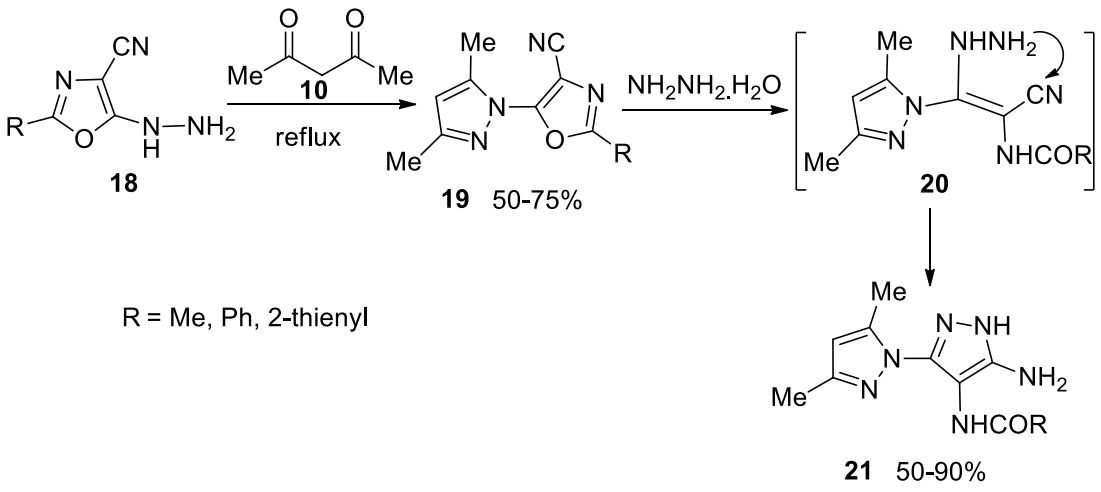
Scheme 4

Bromination of a cold solution of the silver salt of pyrazole **16** in ether at 0 °C resulted in the formation of 1,3'-bipyrazole derivative **17** as outlined in Scheme 5.[32]



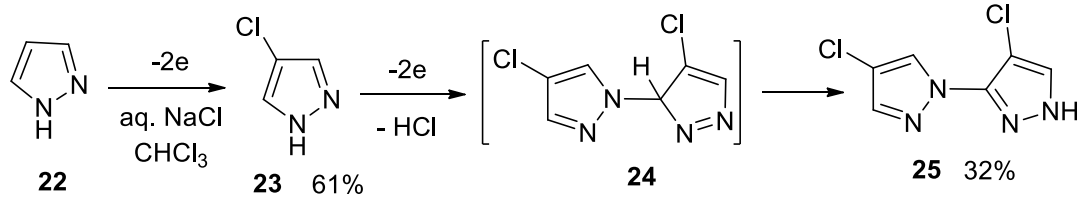
Scheme 5

Transformation of the 5-hydrazino-1,3-oxazole-4-carbonitriles **18** into 5-(pyrazol-1-yl)-1,3-oxazole-4-carbonitriles **19,** in good yields, was achieved upon its heating with acetylacetone **10**. Further treatment of 5-(pyrazol-1-yl)-1,3-oxazole-4-carbonitriles **19** with hydrazine hydrate in refluxing ethanol resulted in the opening of 1,3-oxazole ring of **19** and furnished the corresponding 1,3'-bipyrazoles **21** in moderate to high yields *via* the intermediates **20** as depicted in Scheme 6.[33,34]



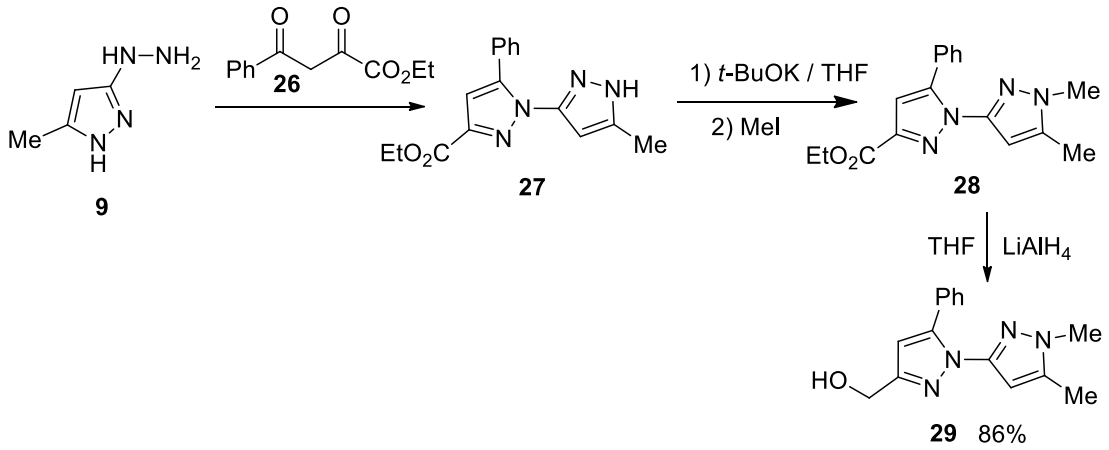
Scheme 6

Electrochlorination of the unsubstituted pyrazole **22** in aqueous NaCl solution in the presence of $CHCl_3$ on Pt anode at a current of 3 A and 15 °C led to the formation of 4-chloropyrazole **23** which underwent further dimerization under the reaction condition to give 4,4'-dichloro-1,3'-bipyrazole **25** in reasonable yield, through the intermediate **24** (Scheme 7).[35]



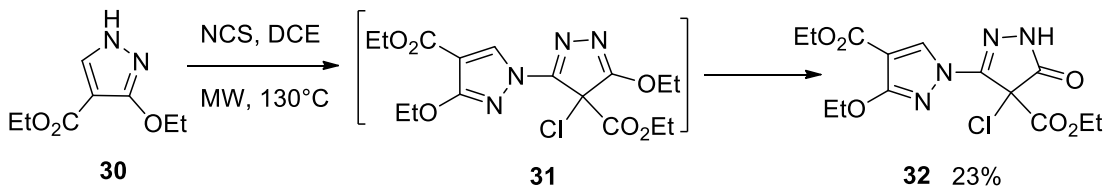
Scheme 7

Treatment of 3-hydrazinopyrazole **9** with the benzoylpyruvate ester **26** yielded the 1,3'-bipyrazole ester derivative **27** in 36% yield. Methylation of **26** in the presence of *t*-BuOK gave the 1,3'-bipyrazole derivative **28** in 29%. Finally, reduction of **28** using $LiAlH_4$ in THF afforded 1,5'-dimethyl-3-hydroxymethyl-5-phenyl-1,3'-bipyrazole **29** in 86% yield (Scheme 8).[36]



Scheme 8

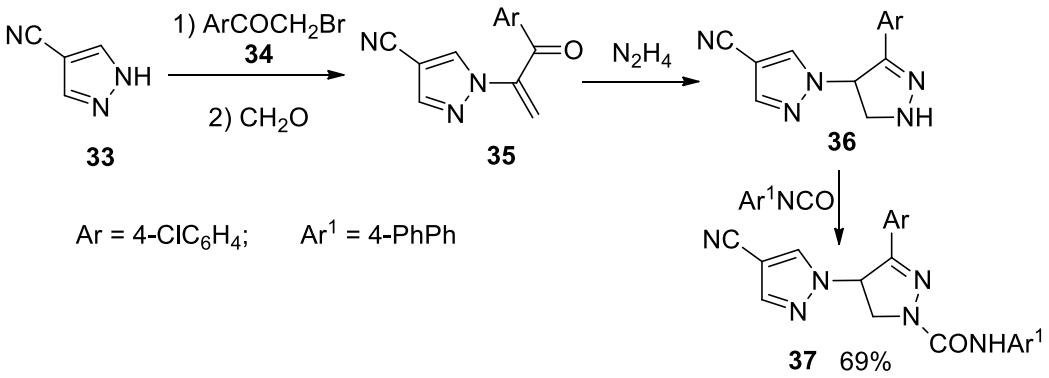
5-Chlorination of ethyl 3-ethoxypyrazole-4-carboxylate **30** with *N*-chlorosuccinimide (NCS) under microwave irradiation at 130 °C in dichloroethane (DCE) led to the formation of the 1,3'-bipyrazole derivative **32** in 23%. Mechanistically, occurrence of **32** was suggested *via* the hydrolysis of the 4-chlorinated ethoxypyrazole moiety of the intermediate **31** upon working-up of the reaction (Scheme 9).[37,38]



Scheme 9

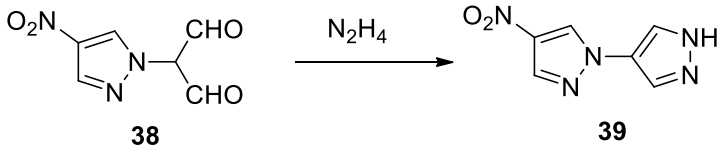
2.3. 1,4'-Bipyrazoles

Reaction of 1*H*-pyrazole-4-carbonitrile **33** with 4-chlorophenacyl bromide **34** followed by condensation with formaldehyde resulted in the formation of the pyrazole derivative **35**. When the latter compound was heated with hydrazine, the 1,4'-bipyrazole **36** was obtained. Reaction of the 1,4'-bipyrazole **36** 4-phenylphenylisocyanate afforded the 1,4'-bipyrazole derivative **37** in 69% yield (Scheme 10).[39,40]



Scheme 10

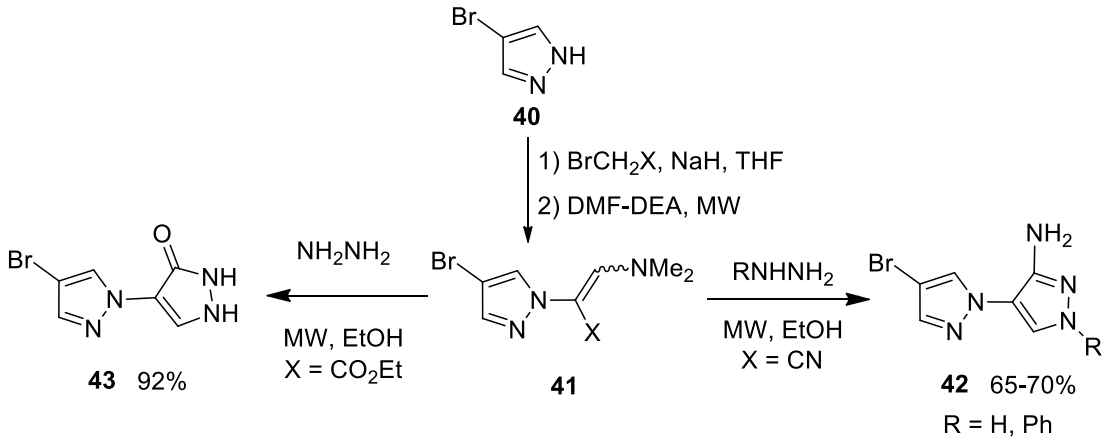
4-Nitro-1'*H*-1,4'-bipyrazole **39** was obtained *via* condensation reaction of 2-(4-nitro-1*H*-pyrazol-1-yl)malonaldehyde **38** with hydrazine hydrate (Scheme 11).[41]



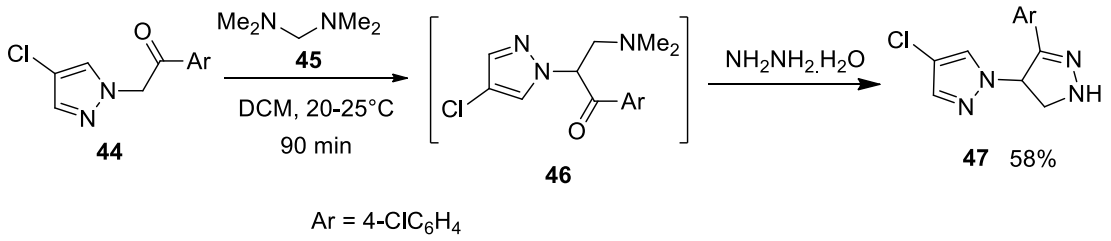
Scheme 11

Alkylation of 4-bromopyrazole **40** with ethyl bromoacetate or bromoacetonitrile in anhydrous THF, followed by formylation with dimethyl formamide-diethyl acetal (DMF-DEA) under microwave irradiating condition gave the 2-(4-bromopyrazol-1-yl)-3-dimethylaminoacrylic acid derivatives **41** (X = CN, CO_2Et)**.** Further microwave irradiation of **41** (X = CN) with hydrazines in ethanol afforded the corresponding 1,4'-bipyrazoles **42** in good yields. Similar heating of **41** (X = CO_2Et) and hydrazine gave the 1,4'-bipyrazole derivative **43** in excellent yield (Scheme 12).[42]

Keeping a mixture of *bis*(dimethylamino)methane **45** and α-(4-chloro-1-pyrazolyl)-4-chloroacetophenone **44** in dichloromethane at 20-25 °C for 90 min gave the non-isolable intermediate **46** which upon treatment with hydrazine hydrate gave the 1,4'-bipyrazole derivative **47** in 58% yield (Scheme 13).[43]

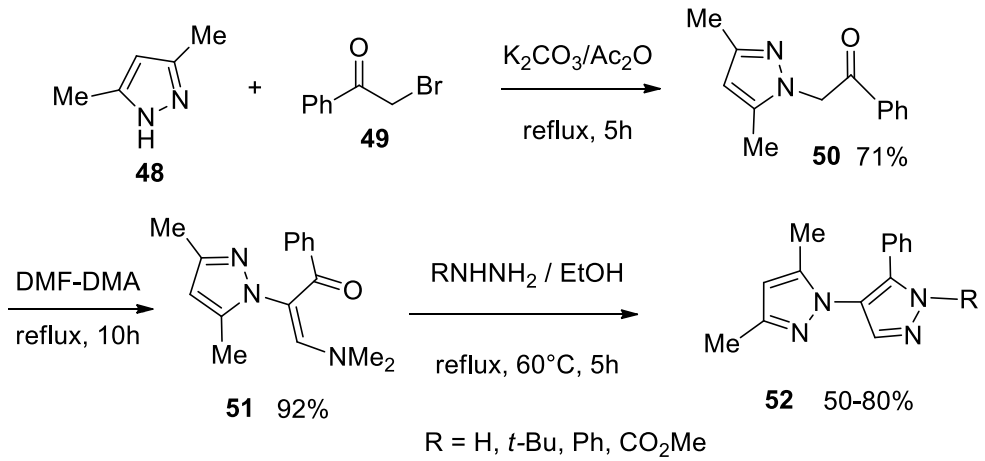


Scheme 12



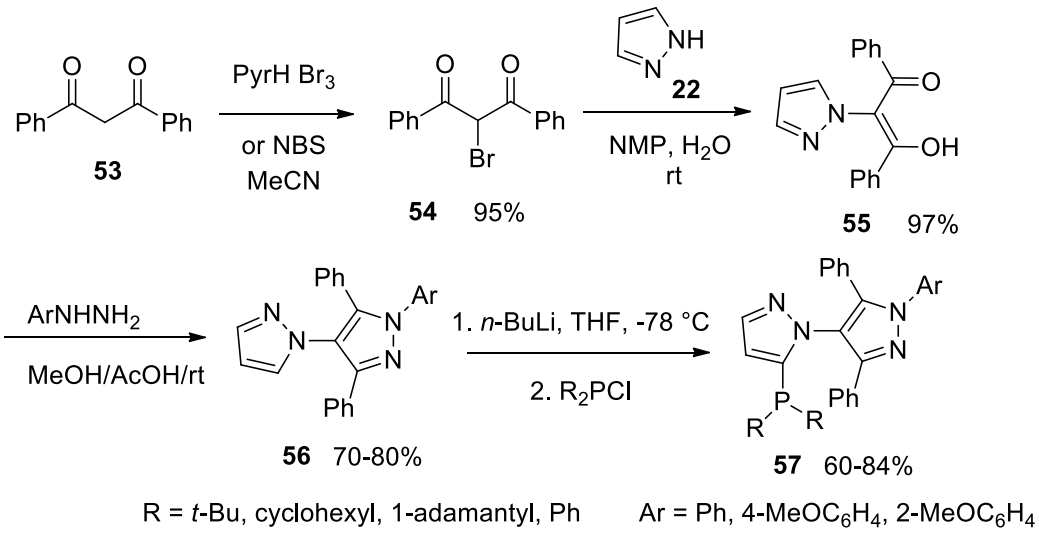
Scheme 13

2-(3,5-Dimethyl-1*H*-1-pyrazolyl)acetophenone **50** was prepared in 71% yield through the alkylation reaction of 3,5-dimethyl-1*H*-pyrazole **48** with phenacyl bromide **49** under reflux of anhydrous acetone containing potassium carbonate. Condensation of the latter compound with 1.2 equivalent of neat *N*,*N*-dimethylformamide-dimethylacetal (DMF-DMA) under reflux gave 3-dimethylamino-2-(3,5-dimethyl-1*H*-1-pyrazolyl)-1-phenyl-2-propen-1-one **51** in 92% yield. The dimethylaminoenone **51** was converted into 1,4'-bipyrazoles **52** by its reaction with hydrazine derivatives (Scheme 14).[44]



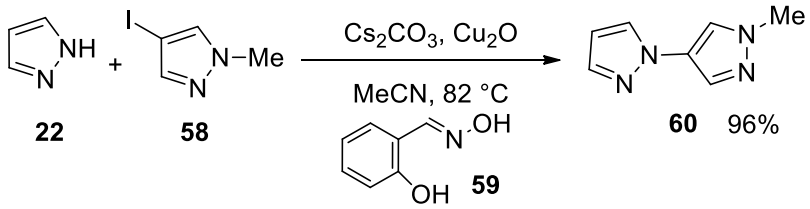
Scheme 14

Next, the synthesis 5-(di-*tert*-butylphosphino)-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1*H*-pyrazole (Bippyphos) **57** and its derivatives has been reported in four steps. The key precursor to Bippyphos **57** was the preparation of the bipyrazole derivative **56** *via* a one-pot bromination of 1,3-diphenylpropane-1,3-dione **53** followed by alkylation with pyrazole **54** in *N*-methyl-2-pyrrolidinone (NMP) followed by condensation of the product **55** with phenylhydrazine. Lithiation of **56** followed by trapping with di-alkylchlorophosphine afforded the Bippyphos derivatives **57** in good yields (Scheme 15).[45,46]



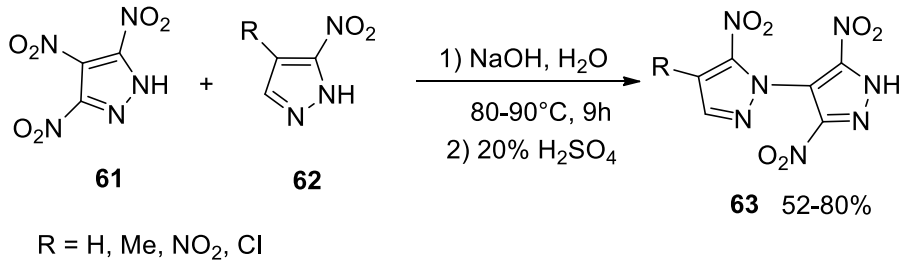
Scheme 15

N-Hetarylation of 1*H*-pyrazole **22** through its coupling with 4-iodo-1-methylpyrazole **58** using cesium carbonate as a base, in the presence of Cu_2O as co-catalyst and salicylaldoxime **59** as ligand, in acetonitrile furnished 96% yield of the 1,4'-bipyrazole derivative **60** (Scheme 16).[47]



Scheme 16

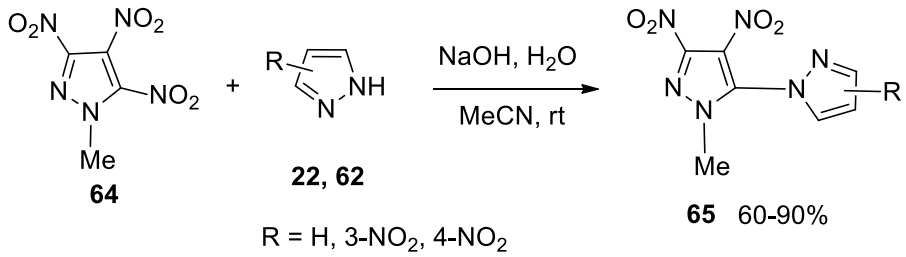
The reaction of 3,4,5-trinitro-1*H*-pyrazole (TNP) **61** with 1*H*-pyrazoles **62** in water in the presence of 2 equiv. NaOH at 80–90 °C followed by acidification gave the corresponding 1,4´-bipyrazoles **63** in good yields, where the 1*H*-pyrazoles **62** selectively substitute the 4-positioned nitro group in the TNP **61** (Scheme 17).[48]



Scheme 17

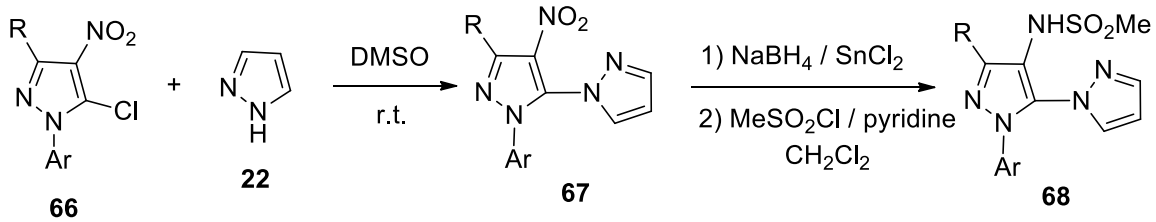
2.4. 1,5'-Bipyrazoles

In contrast to the behavior of 3,4,5-trinitro-1*H*-pyrazole (TNP) **61** towards 1*H*-pyrazoles where the substitution took place at the 4-positioned nitro group, the reactivity of 1-methyl-3,4,5-trinitropyrazole (MTNP) **64** behaved completely different compared to TNP **61** and the nucleophilic substitution proceeded regiospecifically at the 5-position. Thus, reaction of MTNP **64** with 1*H*-pyrazole **22** or nitropyrazoles **62** in the presence of NaOH at room temperature afforded the corresponding 1,5´-bipyrazole derivatives **65** in high yields (Scheme 18).[49]



