

REVIEW

A review on *bis*-hydrazonoyl halides: Recent advances in their synthesis and their diverse synthetic applications leading to *bis*-heterocycles of biological interest

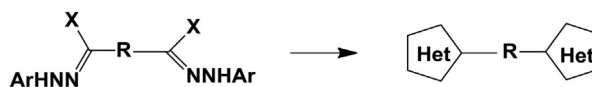


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GRAPHICAL ABSTRACT

Recent Advances in Synthesis of *Bis*-hydrazonoyl halides and their Diverse Synthetic Applications Leading to *Bis*-heterocycles of Biological Interest.



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ABSTRACT

This review covers a summary of the literature data published on the chemistry of *bis*-hydrazonoyl halides over the last four decades. The biological activities of some of the *bis*-heterocyclic compounds obtained from these *bis*-hydrazonoyl halides are also reviewed and discussed.

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Bis-nitrilimines
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 Biological activities



Prof. Ahmad Sami Shawali is an Emeritus Professor of Physical Organic Chemistry, Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt. He graduated with B.Sc. from the University of Cairo in 1958. He received his M.Sc. and Ph.D. degrees in 1962 and 1966, respectively, from Lowell Technological Institute, presently the University of Lowell, Massachusetts, USA. He was awarded the degree of Doctor of Science (D.Sc.) from the University of Cairo

after recommendation from a British committee from the Royal Chemical Society in 1995. Prof. Shawali has been the recipient of the state award and Egypt State Medal of Science and Arts in 1977. He holds several national and international certificates of merit for his distinguished services. He was appointed Vice-Dean for student affairs in 1989 and he was elected Dean of the Faculty of Science in 1991. He was visiting professor at the University of Texas at El Paso, Texas, USA, from 1979 to 1980, University of Kuwait from 1973 to 1977 and King Abdulaziz University, Jeddah, Saudi Arabia, from 1982 to 1988. He has published 255 scientific papers including 21 review articles, all in international journals. At present, Google Scholar indicates that there are more than 3170 citations of his work from 1970 until mid 2015 (i.e. about 70 citations/year or 12 citations/paper) with h-index = 28 and i10 = 95. So far, he supervised 48 M.Sc. and 17 Ph.D. graduate theses. He was invited to present plenary lectures at 29 conferences. His research interests are in the fields of reaction mechanisms, applications of LFERs, chemistry of hydrazoneic acid derivatives, 1,3-dipolar cycloadditions and 1,5-electrocyclizations.

Introduction

Bis-hydrazoneyl halides are compounds that have the general formula **A** or **B** (Fig. 1), where X = Cl or Br. The first *bis*-hydrazoneyl halides, namely N,N'-diaryl 1,2-ethane-*bis*-

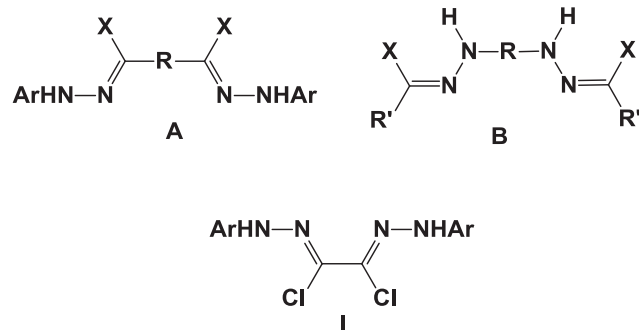


Fig. 1 Chemistry of *bis*-hydrazoneyl halides **A** and **B**.

hydrazoneyl chlorides **I** (Chart 1) have been reported by Chattaway and Farinholt in 1930 in the course of their studies on direct halogenations of *bis*-hydrazones [1]. Although such compounds have been known for more than 85 years, they have recently reawakened interest in their chemistry as they proved to be useful building blocks for one-pot synthesis of a wide variety of *bis*-heterocycles such as *bis*-pyrazoles [2,3], *bis*-1,3,4-thiadiazoles [4], *bis*(1,3,4-selenadiazoles) [5] and pyrrolo[2,1-*b*]benzothiazole [6]. The interest in such *bis*-heterocycles is due to the fact that many of them exhibit more potent biological activities than the monoheterocyclic analogues [7–13]. In addition, many *bis*-pyrazole [14–17] and *bis*-1,3,4-thiadiazole [18–20] derivatives were reported to exhibit various pharmaceutical, agrochemical and many other applications including antibacterial, fungicidal, tuberculostatic, antiamebic, and plant growth regulative properties [21].

At present, there are several review articles by the author covering the data published on reactions of monohydrazoneyl halides of type, R-C(X) = NNHR' [22–27]. In contrast, few data concerning the chemistry of *bis*-hydrazoneyl halides **A** and **B** (Fig. 1), if there is any, have been covered in such reviews. Hence, this review offers a systematic and rational survey of the synthesis and chemical reactions of

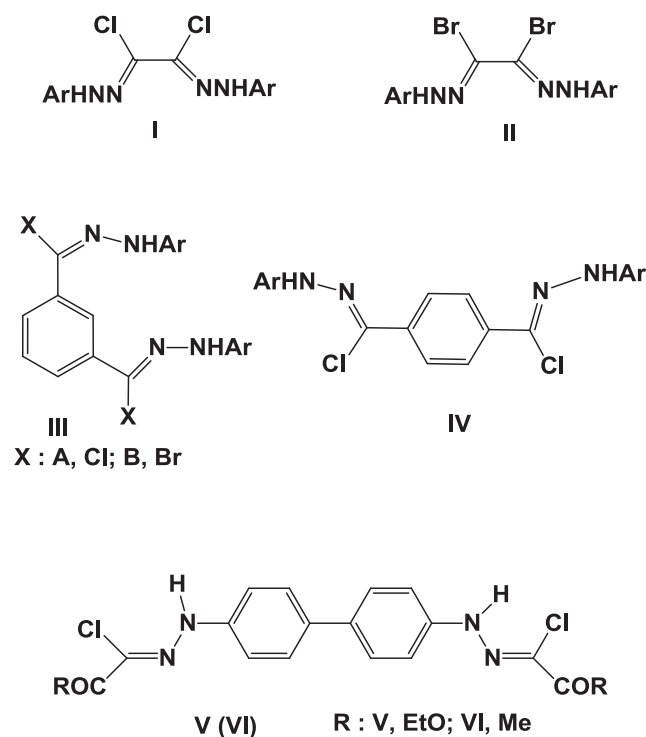


Fig. 2 General structural formulas of the various *bis*-hydrazoneyl halides.

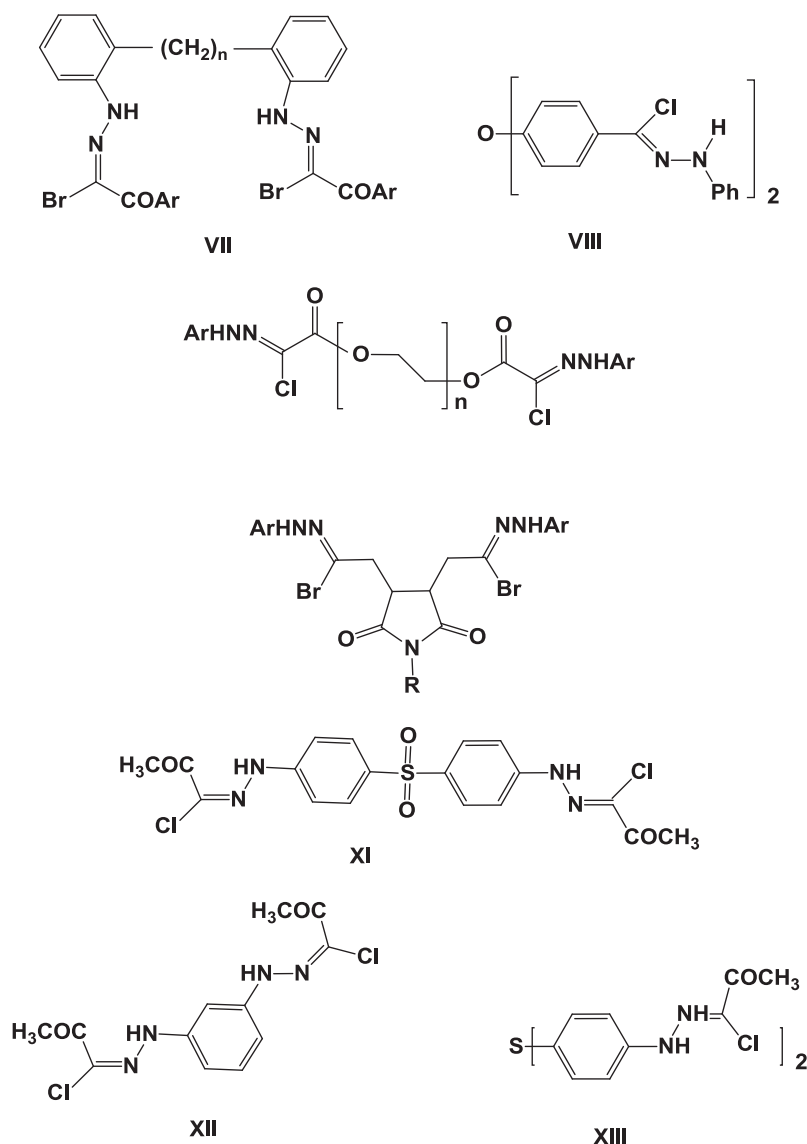


Fig 2. (continued)

different *bis*-hydrazoneyl halides that have been reported during the period from 1930 till mid 2015. In addition, the various biological activities of the products of the reactions of such halides are presented.

Synthesis of *bis*-hydrazoneyl halides

At present, there are four methods for synthesis of *bis*-hydrazoneyl halides. The general structural formulas of the various *bis*-hydrazoneyl halides that have been prepared by such methods and reported hitherto are depicted in Fig. 2.

Halogenation of *bis*-(*aryl*hydrazines)

Reactions of *bis*-hydrazide derivatives of dicarboxylic acids with phosphorous pentachloride, thionyl chloride or triphenyl phosphine/carbon tetrachloride reagent were reported to yield the corresponding *bis*-hydrazoneyl chlorides. For example,

1,3- and 1,4-phenylene-*bis*(carbohydrazoneyl chlorides) **III** (**IV**) were prepared by the reaction of iso- and terphthaloylhydrazides **1a,b**, each with phosphorus pentachloride (**Scheme 1**) [28].

Grundmann et al. [29] reported also the synthesis of *N,N'*-diphenyl ethane-1,2-*bis*-hydrazoneyl chloride **Ia**, by heating oxalic acid *bis*-(*N*-phenylhydrazide) **2a** with a mixture of phosphorus pentachloride and phosphorus oxychloride (**Scheme 2**).

Other *N,N'*-diaryl ethane-1,2-*bis*-hydrazoneyl chlorides **Ia-e** were synthesized by treatment of oxalic *bis*-(*N*-arylhydrazides) **2a-e** with triphenylphosphine and carbon tetrachloride in refluxing acetonitrile (**Scheme 3**) [3,4,30,31]. Recently, *N*¹,*N*³-diphenyl-1,3-benzene-*bis*-carbohydrazoneyl bromide **IIIB** was prepared by reaction of *N*¹,*N*³-diphenylisophthalohydrazide with triphenylphosphine and carbon tetrabromide in acetonitrile at room temperature (**Scheme 3**) [32].

Also, heating the *bis*-hydrazide **3** with phosphorus pentachloride in anhydrous ether under reflux for 24 h gave the *bis*-hydrazoneyl chloride **VIII** in 57% yield (**Scheme 4**) [33].

Direct halogenation of bis(aldehyde arylhydrazones)

Chattaway and his coworkers [1] were the first to report that reaction of glyoxal-osazones **4a-c** each with chlorine in acetic acid yielded 1,2-dichloroglyoxal bis(2,4-dichlorophenylhydrazone) **1a-c**, respectively (Scheme 5). Similar chlorination of **4d** yielded the bis-hydrazoneyl chloride **1d** (Scheme 5) [1]. The product **1a** was also obtained in 30% yield by treatment of **4a** with sulfuryl chloride in chloroform [29].

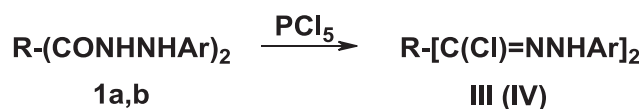
Similarly, direct bromination of bis-hydrazones **4a-c** each with bromine in acetic acid afforded the corresponding bis-hydrazoneyl bromides **11a-c** (Scheme 6) [1].

Farag et al. [4] and Shawali et al. [34] synthesized N,N-di(*p*-nitrophenyl) ethane-1,2-bis-hydrazoneyl bromide **11d** in 86% yield by direct bromination of the corresponding bis-hydrazone **4d** with bromine in acetic acid (Scheme 7).

Treatment of bis-(2-chlorophenylhydrazones) **5a,b** with N-bromosuccinimide (NBS) in tetrahydrofuran (THF) at room temperature gave the corresponding bis-hydrazoneyl bromides **Xa,b**, respectively (Scheme 8) [35].

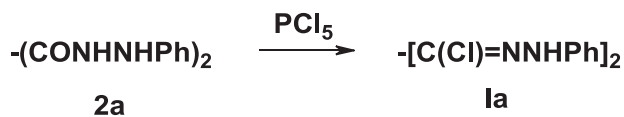
Diazo coupling with activated α -halo-methinyl compounds

α -Halo-methinyl compounds activated by two electron withdrawing groups, such as COCH₃, CN, and COOR couple readily with arene-diazonium salts in basic aqueous media to

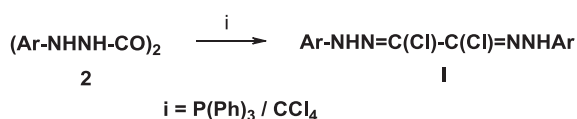


R : 1a (III), 1,3-C₆H₄ ; 1b(IV), 1,4-C₆H₄

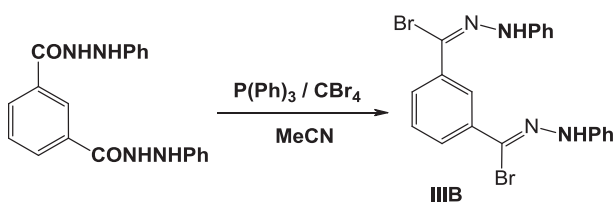
Scheme 1



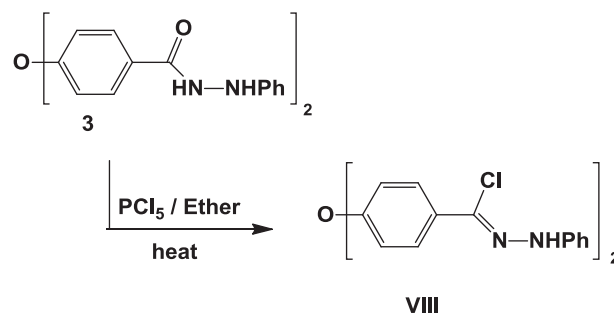
Scheme 2



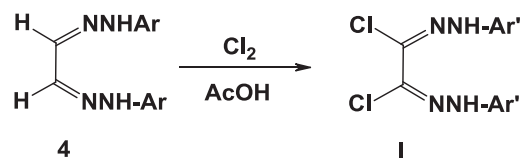
**Ar : X_nC₆H_{5-n}; X : a, H; b, 2-Me; c, 4-Me; d, 4-Cl; e, 2,4-Cl₂;
f, 2,6-Me₂**



Scheme 3

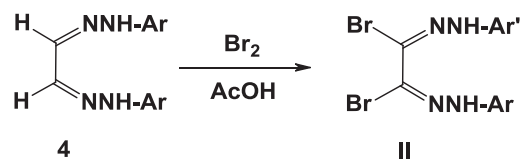


Scheme 4



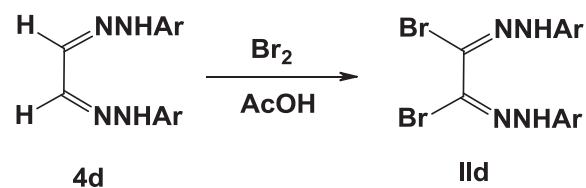
**Ar : a, C₆H₅; b, 4-ClC₆H₄; c, 2,4-Cl₂C₆H₃; d, 2,4,6-Cl₃C₆H₂
Ar' = 2,4-Cl₂C₆H₃**

Scheme 5



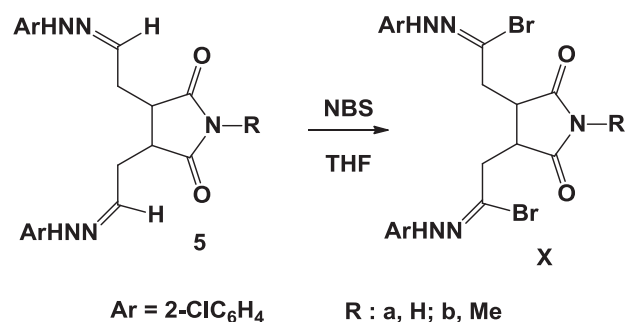
**Ar : a, C₆H₅; b, 4-BrC₆H₄; c, 2,4-Br₂C₆H₃
Ar' = 2,4-Br₂C₆H₃**

Scheme 6

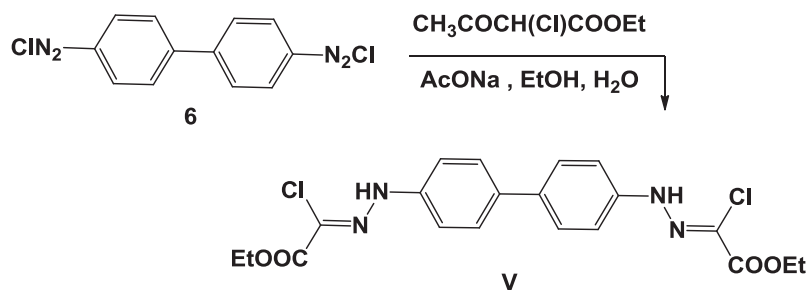


Ar = *p*-O₂NC₆H₄

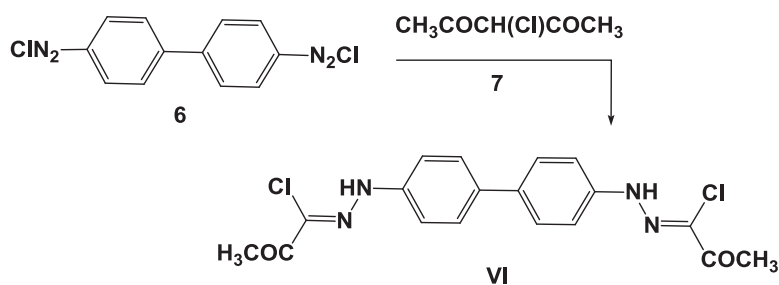
Scheme 7



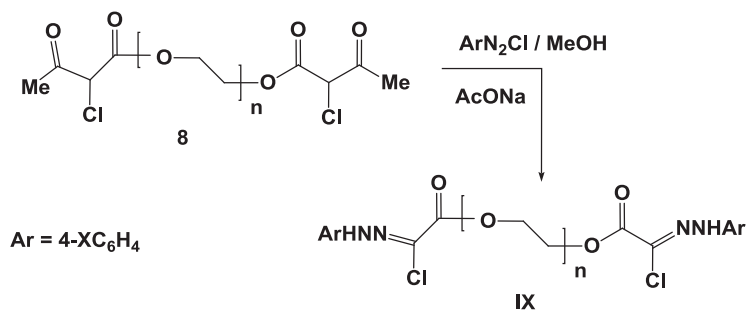
Scheme 8



Scheme 9



Scheme 10



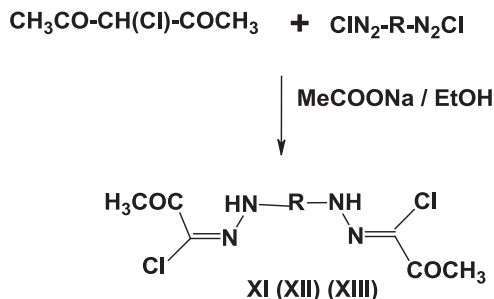
X / n : a, Cl / 1; b, Cl / 2; c, Me / 2; d, Me / 2

