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Synthesis and applications of bi- and bis-triazole systems

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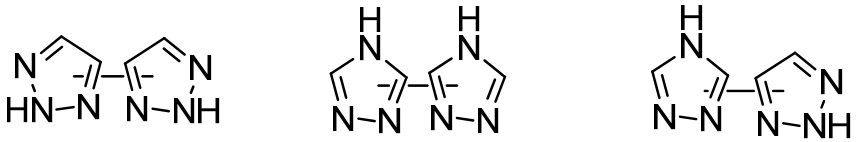
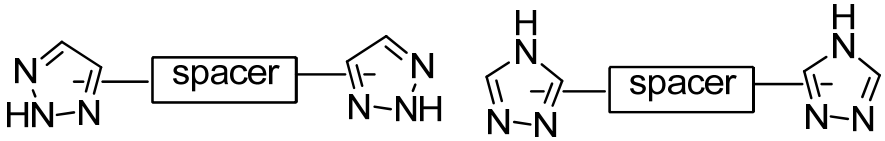
Abstract

The current review article represents the synthetic routes to all possible classes of bi- and bis-triazole systems along with their research and biological applications. The classification is based on the connection between the two triazole rings.

bi-triazoles:



bis-triazoles:



Keywords: Bi-triazoles, bis-triazoles, synthesis, applications, heterocycles

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1. Introduction

1,2,3- and 1,2,4-Triazoles are important heterocyclic scaffolds of interesting chemical and biological applications. Several therapeutically active compounds containing 1,2,3-triazole moiety have been reported as antimicrobials, anti-HIV agents and kinase inhibitors.[1-4] Some 1,2,4-triazole derivatives have antibacterial[5-7] and antifungal[8,9] properties. Triazole units were incorporated in the core structure of some commercial drugs in the market. For example, Cefatrizine is using as antibiotic, Tazobactum as anti-bacterial agent[10,11] and Suvorexant for the treatment of insomnia, was approved by the US-FDA[12] in 2014 (Figure 1). 1,2,3- and 1,2,4-triazoles were also employed as efficient corrosion inhibitors in an acid aqueous medium.[13,14] Considerable interest is also focused on the synthesis of bi-heterocycles, due to their wide range of applications. For example, 3,3`-bi-1,2,4-triazoles have proved to possess bactericidal, fungicidal, and anthelmintic activities.[15] Some bis-triazole-based commercial drugs are also available in the market, for example Fluconazole, Itraconazole and Posaconazole were used as antifungal drugs and Vorozole as antineoplastic drug (Figure 1).

Fluconazole was the first-line bis-triazole-antifungal drug recommended by World Health Organization (WHO).[16-19] Nonsymmetric 1,3`-Bitriazole derivatives were reported to have antiviral activity against tobacco mosaic virus and exhibited powerful antiproliferative effects on different cancer cell lines.[20] The application of bitriazoles as chelating N-heterocyclic carbene ligands for ruthenium(II), palladium(II), and rhodium and their applications in catalytic organic synthesis have also been reported.[21,22] The coordination chemistry of the π-electron excessive bi-1,2,4-triazole ligands was also intensively explored for synthesis of coordination polymers with unique properties.[23-27] In the view of the above results and in connection with our previous review articles about biologically active heterocyclic systems,[28-33] we prepared this review to disclose the intensive survey on the synthetic routes to symmetrical and nonsymmetrical bi- and bis- triazole systems (Figure 2) and their applications reported in the literature until the end of 2017.

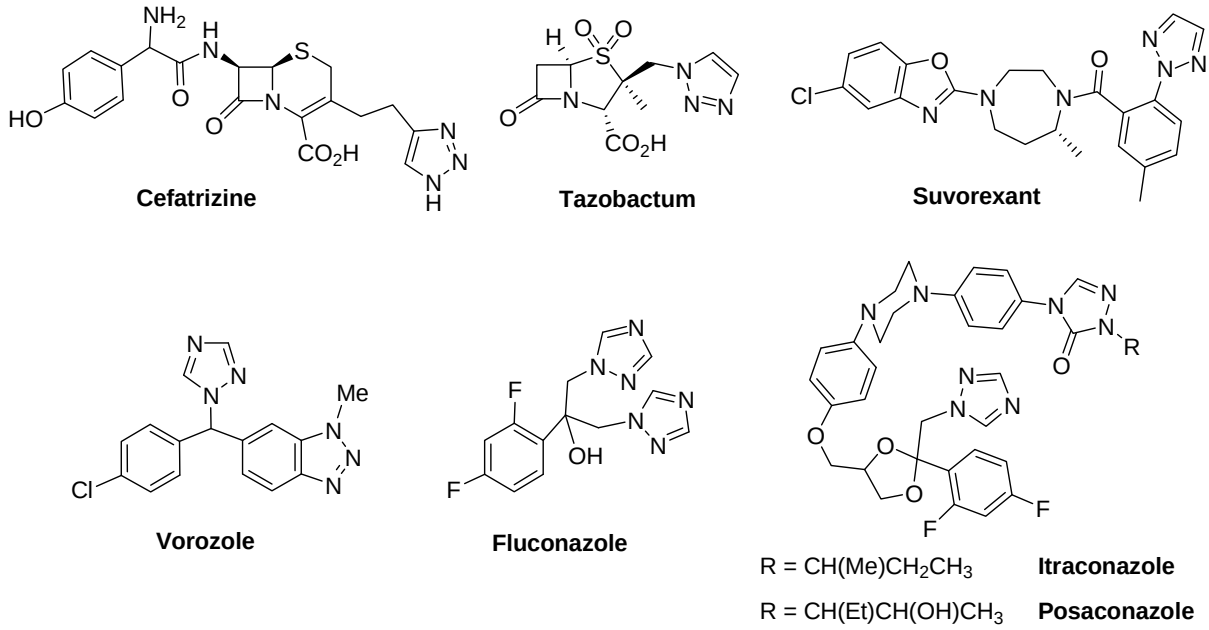


Figure 1. Triazole-based commercial drugs.

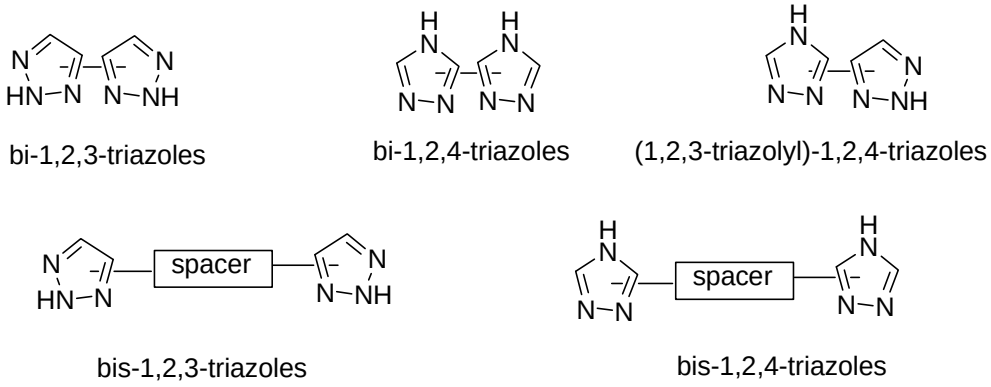
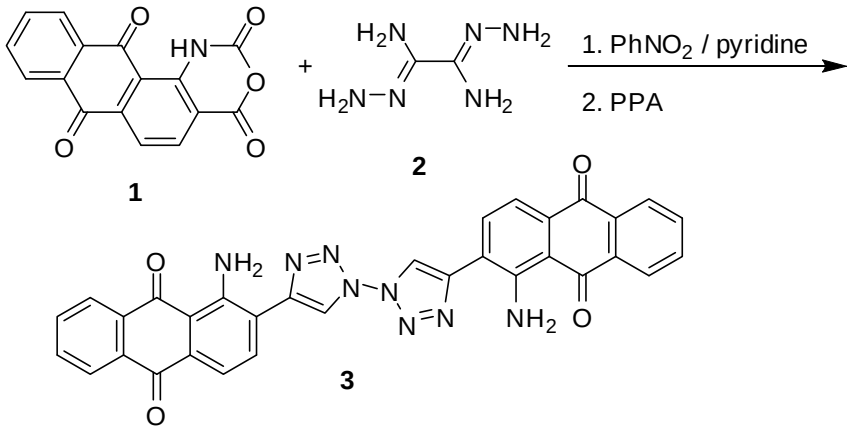


Figure 2. Structures of bi- and bis- triazole systems.

2. Synthesis and Application of Bitriazole Systems

2.1. 1,1`-Bi-triazoles

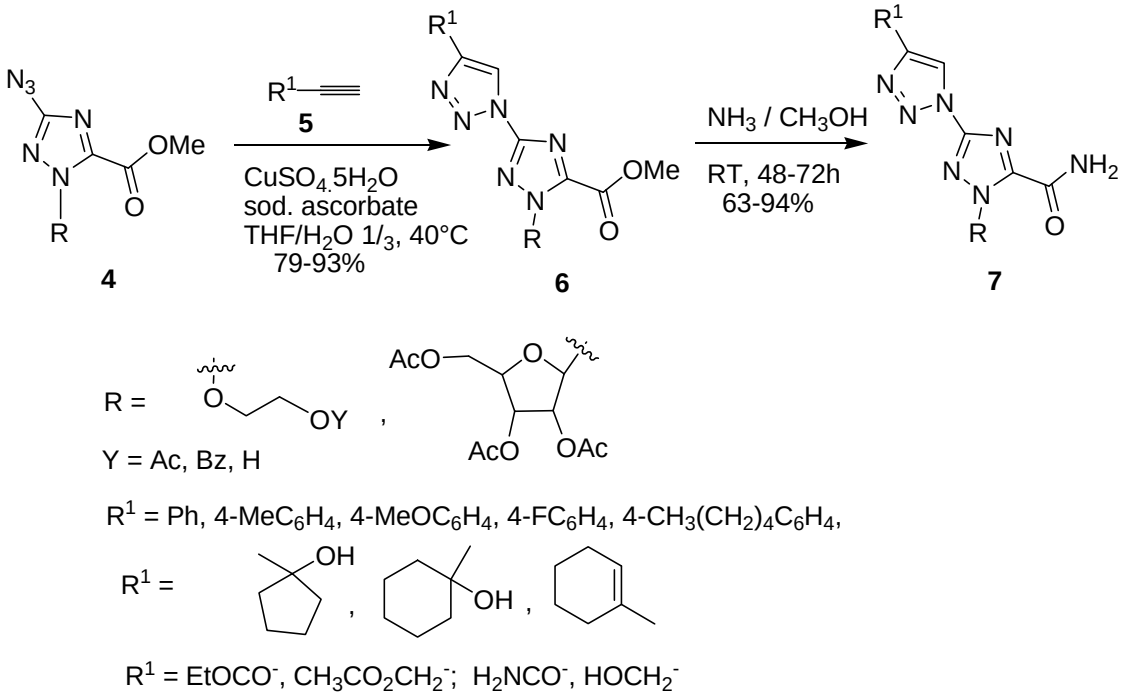
Treatment of 3,4-phthaloylisatoic anhydride **1** with oxamide-dihydrazone **2** in nitrobenzene and pyridine at 150 °C, followed by treatment with polyphosphoric acid at 130 °C, then 175°C afforded the 5,5'-bis(1-amino-2-anthraquinonyl)-1,1`-bi-1,2,3-triazole derivative **3** (Scheme 1).[34]



Scheme 1

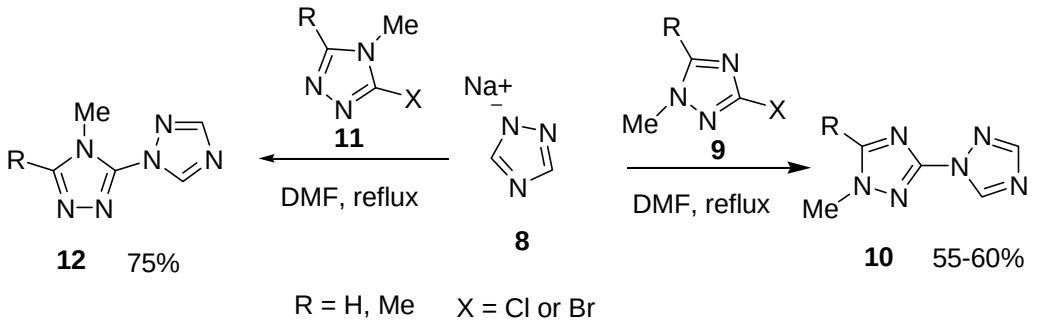
2.2. 1,3`-Bi-triazoles

The 1,3`-bitriazole compounds **6** were synthesized in good to excellent yields *via* the copper(I)-catalyzed Huisgen reaction of the azidotriazole **4** with alkynes **5**. Treatment of **6** with $NH_3$/MeOH at room temperature resulted in the formation of the 1,3`-bitriazole derivatives **7** (Scheme 2).[35,36] The bitriazole compounds **6** showed high antiviral activity against tobacco mosaic virus.



Scheme 2

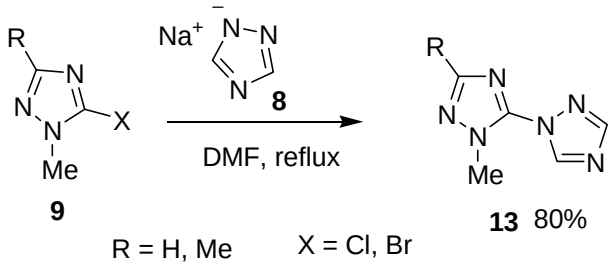
The 1,3`-bi-triazoles **10** and **12** were prepared by a nucleophilic substitution reaction of the sodium salt of 1,2,4-triazole **8** with the halotriazole derivatives **9** and **11**, respectively (Scheme 3).[37]



Scheme 3

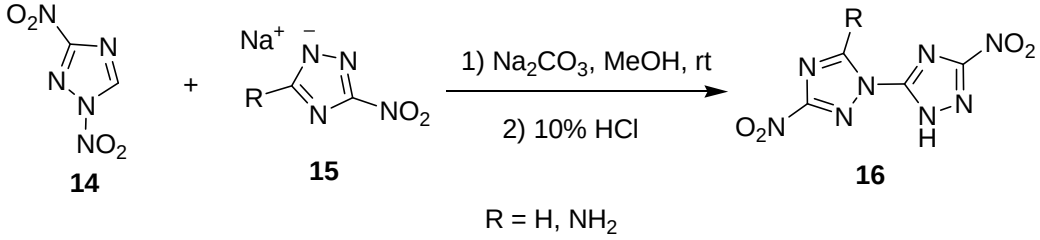
2.3. 1,5`-Bi-triazoles

Treatment the sodium salt of 1,2,4-triazole **8** with the halotriazole derivatives **9** yielded the 1,5`-bitriazole **13** in high yield (Scheme 4).[37]



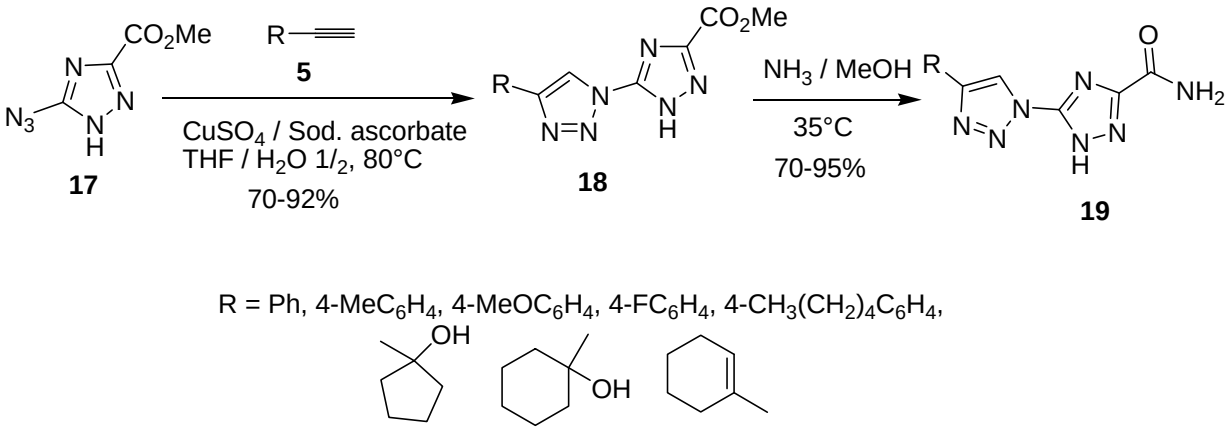
Scheme 4

The nucleophilic aromatic substitution reaction of 1,3-dinitro-1,2,4-triazole **14** with sodium salt of 3-nitro-1,2,4-triazoles **15** in methanol and sodium carbonate at room temperature furnished the 1,5`-bi-1,2,4-triazole derivatives **16** (Scheme 5).[38] The bi-triazoles **16** exhibited various energetic properties with high thermal stability and low sensitivity.