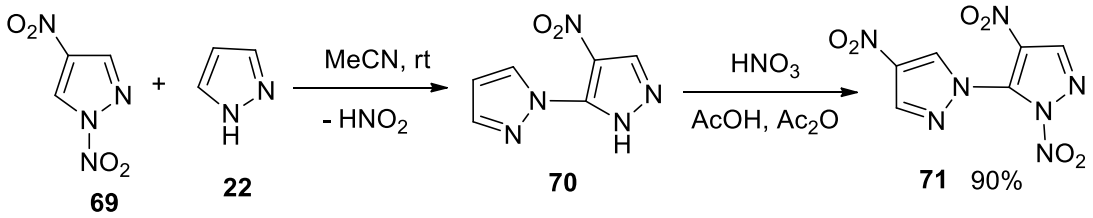
Scheme 18

The activated 5-chloropyrazoles **66** underwent nucleophilic substitution of its chlorine atom with pyrazole **22** (as a nucleophile) in dimethylsulfoxide (DMSO) at room temperature led to the formation 1,5'-bipyrazole derivatives **67** in good yields. Further reduction of the nitro group in compounds **67** using $NaBH_4/SnCl_2$ followed by treatment with methanesulfonyl chloride and pyridine in dichloromethane afforded 4'-(methylsulfonylamino)-1,5'-bipyrazole **68** (Scheme 19).[50,51]



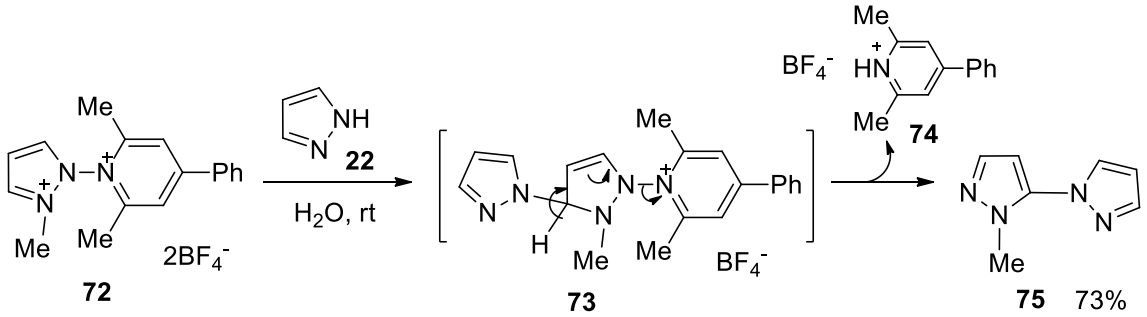
Scheme 19

Reaction of pyrazole **22** with 1,4-dinitropyrazole **69** in acetonitrile at room temperature resulted in the formation of 4'-nitro-1,5'-bipyrazole **70** in excellent yield through *cine*-substitution reaction where the entering group (pyrazole **22**) occupied position-2 adjacent to the leaving group (NO_2). Further, nitration of **70** with nitric acid in a mixture of acetic acid and acetic anhydride at reflux led to the formation of 1',4',4-trinitro-1,5'-bipyrazole **71** in 90% yield (Scheme 20).[52,53]



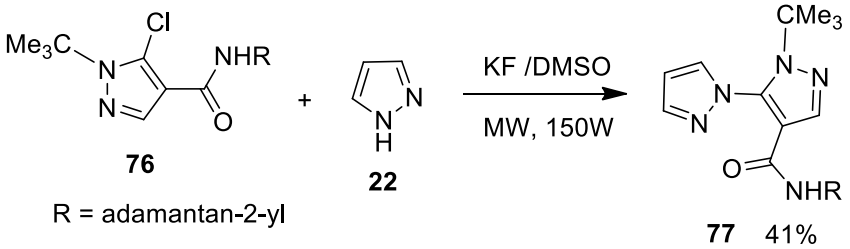
Scheme 20

Reaction of pyrazole **22** with 2,6-dimethyl-1-(2-methylpyrazol-1-yl)-4-phenylpyridinium bistetrafluoroborate **72**, in water at room temperature afforded 1´-methyl-1,5´-bipyrazole **75** in 73% yield *via* loss of pyridinium tetraflouroborate **74** from the intermediate **73** under the reaction conditions (Scheme 21).[54]



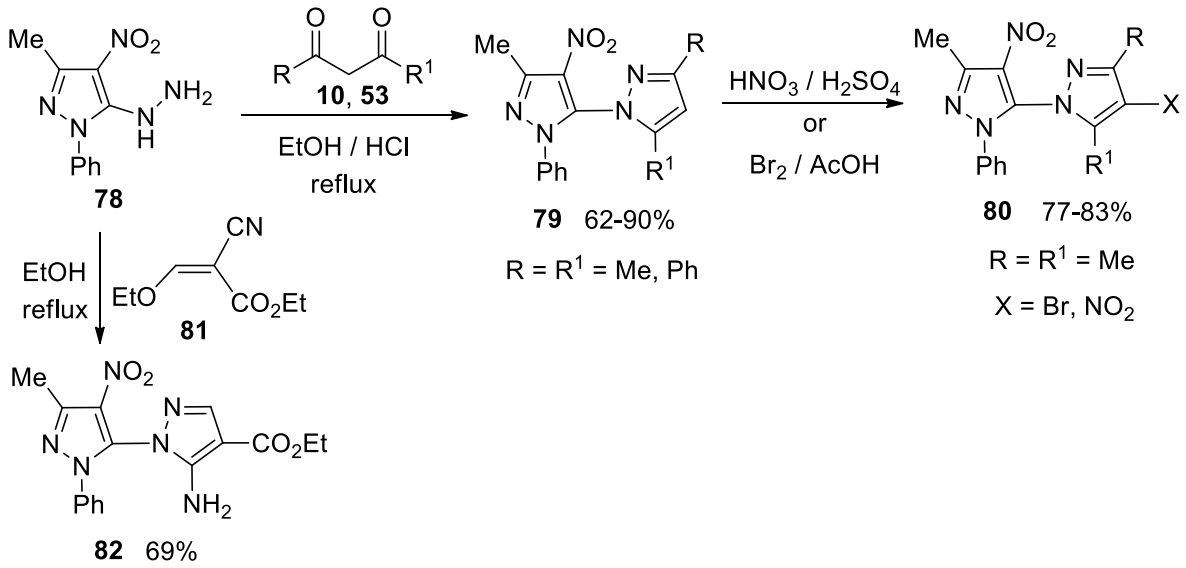
Scheme 21

1'-*tert*-Butyl-1,5'-bipyrazolyl-4'-carboxylic acid-*N*-(adamantan-2-yl)amide **77** was prepared through the microwave irradiation of a mixture of 1-*tert*-butyl-5-chloro-1*H*-pyrazole-4-carboxylic acid-*N*-(2-adamantyl)amide **76** with pyrazole **22** using KF as a base and DMSO solvent (Scheme 22).[55]



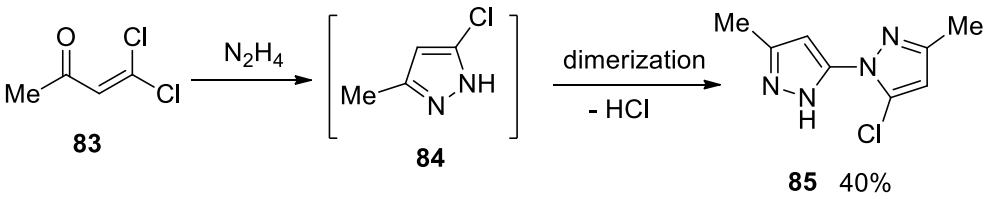
Scheme 22

Cyclocondensation of 5-hydrazinopyrazole derivative **78** with 1,3-dicarbonyl compounds **10** and **53** gave the corresponding 1,5'-bipyrazoles **79**. The latter 1,5'-bipyrazole **79** (R = R^1 = Me) underwent electrophilic substitution reactions (nitration and bromination) at the position-4 of the pyrazole ring to give the corresponding 1,5'-bipyrazole derivatives **80** in high yield. Condensation of the pyrazol-5-ylhydrazine **78** with ethyl 2-cyano-3-ethoxyacrylate **81** afforded the 1,5'-bipyrazole derivative **82** in 69% yield (Scheme 23).[56]



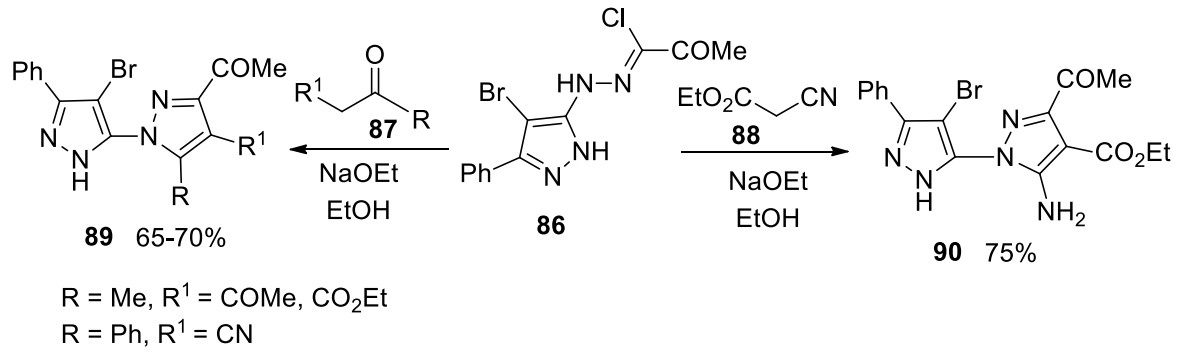
Scheme 23

The treatment of 3,3-dichlorovinyl methyl ketone **83** with hydrazine led to the formation of the 1,5´-bipyrazole derivative **85** in 40% yield. The reaction proceeded through initial formation of 5-chloro-3-methylpyrazole **84** followed by its dimerization under the basic reaction condition with loss of HCl (Scheme 24).[57]



Scheme 24

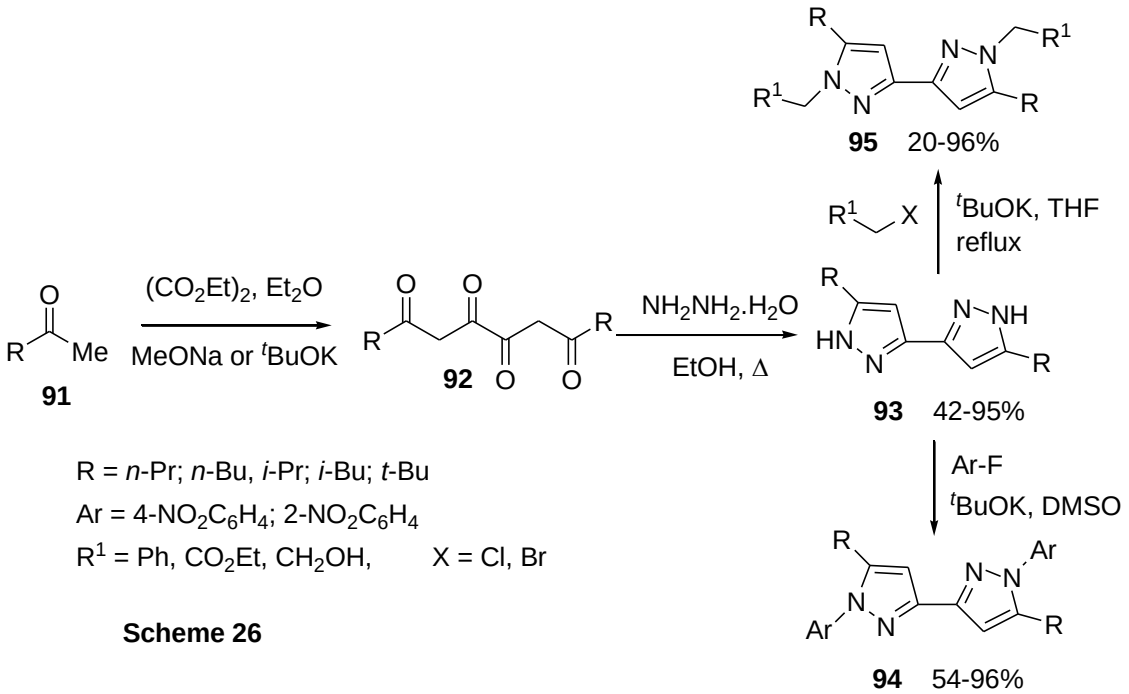
The 4-bromo-3-phenylpyrazol-5-ylhydrazonyl chloride **86** was reported to react with the active methylene compounds **87** and **88** in ethanolic sodium ethoxide solution at room temperature to give the 1,5'-bipyrazole derivatives **89** and **90**, respectively (Scheme 25).[58-60]



Scheme 25

2.5. 3,3'-Bipyrazoles

Treatment of the methyl ketones **91** with diethyl oxalate in the presence of an alkoxide base gave the corresponding 1,3,4,6-tetraketones **92** *via* a double Claisen condensation. Reaction of **92** with hydrazine hydrate in refluxing ethanol afforded the 5,5'-disubstituted-3,3'-bipyrazoles **93**. Further *N*,*N*'-arylation of **93** with fluoronitrobenzenes under microwave irradiation and under classical heating conditions, afforded high yields of 1,1´-diaryl-3,3´-bipyrazole derivatives **94** (Scheme 26).[11,61,62] Treatment of the bipyrazole derivatives **93** with benzylbromide and ethyl chloroacetate in refluxing THF gave the corresponding alkylated 3,3´-bipyrazole derivatives **95** in moderate to good yields (Scheme 26).[63-69]

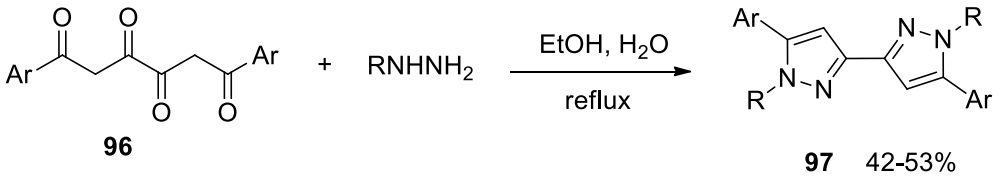


Scheme 26

Scheme 26

Reaction of 1,6-aryl-2,4,6,7-hexanetetrones **96** with hydrazine and arylhydrazines in refluxing ethanol afforded the corresponding 3,3'-bipyrazole derivatives **97** in moderate yields

(Scheme 27).[70-72]

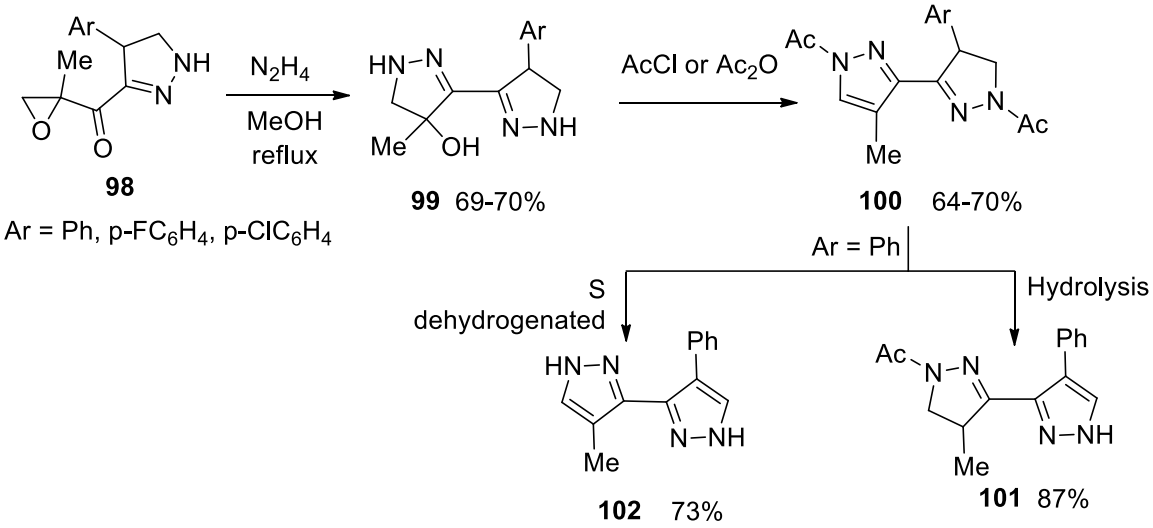


Ar = Ph, 4-MeC_6H_4, 2,4-$Me_2C_6H_3$, 4-C_6H_4OH

R = H, Ph, 2-MeC_6H_4

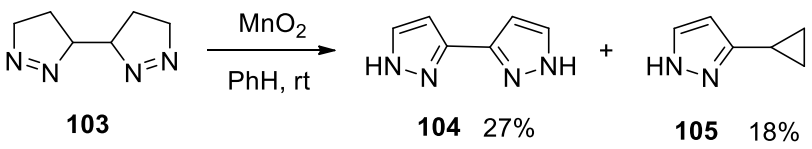
Scheme 27

Treatment of 3-epoxypropionyl-2-pyrazolines **98** with hydrazine hydrate in refluxing methanol gave 69-70% of 3,3'-bipyrazolines **99**, which were acetylated by acetylchloride to give 64-70% of **100**. Hydrolysis of **100** gave 87% of 1-acetyl-4'-methyl-4-phenyl-4,5-dihydro-3,3'-bipyrazole **101**. Dehydrogenation of compound **100** by sulfur gave 73% of 4-methyl-4'-phenyl-3,3'-bipyrazole **101** (Scheme 28).[73]



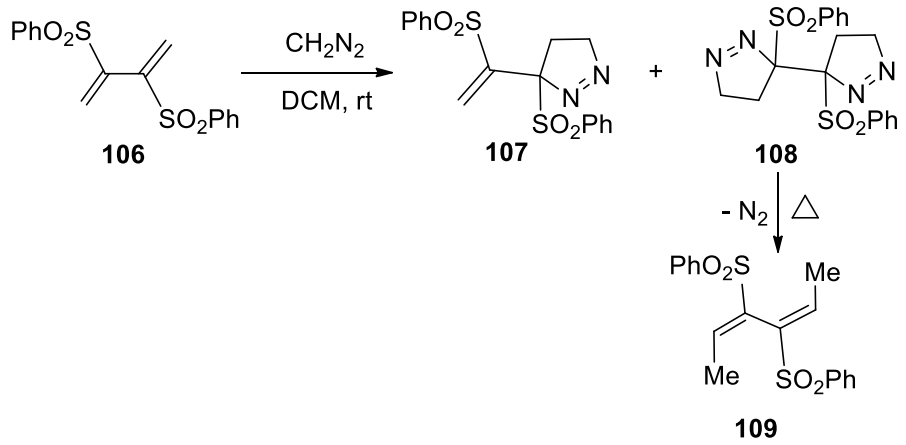
Scheme 28

Oxidative dehydrogenation of 3,3′,4,4′,5,5′-hexahydro-3,3′-bipyrazole **103** with MnO_2, in benzene at room temperature, led to the formation of a mixture of 3,3'-bipyrazole **104** and 3-cyclopropyl-1*H*-pyrazole **105** in 27 and 18% yields, respectively (Scheme 29).[74,75]



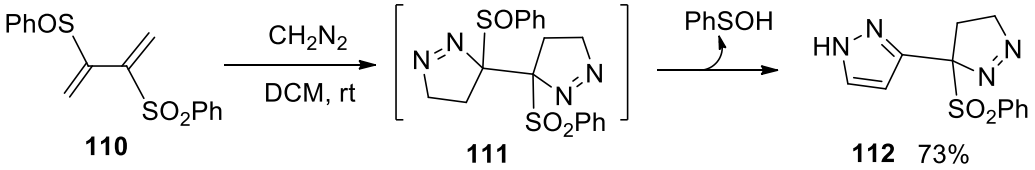
Scheme 29

Reaction of 2,3-*bis*(phenylsulfonyl)-l,3-butadiene **106** with diazomethane in dicholomethane (DCM) at room temperature under nitrogen gave a 1:1 mixture (98%) of the pyrazoline **107** and 3,3'-bipyrazoline **108** derivatives. Thermal extrusion of nitrogen occurred from the 3,3'-bipyrazoline **108** producing mainly the *E*,*E*-diene **109** (Scheme 30).[76]



