Synthesis of 1,4-phenylene bridged bis-heterocyclic compounds

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Abstract

The synthesis of 1,4-phenylene bis-heterocyclic compounds is comprehensively reviewed.

Keywords: Synthesis, 1,4-phenylene, bis-heterocyclic compounds, terephthalaldehyde

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Contents

1. Introduction

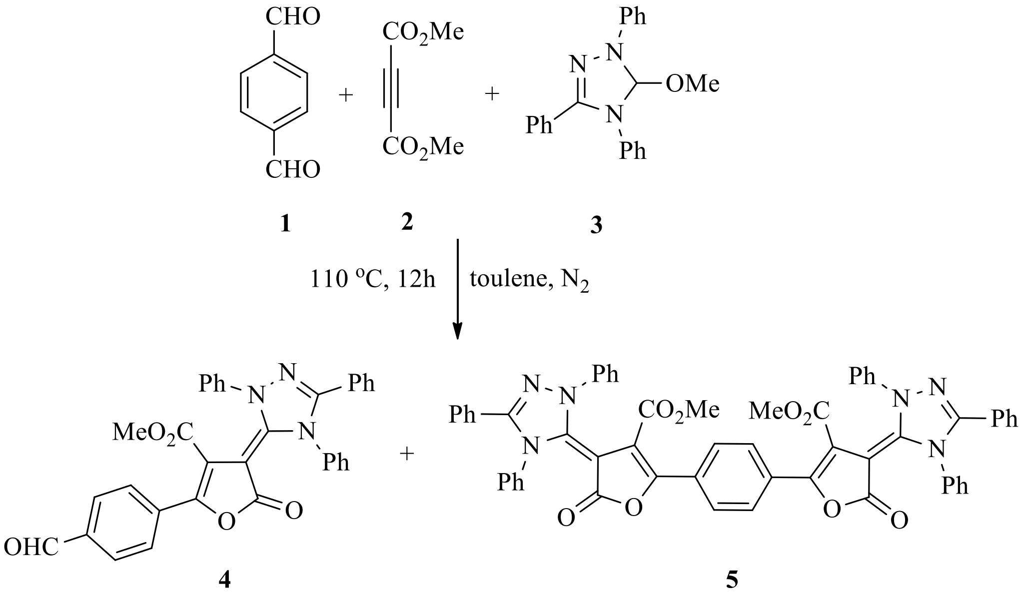
Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. The large number of biologically active molecules that contain heterocyclic rings has made synthetic studies of new heterocyclic rings very attractive,[1-5] particularly, polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles.[6-12] Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention. In recent years, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds which exhibit various biological activities,[13-20] including antibacterial, fungicidal, tuberculostatic, antiamoebic, and plant growth regulative properties. The current first specialized review covers the synthesis of 1,4-phenylene-bis-heterocyclic compounds from the late 1972 until 2011, and our survey of the literature on the synthesis of these heterocyclic has been divided according to the number of heteroatom in the heterocyclic.

2. Five-membered Rings with One Heteroatom

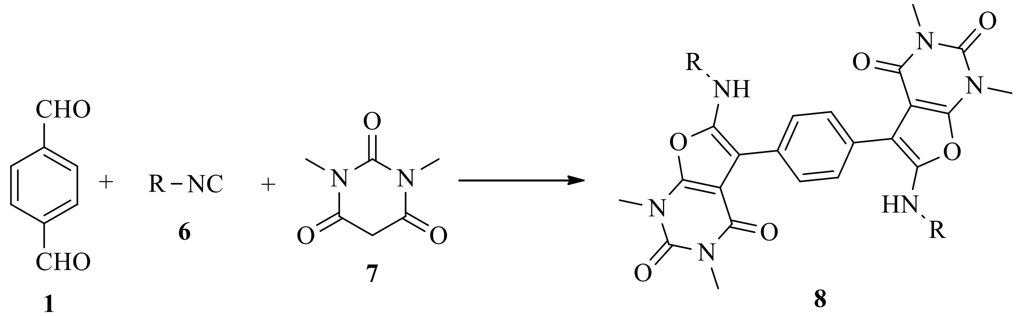
2.1. 1,4-Phenylene-bis-furans and their fused derivatives

Terephthalaldehyde **1** when treated with two equivalents of dimethyl acetylenedicarboxylate (DMAD) **2** and methoxytriazoline **3** afforded both mono- and bis-adducts **4** and **5**, respectively, (Scheme 1).[21]

The 5,5′-(1,4-phenylene)bis(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione) derivatives **8** were obtained from the reaction of isocyanides **6**, terephthalaldehyde **1** and *N*,*N*-dimethylbarbituric acid **7** *via* efficient one-pot three-component condensation reactions (Scheme 2).[22]



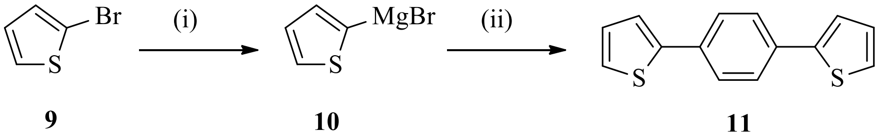
Scheme 1



Scheme 2

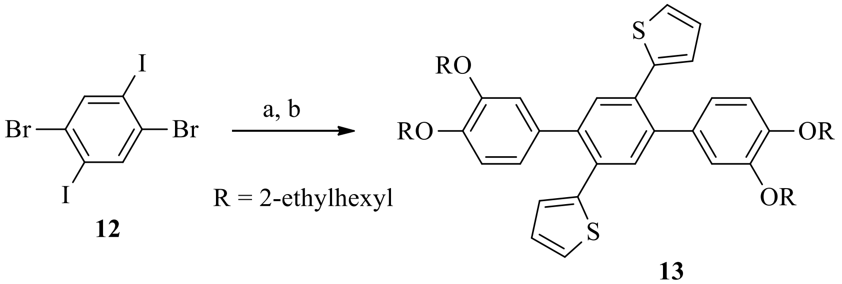
2.2. 1,4-Phenylene-bis-thiophenes

The 1,4-bis(thiophen-2-yl)benzene **11** was synthesized according to the procedure reported by Yang *et al.*[23] As shown in Scheme, 3, 2-bromothiophene **9** is reacted with magnesium to afford Grignard reagents **10** which are then cross-coupled to 1,4-dibromobenzene in the presence of catalytic bis(triphenylphosphino)dichloronickel (II) ($NiCl_2(PPh_3)_2$) (Scheme 3).



Scheme 3. Reagents: (i) Mg, Et_2O; (ii) 1,,4-dibromobenzere, $NiCI_2(PPh_3)_2$, THF.

Suzuki cross-couplings onto the isomeric 1,4-dibromo-2,5-diiodobenzene **12** afforded the thienyl-substituted terphenyl **13** (Scheme 4).[24]



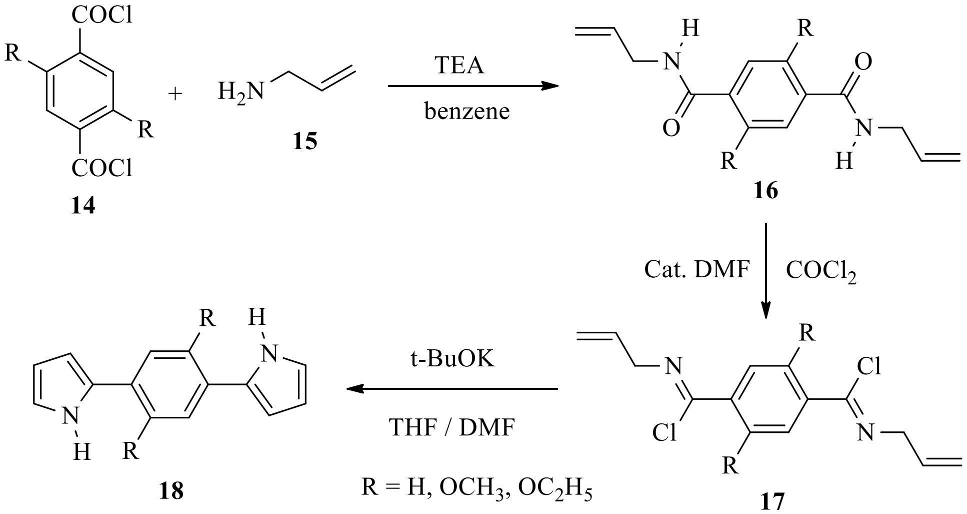
12

13

Scheme 4. Reagents: (a) 2-tridutylstannythiopene, $(Ph_3P)_2PdCI_2$, DMF, 80 °C. (b) 3,4-di (2-tthylhexyloxy)phenylpinacolatoborane, $Pd(PPh_3)_4$, Na_2CO_3, PhMe, EtOH, H_2O, 90 °C.

2.3. 1,4-Phenylene-bis-pyrroles

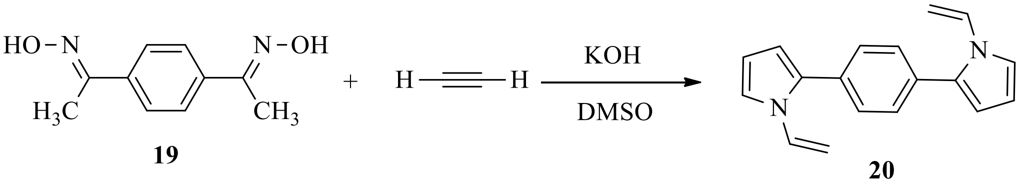
The 1,4-bis(1*H*-pyrrol-2-yl)benzene derivatives **18** were prepared by modification of the method of Engel and Steglich,[25] in accordance with the general pathway set out in Scheme 5. The acid chlorides **14** were reacted with allylamine **15** to give aryl bis(allylamides) **16**. Subsequent treatment with phosgene furnished the aryl bis(allylimino chlorides) **17**, which were used without isolation or purification in the following step. Compounds **17** were cyclized under basic conditions to form **18** (Scheme 5).[26,27]



14 **15** **16** **17** **18**

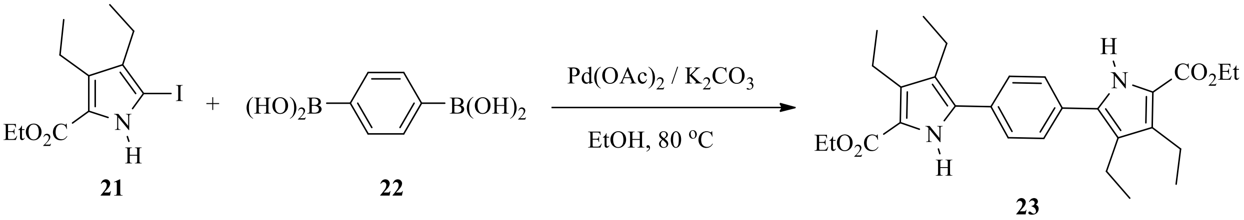
Scheme 5

The 1,4-bis(1-vinyl-1*H*-pyrrol-2-yl)benzene **20** was synthesized by the Trofimov reaction from 1,4-diacetylbenzene dioxime **19** and acetylene in a KOH - DMSO system (Scheme 6).[28-30]



Scheme 6

When a mixture of 3,4-diethyl-2-ethoxycarbonyl-5-iodopyrrole **21** (2.0 mmol), 1,4-phenylene-bisboronic acid **22** (1.0 mmol), K_2CO_3 (6.6 mol), $Pd(OAc)_2$ (0.10 mmol), and PPh_3 (0.20 mmol) in ethanol was heated under argon for 24 h at reflux, diethyl 5,5′-(1,4-phenylene)bis(3,4-diethyl-1*H*-pyrrole-2-carboxylate) **23** was obtained (Scheme 7).[31]



Scheme 7

The oxidative electropolymerization of these 1,4-bis(1*H*-pyrrol-2-yl)benzene **18** (R=H) gave the polymer **24** (Figure 1).[26,27]

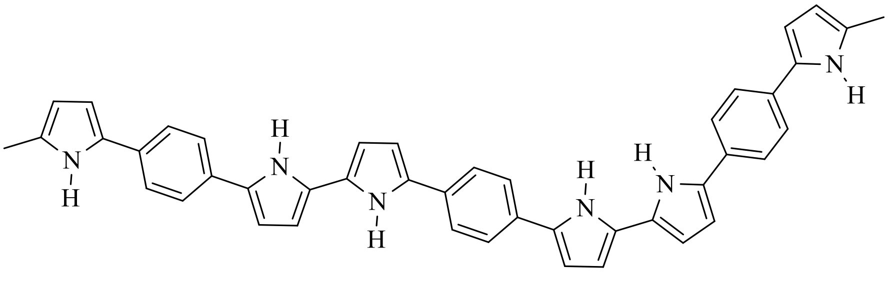
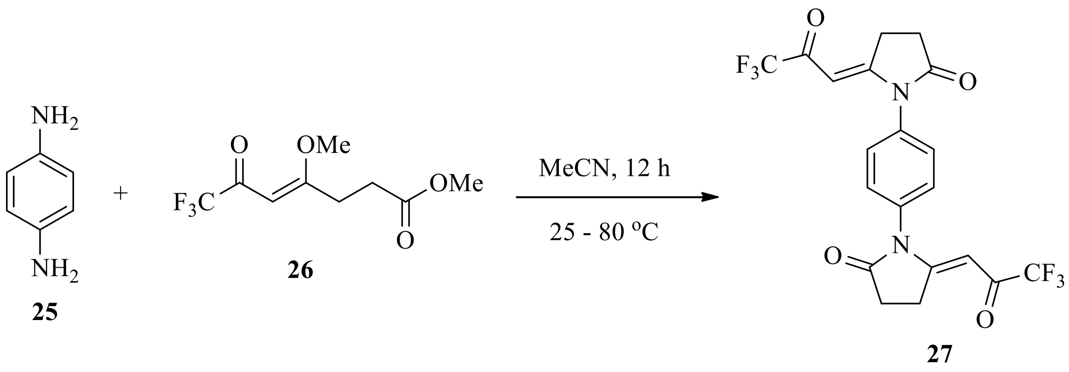


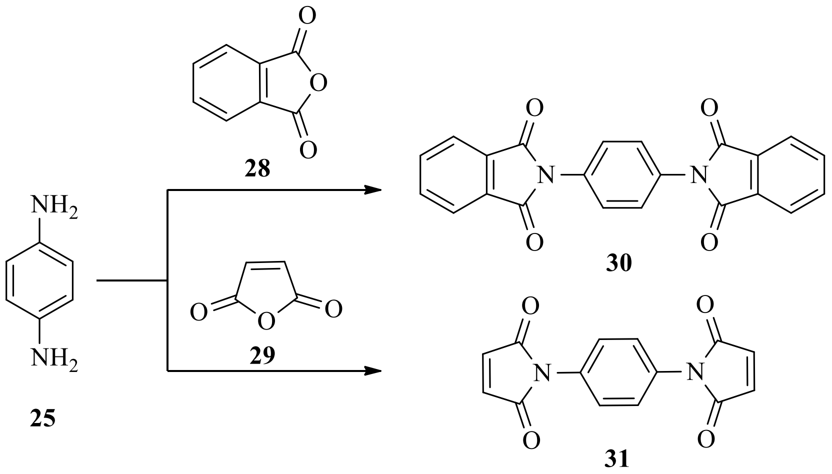
Figure 1

In the reaction of 1,4-diaminobenzene **25** with methyl 4-methoxy-6-oxo-7,7,7-trifluoro-4-heptenoate **26** in a stoichiometric ratio 2:1 mol-equiv ratio in MeCN under reflux conditions the intramolecular cyclisation took place with the formation of 1,1′-(1,4-phenylene)bis(5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one) **27** (Scheme 8).[32]



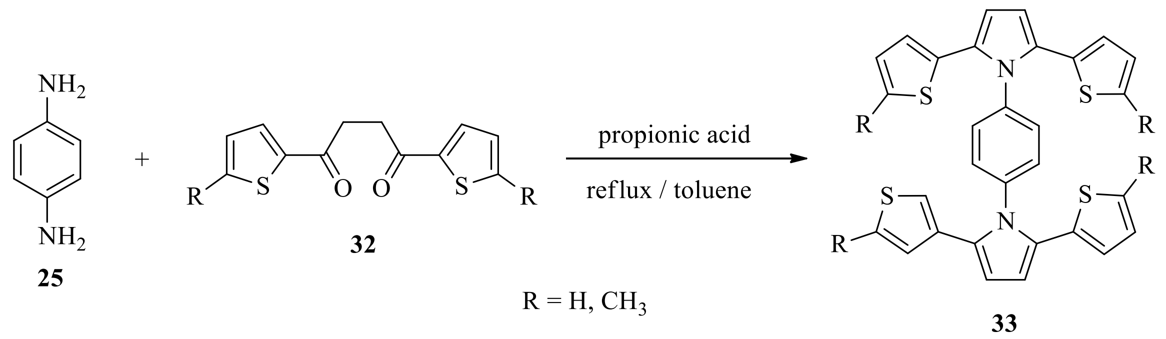
Scheme 8

The reaction of *cis*-1,2,3,6-tetrahydrophthalic anhydride **28** and maleic anhydride **29** with 1,4-diaminobenzene **25** on montmorillonite K-10 under microwave irradiation afforded 2,2′-(1,4-phenylene)bis(isoindoline-1,3-dione) **30** and 1,1′-(1,4-phenylene)bis(1*H*-pyrrole-2,5-dione) **31**, respectively (Scheme 9).[33]