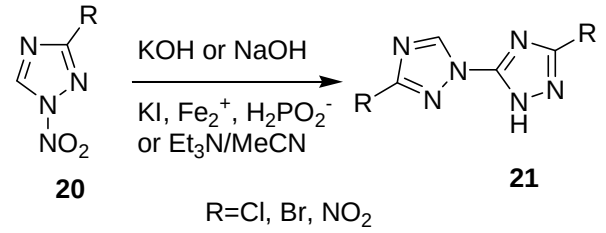
Scheme 5

The synthesis of the 1,5`-bitriazole derivatives **18** was conducted under mild conditions, where the azido-triazole derivative **17** was readily engaged in a copper(I)-catalyzed Huisgen reaction with various terminal acetylenes **5**. Treatment the bi-triazolyl compounds **18** with NH_3/MeOH led to the formation of the corresponding amides **19** (Scheme 6).[39,40] The 1,5`-bitriazole derivatives **18** and **19** constituted interesting leads for the development of new antiviral candidates where they were more potent antiviral than the commercial products, DHT and ribavirin.



Scheme 6

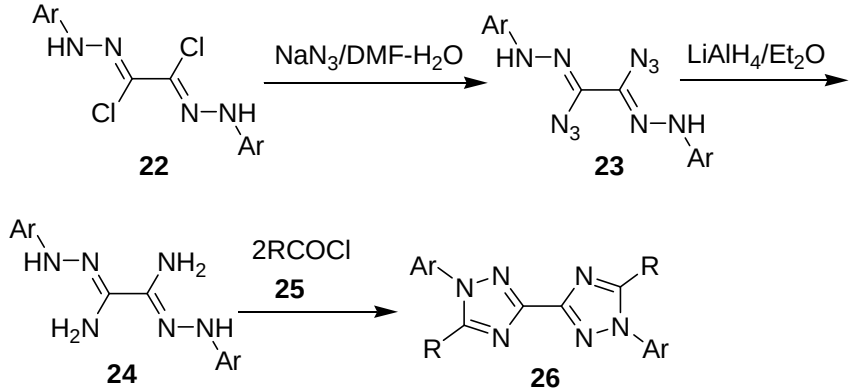
1,5`-Bi-1,2,4-triazoles **21** were obtained in 20–70% yields by the reaction of 1-nitro-1,2,4-triazoles **20** with aqueous alkali hydroxides and reducing agents (KI, Fe^{2+}, $H_2PO_2^-$) or with triethylamine in acetonitrile (Scheme 7).[41]



Scheme 7

2.4. 3,3`-Bi-triazoles

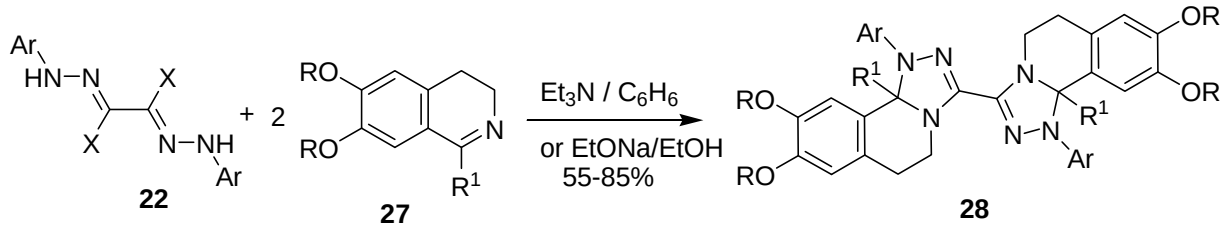
Reaction of the oxalodihydrazonyl dihalide derivatives **22** with sodium azide in aqueous dimethylformamide at room temperature afforded the corresponding *N*,*N*`-diaryloxalodihydrazonyl diazides **23** in 80-85% yields. Reduction of **23** with lithium aluminum hydride in ether yielded the diamidrazone derivatives **24** in 65-72% yields. Reactions of **24** with acyl chlorides **25** in refluxing benzene gave the 3,3`-bi-1,2,4-triazole derivatives **26** in 43-60% yields (Scheme 8).[42]



Ar = Ph, 4-ClC_6H_4, R = Ph, 4-XC_6H_4, 3-$O_2NC_6H_4$, $ClCH_2$

Scheme 8

3,3`-Bi-1,2,4-triazolo[3,4-*a*]isoquinolines **28** were prepared in good yields *via* 1,3-dipolar cycloaddition reaction of dihydrazonoyl dihalides **22** with 3,4-dihydroisoquinolines **27** (Scheme 9).[43]

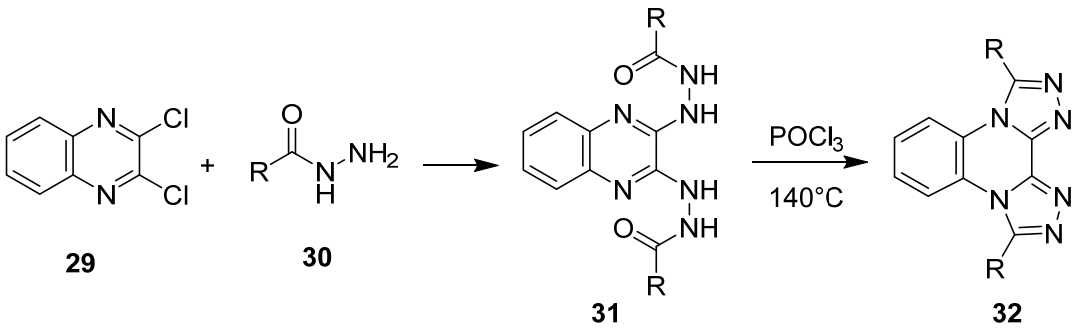


22 **27** **28**

R=Me, Et; R^1= H, Me; Ar= Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-NOC_6H_4, 2,4-$Cl_2C_6H_3$; X = Br, Cl

Scheme 9

The bi-1,2,4-triazolo[a,c]quinoxaline derivatives **32** were prepared *via* reaction of 2,3-dichloroquinoxaline **29** with the acid hydrazide derivatives **30**, followed by thermal cyclization *via* refluxing the resulting quinoxaline derivatives **31** with phosphorus oxychloride in an oil bath at 140 °C (Scheme 10).[44]

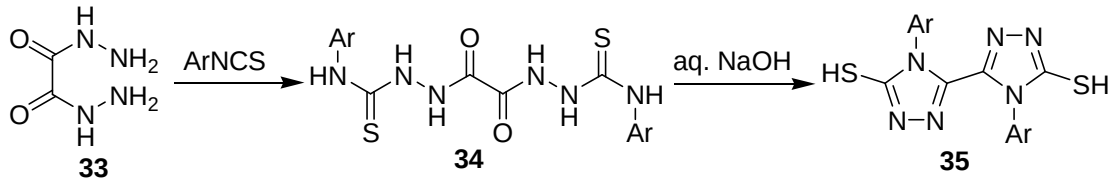


29 **30** **31** **32**

R = Me, Ph, 2-ClC_6H_4, 2-OHC_6H_4, 4-$NH_2C_6H_4$, 2-OH-4-$SO_3HC_6H_3$

Scheme 10

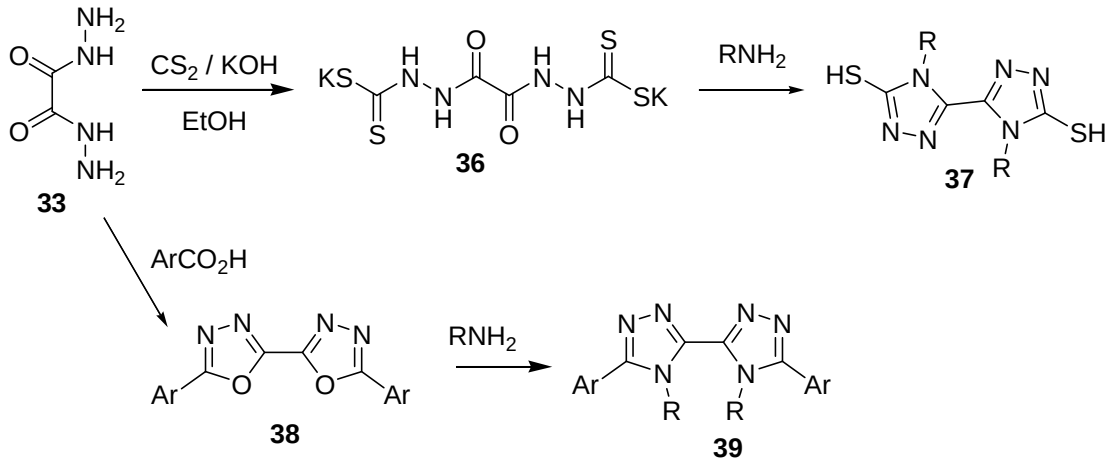
Reaction of oxalic acid dihydrazide **33** with isothiocyanates yielded the respective thiosemicarbazide derivatives **34**. Cyclization of **34** in alkaline medium afforded the corresponding 4,4'-substituted-5,5'-mercapto-3,3`-bi-1,2,4-triazole **35** (Scheme 11).[45]



33 **34** **35**

Scheme 11

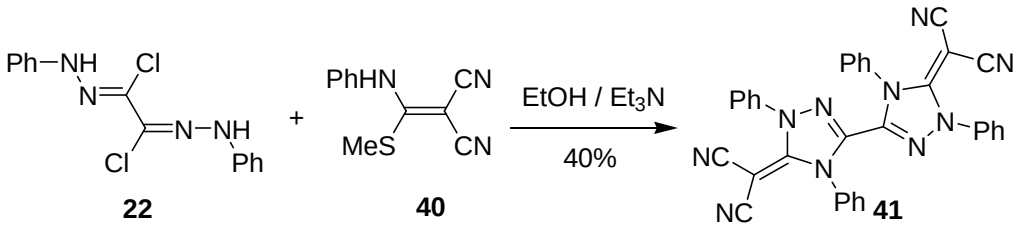
Reaction of oxalo-bis-hydrazide **33** with carbon disulfide followed with hydrazines afforded the 3,3`-bi-1,2,4-triazoles **37**. Also reaction of the oxalo-bishydrazide **33** with carboxylic acids gave the bioxadiazoles **38** which on treatment with hydrazines or amines yielded the 3,3`-bi-1,2,4-triazole derivatives **39** (Scheme 12).[15]



Ar = 2-ClC_6H_4, 4-ClC_6H_4; R = NH_2, NHPh

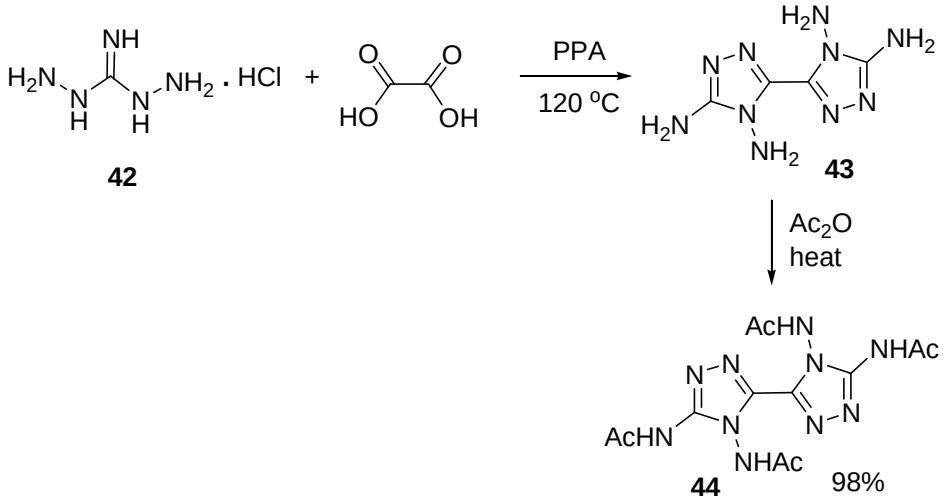
Scheme 12

The 3,3`-bi-1,2,4-triazole derivative **41** was prepared in moderate yield by reaction of *N*,*N*`-diphenyloxalohydrazonoyl dichloride **22** with 2-(methylthio(phenylamino)methylene)-malononitrile **40** in refluxing ethanol and triethylamine (Scheme 13).[46]



Scheme 13

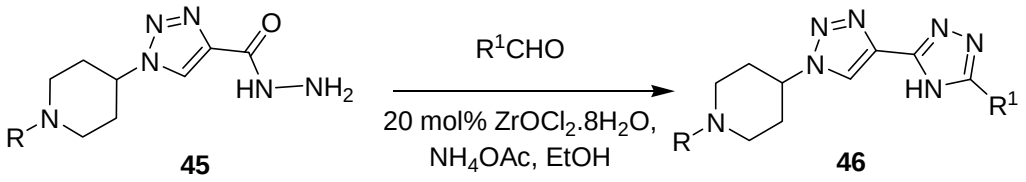
4,4`,5,5`-Tetraamino-3,3`-bi-1,2,4-triazole **43** was synthesized from heating 1,3-diaminoguanidine monohydrochloride **42** with oxalic acid in the presence of polyphosphoric acid (PPA). Heating of **43** in the presence of acetic anhydride, yielded the corresponding tetracetamido-3,3`-bi-1,2,4-triazole derivative **44** in 98% (Scheme 14).[47-49]



Scheme 14

2.5. 3,4`-Bi-triazoles

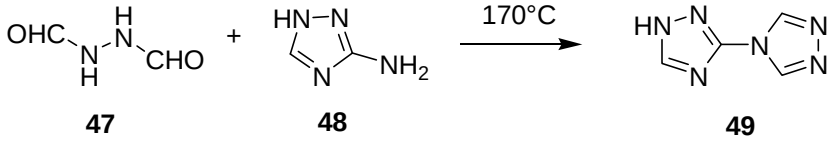
Heating of the 1,2,3-triazolylhydrazides **45** with ammonium acetate and aromatic aldehydes in ethanol catalyzed by 20 mol% $ZrOCl_2.8H_2O$, afforded the corresponding 3,4`-bitriazole derivatives **46** in 80-85% yields (Scheme 15).[50]