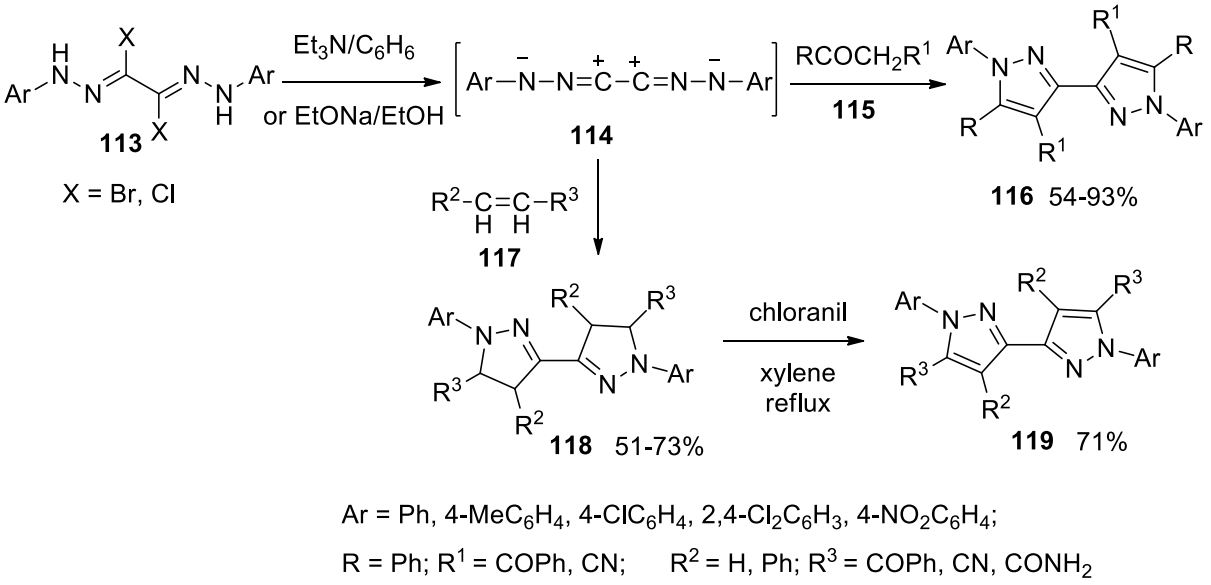
Scheme 30

When an excess of diazomethane was allowed to react with 2-phenylsulfinyl-3-phenylsulfonyl-1,3-butadiene **110** and for longer periods of time furnished only dihydro-3H,l'H-3,3'-bipyrazole **112** in 73% yield. The formation of **112** was explained by reaction of diazomethane (excess) with both π-bonds in a sequential manner giving the 2:l-adduct **111** as a transient species. This intermediate underwent a subsequent *syn* elimination of PhSOH followed by a 1,5-sigmatropic hydrogen shift (Scheme 31).[76]



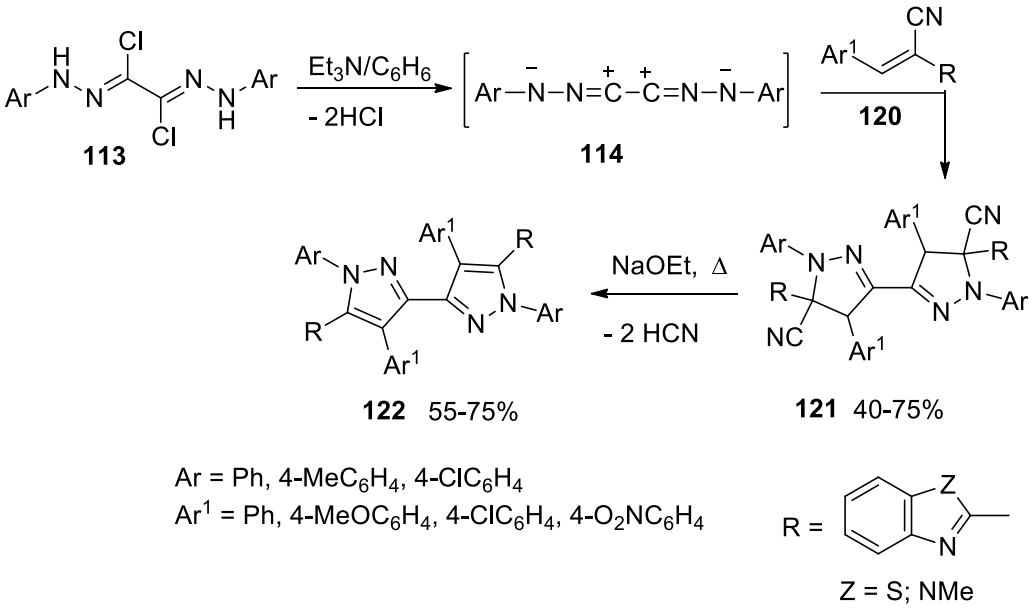
Scheme 31

Treatment of the *bis*-arylnitrilimines **114** [generated *in situ* from treatment of *bis*-hydrazonyl halides **113** with triethylamine in dry benzene] with active methylene compounds **115** furnished the polysubstituted 3,3'-bipyrazole derivatives **116** in good to high yields. Furthermore, the *bis*-arylnitrilimines **114** underwent 1,3-dipolar cycloaddition reactions with some olefins **117** to give the corresponding 3,3'-bi(2-pyrazolines) **118** in good yield. Oxidation of the latter compound **118** (R^2 = Ph, R^3 = COPh, Ar = Ph) with chloranil afforded the corresponding 3,3'-bipyrazole derivative **119** in 71% yield (Scheme 32).[77]



Scheme 32

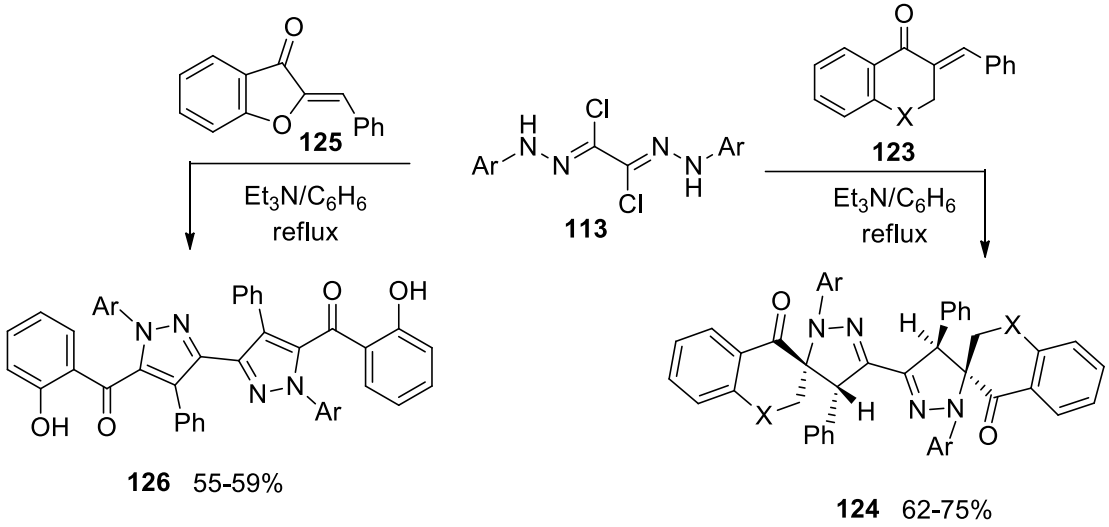
Regioselective synthesis of polysubstituted 3,3'-bi-1*H*-pyrazole derivatives **122** *via* 1,3-dipolar cycloaddition reactions has also been reported. Thus, the *bis*-arylnitrilimines **114** reacted regioselectively with the cinnamonitriles **120** to yield the cycloadducts 5,5'-dicyano-4,4',5,5'-tetrahydro-3,3'-bi-1*H*-pyrazoles **121** in 40-75% yields. Compounds **121** underwent aromatization *via* thermal elimination of hydrogen cyanide under the basic reaction conditions and afforded the corresponding 3,3'-bi-1*H*-pyrazole derivatives **122** in 55-75% yields (Scheme 33).[78]



Scheme 33

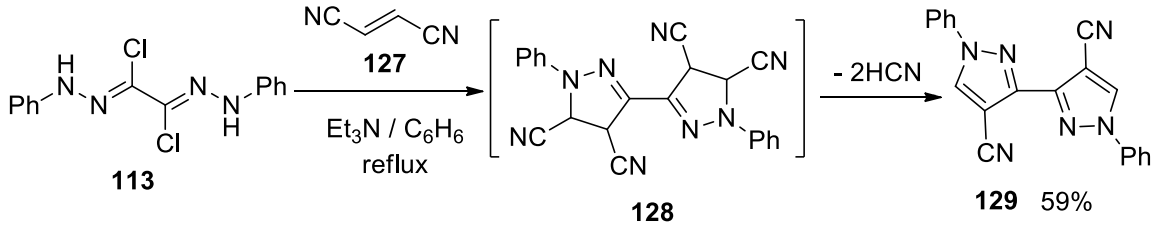
Furthermore, regioselective 1,3-dipolar cycloaddition of the *bis*-hydrazonyl halides **113**

with the benzylidene chroman-4-one and thiochroman-4-one derivatives **123** afforded the corresponding *bis*-spiropyrazoline-5,3'-chroman(thiochroman)-4-one derivatives **124** in good yields. The regio- and stereoselective cycloaddition was elucidated using X-ray analysis. Similar reaction of the *bis*-hydrazonyl halides **113** with 2-benzylidene-3-coumaranone **125** furnished the 3,3'-bipyrazole derivatives **126** in moderate yields (Scheme 34).[79]



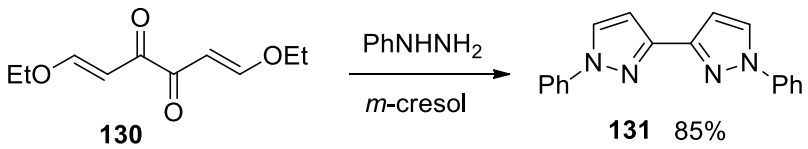
Scheme 34

Bis-hydrazonyl halides **113** underwent similar cycloaddition reaction with fumaronitrile **127** in benzene under reflux in the presence of triethylamine to afford 1,1'-diphenyl-3,3'-bipyrazole-4,4'-dicarbonitrile **129** in 59% yield through loss of two molecules of HCN from the cycloadduct intermediates **128** (Scheme 35).[80]



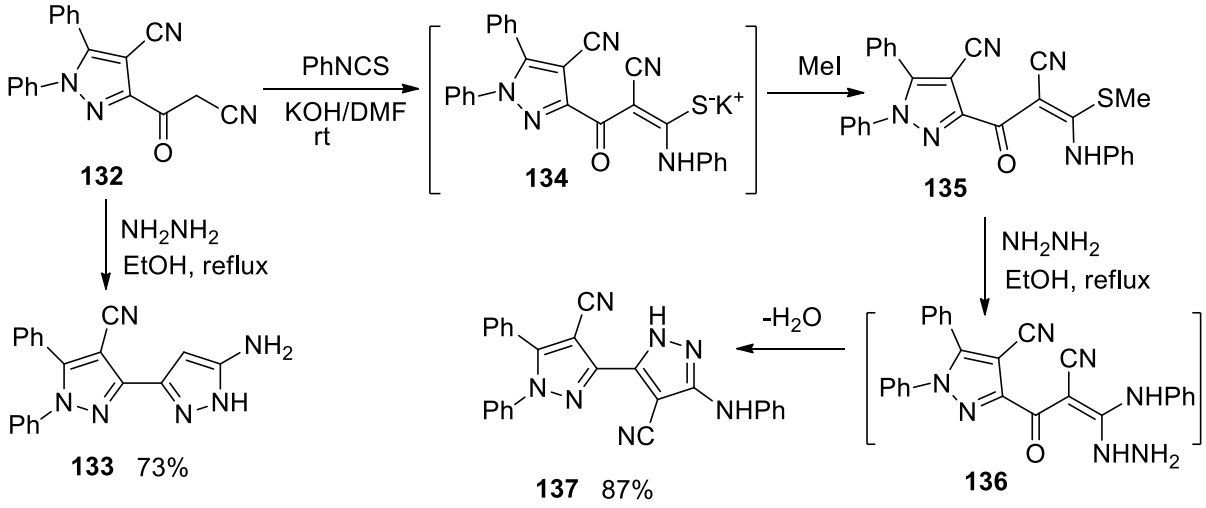
Scheme 35

Cyclocondensation of 1,6-diethoxyhexa-1,5-diene-3,4-dione **130** with phenylhydrazine in *m*-cresol provided 1,1'-diphenyl-3,3'-bipyrazole **131** in 85% yield (Scheme 36).[81]



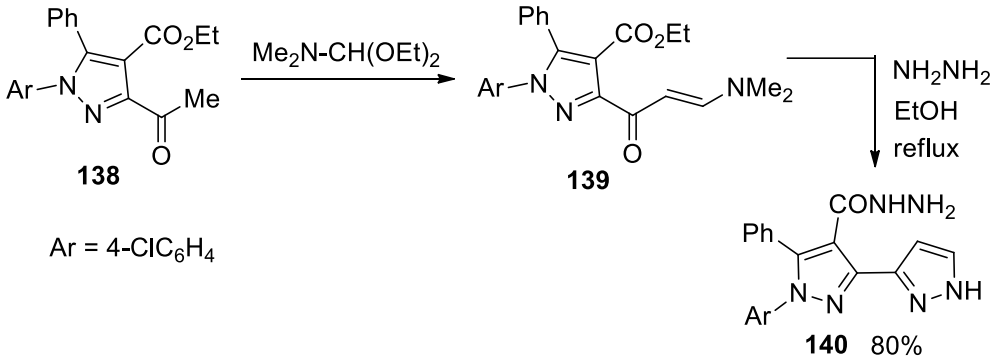
Scheme 36

Treatment of the cyanoacetylpyrazole derivative **132** with hydrazine hydrate, in refluxing ethanol afforded the corresponding 3,3'-bipyrazole derivative **133** (Scheme 36).[82] Reaction of the cyanoacetylpyrazole **132** with phenyl isothiocyanate, in the presence of potassium hydroxide, at room temperature followed by addition of methyl iodide afforded 3-(2-cyano-3-methylthio-3-phenylaminoacryloyl)-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile **135**. When compound **135** was treated with hydrazine hydrate in refluxing ethanol it afforded 1,5-diphenyl-5'-phenylamino-3,3'-bipyrazolyl-4,4'-dicarbonitrile **137** in high yield (Scheme 37).[83]



Scheme 37

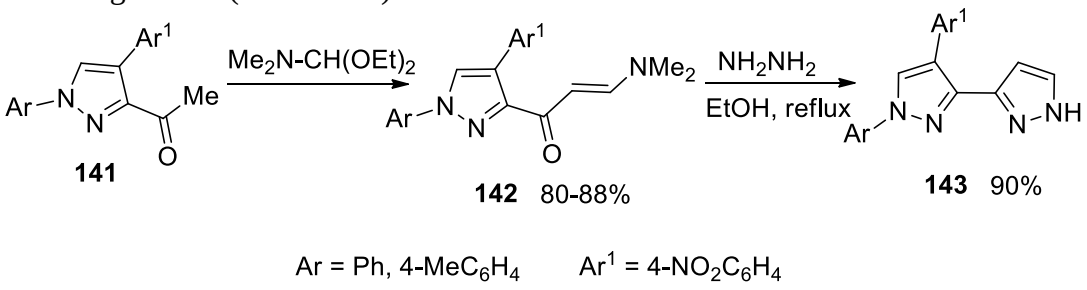
3-[(*E*)-3-(*N*,*N*-Dimethylamino)acryloyl]-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate **139** was prepared *via* condensation of the pyrazole derivative **138** with dimethylformamide-dimethylacetal (DMF-DMA). Treatment of **139** with hydrazine hydrate in ethanol under reflux yielded 3-(1*H*-pyrazol-3-yl)-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-4-carbohydrazide **140** in 80% yield (Scheme 38).[84,85]



Scheme 38

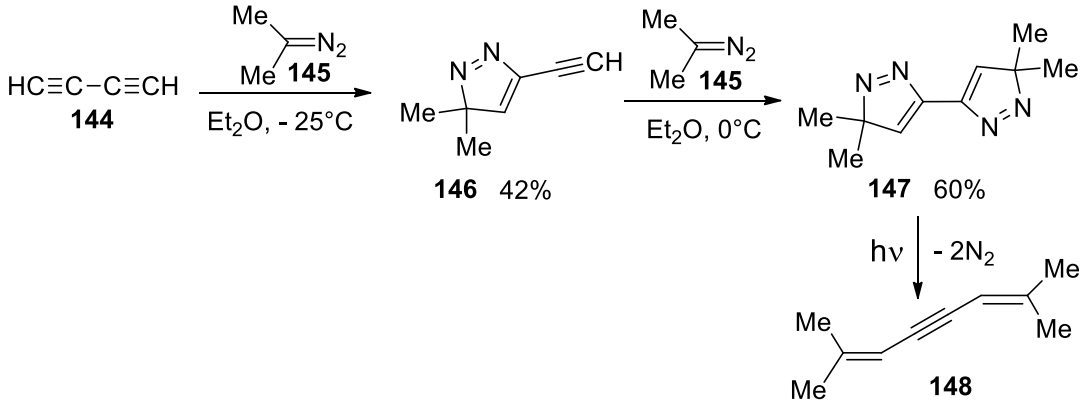
Heating a mixture of 3-acetyl-4-(4-nitrophenyl)-1-aryl-1*H*-pyrazoles **141** and dimethylformamide dimethylacetal gave the corresponding enaminone **142** in 80-88% yields. Treatment of the enaminones **142** with hydrazine hydrate in ethanol under reflux afforded the

3,3'-bipyrazoles **143** in 90% yield. The products were formed *via* initial addition of hydrazine to the enaminone double bond, followed by elimination of dimethylamine and water molecules to give **143** (Scheme 39).[86]



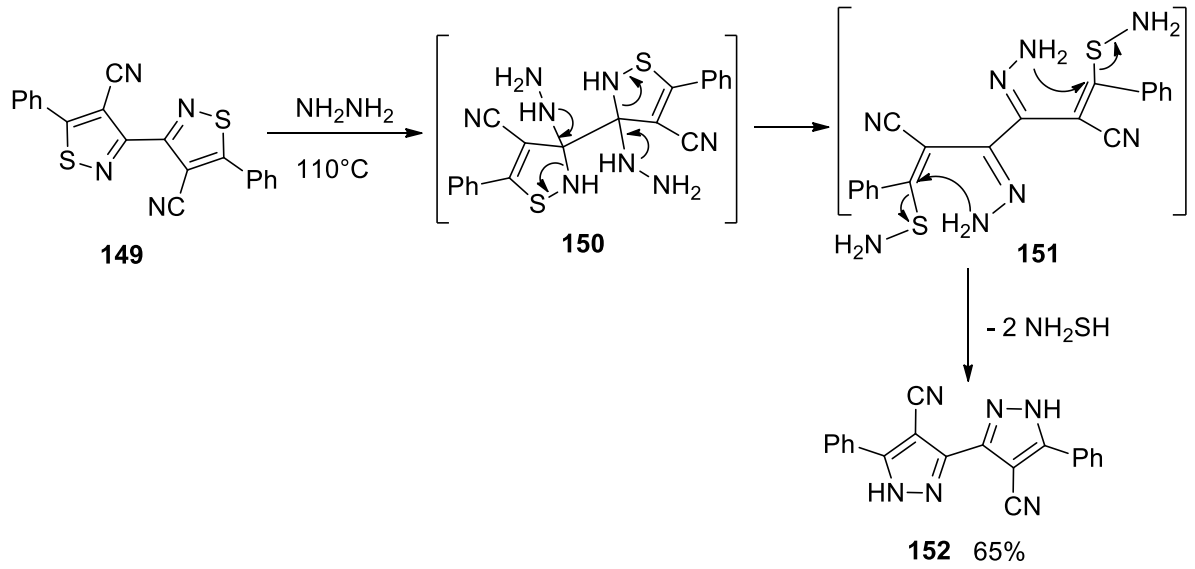
Scheme 39

The reaction of diacetylene **144** with 2-diazopropane **145** took place in two steps to give at first the acetylenic pyrazole **146** which underwent further cycloaddition to 2-diazopropane **145** in diethyl ether at 0°C to afford the 5,5,5',5'-tetramethyl-3,3'-bipyrazole **147** in 60% yield. Photolysis of the latter bipyrazole **147** led to the formation of 2,7-dimethylocta-2,6-dien-4-yne **148** *via* loss of two N_2 molecules (Scheme 40).[87]



Scheme 40

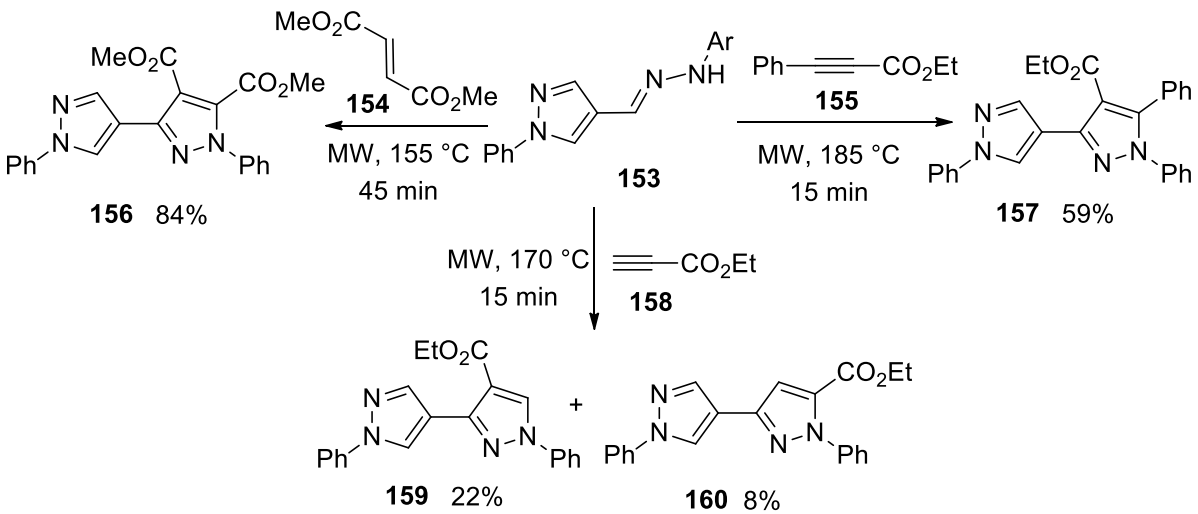
The conversion of isothiazoles into pyrazoles using neat anhydrous hydrazine was also reported. Thus, 5,5'-diphenyl-3,3'-biisothiazole-4,4'-dicarbonitrile **149** was easily transformed into 5,5'-diphenyl-3,3'-bi(1*H*-pyrazole)-4,4'-dicarbonitrile **152** in 65% yield upon heating in neat anhydrous hydrazine according to the mechanism outlined in Scheme 41.[88]