Scheme 11

generate the corresponding hydrazoneyl halides. This coupling reaction occurs in the presence of a base such as pyridine or sodium acetate to give primarily the azo intermediate, which is then converted into the desired hydrazoneyl halide in high yield (80–95%) *via* the loss of one of the groups according to the following order: COOH > CHO > COMe > COAr > COOR > CONH₂ > CN. For example, the *bis*-hydrazoneyl chloride **V** was recently prepared by coupling of benzidine dia-

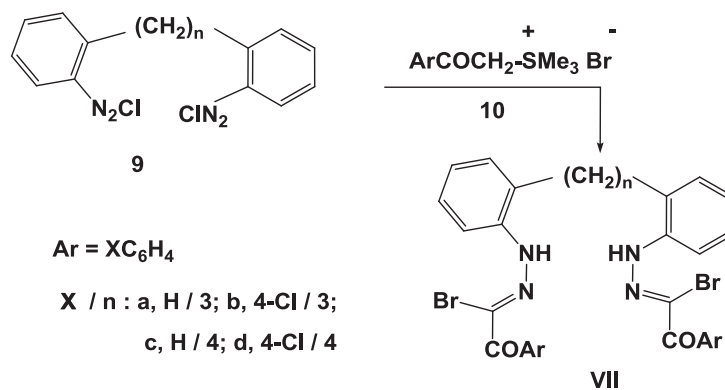
zonium chloride **6** with ethyl 2-chloro-3-oxobutanoate in aqueous-ethanolic sodium acetate solution (Scheme 9) [36].

Similarly, the coupling of 3-chloro-2,4-pentanedione **7** with diazonium chloride of benzidine **6** in ethanol, in the presence of sodium acetate afforded *N,N'*-(biphenyl-4,4'-diyl)-*bis*-(2-oxopropanehydrazoneyl chloride) **VI** (Scheme 10). The results of evaluating the anticancer activity of **VI** against colon carcinoma (HCT) revealed that it has moderate activity [37].

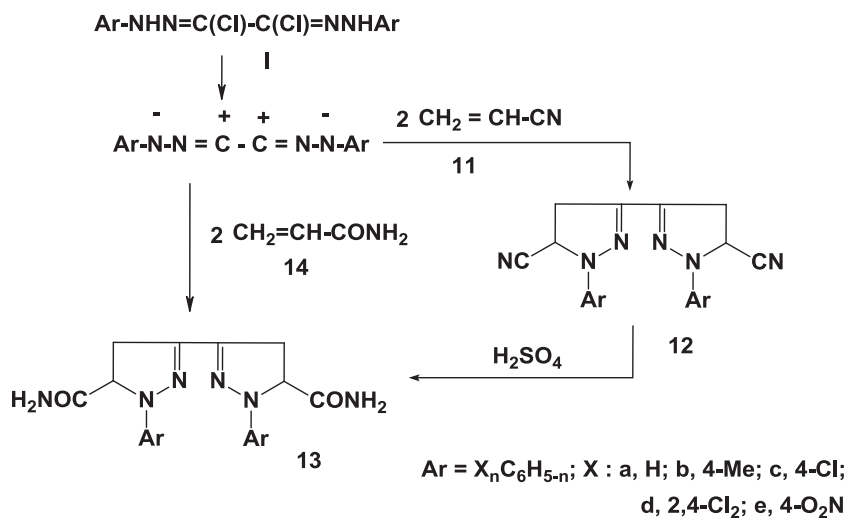


R : XI, 1,4-C₆H₄-SO₂-C₆H₄-1,4; XII, 1,3-C₆H₄; XIII, 1,4-C₆H₄-S-C₆H₄-1,4

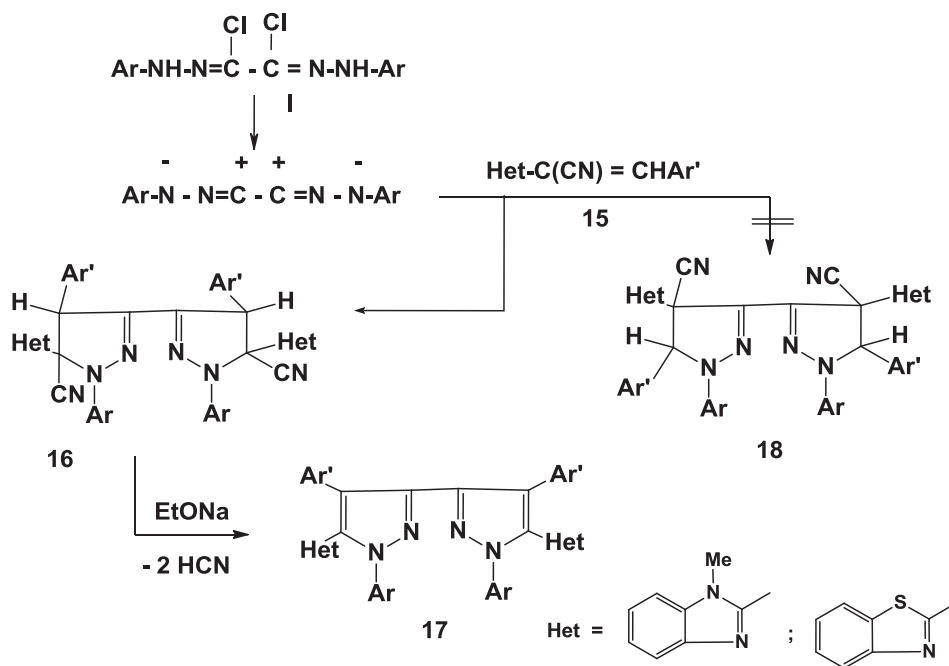
Scheme 12



Scheme 13



Scheme 14



$\text{Ar}' : \text{a, Ph}; \text{b, 4-ClPh}; \text{c, 4-O}_2\text{NPh} \quad \text{Ar} : \text{a, Ph}; \text{b, 4-MePh}; \text{c, 4-ClPh}$

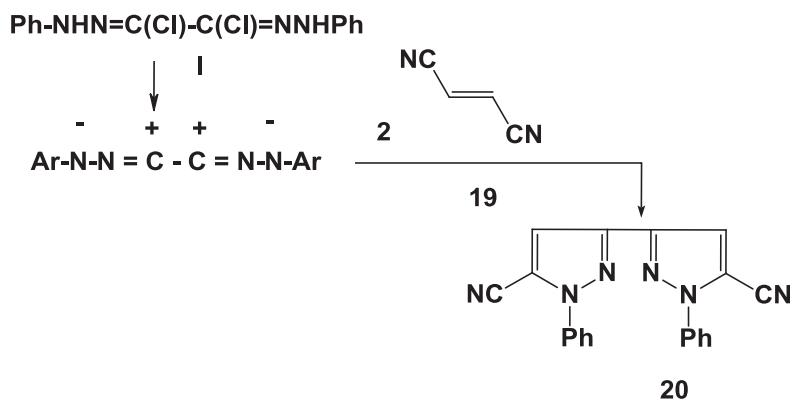
Scheme 15

Also, the reactions of aryldiazonium chlorides with each of compounds **8a-d** in ice cold methanol in the presence of sodium acetate yielded the corresponding *bis*-hydrazoneyl chlorides **IXa-d** in 51–83% yield (Scheme 11) [38].

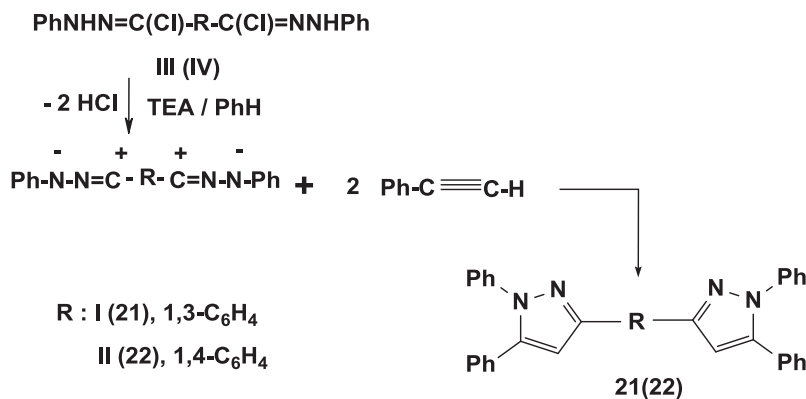
The *bis*-hydrazoneyl halides **XI-XIII** were prepared by coupling of 3-chloro-2,4-pentanedione with each of the corresponding diazotized diamines in ethanol in the presence of sodium acetate trihydrate (Scheme 12) [55].

Coupling of phenacyl trimethylsulfonium bromides with diazotized bis-amines

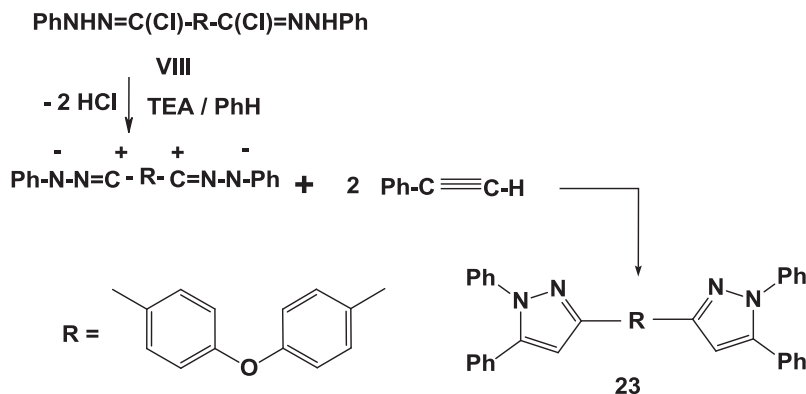
Coupling of the *bis*-diazonium salts **9a,b** each with the appropriate sulfonium bromide **10b** in ethanol in the presence of sodium acetate gave the *bis*-hydrazoneyl bromides **VIIa-d** in 60–75% yields (Scheme 13) [39].



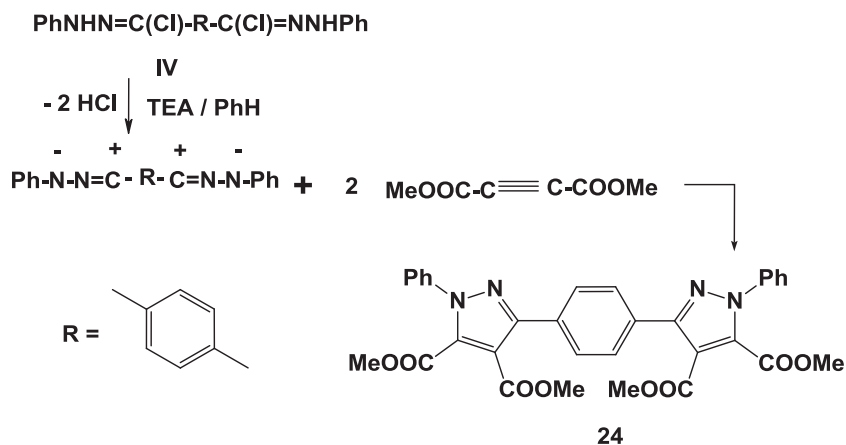
Scheme 16



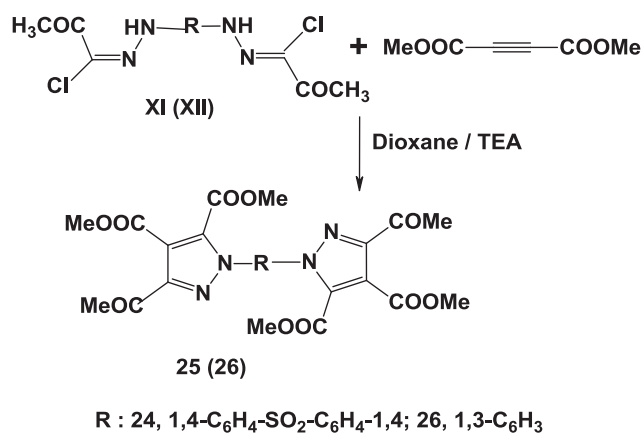
Scheme 17



Scheme 18



Scheme 19



Scheme 20

Reactions

Cycloaddition reactions

Reaction with acrylonitriles

Reaction of *bis*-nitrilimines, generated by treatment of the corresponding *bis*-hydrazonoyl halides **I**, with acrylonitrile **11** was found to give regioselectively the *bis*-cycloadduct **12** (Scheme 14) as the sole product in 51–73% yield [34]. The structure assigned was evidenced by ¹H NMR data and was confirmed by conversion into **13** which was prepared by reaction of the same *bis*-nitrilimine with acrylamide **14** as outlined in Scheme 14.

Similar reactions of 3-aryl-2-heteroaryl-acrylonitriles **15** with *bis*-nitrilimines derived from the *bis*-hydrazonoyl chloride **I** in benzene at reflux were reported to give exclusively the *bis*-cycloadducts namely 5,5'-dicyano-4,4', 5,5'-tetrahydro[3,3'-bi-1*H*-pyrazole] **16** (Scheme 15) [2]. The structures of the isolated cycloadducts were elucidated on the basis of their spectral (IR, ¹H NMR and ¹³C NMR) data. The formation of **16** and exclusion of its regio-isomer **18** were confirmed by chemical transformation. For example, treatment of the cycloadducts **16** with sodium ethoxide in refluxing ethanol resulted in elimination of hydrogen cyanide and the formation of the respective *bis*-3,3'-pyrazole derivatives **17** (Scheme 15) [2].

Also, it was reported that reaction of *bis*-hydrazonoyl chloride **I** with 1,2-dicyanoethylene **19** in 1: 2 molar ratio in refluxing benzene in the presence of triethylamine yielded 1,1'-diphenyl-3,3'-bipyrazole-4,4'-dicarbonitrile **20** (Scheme 16) [40].

Reaction with phenylacetylene

Reactions of *bis*-hydrazonoyl chlorides **III** (**IV**) each with phenylacetylene in refluxing benzene in the presence of triethylamine yielded the corresponding 1,3- and 1,4-*bis*-(1,5-diphenylpyrazol-3-yl)-benzene derivatives **21**(**22**), respectively in 55–57% (Scheme 17) [28,41].

Similar reaction of *bis*-hydrazonoyl chloride **VIII** with phenylacetylene in refluxing benzene in the presence of triethylamine yielded the corresponding *bis*-cycloadduct **23** in 55–57% (Scheme 18) [33].

The reactions of the *bis*-hydrazonoyl chlorides **IV** [42], **XI** and **XII** [55] each with dimethyl acetylenedicarboxylate in dioxane in the presence of triethylamine yielded the corresponding *bis*-cycloadduct **24** (Scheme 19).

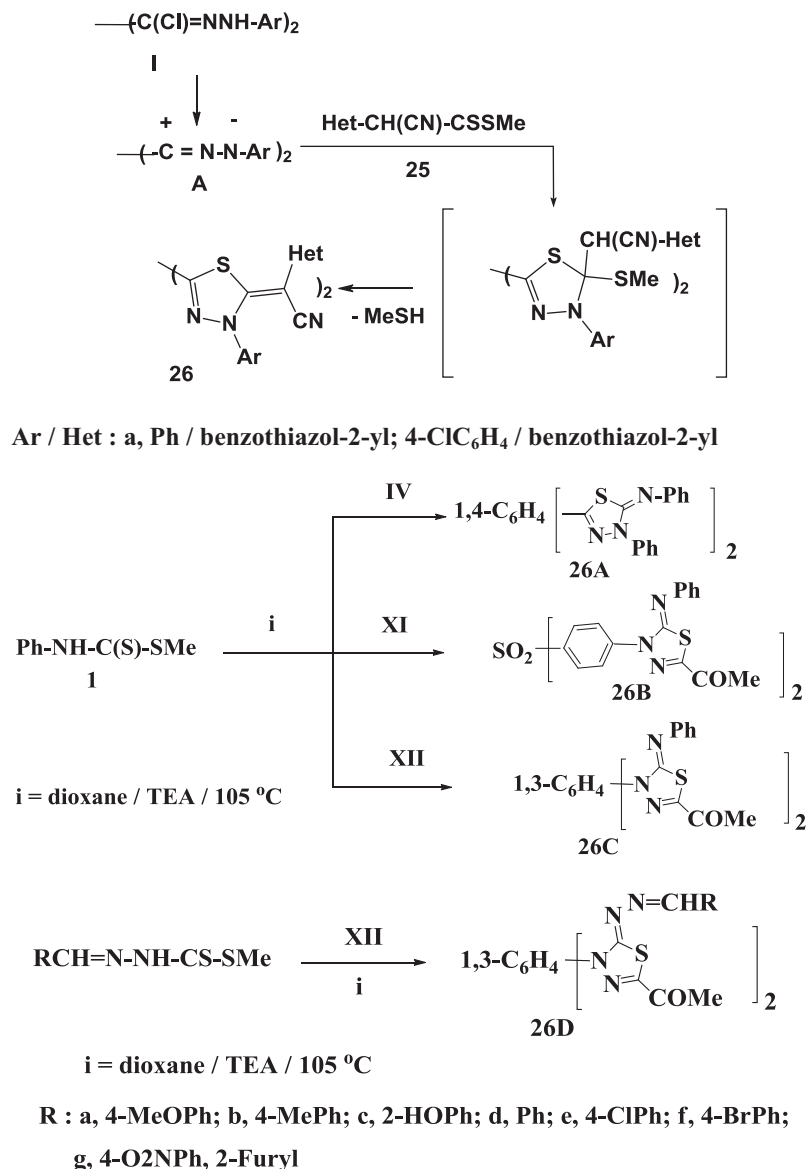
Also, the reactions of the *bis*-hydrazonoyl chlorides **XI** and **XII** [54] each with dimethyl acetylenedicarboxylate in dioxane in the presence of triethylamine afforded the corresponding *bis*-cycloadducts **25** and **26** (Scheme 20).