R =Boc, SO_2Me, $COCH_3$; R^1= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$

Scheme 15

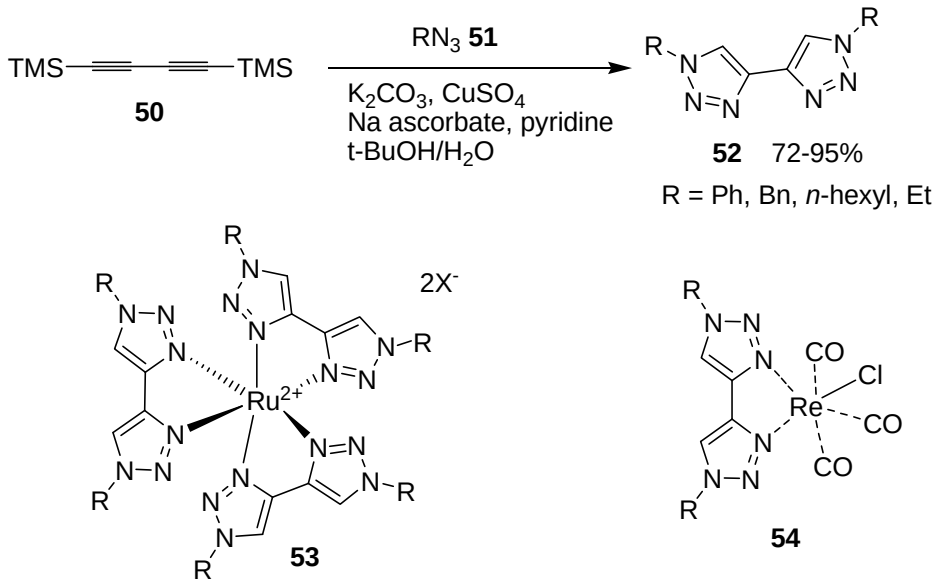
Heating diformylhydrazine **47** and 3-amino-1*H*-1,2,4-triazole **48** in a Teflon-lined stainless steel autoclave in a furnace at 170°C for 3 days yielded the 3,4`-bitriazole derivative **49** in 80% yield (Scheme 16).[51]



Scheme 16

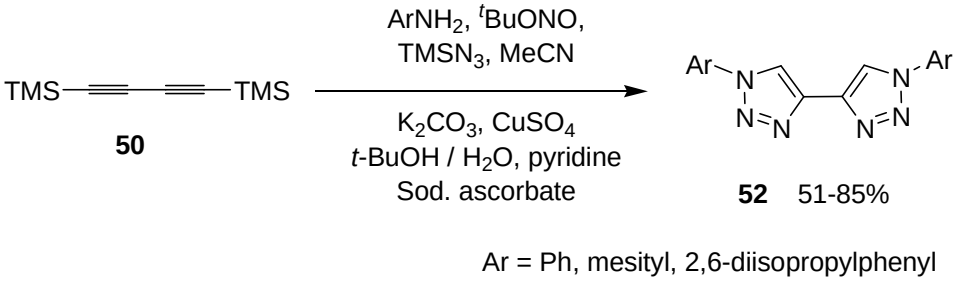
2.6. 4,4`-Bi-triazoles

The 4,4`-bi(1,2,3-triazole) derivatives **52** were prepared in high yields directly from 1,4-bis(trimethylsilyl)butadiyne **50** by reaction with two equivalents of the azides **51** in H_2O/*t*-BuOH in the presence of K_2CO_3 and a catalytic amount of $CuSO_4$. The reaction proceeded *via* tandem deprotection/click transformations and the presence of K_2CO_3 allowed the *in situ* removal of the TMS group of the alkyne reactants (Scheme 17). The 4,4`-bi(1,2,3-triazole) derivatives **52** were reported as bidentate chelators by forming stable Ru(II) complexes **53** which are coordinatively symmetrical, largely optically transparent and nonfluorescent. Compound **52** (R = Et) formed Re(I) complex **54** by its reaction with Rhenium(I) pentacarbonyl chloride $Re(CO)_5Cl$, which was useful for homogeneous- and electro-catalysis fields (Scheme 17).[52-56]



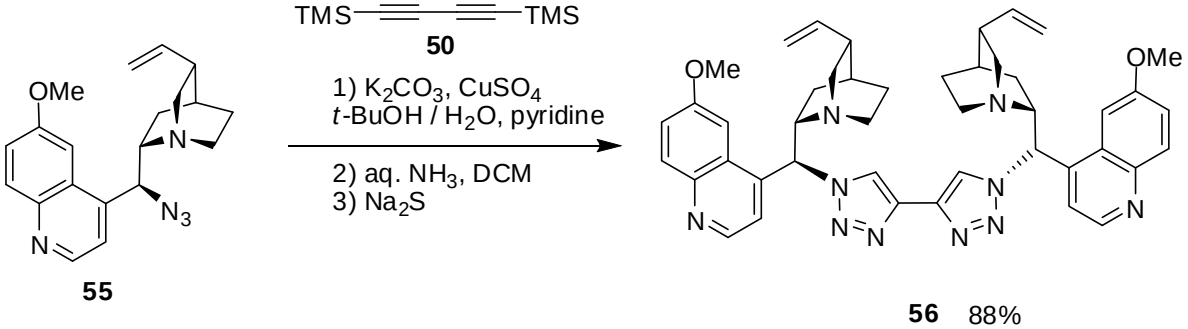
Scheme 17

An alternative synthesis of 1,1`-diphenyl-4,4`-bi(1,2,3-triazole) **52** (R = Ph) was reported in two steps; firstly reaction of anilines with tert-butyl nitrite then trimethylsilyl azide to obtain aryl azide. Afterward, 1,4-bis(trimethylsilyl)buta-1,3-diyne **50**, pyridine, potassium carbonate, $CuSO_4.5H_2O$ and sodium ascorbate in H_2O were added to give **55** in 51-85% yield (Scheme 18).[57]



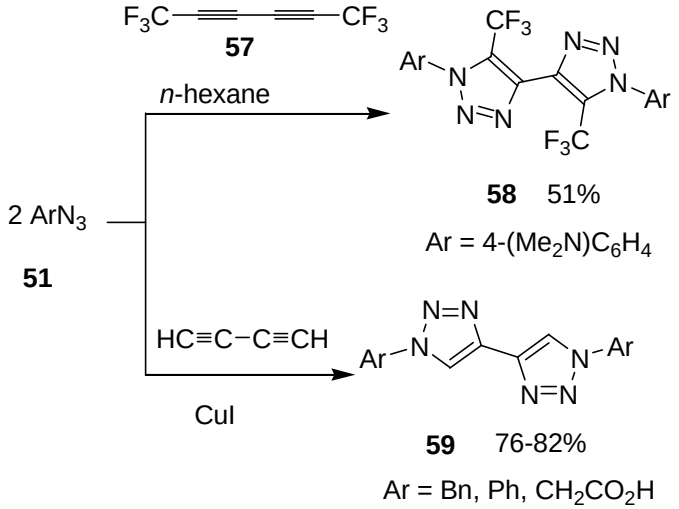
Scheme 18

Using the *click* copper-catalyzed azide alkyne cycloaddition (CuAAC) condition, the reaction of 1,4-bis(trimethylsilyl)butadiyne **50** with two equivalents of epi-azido quinine **55** led to the formation of the 4,4`-bi(1,2,3-triazole) derivative **56** in excellent yield (Scheme 19). The bitriazole **56** was applied as ligand in several copper-catalyzed asymmetric Michael-type addition reactions. [58]



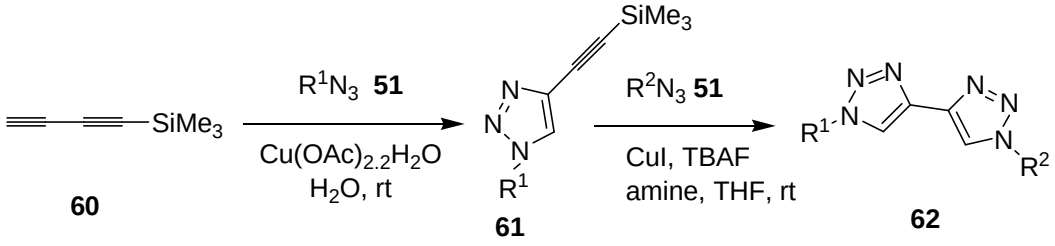
Scheme 19

Dipolar cycloaddition of perfluorohexa-2,4-diyne **57** with azides **51** in hexane afforded the 4,4`-bi-1,2,3-bitriazole derivatives **58** in good yields. In addition, the 4,4'-bi-1*H*-1,2,3-triazole derivatives **59** were synthesized by the CuI-catalyzed click reaction between buta-1,3-diyne and the aryl azides **51** (Scheme 20).[59,60]



Scheme 20

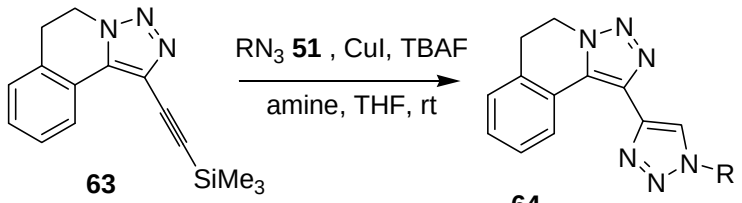
Fiandanese *et al.* reported the synthesis of the unsymmetrically substituted 4,4`-bi-1,2,3-triazole derivatives **62** from the reaction of 1-trimethylsilyl-1,3-butadiyne **60** with the azide derivatives **51**. Reaction of the azides **51** with compound **60** in the presence of $Cu(OAc)_2$, as a catalyst, in water provided 51–92% yields of the corresponding 1,4-triazole adducts **61**. Treatment of compounds **61** with the azides **51** in THF, at room temperature employing CuI catalyst and TBAF, in the presence of 1,1,4,7,7-pentamethyl-diethylenetriamine, led to the formation of the 4,4`-bitriazole derivatives **62** in 52-86% yields (Scheme 21).[61]



R^1 = $PhCH_2$; R^2 = $Ph(CH_2)_2$, $Ph(CH_2)_3$, $CH_3(CH_2)_7$, $CH_3(CH_2)_9$
R^1 = $CH_3(CH_2)_7$, R^2 = $PhCH_2$, $Ph(CH_2)_3$, $CH_3(CH_2)_9$, 4-$MeOC_6H_4$

Scheme 21

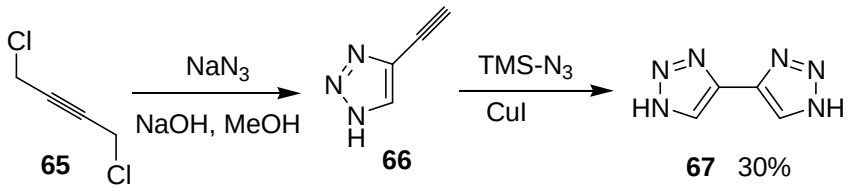
The 4,4`-bi-1,2,3-triazole derivatives **64** were obtained smoothly and in high yields by cycloaddition reactions of compound **63** with alkyl azides **51** (Scheme 22).[62]



R = $CH_3(CH_2)_7$, $CH_3(CH_2)_9$, $Ph(CH_2)_2$, 2-$BrC_6H_4(CH_2)_2$, 2-$IC_6H_4(CH_2)_2$, $Ph(CH_2)_3$

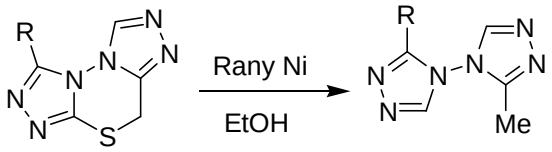
Scheme 22

4,4`-Bi-1,2,3-triazole **67** was synthesized in two steps from 1,4-dichloro-2-butyne **65** with sodium azide to give 4-ethynyl-1*H*-1,2,3-triazole **66** as an intermediate *via* an azabutatriene type rearrangement. Compound **67** was obtained from **66** *via* "click chemistry" with trimethylsilyl azide (Scheme 23).[63] The 4,4`-1*H*-1*H*-bi-1,2,3-triazole **67** was reported as capable of mimicking the hydrogen bonding of water in the solid state and was able to conduct protons in the presence of poly(ethylene oxides) under anhydrous conditions. The bitriazole **67** was found to have sufficient thermal and electrochemical stability for fuel cell applications. [63]



Scheme 23

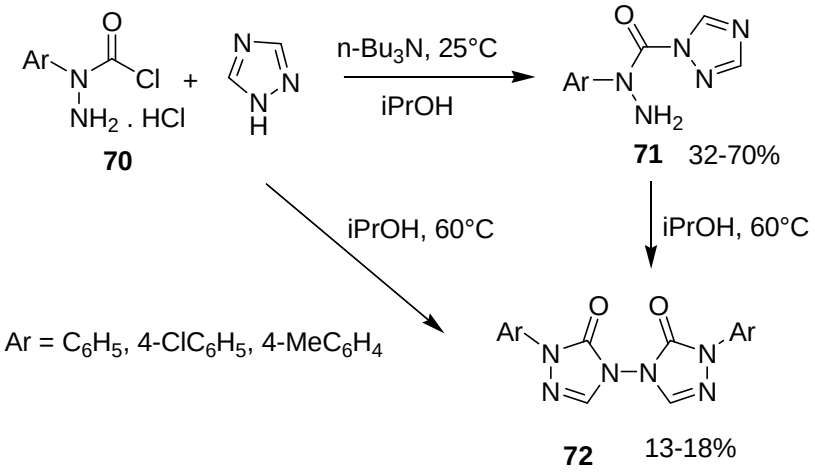
4,4`-Bi-1,2,4-triazole derivatives **69** were prepared by Raney nickel catalyzed desulfurization reaction of the bis-*s*-triazolothiadiazines **68** (Scheme 24).[37]



