

CHEMISTRY OF BIPYRAZOLES: SYNTHESIS AND APPLICATIONS



Kamal M. Dawood
Ashraf A. Abbas

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Chemistry of Bipyrazoles: Synthesis and Applications

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CONTENTS

PREFACE	i
CONSENT FOR PUBLICATION	i
CONFLICT OF INTEREST	i
ACKNOWLEDGEMENT	i
CHAPTER 1 CHEMISTRY OF N,N- AND C,N-LINKED BIPYRAZOLE DERIVATIVES	1
1. INTRODUCTION	1
2. SYNTHESIS OF BIPYRAZOLE SYSTEMS	2
2.1. Synthesis of 1,1'-Bipyrazoles	2
2.2. Synthesis of 1,3'-bipyrazoles	3
2.3. Synthesis of 1,4'-bipyrazoles	12
CONCLUSION	17
REFERENCES	17
CHAPTER 2 CHEMISTRY OF 3,3'-BIPYRAZOLE DERIVATIVES	22
1. INTRODUCTION	22
2. SYNTHESIS OF 3,3'-BIPYRAZOLE SYSTEMS	24
2.1. From 1,3-Dipolar Cycloaddition Reactions	24
2.2. <i>Via</i> Cyclocondensation Reactions	34
2.3. From Metal Catalyzed C-H Activation Reactions	45
3. REACTIONS OF 3,3'-BIPYRAZOLE DERIVATIVES	46
3.1. Nitration of 3,3'-Bipyrazole Derivatives	46
3.2. Miscellaneous Reactions	50
CONCLUSIONS	51
REFERENCES	52
CHAPTER 3 CHEMISTRY OF 3,4'-BIPYRAZOLES	57
1. INTRODUCTION	57
2. SYNTHESIS OF 3,4'-BIPYRAZOLE DERIVATIVES	59
2.1. From 1,3-dipolar Cycloaddition Reactions	59
2.2. From Cyclocondensation of 4-pyrazolylchalcones	63
2.3. From Cyclocondensation of 4-pyrazolyl-bifunctional Side-arm with Hydrazines	77
2.4. From C-C Cross Coupling Between Two Pyrazole Units	90
CONCLUSION	91
REFERENCES	91
CHAPTER 4 CHEMISTRY OF 4,4'-BIPYRAZOLES	100
1. INTRODUCTION	100
2. SYNTHESIS OF 4,4'-BIPYRAZOLE DERIVATIVES	102
2.1. From Dimerization of Pyrazoles	102
2.2. From 1,3-dipolar Cycloaddition	105
2.3. From Functionalized Pyrazoles	106
CONCLUSION	110
REFERENCES	111
CHAPTER 5 APPLICATIONS OF BIPYRAZOLE DERIVATIVES	114
1. INTRODUCTION	114
2. APPLICATIONS OF BIPYRAZOLE DERIVATIVES	114
2.1. Bipyrazoles as Ligands	114
2.2. Bipyrazoles in Synthesis of Polybipyrazoles	116
2.3. Bipyrazoles as Energetic Materials	117
2.4. Bipyrazoles as Corrosion Inhibitors	120

2.5. Bipyrazoles as Therapeutics	121
2.6. Bipyrazoles in Metal–organic Frameworks (MOFs)	122
CONCLUSION	136
REFERENCES	137
SUBJECT INDEX	145

PREFACE

Pyrazole is one of the most valuable nitrogen-based heterocycles and is incorporated in the constitution of a wide range of pharmaceuticals and agrochemicals. Direct connection of two pyrazole units produces six different bipyrazole skeletons that can be classified as i) *N-N* bond connected 1,1'-bipyrazoles; ii) *C-N* bond connected 1,3'- and 1,4'-bipyrazoles and iii) *C-C* bond connected 3,3'-, 3,4'- and 4,4'-bipyrazoles.

This book presents the recent achievements in the synthetic platforms toward the directly connected bipyrazole systems and their applications in academic, industrial, and material science fields. The construction of the targeted bipyrazole heterocycles was carried out *via* a wide-range of synthetic routes that grasp the attention of graduate and postgraduate chemists and pharmacists and material science researchers to make more efforts in this area to reach high impact findings for their applications in our life.

Most of the reported bipyrazoles are highly bioactive heterocycles demonstrating a broad array of significant inhibitory activities against several human diseases and agricultural pesticides and herbicides. They also have considerable applications in the material science area *via* involvement in the construction of metal-organic frameworks (MOFs) with distinguished industrial applications.

This book is presented in five chapters describing the synthesis of six connected bipyrazole systems and their brilliant and vibrant applications. As a result, we expect that the provided book chapters will be of pronounced support and a valuable source for the scientific community for developing new bipyrazole-based fascinating candidates towards optimization of their pharmacological benefits in the treatment of diseases as well as building up new MOFs for daily life applications that serve the humanity and industry.

We hope that the researchers and readers will find new ideas based on the provided work. Finally, we are very thankful to the Bentham Science Publishers for giving us the chance to publish this book.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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CHAPTER 1

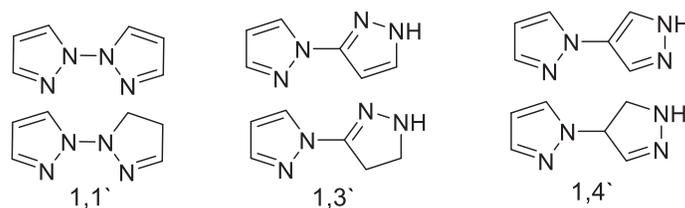
Chemistry of *N,N*- and *C,N*-Linked Bipyrazole Derivatives

Abstract: The synthetic routes to three differently connected bipyrazole systems, namely; 1,1'-, 1,3'- and 1,4'-bipyrazoles were reported. The main synthetic platforms were cyclocondensation reactions. Many of the reported bipyrazole derivatives had potent applications in material science as well as in pharmaceutical fields.

Keywords: 1,1'-bipyrazoles, 1,3'-bipyrazoles, 1,4'-bipyrazoles, Cross-coupling, Cyclocondensation, Nitrilimines.

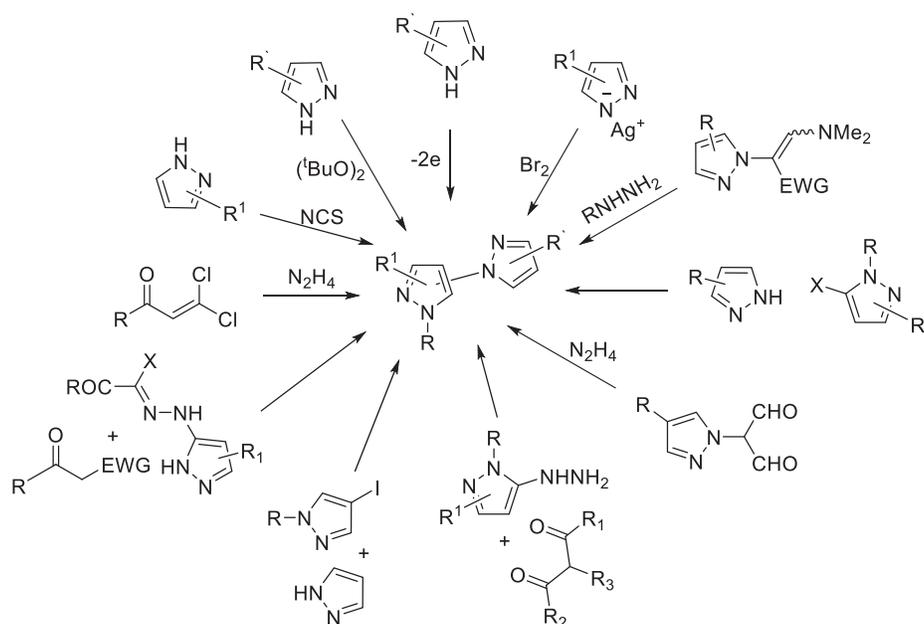
1. INTRODUCTION

Bipyrazoles are nitrogen heterocycles that are consisted of two pyrazole moieties connected directly by a covalent sigma bond without any space linker. In this chapter, the considered connections are either *N,N*- or *C,N*-connection types. The *N,N*-linked bipyrazoles are named as 1,1'-bipyrazoles, and those *C,N*-bonded compounds are named as either 1,3'-bipyrazoles or 1,4'-bipyrazoles as shown in Scheme (1).