Scheme 41

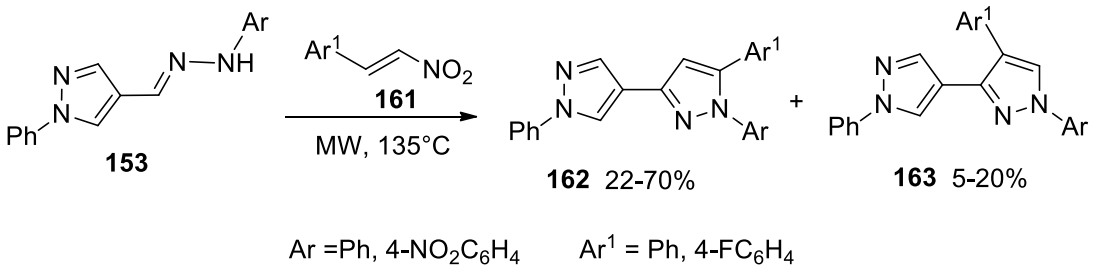
2.6. 3,4'-Bipyrazoles

1,3-Dipolar cycloaddition of 4-pyrazolylformylhydrazone **153** with electron-poor dipolarophiles namely; dimethyl fumarate **154** and ethyl 3-phenylpropiolate **155** under microwave irradiation in solvent-free conditions within 15-45 min afforded the corresponding 3,4'-bipyrazoles **156** and **157**, respectively. Similar microwave heating of the hydrazone **153** with ethyl propiolate **158** at 170 °C for 15 min gave a mixture of the 3,4'-bipyrazole derivatives **159** and **160** (Scheme 42).[89,90]



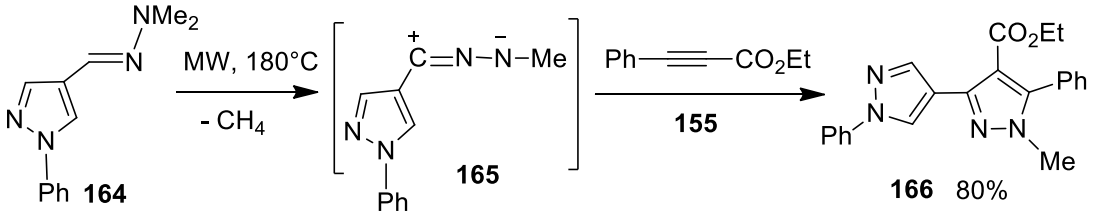
Scheme 42

Conducting the 1,3-dipolar cycloaddition of the 4-pyrazolylformylhydrazones **153** with β-nitrostyrenes **161** under solvent-free microwave irradiation at 130°C for 10 min was reported to afford a mixture of the 3,4'-bipyrazoles **162** and **163** (Scheme 43).[89,91]



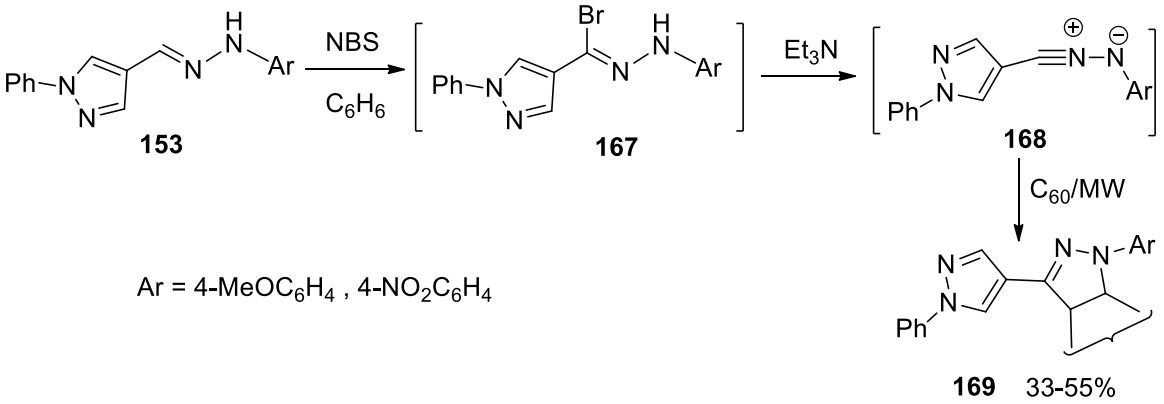
Scheme 43

Similar 1,3-dipolar cycloaddition reactions of the pyrazolylhydrazone **164** with ethyl 3-phenylpropiolate **155** under microwave irradiation for 10 min gave the 3,4'-bipyrazole **166** in 80% yield, *via* the formation of the nitrilimine intermediate **165** generated by elimination of methane from **164**. In contrast, it was reported that heating the same mixture under classical heating did not proceed at all (Scheme 44).[89,92]



Scheme 44

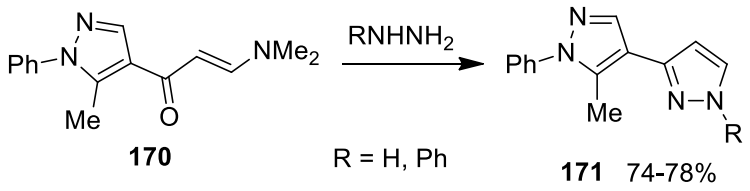
The formation of several fullereno-3,4'-bipyrayole adducts **169** from nitrilimines has been also reported. Thus, treatment of the pyrazolylhydrazone **153** with *N*-bromosuccinimide (NBS) followed by Et_3N then addition of C_{60} under microwave irradiation conditions resulted in the formation of **169** in moderate yields (Scheme 45).[93]



Scheme 45

Reaction of 1-(5-methyl-1-phenylpyrazol-4-yl)-3-(*N*,*N*-dimethylamino)-2-propen-1-one **170** with hydrazine or phenyl hydrazine afforded the corresponding 3,4'-bipyrazoles **171** in

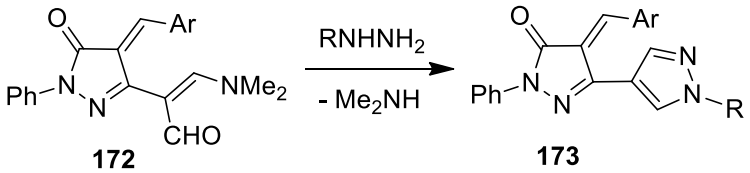
good yields (Scheme 46).[94]



170 **171** 74-78%

Scheme 46

The reaction of the pyrazolylenamine derivatives **172** with hydrazine or phenylhydrazine led to the formation of 3,4'-bipyrazoles **173** (Scheme 47).[95]

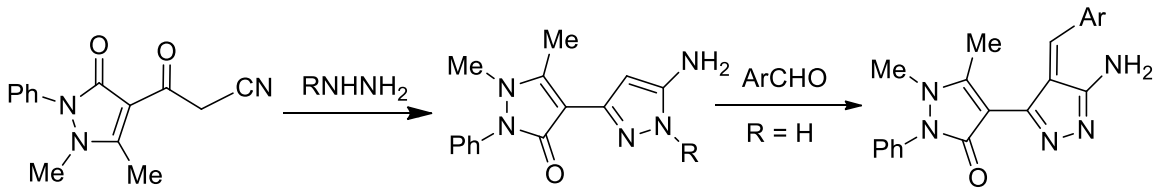


172 **173**

Ar, R= Ph, H; Ph, 4-ClC_6H_4

Scheme 47

Reaction of cyanoacetylpyrazole **174** with hydrazines gave the corresponding 3,4'-bipyrazoles **175.** Heating a mixture of the bipyrazole derivatives **175** and aromatic aldehydes in ethanol at reflux in the presence of piperidine gave the corresponding 5-amino-4-arylidenepyrazoles **176** in good yields (Scheme 48).[96-98]

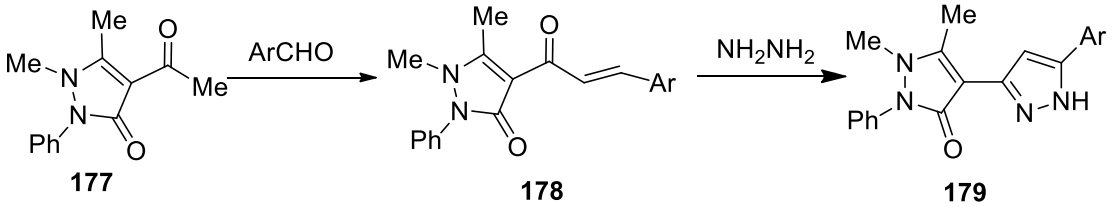


174 **175** **176**

Ar = Ph, 4-BrC_6H_4 R = H, Ph

Scheme 48

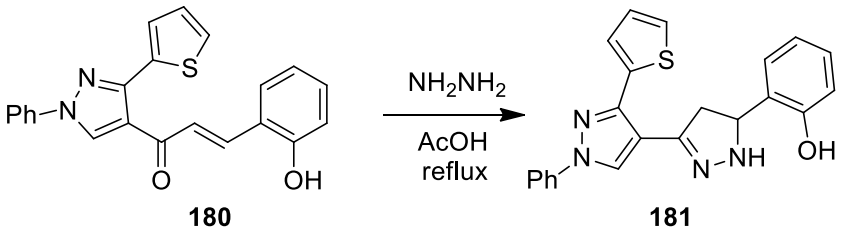
Treatment of 4-acetylpyrazolone derivative **177** with aromatic aldehydes gave the corresponding chalcones **178** which upon heating with hydrazine hydrate yielded the 3,4'-bipyrazoles **179** (Scheme 49).[99]



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

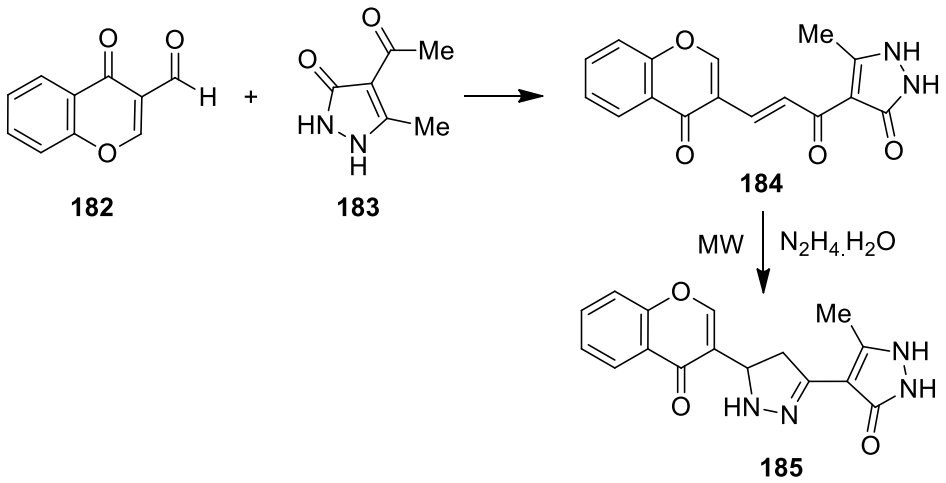
Scheme 49

The 3,4'-bipyrazole derivative **181** was prepared in moderate yield by condensation of 3-(2-hydroxyphenyl)-1-(1-phenyl-3-(2-thienyl)-1*H*-pyrazol-4-yl)prop-2-en-1-one **180** with hydrazine hydrate in refluxing acetic acid (Scheme 50).[100]



Scheme 50

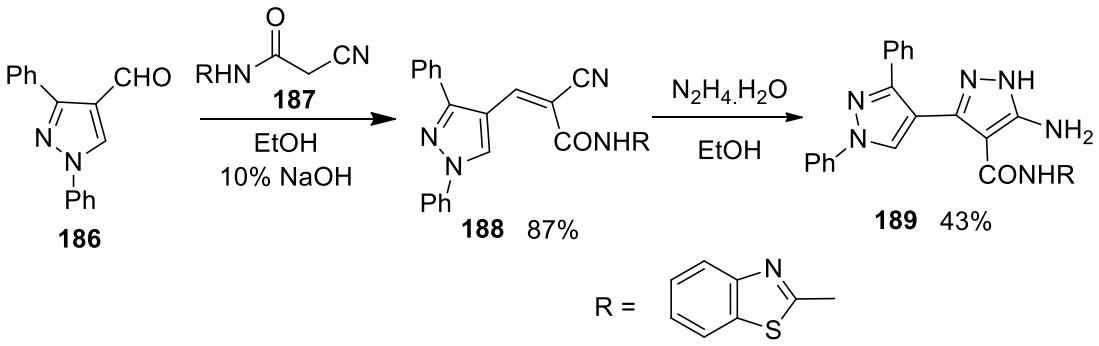
Reaction of 4-oxo-3-chromenecarboxaldehyde **182** with 4-acetyl-5-methyl-1,2-dihydro-3-pyrazolone **183** gave the corresponding enone **184**. Subsequent cyclocondensation of **184** with hydrazine hydrate under microwave irradiation conditions gave the 3,4'-bipyrazole derivative **185** (Scheme 51).[101]



Scheme 51

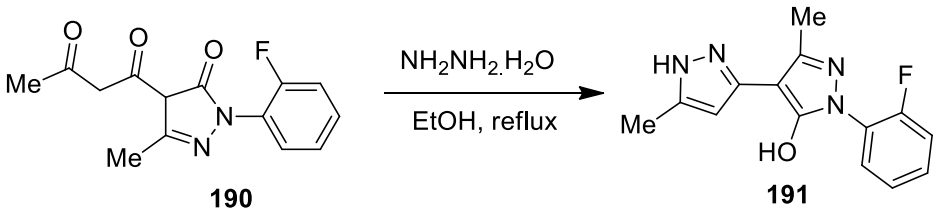
Knoevenagel condensation of *N*-(benzothiazol-2-yl)-2-cyanoacetamide **187** with 1,3-

diphenylpyrazole-4-carboxaldehyde **186** in ethanolic sodium hydroxide (10%) afforded 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamide **188**. The addition of hydrazine hydrate to the activated double bond of compound **188** in boiling ethanol afforded 5-amino-1',3'-diphenyl-3,4'-bipyrazole-4-carboxamide **189** in a reasonable yield (Scheme 52).[102]



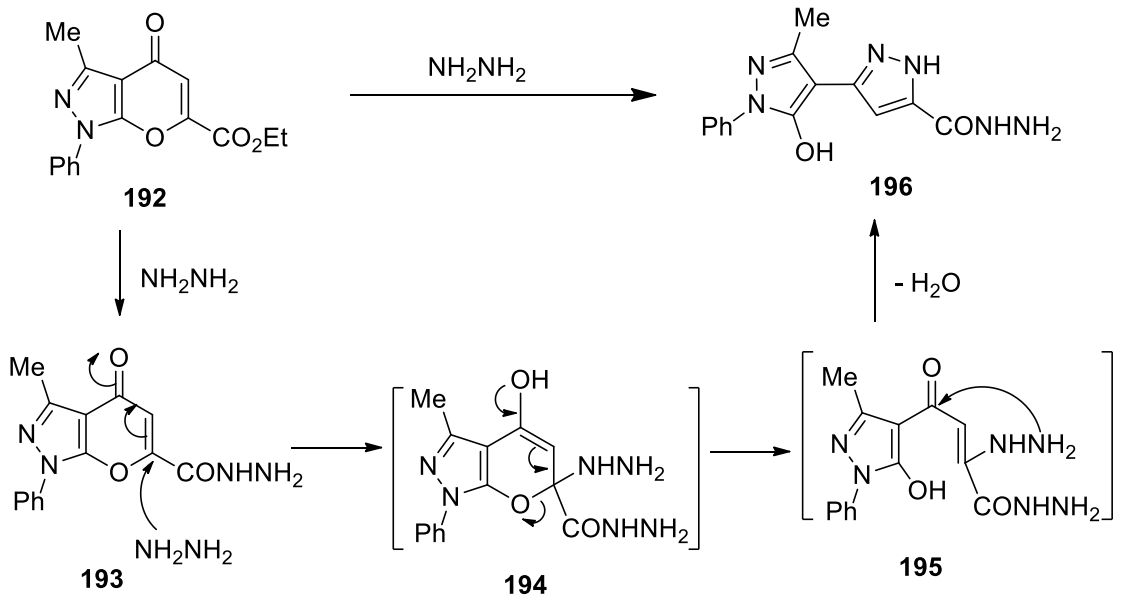
Scheme 52

Heating a mixture of 1-(pyrazol-4-yl)butane-1,3-dione **190** and hydrazine hydrate in ethanol furnished 1'-(2-fluorophenyl)-5,3'-dimethyl-3,4'-bipyrazolyl-5'-ol **191** which is useful as central nervous system agents (Scheme 53).[103]



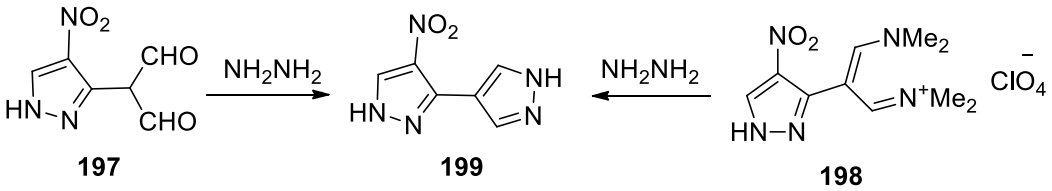
Scheme 53

Treatment of the γ-pyrone derivative **192** with two equivalents of hydrazine resulted in the formation of the 3,4'-bipyrazole derivative **196**. A proposed mechanism for the formation of **196** is outlined in Scheme 54 where hydrazinloysis of ester group was firstly attempted followed by nucleophilic attack of another hydrazine molecule resulting in ring opening then closing *via* loss of water molecule to give the 3,4'-bipyrazole derivative **196** (Scheme 54).[104]



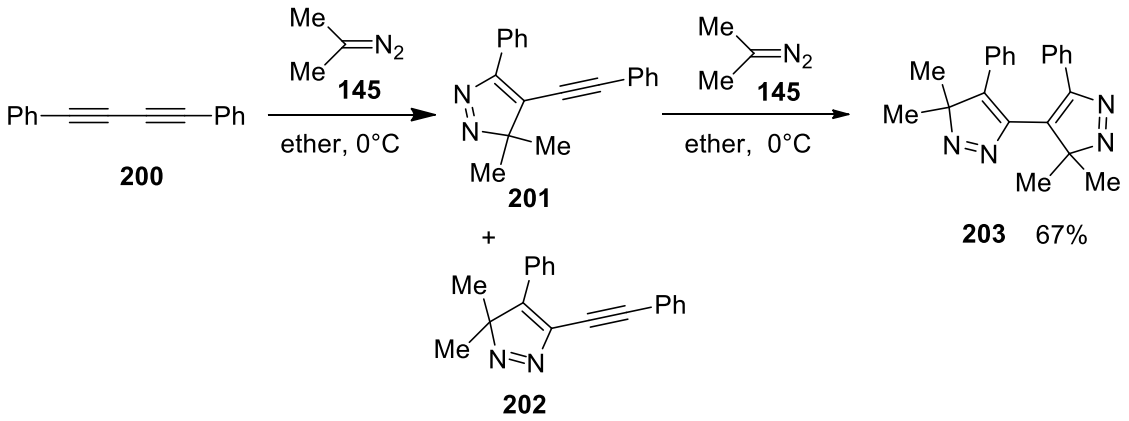
Scheme 54

3,4'-Bipyrazole derivative **199** was obtained from the reaction of 3-(diformylmethyl)-4-nitropyrazole **197** with hydrazine hydrochloride in basic aqueous solution. The same compound **199** was more conveniently obtained from the reaction of the perchlorate trimethinium salt **198** under similar condition using a double amount of the base (Scheme 55).[105]



Scheme 55

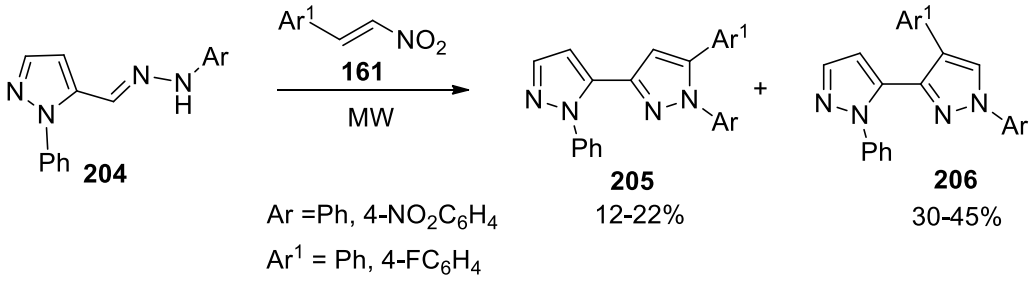
The 1,3-cycloaddition reaction of diphenyldiacetylene **200** with 2-diazopropane **145** led to a mixture of 3,3-dimethy-5-phenyl-4-phenylethynyl-3*H*-pyrazole **201**, 3,3-dimethyl-4-phenyl-5-phenylethynyl-3*H*-pyrazole **202**. Treatment of the pyrazole derivative **201** with 2-diazopropane **145** gave the 3,4'-bipyrazole derivative **203** with 67% yield (Scheme 56).[106,107]