Scheme 9

The Knorr-Paal reaction 1,4-diaminobenzene **25** with 1,4-bis(2-thienyl)-1,4-butanedione **32** in the presence of propionic acid catalysts afforded 1,4-bis[2,5-di(2-thienyl)-1*H*-1-pyrrolyl]benzene **33** (Scheme 10).[34]



Scheme 10

3. Five-membered Rings with Two Heteroatoms

3.1. 1,4-Phenylene-bis-pyrazoles and their fused derivatives

In the reaction between diarylidene-1,4-diacetylbenzenes **34** and phenylhydrazine hydrochloride, 1,4-bis(4,5-dihydro-1*H*-pyrazol-3-yl)benzene derivatives **35** were obtained which possess a bright green or blue luminescence (Figure 2).[35]

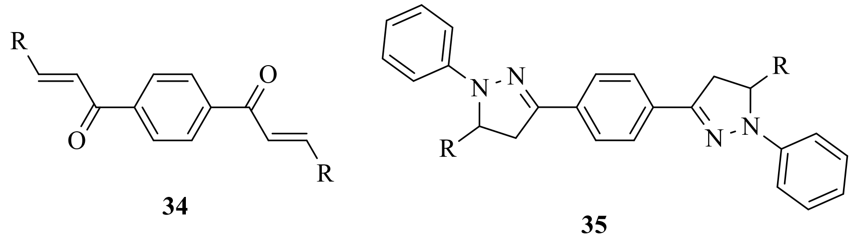
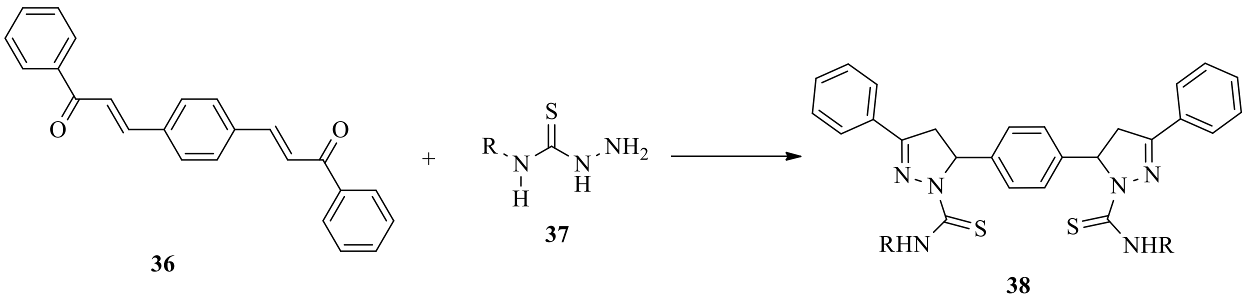


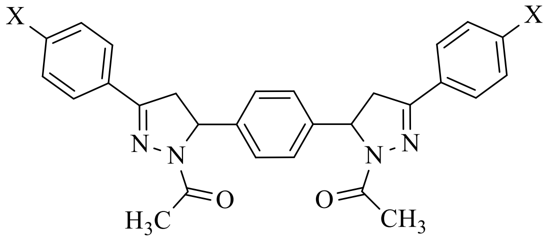
Figure 2

The cyclization of bischalcone **36** with *N*-4 substituted-thiosemicarbazides **37** under basic condition led to the formation of 5,5′-(1,4-phenylene)bis(4,5-dihydro-1*H*-pyrazole-1-carbothioamide) **38** (Scheme 11).[18]



Scheme 11

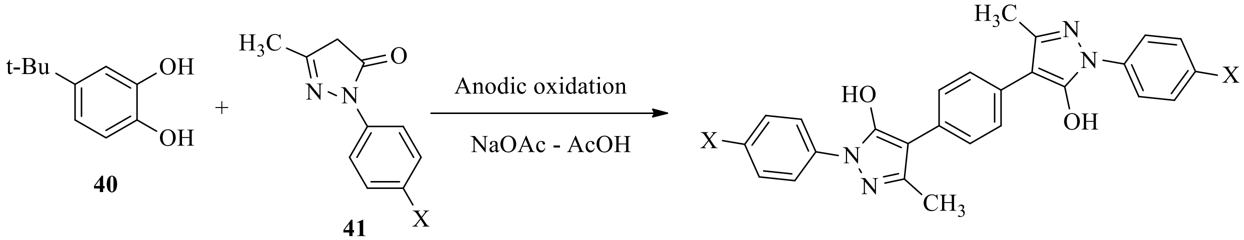
The 5,5′-(1,4-phenylene)bis(3-aryl-1*H*-pyrazole) **39** are synthesized by the reaction of bischalcone **35** with hydrazine hydrate catalyzed by anhydrous sodium acetate/acetic anhydride under ultrasonic irradiation method at 45 °C within 10–20 min (Figure 3).[36]



39 (X = H, Cl, Br, CH_3, OCH_3)

Figure 3

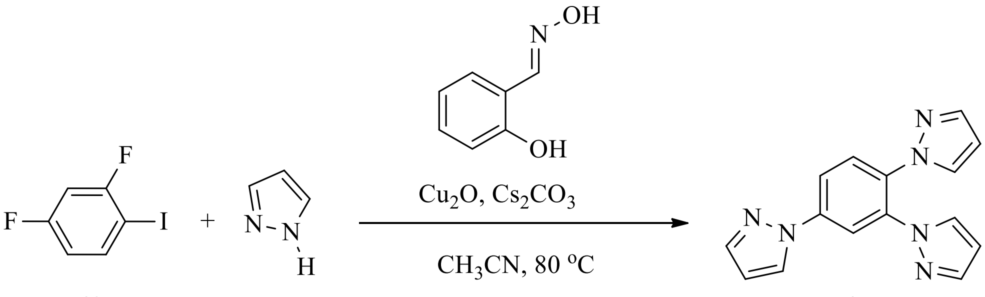
The anodic oxidation of 4-*tert*-butylcatecol **40** in the presence of pyrazol-5-ones **41** in 2:1 volume ratio of acetate buffer to acetonitrile, gave 4,4′-(1,4-phenylene)bis(1-aryl-3-methyl-1*H*-pyrazol-5-ol) **42** (Scheme 12).[37]



42 (X = H, Cl, CH_3, OCH_3)

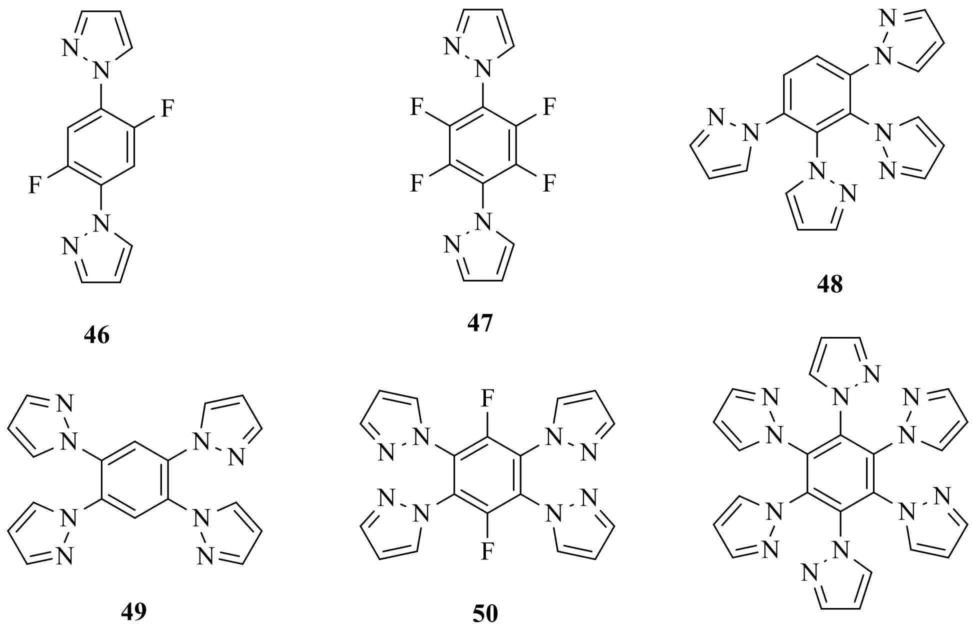
Scheme 12

The 1,2,4-tris(1*H*-pyrazolyl)benzene **45** was synthesized by the reaction of 2,4-difluoroiodobenzene **43** with pyrazole **44** catalyzed by Cu_2O (5 mol%) 20% salicylaldoxime (20 mol%) and Cs_2CO_3 (2 equiv) in acetonitrile (Scheme 13).[38]



Scheme 13

Also, the 1,1′-(2,5-difluoro-1,4-phenylene)bis(1*H*-pyrazole) **46**,[39] 1,1′-(perfluoro-1,4-phenylene)bis(1*H*-pyrazole) **47**,[39] 1,2,3,4-tetrakis(pyrazol-1-yl)benzene **48**,[39] 1,2,4,5-tetrakis(pyrazol-1-yl)benzene **49**,[39,40] 1,4-difluoro-2,3,5,6-tetrakis(pyrazol-1-yl)benzene **50**[39] and hexakis(pyrazol-1-yl)benzene **51**,[39-42] were prepared by nucleophilic substitution of fluorine in 1,2,3,4-tetrafluoro-, 1,2,4,5-tetrafluoro, and hexafluorobenzene, respectively (Figure 4).

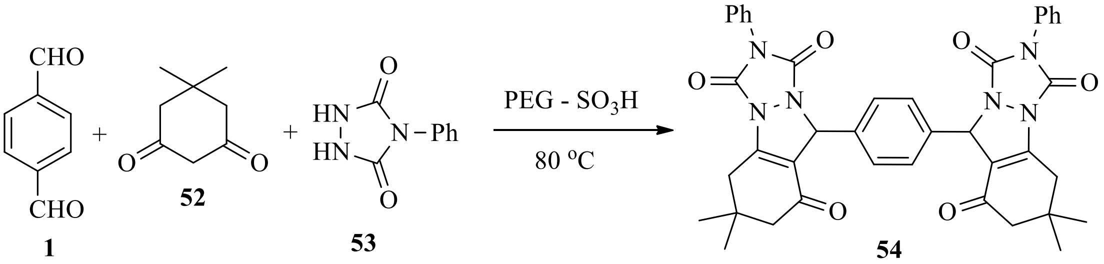


46 **47** **48**

49 **50** **51**

Figure 4

The condensation reaction between terephthalaldehyde **1**, dimedone **52** and 4-phenylurazole **53** gave 9,9′-(1,4-phenylene)bis(6,7-dihydro-[1,2,4]triazolo[1,2-*a*]indazole-trione) **54** (Scheme 14).[43]

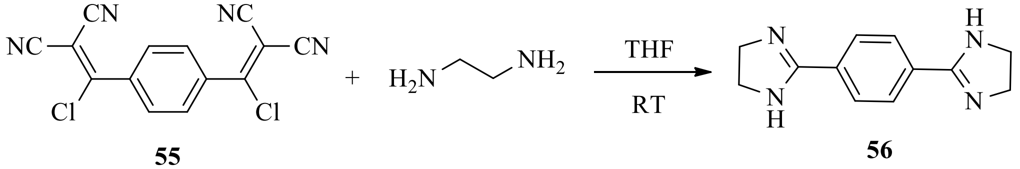


1 **52** **53** **54**

Scheme 14

3.2. 1,4-Phenylene- bis-imidazoles and their fused derivatives

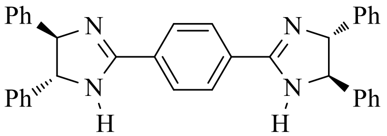
The 1,4-bis(1-chloro-2,2-dicyanovinyl)benzene **55** reacts with excess amount of ethylenediamine to give 1,4-bis(4,5-dihydro-1*H*-imidazol-2-yl)benzene **56** at room temperature (Scheme 15).[44]



55 **56**

Scheme 15

Similarly, the condensation of enantiopure 1,2-diamines with terephthalaldehyde (**1**), in toluene followed by treatment with *N*-bromosuccinimide in dichloromethane gives direct access to enantiopure 1,4-bis[4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl]benzene **57** and 1,4-bis[4,5-dimesyl-4,5-dihydro-1*H*-imidazol-2-yl]benzene **58** (Figure 5).[45]



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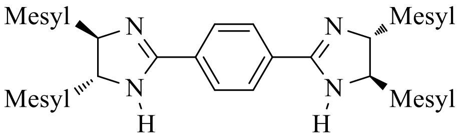
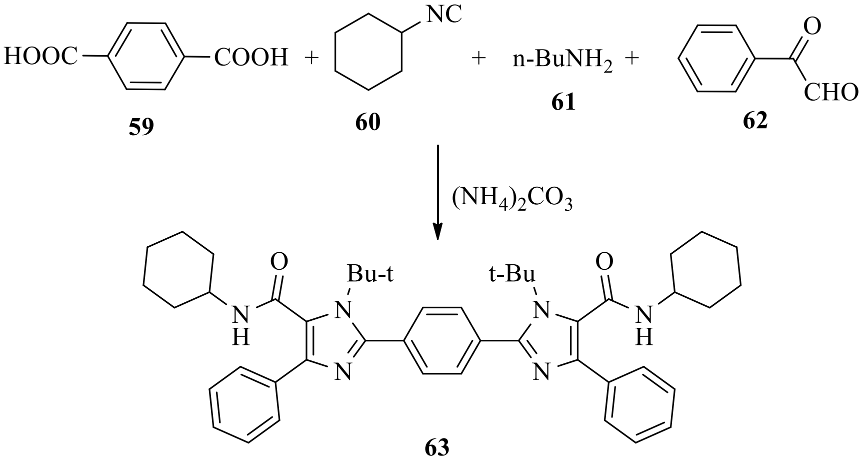


58

Figure 5

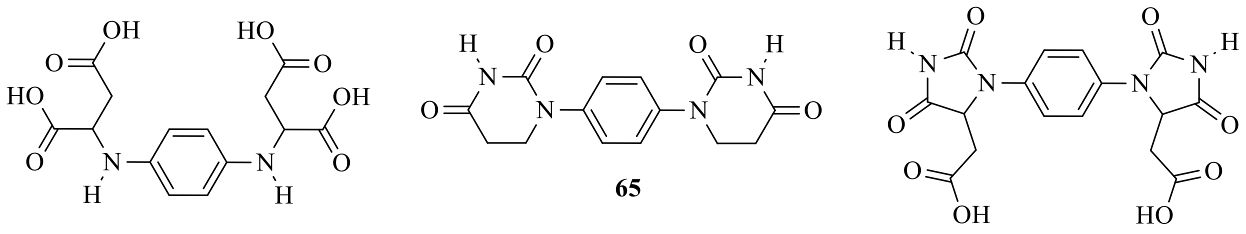
The 2,2′-(1,4-phenylene)bis(1*H*-imidazole-5-carboxamide) **63** was prepared by multi-component reaction of terephthalic acid **59**, cyclohexylisocyanide **60**, *n*-butylamine **61** and phenylglyoxal hydrate **62** (Scheme 16).[46]



59 **60** **61** **62** **63**

Scheme 16

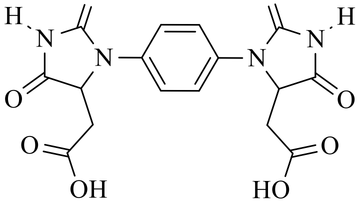
The 1,1′-(1,4-phenylene)bis(dihydropyrimidine-2,4(1*H*,3*H*)-dione) **65** was also obtained along with 2,2′-(3,3′-(1,4-phenylene)bis(2,5-dioxoimidazolidine-4,3-diyl))diacetic acid **66** by heating aspartic acid dimer **64** with urea (Figure 6).[47]



64 **65** **66**

Figure 6

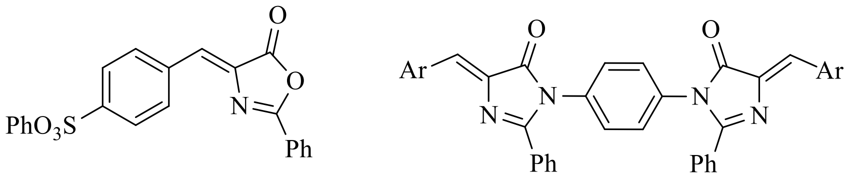
Heating the tetracarboxylic acid **64** with potassium thiocyanate in acetic acid and subsequent addition of hydrochloric acid gave 2,2′-(3,3′-(1,4-phenylene)bis(5-oxo-2-thioxoimidazolidine-4,3-diyl))diacetic acid **67** (Figure 7).[47]