Scheme (1). The directly connected *N,N*- and *C,N*- bipyrazole systems.

The fulfilling pathways are: 1) reactions of tetracarbonyl or dihydroxydicarbonyl building units with hydrazines, 2) reaction of pyrazoles having a difunctional-side arm with hydrazines, 3) reaction of pyrazolyl-hydrazines with difunctional compounds (*e.g.* dicarbonyl, hydroxycarbonyl, ketonitrile or dinitrile substrates), and 4) metal catalyzed C-C cross coupling reactions of pyrazoles *via* C-H activation (Scheme 2).



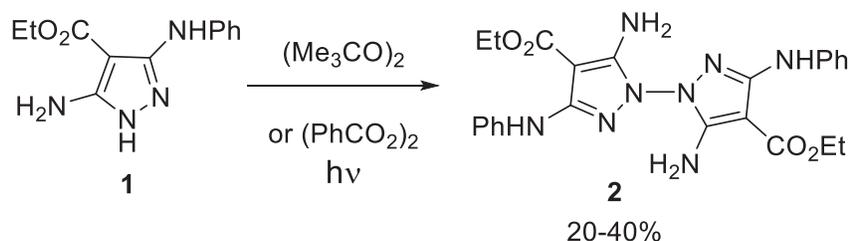
Scheme (2). The possible synthetic routes to *N,N*- and *C,N*-bipyrazoles.

Pyrazoles are one of the most abundant nitrogen heterocyclic compounds that have huge pharmaceutical and agro-chemical industrial applications [1 - 6]. Bipyrazoles are also a very interesting bioactive class of heterocycles that had pronounced biological activities. Particularly, 1,3'-bipyrazole derivatives had potent inhibitory activities against various diseases. For example, they exhibited cytotoxic [7], antimicrobial [8], anti-inflammatory [9] and antidiabetic activities [10] as well as herbicidal activities with excellent weed-controlling effects [11 - 13], potential agricultural pesticides [14, 15]. On the other hand, several 1,4'-bipyrazole derivatives were reported to have pronounced cytotoxicity activities [16] and for the treatment of Parkinson's disease [17]. The 1,4'-bipyrazole derivatives were employed as efficient ligands in the palladium-catalyzed C-N and C-O cross-coupling reactions of aryl halides with urea and with primary alcohols derivatives [18 - 22].

2. SYNTHESIS OF BIPYRAZOLE SYSTEMS

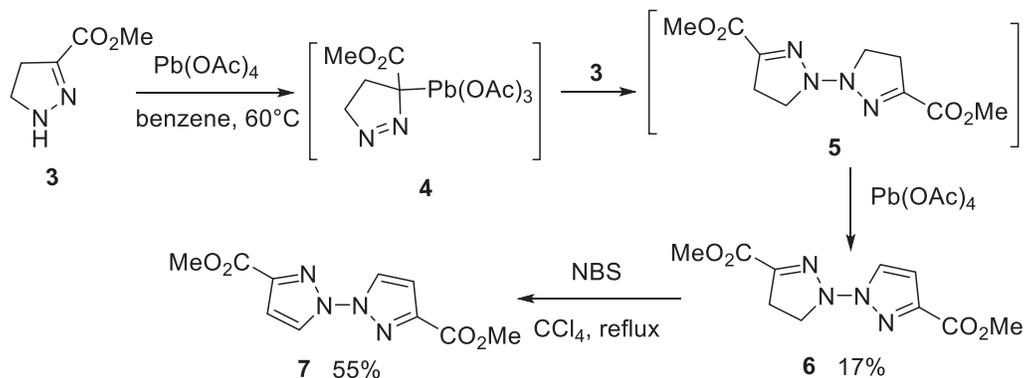
2.1. Synthesis of 1,1'-Bipyrazoles

Formation of the 1,1'-bipyrazole derivative **2** was performed by photolysis of ethyl 5-amino-3-(phenylamino)pyrazole-4-carboxylate **1** with *tert*-butyl peroxide or with dibenzoyl peroxide under mild reaction conditions. The reaction took place *via* radical dimerization of the pyrazole **1** (Scheme 3) [23].



Scheme (3). Synthesis of 1,1'-bipyrazole **2**.

The dihydro-1,1'-bipyrazole derivative **6** was obtained from the reaction of 3-methoxycarbonyl-2-pyrazoline **3** with lead tetraacetate in benzene at 60°C. The reaction proceeded *via* the pyrazoline intermediate **4** which underwent further attack on **3** to give **6** in 17% yield. The ¹³C NMR of compound **6** showed five peaks δ 52.3, 109.1 129.4 142.3 161.3 ppm due to OCH₃, pyrazole-carbons (C-4, C-5 and C-3) and C=O, respectively. The oxidation of **6** with *N*-bromosuccinimide (NBS) in refluxing carbon tetrachloride in the presence of a few drops of dry pyridine resulted in the formation of the symmetrical 1,1'-bipyrazole **7** in 55% yield (Scheme 4) [24].



Scheme (4). Synthesis of 1,1'-bipyrazole **7**.

2.2. Synthesis of 1,3'-bipyrazoles

The 1,3-bipyrazole derivative derivatives **10** were synthesized, in good yields, from the reaction of the hydrazino-pyrazole derivative **8** with various symmetrical and unsymmetrical 1,3-dicarbonyl compounds **9** in the presence of 5% HCl (Scheme 5) [7]. The ¹H NMR spectrum of compound **10** (R₁=R₂= Me, R₃= H) displayed five singlet peaks at δ 2.16, 2.61, 3.32, 3.67 (due to four CH₃ protons) and 6.11 due to CH-proton and its ¹³C NMR exhibited nine peaks at δ 11.0

Chemistry of 3,3'-Bipyrazole Derivatives

Abstract: Synthesis of 3,3'-bipyrazole systems was achieved *via* interesting synthetic methodologies such as 1,3-dipolar cycloaddition reactions, cyclocondensation reactions and metal catalysed C-H activation reactions. Construction of the structurally related 3,3'-bipyrazolines or 3-(pyrazol-3-yl)pyrazolines is described.

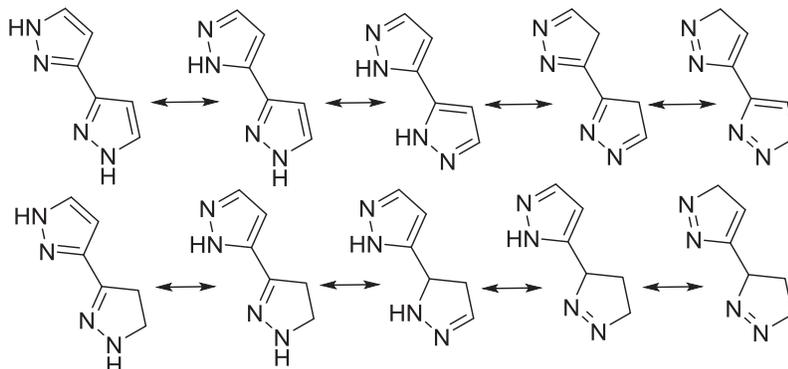
Keywords: 3,3'-bipyrazoles, 3,3'-bipyrazolines, Cyclocondensation, Cyclo addition, Cross-coupling, Nitrilimines.