Scheme 56

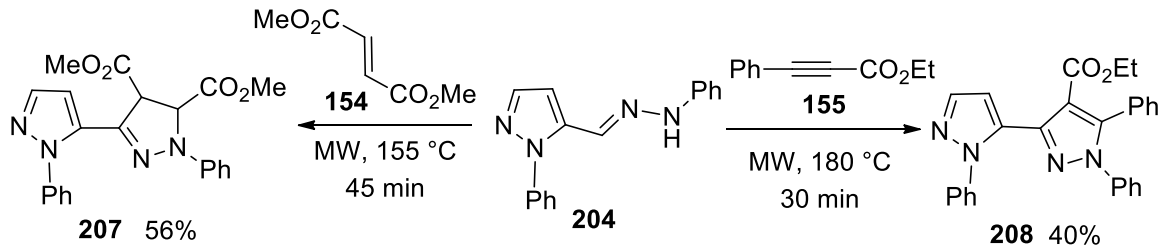
2.7. 3,5'-Bipyrazoles

Heating 5-pyrazolylformylhydrazones **204** with β-nitrostyrenes **161** under microwave irradiation at 130 °C, without solvent, afforded a mixture of the 3,5'-bipyrazoles **205** and **206** *via* 1,3-dipolar cycloaddition in overall moderate yields (Scheme 57).[89,91]



Scheme 57

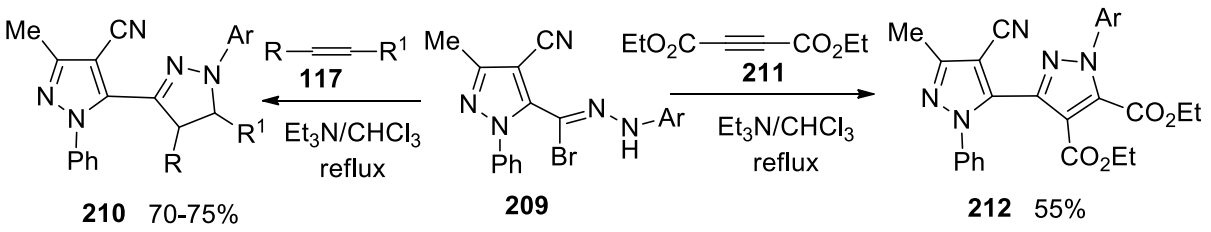
3,5'-Bipyrazole derivatives **207** and **208** were prepared in reasonable yields *via* 1,3-dipolar cycloaddition of 5-pyrazolylformylhydrazone **204** with the electron poor dipolarophiles; dimethyl fumarate **154** and ethyl 3-phenylpropiolate **155**, respectively, under microwave irradiation condition (Scheme 58).[89]



Scheme 58

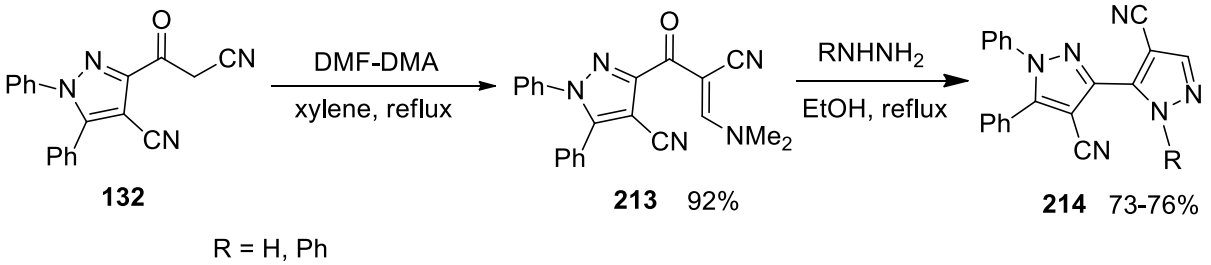
A regioselective 1,3-dipolar cycloaddition of the activated alkenes **117** with 4-pyrazolylhydrazonoyl bromides **209** furnished the corresponding unsaturated 3,5'-bipyrazole

derivatives **210** in good yields. Similar cycloaddition of acetylenedicarboxylate ester **211** gave the 3,5'-bipyrazole **212** (Scheme 59).[108]



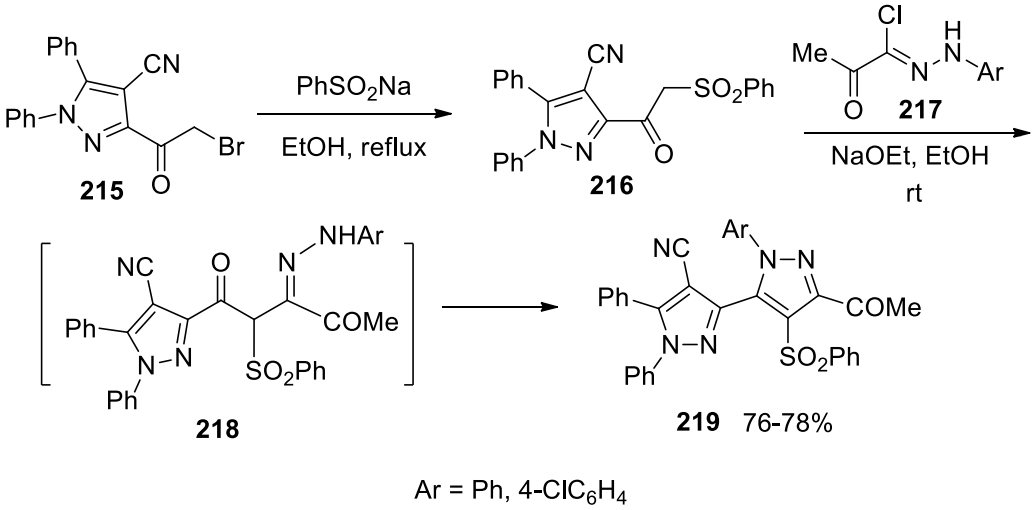
Scheme 59

Reaction of 3-(pyrazol-3-yl)-3-oxo-propanenitrile derivative **132** with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene gave the enaminonitrile derivatives **213** in 92% yield. Treatment of the latter compounds **213** with hydrazine derivatives afforded the 3,5'-bipyrazole derivatives **214** in good yields (Scheme 60).[82]



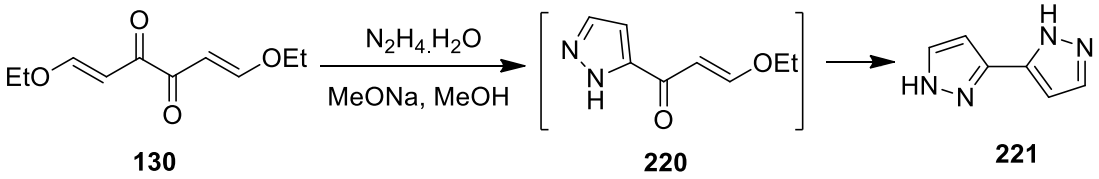
Scheme 60

3-Bromoacetyl-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile **215** was reported to react with sodium benzenesulfinate in refluxing ethanol and afforded 1,5-diphenyl-3-(2-(phenylsulfonyl)acetyl)-1*H*-pyrazole-4-carbonitrile **216**. Reaction of the ketosulfone **216** with hydrazonoyl chlorides **217** in ethanolic sodium ethoxide solution at room temperature afforded 5'-acetyl-1-aryl-2',5-diphenyl-4'-(phenylsulfonyl)-3,3'-bipyrazole-4-carbonitriles **219** in good yields (Scheme 61).[109]



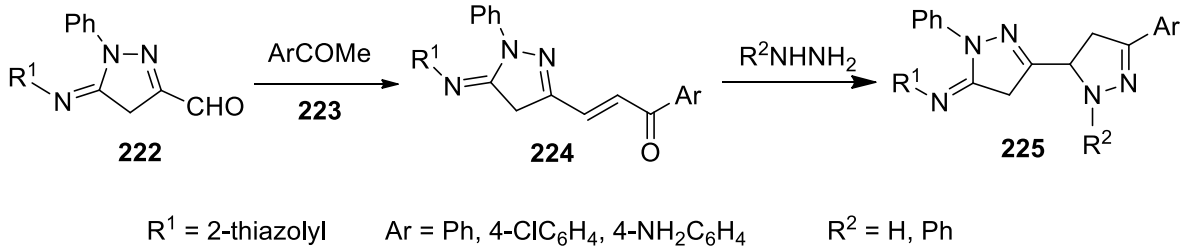
Scheme 61

The unsubstituted 3,5'-bipyrazole **221** was prepared by Effenberger, in 75% yield, from 1,6-diethoxy-1,5-hexadiene-3,4-dione **130** and hydrazine hydrate in THF at room temperature, in the presence of *p*-toluenesulfonic acid (Scheme 62).[110]



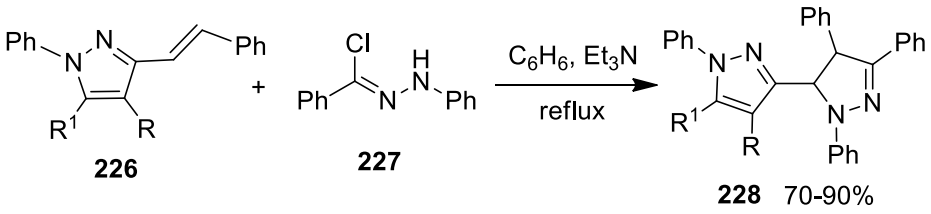
Scheme 62

3-Formyl-1-phenyl-5-(2-thiazolylimino)pyrazole **222** was condensed with arylketones **223** to give the α,β-unsaturated ketones **224** which underwent cyclocondensation with hydrazines afforded the 3,5'-bipyrazoline derivatives **225** (Scheme 63).[111]



Scheme 63

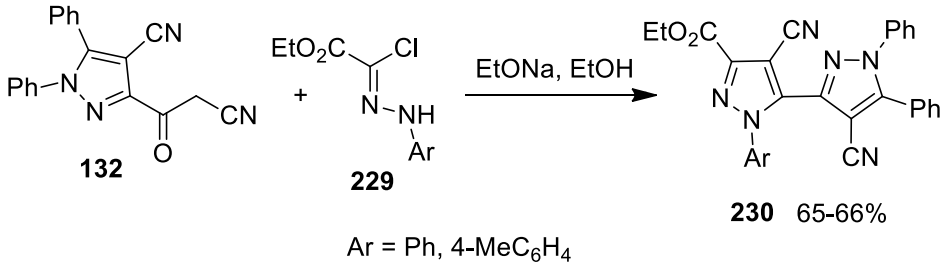
1,3-Dipolar cycloaddition of 3-styrylpyrazoles **226** with the hydrazonyl chloride **227**, in benzene at reflux, in in the presence of triethylamine, gave the corresponding 3,5'-bipyrazole derivatives **228** in high yields (Scheme 64).[112]



R^1 / R = H/CN, Ph/CN, COMe/Me, CO_2Et/Me, CO_2Et/Ph, CN/Ph, COPh/Ph

Scheme 64

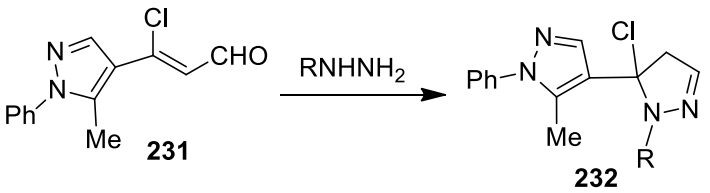
The reaction of 3-cyanoacetylpyrazole **132** with hydrazonoyl chlorides **229** in ethanol and sodium ethoxide at room temperature afforded the 3,5'-bipyrazole derivatives **230** in acceptable yields (Scheme 65).[83]



Ar = Ph, 4-MeC_6H_4

Scheme 65

Reaction of the 3-(1-phenyl-5-methylpyrazol-4-yl)-3-chloropropenal **231** with arylhydrazines led to the formation of 3,4'-bipyrazole derivatives **232** (Scheme 66).[113]

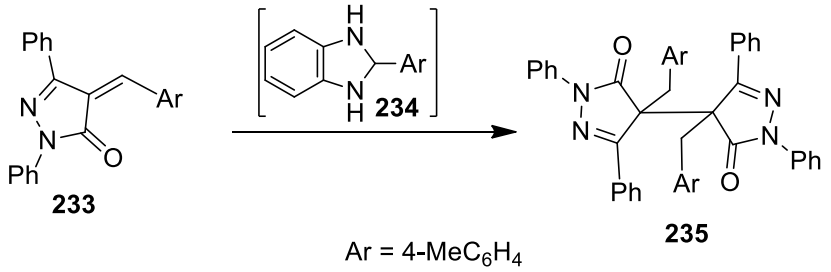


R = Ph, 2,4-$(NO_2)_2C_6H_3$

Scheme 66

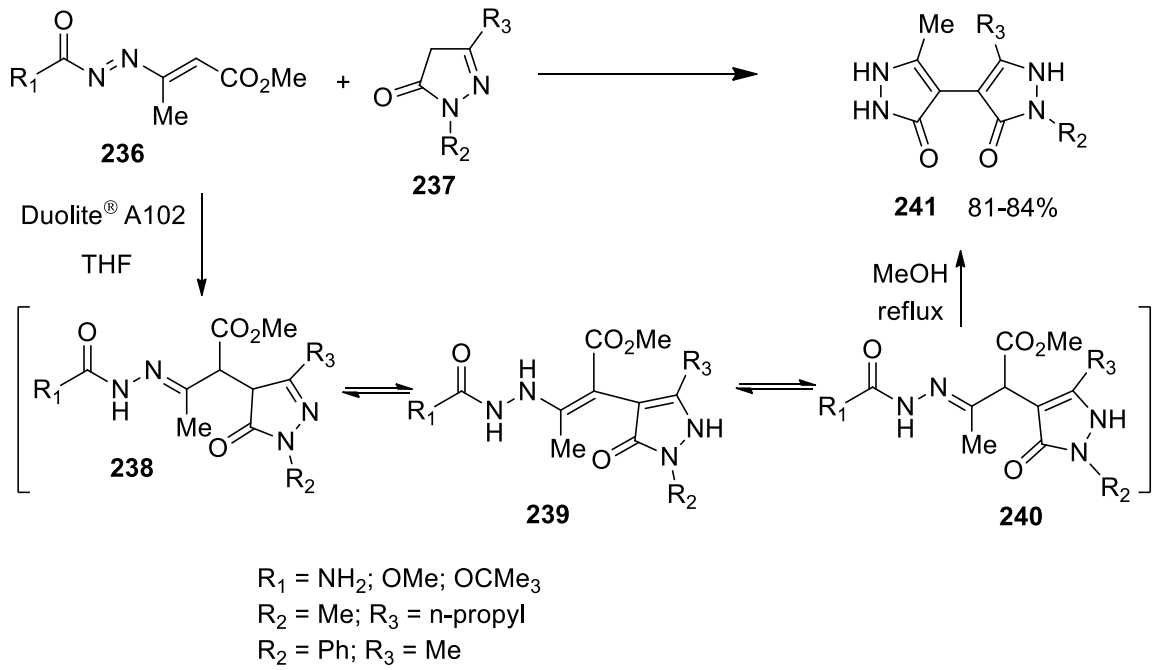
2.8. 4,4'-Bipyrazoles

Bruno *et al.* reported the diastereoselective reductive dimerization 4-tolylmethylene-3-phenylpyrazol-5-one **233,** *via* single electron transfer generated *in situ* using 2-arylbenzimidazoline **234** as catalyst, to afford the corresponding 4,4'-bipyrazoline derivative **235** (Scheme 67).[114]



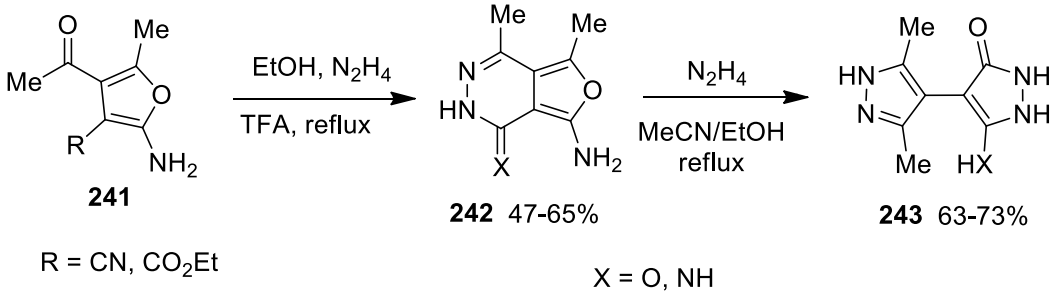
Scheme 67

4,4'-Bipyrazolin-3,3'-ones **241** were prepared by direct nucleophilic 1,4-addition of 2-pyrazolin-5-ones **237** to the conjugated azoalkenes **236** in the presence of the strong base anion exchanger resin Duolite® $A10_2$. This reaction proceeded *via* the intermediate *CH*-hydrazone **238** and then *NH*-hydrazone form **239** in tautomeric equilibrium with the relevant *NH*-hydrazine form **240** (Scheme 68).[115]

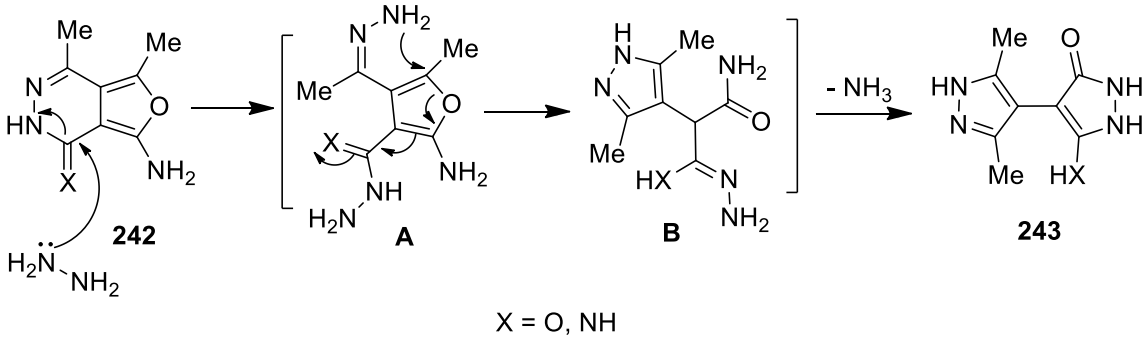


Scheme 68

The addition of hydrazine to functionalized furans led also to the formation of 4,4'-bipyrazoles. Thus, 4-acetyl-2-amino-5-methylfurans **241** were converted into 7-amino-4,5-dimethylfuro[3,4-d]pyridazines **242**, which were then transformed into the 4,4'-bipyrazole derivatives **243** upon treatment of **242** with hydrazine (Scheme 69). Conversion of the furo[3,4-d]pyridazine **242** into 4,4'-bipyrazole **243** was undertaken *via* ring opening followed by ring closure according to the mechanism outlined in Scheme 70.[116]

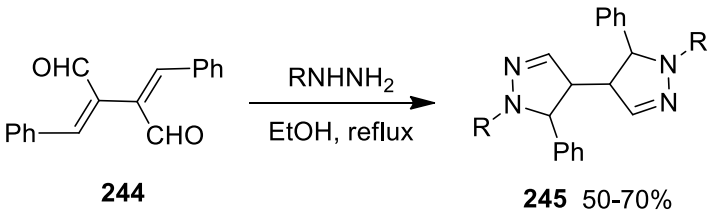


Scheme 69



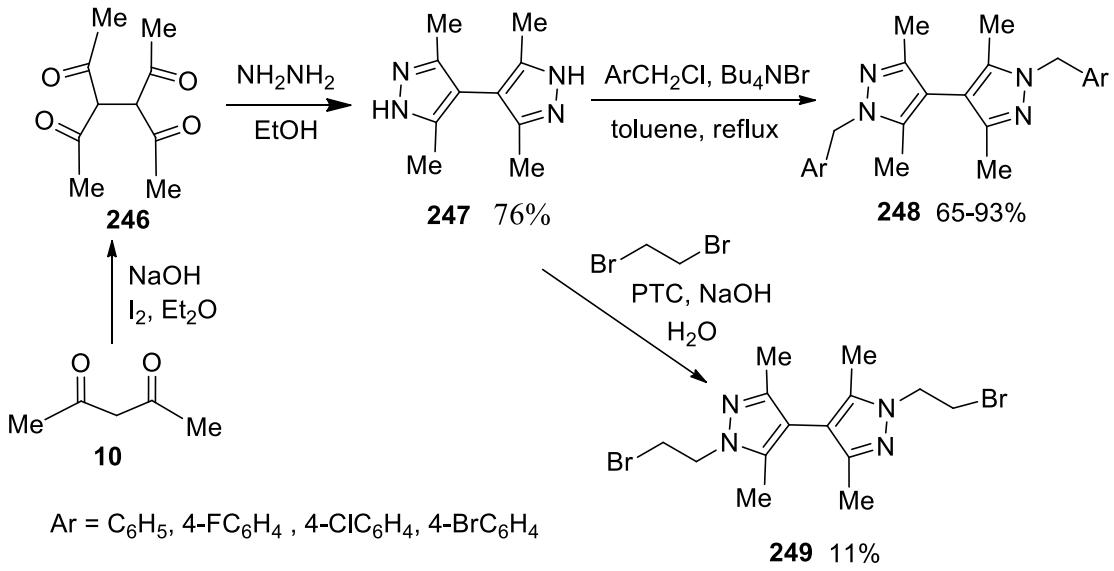
Scheme 70

Cyclocondensation of 1,4-diphenyl-2,3-diformylbutadiene **244** with variety of hydrazines in refluxing ethanol gave the corresponding 4,4´-bipyrazoline derivatives **245** in moderate yields (Scheme 71).[117]