67

Figure 7

Treatment of 4-(benzylidene-4-benzenesulphoate)-2-phenyl-2-oxazolin-5-one **68** with 1,4-diaminobenzene **25** in acetic acid containing catalytic amounts of freshly fused sodium acetate gave the corresponding 1,1′-(1,4-phenylene)bis(4-arylidene-2-phenyl-1*H*-imidazol-5(4H)-one) **69** (Figure 8).[48]

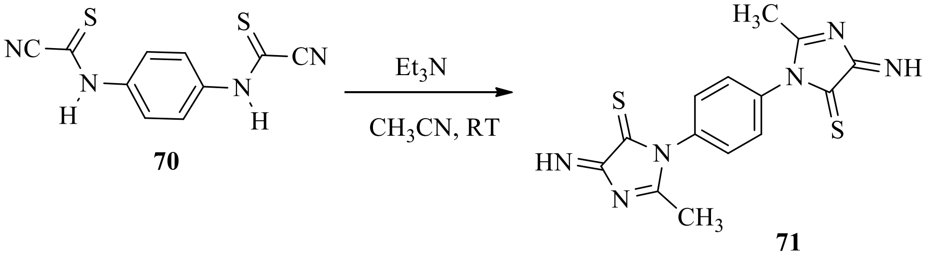


68 **69**

Ar = -C_6H_4-SO_3-Ph

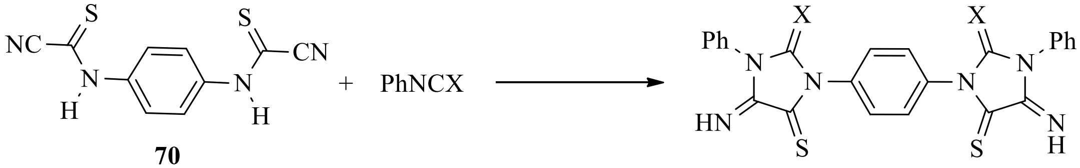
Figure 8

When 1,4-phenylenedicarbamothioyl cyanide **70** was reacted with two moles of acetonitrile in tetrahydrofuran containing triethylamine at room temperature cyclization occurred to afford 1,1′-(1,4-phenylene)bis(4-imino-2-methyl-1*H*-imidazole-5(4*H*)-thione) **71** (Scheme 17).[49]



Scheme 17

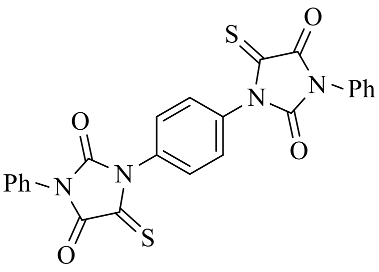
Also, the 1,4-phenylenedicarbamothioyl cyanide **70** underwent cyclization upon its reaction with phenyl iso(thio)cyanate in tetrahydrofuran containing a catalytic amount of triethylamine giving the corresponding 3,3′-(1,4-phenylene)bis(4-thioxoimidazolidin-2-one) **72a** and/or 3,3′-(1,4-phenylene)bis(imidazolidine-2,4-dithione) **72b**, respectively (Scheme 18).[49]



72a, X = O
b, X = S

Scheme 18

Reaction of **72a** with DMF/HCl and with phenyl hydrazine gave the corresponding 1,1′-(1,4-phenylene)bis(5-thioxoimidazolidine-2,4-dione) **73** and 3,3′-(1,4-phenylene)bis(5-imino-1-phenyl-4-(2-phenylhydrazono)imidazolidin-2-one) **74** (Figure 9).[49]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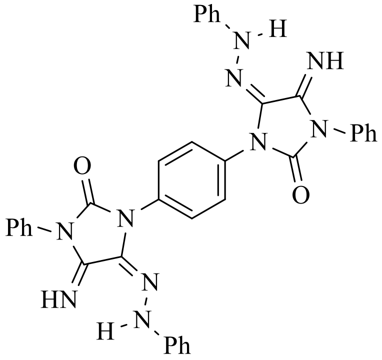
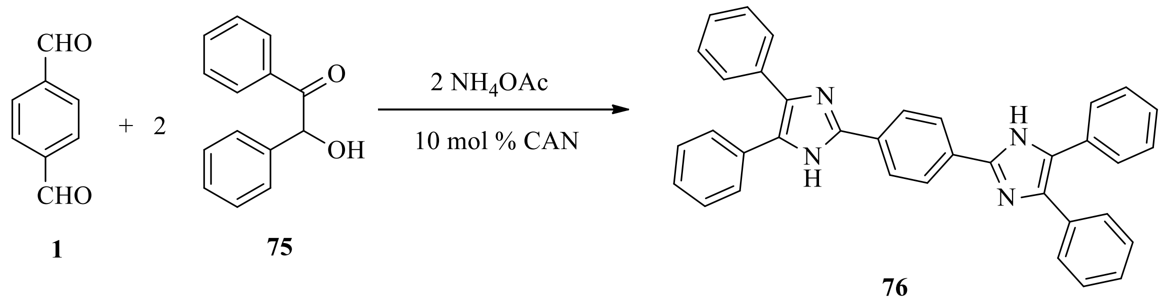

74

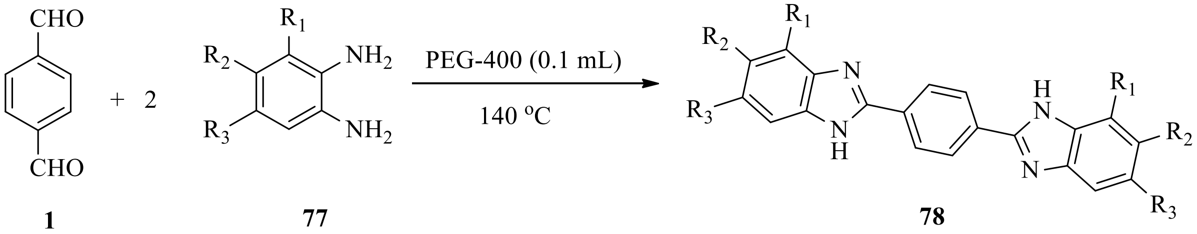
Figure 9

Ceric ammonium nitrate (CAN) is used as an efficient catalyst for the synthesis of 1,4-bis(4,5-diphenyl-1*H*-imidazol-2-yl)benzene **76** *via* condensation of terphthaldehyde **1**, benzoin **75**, and ammonium acetate (Scheme 19).[50]



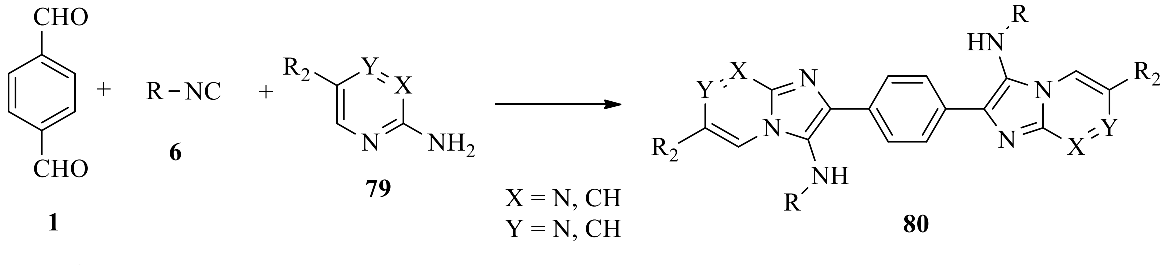
Scheme 19

The reaction of two moles of 1,2-phenylenediamine derivatives **77** with terphthalaldehyde **1** gave the 1,4-bis(1*H*-benzo[*d*]imidazol-2-yl)benzene **78** by PEG-mediated catalyst-free synthesis under solvent-less conditions (Scheme 20).[51]



Scheme 20

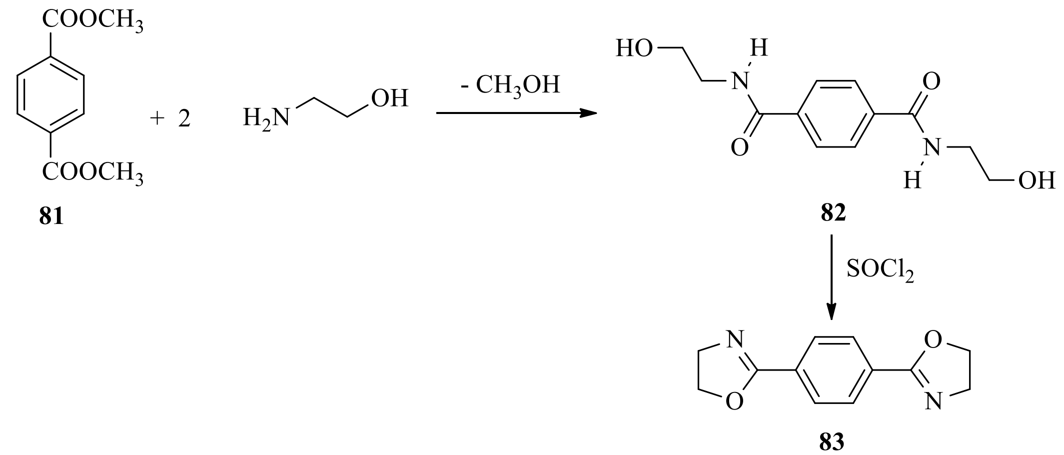
Shaabani *et al.*[52] have described the synthesis of 1,4-phenylene-bis(imidazo[1,2-*a*]pyridines), 1,4-phenylene- bis-pyrimidines, and 1,4-phenylene-bis-pyrazines **80** by a pseudo-five-component condensation of 2-amino-pyridines or 2-amino-pyrimidines and/or 2-amino-pyrazines **79** with terephthalaldehyde **1** and isocyanides **6** in the presence of *p*-toluenesulfonic acid in methanol (Scheme 21).



Scheme 21

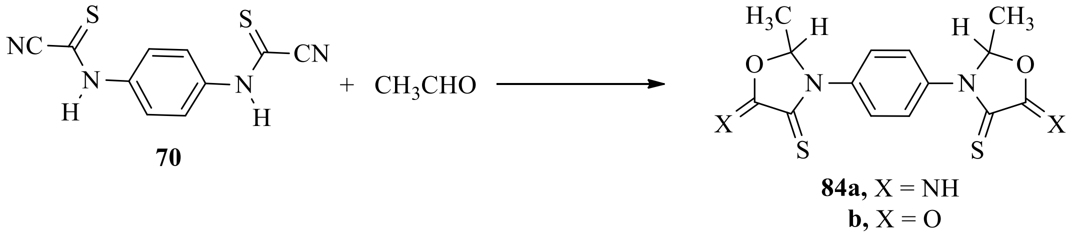
3.3. 1,4-Phenylene- bis-oxazoles

The 1,4-bis(4,5-dihydrooxazol-2-yl)benzene **83** was prepared in two-steps. The dimethyl-terephthalate **81** reacted with 2-aminoethanol to give the *N*,*N′*-bis(2-hydroxyethyl)-terephthalamide **82**. Subsequent treatment with thionyl chloride furnished **83** (Scheme 22).[53,54]



Scheme 22

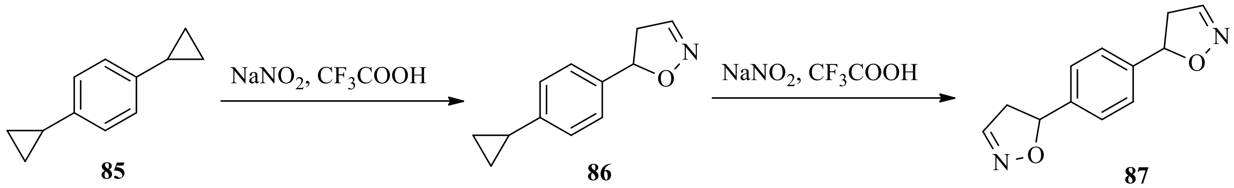
When 1,4-phenylenedicarbamothioyl cyanide **70** was treated with two moles of acetaldehyde in tetrahydrofuran containing a catalytic amount of triethylamine a product was formed which was formulated as 3,3′-(1,4-phenylene)bis(5-imino-2-methyloxazolidine-4-thione) **84a**. Hydrolysis of **84a** by DMF/HCl gave 3,3′-(1,4-phenylene)bis(4-thioxooxazolidin-5-one) **84b** (Scheme 23).[49]



Scheme 23

3.4. 1,4-Phenylene- bis-isoxazoles

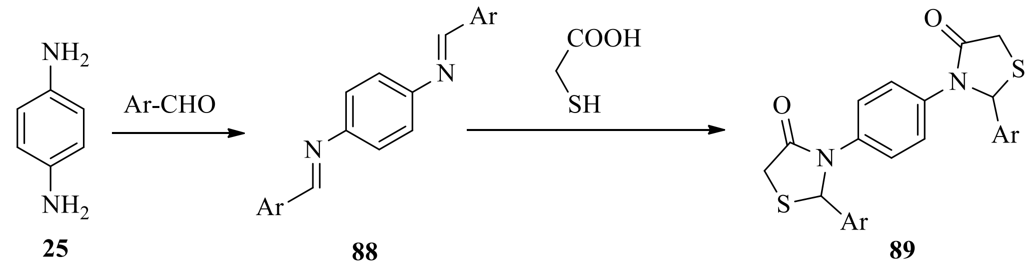
Shabarov and coworkers[55] found that under the influence of nitrosyl cation 1,4-dicyclopropylbenzene **85** is converted with high yields into 5-(4-cyclopropylphenyl)-4,5-dihydroisoxazole **86**. It should be noted[56-58] that the second three-carbon ring is not transformed with the initially employed reagent ratio and is, therefore, converted into the 1,4-bis(4,5-dihydroisoxazol-5-yl)benzene **87** only with extreme difficulty (Scheme 24).



Scheme 24

3.5. 1,4-Phenylene- bis-thiazoles and their fused derivatives

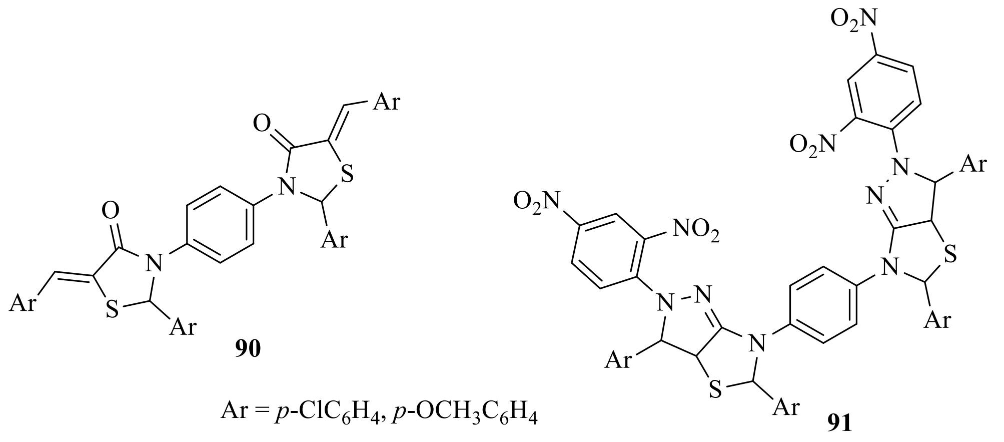
Condensation of 1,4-diaminobenzene **25** with arylaldehyde in aqueous ethanol gave the corresponding diarylidenebenzene-1,4-diamine **88**, which on condensation with thioglycollic acid furnished 3,3′-(1,4-phenylene)bis(2-aryl-thiazolidin-4-one) **89** (Scheme 25).[59,60]



Ar = C_6H_5, p-ClC_6H_4, p-$OCH_3C_6H_4$

Scheme 25

Condensation of **89** with arylaldehyde yielded 3,3′-(1,4-phenylene)bis(5-arylidene-thiazolidin-4-one) **90**, which when treated with 2,4-dinitrophenylhydrazine afforded the cyclized product, 1,4- bis(pyrazolo[3,4-*d*]thiazol-6(5*H*)-yl)benzene **91**, in one step (Figure 10).[60]



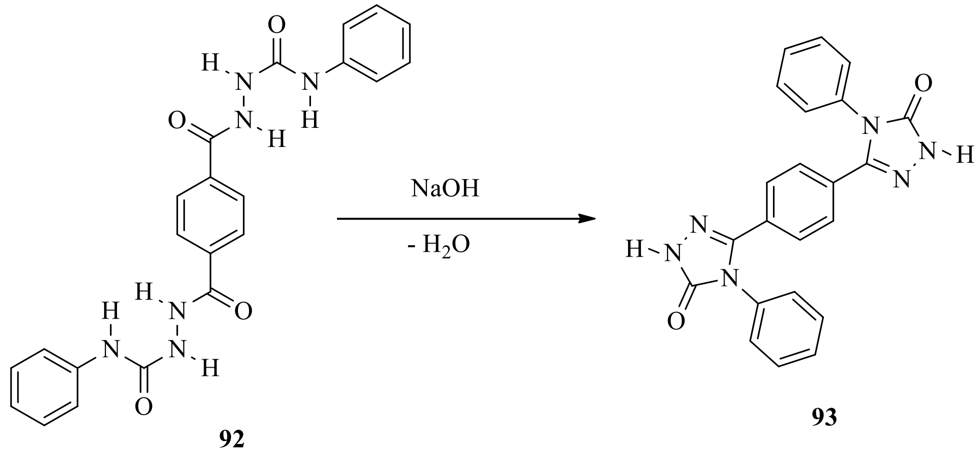
Ar = p-ClC_6H_4, p-$OCH_3C_6H_4$

Figure 10

4. Five-membered Rings with Three Heteroatoms

4.1. 1,4-Phenylene- bis-triazoles and their fused derivatives

Shaker *et al*.[61] reported that the bis-semicarbazide **92** on treatment with NaOH underwent cyclization to the 3,3′-(1,4-phenylene)bis(1*H*-1,2,4-triazol-5(4*H*)-one) **93** (Scheme 26).