R= H, Me

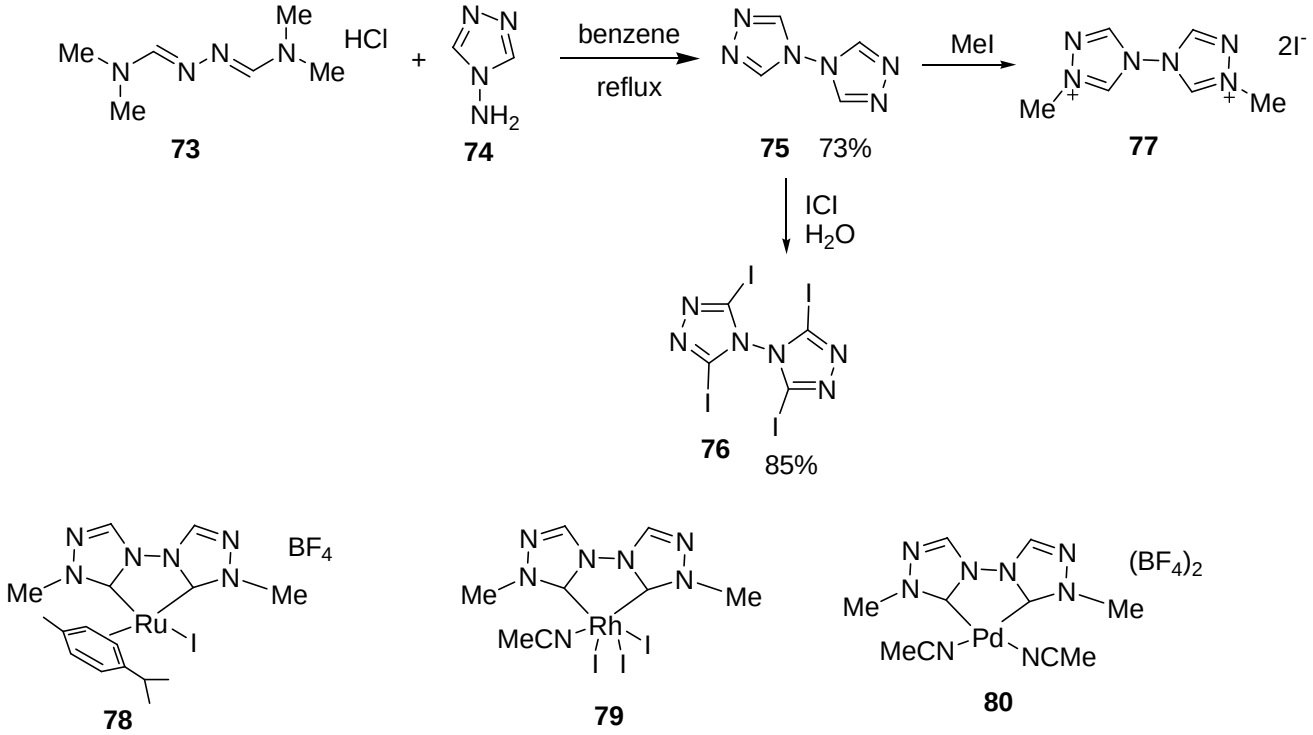
Scheme 24

α-1,2,4-Triazolylcarbonyl arylhydrazines **71** were synthesized *via* nucleophilic substitution reaction of the corresponding α-(chloroformyl)arylhydrazine hydrochlorides **70** with 1*H*-1,2,4-triazole. Cycloaddition of **71** with 1,2,4-triazole at 60 °C and in the absence of base gave the 2,2'-diaryl-4,4`-bi-1,2,4-triazole derivatives **72** in low yields (13-18%) (Scheme 25) .[64]



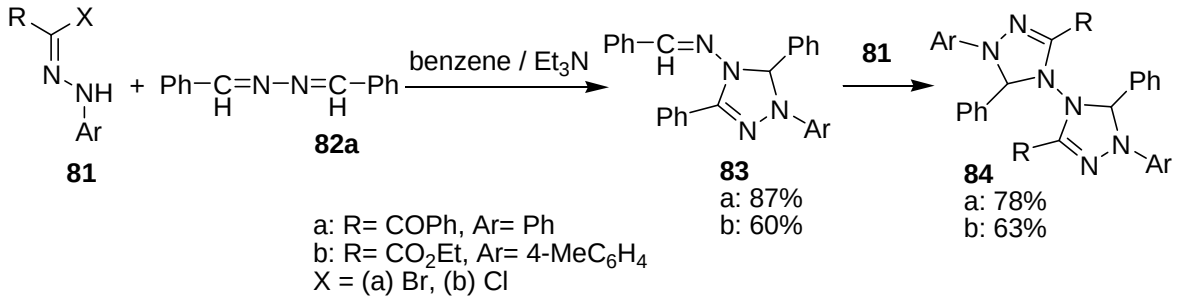
Scheme 25

Heating of *N*,*N*-dimethylformamide azine dihydrochloride **73** with 4-amino-1,2,4-triazole **74** in benzene gave 4,4`-bi-1,2,4-triazole **75** in significant yield (73%) *via* direct transamination. Treatment of **75** with iodine monochloride in water at r.t., resulted in the formation of tetraiodo-4,4`-bi-1,2,4-triazole **76** in 85% yield (Scheme 26).[65-67] *N*-Quaternization of the bi-1,2,4-triazole **75** with methyl iodide gave the corresponding iodide salt **77** in high yield.[68] The application of the 1,1`-dimethyl-4,4`-bi-1,2,4-triazolium bitriazolium diiodide as chelating *N*-heterocyclic carbene ligand for ruthenium(II), palladium(II), and rhodium(II) to form the corresponding complexes **78-80** was reported.[21]



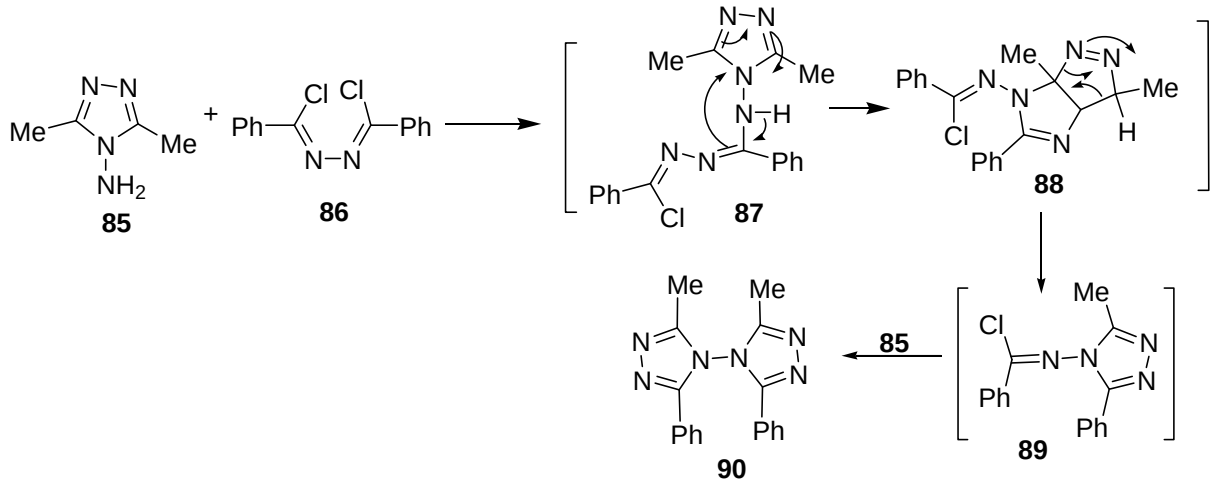
Scheme 26

When an equimolar mixture of appropriate hydrazonoyl halide **81** and 1,4-diphenyl-2,3-diaza-l,3-butadiene **82a** was refluxed in dry benzene in the presence of triethylamine, it afforded the cycloadduct 4-(phenylmethylene)amino-1,2,4-triazole derivatives **83**. Treatment of the cycloadducts **83** with the hydrazonoyl halides **81** afforded the corresponding 5,5`-diphenyl-1,1',3,3'-tetrasubstituted 4,4`-bi-1*H*-1,2,4-triazole derivatives **84** in good yields (Scheme 27).[69]



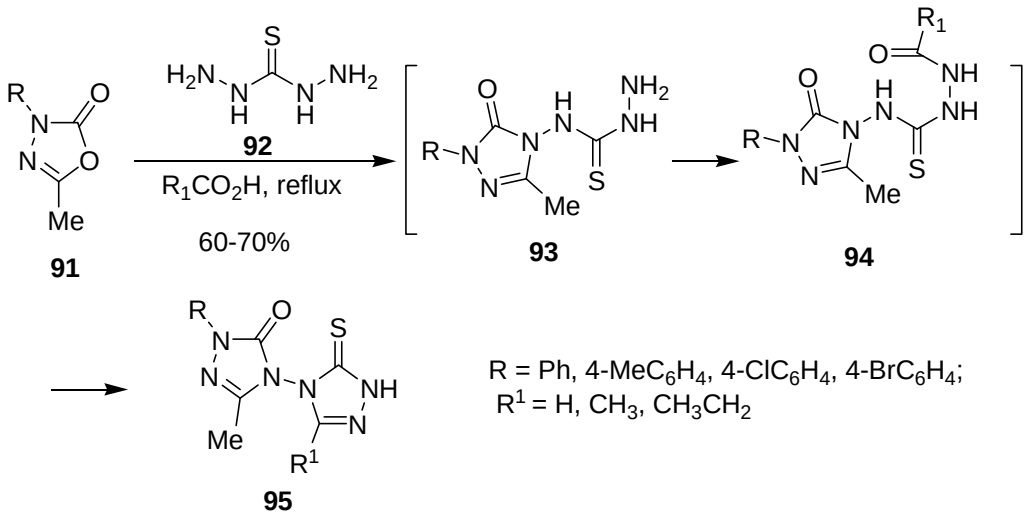
Scheme 27

The reaction between 4-amino-3,5-dimethyl-4*H*-1,2,4-triazole **85** and bis(α-chlorobenzylidene)hydrazine **86** in refluxing xylene yielded 3,3`-dimethyl-5`,5`-diphenyl-4,4`-bi-4*H*-1,2,4-triazole **87**. Initial nucleophilic displacement of chlorine in **86** by the amino group followed by an intramolecular ring closure and subsequent elimination of diazoethane to give **89** was disclosed. Repeating this reaction at the second imidoyl chloride centre yielded the 4,4`-bi-1,2,4-triazole derivative **90** (Scheme 28).[70]



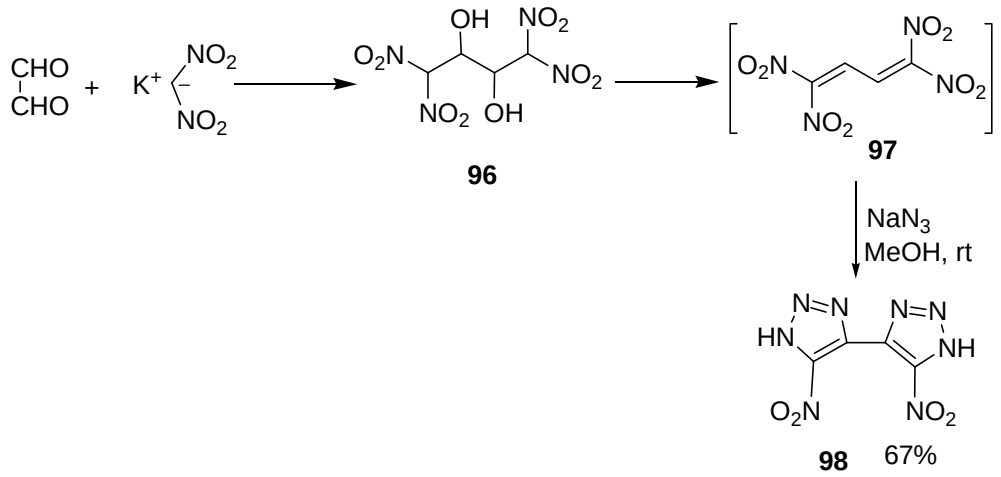
Scheme 28

Heating the three component reaction of 3-aryl-5-methyl-1,3,4-oxadiazol-2(3*H*)-ones **91** with thiocarbazide **92** and aliphatic carboxylic acids, resulted in the formation of the 4,4`-bi-1,2,4-triazole derivatives **95** *via* the intermediates **93** and **94** as shown in Scheme 29.[71]



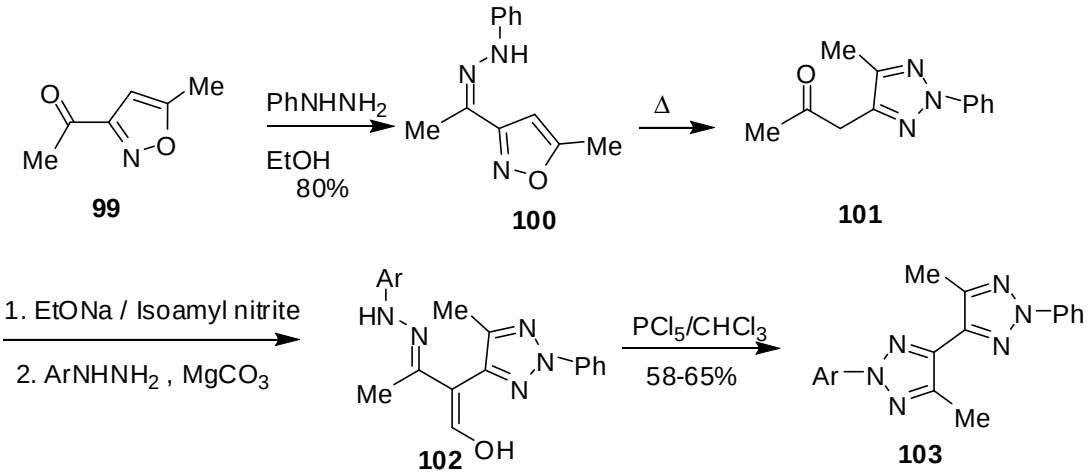
Scheme 29

Condensation of dinitromethane with glyoxal afforded 1,1,4,4-tetranitro-1,3-butadiene **96**. Reaction of the latter compound with sodium azide led to formation of 4,4`-bi-1,2,3-triazole derivative **98** *via* 1,1,4,4-tetranitro-2,3-butanediol intermediate **97** (Scheme 30).[72]



Scheme 30

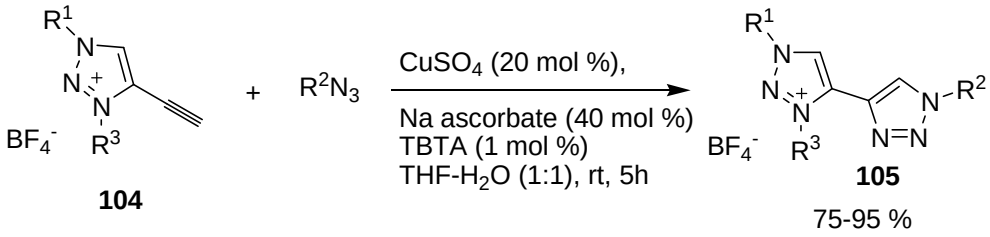
Thermal rearrangement of 3-acylisoxazole arylhydrazones **100**, prepared by heating of 1-(5-methylisoxazol-3-yl)ethanone **99** with phenylhydrazine in ethanol, allowed facile preparation of 1-(1,2,3-triazol-4-yl)propan-2-ones **101**. Reaction of the 1,2,3-triazolylpropanone derivatives **101** with isoamyl nitrite then arylhydrazine produced α-hydroxyiminohydrazones **102**. Reaction of **102** with phosphorus pentachloride afforded 4,4`-bi-1,2,3-triazoles **103** (Scheme 31).[73]



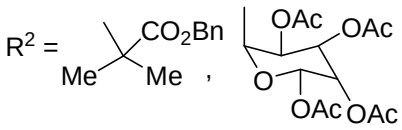
Ar= Ph; 2-Cl, 3-Cl, 4-Cl(C_6H_4); 2-Br, 3-Br, 4-Br(C_6H_4); 4-$O_2NC_6H_4$

Scheme 31

Copper(I)-catalyzed alkyne–azide 'click' [2+3] cycloaddition reactions (CuAAC) method was applied in the synthesis of nonsymmetrical-substituted 4,4`-bis(1,2,3-triazolium) salts **105** by reaction of 3-alkyl-4-ethynyl-1,2,3-triazolium salts **104** with alkyl and aryl azides (Scheme 32).[74]