1. INTRODUCTION

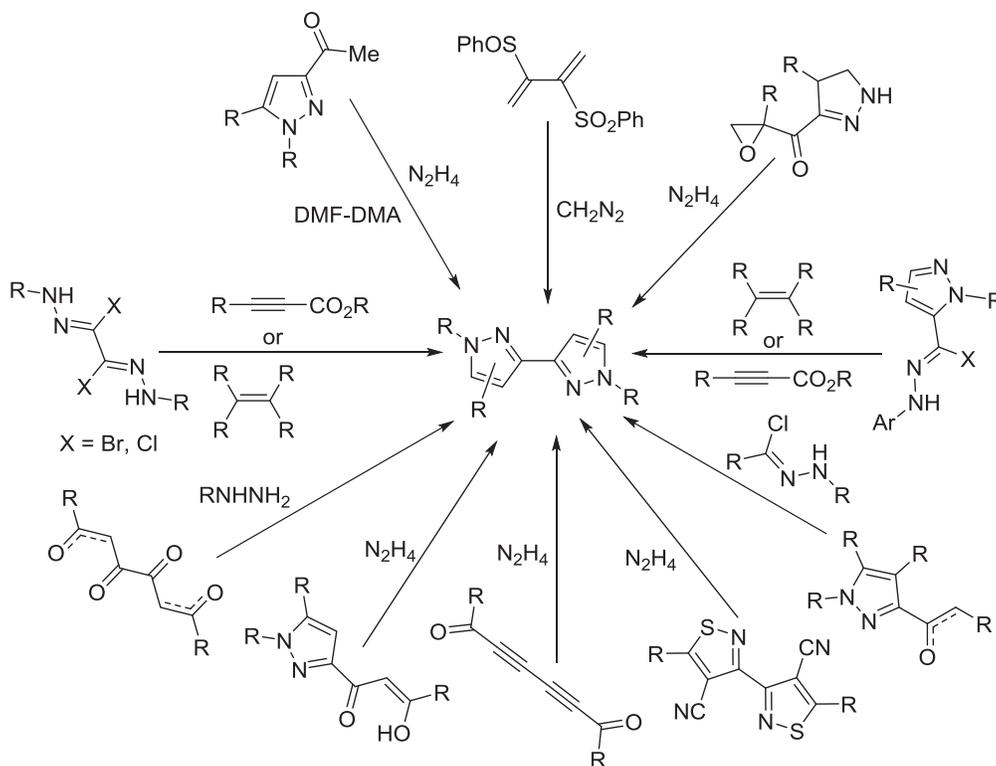
3,3'-Bipyrazoles, 3,3'-bipyrazolines and 3-(pyrazol-3-yl)pyrazolines are all structurally related C-C directly connected two pyrazole units by sigma bond between 3,3'-positions without any spacer. There are several tautomeric structural formulae that can be drawn for such 3,3'-bipyrazole derivatives, as depicted in Scheme (1). The synthetic pathways for the 3,3'-bipyrazole structures are briefly summarized in Scheme (2). Such routes are: 1) reactions of tetracarbonyl or dihydroxydicarbonyl building units with hydrazines, 2) reaction of pyrazoles having a difunctional-side arm at position 3 with hydrazines, 3) reaction of 3-pyrazolyldiazines with difunctional compounds, 4) 1,3-dipolar cycloaddition of pyrazolyl-nitrilimines with olefins or acetylenes, and 5) 1,3-dipolar cycloaddition of bis-nitrilimines with two equivalents of olefins or acetylenes.

The 3,3'-bipyrazole derivatives had several academic and industrial applications. They formed complexes with copper(I/II) that were efficiently used for oxidation of catechol to o-quinone with the atmospheric dioxygen [1]. Their ruthenium(II) complexes showed good catalytic activity and transfer of hydrogen in catalyzed hydrogenation reactions [2, 3], and their palladium(II)-complexes were reported as good precatalysts for Suzuki-Miyaura C-C cross-coupling reactions in aqueous media [4]. They have involved in the synthesis of poly(3,3'-bipyrazole) derivatives with high thermal stability and electrochemical activity [5]. Nitration of 3,3'-bipyrazole gave several polynitro-3,3'-bipyrazole derivatives that were found to be metal-free primary explosives with high energetic properties and excellent thermal stability [6 - 8].

The 3,3'-bipyrazole derivatives also had solvatochromic behaviour [9] The platinum and osmium complexes of 3,3'-bipyrazoles were also useful as emitting materials for organic light-emitting diode (OLED) [10 - 12]. 3,3'-Bipyrazole derivatives were also reported to have high antitumor inhibitory activity [13].



Scheme (1). The possible tautomeric forms of 3,3'-bipyrazoles.

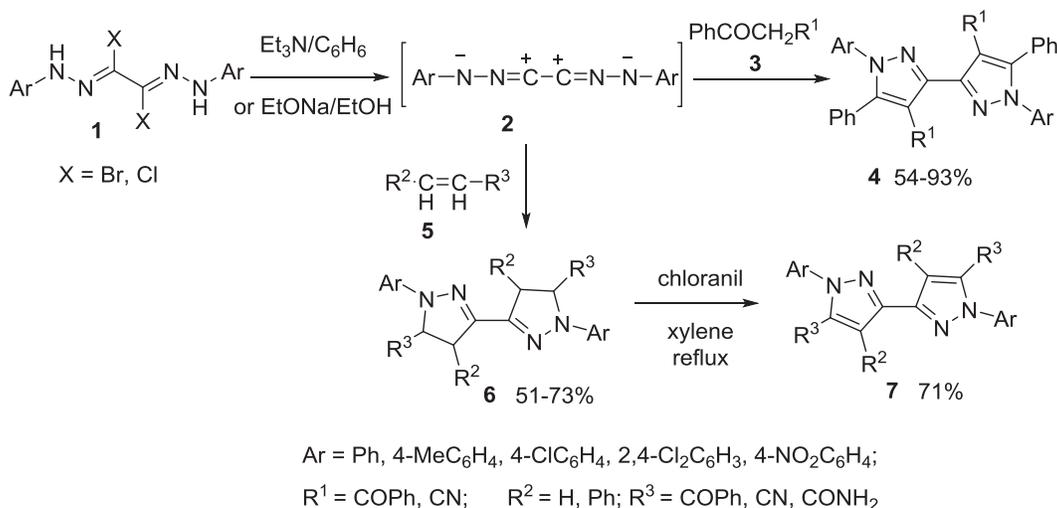


Scheme (2). The possible synthetic routes to 3,3'-bipyrazoles.

2. SYNTHESIS OF 3,3'-BIPYRAZOLE SYSTEMS

2.1. From 1,3-Dipolar Cycloaddition Reactions

When the *bis*-arylnitrilimines **2** (generated *in situ* from the treatment of *bis*-hydrazonyl halides **1** with triethylamine in dry benzene) was treated with the active methylene compounds **3**, they resulted in the formation of the 3,3'-bipyrazole derivatives **4** in high yields. Similarly, the *bis*-arylnitrilimines **2** underwent 1,3-dipolar cycloaddition reactions with the activated olefins **5** to give the 3,3'-bi(2-pyrazolines) **6**. Oxidation of compound **6** ($R^2 = \text{Ph}$, $R^3 = \text{COPh}$, $\text{Ar} = \text{Ph}$) with chloranil afforded the corresponding 3,3'-bipyrazole derivative **7** in 71% yield (Scheme 3) [14].



Scheme (3). Synthesis of 3,3'-bipyrazole **4** and **7**.

