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; \textit{N,N-}, \textit{C,N-}, and \textit{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.
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).
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](image)

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-1H-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](image)

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).\textsuperscript{16,31}

\begin{equation*}
\text{HN-}NH_2 \quad \begin{array}{c}
\text{MeS} \\
\text{CN}
\end{array} \quad \begin{array}{c}
\text{EtOH, } K_2 CO_3 \\
\text{reflux}
\end{array} \quad \begin{array}{c}
\text{NH}_2 \\
\text{NN}
\end{array} \\
\text{R}^3 \quad \text{X} \quad \text{R}^1 \\
\text{R}^2 \quad \text{R}^4 \\
\text{R}^1 = H, \text{Me, Et}; \quad \text{R}^2 = H, \text{Me, OMe, SMe, CF}_3; \quad \text{R}^3 = H, \text{Cl, Br, CN, CO}_2 \text{Et} \quad \text{X} = H, \text{CN, CO}_2 \text{Et}
\end{equation*}

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.\textsuperscript{32}

\begin{equation*}
\text{R, R}^1 = \begin{array}{c}
\text{R} \\
\text{R}^1
\end{array}
\end{equation*}

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.\textsuperscript{33,34}

\begin{equation*}
\text{R = Me, Ph, 2-thienyl}
\end{equation*}

Scheme 6
Electrochlorination of the unsubstituted pyrazole 22 in aqueous NaCl solution in the presence of CHCl₃ 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'-bipyrzyazole 25 in reasonable yield, through the intermediate 24 (Scheme 7).³⁵

![Scheme 7](image)

**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 LiAlH₄ in THF afforded 1,5'-dimethyl-3-hydroxymethyl-5-phenyl-1,3'-bipyrazole 29 in 86% yield (Scheme 8).³⁶

![Scheme 8](image)

**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'-bipyrzyazole 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](image)

**Scheme 9**
2.3. 1,4'-Bipyrazoles

Reaction of 1H-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 with 4-phenylphenylisocyanate afforded the 1,4'-bipyrazole derivative 37 in 69% yield (Scheme 10).\(^{39,40}\)

\[
\begin{align*}
\text{33} & \xrightarrow{1) \text{ArCOCH}_2\text{Br}} \text{34} \quad \text{35} \quad \text{36} \\
\text{NC} & \quad \text{Ar} \quad \text{Ar}^1 \quad \text{NC} \\
\text{NH} & \quad \text{N} \quad \text{O} \quad \text{N} \\
\text{1H-pyrazole-4-carbonitrile} & \quad \text{4-chlorophenacyl bromide} \quad \text{formylated} \\
2) \text{CH}_2\text{O} & \\
\text{N}_2\text{H}_4 & \quad \text{36} \\
\end{align*}
\]

\[\text{Ar} = 4-\text{ClC}_6\text{H}_4; \quad \text{Ar}^1 = 4-\text{PhPh}\]

Scheme 10

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

\[
\begin{align*}
\text{38} & \xrightarrow{\text{N}_2\text{H}_4} \text{39} \\
\text{O}_2\text{N} & \quad \text{NH} \\
\text{N} & \quad \text{N} \\
\text{CHO} & \quad \text{CHO} \\
\end{align*}
\]

Scheme 11

Alkylation of 4-bromopyrazole 40 with ethyl bromoacetate or bromoacetanitrile 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\(_2\)Et). 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\(_2\)Et) 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).\(^{43}\)
2-(3,5-Dimethyl-1H-1-pyrazolyl)acetophenone 50 was prepared in 71% yield through the alkylation reaction of 3,5-dimethyl-1H-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-1H-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).
Next, the synthesis 5-(di-tert-butylphosphino)-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-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).

\[
\begin{align*}
\text{Ph}_2\text{C}=\text{O} & \xrightarrow{\text{PyrHBr}_3 \text{ or NBS}} \text{Ph}_2\text{C}=\text{O} \xrightarrow{\text{NMP, H}_2\text{O}} \text{Ph}_2\text{C}=\text{O} \\
\text{Ph}_2\text{C}=\text{Br} & \xrightarrow{\text{NMP, H}_2\text{O}} \text{Ph}_2\text{C}=\text{O} \\
\text{ArNHNNH}_2 & \xrightarrow{\text{MeOH/AcOH/rt}} \text{ArNHNHO} \\
\text{NMP,H} & \xrightarrow{\text{BuLi, THF, -78°C}} \text{NMP,H} \\
\text{R} = \text{t-Bu, cyclohexyl, 1-adamantyl, Ph} & \quad \text{Ar} = \text{Ph, 4-MeOC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4
\end{align*}
\]