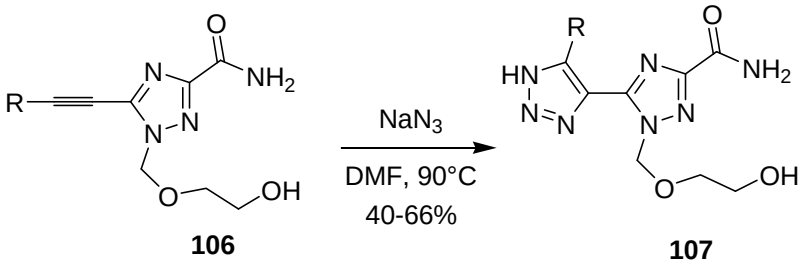
R^1= Bn, 4-t-Bu$C_6H_4CH_2$, 4-NCC_6H_4; R^2 = Bn, $CH_2C_6H_4$-t-Bu, ph; R^3 =Me, Et



Scheme 32

2.7. 4,5`-Bi-triazoles

The 4,5`-bitriazolyl acyclonucleosides **107** were synthesized in good yields *via* a one-step Huisgen cycloaddition reaction using sodium azide and the 5-alkynylyltriazole acyclonucleosides **106** in DMF at 90°C (Scheme 33). The synthesized bitriazolyl compounds exhibited potent antiviral activity against tobacco mosaic virus and were devoid of any notable toxicity.[75]

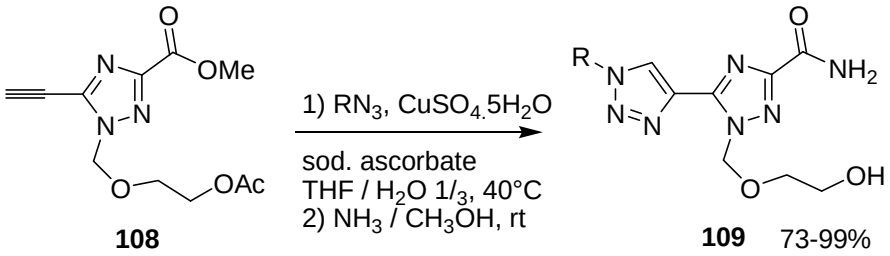


106 **107**

R= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$CH_3(CH_2)_3C_6H_4$
4-$CH_3(CH_2)_4C_6H_4$, 4-$F_3CC_6H_4$, 3-$F_3CC_6H_4$, 2-thienyl, 1-cyclohexenyl

Scheme 33

The 4,5`-bitriazolyl acyclonucleosides **109** were synthesized in excellent yields *via* the copper catalyzed cycloaddition reaction of aryl azides and the 5-acetynylyltriazole acyclonucleoside **108** in THF-water followed by ammonolysis with NH_3/MeOH mixture (Scheme 34). The synthesized compounds exhibited powerful antiproliferative effects on numerous cancer cell lines.[76]



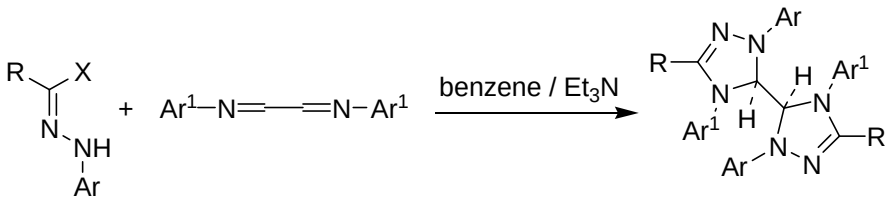
108 **109** 73-99%

R= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 3-$F_3CC_6H_4$, benzyl,
1-naphthalenyl, 1-methylpyrenyl

Scheme 34

2.8. 5,5`-Bitriazoles

Reaction of the 1,4-diazabutadiene derivative **82b** with a 1:2 molar amount of the hydrazonoyl chlorides **81** resulted in the formation of the 5,5`-bi-1,2,4-triazoline derivatives **110** in moderate yields (Scheme 35).[69]

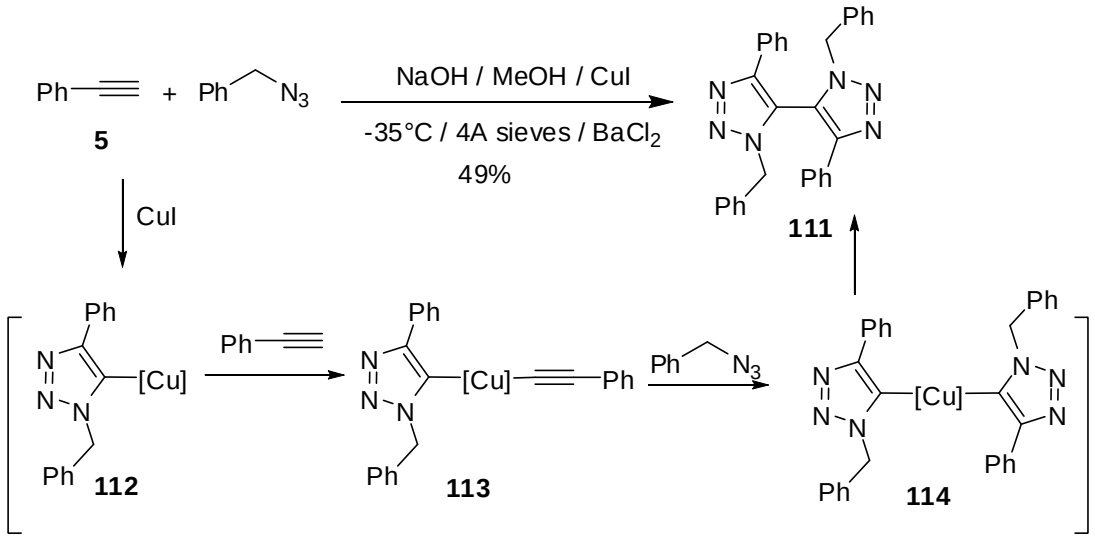


81 **82b** **110a**: 42%
Ar^1 = 4-MeC_6H_4 **110b**: 33%

a: R= CO_2Et, Ar = 4-MeC_6H_4
b: R= $COCH_3$, Ar = 4-ClC_6H_4

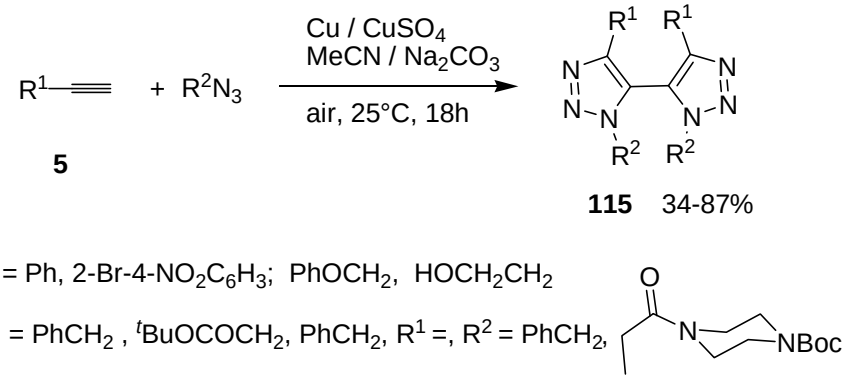
Scheme 35

Cycloaddition of phenylacetylene **5** and benzyl azide using catalytic amount of copper(I) iodide in the presence of NaOH yielded the 5,5`-bi-1,2,3-triazole derivative **111** *via* the intermediates **112**-**114** according to the reaction mechanism depicted in Scheme 36.[77]



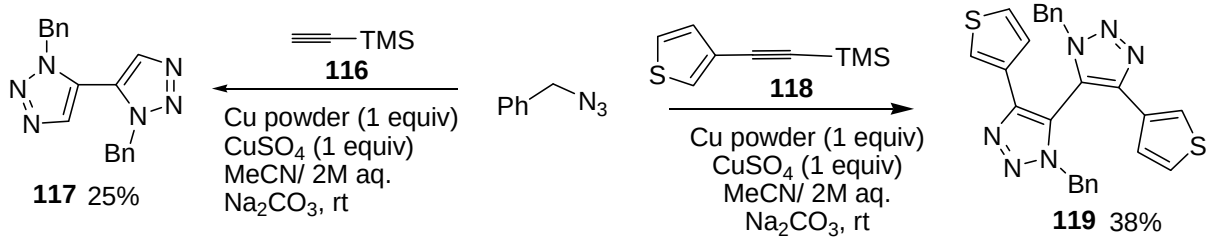
Scheme 36

The oxidative dimerization was extrapolated in the copper-mediated Huisgen reaction of the terminal alkynes **5** with azides **51** to yield the 5,5`-bi-1,2,3-triazole derivatives **115** under basic reaction conditions (Scheme 37).[78]



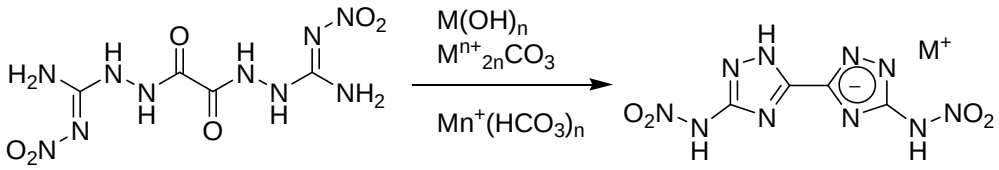
Scheme 37

Trimethylsilylacetylene **116** and 2-(3-thienyl)ethynyltrimethylsilane **118** were also reported as effective substrates for the cycloaddition with benzyl azide and oxidative dimerization to give the corresponding 5,5`-bitriazole derivatives **117** and **119** in 25 and 38% yields, respectively (Scheme 38).[78]



Scheme 38

Heating the oxalo-bis-hydrazide derivative **120** in water in the presence of bases, (alkali metal carbonates, or guanidinium or aminoguanidinium carbonates) at a molar ratio of 1:2 and subsequent acidification of the mixture resulted in the formation of the corresponding 5,5`-bi(3-nitroamino-1,2,4-triazole) salts **121** in excellent yields (Scheme 39).[79-81]

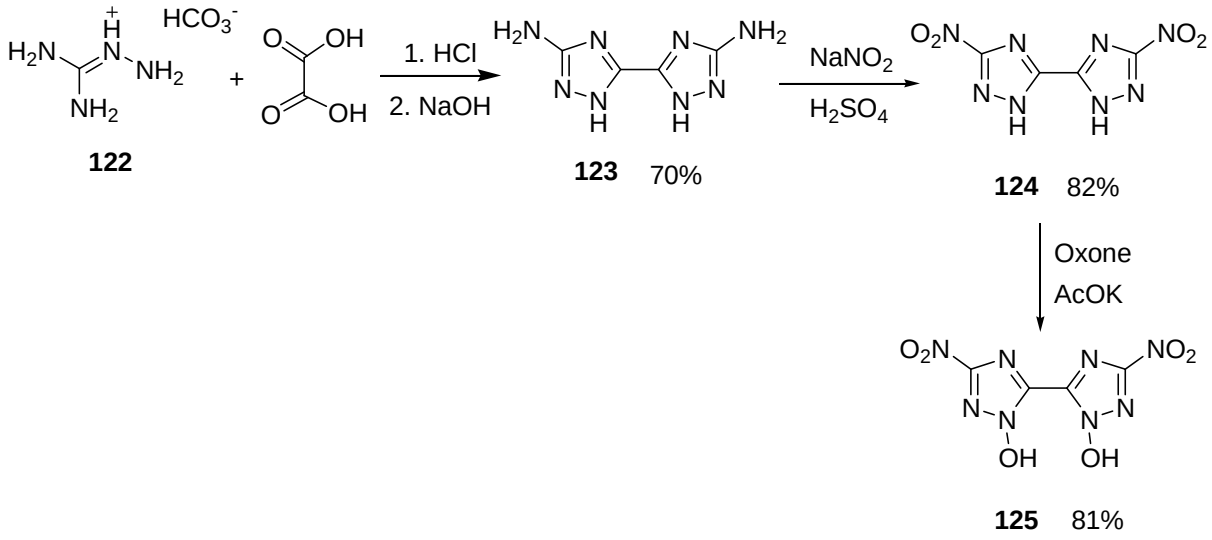


M = Na, K, NH_4, $NH_3C(=NH)NH_2$, $NH_3NHC(=NH)NH_2$

Scheme 39

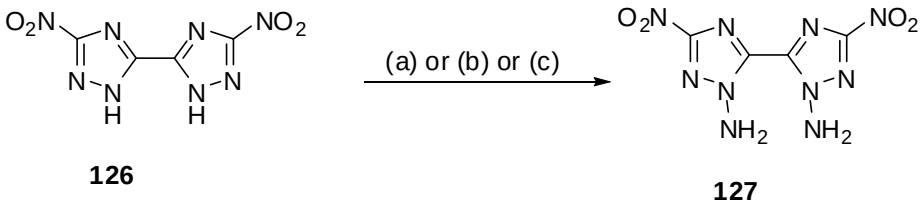
3,3`-Diamino-5,5`-bi-1,2,4-triazole **123** (DABT) was synthesized from the reaction of oxalic acid and aminoguanidinium bicarbonate **122** in concentrated hydrochloric acid and subsequent cyclization in basic media. Oxidation of DABT **123** by Sandmeyer reaction *via* diazotization in sulfuric acid and subsequent reaction with sodium nitrite yielded 3,3′-dinitro-5,5′-bi-1,2,4-triazole (DNBT) **124** (Scheme 40). Oxidation of 3,3′-dinitro-5,5`-bi-1,2,4-triazole **124** in an buffered aqueous solution of oxone at 40 °C led to the selective oxidation to 3,3′-dinitro-5,5`-bi-1,2,4-triazole-1,1′-diol **125** (Scheme 40). The DNBT, as nitrogen-rich ligand, was employed in the development of energetic metal-organic frameworks (MOFs) of high density and thermal stability.[82-87]

Synthesis of 3,3`-dinitro-5,5`-bi-1,2,4-triazole-1,1`-diamine **127**, as new explosive and energetic material, was reported employing amination conditions using either *O*-tosylhydroxylamine or *O*-mesitylenesulfonyl hydroxylamine reagents of the in situ ammonium salts of the 3,3`-dinitro-5,5`-bi-1,2,4-triazole **126** as outlined in Scheme 41.[88-90]



122 **123** 70% **124** 82% **125** 81%

Scheme 40



126 **127**

(a) Et_4NOH/H_2O then O-mesitylenesulfonyl hydroxylamine/MeCN, yield 80%

(b) NH_3/H_2O then O-tosylhydroxylamine/DMF/$CHCl_3$ yield 45%

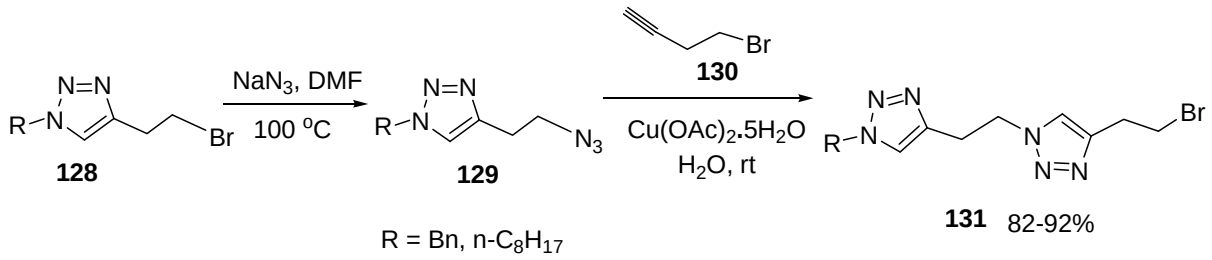
(c) DBU/CH_3CN then O-tosylhydroxylamine /CH_2Cl_2, yield 56%