Regioselective synthesis of polysubstituted 3,3'-bi-1*H*-pyrazole derivatives **10** was carried out *via* 1,3-dipolar cycloaddition reaction of the *bis*-arylnitrilimines **2** with the cinnamionitriles **8** to yield the cycloadducts 5,5'-dicyano-4,4',5,5'-tetrahydro-3,3'-bi-1*H*-pyrazoles **9** in 40-75% yields. Aromatization of compounds **9** *via* thermal elimination of hydrogen cyanide under the basic reaction conditions afforded the 3,3'-bi-1*H*-pyrazole derivatives **10** in good yields (Scheme 4) [15].

Chemistry of 3,4'-Bipyrazoles

Abstract: All the possible synthetic routes to the 3,4'-bipyrazole systems were thoroughly reported. Such synthetic platforms include: cyclocondensation and 1,3-dipolar cycloaddition reactions. Many of the reported 3,4'-bipyrazoles have potent applications in the field of pharmaceutical and material science.

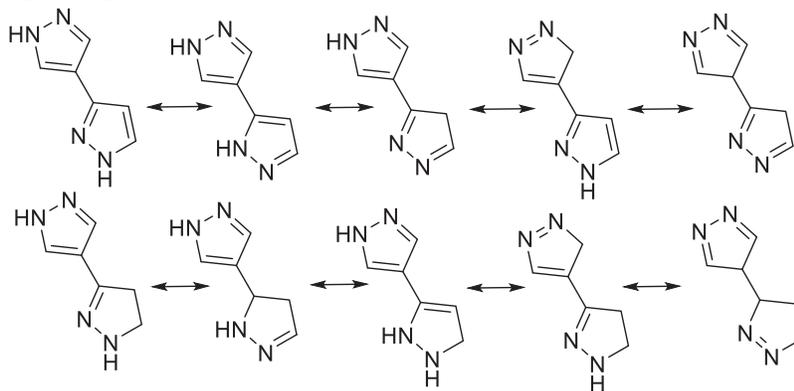
Keywords: 1,3-dipolar cycloaddition, 3,4'-bipyrazoles, 3,4'-bipyrazolines, Cross-coupling, Cyclocondensation, Pyrazolyhydrazones.

1. INTRODUCTION

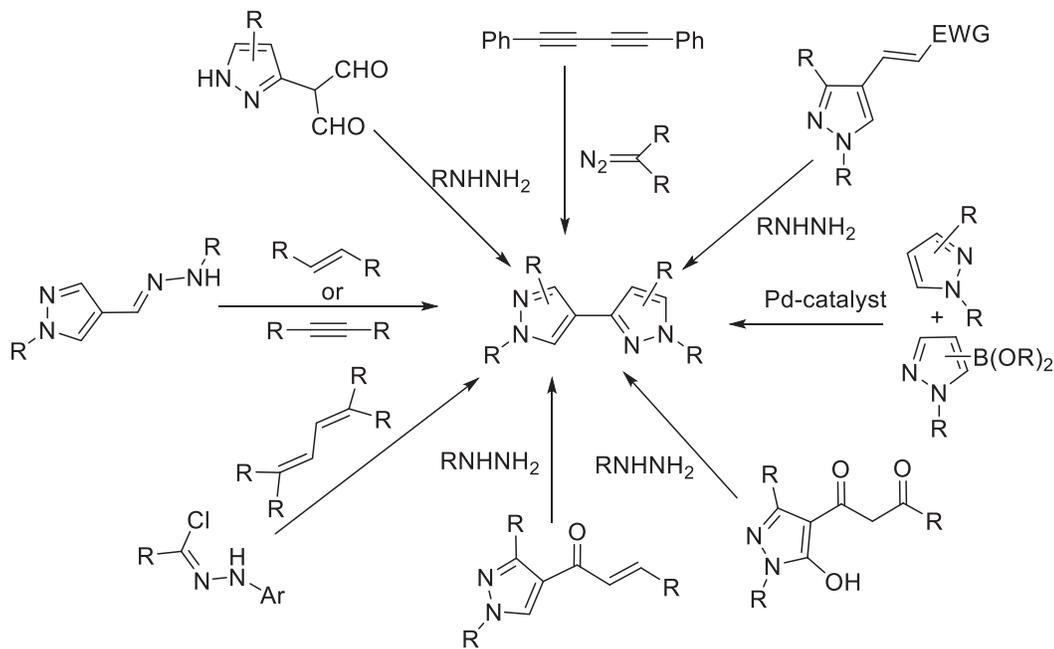
Various 3,4'-bipyrazoles ring skeletons were reported in the literature. They are composed of either two aromatic pyrazole units or 4-pyrazolyl attached with pyrazoline at C-3 or 4-pyrazolinyl attached to pyrazole at C-3. As a result, there will be the aromatic 3,4'-bipyrazole skeleton or partially aromatic pyrazolylpyrazoline skeleton. The two pyrazole units are connected directly with a sigma bond between the two units. A number of tautomeric forms can be constructed, as shown in Scheme (1). Synthesis of such 3,4'-bipyrazole skeletons was achieved *via* several synthetic routes as outlined in Scheme (2). Such synthetic routes include: 1) cyclocondensation of an activated 4-pyrazole ring having chalcones or 1,3-dicarbonyl functions with hydrazines; 2) 1,3-dipolar cycloaddition of pyrazolyhydrazones with activated olefins or acetylenes; 3) 1,3-dipolar cycloaddition of nitrilimines with bis-olefines with nitrilimines or diazoalkanes; and 4) C-C cross coupling reactions of pyrazolylboronic acids with halopyrazoles or pyrazoles themselves *via* C-H activation using palladium catalysts.

The fully aromatic 3,4'-bipyrazoles and their partially aromatic ones (pyrazolylpyrazolines) are potent inhibitory active heterocycles with significant biological potentialities. The 3,4'-bipyrazole derivatives were also considered to have anticancer [1 - 5], antimicrobial [6 - 12], anti-inflammatory [13 - 19], antioxidant [20], antitubercular [21 - 23] and antimalarial activities [24]. They

were found to be effective enzyme inhibitors against carbonic anhydrase inhibitory activity [25], human Tropomyosin-related kinase A (TrkA) [26 - 30], and Janus kinase (JAK1/JAK2) [31]. 3,4'-Bipyrazole-based metal coordination complexes were reported to display remarkable pharmaceutical applications. For example, gold(III) and iridium(II) complexes of 3,4'-bipyrazoles were useful as anticancer agents [4, 5]. In addition, the palladium(II) and platinum(II) complexes of 3,4'-bipyrazoles were found to have excellent antibacterial and antifungal activities [6, 32].