Scheme 15

*N*-Hetarylation of 1H-pyrazole 22 through its coupling with 4-iodo-1-methylpyrazole 58 using cesium carbonate as a base, in the presence of Cu₂O as co-catalyst and salicylaldoxime 59 as ligand, in acetonitrile furnished 96% yield of the 1,4’-bipyrazole derivative 60 (Scheme 16).

\[
\begin{align*}
\text{Pyraz} \xrightarrow{\text{Cs}_2\text{CO}_3, \text{Cu}_2\text{O}, \text{MeCN, 82°C}} \text{Pyraz} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{Me} & \xrightarrow{\text{Me}} \text{Me}
\end{align*}
\]

Scheme 16

The reaction of 3,4,5-trinitro-1H-pyrazole (TNP) 61 with 1H-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 1H-pyrazoles 62 selectively substitute the 4-positioned nitro group in the TNP 61 (Scheme 17).
Scheme 17

2.4. 1,5'-Bipyrazoles

In contrast to the behavior of 3,4,5-trinitro-1H-pyrazole (TNP) 61 towards 1H-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 1H-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).\(^4^9\)

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'-(methylsulfonlamino)-1,5'-bipyrazole 68 (Scheme 19).\(^5^0,5^1\)

Scheme 19

\(Ar = \text{Ph, 4-MeOC}_{6}H_{4}, 4-\text{BrC}_{6}H_{4}, 4-\text{ClC}_{6}H_{4}, 4-\text{FC}_{6}H_{4}, 4-\text{NO}_{2}C_{6}H_{4}\)

\(R = \text{H, Me}\)
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 (NO₂). 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](image_url)

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 tetrafluoroborate 74 from the intermediate 73 under the reaction conditions (Scheme 21). ⁵⁴

![Scheme 21](image_url)

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-1H-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](image_url)
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 = R¹ = 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).

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).

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).
Scheme 25

2.5. 3,3'-Bipyrazoles

Treatment of the methyl ketone 91 with diethyl oxalate in the presence of an alkoxide base gave the corresponding 1,3,4,6-tetraacetones 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).\textsuperscript{11,61,62} Treatment of the bipyrazole derivatives 93 with benzylbromide and ethyl chloroacetate in refluxing THF gave the corresponding alkyalted 3,3'-bipyrazole derivatives 95 in moderate to good yields (Scheme 26).\textsuperscript{63-69}

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).\textsuperscript{70-72}

\[
\begin{align*}
\text{ArCOCOAr} + \text{RNHNH}_2 &\xrightarrow{\text{EtOH, H}_2\text{O, reflux}} \text{Ar}^\text{N-N} \text{Ar} \\
\text{Ar} &\equiv \text{Ph, 4-MeC}_6\text{H}_4, 2,4-\text{Me}_2\text{C}_6\text{H}_3, 4-\text{C}_6\text{H}_4\text{OH} \\
R &\equiv \text{H, Ph, 2-MeC}_6\text{H}_4
\end{align*}
\]

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 acetyl chloride 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).\textsuperscript{73}

\[
\begin{align*}
\text{ArCOCOAr} + \text{N}_2\text{H}_4 \xrightarrow{\text{MeOH, reflux}} \text{HN-N} \text{Me} \text{OH} \\
\text{AcCl or Ac}_2\text{O} &\xrightarrow{} \text{Ar}^\text{N-N} \text{Ar} \\
\text{Ar} &\equiv \text{Ph, p-FC}_6\text{H}_4, p-\text{ClC}_6\text{H}_4
\end{align*}
\]

Scheme 28

Oxidative dehydrogenation of 3,3',4,4',5,5'-hexahydro-3,3'-bipyrazole 103 with MnO\textsubscript{2}, in benzene at room temperature, led to the formation of a mixture of 3,3'-bipyrazole 104 and 3-cyclopropyl-1H-pyrazole 105 in 27 and 18\% yields, respectively (Scheme 29).\textsuperscript{74,75}

\[
\begin{align*}
\text{HN-N} \text{N} \xrightarrow{\text{MnO}_2, \text{PhH}, \text{rt}} \text{HN-N} \text{N-N} + \text{HN-N} \text{N} \\
\text{103} &\xrightarrow{} \text{104} 27\% + \text{105} 18\%
\end{align*}
\]