Scheme 41

3. Synthesis and Application of Bistriazole Systems

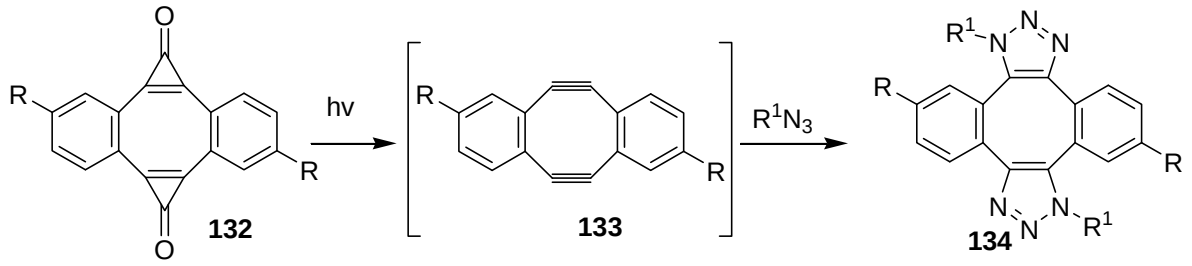
3.1. Bis-(1,2,3-triazoles)

Copper promoted click chemistry was reported to be useful tool for the facile formation of bis(1,2,3-triazoles).[91] Copper catalyzed cycloaddition reaction between the alkyl azides **129**, prepared by heating of bromide **128** with sodium azide in DMF at 100 °C, and 4-bromo-1-butyne **130** in H_2O at room temperature in the presence of $Cu(OAc)_2.H_2O$, led regioselectively to 4-(2-bromoethyl)-1,2,3-triazoles **131** in excellent yields (Scheme 42).[92]



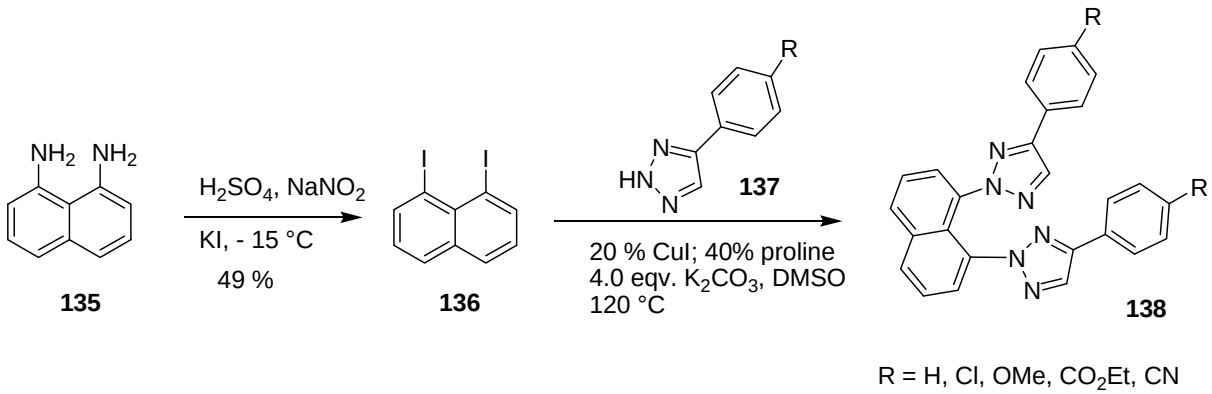
Scheme 42

Photo irradiation of dibenzo[a,e]cyclooctadiyne (DIBOD) **132** with 350 or 420 nm fluorescent lamps in the presence of the appropriate azide resulted in the efficient formation of the bis-triazole derivatives **134** *via* the intermediate **133** (Scheme 43).[93,94]



Scheme 43

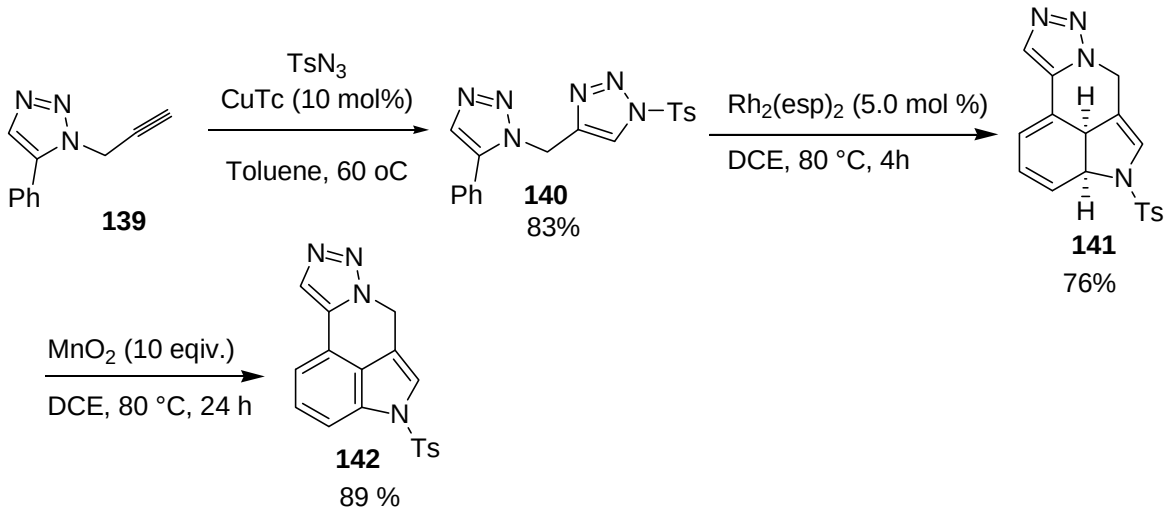
1,8-Diiodonaphthalene **136**, prepared from naphthalene-1,8-diamine **135**, reacted with 4-aryl-1,2,3-triazoles **137** in dry DMSO in the presence of CuI and K_2CO_3 under N_2 atmosphere to give the naphthalene-bridged bis-triazole derivatives **138** in 42-66% yields (Scheme 44).[95] The naphthalene-bridged bis-triazole derivatives **138** were reported to be potential fluorophores for chemical and biological applications and showed high fluorescence efficiency and large Stokes shifts.



Scheme 44

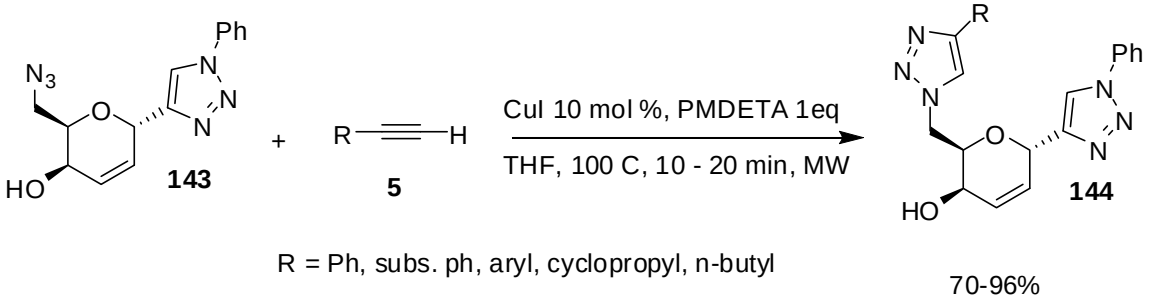
The bis(1,2,3-triazole) **140**, was synthesized in 83% from *N*-propargyl-5-phenyltriazole **139** with tosyl azide in the presence of copper(I) thiophene-2-carboxylate (CuTc) catalyst in dry toluene under N_2 atmosphere. Treatment of **140** with Rh(II) catalyst led to selective decomposition of the 1,4-disubstituted

1,2,3-triazole core, leading to a 3,4-fused dihydroindole **141** in 76% *via* intramolecular [3+2]-annulation reaction. Further treatment of **141** with MnO_2 at 80 °C afforded fused indole of bis(1,2,3-triazole) **142** in good yield (Scheme 45).[96]



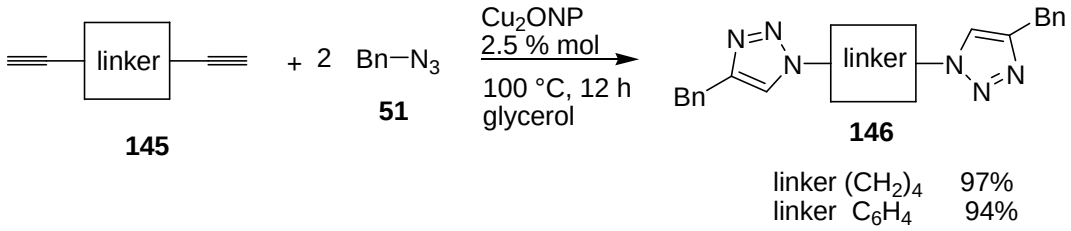
Scheme 45

Synthesis of the bis-1,2,3-triazole derivatives **144** was conducted starting from a azido-glycoside derivative **143** using CuI-catalyst under microwave irradiation condition. The azide **143** was treated with different terminal alkynes **5** using PMDETA (*N,N,N,N,N*-pentamethyldiethylenetriamine) as the base in THF (Scheme 46).[97]



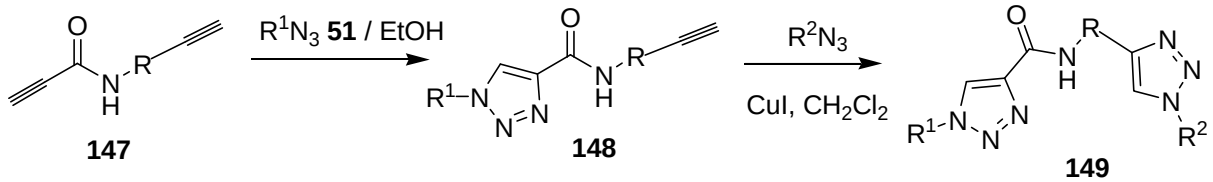
Scheme 46

Symmetrically substituted bis(1,2,3-triazoles) **146** having butyl or phenyl spacer groups were synthesized in high yields from reaction of the corresponding dialkynes **145** and benzyl azide using copper(I) oxide nanoparticles (Cu_2ONP) in glycerol (Scheme 47).[98]



Scheme 47

The copper-catalyzed coupling bis-alkynes **147** with various organic azides **51** afforded the corresponding bis(1,2,3-triazole) derivatives **149** *through* **148** using the polymer-supported catalyst Amberlyst A-21•CuI in DCM at room temperature (Scheme 48).[99] Some of the bis-triazole products **149** showed noteworthy activity against B16 melanoma included in the range 1-20 μM.

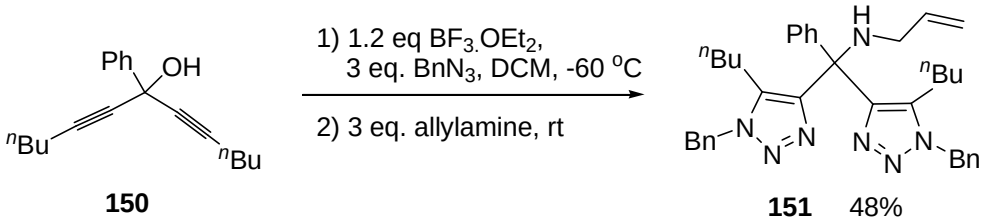


R^1 =R^2=Bn; R^1= Bn, R^2=CH_2CO_2Et; R^1= Bn,R^2= $(CH_2)_2OAc$

R = CH_2, *m*-phenylene, *p*-phenylene

Scheme 48

One-pot three-component coupling reactions of **150** consisted by double [3+2] reactions followed by substitutions with allylamine, as nucleophile, successfully afforded the bis(1,2,3-triazole) derivative **151** in moderate yield (Scheme 49).[100]

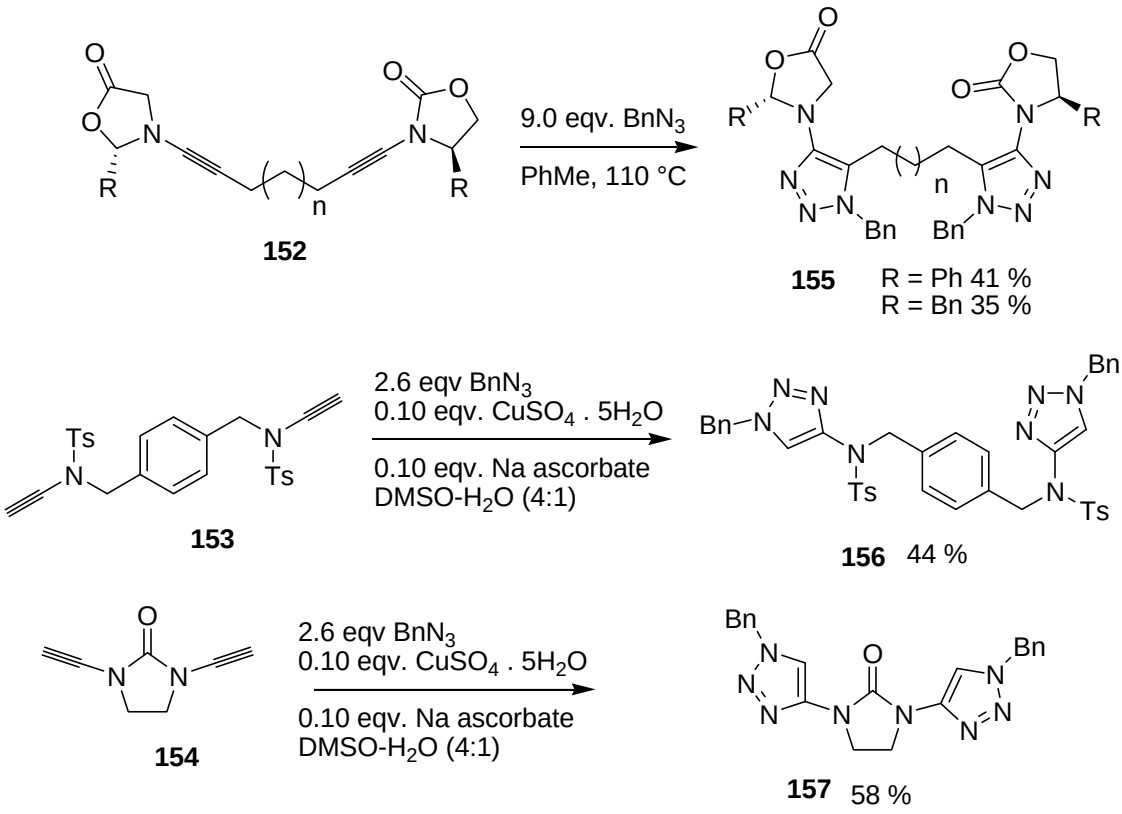


Scheme 49

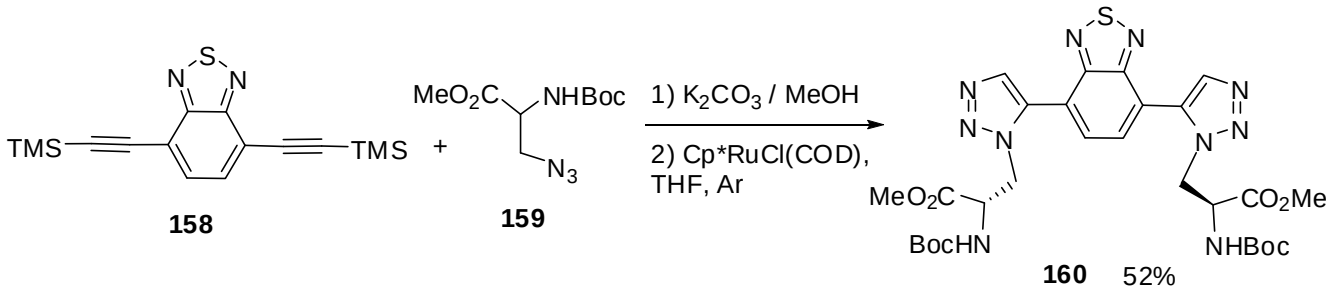
Thermally driven [3+2] cycloadditions of internal bis-ynamides **152-154** with benzyl azide led to the formation of the bis(1,2,3-triazole) derivatives **155-157** in moderate yields (Scheme 50).[101]