Scheme (1). The possible direct connected 3,4'-bipyrazole derivatives

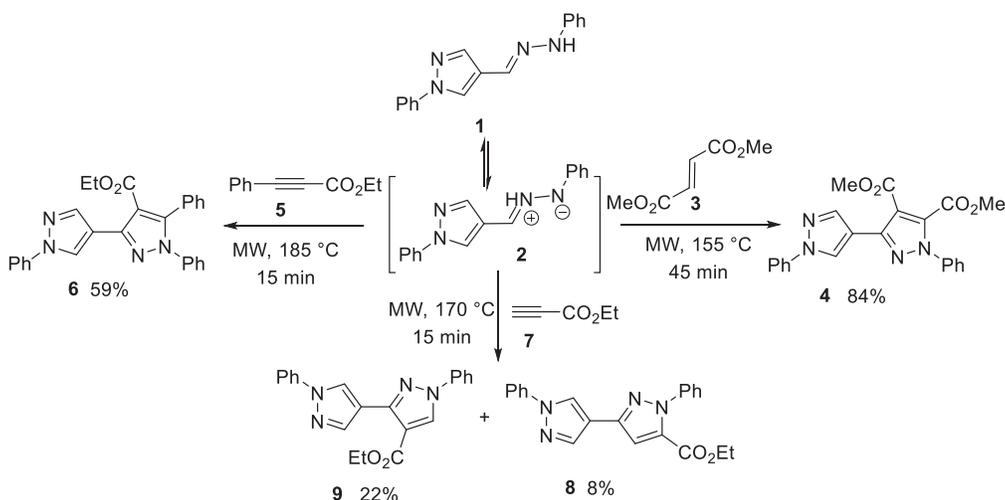


Scheme (2). The possible synthetic routes to 3,4'-bipyrazoles systems

2. SYNTHESIS OF 3,4'-BIPYRAZOLE DERIVATIVES

2.1. From 1,3-dipolar Cycloaddition Reactions

1,3-Dipolar cycloaddition of 4-pyrazolylformylhydrazone **1** with some activated dipolarophiles such as dimethyl fumarate **3** and ethyl 3-phenylpropiolate **5** under solvent-free conditions using microwave irradiation technique resulted in the construction of the corresponding 3,4'-bipyrazoles **4** and **6**, respectively. Similar reaction of the hydrazone **1** with ethyl propiolate **7** under microwave heating at 170 °C afforded a mixture of the 3,4'-bipyrazole derivatives **8** and **9** (Scheme 3). The ¹H NMR analysis of structure **9** presented the following data: δ 5 1.37 (t, *J* = 7.1 Hz, 3H, CH₃), 4.33 (q, *J* = 7.1 Hz, 2H, CH₂), 7.35 (s, 1H, H-5'), 7.28-7.48 (m, 8H, ArH's) 7.64 (d, *J* = 8.6 Hz, 2H, *o*-H 1-Ph), 8.17 (s, 1H, H-3), 8.40 (s, 1H, H-5). Mechanistically, the regioselective cycloaddition process proceeded *via* the addition of the dipolarophiles **3** and **5** to the dipolar intermediate **2** followed by aromatization *via* air oxidation [33, 34]. Carrying out the 1,3-dipolar cycloaddition of the pyrazolylhydrazone **1** with dimethyl fumarate (**3**) under classical thermal heating at same temperature and reaction time on an oil bath led to the formation of the bipyrazole **4** in only 17% yield. The obtained result confirmed the advantage of microwave radiation in organic synthesis compared with classical heating.



Scheme (3). Synthesis of the 3,4'-bipyrazoles **4**, **6**, **8** and **9**.

The 4-pyrazolylformylhydrazones **1** underwent similar 1,3-dipolar cycloaddition with β -nitrostyrenes **10** under solvent-free microwave irradiation condition (at 130°C for 10 min) to give a mixture of the 3,4'-bipyrazole derivatives **11** and **12** (Scheme 4) [33, 35].

Chemistry of 4,4'-Bipyrazoles

Abstract: Synthesis of a huge number of 4,4'-bipyrazole derivatives was achieved employing various synthetic platforms. This chapter outlines all possible routes (such as cyclocondensation, 1,3-dipolar cycloaddition and dimerization reactions) towards the construction of the 4,4'-bipyrazole heterocycles.

Keywords: 1,3-dipolar cycloaddition, 4,4'-bipyrazoles, Cross-coupling, Cyclocondensation, Hydrazonoyl halides.

1. INTRODUCTION

The 4,4'-bipyrazole ring skeletons can have the possible tautomeric forms that are constructed in Fig. (1). Synthesis of 4,4'-bipyrazoles was achieved through a number of synthetic routes as outlined in Fig. (2). The reported synthetic routes are as follows: 1) cyclocondensation of the activated 4-pyrazole ring having dicarbonyl functions with hydrazines; 2) cyclocondensation of tetraketones or bis-enals with hydrazines; 3) 1,3-dipolar cycloaddition of nitrilimines or diazomethane with bis-olefines, and 4) dimerization of pyrazole ring *via* electrolysis or homocoupling reactions using palladium catalysts.

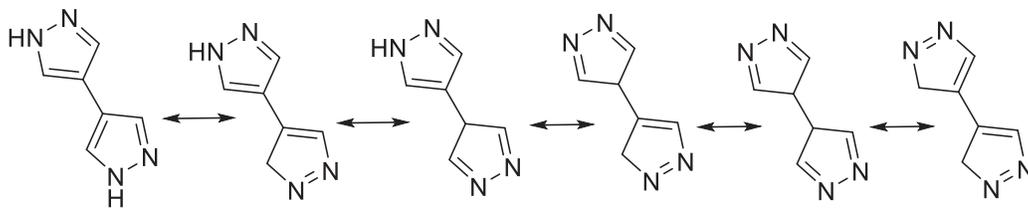


Fig. (1). The possible tautomeric forms of 4,4'-bipyrazole systems.

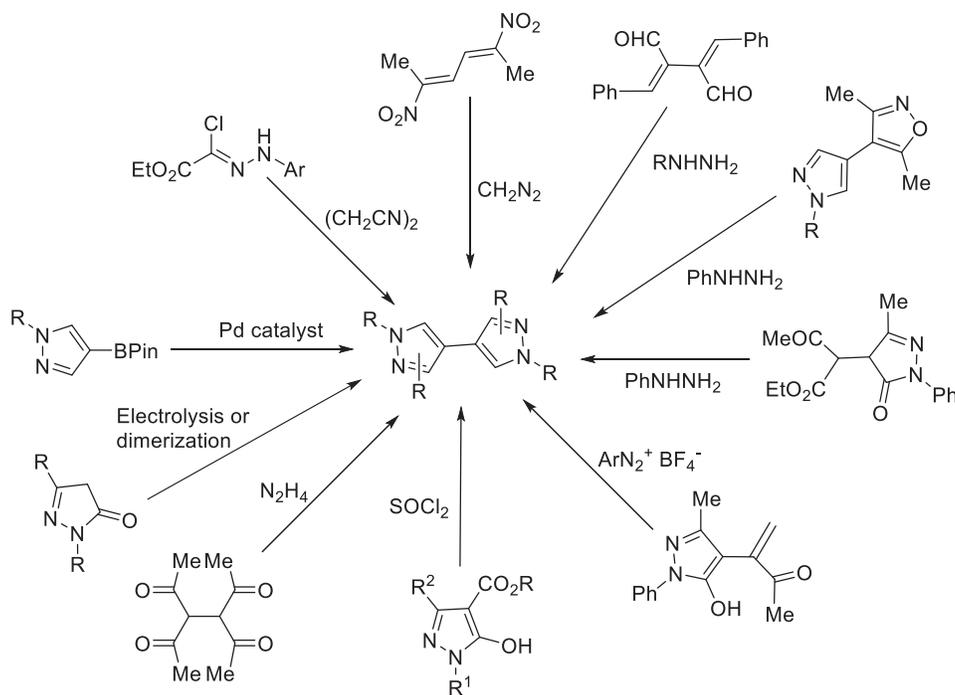


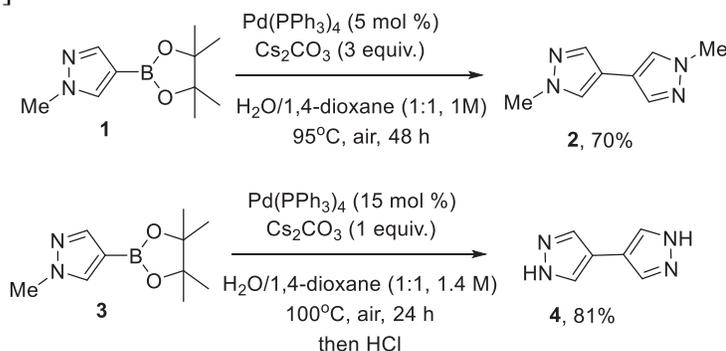
Fig. (2). The possible synthetic routes to 4,4'-bipyrazole systems.