Scheme 26

Smith *et al.*[62] accomplished the reaction of the corresponding dienamines with dimethyl ester tetrazine **94** to yield the corresponding 5,5′-(1,4-phenylene)bis(2*H*-1,2,3-triazole) **95** and 3,3′-(1,4-phenylene)bis(1H-1,2,4-triazole) **96** (Figure 11).

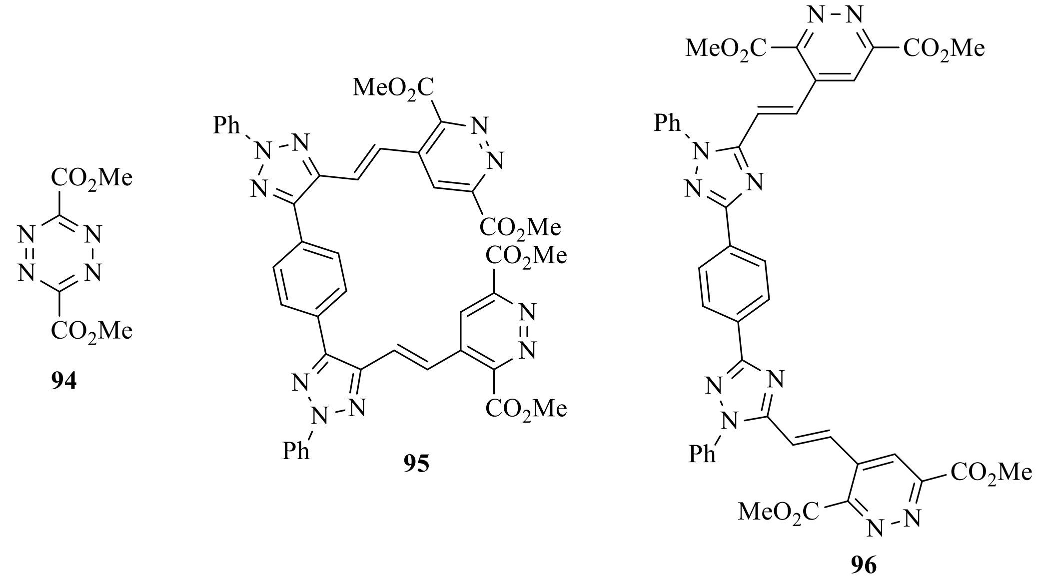
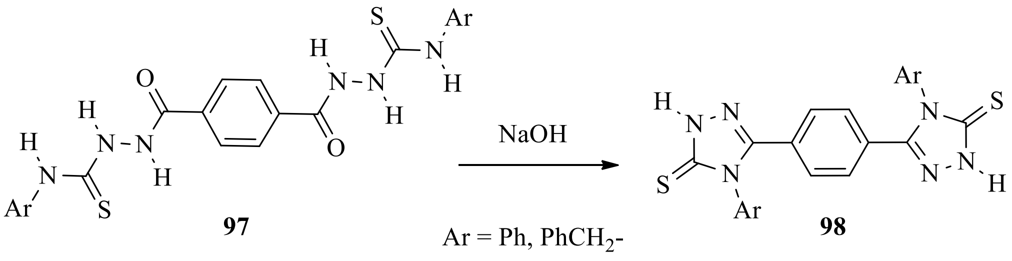


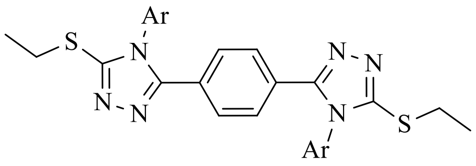
Figure 11

Shaker *et al*.[61] reported that the treatment of 1,4-phenylene-bis-thiosemicarbazide **97** with sodium hydroxide gives 3,3′-(1,4-phenylene)bis(1*H*-1,2,4-triazole-5(4*H*)-thione) **98** (Scheme 27).



Scheme 27

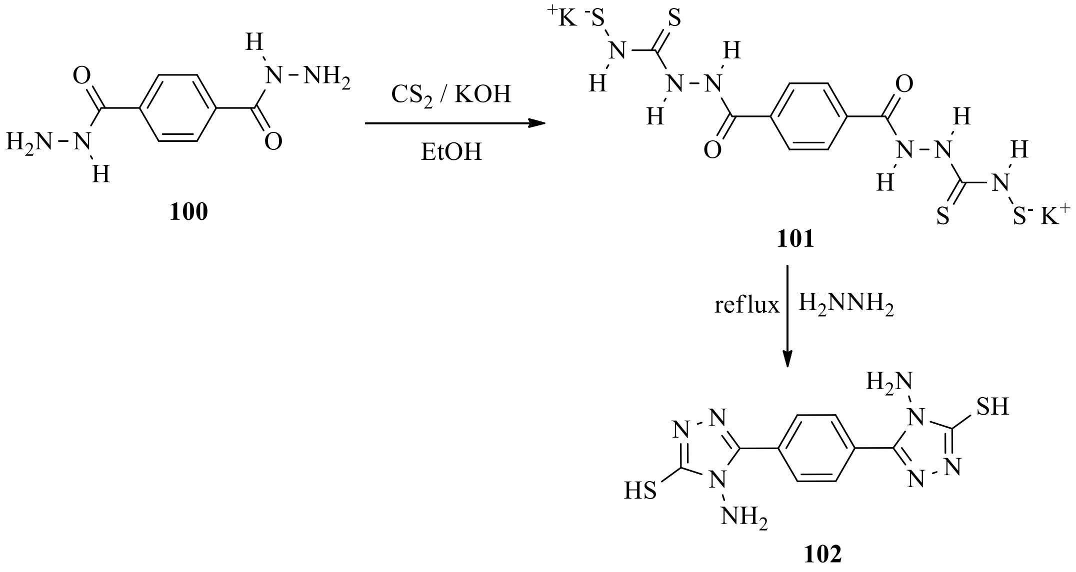
The reaction of **98** with ethyl iodide in DMF at room temperature and in the presence of anhydrous potassium carbonate gave 1,4-bis(4*H*-1,2,4-triazol-3-yl)benzene **99** (Figure 12).[61]



99

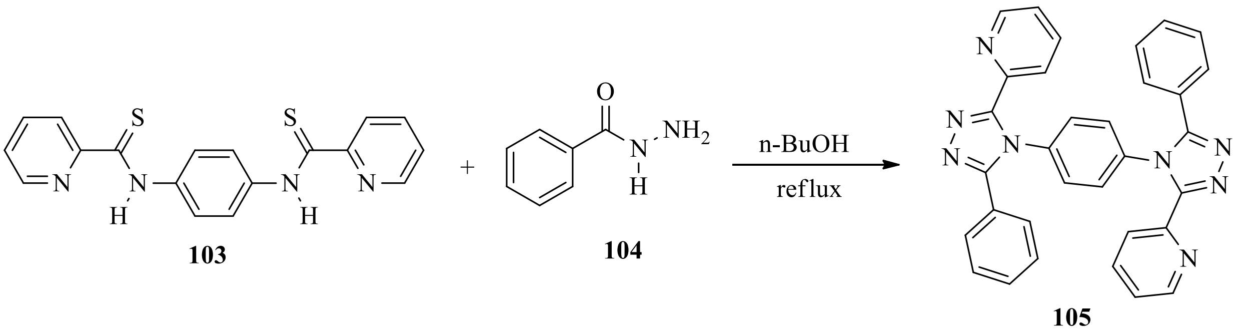
Figure 12

The bis-dithiocarbazinate **101** was synthesized by reacting dihydrazide **100** with carbon disulfide and potassium hydroxide in ethanol. This salt **101** underwent ring closure with an excess of 99% hydrazine hydrate to give the 5,5′-(1,4-phenylene)bis(4-amino-4*H*-1,2,4-triazole-3-thiol) **102** (Scheme 28).[63]



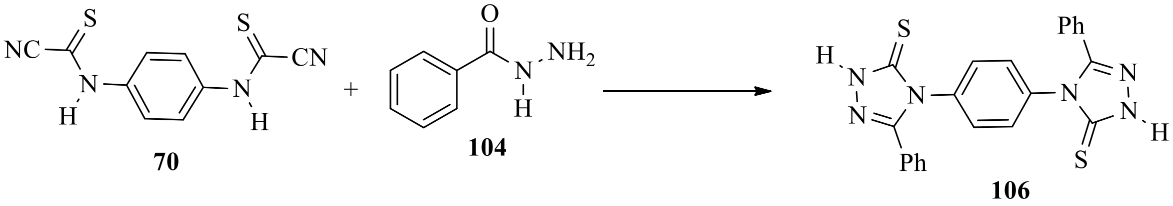
Scheme 28

The 1,4-bis(4*H*-1,2,4-triazol-4-yl)benzene **105** was prepared from the reaction of *N*,*N′*-(1,4-phenylene)bis-2-pyridinecarbothioamide **103** with benzoylhydrazine **104** (Scheme 29).[64,65]



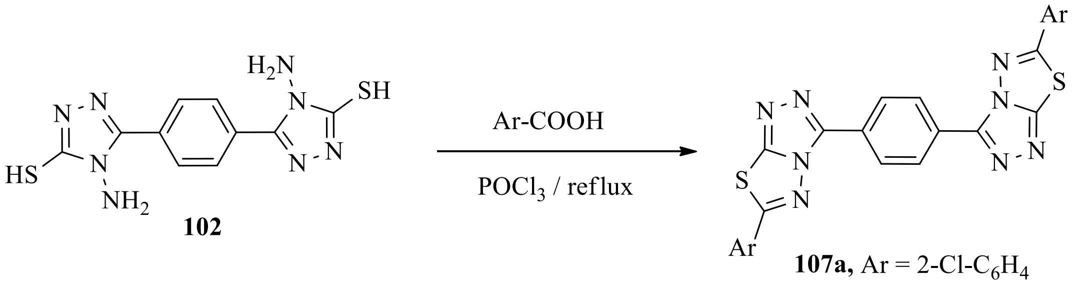
Scheme 29

When two moles of benzoylhydrazine **104** was reacted with 1,4-phenylenedicarbamothioyl cyanide **70** the 4,4′-(1,4-phenylene)bis(3-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione) **106** was obtained (Scheme 30).[49]



Scheme 30

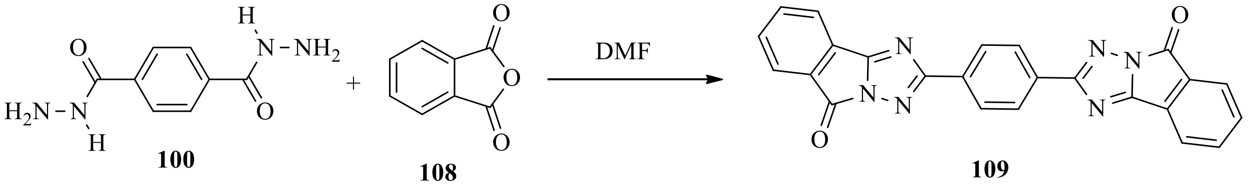
The 1,4-phenylene-bis(4-amino-4*H*-1,2,4-triazole-3-thiol) **102** was converted to 1,4-bis(1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)benzene **107a,b** in a one pot reaction, by condensation with aromatic acids in the presence of $POCl_3$ (Scheme 31).[63]



107a, Ar = 2-Cl-C_6H_4
b, Ar = 4-NO_2-C_6H_4

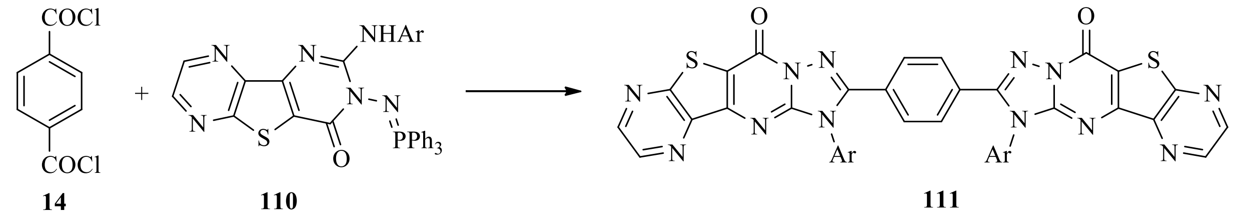
Scheme 31

The condensation of dihydrazide **100** with phthalic anhydride **108** leads to the formation of 2,2′-(1,4-phenylene)bis(5*H*-[1,2,4]triazolo[5,1-*a*]isoindol-5-one) **109** (Scheme 32).[66]



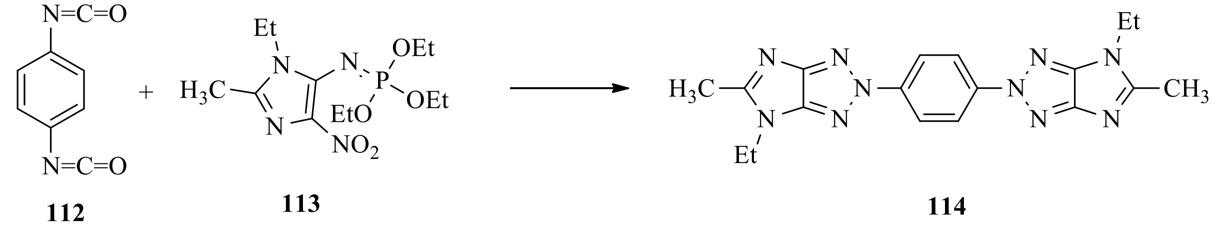
Scheme 32

The 1,4-bis(pyrazinothienotriazolopyrimidinones)benzene **111** was synthesized by the intermolecular aza-Wittig reaction of phosphazenes **110** with acid chloride **14** (R=H) followed by heterocyclization (Scheme 33).[67]



Scheme 33

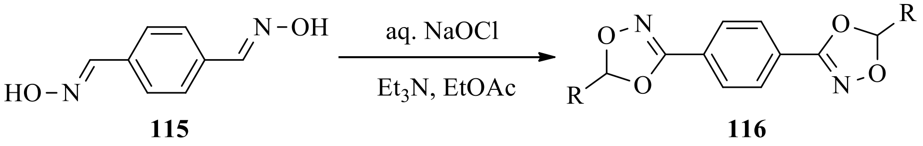
The reaction with 1,4-phenylene diisocyanate **112** and two equivalents of the phosphorimidate **113** led to the formation of 1,4-bis(imidazo[4,5-*d*][1,2,3]triazol-2(4*H*)-yl)benzene **114** (Scheme 34).[68]