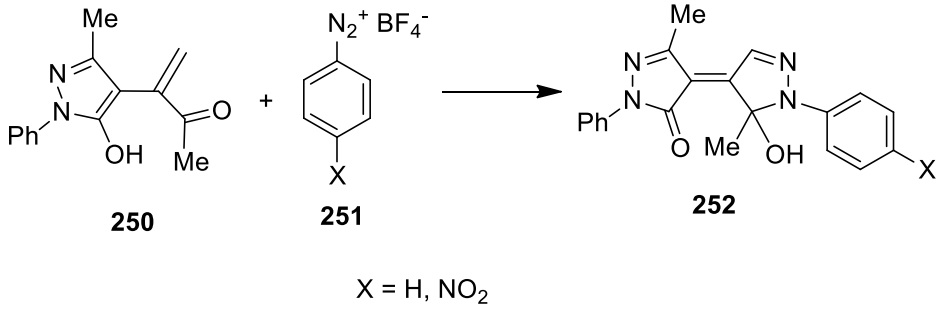
Scheme 71

Dimerization of acetylacetone **10** was conducted using iodine and NaOH to give 3,4-diacetylhexan-2,5-dione **246** which upon reaction with hydrazine hydrate afforded 3,3',5,5'-tetramethyl-4,4'-bipyrazole **247** in good yield (Scheme 72).[118,119] Alkylation of 4,4'-bipyrazole **247** with benzyl chlorides using tetrabuylammonium bromide, as phase transfer catalyst, in refluxing toluene gave the corresponding 1,1´-dialkylated 4,4'-bipyrazoles **248**.[10] 5,5´-Bi(2-bromoethylpyrazole) **249** was prepared in 11% yield by reaction of 4,4'-bipyrazole **247** with an excess of 1,2-dibromoethane using liquid-liquid phase transfer catalysis (Scheme 72).[120]



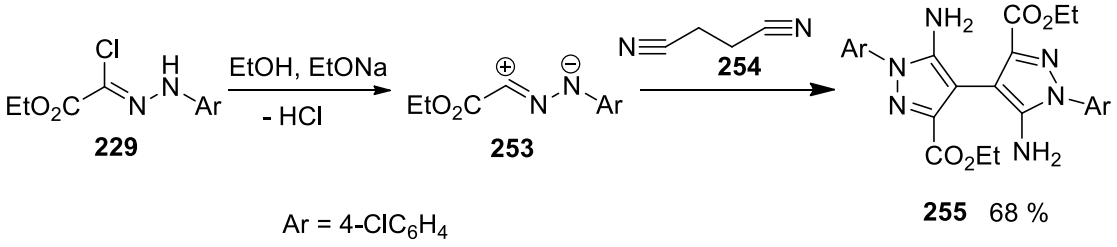
Scheme 72

Lycka *et. al* reported the synthesis of 5'-hydroxy-5,5'-dimethyl-2-phenyl-1'-aryl-1',5'-dihydro-4,4'-bipyrazolylidene-3-one **252** from the coupling reaction between 4-(α-acetylethylidene)pyrazole **250** and aryldiazonium fluoroborates **251** (Scheme 73).[121]



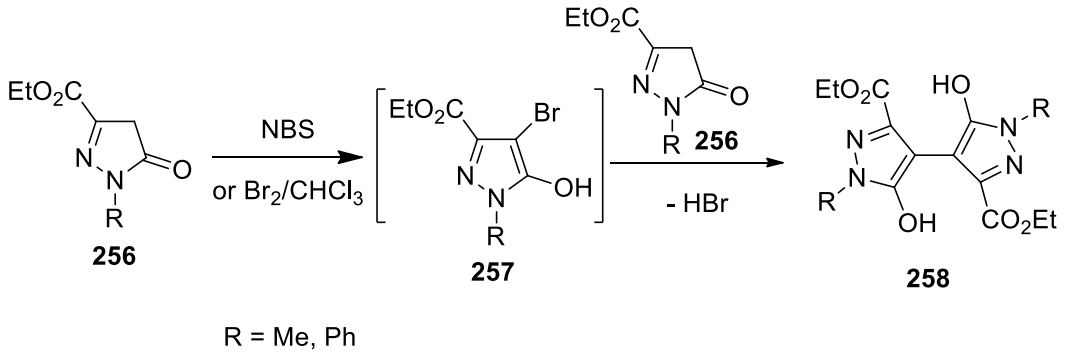
Scheme 73

The reaction of succinonitrile **254** with two equivalents of the hydrazonoyl chloride **229**, in the presence of sodium ethoxide at room temperature, resulted in the formation of the 4,4′-bipyrazole derivative **255** in 68% yield. The reaction took place *via* 1,3-dipolar cycloaddition of the nitrilimine intermediate **253** on the nitrile function of **354** (Scheme 74).[122]



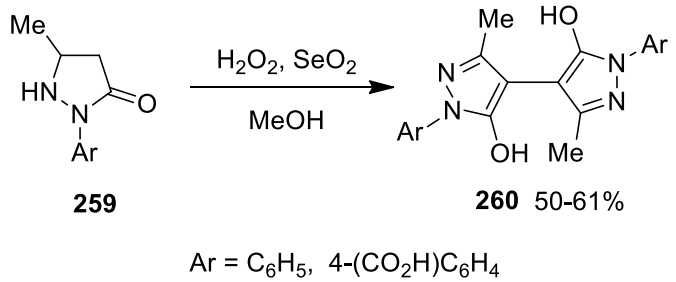
Scheme 74

The 5,5'-dihydroxy-4,4'-bipyrazole derivatives **258** were obtained as a dimerization product during the bromination of the pyrazolone **256** with *N*-bromosuccinimide (NBS) or bromine in chloroform (Scheme 75).[123]



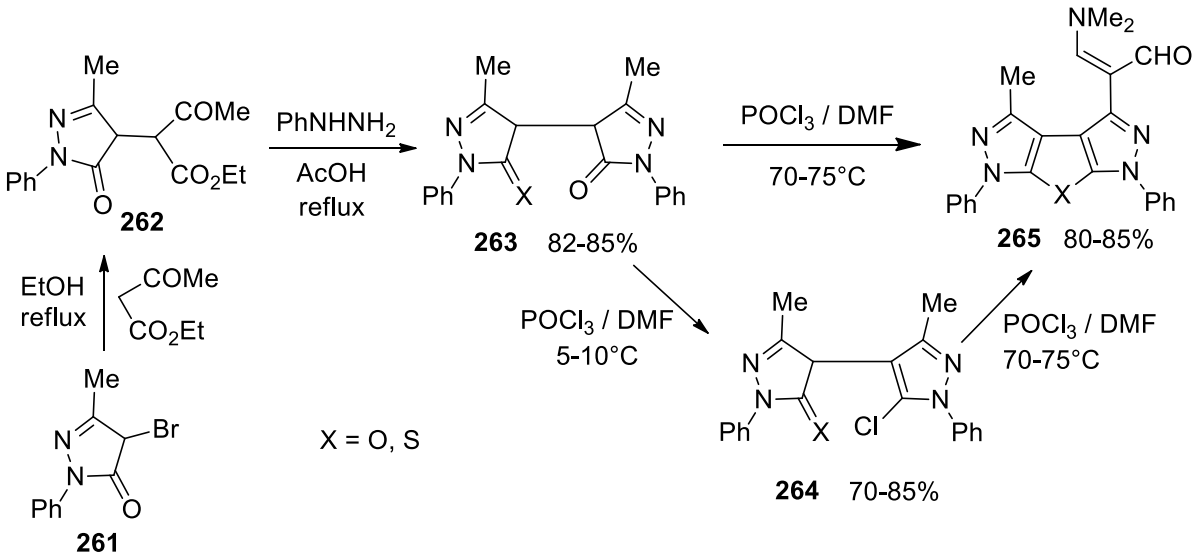
Scheme 75

Dimerization of the pyrazolinone derivative **259** resulted in the formation of the 5,5'-dihydroxy-4,4'-bipyrazole derivatives **260** in 50-61% yields when **259** was treated with 30% hydrogen peroxide in the presence of selenium oxide in methanol at 0°C under a nitrogen atmosphere (Scheme 76).[25]



Scheme 76

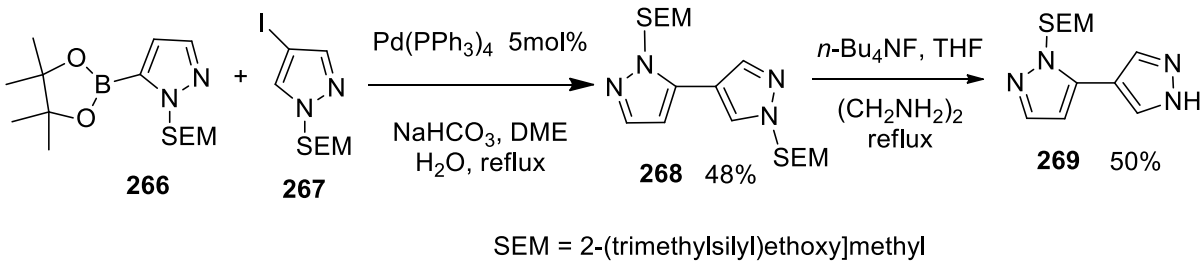
Heating a mixture of 4-bromopyrazolone **261** with ethyl acetoacetate gave the pyrazole ester **262** which upon reaction with phenylhydrazine gave the 4,4'-bipyrazole-5,5'-dione **263** (X = O). Compound **263** (X = O) was converted into **263** (X = S) by the action of P_2S_5. Reaction of Vilsmeier reagent (DMF/$POCl_3$) with 4,4'-bipyrazole **263** (X = S, O) at 5-10 °C afforded 5-chloro-4,4'-bipyrazole derivatives **264**. However, when the reaction was carried out on hot at 70-75 °C, the tricyclic fused compound 1,6-diphenylthieno[2,3-c:5,4-c']dipyrazole **265** was obtained. (Scheme 77).[124-126]



Scheme 77

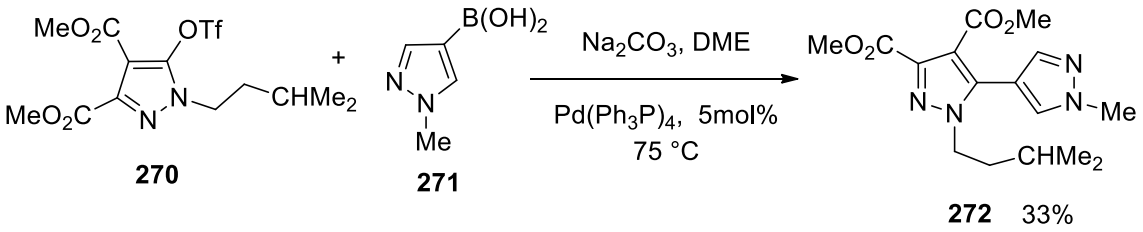
2.9. 4,5'-Bipyrazoles

Suzuki cross-coupling reaction of 5-pyrazolylboronic ester **266** with 4-iodo-1-[2-(trimethylsilyl)ethoxy]methyl pyrazole **267** in the presence of $Pd(PPh_3)_4$ and $NaHCO_3$ in refluxing dimethoxyethane (DME)/water gave the 1,1'-di(SEM)-4,5'-bipyrazole derivative **268** in 48% yield; [2-(trimethylsilyl)ethoxy]methyl = SEM]. Deprotection of **268** using *n*-Bu_4NF and ethylenediamine in refluxing THF resulted in removing only one SEM group of the 4,5'-bipyrazole **268** to give the mono-protected 4,5'-bipyrazole **269** in 50% yield (Scheme 78).[127]



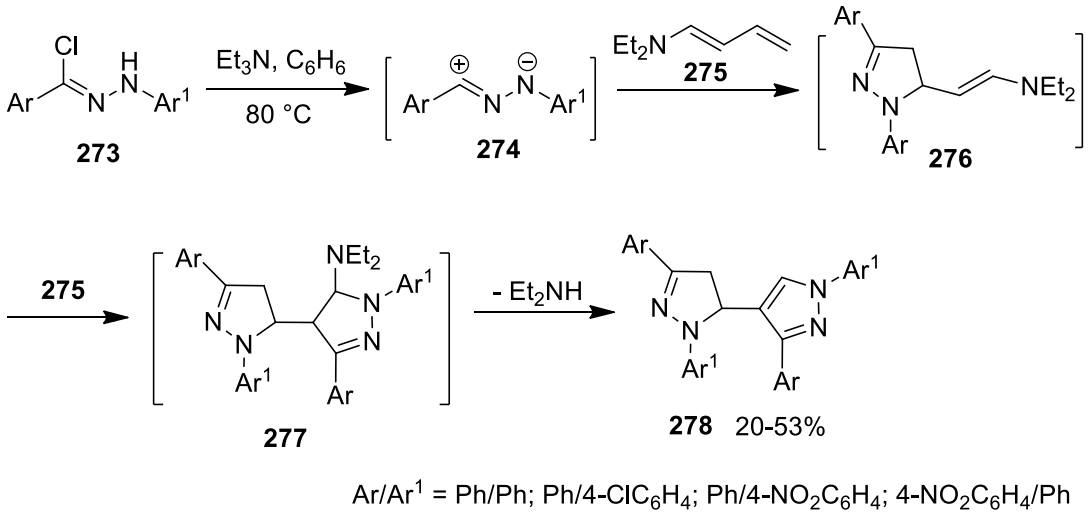
Scheme 78

Dimethyl 1-methyl-1'-(3-methylbutyl)-4,5'-bipyrazole-3,4-dicarboxylate **272** was prepared in 33% *via* the Suzuki cross-coupling of the pyrazolyl triflate derivative **270** with 4-pyrazolylboronic acid **271** catalyzed by 5 mol% of $Pd(PPh_3)_4$ in anhydrous DME using Na_2CO_3 as a base (Scheme 79).[128]



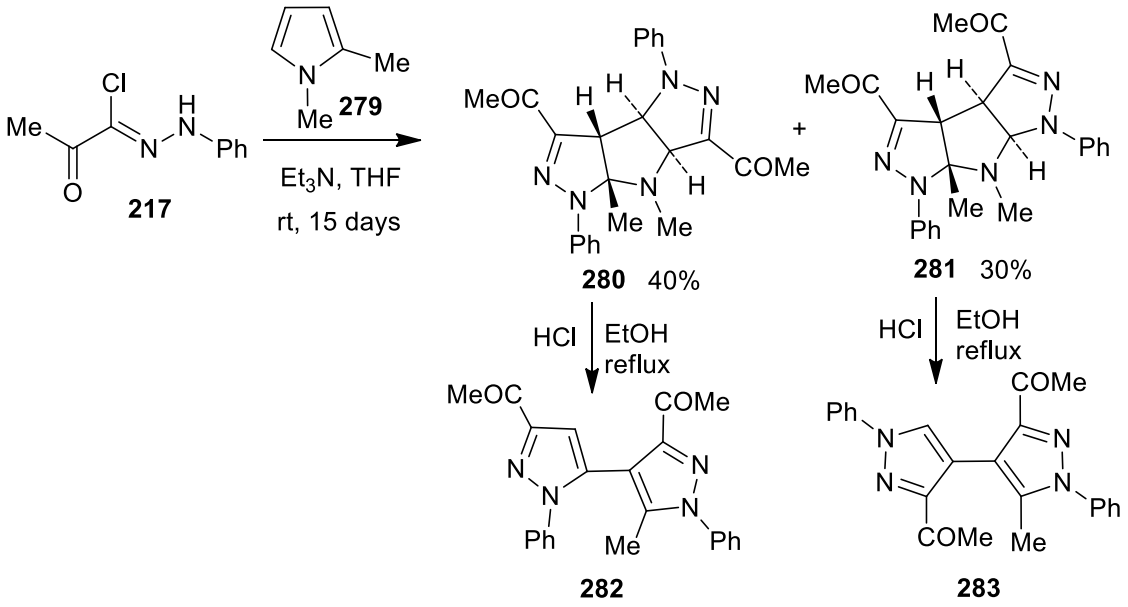
Scheme 79

The reaction of *N*,*N*-diethylbuta-1,3-dien-1-amine **275** with two equivalents of diarylnitrilimines **274** [derived from the hydrazonyl chloride **273** under the effect of Et_3N] in benzene at 80°C gave the corresponding 4,5'-bipyrazole derivatives **278** in 20-53% yields. The reaction took place *via* the intermediates **276** and **277** as depicted in Scheme 80.[129]



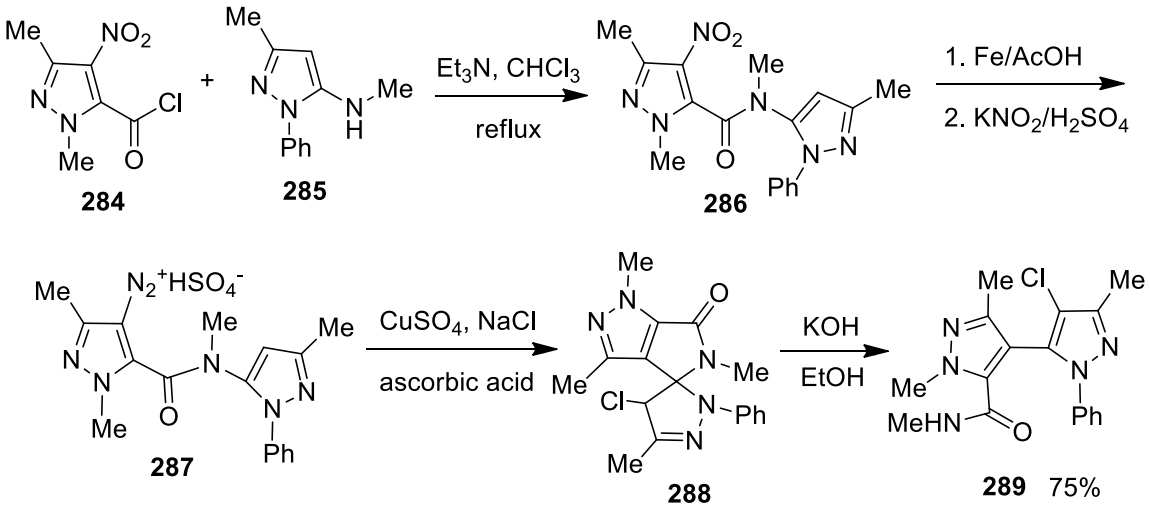
Scheme 80

Reaction of 1,2-dimethylpyrrole **279** with two equivalents of the hydrazonoyl chloride **217** yielded two products: the *bis*-cycloadducts **280** and **281** in 40 and 30% yields, respectively. Ring transformation of the cycloadducts **280** and **281** into the 4,5'-bipyrazole **282** and 4,4'-bipyrazole **283** derivatives, respectively in high yields, was achieved in refluxing ethanol in the presence of hydrochloric acid (Scheme 81).[130]



Scheme 81

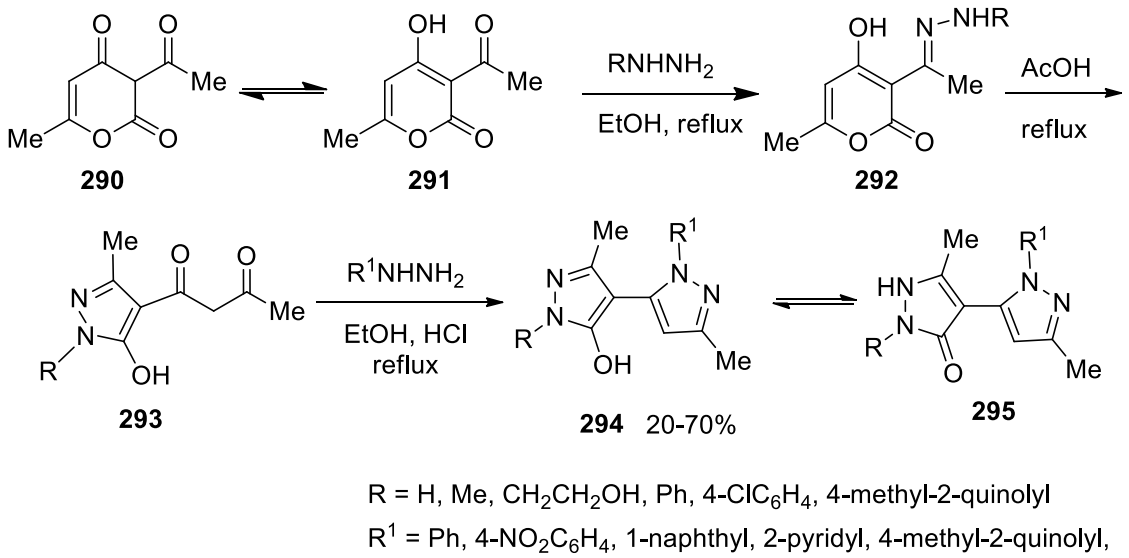
Heating of nitropyrazolecarbonyl chloride **284** with *N*,3-dimethyl-1-phenylpyrazol-5-amine **285** gave the nitropyrazolylamide derivative **286**, in which the nitro function was reduced to the corresponding amine and then converted into the diazonium salt **287** as outlined in Scheme 82. Treatment of **287** with $CuSO_4$ and NaCl in the presence of ascorbic acid afforded the tricyclic chlorinated spiroheterocycle **288**. Reaction of **288** with KOH in EtOH at room temperature gave 75% yield of the 4,5'-bipyrazole derivative **289** (Scheme 82).[131]