Reactions with dithiocarboxylate esters

Reactions of *bis*-nitrilimines, derived from the *bis*-hydrazonoyl chlorides **I** with methyl 2-cyano-2-(hetaryl)dithiocarboxylates **25** gave the corresponding *bis*-2,2'-(1,3,4-thiadiazole) derivatives **26** in 83–90% yield (Scheme 21) [43].

The reaction of *bis*-hydrazonoyl dichlorides (**IV**, **XI** and **XII**) with the methyl-*N*-phenylethanimidiothioate in dioxane in the presence of triethylamine at 105 °C was reported to afford the corresponding acyclic thiohydrazonates which underwent *in situ* elimination of methanethiol to give the compounds (**26A-C**) as final products, respectively (Scheme 21) [59].

Similar reaction of methyl-2-arylidene hydrazine-carbodithioates with the *bis*-hydrazonoyl chloride **XII** in dioxane and in the presence of triethylamine by heating until complete elimination of methanethiol gas was reported to give the corresponding *bis*-(5-((arylidene)hydrazono)-4,5-dihydro-1,3,4-thiadiazole-4,2-diyl)diethanone **26D** (Scheme 21) [59].



Scheme 21

Reactions with thiocarboxamides

Bis-2,2'-(1,3,4-thiadiazole) derivatives **28** have been obtained in 83–90% yield by reaction of the bis-nitrilimines, derived from the respective bis-hydrazoneyl chlorides **I**, with *N*-phenyl 2-cyano-2-(benzothiazol-2-yl)thioamide **27** under the same reaction conditions (Scheme 22) [43].

Also, it was reported that reactions of the bis-hydrazoneyl chloride **I** with the potassium salt each of the acyl-substituted thioanilides **29A** was also reported to give the bis(1,3,4-thiadiazole) derivatives **30A**, respectively (Scheme 23) [40].

Treatment of the bis-hydrazoneyl chloride **I** with potassium salts of active methinethioanilides **29A** was also reported to give the bis(1,3,4-thiadiazole) derivatives **30A**, respectively (Scheme 23) [58].

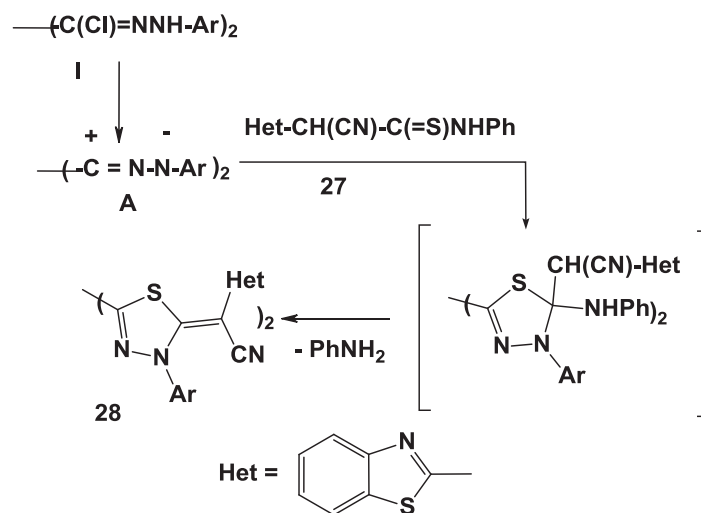
Similarly, it was reported recently that treatment of *N,N'*-(biphenyl-4,4'-diyl)bis(2-oxopropanehydrazoneyl chloride) **VI** (1 mol) with 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-mercapto-3-(phenylamino)-acrylamide (2 mol) in ethanol, in the presence of catalytic amount of

triethylamine, furnished 2,2'-[3,3'-(biphenyl-4,4'-diyl)bis(5-acetyl-1,3,4-thiadiazole-3(3*H*)-yl-2(3*H*)-ylidene)]bis[2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide] **33** (Scheme 24) [37]. The reaction was considered to proceed *via* *S*-alkylation to give bis(*S*-alkylated) intermediate **31** which undergoes intramolecular Michael type addition under the employed reaction conditions to afford the bis-cycloadduct **32**. Elimination of two moles of aniline from **32** yielded the final product **33**. The latter product was reported to exhibit moderate anticancer activity against the colon carcinoma (HCT) cell line [37] (Scheme 24).

Recently, it was reported that reaction of the thiocarboxamides **34a,b** each with the bis-hydrazoneyl chloride **XI** in boiling DMF in the presence of triethylamine yielded the bis-thiazoline derivatives **35a,b**, respectively (Scheme 25) [55].

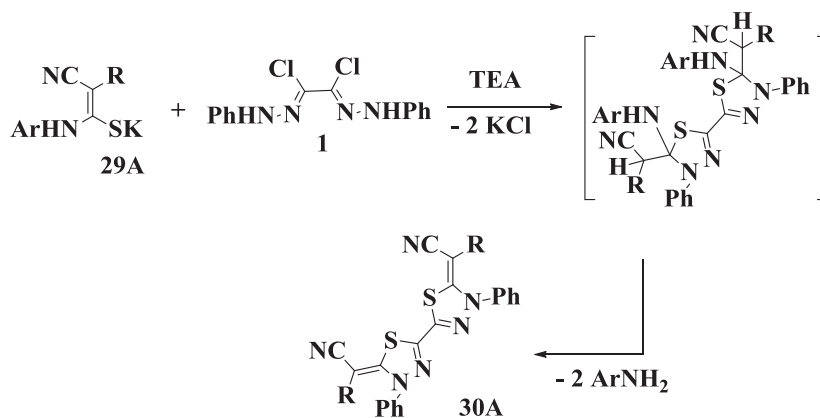
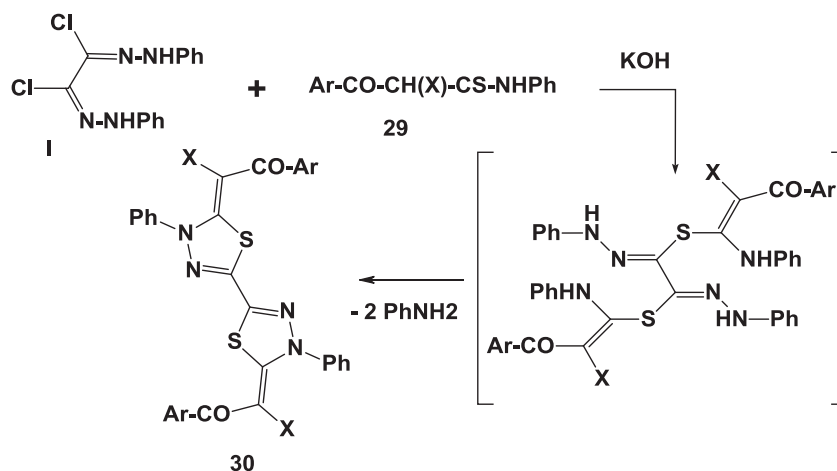
Reactions with carbonothioic dihydrazides

Similarly, reactions of carbonothioic dihydrazide **36** with the bis-hydrazoneyl chlorides **IV** in DMF in the presence of

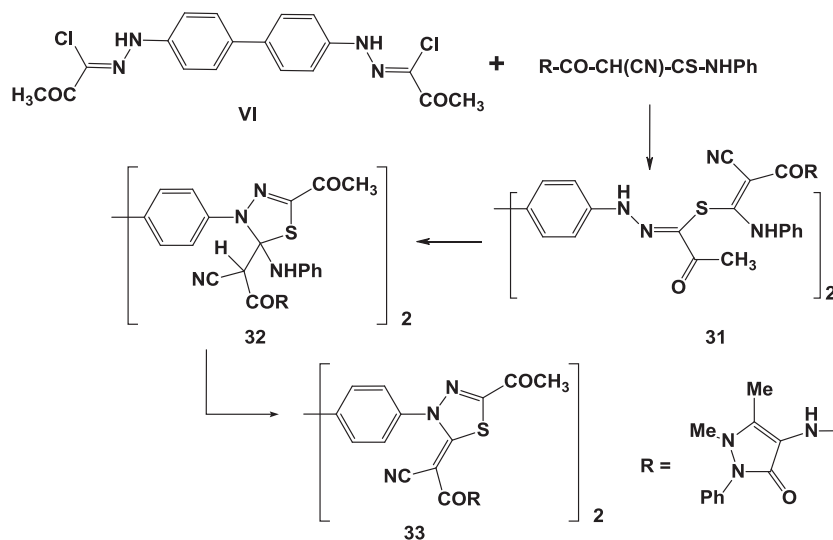


Ar / Het : a, Ph / Benzothiazol-2-yl; b, 4-ClPh / Benzothiazol-2-yl

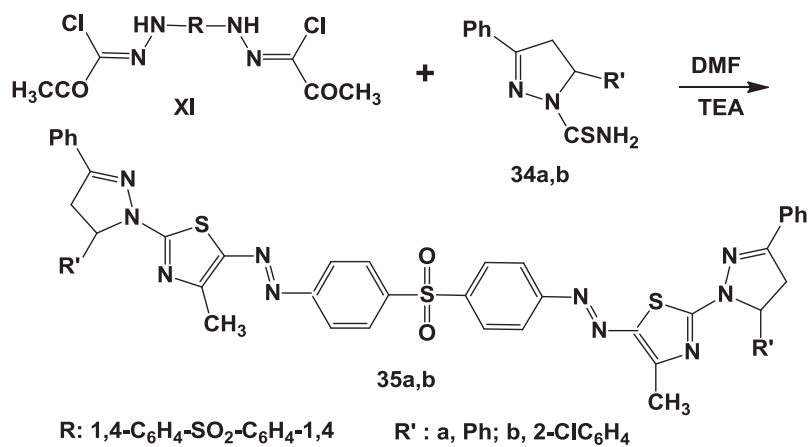
Scheme 22



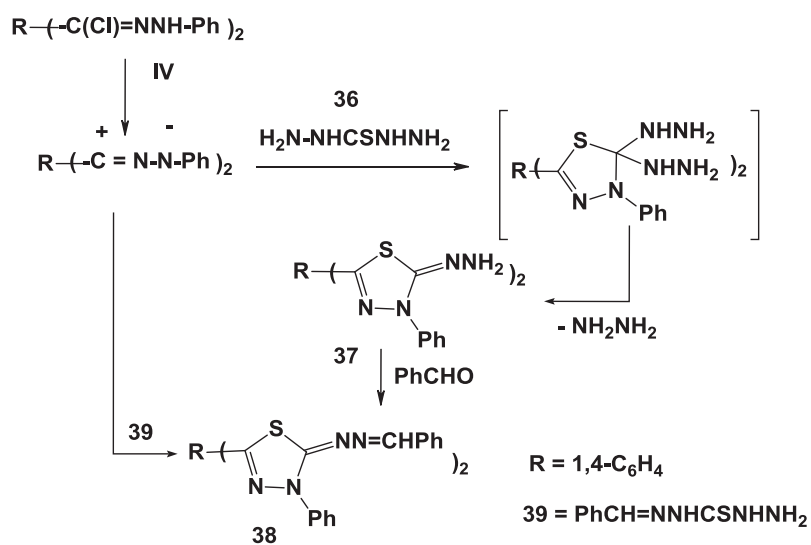
Scheme 23



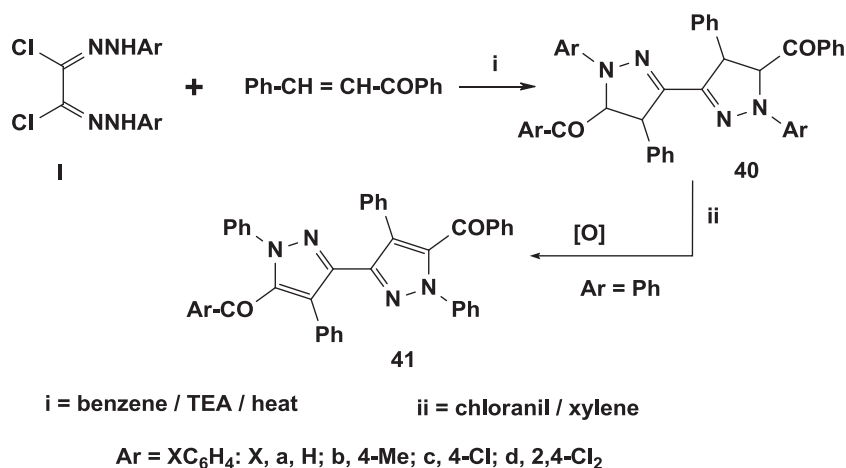
Scheme 24



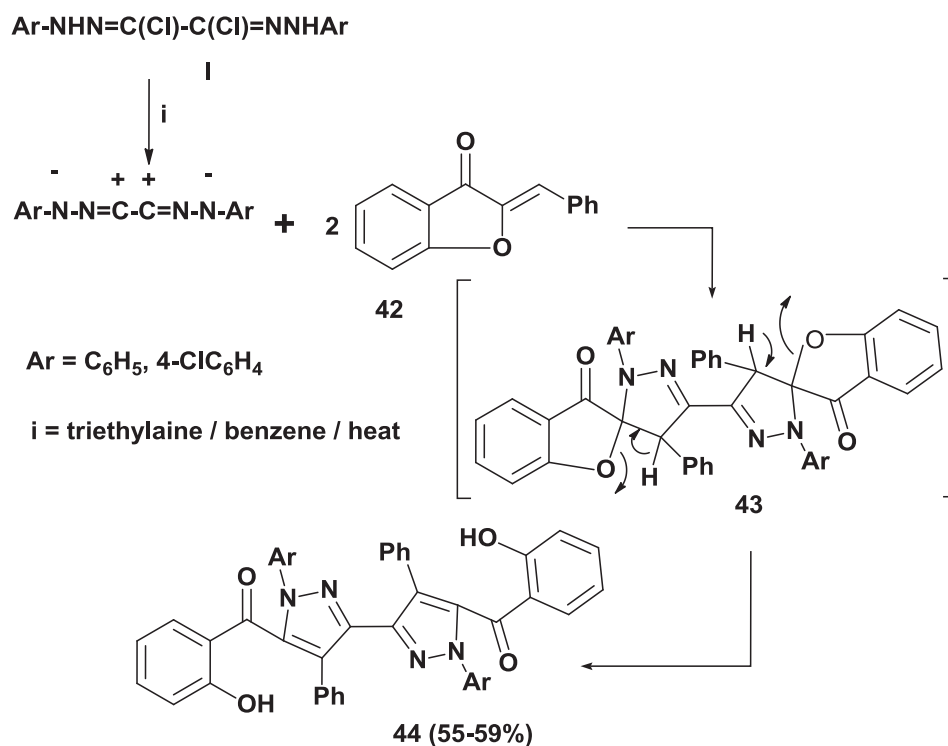
Scheme 25



Scheme 26



Scheme 27



Scheme 28

triethylamine furnished the corresponding 2,2'-bis(1,3,4-thiadiazole) derivatives **37** in about 60% yield (Scheme 26) [44,45]. Compound **37** reacted with benzaldehyde to give the bis-hydrazone **38**. The latter was also obtained by reaction of the bis-hydrazoneyl chloride **IV** with 2-(phenylmethylene)carbothioic dihydrazide **39** in ethanolic triethylamine (Scheme 26) [45].

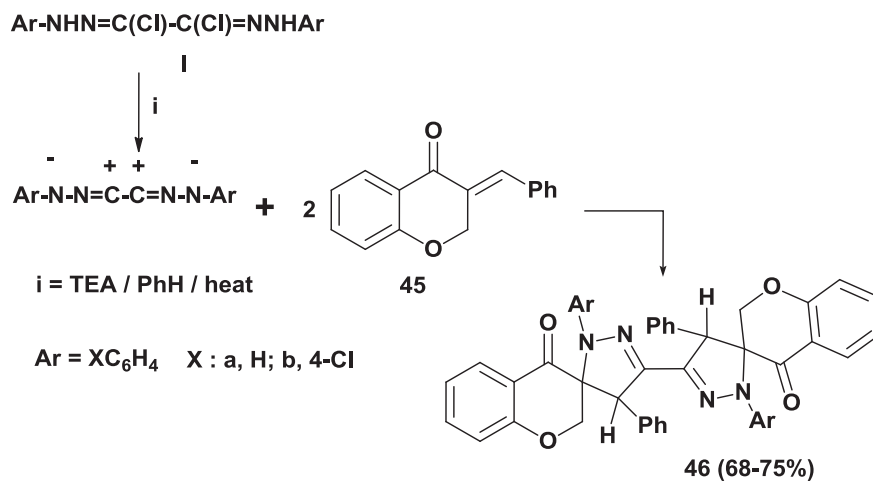
Reactions with enones

Reactions of the bis-hydrazoneyl chlorides **Ia-d** each with benzalacetophenone in refluxing benzene in the presence of triethylamine were reported to afford the corresponding 3,3'-bispyrazoline derivatives **40a-d** [34]. Treatment of **40a** with chloranil in xylene resulted in their oxidation to yield the bis-pyrazole derivative **41a** (Scheme 27) [34].

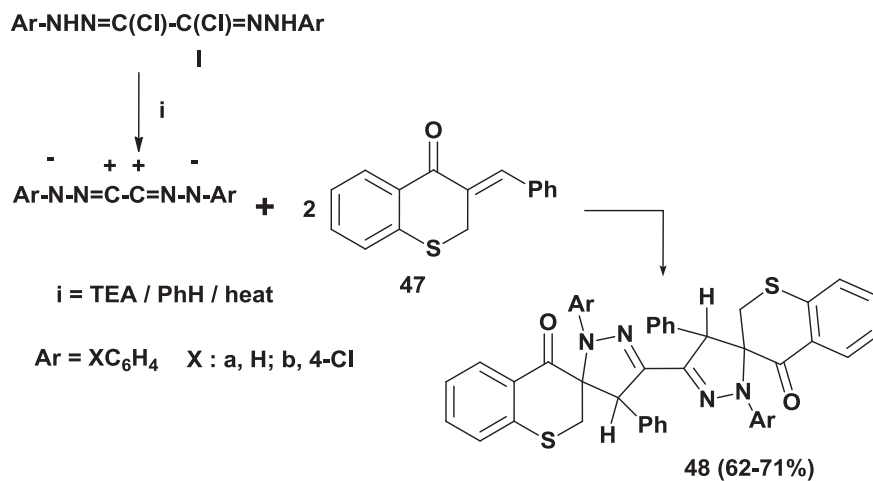
Similarly, the reaction of each of the hydrazoneyl chlorides **I** with 2-benzylidene-coumaranone **42** in refluxing benzene in the presence of triethylamine was reported to give 5,5'-di-(2-hydroxybenzoyl)-1,1',4,4'-tetraphenyl-3,3'-bipyrazoles **44**. The formation of the latter products was assumed to result *in situ* ring opening of the initially formed bis-spiropyrazolocoumaranone derivatives **43** (Scheme 28) [46].