The bis-1,2,3-triazolyl benzothiadiazole derivative **160** was synthesized by ruthenium-catalyzed azide-alkyne cycloaddition between the benzothiadiazole bis-alkyne **158** and azido alanine **159** in 52% yield as shown in Scheme 51. Photophysical studies demonstrated the crucial role of the prepared bistriazole **160** in the design of new fluorescent chemosensors.[102]

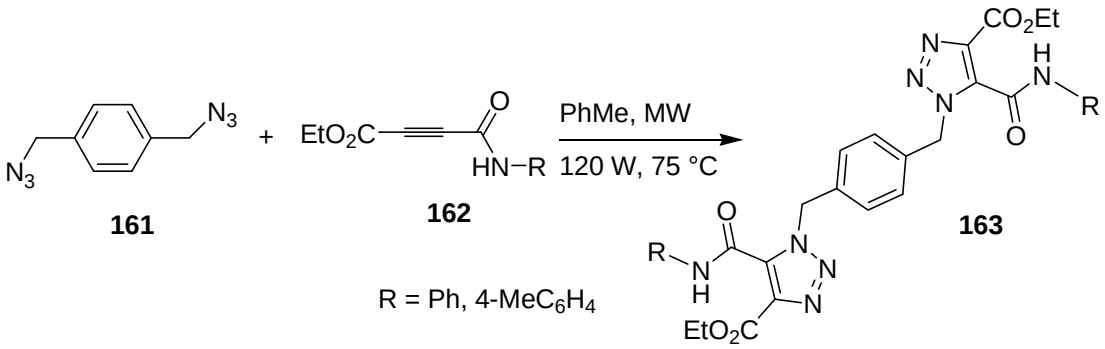
The reaction of 1,4-bis(azidomethyl)benzene **161** with 2 equiv. of ethyl 4-anilino-4-oxo-2-butynoate **162** in toluene under microwave irradiation furnished the mixed regioisomeric bis(1,2,3-triazole) derivatives **163** in 65% yield (Scheme 52).[103]



Scheme 50

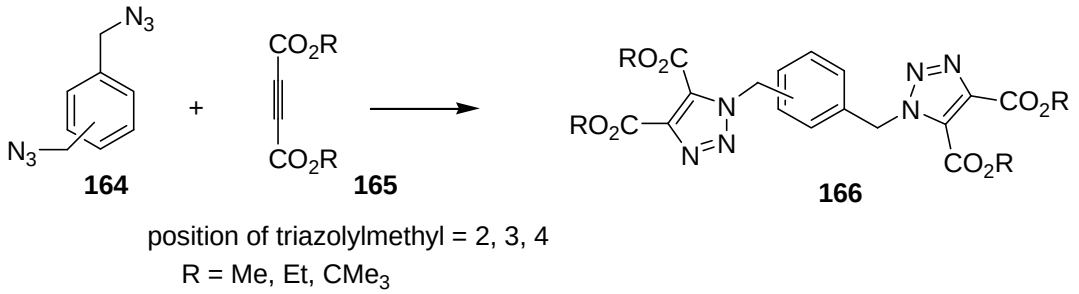


Scheme 51



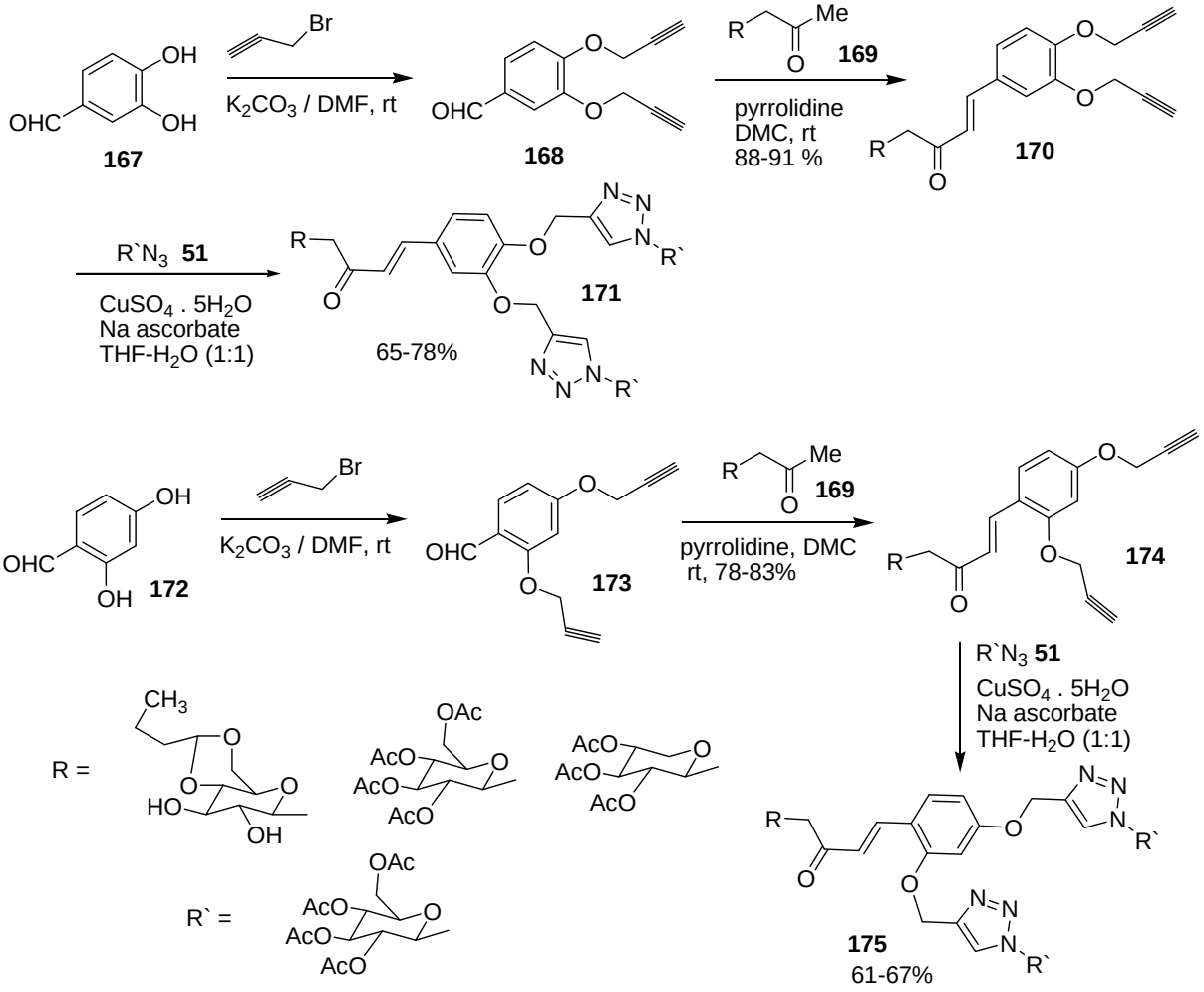
Scheme 52

Reaction of 1,2-, 1,3- and 1,4-bis(azidomethyl)benzenes **164** with acetylenedicarboxylate esters **165** afforded the corresponding bis(1,2,3-triazole) derivatives **166** (Scheme 53).[104]



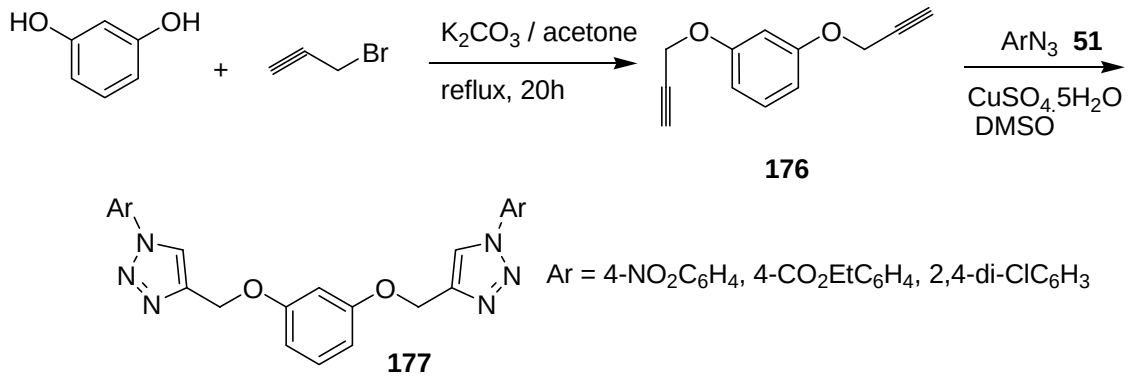
Scheme 53

Click reaction of the sugar azides **51** with chalcogeno bis-propargylated catechols and resorcinol derivatives **170** and **174**, [prepared by reaction of **167** or **172**, with propargyl bromide to afford **168** or **173** which then reacted with methyl ketones **169**] using tetrahydrofuran and water as solvent resulted in the formation of the sugar-chalcone based bis-triazole derivatives **171** and **175** in high yields (Scheme 54).[105]



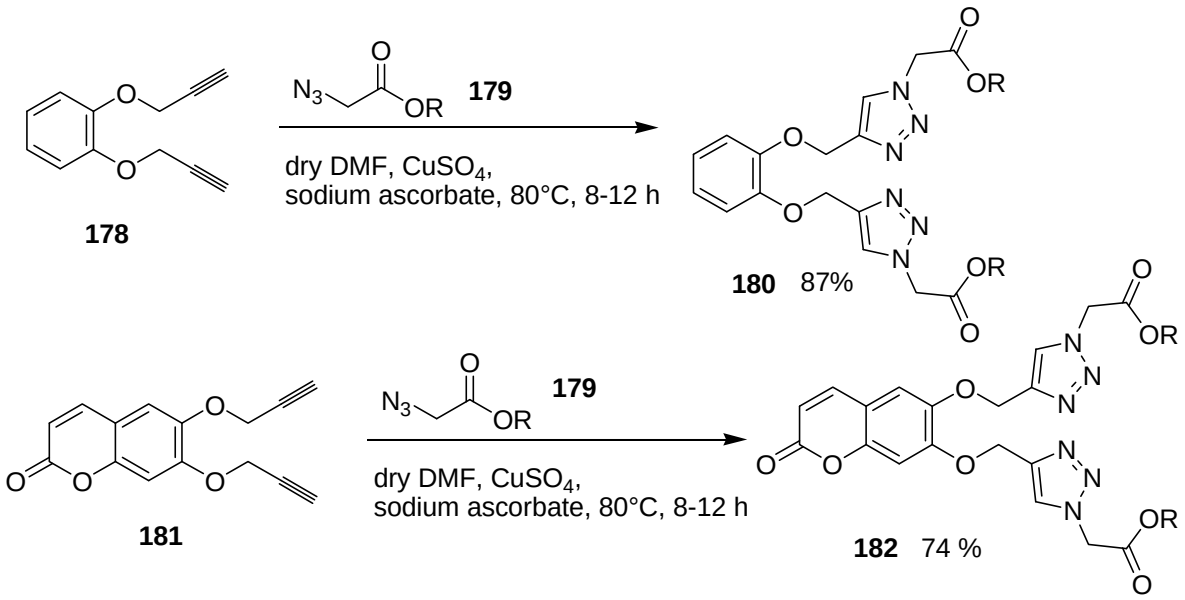
Scheme 54

Synthesis of bis-1,2,3-triazoles **177** *via* Cu(I)-catalyzed click reaction of aryl azides and 1,3-bis(prop-2-yn-1-yloxy)benzene **176**. The latter were synthesized from the reaction of resorcinol with propargyl bromide in the presence of potassium carbonate (Scheme 55).[106]



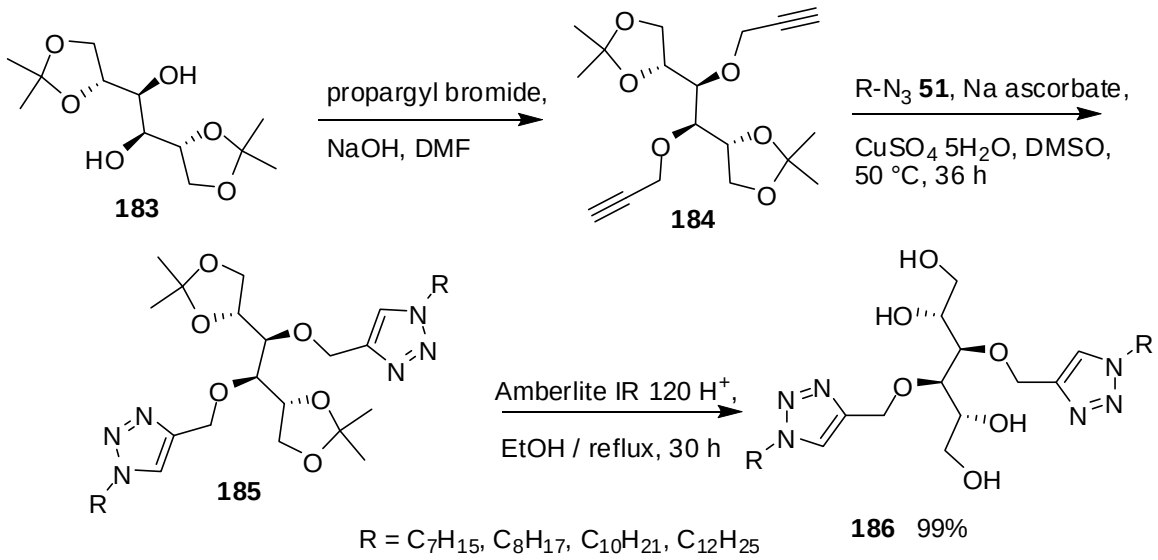
Scheme 55

Copper(I)-catalyzed click reaction of the bis-alkyne derivatives of catechol **178** or 6,7-dihydroxycoumarin **181** with the azide esters **179** yielded the corresponding bis-1,2,3-triazole derivatives **180** and **182** respectively in high yields (Scheme 56).[107]