Scheme 34

4.2. 1,4-Phenylene- bis-dioxazoles

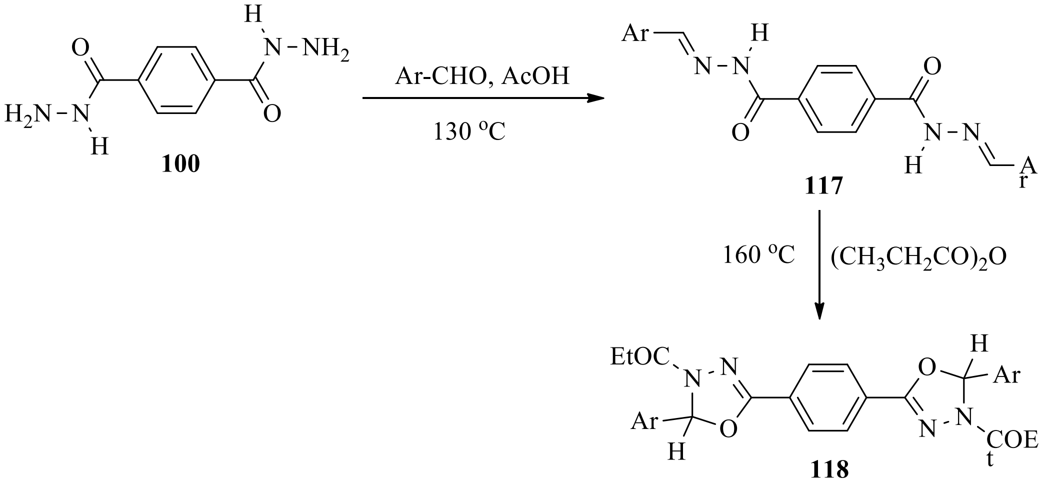
Cyclization of benzene-1,4-dicarbaldehyde dioxime **115** with different aromatic aldehydes in inert atmosphere yielded 1,4-bis(1,4,2-dioxazol-3-yl)benzene **116** (Scheme 35).[20]



Scheme 35

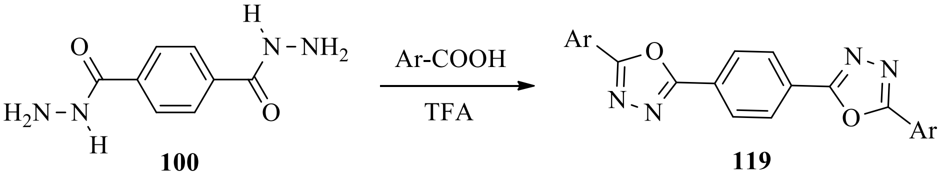
4.3. 1,4-Phenylene- bis-oxadiazoles

The condensation of dihydrazide **100** with aromatic aldehydes afforded corresponding hydrazones **117**, respectively. Cyclization of **117** with propionic anhydride at 160 °C yielded 1,4-bis[3-*N*-propionyl-2-aryl-1,3,4-oxadiazo-5-yl]benzene **118** (Scheme 36).[69]



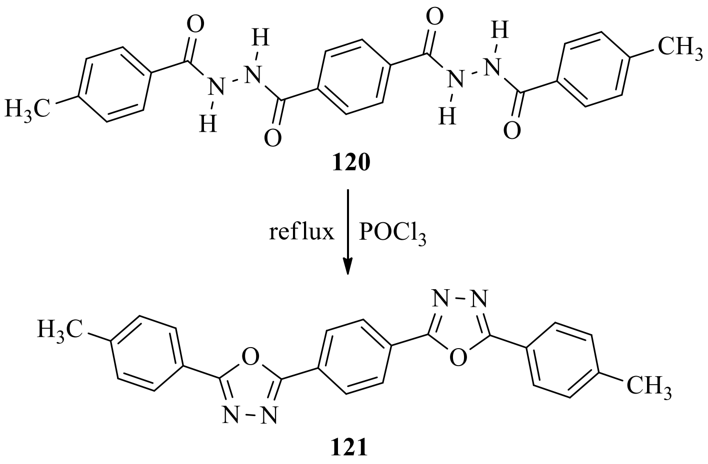
Scheme 36

Various 1,4-bis(5-aryl-1,3,4-oxadiazol-2-yl)benzene **119** were prepared by treatment of dihydrazide **100** with aromatic acids in the presence of trifluoroacetic acid (Scheme 37).[63]



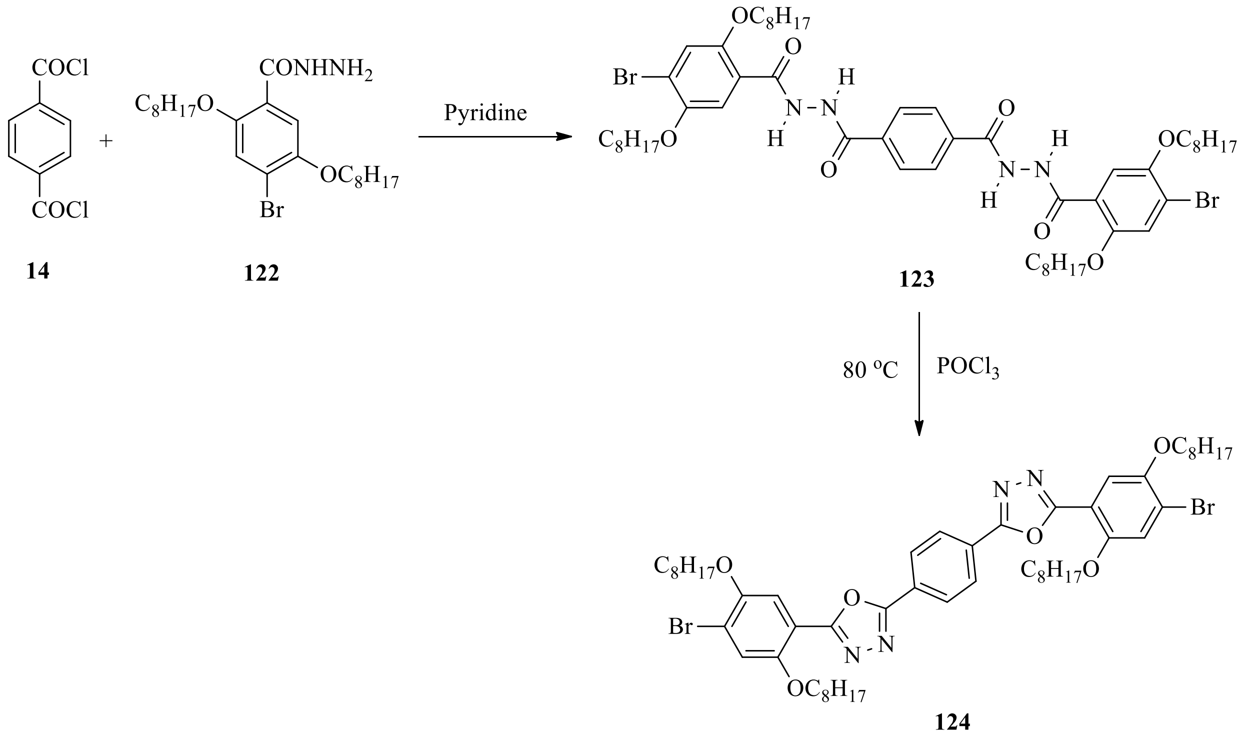
Scheme 37

The synthesis, optical properties and electrochemical properties, of 1,4-bis(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)benzene **121** are reported (Scheme 38).[70]



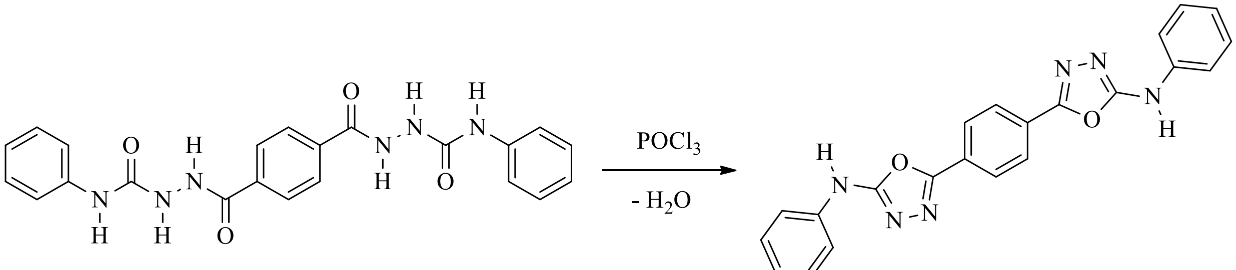
Scheme 38

The N'^1,N'^4-bis(4-bromo-2,5-bis(octyloxy)benzoyl)terephthalohydrazide **123** was obtained from the reaction of acid chloride **14** (R=H) with 4-bromo-2,5-bis(octyloxy)benzohydrazide **122**. After cyclodehydration of compound **123**, the 1,4-bis(1,3,4-oxadiazol-2-yl)benzene **124** was obtained (Scheme 39).[71]



Scheme 39

Shaker *et al.*[61] reported that the bis-semicarbazide **92** on treatment with NaOH underwent cyclization to the corresponding 5,5′-(1,4-phenylene)bis(1,3,4-oxadiazol) **125** (Scheme 40).

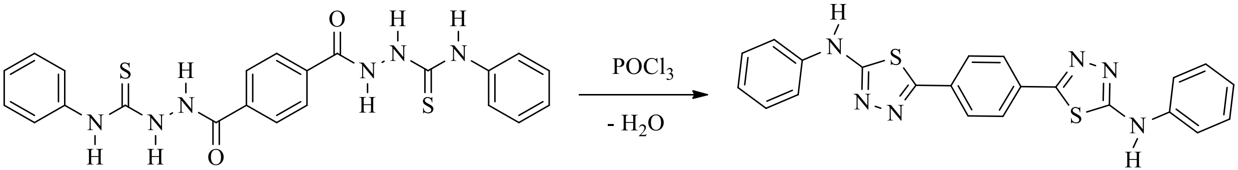


92 **125**

Scheme 40

4.4. 1,4-Phenylene- bis-thiadiazoles

Shaker *et al.*[61] reported that 1,4-phenylene-bis-thiosemicarbazide **97** reacted with phosphoryl chloride at reflux to give 5,5′-(1,4-phenylene)bis(1,3,4-thiadiazol) **126** (Scheme 41).



Ar = Ph, PhCH$_2$-

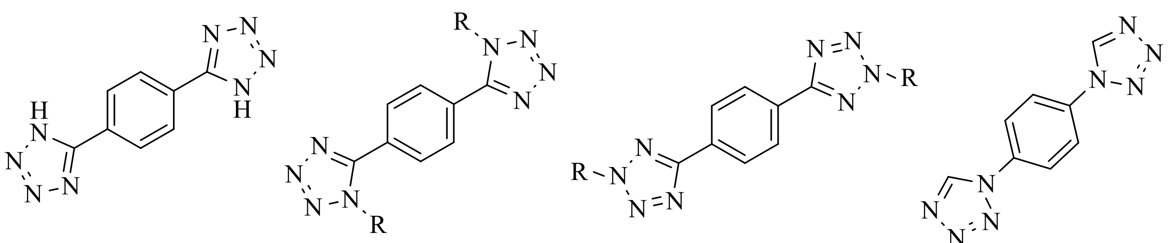
97 **126**

Scheme 41

5. Five-membered Rings with Four Heteroatoms

5.1. 1,4-Phenylene-bis-tetrazoles

A series of 1,4-bis(tetrazole)benzene derivatives **127 – 130** were prepared by different methods (Figure 13).[72-74]



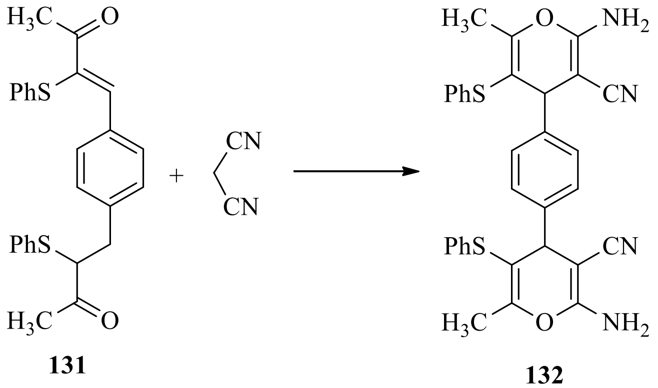
127 **128** **129** **130**

Figure 13

6. Six-membered Rings with One Heteroatom

6.1. 1,4-Phenylene- bis-pyrans and their fused derivatives

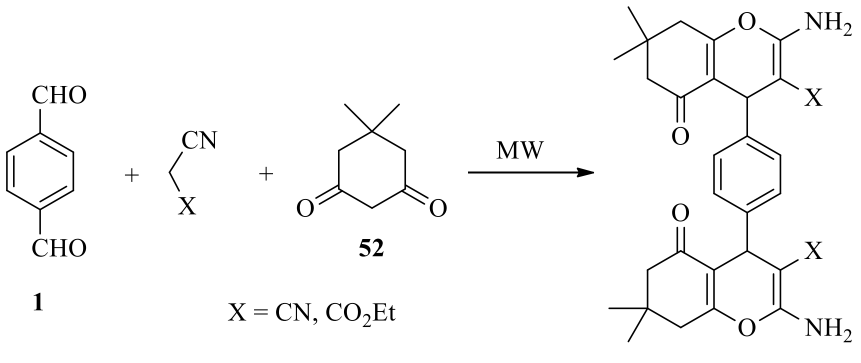
The reaction of phenylthioacetone **131** with malononitrile in a molar ratio of 1:2 carried out in absolute ethanol and catalyzed by piperidine afforded 4,4′-(1,4-phenylene)bis(2-amino-6-methyl-5-(phenylthio)-4*H*-pyran-3-carbonitrile) **132** (Scheme 42).[75]



131 **132**

Scheme 42

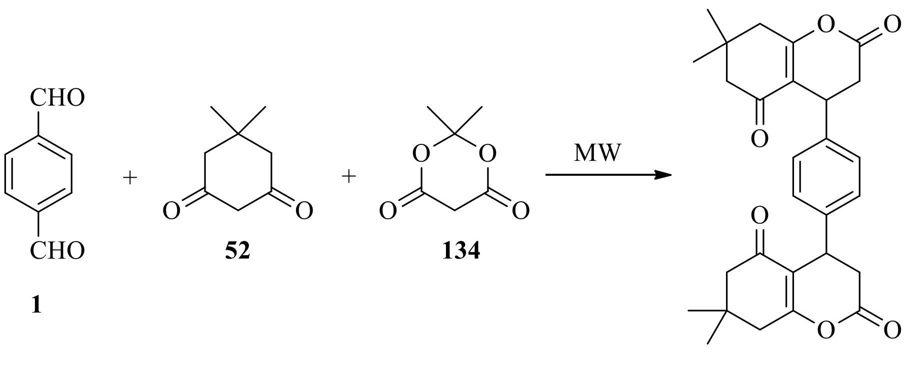
The 4,4′-(1,4-phenylene)bis(7,8-dihydro-4*H*-chromen-5(6*H*)-one) derivatives **133** were prepared from terephthalaldehyde **1**, dimedone **52** and malononitrile or ethyl cyanoacetate under MW irradiation (Scheme 43).[76]



1 **52** **133**

Scheme 43

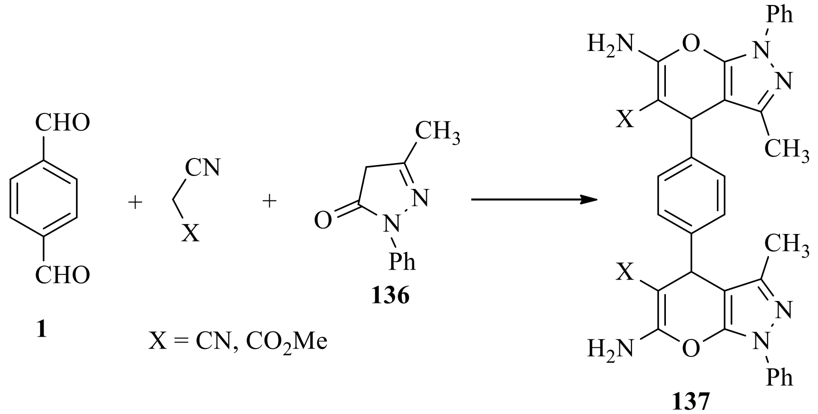
The multi-component approach to the synthesis of 4,4′-(1,4-phenylene)bis(7,7-dimethyl-3,4,7,8-tetrahydro-2*H*-chromene-2,5(6*H*)-dione) **135** is based on the reaction of terephthalaldehyde **1**, dimedone **52** and Meldrum's acid **134** under MW irradiation (Scheme 44).[76]



135

Scheme 44

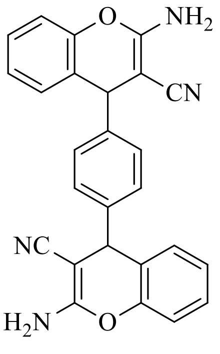
Reaction of terephthalaldehyde **1**, 3-methyl-2-pyrazolin-5-one **136** and malononitrile or methyl cyanoacetate under classical heating[77] or MW irradiation[76] gave the corresponding 4,4′-(1,4-phenylene)bis(1,4-dihydropyrano[2,3-*c*]pyrazole) **137** (Scheme 45).