The 1,3-dipolar cycloaddition of bis-nitrilimines, generated *in situ* by triethylamine catalyzed dehydrochlorination of the respective bis-hydrazoneyl chloride **I** in refluxing benzene, to (E)-3-benzylidene-chroman-4-one **45** was reported to be regioselective as it yielded the corresponding bis-[1,4-diaryl-spiropyrazoline-5,3'-chroman-4-ones **46** (Scheme 29) [46].

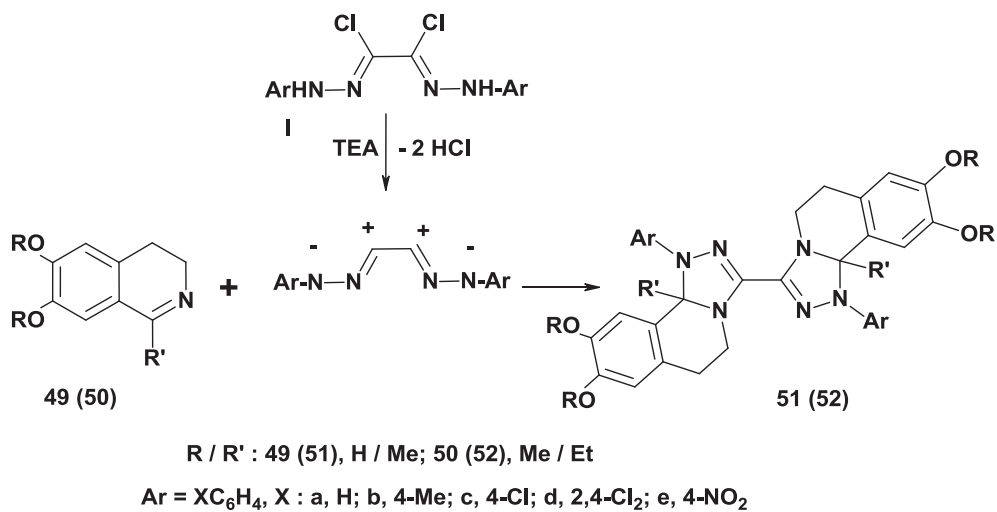
Also, bis-[1,4-diaryl-spiropyrazoline-5,3'-thiochroman-4-ones **48** were easily prepared by reaction of the hydrazoneyl



Scheme 29



Scheme 30



Scheme 31

chlorides **I** with 3-benzylidene-thiochroman-4-one **47** in refluxing benzene in the presence of triethylamine (Scheme 30) [46].

Reaction with endocyclic C=N bond

Two series of 3,3'-(1,3,4-triazolo[3,4-a]isoquinolines) **51(52)** were prepared by reaction with each of the *bis*-hydrazonoyl halides **I** with isoquinolines **49(50)** in refluxing benzene in the presence of triethylamine (Scheme 31) [34].

Reactions with alkenes

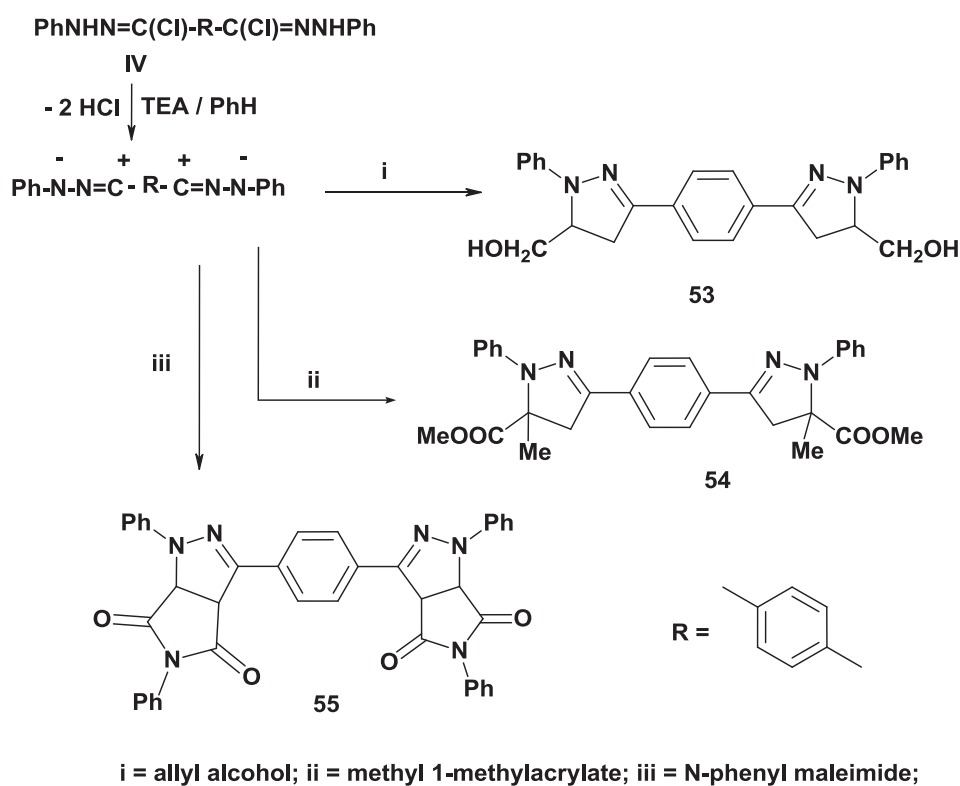
Iwakura et al. [42] reported that the *bis*-hydrazonoyl chloride **IV** reacted with various olefinic dipolarophiles such as allyl alcohol, methyl 1-methylacrylate and *N*-phenyl maleimide in benzene in the presence of triethylamine yielded the corresponding *bis*-cycloadduct **53-55** (Scheme 32).

Reaction of the *bis*-hydrazonoyl chloride **IV** with bicyclo [2.2.1]hept-2-ene in refluxing dimethylformamide in the presence of triethylamine yielded the *bis*-cycloadduct **56** in 71% yield (Scheme 33) [47].

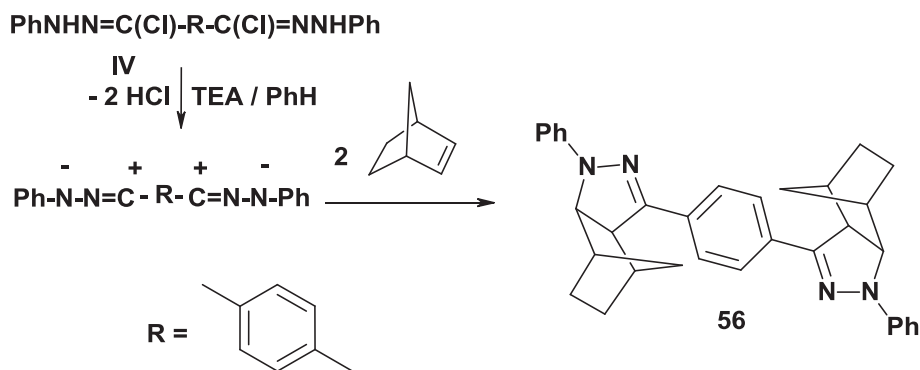
Following the multiple cycloadditive macrocyclization between *bis*-nitrile oxides and bifunctional dipolarophiles introduced by Kim and co-workers [48], it was reported a version of the same methodology based upon the double cycloaddition between *bis*-hydrazonoyl chlorides **IX** and *bis*-dipolarophiles **57** in the presence of silver carbonate as the basic agent yielded macrocyclic products **58** and **59** were obtained with good combined yields (36–59%) (Scheme 34) [38].

Reaction with enamines

Reaction of the *bis*-hydrazonoyl chloride **VI** with 3-(dimethylamino)-1-propene-2-one **60** in refluxing benzene in



Scheme 32



Scheme 33

the presence of triethylamine furnished the *bis*-pyrazole derivative **61** (Scheme 35) [50]. The latter product showed moderate activity against *Aspergillus fumigates* (AF), *Candida albicans* (CA) and *Geotrichum candidum* (GC) fungi [49].

Reactions with thiosemicarbazones

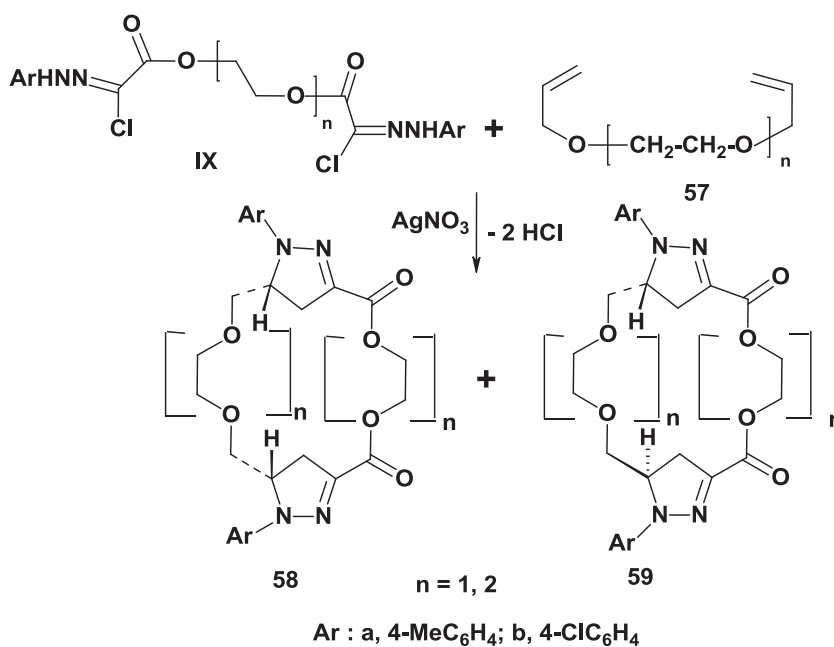
Reactions of the *bis*-hydrazoneyl chlorides **IX** with each of the appropriate thiosemicarbazone derivatives **62a-d** in dioxane in the presence of triethylamine were reported to yield the *bis*-thiazole derivatives **63a-d**, respectively [55] (Scheme 36).

Also, the *bis*-hydrazoneyl chloride **XII** was reported to react similarly with each of the appropriate thiosemicarbazone **64** in dioxane in the presence of triethylamine at 105 °C to yield the corresponding *bis*-thiazole derivatives **65a-d**, respectively [55] (Scheme 37).

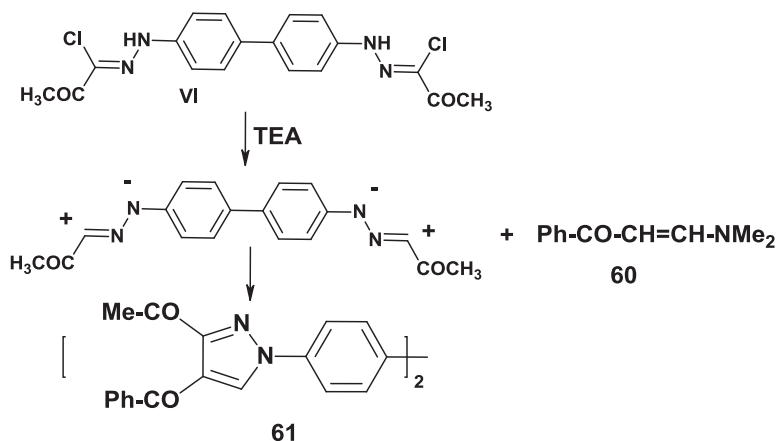
Reactions with nucleophiles

Reaction with sodium azide

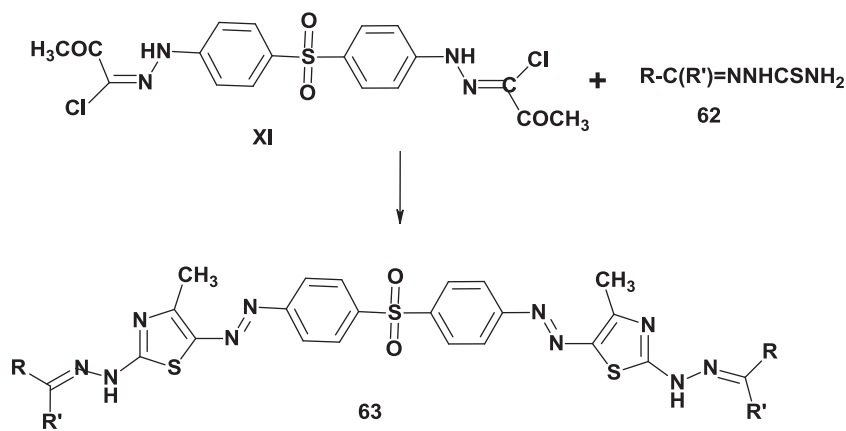
Shawali et al. [3] reported that treatment of the *bis*-hydrazoneyl halides **I** each with sodium azide in dimethylformamide at room temperature yielded the *bis*-azide derivatives **66**. The latter were reduced by lithium aluminum hydride in ether to afford the corresponding *bis*-amidrazones **67** in almost quantitative yield. Reaction of the latter with acyl chlorides in refluxing benzene afforded 3,3'-*bis*(1,5-disubstituted-1,2,4-triazoles) **68** (Scheme 38) [3]. The latter products **68** were also obtained by treatment of the *bis*-azide derivatives **66** with triphenylphosphine in refluxing benzene followed by reaction



Scheme 34

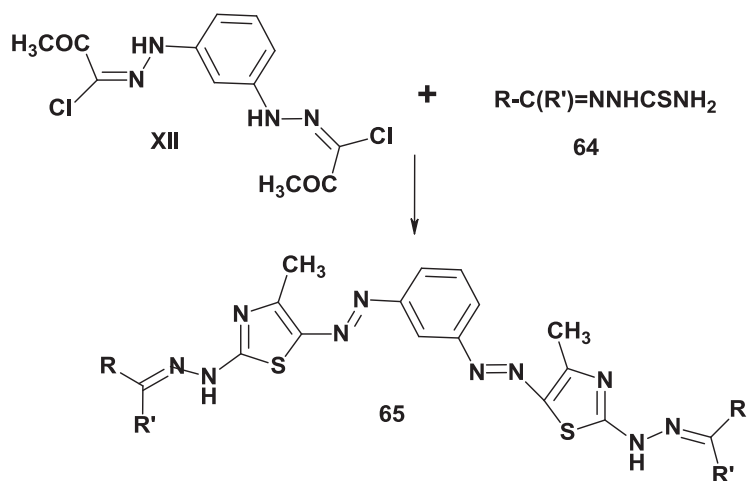


Scheme 35



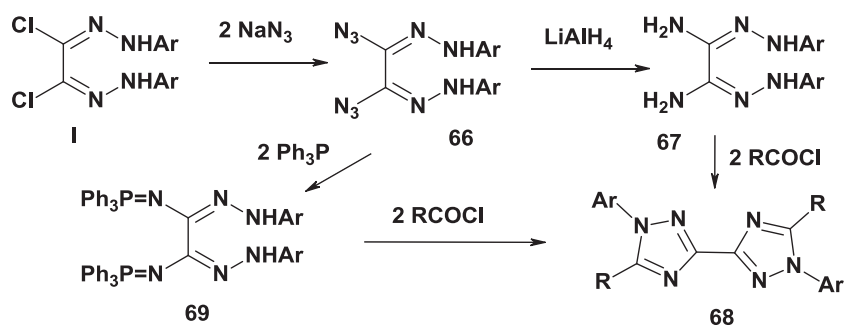
$\text{R / R' : a, H / XC}_6\text{H}_4$; b, H / 2-furyl ; c, H / 2-pyridyl ; d, Me / 2-thienyl
 $\text{X = H; 4-Me; 4-Br; 2-HO}$

Scheme 36



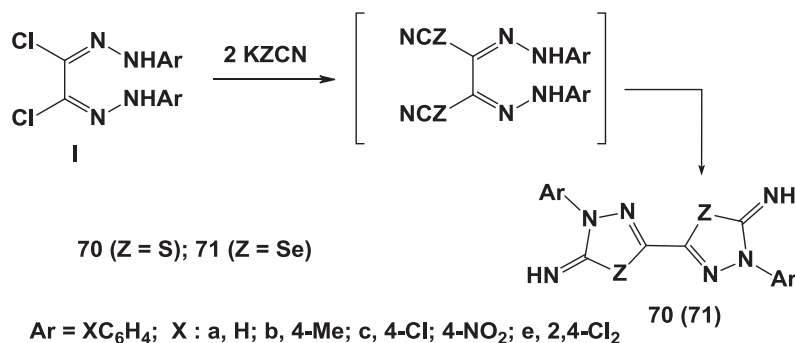
$\text{R / R' : a, H / XC}_6\text{H}_4$; b, H / 2-furyl ; c, H / 2-pyridyl ; d, Me / 2-thienyl
 $\text{X = H; 4-Me; 4-Br; 2-HO}$

Scheme 37

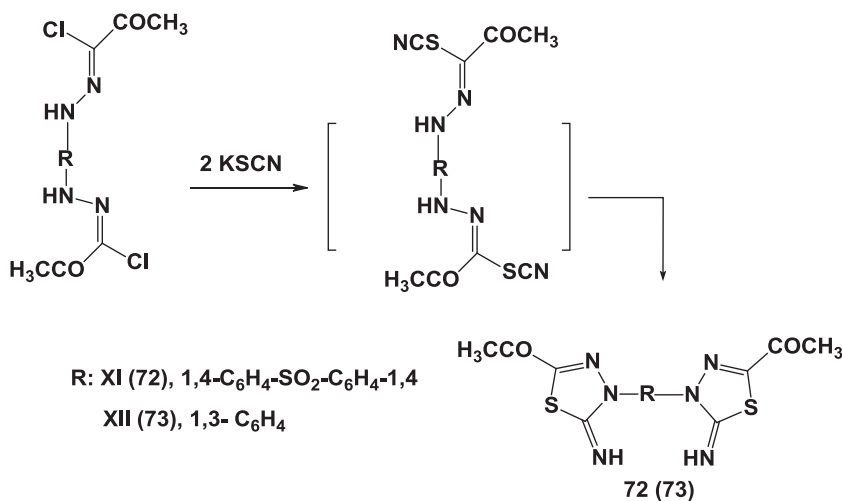


$\text{Ar = XC}_6\text{H}_4$; X : H; 4-Cl
 $\text{R = YC}_6\text{H}_4$; ClCH_2 ; $\text{Y : a, H; b, 4-Me; c, 4-Cl; d, 3-NO}_2$

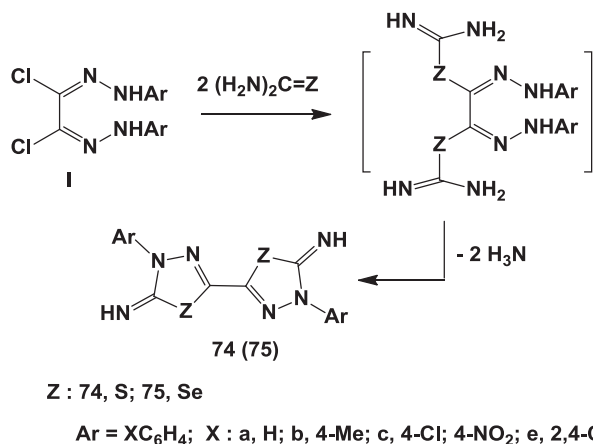
Scheme 38



Scheme 39



Scheme 40



Scheme 41

of the resulting bis-phosphonimines **69** with acyl chlorides (Scheme 38) [3].