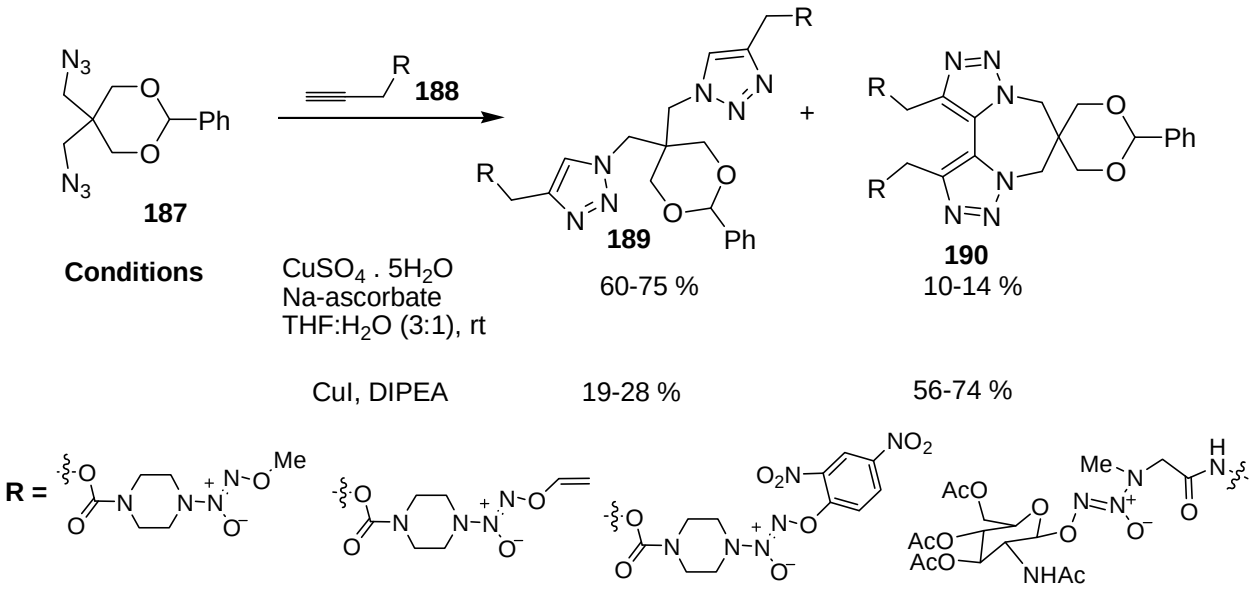
Scheme 56

1,2,5,6-Di-*O*-isopropylidene-D-mannitol **183** reacted with propargyl bromide in NaOH and DMF solvent to give the bis-alkyne **184**. The Cu(I)-catalyzed 1,3-dipolar cycloaddition of the bis-alkyne **185** with alkyl azides **51** in DMSO at 50 °C gave the corresponding bis-triazoles **186** in quantitative yields (Scheme 57).[108]



Scheme 57

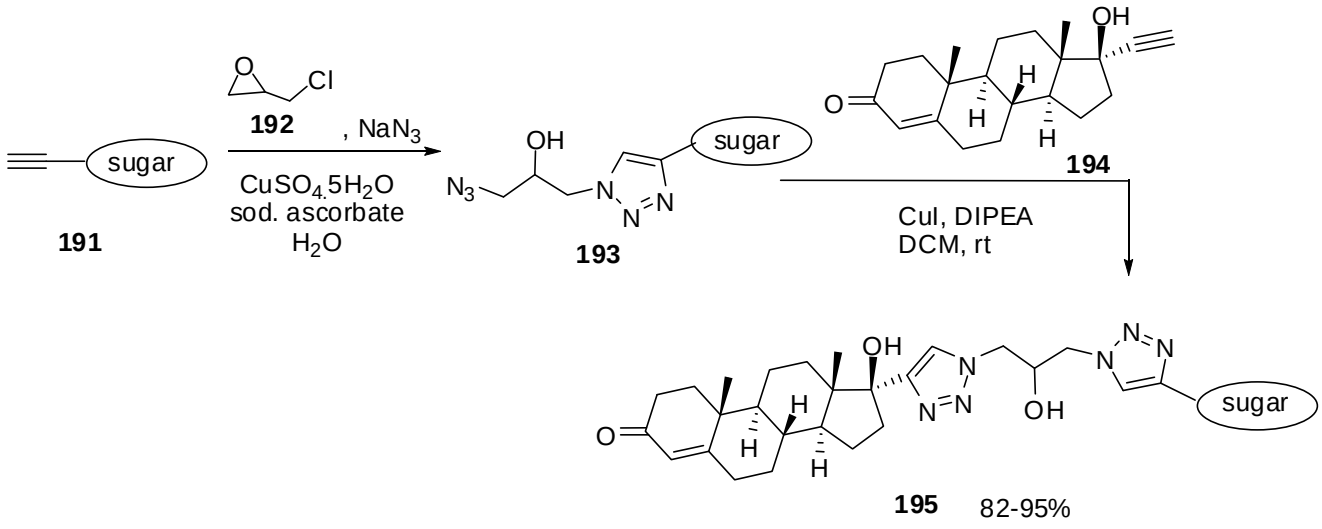
The "click" reaction of diazeniumdiolate prodrugs having terminal alkyne groups **188** with the bis-azide **187** was performed using $CuSO_4$/Na-ascorbate in THF/water. The reaction proceeded quickly (15-45 min) and gave a mixture of two products. The major product was in each case the bis-triazole derivative **189** and the minor product was 5,5′-triazolo-triazole **190**. The use of CuI and diisopropylethylamine (DIPEA) as base predominantly gave the cycloaddition/oxidative coupling products; 5,5′-triazolo-triazole **189** as major products (Scheme 58).[109] The products were reported to have potential biological applications as NO-donors.



Scheme 58

Synthesis of the bis-triazolyl ethisterone glycoconjugates **195** was reported using CuAAC reaction condition. At first, the sugar based triazolyl azido-alcohols **195** were synthesized *via* one pot click reaction of glycosyl alkynes **193** with epichlorohydrin **192** in aqueous medium. Treatment of the triazolyl azido-alcohols **193** with the naturally occurring steroid alkyne (ethisterone) **194** yielded the bis-triazolyl ethisterone

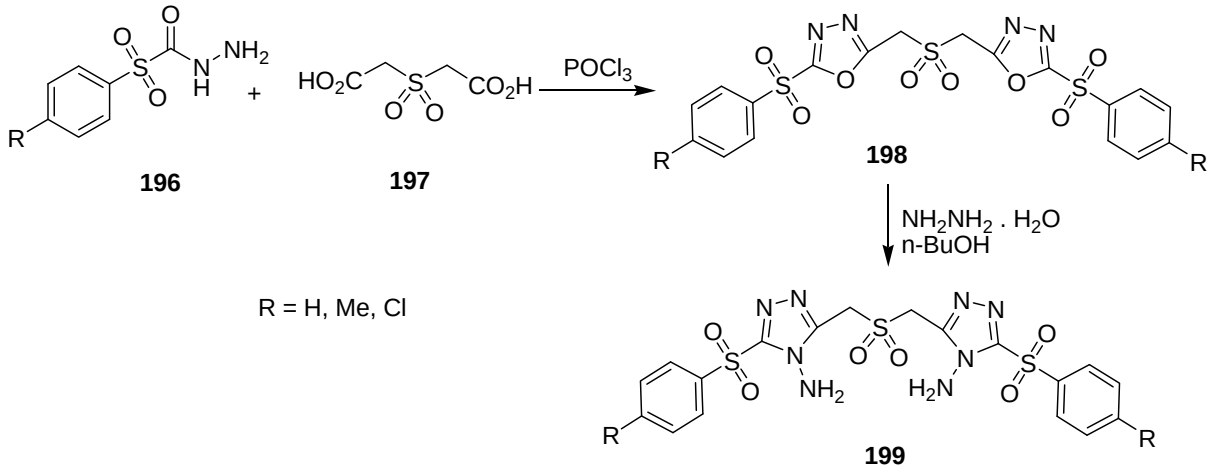
glycoconjugates **195** regioselectively in good yields (Scheme 59). The products **195** were of potential application in androgen receptor pharmacology and chemical biology.[110]



Scheme 59

3.2. Bis-(1,2,4-triazoles)

Reaction of arylaminosulfonylacetic acid hydrazide **196** with sulfonyldiacetic acid **197** in the presence of $POCl_3$ resulted in the formation of bis(1,3,4-oxadiazole) derivatives **198**. Treatment of the latter compounds with hydrazine hydrate in *n*-butanol gave the bis(1,3,4-triazole) derivatives **199** (Scheme 60).[111] Compounds **199** exhibited good antioxidant activity using DPPH, nitric oxide (NO), and hydrogen peroxide (H_2O_2) methods at 50, 75, and 100 μM concentration.



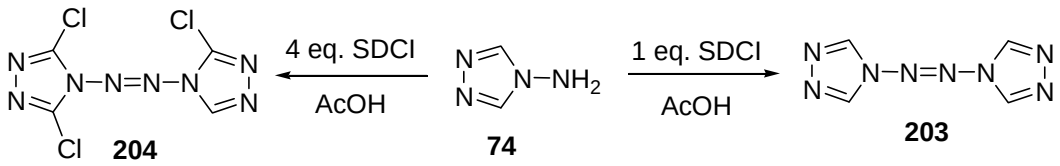
Scheme 60

The bis(1,2,4-triazole) derivative **202** was synthesized in 42% yield from the reaction of 2-cyano-3-methylthio-3-phenylaminoacrylonitrile **201** with the bis-hydrazonoyl halide **200** in refluxing DMF/EtOH in the presence of triethylamine (Scheme 61).[112]

200 **201** **202**

Scheme 61

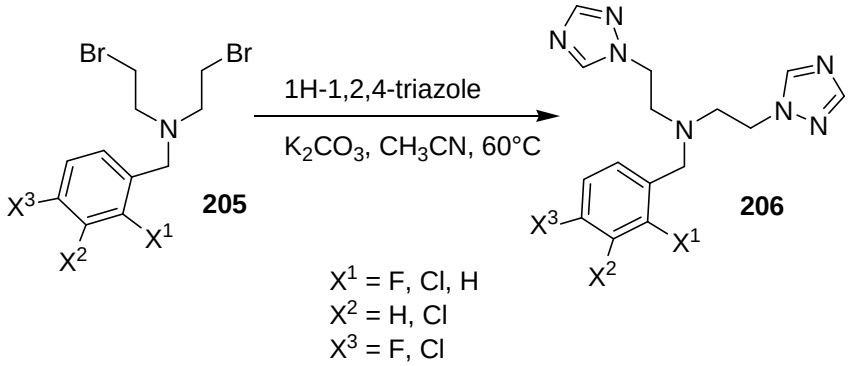
The reaction of 4-amino-1,2,4-triazole **74** with sodium dichloroisocyanurate (SDCI) afforded the bis(1,2,4-triazole) derivaive **203** in 90% yield. Increasing the molar ratio of SDCI to 4-amino-1,2,4-triazole, the chlorinated bis(1,2,4-triazole) **204** was formed in 45% yield (Scheme 62).[113]



204 **74** **203**

Scheme 62

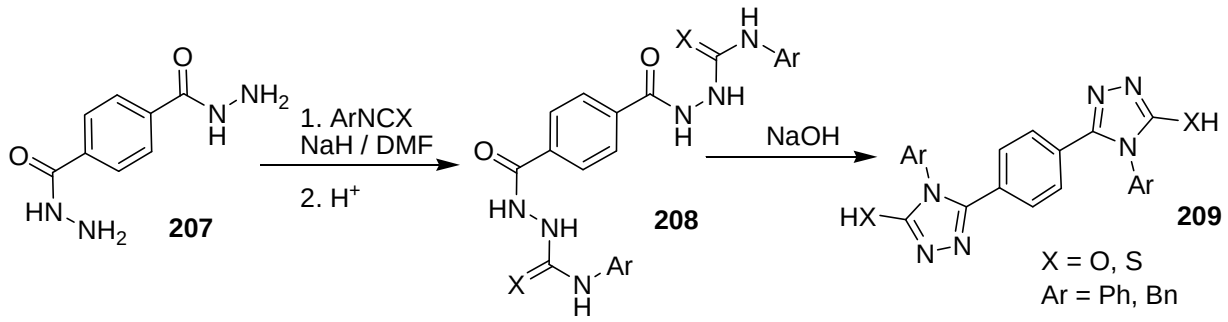
Reaction of the amine bis-bromide compounds **205** reacted with 1*H*-1,2,4-triazole in the presence of potassium carbonate in acetonitrile at 40-70 °C to give the corresponding amine bis(1,2,4-triazole) derivatives **206** in 67-75% yields (Scheme 63).[114] The obtained bis-triazoles **206** exhibited more potent antifungal activity than the clinically prevalent antifungal drug Fluconazole against *C.* albicans with MIC value of 0.25 mg/mL.



205 **206**

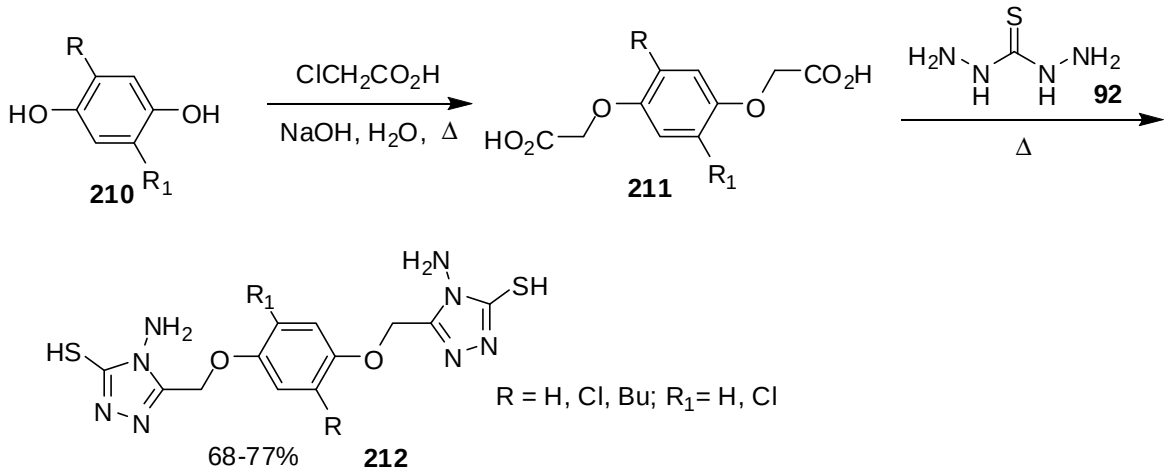
Scheme 63

Reaction of terephthalic acid bis-hydrazide **207** with aryl iso(thio)cyanate in DMF in the presence of sodium hydride followed by treatment with concentrated HCl afforded the corresponding (thio)semicarbazide **208**. The bis-(thio)semicarbazides on treatment with sodium hydroxide led to the formation of the bis(1,2,4-triazole) derivatives **209** in 64-69% yields (Scheme 64).[115]



Scheme 64

Fusion of 1,4-bis-phenoxyacetic acids **211**, prepared by heating of **210** with chloroacetic acid and sodium hydroxide in water, with thiocarbazide **92** afforded 1,4-bis-(1,2,4-triazol-3-ylmethoxy)phenylenes 2**12** in a one pot reaction in good yields (Scheme 65).[116]



Scheme 65

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