Scheme 29
Reaction of 2,3-bis(phenylsulfonyl)-1,3-butadiene 106 with diazomethane in dichloromethane (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).\textsuperscript{76}

![Scheme 30](image)

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,1'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 2:1-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).\textsuperscript{76}

![Scheme 31](image)

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\textsubscript{2} = Ph, R\textsubscript{3} = COPh, Ar = Ph) with chloranil afforded the corresponding 3,3'-bipyrazole derivative 119 in 71% yield (Scheme 32).\textsuperscript{77}
Regioselective synthesis of polysubstituted 3,3'-bi-1H-pyrazole derivatives 122 via 1,3-dipolar cycloaddition reactions has also been reported. Thus, the bis-arylnitrilimines 114 reacted regioselectively with the cinnamoylitriles 120 to yield the cycloadducts 5,5'-dicyano-4,4',5,5'-tetrahydro-3,3'-bi-1H-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-1H-pyrazole derivatives 122 in 55-75% yields (Scheme 33).

Furthermore, regioselective 1,3-dipolar cycloaddition of the bis-hydrazonyl halides 113
with the benzyldiene chroman-4-one and thiocroman-4-one derivatives 123 afforded the corresponding bis-spiropyrazoline-5,3'-chroman(thiocroman)-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-benzyldiene-3-coumaranone 125 furnished the 3,3'-bipyrazole derivatives 126 in moderate yields (Scheme 34).®

\[
\text{Scheme 34}
\]

**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).®

\[
\text{Scheme 35}
\]

Cyclocondensation of 1,6-diethoxyhexa-1,5-diene-3,4-dione 130 with phenylhydrazine in \textit{m}-cresol provided 1,1'-diphenyl-3,3'-bipyrazole 131 in 85% yield (Scheme 36).®
Treatment of the cyanoacetylpyrazole derivative 132 with hydrazine hydrate, in refluxing ethanol afforded the corresponding 3,3′-bipyrazole derivative 133 (Scheme 36). 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-1H-pyrazole-4-carbonitrile 135. When compound 135 was treated with hydrazine hydrate in refluxing ethanol it afforded 1,5-diphenyl-5′-phenylamino-3,3′-bipyrrozol-4,4′-dicarbonitrile 137 in high yield (Scheme 37).

Scheme 37

3-[\((E)\)-3-(N,N-Dimethylamino)acryloyl]-1-(4-chlorophenyl)-5-phenyl-1H-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-(1H-pyrazol-3-yl)-1-(4-chlorophenyl)-5-phenyl-1H-pyrazole-4-carbohydrazide 140 in 80% yield (Scheme 38).

Scheme 38

Heating a mixture of 3-acetyl-4-(4-nitrophenyl)-1-aryl-1H-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).  

![Scheme 39](image)

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 N₂ molecules (Scheme 40).  

![Scheme 40](image)

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(1H-pyrazole)-4,4'-dicarbonitrile 152 in 65% yield upon heating in neat anhydrous hydrazine according to the mechanism outlined in Scheme 41.
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-pyrazolylformylhydrzones 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). \(^{89,91}\)
Similar 1,3-dipolar cycloaddition reactions of the pyrazolylhydrazone 164 with ethyl 3-phenylpropionate 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).\(^a,92\)

The formation of several fullereno-3,4'-bipyrazole adducts 169 from nitrilimines has been also reported. Thus, treatment of the pyrazolylhydrazone 153 with N-bromosuccinimide (NBS) followed by Et\(_3\)N then addition of C\(_{60}\) under microwave irradiation conditions resulted in the formation of 169 in moderate yields (Scheme 45).\(^93\)

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).\textsuperscript{94}

![Scheme 46](image)

The reaction of the pyrazolylamine derivatives 172 with hydrazine or phenylhydrazine led to the formation of 3,4′-bipyrazoles 173 (Scheme 47).\textsuperscript{95}

![Scheme 47](image)

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).\textsuperscript{96-98}

![Scheme 48](image)

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).\textsuperscript{99}
The 3,4'-bipyrazole derivative 181 was prepared in moderate yield by condensation of 3-(2-hydroxyphenyl)-1-(1-phenyl-3-(2-thienyl)-1H-pyrazol-4-yl)prop-2-en-1-one 180 with hydrazine hydrate in refluxing acetic acid (Scheme 50). 100

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

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-1H-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-pyrene 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 hydrazinolysis 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).

Scheme 55

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

2.7. 3,5'-Bipyrazoles

Heating 5-pyrazolyformylhydrazones 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).  