4,4'-Bipyrazole derivatives were found to possess high biological potency and industrial applications. Some 4,4'-bipyrazole derivatives had a selective Janus kinase-1 (JAK1) inhibitory activity [1, 2]. Some 5,5'-dihydroxy-4,4'-bipyrazole derivatives were found to be useful for treatment of cerebral ischemia, heart diseases, gastrointestinal diseases, cancer, aging and inflammation, where they are effective in capturing the active oxygen and free radicals that are responsible for adult diseases [3 - 5]. Palladium(II) and platinum(II) complexes of 4,4'-bipyrazole were reported as potential anticancer agents [6], and the 4,4'-bipyrazol-Gadolinium(III) complexes were effective Paramagnetic Contrast Agent for clinical Magnetic Resonance Imaging (MRI) [7]. The nitrated 4,4'-bipyrazoles were classified as energetic and explosive materials [8, 9]. 4,4'-Bipyrazole systems were incorporated in the construction of several metal-organic frameworks (MOF). The MOF had promising diverse applications in drug delivery, gas separations, sensing, electrical conductivity, energy storage. and participated in forming porous coordination polymers with potential uses as solid sorbents, ion exchangers and heterogeneous catalysts [10 - 23].

2. SYNTHESIS OF 4,4'-BIPYRAZOLE DERIVATIVES

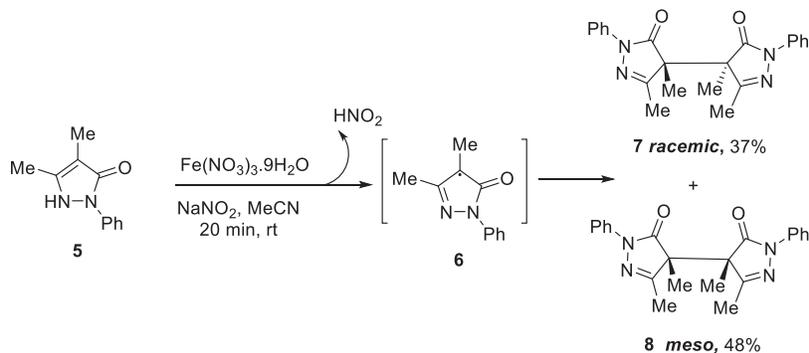
2.1. From Dimerization of Pyrazoles

Homocoupling of the pyrazolylboronic esters **1** and **3** catalyzed by $\text{Pd}(\text{PPh}_3)_4$ (5 mol%), in water solvent using Cs_2CO_3 as a base in the open air, led to the production of the symmetric 4,4'-bipyrazoles **2** and **4** in good yields, respectively (Scheme 1) [11].



Scheme (1). Synthesis of the 3,4'-bipyrazole derivatives **2** and **4**.

Treatment of the pyrazolin-5-one **5** with $\text{Fe}(\text{ClO}_4)_3$ at ambient temperature led to its oxidative dimerization and formation of a diastereomeric mixture of 4,4'-bipyrazole-3,3'-diones **7** (*racemic*, 32% yield) and **8** (*meso*, 44% yield). The ^1H NMR spectral data of the *racemic* product **7** in CDCl_3 were as following: δ 1.60 (s, 6H, 2Me), 2.19 (s, 6H, 2Me), 7.18 (t, $J = 7.3$ Hz, 2H, ArH's), 7.45–7.31 (m, 4H, ArH's), 7.85 (d, $J = 7.9$ Hz, 4H, ArH's); however the ^1H NMR spectrum of the *meso*-compound **8** showed the following data: δ 1.73 (s, 6H, 2Me), 1.93 (s, 6H, 2Me), 7.22 (t, $J = 7.3$ Hz, 2H, ArH's), 7.49–7.34 (m, 4H, ArH's), 7.89 (d, $J = 8.2$ Hz, 4H, ArH's). The reaction was supposed to take place *via* the pyrazolyl radical intermediate **6** as shown in Scheme (2) [24].



Scheme (2). Synthesis of 4,4'-bipyrazoles diastereomers **7** and **8**.

Applications of Bipyrazole Derivatives

Abstract: Numerous bipyrazole-based metal-organic frameworks (MOF) were synthesized *via* mixing a number of bipyrazole ligands with several transition-metal cations, and the obtained MOF represented interesting applications in the field of material science and pharmaceuticals due to their high degree of crystallinity and internal porosity. There are photo-luminescence, sensing, gas separations, electrical conductivity, and energy storage, among those interesting applications.

Keywords: Bipyrazoles, Energetic organic materials, Gas separation, MOF, Nitropyrazoles, OLED.

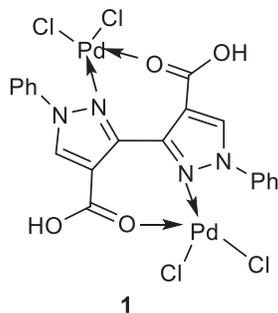
1. INTRODUCTION

Recently, bipyrazole-based *metal coordination compounds* displayed interesting applications in pharmaceuticals and in material science. For example, gold(III) and ruthenium(II) complexes of bipyrazoles were proved to be anticancer agents [1, 2], and copper(I) complexes had excellent antibacterial activity [3], whereas gold(III), platinum(II), osmium(II) and copper(I) complexes were involved in the fabrication of luminescence Organic Light-Emitting Diodes (OLED) and laser materials [4 - 7]. Bipyrazole ligands coordinate up to four different metal centers to give three-dimensional structures known as metal-organic frameworks (MOFs). Such MOFs had promising wide applications in drug delivery, sensing, gas separations, electrical conductivity, and energy storage due to their high degree of crystallinity and internal porosity [8, 9]. Bipyrazoles (especially Bippyphos) played an important role as ligands for palladium-catalyzed cross-coupling reactions of aryl halides [10 - 13].

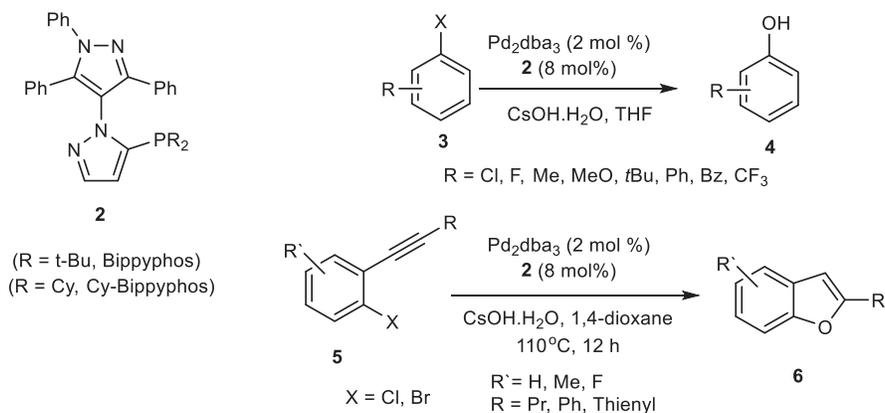
2. APPLICATIONS OF BIPYRAZOLE DERIVATIVES

2.1. Bipyrazoles as Ligands

The 3,3'-bipyrazole-based Pd(II)-complex **1** was synthesized and reported as an efficient precatalyst for Suzuki-Miyaura C-C cross-coupling reactions of aryl halides with arylboronic acids in aqueous media [14].