Reaction with potassium selenocyanate and thiocyanate

Reaction of the bis-hydrazonoyl halides **I** each with potassium thiocyanate [4] and potassium selenocyanate [5] in refluxing ethanol yielded the 2, 2'-bis(4,5-dihydro-1,3,4-thiadiazole)

and 2,2'-bis(4,5-dihydro-1,3,4-selenadiazole) derivatives **70** (**71**), respectively (Scheme 39).

Treatment of the bis-hydrazonoyl chlorides **XI** and **XII** each with potassium thiocyanate [56] in refluxing ethanol yielded the 2,2'-bis(4,5-dihydro-1,3,4-thiadiazole) derivatives **72** (**73**), respectively (Scheme 40) [56].

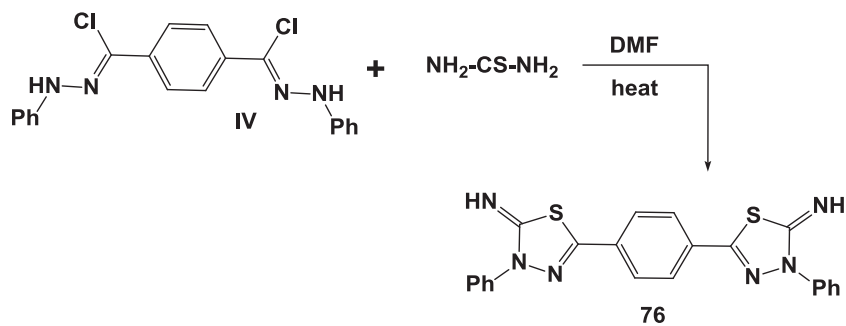
Reaction with thiourea and selenourea

Reaction of the bis-hydrazonoyl chlorides **I** each with thiourea [4] and selenourea [5] in refluxing ethanol yielded the corresponding bis-3,3'-(1-aryl-5-imino[1,3,4]thiadiazoles) **74** and bis-3,3'-(1-aryl-5-imino[1,3,4]selenadiazoles) **75** (Scheme 41).

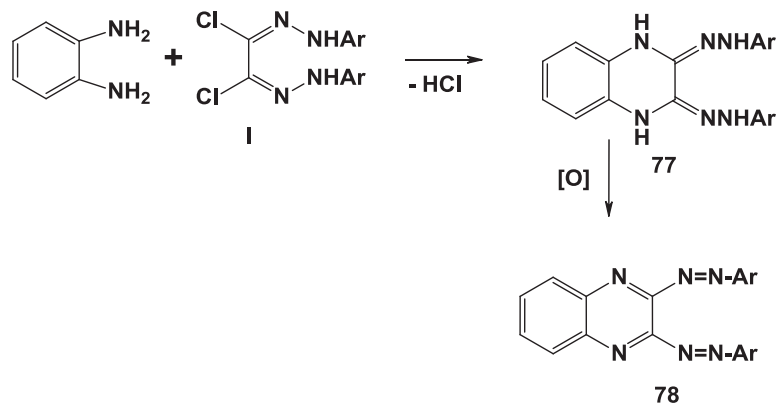
Also, treatment of bis-hydrazonoyl dichlorides **IV** with thiourea in DMF under heating gave 1, 4-bis(3-phenyl-3H-[1,3,4]thiadiazol-5-imino)benzene **76** via elimination of HCl and ammonia as shown in Scheme 42 [50].

Reactions with diamines

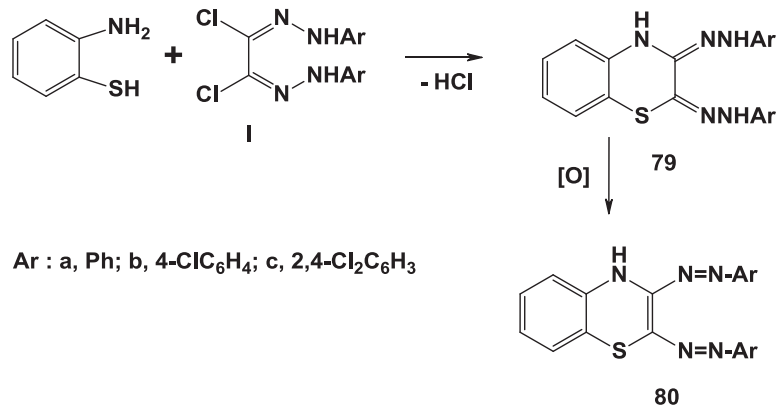
Reaction of the bis-(hydrazonoyl chloride) **I** with *o*-phenylenediamine gives the bis-hydrazone derivative **77** that was converted into 2,3-bis-(aryloxy)quinoxaline **78** upon treatment with iodobenzene bis-trifluoroacetate (Scheme 43) [51].



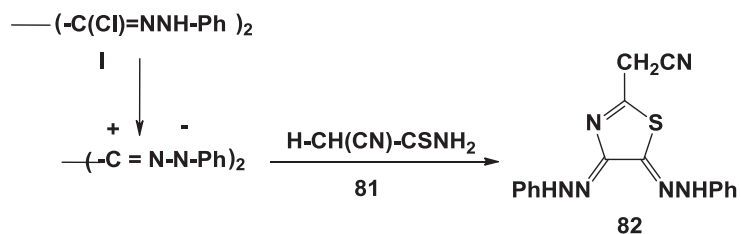
Scheme 42



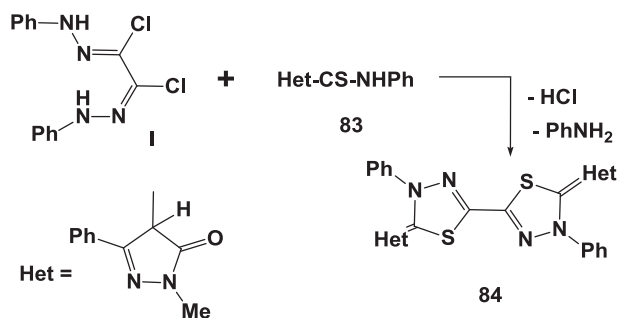
Scheme 43



Scheme 44



Scheme 45



Scheme 46

Reactions with aminothiophenol

Bis-hydrazoneyl chlorides **I** were reported to react with 2-aminothiophenol and give the bis-hydrazone derivatives **79** that were readily oxidized to 2,3-bis-(aryloxy)-1,4-benzothiazines **80** (Scheme 44) [4].

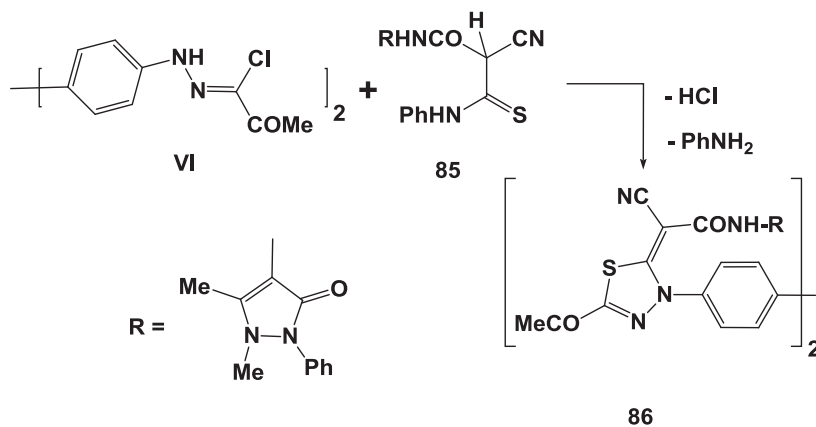
Reactions with thioamides

Reaction of the bis-hydrazoneyl chloride **I** with cyanothioacetamide **81** in refluxing ethanol in the presence of triethylamine was reported twice [40] to yield 2,3-bis(phenylhydrazone)-5-cyanomethylthiazole **82** (Scheme 45).

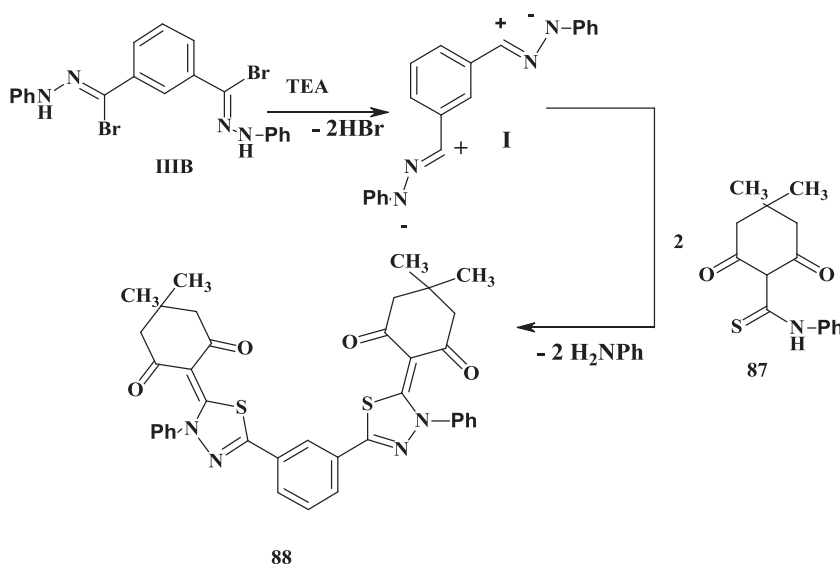
Treatment of the bis-hydrazoneyl chloride **I** with 1-methyl-5-oxo-3-phenyl-2-pyrazolin-4-thiocarboxanilide **83** in ethanol in the presence of triethylamine under ultrasonic irradiation was reported to afford the bis-1,3,4-thiadiazole derivative **84** in 90% yield within 15 min. (Scheme 46) [52]. Repetition of this reaction under the same conditions in the absence of ultrasonic irradiation decreased the yield to 70% and increase in time up to 3 h [52].

Similarly, treatment of the bis-hydrazoneyl chloride **VI** with the thioanilide **85** in ethanol in the presence of triethylamine was reported to furnish the bis-thiadiazole derivative **86** in 68% yield (Scheme 47) [37].

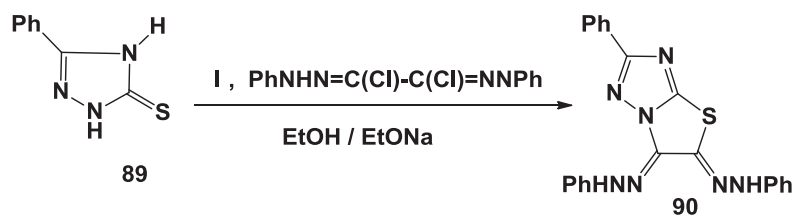
Treatment of the bis-hydrazoneyl bromide **IIIB** with 4,4-dimethyl-2,6-dioxocyclohexane-thiocarboxanilide **87** in refluxing chloroform in the presence of triethylamine gave a single



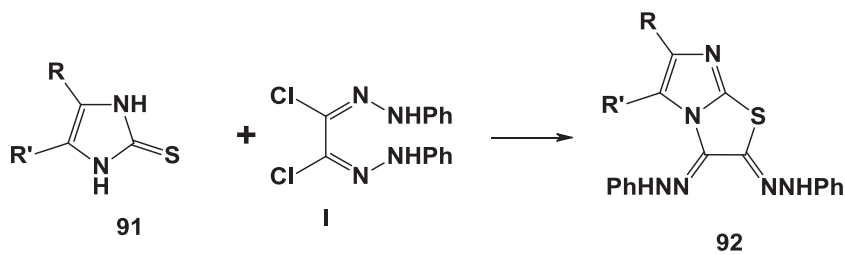
Scheme 47



Scheme 48

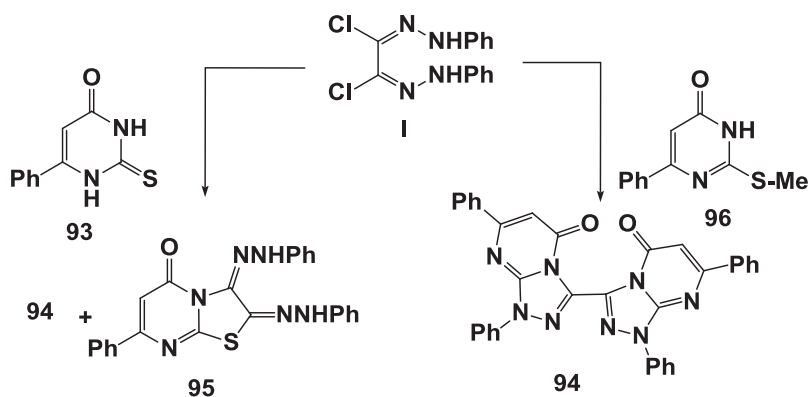


Scheme 49

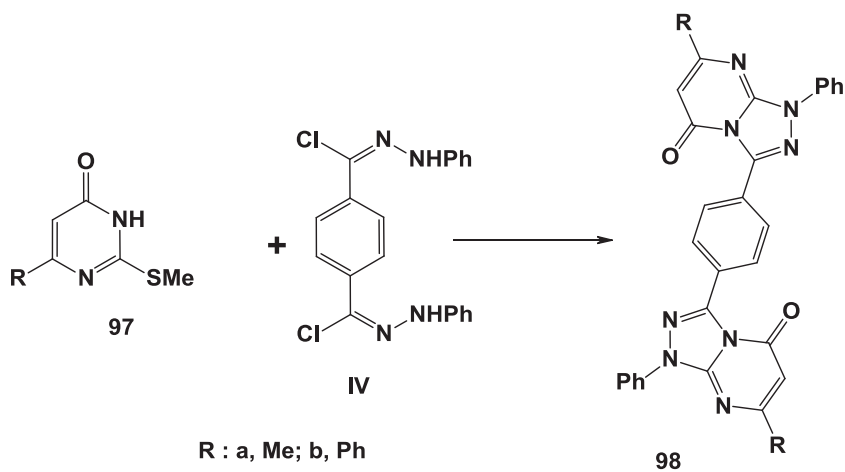


R / R' : a, H / H; b, Ph / Ph

Scheme 50



Scheme 51

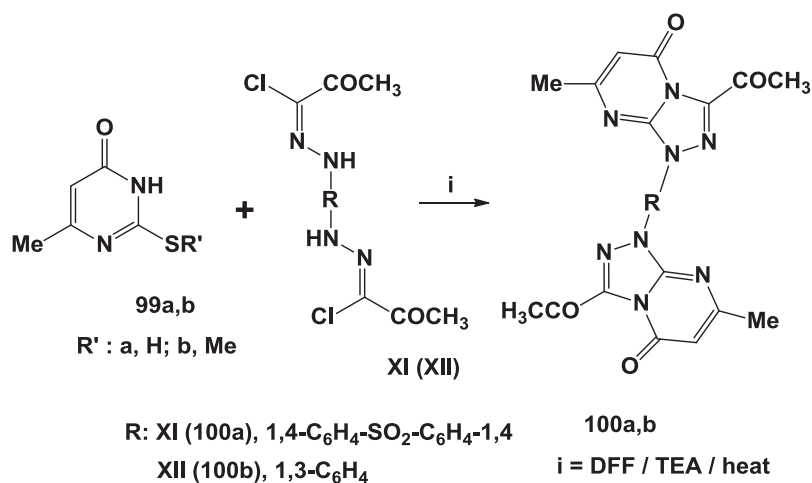


R : a, Me; b, Ph

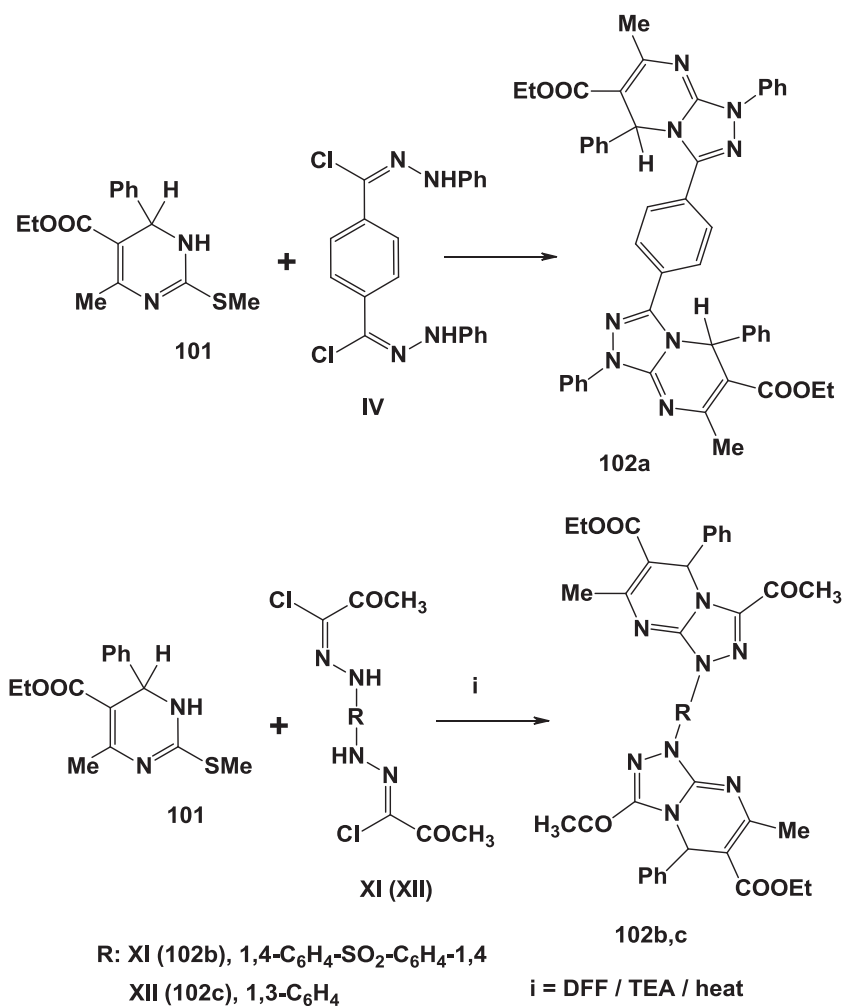
Scheme 52

product identified as 5,5'-(1,3-Phenylene)bis[2-(5,5-dimethylclohexane-1,3-dione)-3-phenyl-3H-[1,3,4]thiadiazole] **88** (Scheme 48) [32]. The formation of latter product **10**, seems to result also *via* initial cycloaddition of the nitrilimine **I** to

the C=S bond to the corresponding cycloadduct which in turn undergoes *in situ* tandem ring opening, recyclization and elimination of two molecules of aniline to give **88** as end products [32].