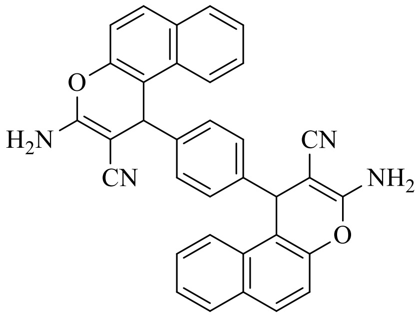
137

Scheme 45

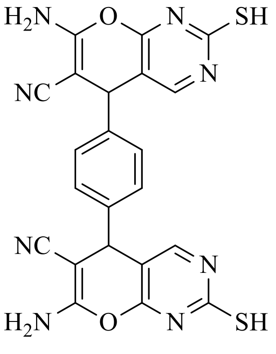
Terephthalaldehyde **1**, on treatment with malononitrile and some phenolic compounds afforded **138-140** (Figure 14).[77]



138



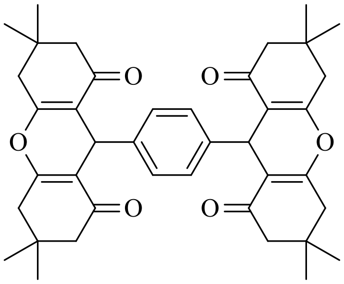
139



140

Figure 14

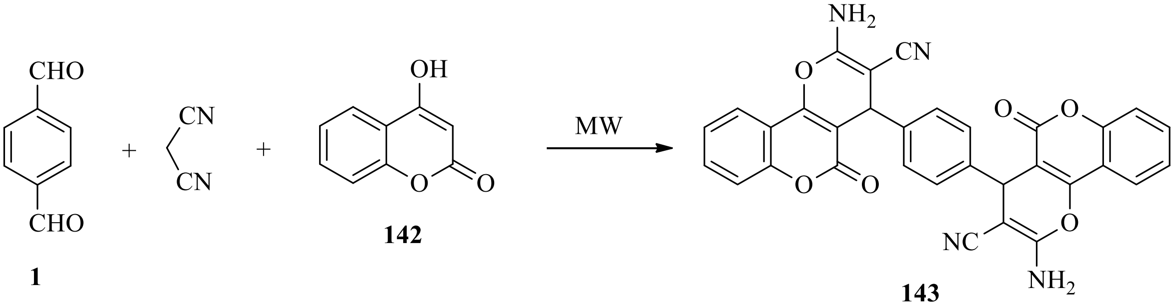
The 9,9′-(1,4-phenylene)bis(3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione) **141** was prepared by condensing terephthalaldehyde **1** with dimedone **52** under different conditions (Figure 15).[76,78,79]



141

Figure 15

The 4,4′-(1,4-phenylene)bis(4,5-dihydropyrano[3,2-*c*]chromene) **143** has been synthesized *via* a one-pot multi-component condensation of terephthalaldehyde **1** with malononitrile and 4-hydroxy-coumarin **142** (Scheme 46).[80]



1

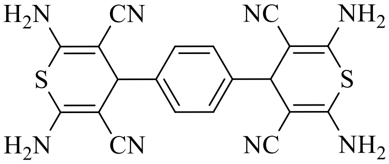
142

143

Scheme 46

6.2. 1,4-Phenylene- bis-thiopyrans

The 4,4′-(1,4-phenylene)bis(4*H*-thiopyran) **144** was synthesized by condensation of terephthalaldehyde **1**, malononitrile and cyanothioacetamide in a 1:2:2 molar ratio (Figure 16).[77]

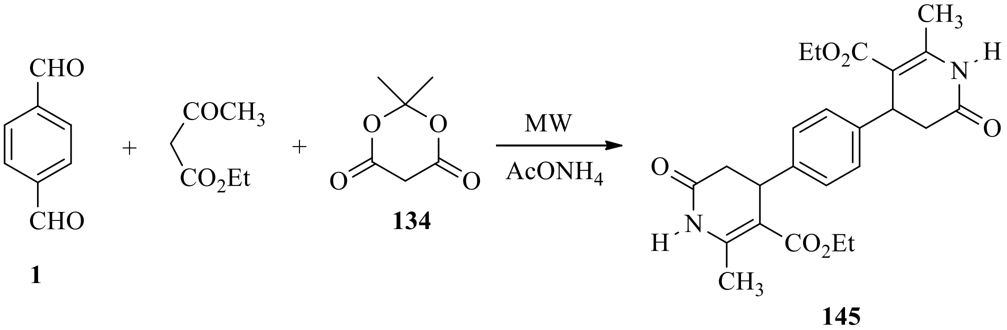


144

Figure 16

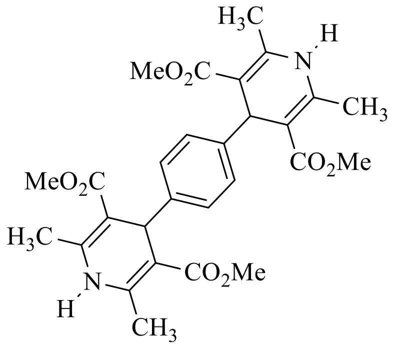
6.3. 1,4-Phenylene- bis-pyridines and their fused derivatives

The multi-component approach to the synthesis of diethyl 4,4′-(1,4-phenylene)bis(2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate) **145** is based on the reaction of terephthalaldehyde **1**, ethyl acetoacetate, Meldrum's acid **134** and ammonium acetate under MW irradiation (Scheme 47).[81]



Scheme 47

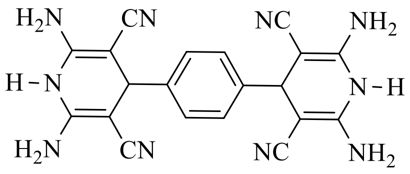
The reaction of terephthalaldehyde **1**, methyl acetoacetate, and ammonium acetate under MW irradiation in a 1:4:3 molar ratio gave 4,4′-(1,4-phenylene)bis(1,4-dihydropyridine) **146** (Figure 17).[81]



146

Figure 17

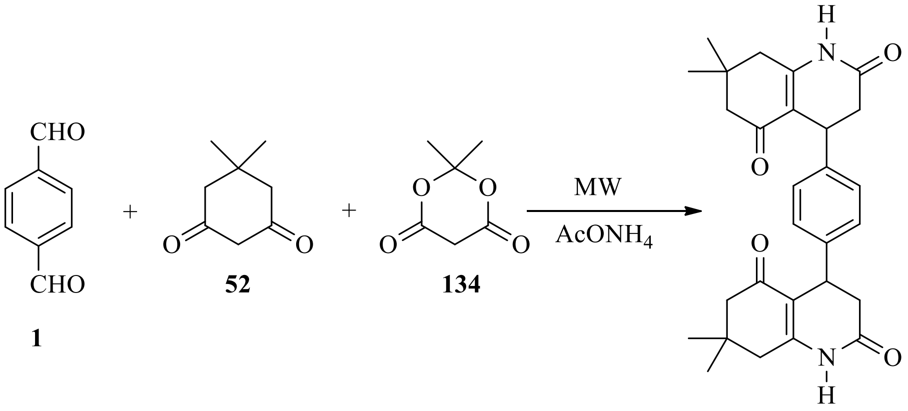
Refluxing an ethanolic solution of terephthalaldehyde **1**, malononitrile and cyanothioacetamide in 1:2:2 molar ratio afforded 4,4′-(1,4-phenylene)bis(2,6-diamino-1,4-dihydropyridine-3,5-dicarbonitrile) **147** (Figure 18).[77]



147

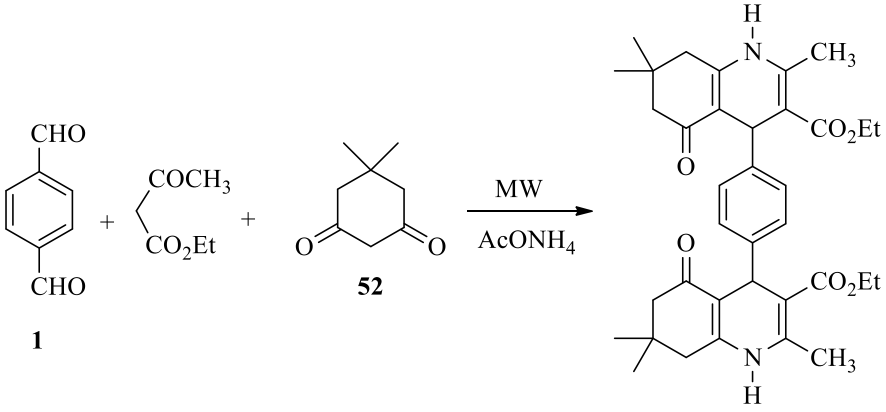
Figure 18

The multi-component approach to the synthesis of 4,4′-(1,4-phenylene)bis(3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione) **148** is based on the reaction of terephthalaldehyde **1**, dimedone **52**, Meldrum's acid **134** and ammonium acetate in a 1:2:2:3 molar ratio under MW irradiation (Scheme 48).[81]



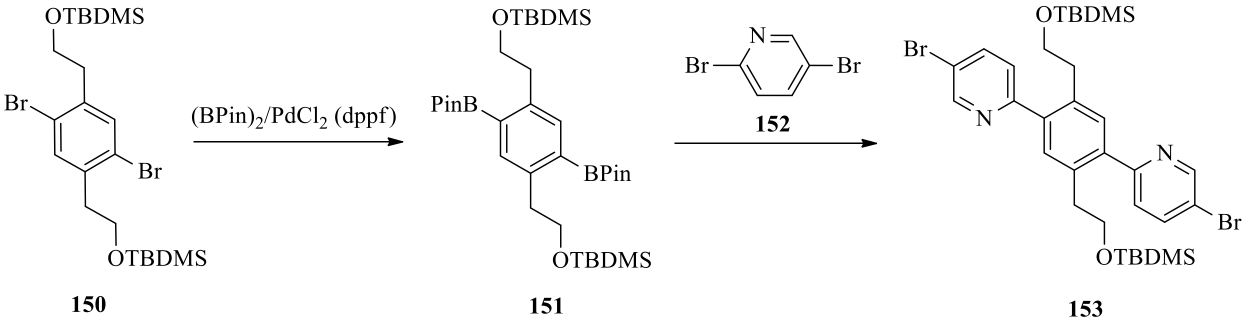
Scheme 48

The 4,4′-(1,4-phenylene)bis(1,4,5,6,7,8-hexahydroquinoline) **149** was prepared from terephthalaldehyde **1**, dimedone **52**, ethyl acetoacetate and ammonium acetate in a 1:2:2:3 molar ratio under MW irradiation (Scheme 49).[81]



Scheme 49

The boronation of 2,5-bis(2-(*tert*-butyldimethylsilyloxy)ethyl)-1,4-benzenedibromide **150** gives the corresponding diboronic acid bis(pinacol) ester **151**. Head-to-head 6,6′-(2,5-bis(2-(*tert*-butyldimethylsilyloxy)ethyl)-1,4-phenylene)bis(3-bromopyridine) **153** was synthesized by regioselective Suzuki coupling of **151** with 2,5-dibromopyridine **152** in 58% yield (Scheme 50).[82]



Scheme 50

The 1,4-bis(terpyridine)benzene **154**[83] and **155**[84] were synthesized by condensation of terephthalaldehyde **1** with a fourfold excess of 4- and/or 2-acetylpyridine in the presence of ammonium acetate in acetic acid (grinding method)[83] and/or under the action of a base in polyethylene glycol (PEG-300)[84] at 0 °C (Figure 19).

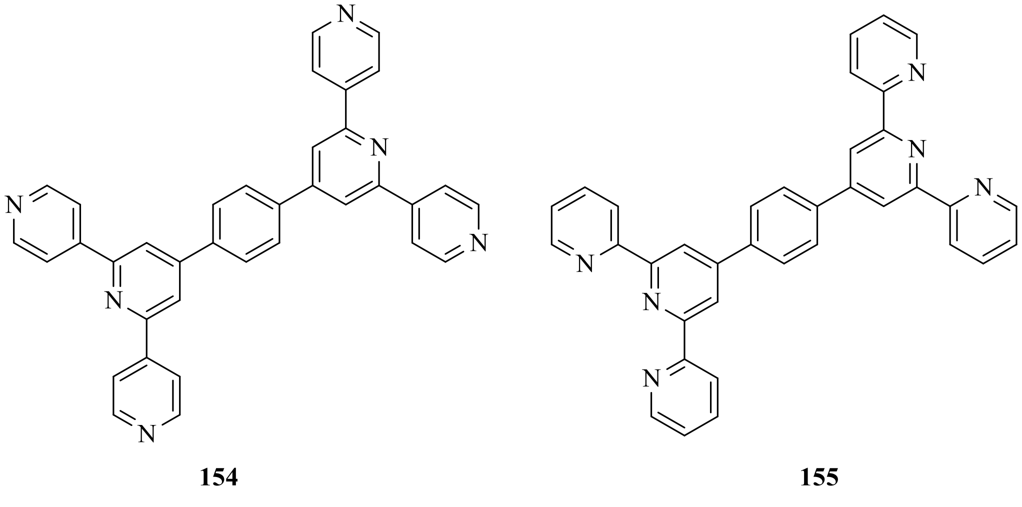
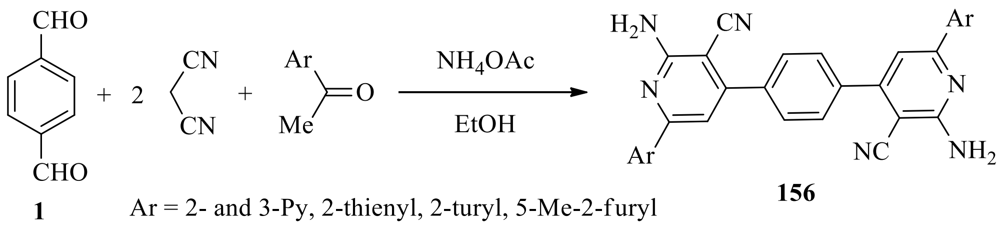


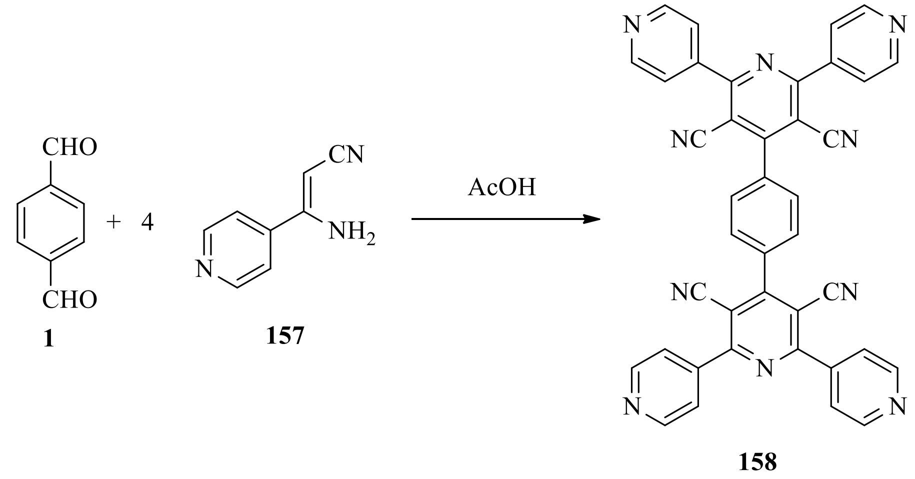
Figure 19

Shaker *et al.*[85] have been reported a synthetic route to 1,4-bis(4-pyridyl)benzenes **156** *via* the reaction of terephthalaldehyde) with two equivalents of malononitrile and acetylhetarenes in the presence of ammonium acetate (Scheme 51).