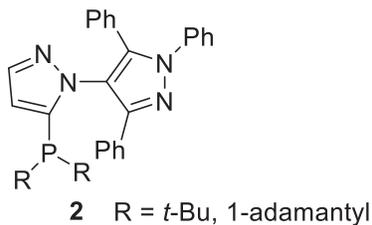


5-(Di-*tert*-butylphosphino)-1',3',5'-triphenyl-1'*H*-[1,4']bipyrazole (Bippyphos) (**2**) was reported as an efficient co-catalyst in the palladium-catalyzed hydroxylation of several (hetero)aryl halides **3** under mild conditions as well as in the synthesis of substituted benzofurans and related heteroaromatic derivatives [11] (Scheme 1).

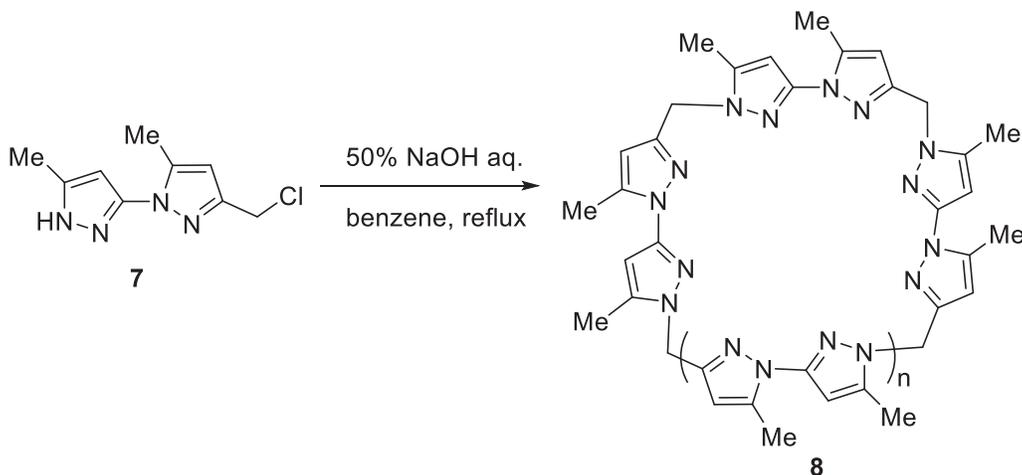


Scheme (1). Synthesis of hydroxyl compounds **4** and substituted benzofurans **6**.

The bipyrazole derivatives (bippyphos) **2** 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 [12, 13, 15 - 17].

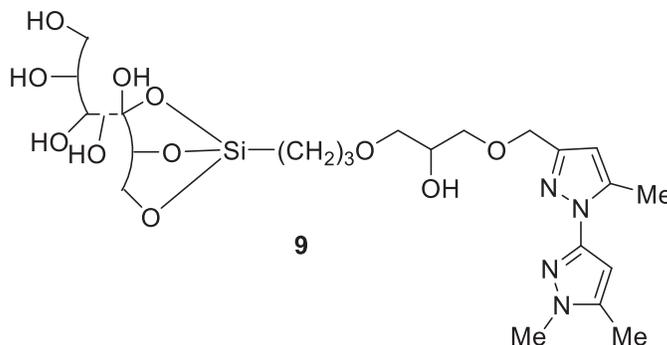


Polycondensation of 5,5'-dimethyl-3-chloromethyl-1,3'-bipyrazole **7** was achieved in refluxing benzene in the presence of 50% NaOH solution and led to the formation of the polypyrazolic macrocycle **8** in 75% yield (Scheme 2). The polypyrazolic macrocycles showed excellent complexing properties as ligands with the alkali metal cations [18].



Scheme (2). Synthesis of the polypyrazolic macrocycle **8**.

The immobilized bipyrazole **9** on the surface of epoxy-silica presented good thermal stability based on the thermogravimetric analysis, and it had good binding and adsorption abilities for Hg^{2+} , Cd^{2+} , Pb^{2+} , Zn^{2+} , K^+ , Na^+ and Li^+ cations [19].



2.2. Bipyrazoles in Synthesis of Polybipyrazoles

Dehalogenative polycondensation of 3,3'-dichloro-5,5'-bipyrazoles **10** using a mixture of $\text{Ni}(\text{cod})_2$ and 2,2'-bipyridine in DMF at 60°C resulted in the formation of poly(5,5'-bipyrazole-3,3'-diyl) derivatives **11** (Scheme 3). The obtained polymers were characterized by their high thermal stability and electrochemical

SUBJECT INDEX

A

Acetates 37, 49, 79, 84, 86, 125
 methyl hydrazine 79
 Acetic acid 10, 66, 67, 71, 79, 81, 84, 86, 90
 refluxing 81
 Acetone 14, 37, 70, 77
 refluxing 14
 Acetophenone derivatives 67, 68, 73, 74, 75
 Acetylacetone 4, 6, 106
 Acetylenecarboxylates 25
 Acetylenic ketones 37
 Acid(s) 10, 45, 46, 47, 49, 25, 62, 67, 79, 81, 82, 84, 91, 105, 108, 110, 114, 125, 126, 127, 134, 136
 arylboronic 114
 ascorbic 91
 biphenyldicarboxylic 125
 chloroacetic 84
 dehydroacetic 79, 81, 82
 diisophthalic 125, 126
 formic 67
 fumaric 134
 fused-ring aromatic multicarboxylic 127
 heating dehydroacetic 82
 hydrochloric 62
 hydrocyanic 25
 isophthalic 125
 maleic 134
 nitric 10, 46, 47, 49, 110
 nitrous 105
 oxy-bis-benzoic 134
 phenylboronic 45
 phosphoric 110
 sebacic 136
 suberic 136
 sulfuric 46
 sulphuric 82
 trans-cyclohexane-dicarboxylic 134
 trifluoroacetic 108
 Acidic hydrolysis 48

Activity 22, 23, 51, 58, 101, 114, 117, 123, 132
 cytotoxic 132
 electrochemical 22
 Anticancer 57, 58, 101, 114, 121
 agents 58, 114
 Antidiabetic activities 2
 Antimalarial activities 57
 Arboxylates 41
 Aromatic 57, 74, 88
 aldehydes 26, 29, 39, 41, 57, 74, 88, 91, 127, 128, 129
 pyrazolylpyrazoline skeleton 57

B

Benzylbromide 35
 Biheterocyclic systems accounting 122
 Bipyrazole-fused heterocyclic systems 26
 Bipyrazoles, -Bipyrazole Derivatives 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51
 Chemistry of 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51
 Bipyrazoles 1, 2, 17, 22, 24, 51, 57, 58, 100, 101, 110, 116
 in synthesis of Polybipyrazoles 116
 systems 1, 2, 17, 22, 24, 51, 57, 58, 100, 101, 110
 Bipyrazoline derivatives 33, 37, 38, 39, 40, 41, 48
 Bis-hydrazoneyl chlorides 25, 28
 Bis-hydroxymethyl-bis-bipyrazole product 5
 Bleaching earth clay (BEC) 84

C

Carbon 48, 124, 129, 131
 anionic 48
 dioxide 131
 monoxide 124
 Catalytic activity 22, 51, 123

Catalyzed 1, 2, 22, 45, 51, 72, 91, 102, 114, 115, 123
 hydrogenation reactions 22, 51, 123
 reaction 72
Chalcone conjugates 64
Chemisorption 124
Conditions 2, 10, 24, 27, 28, 44, 45, 48, 59, 60, 65, 70, 75, 76, 115, 123, 124, 129, 134, 135
 conventional thermal 60
 hydrothermal 134
 photolysis 32
 solvent free 29
 solvothermal 125, 130, 135
 ultrasonic 28
Corrosion Inhibitors 120
Coumarinylpropenone 70
Coupling reactions 1, 2, 22, 57, 114, 115
Cross-coupling reactions 1, 2, 22, 57, 114, 115
 catalyzed 91
 palladium-catalyzed 114
Cyclization 6, 7, 8, 46, 85, 103
 intramolecular 6, 7, 8
Cycloaddition process 32, 59
Cycloaddition reactions 22, 24, 57, 59, 60
 smooth regioselective 105
Cyclocondensation 1, 6, 8, 22, 34, 39, 40, 51, 57, 63, 66, 67, 70, 77, 79, 91, 100