Scheme 53



Scheme 54

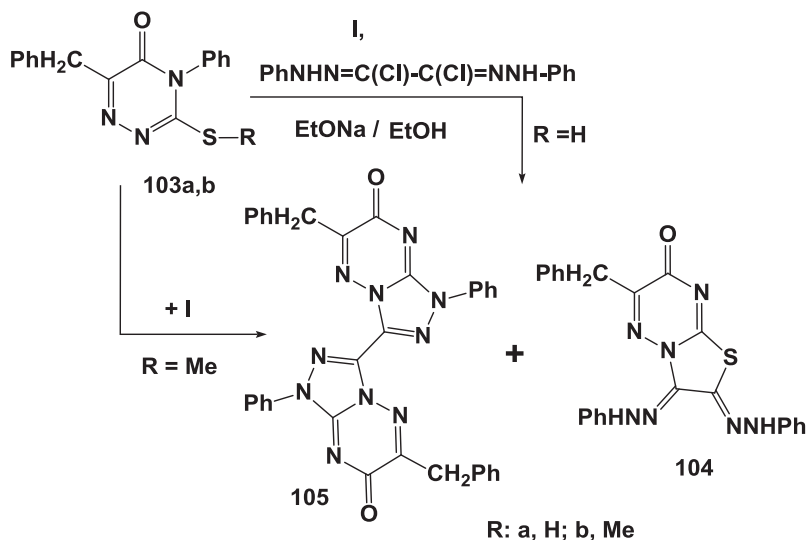
Reactions with heterocyclic thiones

Reaction of 5-phenyl-1,2,4-triazole-3-thione **89** with *bis*-hydrazonoyl chloride **I** in ethanol in the presence of sodium ethoxide at room temperature or in refluxing chloroform in the presence of triethylamine gave the 5,6-*bis*-(phenylhydrazono)-2-phenyl-thiazolo[3,2-*b*,1,2,4]triazole **90** (Scheme 49) [40,53].

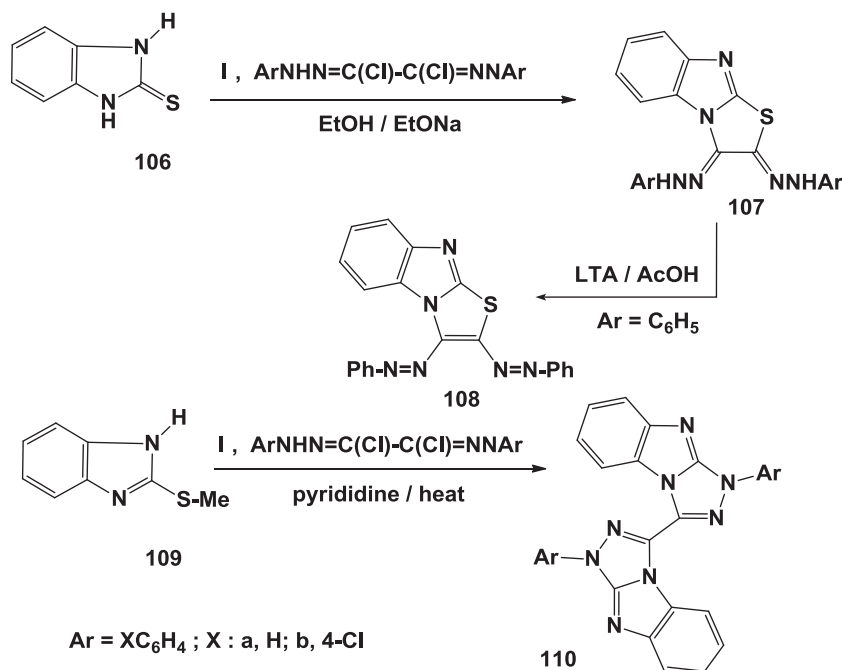
Similarly, reaction of the same *bis*-hydrazonoyl chloride **I** with each of the 5-phenyl-imidazole-2(3*H*)-thiones **91** was reported to afford the corresponding imidazol[2,1-*b*]thiazole derivatives **92** (Scheme 50) [40].

Bis-hydrazonoyl chloride **I** was reported to react regioselectively with 2-thiouracil **93** to give a mixture of 2,3-*bis*-(arylhazono)-thiazolo[3,2-*a*]pyrimidine-5-one **94** and 3,3'-*bis*-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one **95**. However, reaction of the same *bis*-hydrazonoyl chloride **I** with 2-methylthiouracil **96** afforded only **94** (Scheme 51) [54].

Similarly, the *bis*-hydrazonoyl halide **IV** was reported to react with 2-methylthiouracil **97** in 1:2 molar ratio in DMF/pyridine at reflux to give the corresponding 1,4-phenylene-*bis* (1,2,4-triazolo[4,3-*a*]pyrimidin-5-one) derivatives **98** (Scheme 52) [50].



Scheme 55



Scheme 56

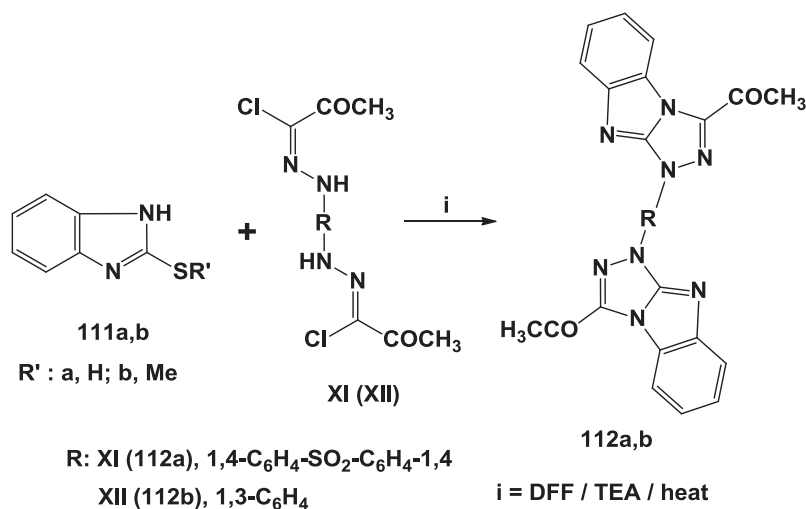
Recently, it was reported [56] that reaction of each of the *bis*-hydrazonoyl chlorides **XI** and **XII** each with 2-mercaptopyrimidine derivative **99a** or its methylthio derivative **99b** in refluxing DMF in the presence of triethylamine yielded the *bis*(3-acetyl-7-methyl-[1,2,4]triazolo[4,3-*a*] pyrimidin-5(1*H*)-one) (**100a,b**), respectively (Scheme 53) [56].

Also, reactions of the *bis*-hydrazonoyl halides **IV** [49] and **XI** (**XII**) [56] with 2-methylthiopyrimidine derivative **101** in 1:2 molar ratio in DMF in pyridine or in the presence of triethylamine under reflux yielded the corresponding *bis*(1,2,4-

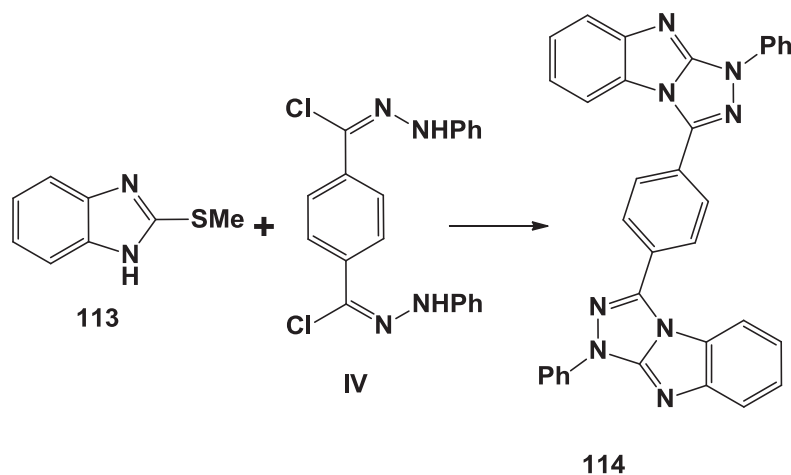
triazolo[4,3-*a*]pyrimidine) derivatives **102a-c**, respectively (Scheme 54) [50,56].

Similarly, reaction of 6-benzyl-2,3-dihydro-3-thioxo-1,2,4-triazin-5(4*H*)-one **103a** with *bis*-hydrazonoyl chloride **I** in ethanol in the presence of sodium ethoxide at room temperature gave a mixture of **104** (72%) and **105** (10%) (Scheme 55) [53]. However, similar reaction of **I** with the methyl thio derivative of **103b** yielded only **105** (Scheme 55) [53].

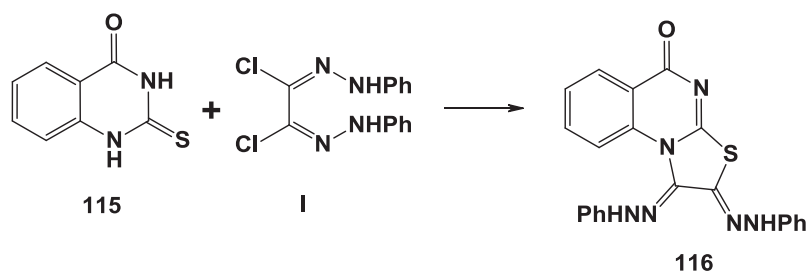
Similarly, reaction of imidazole-2-thione **106** with *bis*-hydrazonoyl chloride **I** in ethanol in the presence of sodium



Scheme 57



Scheme 58

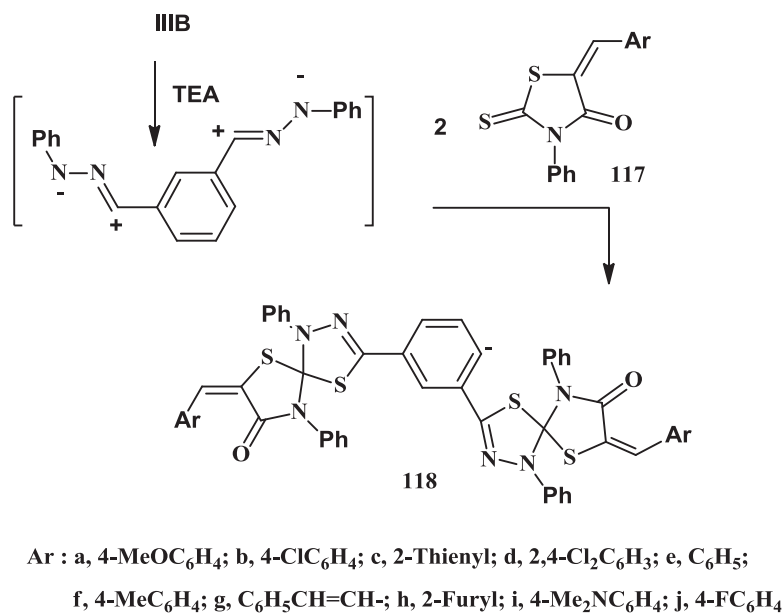


Scheme 59

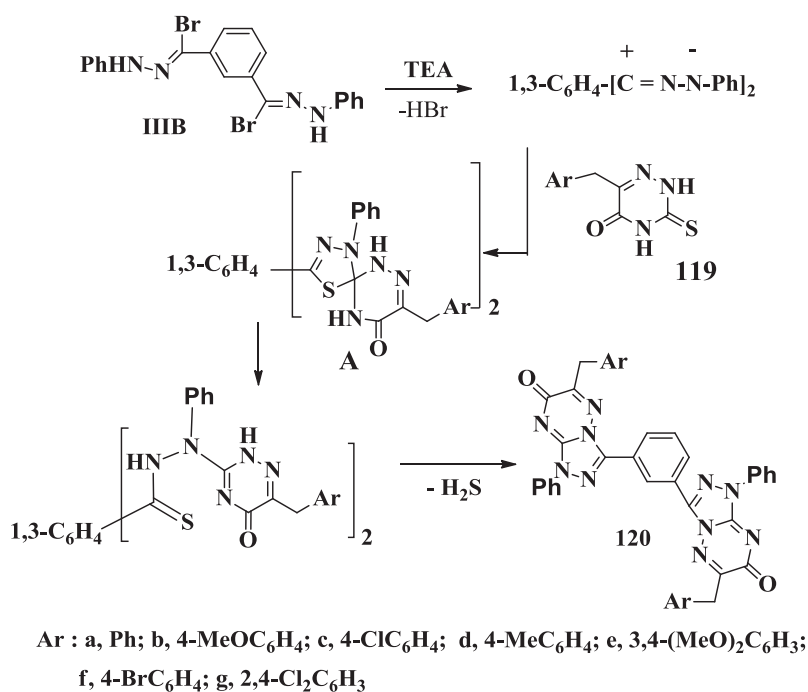
ethoxide at room temperature or in refluxing chloroform in the presence of triethylamine gave the 5,6-bis(phenylhydrazono)-2-phenyl-thiazolo[3,2-*a*]benzimidazole **107** (Scheme 56) [43,53,57]. Oxidation of the latter with lead tetraacetate in acetic acid yielded the *bis*-phenylazo derivative **108**. Similar reaction of the methylthio derivative **109** with **I** in refluxing pyridine yielded **110** [43,53]. When the reactions of **I** with each of **106** and **109** were carried out in ethanol in the presence of triethylamine, they yielded the same products **108** and **110** [43].

Also, it was recently reported [56] that reaction of each of the *bis*-hydrazonoyl chlorides **XI** and **XII** with 2-mercaptobenzimidazole **111a** or its methylthio derivative **111b** in refluxing DMF in the presence of triethylamine yielded the *bis*(3-acetyl-1-phenyl-[1,2,4]triazolo[4,5-*a*]benzimidazole) derivatives (**112a,b**), respectively (Scheme 57) [56].

Similarly, the *bis*-hydrazonoyl halide **IV** was reported to react with 2-methylthio-benzimidazole **113** in 1:2 molar ratio in DMF/pyridine at reflux to give the **114** (Scheme 58) [50].



Scheme 60



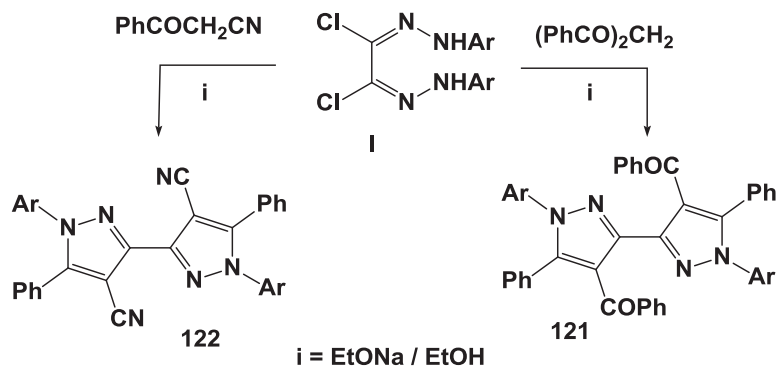
Scheme 61

Reaction of *bis*-hydrazoneyl chloride **I** with 2-thioxoquinazolin-4(1*H*)-one **115** afforded the *bis*-(phenylhydrazone)-thiazoloquinazoline derivative **116** (Scheme 59) [54].

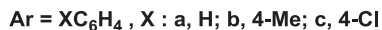
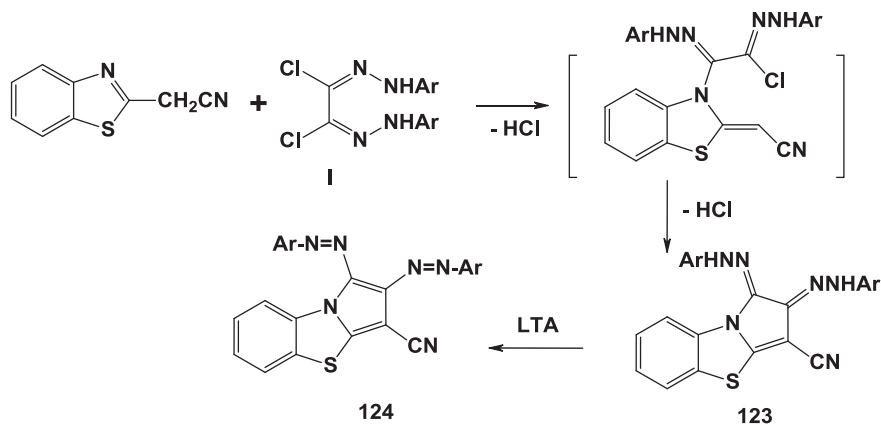
Recently, reaction of the *bis*-hydrazoneyl bromide **IIIB** with each of 3-phenyl-5-arylidene-2-thioxothiazol-4-ones **117** in refluxing chloroform in the presence of triethylamine was reported to be site selective as it led to 3,3'-(1,3-phenylene) *bis*-(1,6-diphenyl-7-oxo-8-substituted-spiro(5H-thiazolo[2,2']-3H-1,3,4-thiadiazole)) **118** (Scheme 60) [32]. Such products

resulted *via* cycloaddition of the generated nitrilimines to the C=S in compounds **117**. This finding indicates that the C=S is more dipolarophilic than both the C=O and the exocyclic C=C groups.