Scheme 82

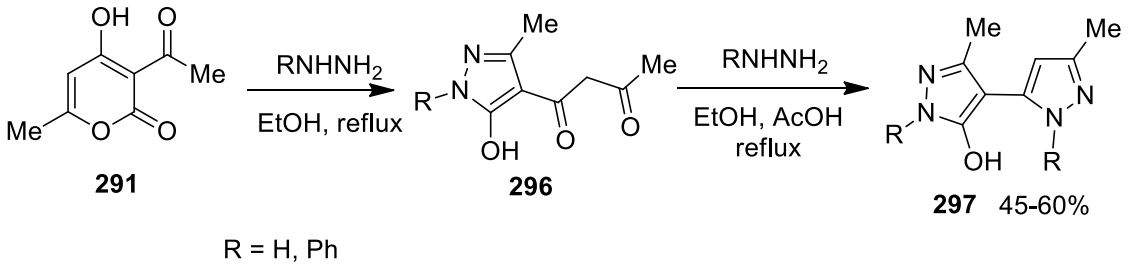
Reaction of 3-acetyl-6-methyl-3*H*-pyran-2,4-dione **290** or its tautomer **291** with aryl- and hetaryl-hydrazines gave the corresponding hydrazones **292** in moderate to good yields. Heating the latter hydrazones **292** in acetic acid underwent smooth skeletal rearrangement to

yield the corresponding 4-acetoacetylpyrazole derivatives **293** (Scheme 83).[132-134] Thereafter, treatment of 4-acetoacetylpyrazole derivatives **293** with aryl- and hetaryl-hydrazines in refluxing ethanol in the presence of HCl furnished a variety of 4,5'-bipyrazoles **294**. The 4,5'-bipyrazoles **294** were available in both the *NH*- and *OH*-tautomers **294** and **295**, respectively (Scheme 83).[135-141]



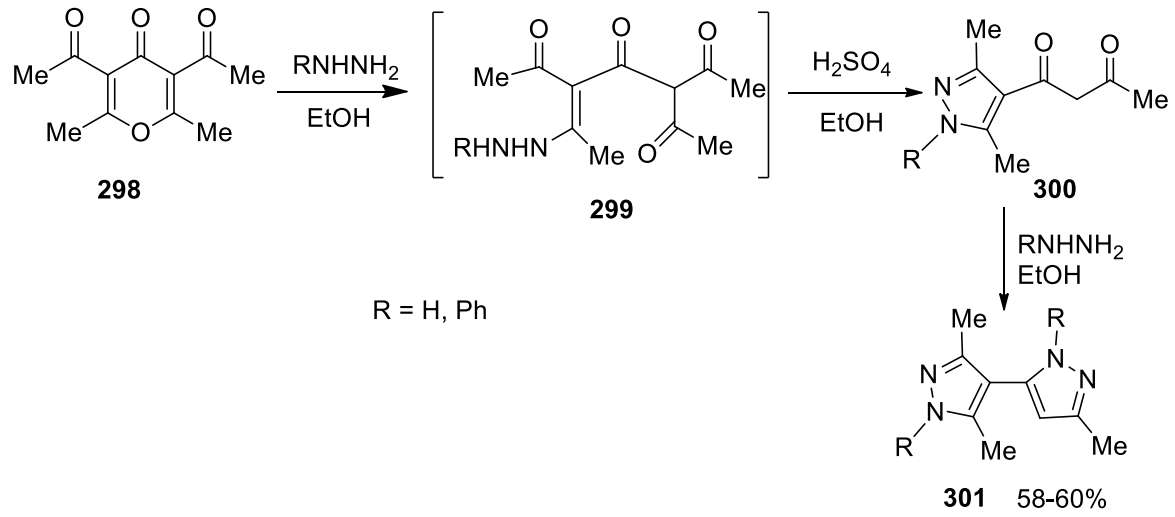
Scheme 83

3-Acetyl-2-pyranone **291** was transformed into 4-(acetoacetyl)-5-hydroxy-3-methylpyrazoles **296** up on its treatment with hydrazine or phenylhydrazine in refluxing ethanol as shown in Scheme 83. In addition, treatment of the latter pyrazoles **296** with hydrazine derivatives resulted in the formation of the corresponding 4,5'-bipyrazoles **297** (Scheme 84).[142]



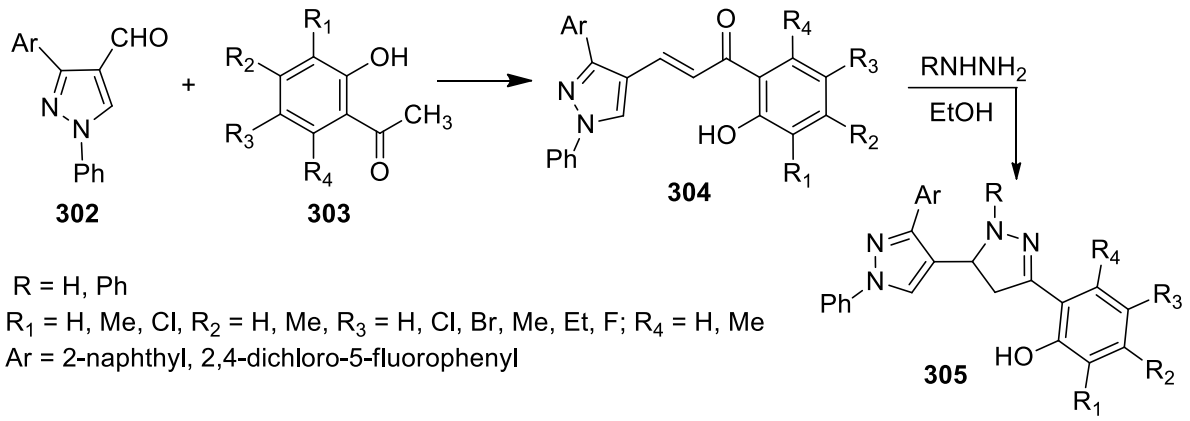
Scheme 84

Treatment of 3,5-diacetyl-4-pyrone **298** with hydrazine and phenylhydrazine at room temperature followed by acidification gave the 4-acetoacetylpyrazole derivatives **300**. Further reaction of the pyrazoles **300** with hydrazines afforded the 4,5'-bipyrazole derivatives **301** in reasonable yields (Scheme 85).[143]



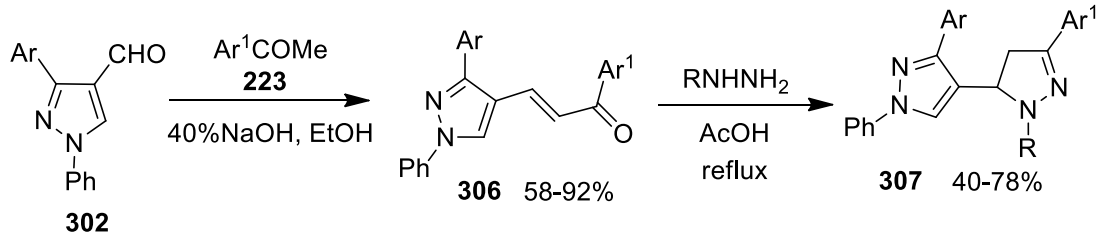
Scheme 85

The base catalyzed condensation of pyrazole-4-carboxaldehydes **302** with 2-hydroxyacetophenones **303** gave the corresponding propenones **304** which upon treatment with hydrazine or phenylhydrazine yielded the 4,5'-bipyrazole derivatives **305** (Scheme 86).[144-146]



Scheme 86

Reaction of pyrazole-4-carboxaldehyde **302** with acetophenones **223** in NaOH and ethanol at 50 °C afforded the 4-pyrazolylpropenones **306** in high yields. Heating the latter propenones **306** with hydrazines yielded the corresponding 4,5'-bipyrazole derivatives **307** (Scheme 87).[147-149]



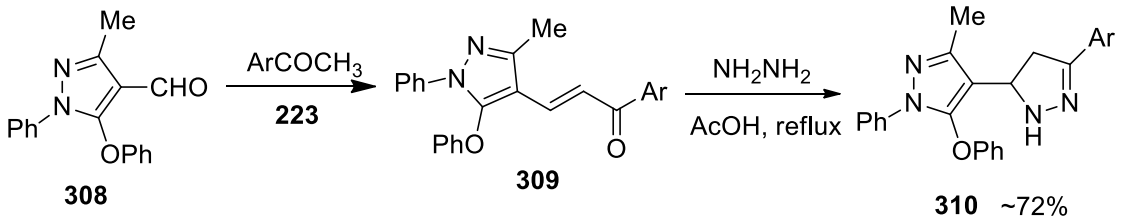
Ar = Ph, 4-$MeSC_6H_4$, 2-thienyl, 3-pyridyl

Ar^1 = Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-$MeSC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 4-OHC_6H_4

R = H, Ph

Scheme 87

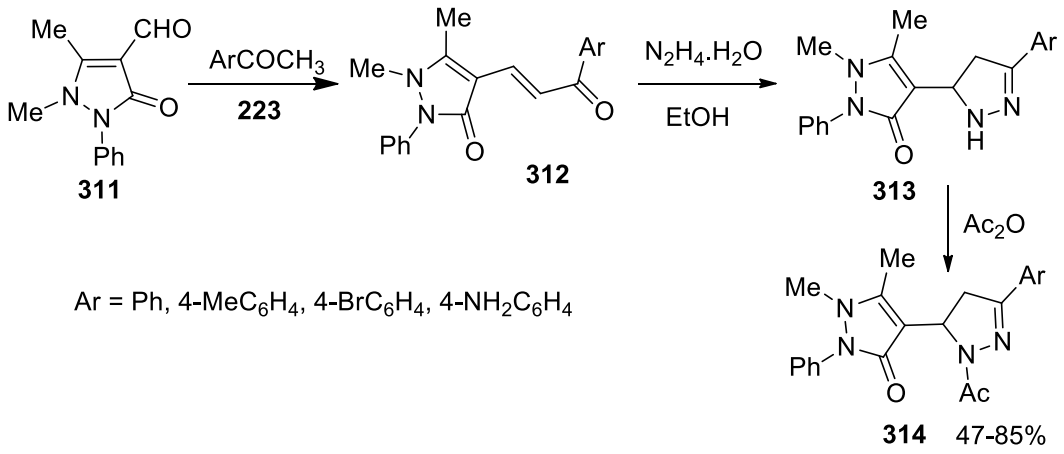
Aldol condensation reaction of acetophenones **223** with the polysubstituted pyrazole-4-carboxaldehyde **308** afforded the corresponding chalcone derivatives **309**. Treatment of the chalcones **309** with hydrazine in glacial acetic acid under reflux conditions gave the 4,5'-bipyrazole derivatives **310** in good yields (Scheme 88).[150-151]



Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 2-thienyl, 2-pyridyl

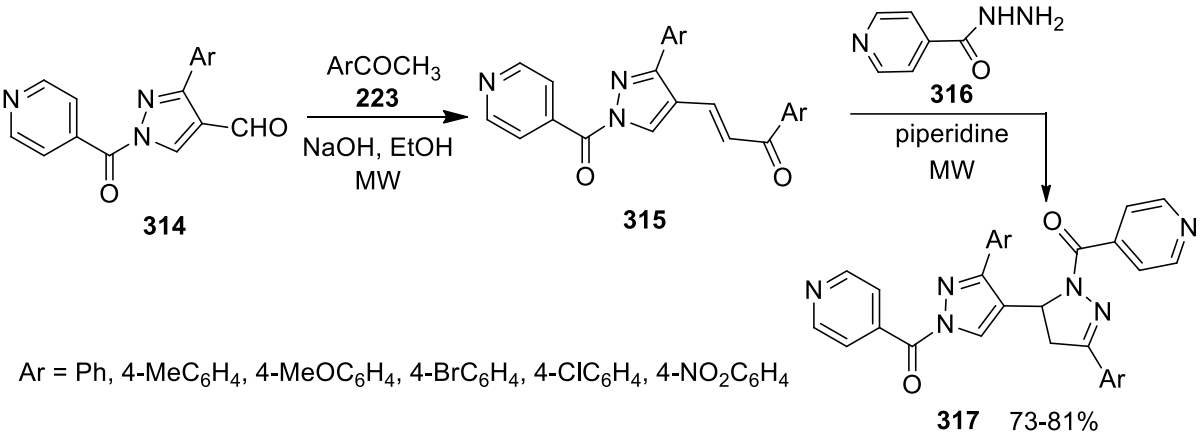
Scheme 88

4-Formylpyrazolone **311** reacted with acetophenones **223** to give the corresponding chalcones **312** which were readily cyclized upon treatment with hydrazine hydrate in ethanol at reflux condition to give the corresponding 4,5'-bipyrazole derivatives **313** in good yields. Acylation of **313** with acetic anhydride at reflux in the presence of pyridine gave the *N*-acylated 4,5'-bipyrazole derivatives **314** (Scheme 89).[152]



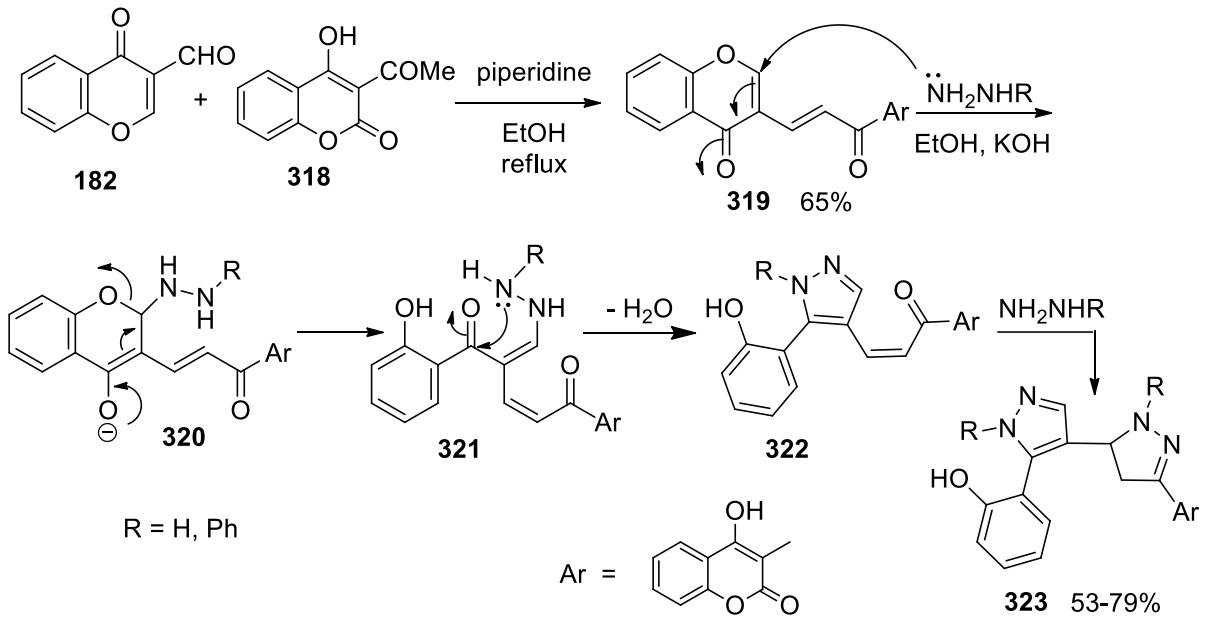
Scheme 89

Microwave irradiation of a mixture of 1-isonicotinoylpyrazole-4-carboxaldehyde **314** and acetophenones **223** in the presence of NaOH in ethanol gave the chalcone derivatives **315**. Reaction of **315** with isonicotinic acid hydrazide **316** under microwave irradiation condition furnished the 1,1'-diisonicotinoyl-4,5'-bipyrazole derivatives **317** in high yields (Scheme 90).[153]



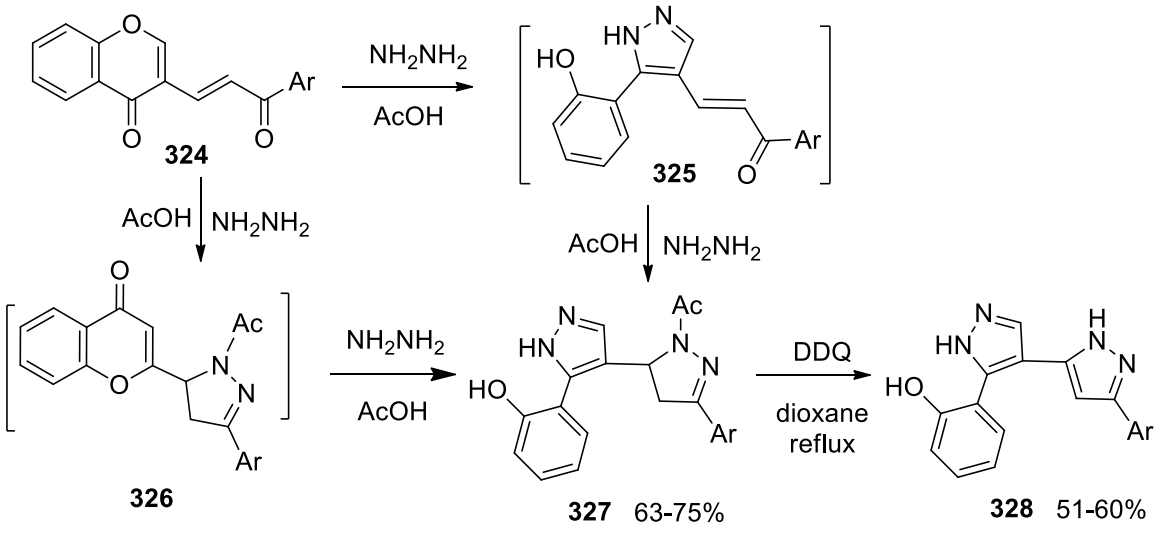
Scheme 90

The propenone derivative **319**, which was synthesized from 3-acetyl-4-hydroxycoumarin **318** and 3-formylchromone **182**, was converted into the 4,5'-bipyrazole derivatives **323** by treatment with hydrazine and phenylhydrazine. The mechanism postulated in Scheme 91 shows that the chromone moiety in **319** underwent ring-opening by the action of hydrazine followed by cyclization to form the pyrazole moiety of **322**. Further molecule of hydrazine reacted with the α,β-unsaturated ketone **322** to form the 4,5'-bipyrazole derivatives **323** (Scheme 91).[154]



Scheme 91

Synthesis of several 1-acetyl-4,5'-bipyrazole derivatives **327** was reported in 63-75% yields by treatment of the 3-(3-aryl-3-oxopropenyl)chromen-4-ones **324** with hydrazine hydrate in hot acetic acid. Oxidation of the 1-acetyl-4,5'-bipyrazole derivatives **327** with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in dioxane at reflux under nitrogen gave the 1*H*,1'*H*-4,5'-bipyrazole derivatives **328** in 51-60% yields. Mechanistically, formation of **327** may be done by reaction between **324** and hydrazine in two different ways, either *via* 1-acetyl-3-aryl-5-(3-chromonyl)-2-pyrazoline **326** or α,β-unsaturated ketone **325** intermediates. Both intermediates could then react with hydrazine to provide the 4,5'-bipyrazole derivatives **328** (Scheme 92).[155,156]

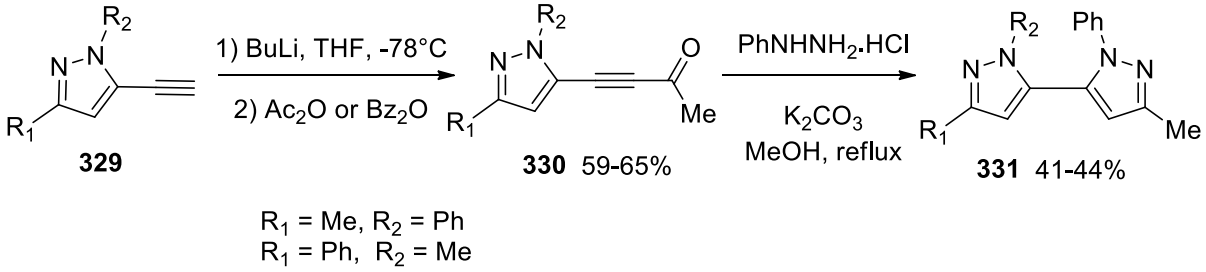


Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 1-naphthyl, 2-naphthyl

Scheme 92

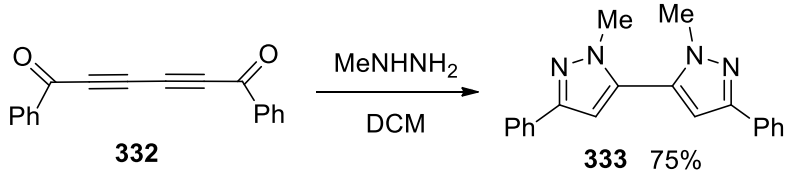
2.10. 5,5'-Bipyrazoles

Lithiation of the pyrazolylacetylenes **329** followed by quenching with acetic or benzoic anhydrides led to formation of the pyrazolylacetylenic ketones **330**. Heating of the acetylenic ketones **330** with phenyl hydrazine hydrochloride and potassium carbonate in methanol led to formation of 5,5'-bipyrazoles **331** in moderate yields (Scheme 93).[157]