D

Dehalogenative polycondensation 116
Dehydrogenation 40, 50, 61, 73
 oxidative 50
 process 73
Derivatives 7, 8, 16, 26, 69, 73, 75, 108, 115, 118
 acetylcoumarin 75
 acrylonitrile 8
 aniline 26, 37
 heteroaromatic 115
 hydrazino-pyrazole 7
 polynitro-bipyrazole 118
 propanedione 16

 pyrazolyl-chalcone 69
 pyrazolylpyrazoline 73
 pyridazine 108
Dichloromethane 9, 14, 15, 31, 37, 73
Difunctional compounds 1, 17, 22
Dihydroxydicarbonyl building units 1, 22
Dimerization reactions, homocoupling 110
Dimethoxyethane 90
Dimethyl acetylenedicarboxylate 25
Diseases 2, 17, 80, 101, 121
 central nervous system 80
 gastrointestinal 101, 121

E

Electrochemical 8, 22, 104, 116, 133
 chlorination 8
 oxidative coupling 104
 process 133
Electrophilic substitution reactions 6
Emission 127, 129, 131, 132, 134, 136
 interesting solid-state fluorescent 134
Energetic 22, 52, 101, 114, 118, 119, 120
 nitrogen heterocyclic material, green 120
 organic materials 114
 properties 118
Energetic materials 117, 119
 high-temperature 117
Energy 101, 114, 119, 120, 130, 132, 137
 density oxygen-carrier material, high 120
 storage materials 137
Enzymatic inhibitions 121
Esters 26, 29, 37, 79, 99, 102, 103
 bipyrazole 4, 79
 dicarboxylate 90, 103, 128
 pyrazolylboronic 57, 90, 102

F

Fluorescence, green 135
Fluorescent sensors 123
Framework topology 129
Friction sensitivities (FS) 117, 118
Functions 48, 57, 91, 100, 105, 129

Subject Index

cyano 48
Fused-ring system 48

G

Gas separation 101, 114, 136

H

Halopyrazoles 51, 57
Heat, insensitive 117
Heating 27, 28, 35, 39, 65, 66, 67, 68, 69, 70, 74, 76, 77, 79, 80, 85, 106
 conventional 27, 28, 35, 76
Heating mode, conventional thermal 27
Herbicidal activities 2
Heterocycles 1, 2, 57, 86, 100, 108
 bipyrazole 100
 three-ring fused 86
Heterocyclization 70
Heterogeneous 101, 122, 133
 catalysts 101, 122
 lyophobic system (HLS) 133
High energetic density materials (HEDM) 118
Homocoupling reactions 100
Hydrazine 14, 39, 79, 81, 89
 derivatives 14, 81
 hydrochloride 39, 79, 89
Hydrazinolysis 79
Hydrazinolysis 37
Hydrazonoyl halides 17, 100
 pyrazole-based 17
Hydrogen 24, 61, 104
 cyanide 24, 61
 peroxide 104
Hydrothermal reaction 127
 of cadmium sulfate octahydrate 127

I

Industrial applications 2, 22, 51, 101, 111
 agro-chemical 2
Inhibitors 58, 120
 effective enzyme 58

Chemistry of Bipyrazoles: Synthesis and Applications 147

Inhibitory activities 2, 17, 121
 carbonic anhydrase 58

J

Janus kinase 58, 101

K

Knoevenagel condensation 88

L

Layered nickel-based MOF material 133
Ligands 2, 51, 114, 116, 123, 124, 128, 130, 131, 135
 auxiliary 135
 bipyrazole 51, 114, 128, 131
 bipyrazole-based 124
 conjugated multidentate 130
 neutral bidentate 122
Liquid-liquid phase transfer catalysis 106
Lithium aluminium hydride 4, 5
Luminescence 114, 124, 126, 129
 organic light-emitting diodes 114
 solid-state 129
Luminescent property 127

M

Magnetic resonance imaging (MRI) 101, 111, 121
Metal 45, 101, 114, 122, 123, 124, 125, 126, 128, 129, 130, 131, 132, 133, 134, 136
 catalyzed C-H activation reactions 45
 ligand bonding interaction 132
 ligand charge transition (MLCT) 129
 organic frameworks (MOFs) 101, 114, 122, 123, 125, 126, 128, 130, 134, 136
Microwave irradiation 9, 11, 13, 29, 59, 60, 70, 74, 76
 technique 59, 76
Microwave radiation 59

N

Negishi reaction conditions 45
Nitrated bipyrazole derivatives 117
NMR 41, 59, 90, 102
 analysis 59
 spectral data 41, 90, 102

O

Organic light-emitting diode (OLED) 23, 114, 132
Oxidative addition 46
Oxidizing agents 124
Oxygen 101, 120, 121, 123, 124, 128, 135
 atmospheric 123
 atoms 128
 rich high energetic material 120

P

Palladium 2, 22, 50, 57, 58, 100, 101, 111, 114, 115
 catalysts 57, 100
 catalyzed hydroxylation 115
Paramagnetic Contrast Agent 101, 121
Parkinson's disease 2
Pathways 1, 22, 25, 27, 31, 42, 51, 62, 71, 79, 103
 cycloaddition 27
 mechanistic 42
 radical 103
 ring-closing 79
 synthetic 22, 51
Photodecomposition 129
Photoluminescence 134, 135, 136
Polyfunctionalized furan derivatives 108
Polypyrazolic macrocycles 116
Properties 111, 121, 126, 127
 hydrogen-bonding 121
 photocatalytic 126
 solid state emission 127
Pyrazolylchalcones 63, 66, 67, 74

Pyrazolyl-enamine aldehydes 88
Pyrazolylpyrazolines 57, 69, 73, 91

R

Racemic product 102
Reaction pathway 31, 62

S

Single-crystal 27, 136
 analyses 136
 X-ray analysis 27
Solvothermal reaction 125, 127, 129, 133
 of Cd 127
Solvothermal synthesis 129
Spacers 22, 129, 130
 nitro-functionalized 130
Supramolecular 134, 135, 136
 networks 134
 solids 136
Suzuki 22, 45, 90, 114
 cross-coupling reaction 90
 Miyaura C-C cross-coupling reactions 22, 114
 reaction 45
Synthesis 2, 115, 116, 124
 of bipyrazole systems 2
 of copper 124
 of hydroxyl compounds 115
 of Polybipyrazoles 116

T

Tautomeric forms 57, 100
Temperatures, refluxing 42, 63
Tert-butyl 2, 48
 hypochlorite 48
 peroxide 2
Tetranitrobipyrazoles 119
Thermal heating 27, 28, 59, 60, 76
 conventional 28

Thermal stability 22, 52, 116, 117, 118, 129,
130, 134
preserved 129
Thermogravimetric analysis 116
THF 4, 13, 35, 39, 45, 90
refluxing 35
solution 45
Thiochroman 27
Thiosemicarbazide 64, 65, 66, 82, 83, 84
TMBP 123, 125, 126, 127, 128, 129, 131, 133,
134, 135, 136
frameworks 133
ligand 127
Triphenylphosphane 51, 123
Triphenylphosphine 48

U

Ultramicroporous diamondoid metal 123
Ultrasound 76
UV 124, 125, 126, 129
irradiation 125, 126
light 129
radiation 124

V

Valence ground states 130
Variable-temperature X-ray 129
Vilsmeier reaction 109

W

Water 10, 17, 31, 37, 39, 42, 46, 69, 79, 82,
83, 85, 90, 102, 126, 133, 134, 136
bromine 69
polluted 126

Z

Zn-based metal 129



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