Scheme 57

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

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).\textsuperscript{108}

![Scheme 59](image)

**Scheme 59**

Reaction of 3-(pyrazol-3-yl)-3-oxo-propanenitrile derivative 132 with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene gave the enaminoitrile 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).\textsuperscript{82}

![Scheme 60](image)

**Scheme 60**

3-Bromoacetyl-1,5-diphenyl-1\textsubscript{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\textsubscript{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).\textsuperscript{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 \(\alpha,\beta\)-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).\(^{112}\)
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).\(^\text{83}\)

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).\(^\text{113}\)

Scheme 66

2.8. 4,4'-Bipyrazoles

Bruno \textit{et al.} reported the diastereoselective reductive dimerization 4-tolylmethylene-3-phenylpyrazol-5-one 233, via single electron transfer generated \textit{in situ} using 2-arylbenzimidazoline 234 as catalyst, to afford the corresponding 4,4'-bipyrazoline derivative 235 (Scheme 67).\(^\text{114}\)
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® A102. This reaction proceeded via the intermediate CH-hydrazine 238 and then NH-hydrazone form 239 in tautomeric equilibrium with the relevant NH-hydrazine form 240 (Scheme 68).115

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
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).\textsuperscript{117}

\[ X = \text{O, NH} \]

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).\textsuperscript{117}

\[ R = \text{H, Ph, 4-NO}_2\text{C}_6\text{H}_4, 2,4-(\text{NO}_2)_2\text{C}_6\text{H}_3 \]

Scheme 71

Dimerization of acetylacetone 10 was conducted using iodine and NaOH to give 3,4-diacylhexan-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).\textsuperscript{118,119} Alkylation of 4,4'-bipyrazole 247 with benzyl chlorides using tetrabutylammonium bromide, as phase transfer catalyst, in refluxing toluene gave the corresponding 1,1'-dialkylated 4,4'-bipyrazoles 248.\textsuperscript{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).\textsuperscript{120}
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 aryl diazonium fluoroborates 251 (Scheme 73).\textsuperscript{121}

\begin{center}
\textbf{Scheme 73}
\end{center}

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).\textsuperscript{122}

\begin{center}
\textbf{Scheme 74}
\end{center}
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).\(^{123}\)

\[
\begin{align*}
\text{EtO}_2\text{C} & \xrightarrow{\text{NBS}} \text{EtO}_2\text{C} \\
\text{N} & \xrightarrow{\text{Br}_2/\text{CHCl}_3} \text{N} \\
256 & \xrightarrow{\text{HBr}} 258 \\
\end{align*}
\]

\(R = \text{Me, Ph}\)

**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).\(^{25}\)

\[
\begin{align*}
\text{Me} & \xrightarrow{\text{H}_2\text{O}_2, \text{SeO}_2} \text{Me} \\
\text{N} & \xrightarrow{\text{MeOH}} \text{N} \\
259 & \xrightarrow{\text{50-61%}} 260 \\
\text{Ar} = \text{C}_6\text{H}_5, 4-(\text{CO}_2\text{H})\text{C}_6\text{H}_4 \\
\end{align*}
\]

**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 (\(X = \text{O}\)). Compound 263 (\(X = \text{O}\)) was converted into 263 (\(X = \text{S}\)) by the action of \(\text{P}_2\text{S}_3\). Reaction of Vilsmeier reagent (DMF/\(\text{POCl}_3\)) with 4,4′-bipyrazole 263 (\(X = \text{S, O}\)) 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(PPh₃)₄ and NaHCO₃ 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-Bu₄NF 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(PPh₃)₄ in anhydrous DME using Na₂CO₃ as a base (Scheme 79).¹²⁸
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 Et₃N] 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 depicted in Scheme 80.

\[
\begin{align*}
\text{Ar} & \quad \text{Ar} \\
273 & \quad \overset{\text{80 °C}}{\underset{\text{Et}_3\text{N}, \text{C}_6\text{H}_6}{\text{Et}_3\text{N}, \text{C}_6\text{H}_6}} \quad \text{N}^+ \quad \text{N}^- \\
274 & \quad \overset{\text{E} \text{t}_2\text{N}}{\underset{275}{\text{E} \text{t}_2\text{N}}} \\
275 & \quad \overset{\text{E} \text{t}_2\text{N}}{\underset{278}{\text{E} \text{t}_2\text{N}}} \\
277 & \quad \overset{\text{E} \text{t}_2\text{N}}{\underset{278}{\text{E} \text{t}_2\text{N}}} \\
\end{align*}
\]