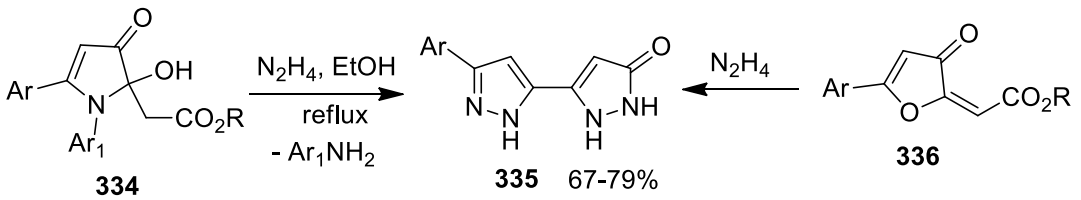
Scheme 93

Treatment of the *bis*-(benzoylacetylene) **332** with methyl hydrazine in DCM gave the symmetric 5,5'-bipyrazole **333** in a good yield (Scheme 94).[157]



Scheme 94

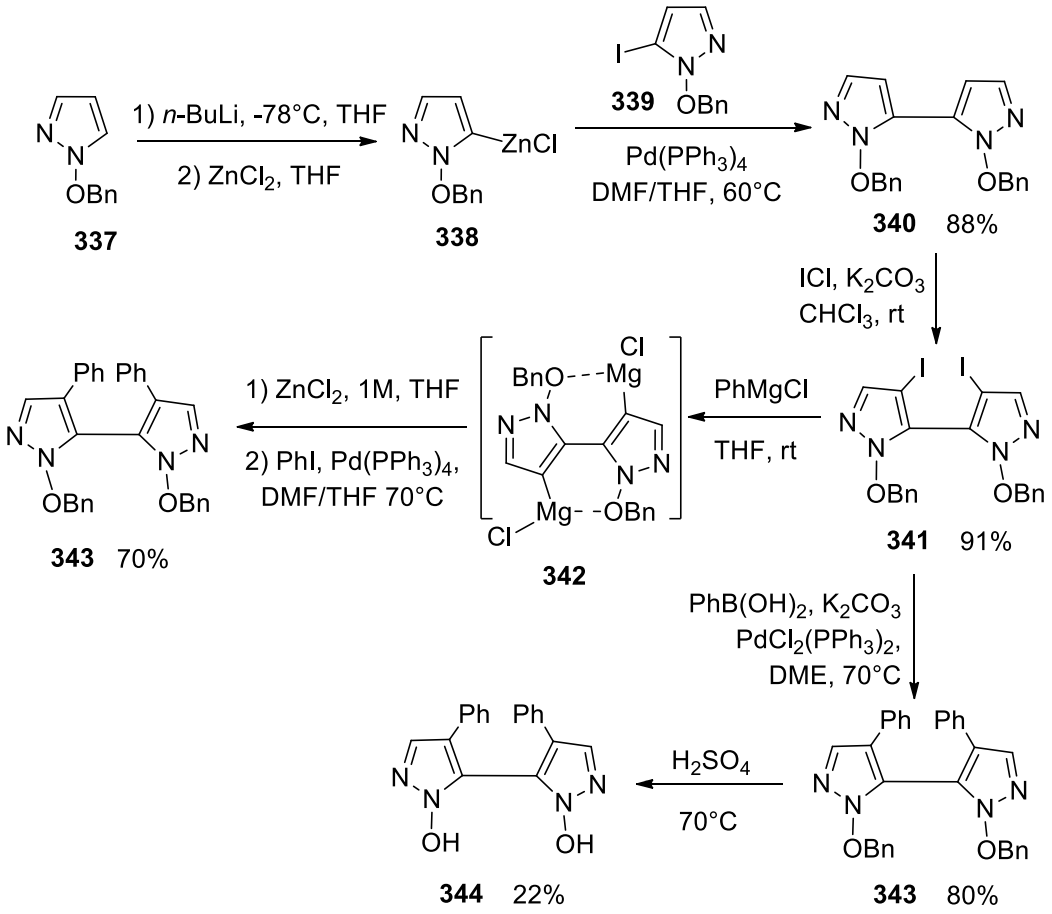
5,5'-Bipyrazole derivatives **335** were obtained in good yields by treating (1,5-diaryl-2-hydroxy-3-oxopyrrolidin-2-yl)acetates **334** with hydrazine hydrate in ethanol at reflux with loss of aniline derivative and water. The 5,5'-bipyrazole derivatives **335** were alternatively synthesized by hydrazinolysis of the 5-aryl-2-alkoxycarbonylmethylene-2,3-dihydro-3-furanones **336** (Scheme 95).[158,159]



Scheme 95

Lithiation of 1-benzyloxypyrazole **337** followed by transmetallation with zinc chloride in THF gave 1-benzyloxypyrazol-5-ylzinc(II) chloride **338** which underwent Negishi cross-

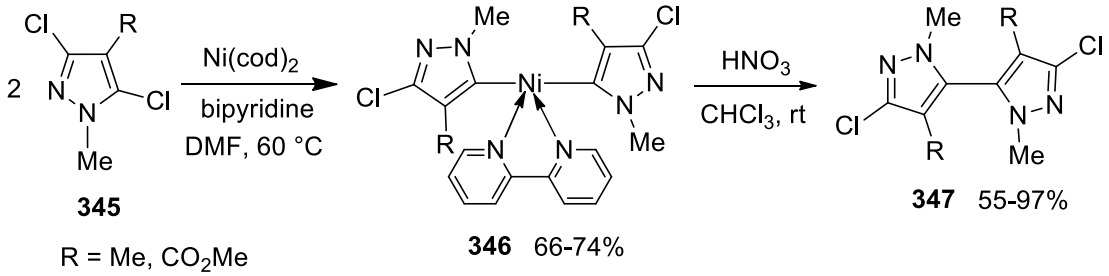
coupling when treated with 5-iodo-1-benzyloxypyrazole **339** to give 1,1'-(dibenzyloxy)-5,5'-bipyrazole **340**. Treating 5,5'-bipyrazole **340** with a large excess of iodine monochloride using potassium carbonate as base resulted in a rapid introduction of the iodine and gave 4,4'-diiodo-1,1'-(dibenzyloxy)-5,5'-bipyrazole **341** in excellent yield. The Negishi conditions were applied for the introduction of phenyl groups at C-4 and C-4' in 5,5'-bipyrazole **341**, however the iodine of **341** did not react. Instead, the reaction occurred by a double iodine–magnesium exchange to the dimagnesium species, followed by magnesium–zinc exchange, and then cross-coupling with iodobenzene, resulted in the formation of 1,1'-(dibenzyloxy)-4,4'-diphenyl-5,5'-bipyrazole **343** in 70% yield but the disadvantage of this method was that a huge excess of phenylmagnesium chloride had to be applied to get the dimagnesium intermediate **342**. Alternatively, Suzuki reaction of 4,4'-diiodo-1,1'-(dibenzyloxy)-5,5'-bipyrazole **341** with phenylboronic acid afforded 1,1'-(dibenzyloxy)-4,4'-diphenyl-5,5'-bipyrazole **343** more efficiently in 80% yield. Heating of **343** in concentrated sulfuric acid led to debenzylation and afforded the corresponding 1,1'-(dihydroxy)-4,4'-diphenyl-5,5'-bipyrazole **344** in low yield (Scheme 96).[160,161]



Scheme 96

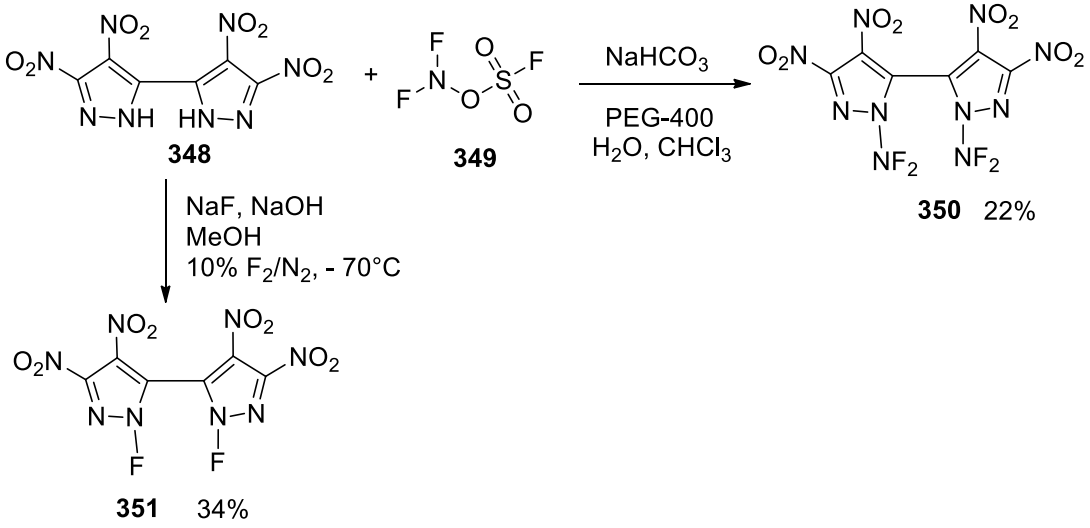
Treatment of 3,5-dichloropyrazoles **345** with $Ni(cod)_2$ [cod = 1,5-cyclooctadiene] in the presence of 2,2'-bipyridine in DMF, had been reported to afford *bis*-(pyrazolyl)nickel(II) complexes **346** in good yields, *via* oxidative addition where the C(5)–Cl bond of the two C–Cl

bonds reacted with Ni(0)L*m*. Treatment of the *bis*(pyrazolyl)nickel(II) complexes **346** with nitric acid resulted in reductive elimination to give the 3,3'-dichloro-5,5'-bipyrazoles **347** (Scheme 97).[162,163]



Scheme 97

1,1'-Difluoroamino-3,3',4,4'-tetranitro-5,5'-bipyrazole **350** have been synthesized in reasonable yield by reacting 3,3',4,4'-tetranitro-1H,1'H-5,5'-bipyrazole **348** with *O*-fluorosulfonyl-*N*,*N*-difluorohydroxylamine **349** under phase-transfer catalysis using PEG-400 in the presence of $NaHCO_3$.[164] However, treatment of **350** with NaF/NaOH in methanol followed by addition of F_2/N_2 at -70 °C resulted in the formation of 1,1'-difluoro-3,3',4,4'-tetranitro-5,5'-bipyrazole **351** (Scheme 98).[165]



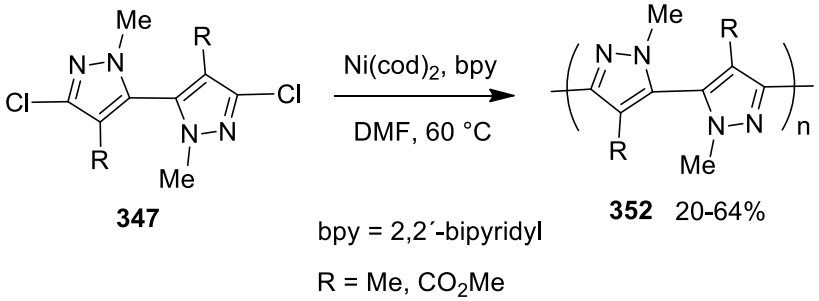
Scheme 98

3. Applications of Bipyrazoles

Bipyrazole derivatives were used as new class of supramolecular complexes, organometallic cage-like structures and self-assembling metallomacrocycles with bipyrazole ligands that are promising as catalysts, molecular mimics, molecular magnetic devices and sensors.[166-168]

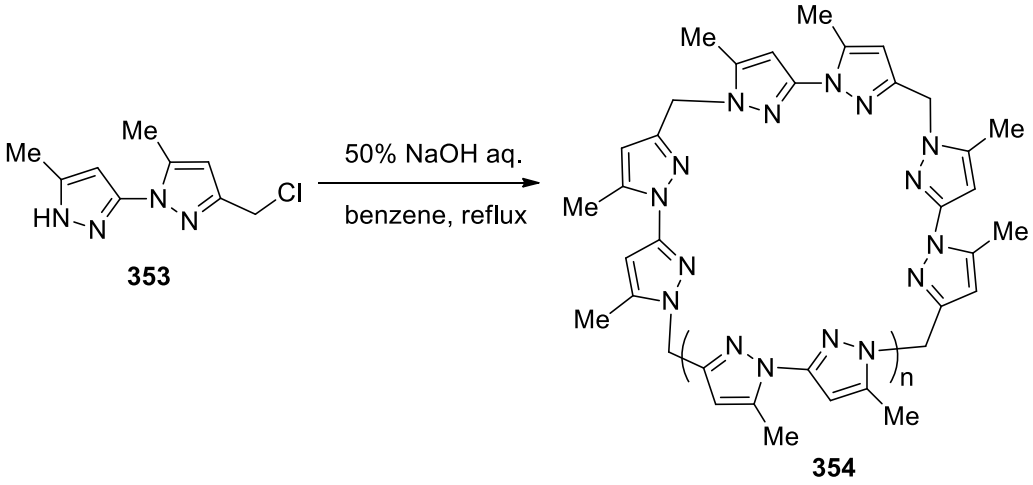
Poly(5,5'-bipyrazole-3,3'-diyl) derivatives **352** were synthesized from 3,3'-dichloro-

5,5'-bipyrazoles **347** through dehalogenative polycondensation using a mixture of $Ni(cod)_2$ and 2,2´-bipyridine in DMF at 60 °C (Scheme 99). The obtained polymers were characterized by their high thermal stability and electrochemical activity.[162]



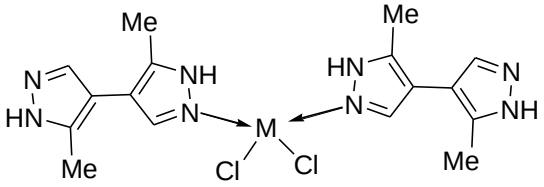
Scheme 99

Polycondensation of 5,5'-dimethyl-3-chloromethyl-1,3'-bipyrazole **353** was achieved in refluxing benzene in the presence of 50% NaOH solution and led to the formation of the polypyrazolic macrocycle **354** in 75% yield (Scheme 100).[30]



Scheme 100

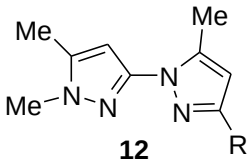
Palladium(II) and platinum(II) complexes of 5,5'-dimethyl-3,3'-bipyrazole **355** were reported to have potential anti-tumor properties.[169]



355 M = Pd, Pt

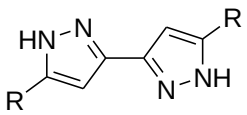
1',3,5,5'-Tetramethyl-1,3'-bipyrazole **12** and 5,5'-disubstituted-3,3'-bipyrazoles **93** were used as inhibitors for the corrosion of steel in 1*M* HCl where the inhibition efficiency

increased with increase in inhibitor concentration. The inhibiting effect of the bipyrazoles **12** and **93** was attributed to their adsorption at the metal–solution interface, owing to the presence of many active centers (several nitrogen atoms and many π-electrons of the pyrazole rings) for adsorption which revealed that inhibitive actions of bipyrazole compounds were mainly due to adsorption on steel surface.[170-172]



12

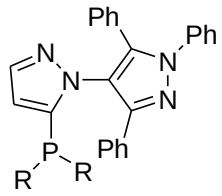
R = Me, CH_2OH, CO_2Et



93

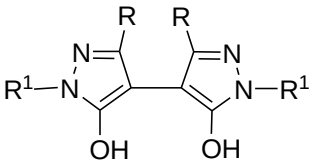
R = Et, Ph, 4-ClC_6H_4

The bipyrazole derivatives (bippyphos) **57** were applied as efficient ligands in the palladium-catalyzed C-O and C-N cross-coupling reactions of aryl halides with primary alcohols and with urea derivatives, respectively.[46,173-176]



57 R = *t*-Bu, 1-adamantyl

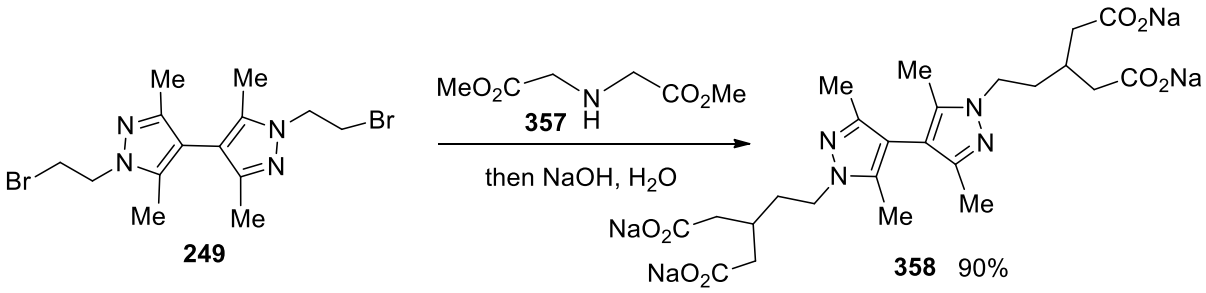
5,5'-Dihydroxy-4,4'-bipyrazoles **356** were reported as useful medicines for treatment of cerebral ischemia, heart diseases, gastrointestinal diseases, cancer, aging and inflammation. These medicines are useful for effectively capturing active oxygen and free radicals which cause adult diseases where singlet oxygen generated in a photo-excited hematoporphyrin system was reacted with 5,5'-dihydroxy-4,4'-bipyrazoles **356** to give ESR signal indicating production of stable free radical.[25,177,178]



R = H, Me, Et, Pr, Bu, Ph **356**

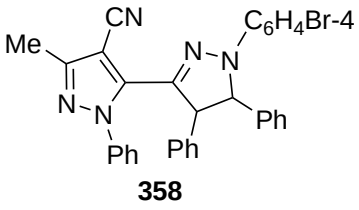
R^1 = H, Me, Et, Pr, Bu, CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, Ph, benzyl, naphthyl

Heating of 5,5'-bi(2-bromoethylpyrazole) **249** with methyl iminodiacetate **357** followed by treatment with aqueous NaOH furnished 90% yield of the tetra-sodium salt of 4,4'-bipyrazole derivative **358** (Scheme 101). The tetra-sodium salt of 4,4'-bipyrazole derivative **358** was used in Gadolonium(III) complex as Paramagnetic Contrast Agent for clinical Magnetic Resonance Imaging (MRI).[120]

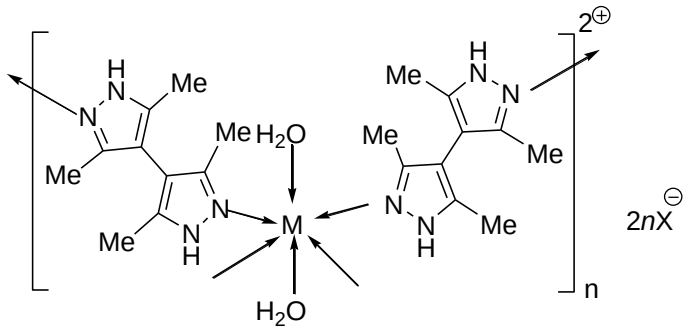


Scheme 101

The solvatochromic behavior of 3,5'-bipyrazole derivatives **358** was reported in various solvents of different polarity. Spectroscopic studies revealed that the solvatochromic behavior depended on both the polarity of the medium and the hydrogen-bonding properties of the solvents. The photophysical study of 3,5'-bipyrazole derivatives **358** in different solvents helped in assessing their potential application in different environments.[179]

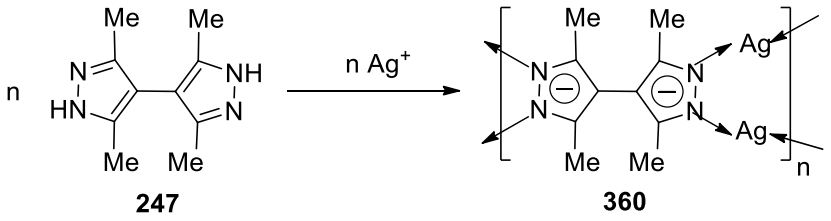


3,3',5,5'-Tetramethyl-4,4'-bipyrazole **247** is an interesting class of bipyrazoles due to its capability to form porous coordination polymers **359** with potential uses as solid sorbents, ion exchangers and heterogeneous catalysts.[119,180-189]



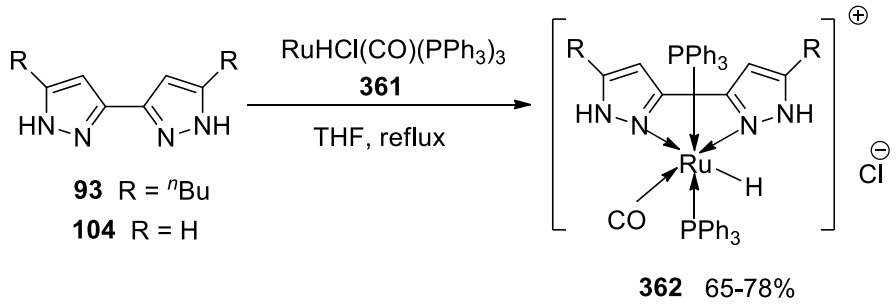
359 M = Cu, Co, Cd, Ni, Pd, Ag, W

Furthermore, 3,3',5,5'-tetramethyl-4,4'-bipyrazole **247** was well-studied as a hydrogen-bonding synthon and neutral bidentate ligand for the synthesis of a flexible porous coordination polymer with two-coordinate Ag centers **360** (Scheme 102).[190-194]



Scheme 102

Treatment of the bidentate 3,3'-bipyrazole ligands **93** and **104** with the monohydrido ruthenium(II) complex **361** gave the corresponding carbonyl(hydrido)*bis*-(triphenylphosphane)ruthenium(II) complexes **362** in 65-78% yields. The ruthenium(II) complexes **362** showed catalytic activity and transfer of hydrogen in catalyzed hydrogenation reactions (Scheme 103).[69,195]



Scheme 103

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