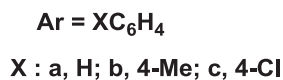
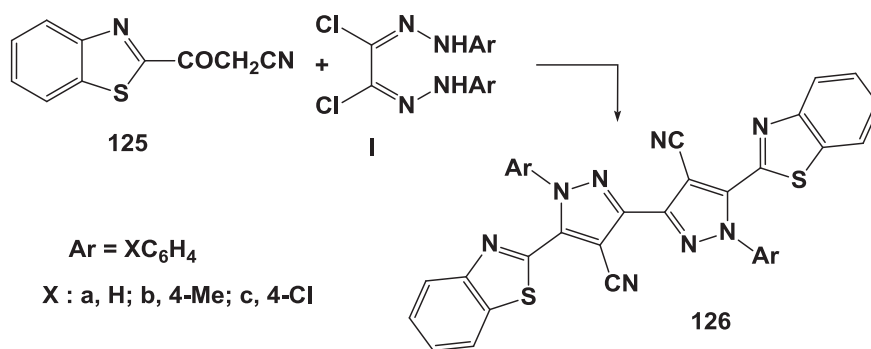
Similar reaction of **IIIB** with each of 6-arylmethylene-2,3-dihydro-3-thioxo-1,2,4-triazin-5(4*H*)-ones **119a-g** in refluxing chloroform in the presence of triethylamine was reported to yield the corresponding products **120** (Scheme 61) [32]. To account for the formation of the latter products **120**, it was



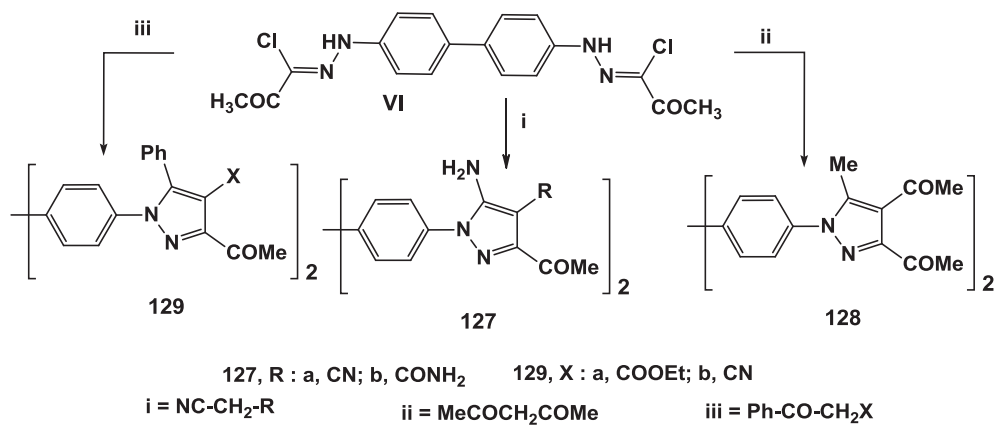
Scheme 62



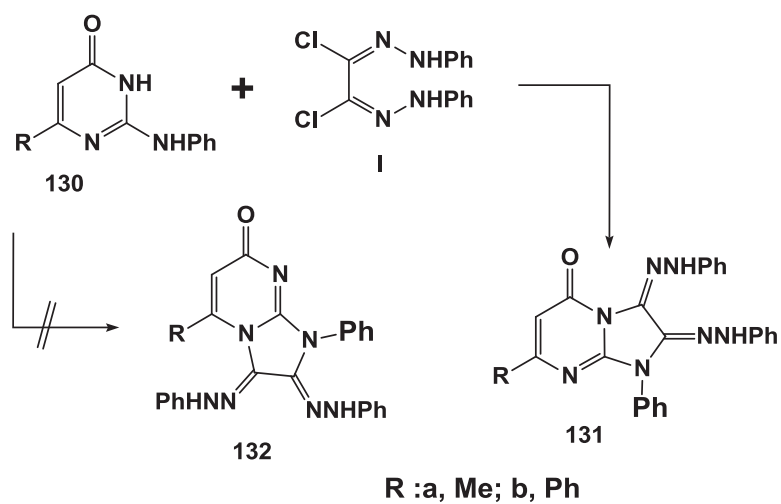
Scheme 63



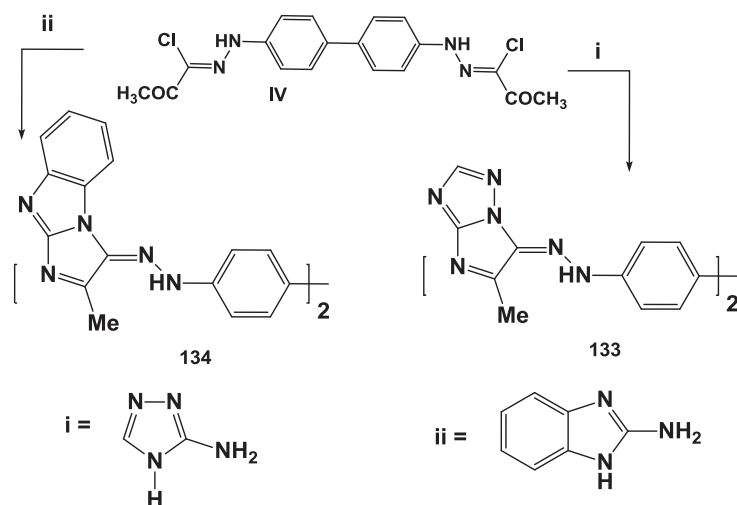
Scheme 64



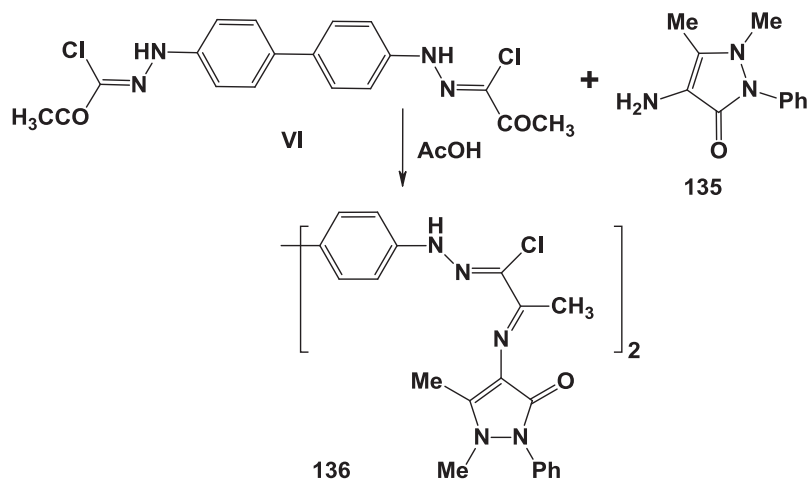
Scheme 65



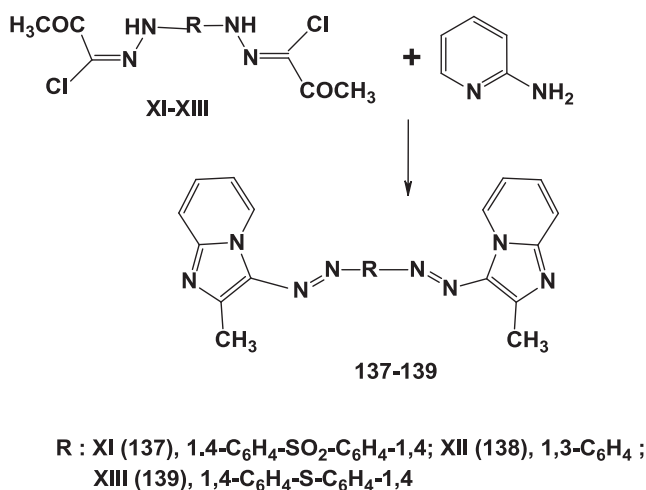
Scheme 66



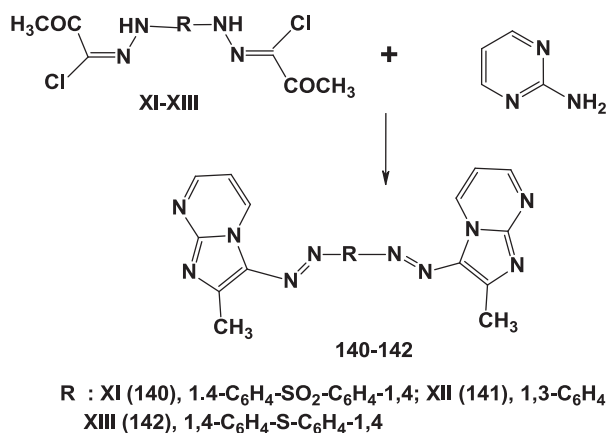
Scheme 67



Scheme 68



Scheme 69



Scheme 70

suggested as depicted in Scheme 2, that the reaction involves an initial cycloaddition of the bis-nitrilimine to C=S of **119** to give the bis-cycloadduct A. The latter then undergoes

in situ tandem ring opening, recyclization and elimination of H₂S to give **120** as end products [32].

Reactions with active methylene compounds

Shawali et al. [34] reported that reaction of the bis-hydrazoneyl chlorides **1a-e** each with dibenzoylmethane in ethanolic sodium ethoxide furnished the 3,3'-bis(1-aryl-4-benzoyl-5-phenyl)pyrazole derivatives **121**. Similar reaction of **1a-e** each with benzoylacetonitrile under the same condition yielded the bis-pyrazole derivatives **122a-e**, respectively (Scheme 62) [34].

2-Cyanomethylbenzothiazole reacted with the bis-hydrazoneyl chloride **1** in ethanol in the presence of sodium ethoxide, and gave the respective bis-hydrazone derivatives **123**. Oxidation of the latter with lead tetraacetate afforded 1,2-bis-(aryloxy)-3-cyanopyrrolo[2,1-b]benzothiazoles **124** (Scheme 63) [6].

Similar reaction of 2-cyanoacetylbenzothiazole **125** with each of the bis-hydrazoneyl chlorides **1a-c** in ethanol in the presence of sodium ethoxide at room temperature yielded the corresponding 3,3'-bis-pyrazole derivatives **126a-c** (Scheme 64) [40].

Reactions of the bis-hydrazoneyl chloride **VI** with each of malononitrile, cyanoacetamide, 2,4-pentanedione, ethyl benzoylacetate and phenacyl cyanide in ethanol in the presence of sodium ethoxide were reported to yield the bis-pyrazole derivatives **127a,b**, **128** and **129a,b**, respectively (Scheme 65) [49]. The compounds **127a**, **128** and **129b** were screened for their anticancer activity against a human live cancer cell line (HEPG2). The results revealed that while **127a** and **128** exhibit promising activity with IC₅₀ 16.4 and 16.6 µg/mL, respectively, compound **129b** showed moderate anticancer activity against such cell line [49]. Also, compound **128** was reported to exhibit no activity against PA and EC gram negative bacteria [49].

Reactions with heterocyclic amines

Treatment of pyrimidinones **130a,b**, each with the bis-hydrazoneyl chloride **1** furnished, in each case, a single product

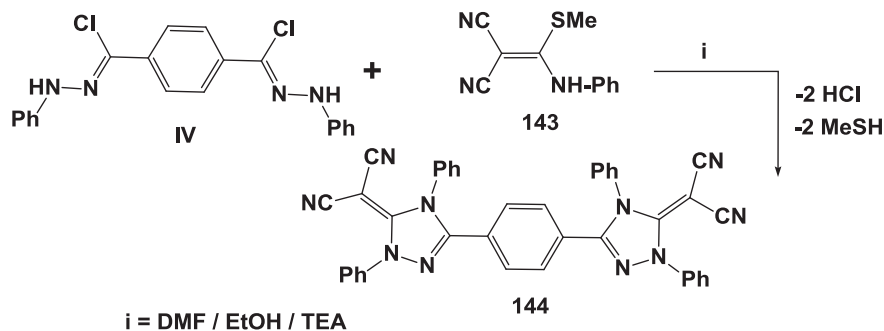
as evidenced by tlc analysis of the crude products. The IR spectra of the isolated products revealed the amide carbonyl band at $1670\text{--}1676\text{ cm}^{-1}$ and their ^{13}C NMR spectra showed the amide carbon signals at $161\text{--}162$. Such spectral data are consistent with structure **131** and not with **132** (Scheme 66) [53].

Reaction of the *bis*-hydrazonoyl chloride **VI** with each of 3-amino-1,2,4-triazole and 2-aminobenzimidazole in refluxing ethanol in the presence of triethylamine was reported to yield the annulated heterocycles **133** and **134**, respectively (Scheme 67) [49].

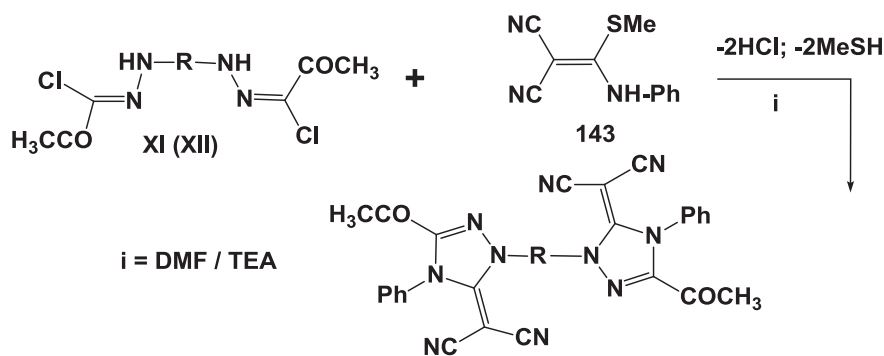
Condensation of *N',N''*-(biphenyl-4,4'-diyl)*bis*(2-oxo-propanehydrazonoyl chloride) **VI** with 4-aminoantipyrine (**135**) in ethanol in the presence of catalytic amount of glacial

acetic acid, under reflux, was reported to give the *bis*-hydrazonoyl halide, namely as *N',N''*-(biphenyl-4,4'-diyl)*bis*[2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)propane-hydrazonoyl chloride] (**136**) (Scheme 68) [37]. The results of anticancer screening revealed that compound **136** has poor inhibitory activity against the colon carcinoma (HCT) cell line [37]. In addition, compound **136** was reported to have high degree of antibacterial activity against Gram-positive bacteria (SA, BS) and Gram-negative bacteria (EC) and exhibited high inhibition effect against (PA) which emerged as one of the most problematic Gram-negative pathogens [37].

Reactions of the *bis*-hydrazonoyl chlorides **XI–XIII** each with 2-aminopyridine in refluxing DMF in the presence of tri-



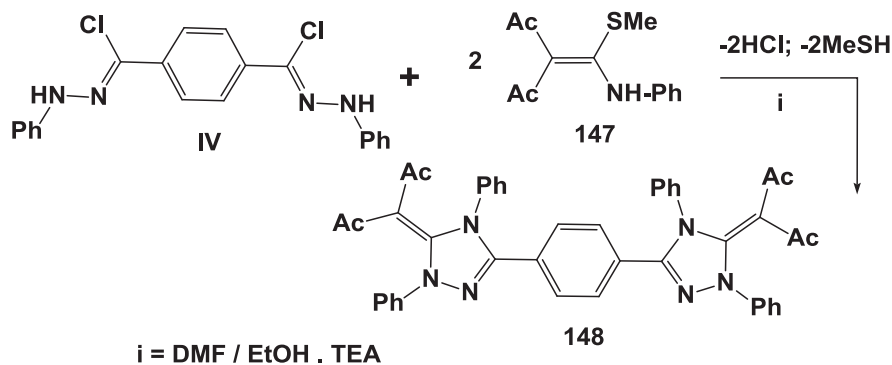
Scheme 71



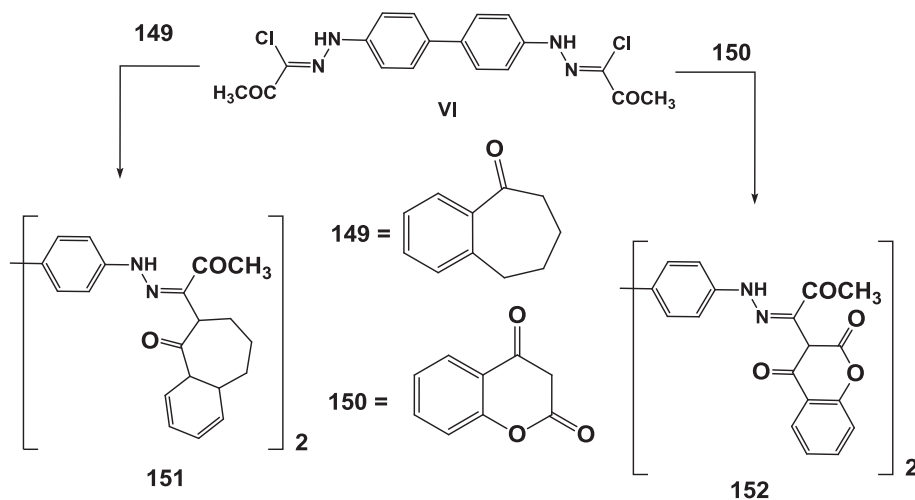
145 (146)

XI (145), 1,4- $\text{C}_6\text{H}_4\text{-SO}_2\text{-C}_6\text{H}_4\text{-1,4}$; XII (146), 1,3- C_6H_4

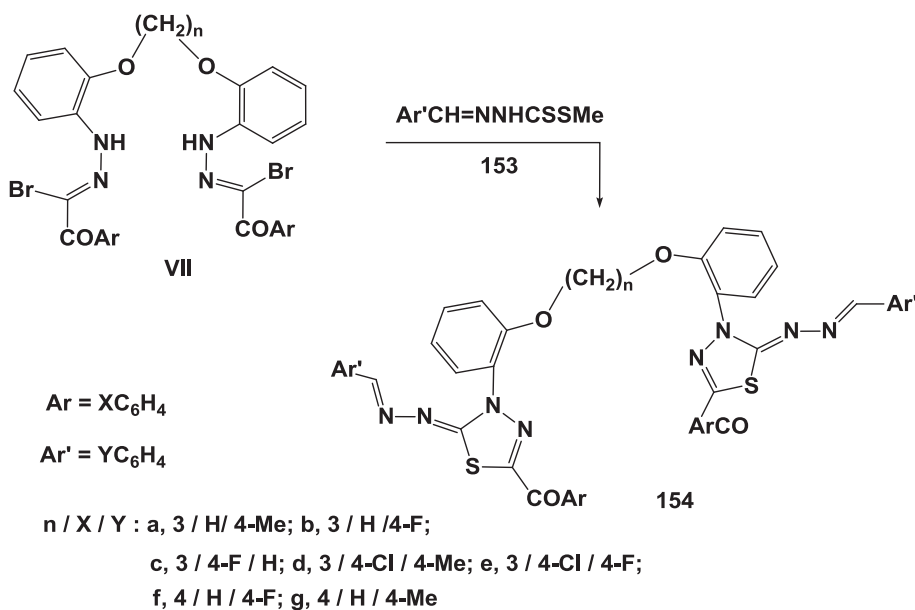
Scheme 72



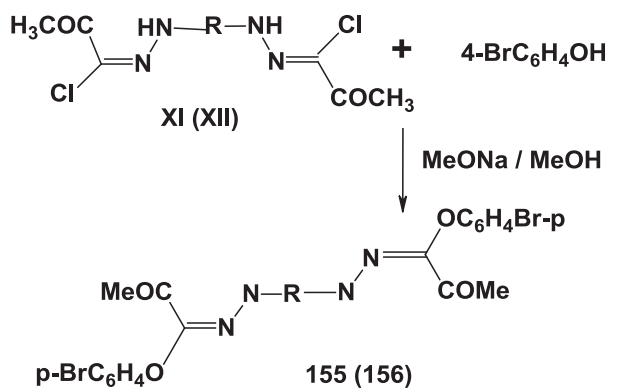
Scheme 73



Scheme 74



Scheme 75



R : 155, 1,4-C₆H₄-SO₂-C₆H₄-1,4; 156, 1,3-C₆H₃

Scheme 76

ethylamine were reported to yield *bis*-imidazo[1,2-*a*]pyridine 137-139, respectively (Scheme 69) [56].