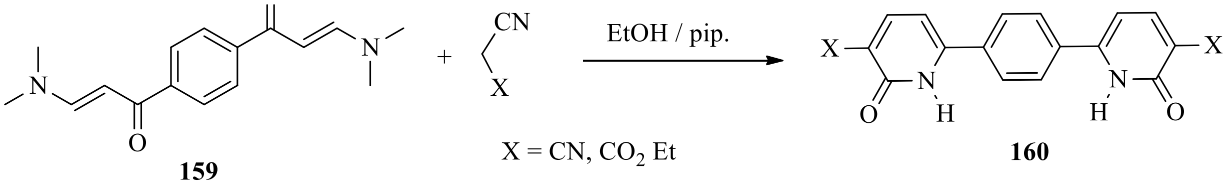
Scheme 51

The reaction of terephthalaldehyde **1** with β-amino-β-(pyrid-4-yl)acrylonitrile **157** in a 4:1 molar ratio carried out in AcOH afforded the desired 4,4′-(1,4-phenylene)bis(pyridine) **158** (Scheme 52).[86]



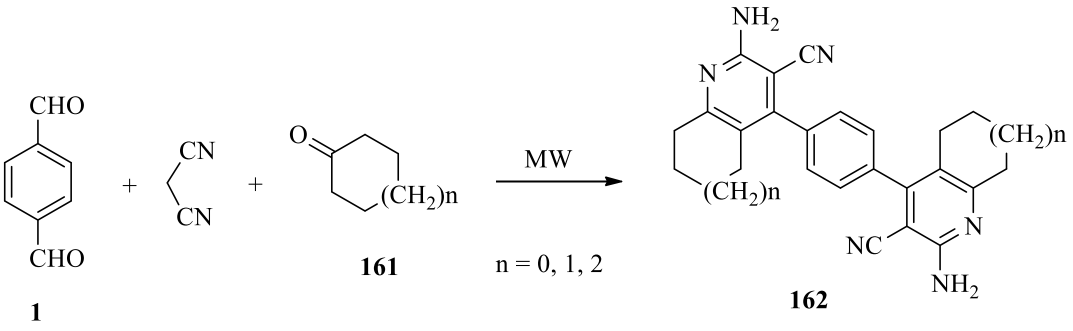
Scheme 52

The reaction of dienaminone **159** with malononitrile or ethyl cyanoacetate at ambient temperature in ethanolic solution and in the presence of piperidine afforded the corresponding 6,6′-(1,4-phenylene)bis(pyridin-2(1*H*)-one) derivatives **160** (Scheme 53).[87]



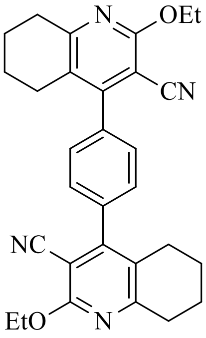
Scheme 53

Treatment of terephthalaldehyde **1** with malononitrile and cycloalkanones **161** in ethanol containing a catalytic amount of ammonium acetate afforded 4,4′-(1,4-phenylene)bis(5*H*-cycloalkan[*b*]pyridine) **162** (Scheme 54).[85]



Scheme 54

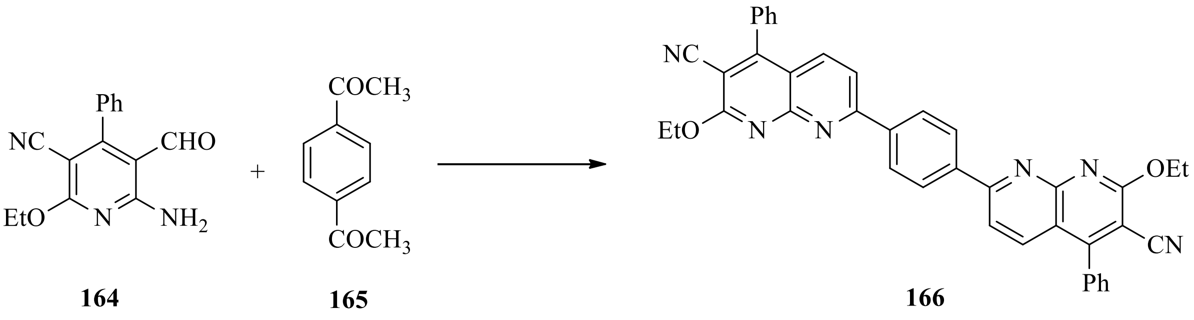
The ternary condensation of terephthalaldehyde **1**, malononitrile and cyclohexanone in refluxing alcoholic sodium ethoxide gave 4,4′-(1,4-phenylene)bis(5,6,7,8-tetrahydroquinoline) **163** (Figure 20).[85]



163

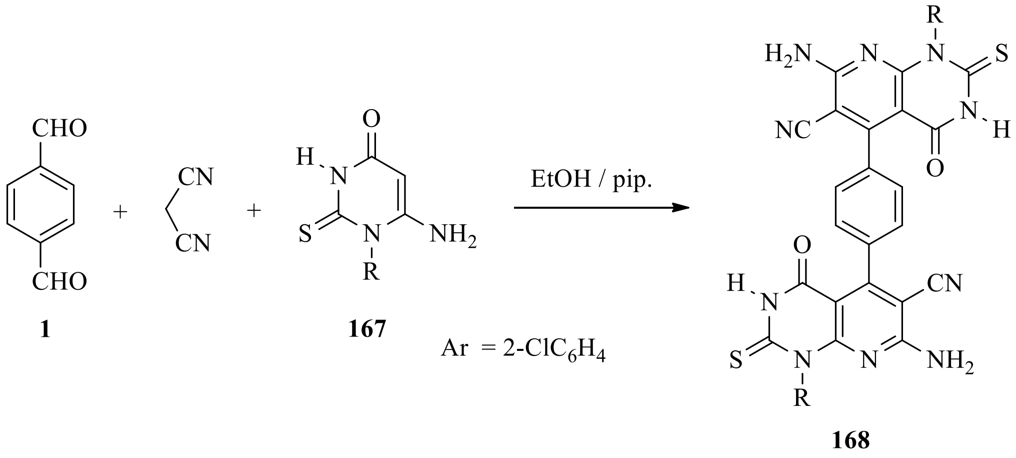
Figure 20

The aminoaldehyde **164** undergoes double Friedländer condensation with 1,4-diacetylbenzene **165** under basic conditions to provide 7,7′-(1,4-phenylene)bis(1,8-naphthyridine) **166** (Scheme 55).[88]



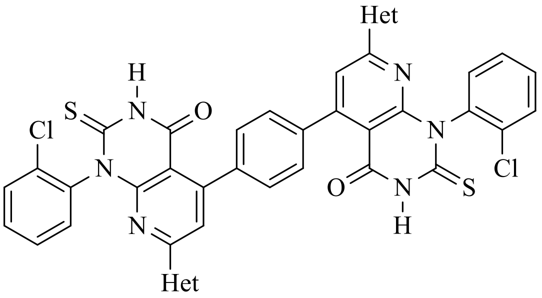
Scheme 55

The condensation of terephthalaldehyde **1**, with malononitrile and 6-amino-2-thiouracil **167** in ethanol containing in the presence of piperidine afforded the corresponding 5,5′-(1,4-phenylene)bis(1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine) **168** (Scheme 56).[89]



Scheme 56

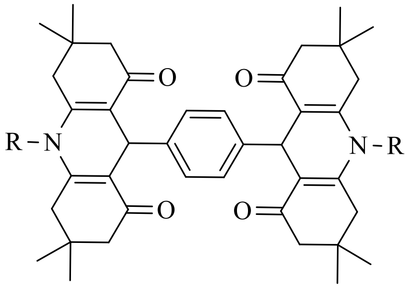
Similarly, 5,5′-(1,4-phenylene)bis(2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one) derivatives **169** were synthesized by treatment of 6-amino-2-thiouracil **167** (R=2-ClC$_6$H$_4$) with terephthalaldehyde **1** and acetylhetarenes (Figure 21).[89]



169, Het = 3-pyridyl, 2-thienyl, 5-methyl-2-furyl

Figure 21

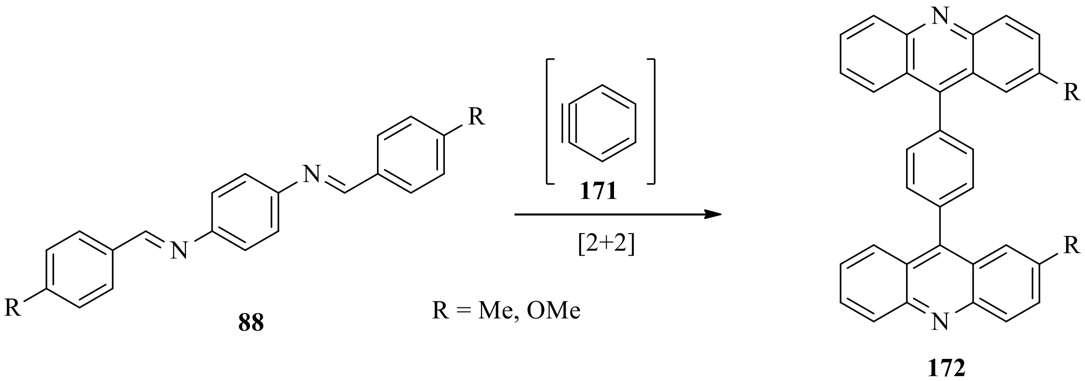
The 9,9′-(1,4-phenylene)bis(3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione) **170** (R=H) has been synthesized by condensation of terephthalaldehyde with dimedone in the presence of ammonium acetate under MW irradiation.[78,81] The *N*-hydroxyacridine **170**[78,90] (R=OH) has been synthesized by using hydroxylamine instead of ammonium acetate (Figure 22).



170 (R = H, OH)

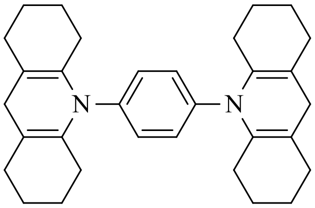
Figure 22

In 1999, it was reported that the reaction between benzyne **171** and diarylidenebenzene-1,4-diamine **88** led to 1,4-bis(acridin-9-yl)benzene **172** *via* [2+2] cycloadditions (Scheme 57).[91]



Scheme 57

The 1,4-bis(1,2,3,4,5,6,7,8-octahydroacridin-10(9*H*)-yl)benzene **173** was synthesized from methylene-2,2′-dicyclohexanone and 1,4-diaminobenzene **25** (Figure 23).[92]



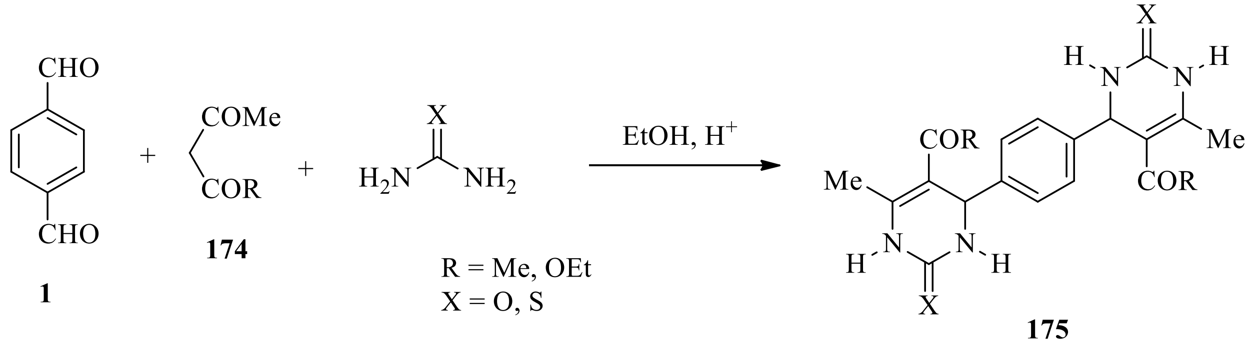
173

Figure 23

7. Six-membered Rings with Two Heteroatoms

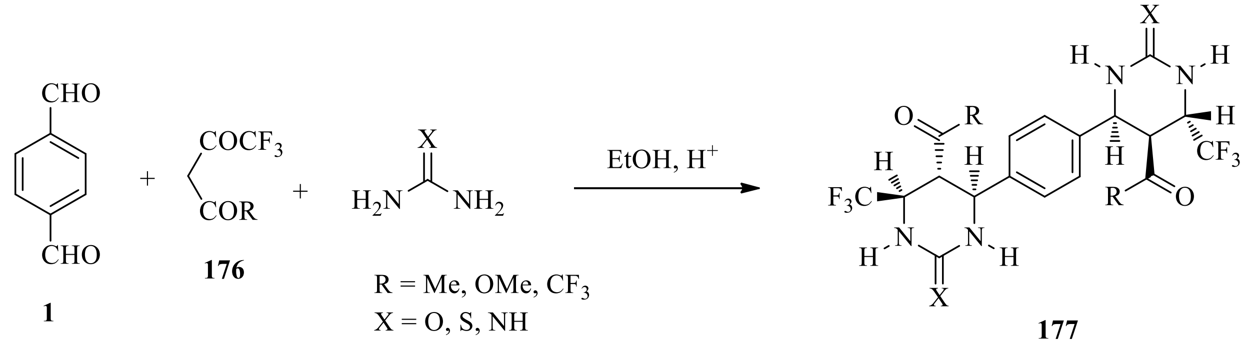
7.1. 1,4-Phenylene- bis-pyrimidines and their fused derivatives

The 4,4′-(1,4-phenylene)bis(3,4-dihydropyrimidine) **175** were prepared from the reaction of terephthalaldehyde **1** with 1,3-dicarbonyl **174** and urea or thiourea in acidic medium[81-85] or using silica-supported tin chloride and titanium tetrachloride as catalyst[93] (Scheme 58).



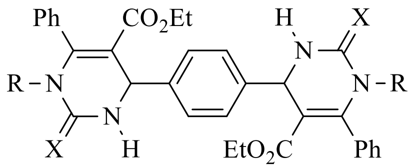
Scheme 58

The trifluoromethyl derivatives of 1,4-bis(tetrahydropyrimidinone-4-yl)benzenes **177** were synthesized *via* one-pot condensation of terephthalaldehyde **1** with (thio)urea or guanidine and fluorinated 1,3-dicarbonyl derivatives **176** at ambient temperature using catalytic quantities of chlorotrimethylsilane (TMSCl) (Scheme 59).[94]



Scheme 59

The ternary condensation of terephthalaldehyde **1**, ethyl benzoylacetate and urea or thiourea or methyl thiourea in a molar ratio 1:2:2, in ethanol containing catalytic amount of hydrochloric acid yielded the corresponding 4,4′-(1,4-phenylene)bis(1,2,3,4-tetrahydropyrimidine) **178** (Figure 24).[89]

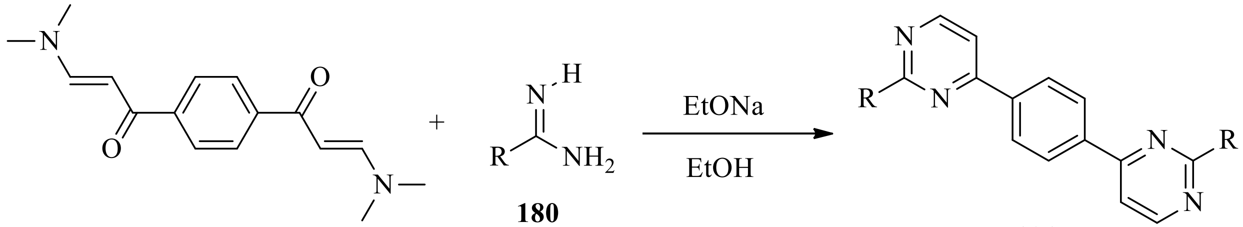


R = H, Me, X = O, S

178

Figure 24

Scheme 60 outlines the synthesis of 4,4′-(1,4-phenylene)bis(2-substituted-pyrimidine) derivatives **181** from the reaction of the 3-dimethylamino-1-[4-(3-dimethylaminoacryloyl)-phenyl]propenone **179** with amidine hydrochlorides **180** and sodium ethoxide.[87]

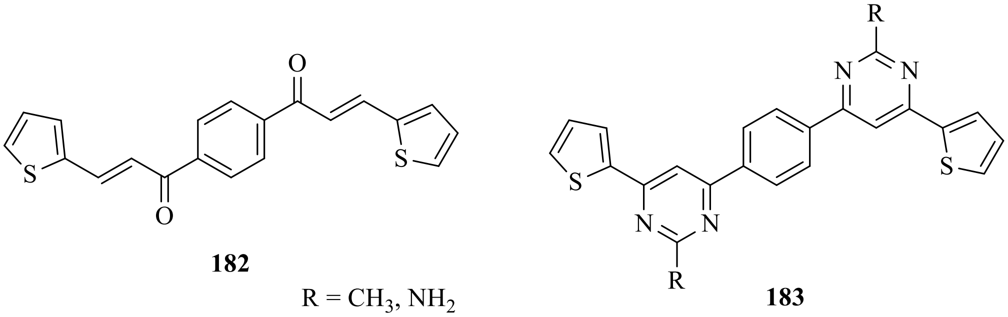


179 **180** **181**

R = CH_3, NH_2

Scheme 60

Also, the reaction of amidine hydrochlorides **180** with 3,3′-(1,4-phenylene)bis[1-(2-thienyl)-2-propen-1-one] **182** and sodium ethoxide carried out in ethanol resulted of 4,4′-(1,4-phenylene)bis(2-substituted-6-(2-thienyl)-pyrimidine) derivatives **183** (Figure 25).[87]