\( \text{Ar/Ar}^1 = \text{PhPh}; \text{Ph/4-ClC}_6\text{H}_4; \text{Ph/4-NO}_2\text{C}_6\text{H}_4; 4-\text{NO}_2\text{C}_6\text{H}_4/\text{Ph} \)

Scheme 80

Reaction of 1,2-dimethylpyrrole 279 with two equivalents of the hydrazonyl 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).
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 CuSO₄ 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-3H-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-acetoacetylpiprazole derivatives 293 (Scheme 83). Thereafter, treatment of 4-acetoacetylpiprazole 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).

Scheme 83

3-Acetyl-2-pyranone 291 was transformed into 4-(acetoacetyl)-5-hydroxy-3-methylpiprazoles 296 upon 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).

Scheme 84

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

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
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

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 1H,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).\(^{155,156}\)

Scheme 92

\(\text{Ar} = \text{Ph}, 4-\text{MeC}_6\text{H}_4, 4-\text{MeOOC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 1-\text{naphthyl}, 2-\text{naphthyl}\)
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).\(^\text{157}\)

\[
\begin{array}{c}
\text{329} \\
\text{N} \quad \text{N} \\
\text{R}_1 \quad \text{R}_2 \\
\text{330} \quad \text{59-65\%} \\
\text{N} \quad \text{N} \\
\text{R}_1 \quad \text{R}_2 \\
\text{331} \quad 41-44\% \\
\end{array}
\]

\[
\begin{aligned}
R_1 &= \text{Me, } R_2 = \text{Ph} \\
R_1 &= \text{Ph, } R_2 = \text{Me}
\end{aligned}
\]

Scheme 93

Treatment of the bis-(benzoylacetylene) 332 with methyl hydrazine in DCM gave the symmetric 5,5'-bipyazole 333 in a good yield (Scheme 94).\(^\text{157}\)

\[
\begin{array}{c}
\text{332} \\
\text{O} \\
\text{Ph} \\
\text{Ph} \\
\text{MeNHNH}_2 \quad \text{DCM} \\
\end{array}
\]

\[
\begin{array}{c}
\text{333} \\
\text{N} \quad \text{N} \\
\text{Me} \quad \text{Me} \\
\text{Ph} \quad \text{Ph}
\end{array}
\]

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 hydrazinolyis of the 5-aryl-2-alkoxycarbonylmethylene-2,3-dihydro-3-furanones 336 (Scheme 95).\(^\text{158,159}\)

\[
\begin{array}{c}
\text{334} \\
\text{Ar} \\
\text{335} \quad \text{67-79\%} \\
\text{N} \quad \text{N} \\
\text{Ar} \\
\text{336} \\
\end{array}
\]

\[
\text{R} = \text{Me, } \text{Ar} = \text{Ph, } 4-\text{MeC}_6\text{H}_4; \quad \text{R} = \text{Et, } \text{Ar} = 4-\text{MeOC}_6\text{H}_4
\]

Scheme 95

Lithiation of 1-benzylxopyrazole 337 followed by transmetallation with zinc chloride in THF gave 1-benzylxopyrazol-5-ylzinc(II) chloride 338 which underwent Negishi cross-
coupling when treated with 5-iodo-1-benzylopyrazole 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).

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)L₉. 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 NaHCO₃. 164 However, treatment of 350 with NaF/NaOH in methanol followed by addition of F₂/N₂ 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](image)

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](image)

Palladium(II) and platinum(II) complexes of 5,5'-dimethyl-3,3'-bipyrazole 355 were reported to have potential anti-tumor properties.$^{169}$

![Scheme 100](image)

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 1M 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 \(\pi\)-electrons of the pyrazole rings) for adsorption which revealed that inhibitive actions of bipyrazole compounds were mainly due to adsorption on steel surface.\(^{170-172}\)

\[
\begin{align*}
12 & \quad \text{R} = \text{Me, CH}_{2}\text{OH, CO}_{2}\text{Et} \\
93 & \quad \text{R} = \text{Et, Ph, 4-ClC}_{6}\text{H}_{4}
\end{align*}
\]

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.\(^{46,173-176}\)

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.\(^{25,177,178}\)

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 Gadolanium(III) complex as Paramagnetic Contrast Agent for clinical Magnetic Resonance Imaging (MRI).\(^{120}\)
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

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).

Scheme 103

4. References


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