Similarly, reaction of each of the *bis*-hydrazoneyl chlorides XI-XIII with 2-aminopyrimidine in refluxing DMF in the presence of triethylamine was reported to yield *bis*-imidazo[1,2-*a*]pyrimidines 140-142, respectively (Scheme 70) [56].

Reaction with ketene-*N,S*-acetal

Reaction of *bis*-hydrazoneyl dichlorides IV with two mol equiv of 143 in refluxing DMF/EtOH in the presence of triethylamine was reported to proceed smoothly to give 3,3'-*bis*-(1,2,4-triazole) derivative 144 (Scheme 71) [50].

Also, it reported recently that each of the *bis*-hydrazoneyl dichlorides XI and XII with two mol equiv of ketene *N,S*-acetal 143 in refluxing DMF in the presence of triethylamine

yielded 3,3'-bis(1,2,4-triazole) derivatives **145** and **146**, respectively (Scheme 72) [56].

Reaction of *bis*-hydrazonoyl chloride **IV** with two mol equivalents of the ketene-N,S-acetal **147** in refluxing DMF/EtOH in the presence of triethylamine was reported to give also 3,3'-bis-(1,2,4-triazole) derivative **148** (Scheme 73) [47].

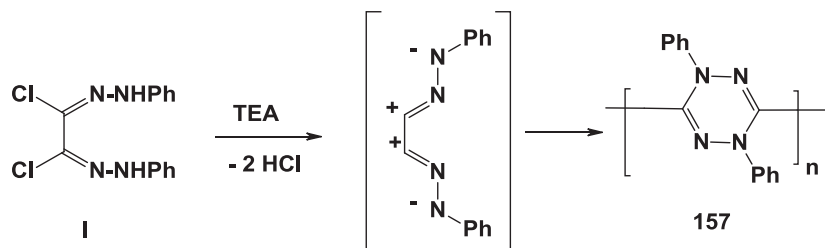
Reactions with ketones

Reaction of *bis*-hydrazonoyl chloride **VI** with each of benzo[b]-cycloheptanone **149** and 4-hydroxycoumarin **150** in ethanolic sodium ethoxide solution afforded the adducts **151** and **152**,

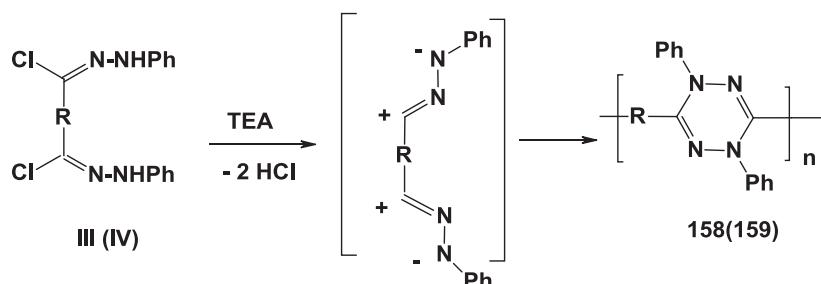
respectively (Scheme 74) [49]. The results of evaluating the anticancer activity of the products **151** and **152** revealed that they have promising activity against HEPG2 cell line with IC50 equals to 14.4 and 15.3, respectively [49].

Reaction with dithiocarbazates

Reaction of the *bis*-hydrazonoyl bromides **VII** with each of methyl N-arylidenedithiocarbazates **153** in ethanol in the presence of triethylamine at room temperature yielded the corresponding *bis*-1,3,4-thiadiazole derivatives **154** in 50–73% (Scheme 75) [39].

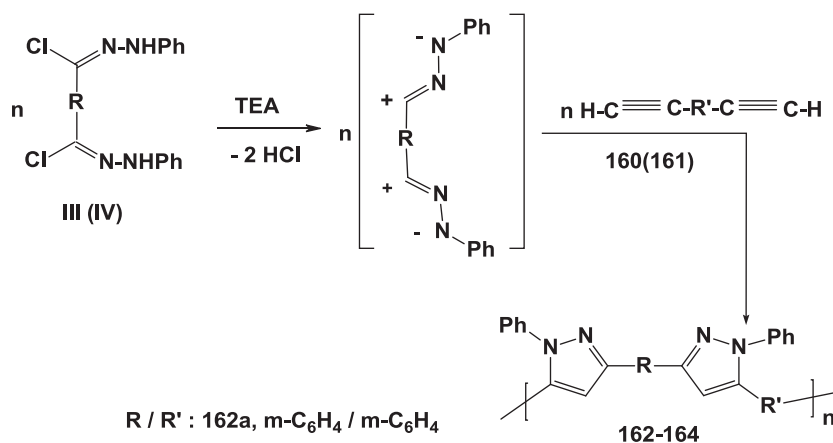


Scheme 77



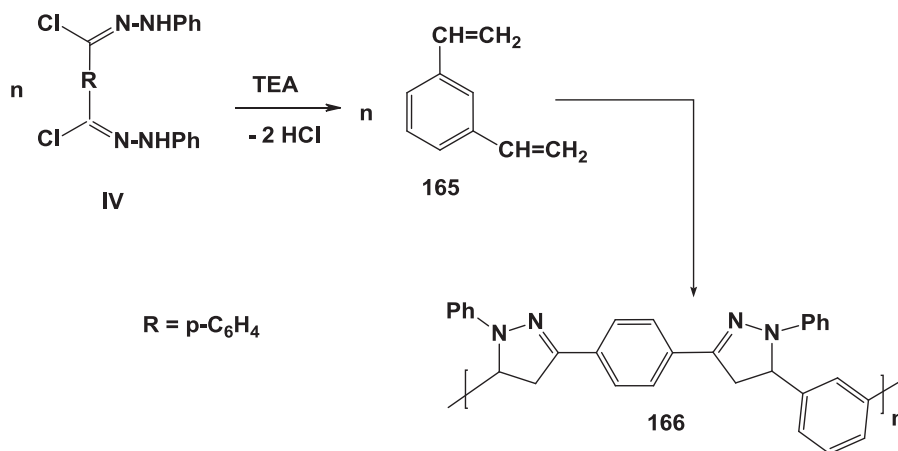
R : III (158), m-C₆H₄; IV (159), p-C₆H₄

Scheme 78

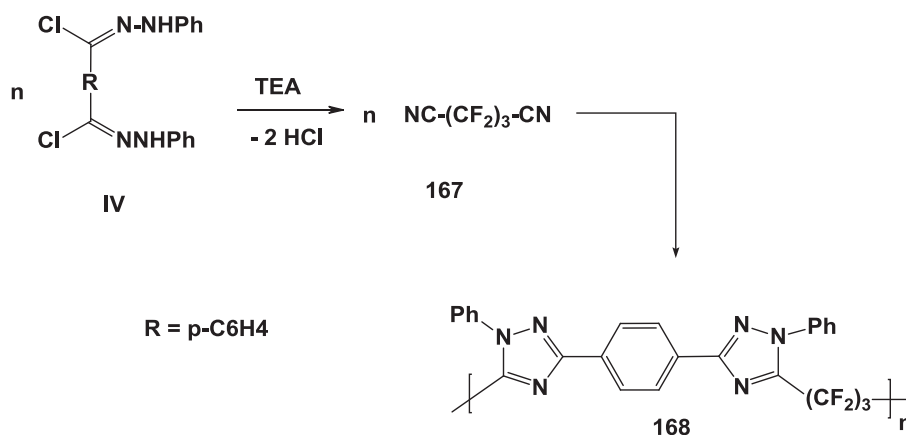


R / R' : 162a, m-C₆H₄ / m-C₆H₄
 162b, m-C₆H₄ / p-C₆H₄
 163a, p-C₆H₄ / m-C₆H₄; 163b, p-C₆H₄ / p-C₆H₄;
 164, p-C₆H₄-O-p-C₆H₄ / p-C₆H₄

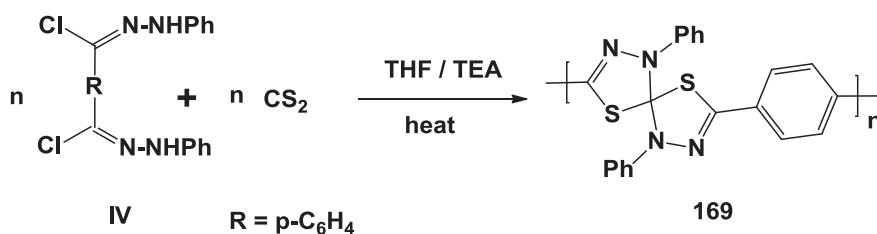
Scheme 79



Scheme 80



Scheme 81



Scheme 82

Reactions with phenols

Treatment of *bis*-hydrazonoyl chlorides **XI** and **XII** each with 4-bromophenol in methanolic sodium methoxide at room temperature gave the hydrazonate esters **155** and **156**, respectively (Scheme 76) [55].

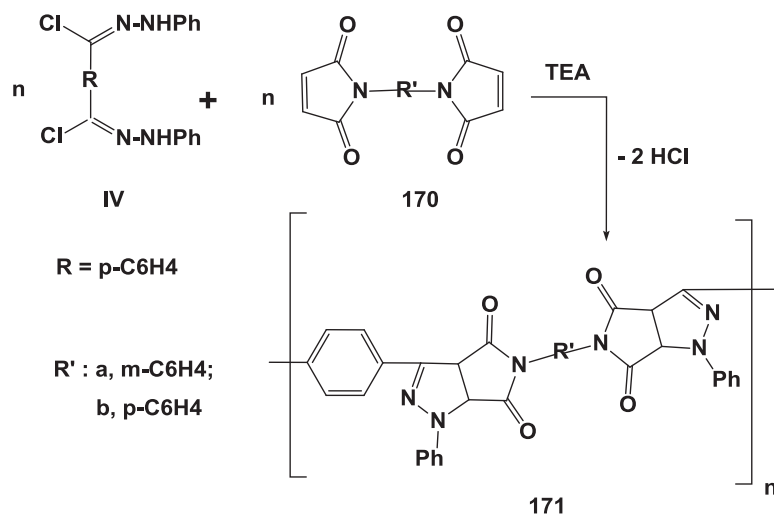
Polymerization

Heating the *bis*-hydrazonoyl chloride **I** in chloroform containing triethylamine was reported to yield sym-1,4-diphenyl-1,4-dihydro-1,2,4,5-polytetrazine **157** in 65% yield *via* polymerization of the initially formed *bis*-nitrilimine (Scheme 77) [31].

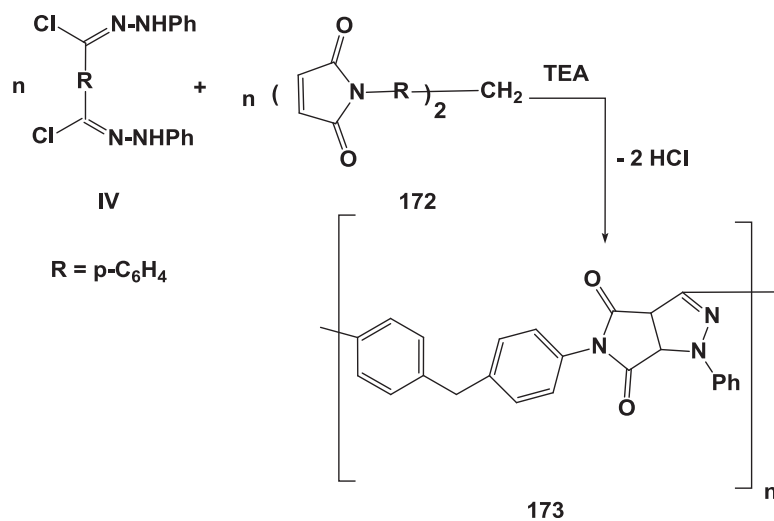
Stille and Harris [33,41] reported that in refluxing pyridine or refluxing benzene in the presence of triethylamine the *bis*-nitrilimines, generated *in situ* from the corresponding *bis*-hydrazonoyl chlorides **III** (**IV**), undergoes self cycloaddition to form poly(1,4-diphenyl-3,6-*m*- and *p*-phenylene-1,4-dihydro-1,2,4,5-tetrazines **158** (**159**) in 90% yield (Scheme 78).

The reactions of the *bis*-hydrazonoyl chlorides **III** (**IV**) each with the diynes **160** (**161**) in refluxing anhydrous tetrahydrofuran in the presence of triethylamine were reported to afford the polypyrazoles **162-164** in 75–94% yield (Scheme 79) [33].

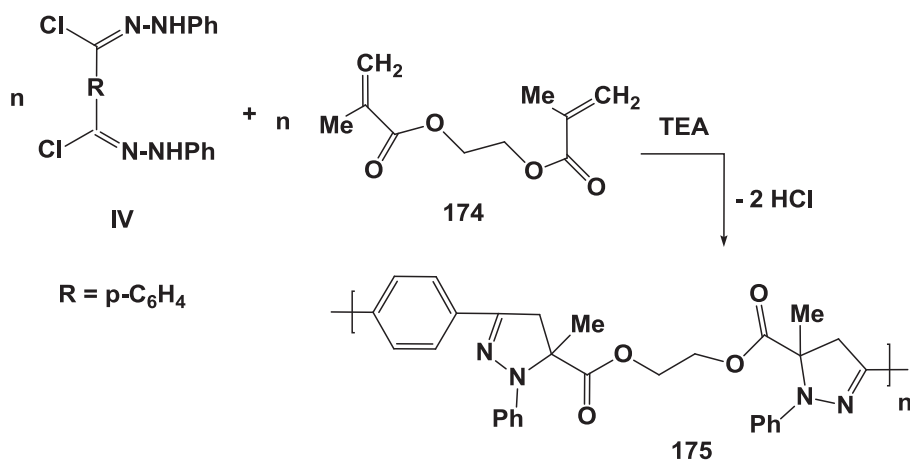
Similarly, the polypyrazoline **166** was formed when *m*-divinylbenzene **165** was refluxed with the *bis*-hydrazonoyl chloride **IV** in tetrahydrofuran in the presence of triethylamine (Scheme 80) [33].



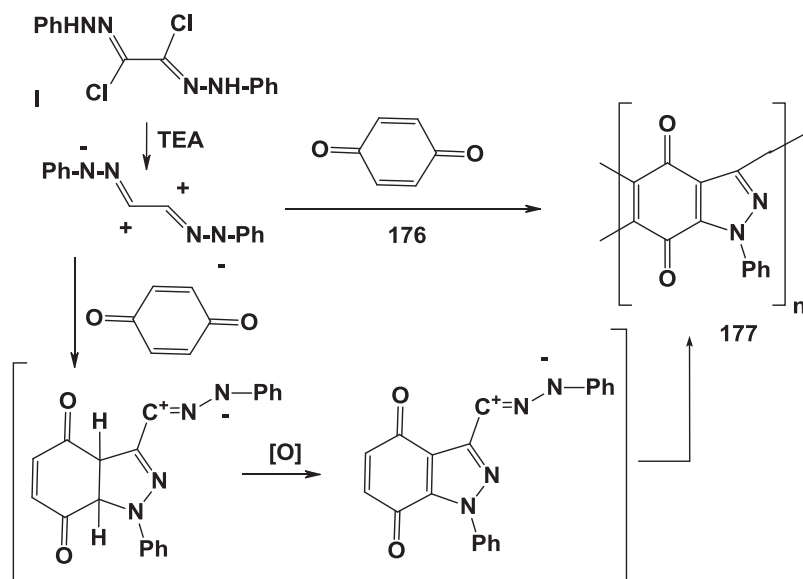
Scheme 83



Scheme 84



Scheme 85



Scheme 86

Also, it was reported that the polytriazole **168** was produced in 75% yield when a mixture of the *bis*-hydrazoneyl chloride **IV** and perfluoroglutaronitrile **167** was heated in sealed tube in anhydrous tetrahydrofuran in the presence of triethylamine (Scheme 81) [33].

Reaction of the *bis*-hydrazoneyl chloride **IV** with carbon disulfide in tetrahydrofuran in the presence of triethylamine gave the spiro-*bis*-thiazoline polymer **169** in 77% yield (Scheme 82) [33].

Reaction of the *bis*-hydrazoneyl chloride **IV** in benzene in the presence of triethylamine with each of *m*- and *p*-phenylenedimaleimides **170a,b** was reported to give the corresponding polyphenylenepyrazolines **171a,b** in almost quantitative yields (Scheme 83) [42].

Very recently, it has been reported that heating a mixture of the *bis*-hydrazoneyl chloride **IV** and *bis*-maleimide **172** in dimethyl formamide the corresponding pyrazole polymer **173** is 67% yield (Scheme 84) [47].

Also, the poly(phenylenepyrazoline) **175** was formed in almost quantitative yield by the reaction of the *bis*-hydrazoneyl chloride **IV** with ethylene dimethacrylate **174** in benzene in the presence of triethylamine (TEA) (Scheme 85) [42].

Polypyrazoles **177** based on *p*-benzoquinone **176** were formed *via* reaction of the latter with *bis*-hydrazoneyl chlorides **I**. In this case, the *bis*-nitrilimine intermediates, generated *in situ* by the action of excess triethylamine on the *bis*-hydrazoneyl chlorides **I**, cycloadd to *p*-benzoquinone **176** to afford final polymer **177** (Schemes 86) [50]. Polymer molecular weights for **177** approached 22,000 g/mol with polydispersity indices of approximately 2.34.

Conclusions

Bis-hydrazoneyl halides are important class of organic compounds and possess versatile chemical reactions. This review covers a summary of the literature data published on the chemistry of such compounds over the last four decades. The bio-

logical activities of some of the *bis*-heterocyclic compounds prepared have also been pointed out. It is hoped that this review will be fruitful base for further development of their chemistry.

Conflict of Interest

The author confirms that this article content has no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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