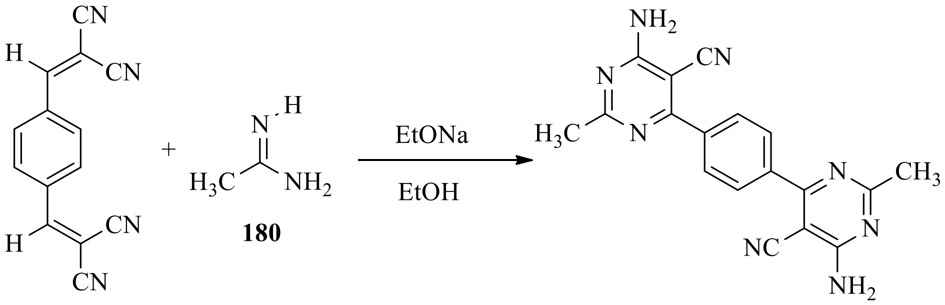
182

R = CH_3, NH_2

183

Figure 25

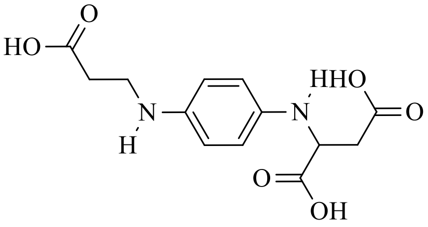
Also, the reaction of amidines **180** ($R=CH_3$) with 2,2′-(1,4-phenylene)bis(1,1-dicyanoethylene) **184** in ethanol containing a catalytic amount of piperidine gave the corresponding 4,4′-(1,4-phenylene)bis(6-amino-5-cyano-2-substituted-pyrimidine) **185** (Scheme 61).[87]



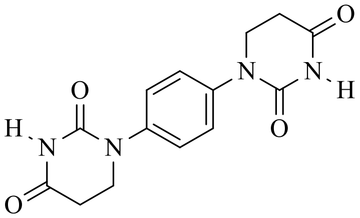
184 **180** **185**

Scheme 61

Heating of the *N*-[4-(2-Carboxyethyl)amino]phenyl-aspartic acid **186** with urea in acetic acid and subsequent addition of HCl gives the 1,1′-(1,4-phenylene)bis(dihydropyrimidine-2,4(1*H*,3*H*)-dione) **187** (Figure 26).[47]



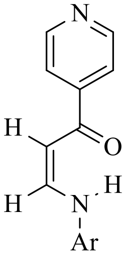
186



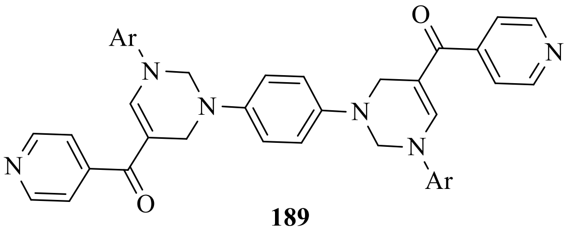
187

Figure 26

Enaminones **188** have also been reacted with 1,4-diaminobenzene **24** and formaldehyde to give 3,3′-(1,4-phenylene)bis(1-alkyl-1,2,3,4-tetrahydropyrimidine) **189** (Figure 27).[95]



188

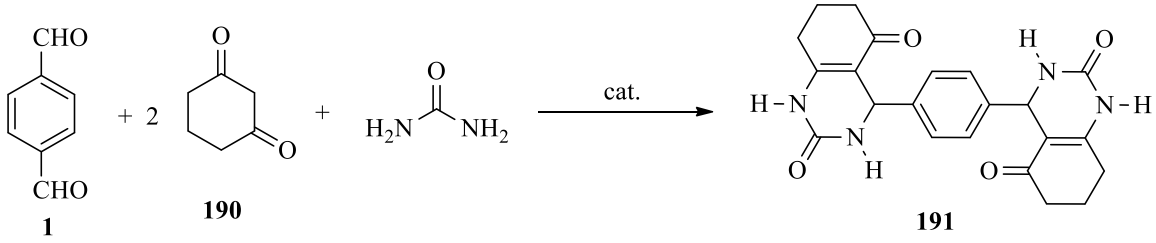


189

Ar = C_6H_5, $C_6H_5CH_2$

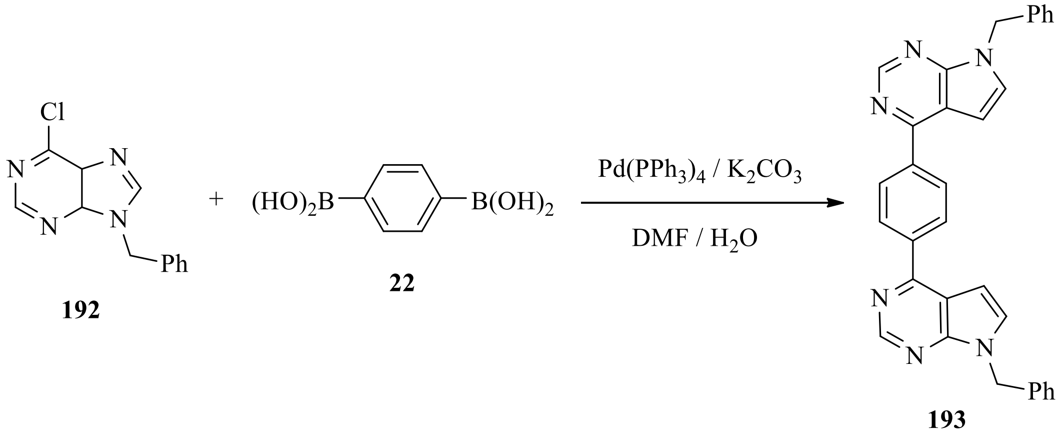
Figure 27

The reaction of 1,3-cyclohexadione **190** with terephthalaldehyde **1**, and urea using silica-supported tin chloride and titanium tetrachloride as catalyst afforded 4,4′-(1,4-phenylene)bis(3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione) **191** (Scheme 62).[93]



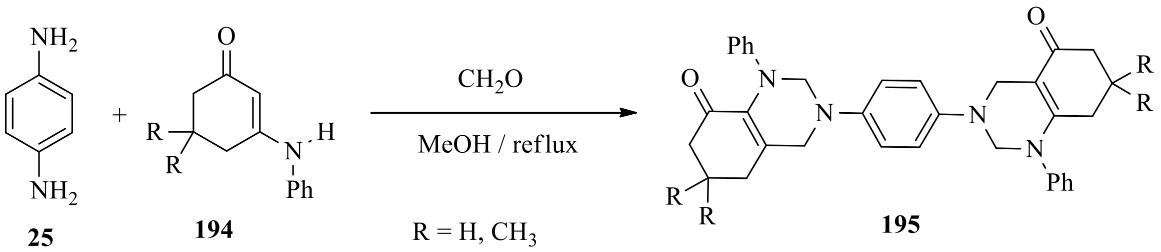
Scheme 62

The reaction of benzene-1,4-diboronic acid **22** with 6-chloropurine **192** in the presence of Pd(PPh_3)$_4$ and K_2CO_3 in DME/H_2O proceeded very smoothly giving the 1,4-bis(7-benzyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)benzene **193** (Scheme 63).[96]



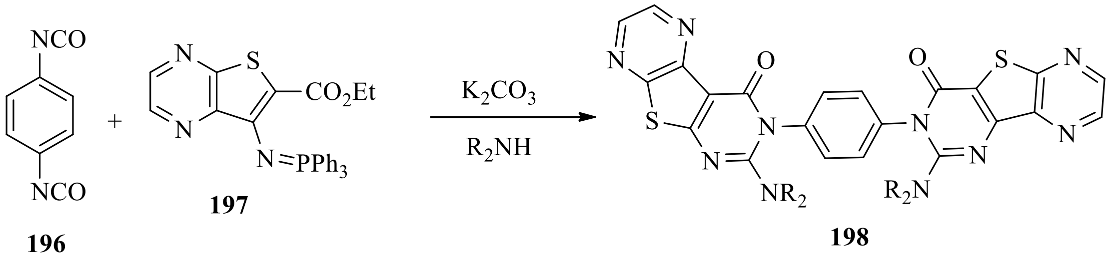
Scheme 63

When a mixture of enaminones **194**, 1,4-diaminobenzene **25** and formaldehyde (2:1:4) in methanol was subjected to MWI yielded 3,3′-(1,4-phenylene)bis(1,2,3,4,7,8-hexahydro-quinazolin-5(6*H*)-one) **195** (Scheme 64).[97]



Scheme 64

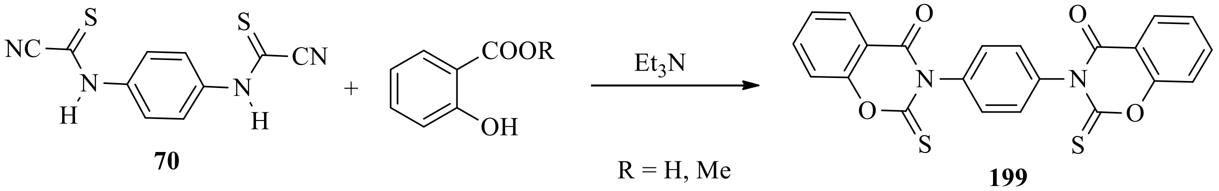
The bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)benzene derivatives **198** were prepared in very good yields (85–95%) by the reaction of 1,4-phenylene diisocyanate **196** with 2 equiv of iminophosphorane **197**, followed by heterocyclization on addition of secondary amines in the presence of a catalytic amount of K_2CO_3 (Scheme 65).[98,99]



Scheme 65

7.2. 1,4-Phenylene- bis-oxazines

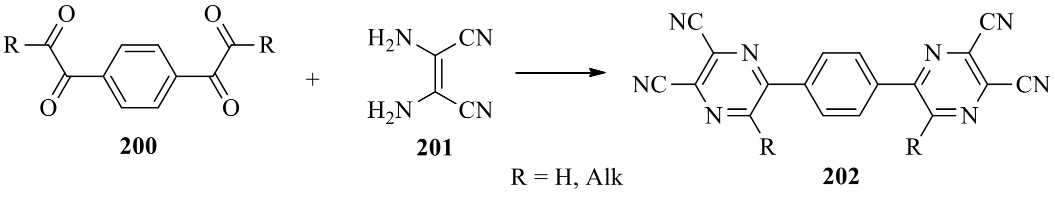
Refluxing 1,4-phenylenedicarbamothioyl cyanide **70** with two moles of salicylic acid or methyl salicylate in DMF containing a catalytic amount of triethylamine, 3,3′-(1,4-phenylene)bis(2-thioxo-2,3-dihydro-benzo[*e*][1,3]oxazine-4-one) **199** was obtained (Scheme 66).[49]



Scheme 66

7.3. 1,4-Phenylene- bis-pyrazines

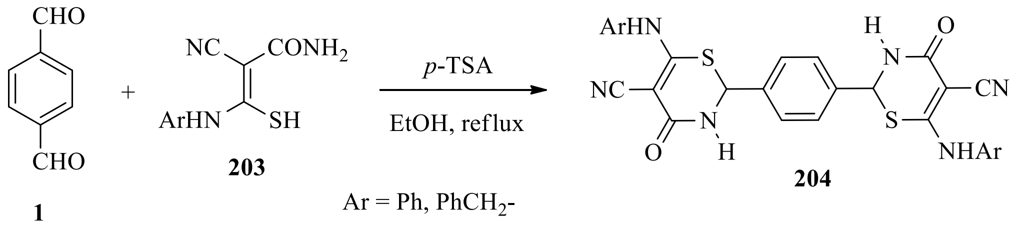
The 6,6′-(1,4-phenylene)bis(5-substituted-pyrazine) **202** are prepared by cyclocondensation of bis(glyoxalyl)benzenes **200** with diaminomaleontrile **201** (Scheme 67).[100]



Scheme 67

7.4. 1,4-Phenylene- bis-1,3-thiazines and their fused derivatives

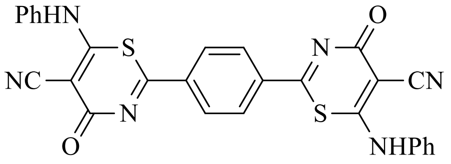
The 2,2′-(1,4-phenylene)bis(3,4-dihydro-2*H*-1,3-thiazine) **204** have been synthesized by the cyclocondensation of terephthalaldehyde **1** with 2 equivalents of **203** in the presence of catalytic amounts of *p*-toluenesulfonic acid in boiling ethanol. High yields of the products **204** also resulted when the reaction was performed in boiling glacial acetic acid (Scheme 68).[101]



Ar = Ph, $PhCH_2$-

Scheme 68

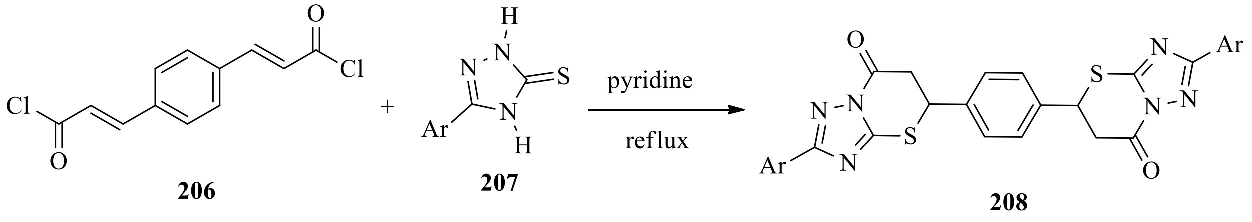
Oxidation of **204** in the presence of nitrobenzene gave 2,2′-(1,4-phenylene)bis(4-oxo-6-(phenylamino)-4*H*-1,3-thiazine-5-carbonitrile) **205** (Figure 28).[101]



205

Figure 28

The condensation of 5-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **207** with benzene-1,4-diylbisacryloyl chloride **206** gave 5,5′-(1,4-phenylene)bis(5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7(6*H*)-one) **208** (Scheme 69).[102]

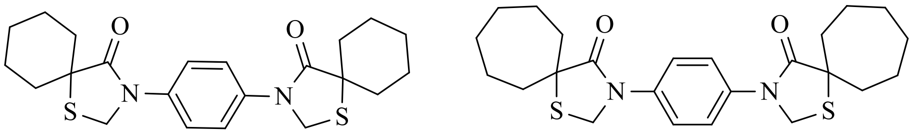


Ar = C_6H_5, 4-H_3CO-C_6H_4, 4-F-C_6H_4, 1-naphthyl

Scheme 69

8. 1,4-Phenylene- Bis-spiroheterocycles

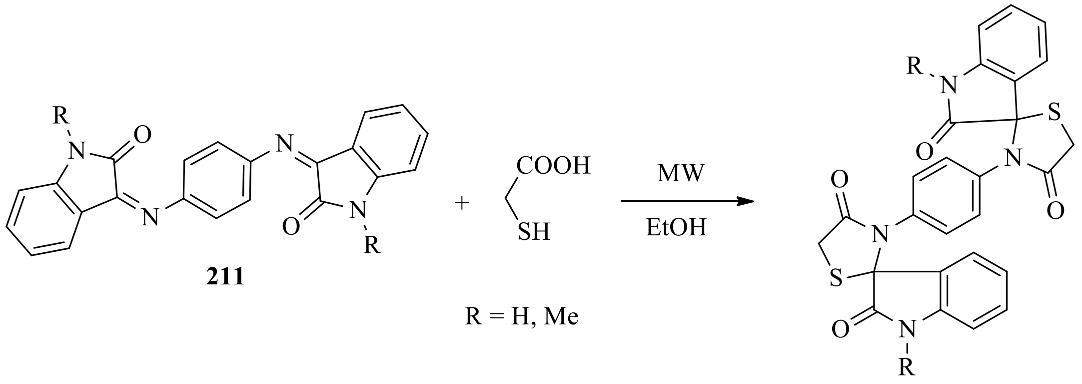
The condensation of 1,4-diaminobenzene **24** with cyclohexanone or cycloheptanone and thioglycollic acid in molar ratio 1:2:2 using dry toluene as a solvent led to 4,4′-(1,4-phenylene)bis[1-thia-4-azaspiro[4.5]decan-3-one] **209** and/or 4,4′-(1,4-phenylene)bis[1-thia-4-azaspiro[4.6]undecan-3-one] **210**, respectively (Figure 29).[59]



209 **210**

Figure 29

Cyclocondensation of mercaptoacetic acid with diimines **211** (prepared from two equivalents of isatin or *N*-methylisatin with one equivalent 1,4-diaminobenzene **25**), was carried out under MWI to yield 3,3′-(1,4-phenylene)bis(spiro[indoline-3,2′-thiazolidinone]) **212** (Scheme 70).[103]



211

R = H, Me

212

Scheme 70

9. Conclusions

Literature data published in the last 40 years have been summarized to help the reader to find information appropriate for the high synthetic potential of 1,4-phenylenebridged bis-heterocyclic compounds. Syntheses of many biologically active heterocyclic compounds belonging to this structural class have been reported.

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