REVIEW

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

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ABSTRACT

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

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Introduction

Bis-hydrazonoyl halides are compounds that have the general formula A or B (Fig. 1), where X = Cl or Br. The first bis-hydrazonoyl halides, namely N,N'-diaryl 1,2-ethane-bis-hydrazonoyl 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 reawaken 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, antiamoebic, and plant growth regulative properties [21].

At present, there are several review articles by the author covering the data published on reactions of monohydrazonoyl halides of type, R-C(X) = NNHR' [22–27]. In contrast, few data concerning the chemistry of bis-hydrazonoyl 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 bis-hydrazonoyl halides.
different bis-hydrazonoyl 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-hydrazonoyl halides**

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

**Halogenation of bis-(aroylhydrazines)**

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-hydrazonoyl chlorides. For example, 1,3- and 1,4-phenylene-bis(carbohydrazonoyl chlorides) III (IV) were prepared by the reaction of iso- and terphthaloylhydrazides Ia,b, each with phosphorus pentachloride (Scheme 1) [28].

Grundmann et al. [29] reported also the synthesis of N,N'-diphenyl ethane-1,2-bis-hydrazonoyl 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-hydrazonoyl 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,N',N'-diphenyl-1,3-benzene-bis-carbohydrazonoyl bromide IIIb was prepared by reaction of N,N',N'-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-hydrazonoyl 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) Ia-c, respectively (Scheme 5). Similar chlorination of 4d yielded the bis-hydrazonoyl chloride Id (Scheme 5) [1]. The product Ia 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-hydrazonoyl bromides IIa-c (Scheme 6) [1].

Farag et al. [4] and Shawali et al. [34] synthesized N,N-di(p-nitrophenyl) ethane-1,2-bis-hydrazonoyl bromide Id 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-hydrazonoyl 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-(CONHNHAr)₂ \[\xrightarrow{PCl₅} \] R-[C(Cl)=NNHAr]₂

Scheme 1

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

-(CONHNHPh)₂ \[\xrightarrow{PCl₅} \] -[C(Cl)=NNHPh]₂

Scheme 2

\[(Ar-NNH-CO)₂ \xrightarrow{i} Ar-NHN=C(Cl)-C(Cl)=NNHAr\]

\(i = P(Ph)₃ / CCl₄\)

Ar : X₆C₆H₄; X : a, H; b, 2-Me; c, 4-Me; d, 4-Cl; e, 2,4,6-Cl₃

\[(CONHNHPh) \xrightarrow{P(Ph)₃ / CBr₄} \]

Scheme 3

ArHNN \[\xrightarrow{NBS / THF} \]

Scheme 8
generate the corresponding hydrazonoyl 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 hydrazonoyl 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-hydrazonoyl chloride V was recently prepared by coupling of benzidine diazonium 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-oxopropanehydrazonoyl chloride) VI (Scheme 10). The results of evaluating the anticancer activity of VI against colon carcinoma (HCT) revealed that it has moderate activity [37].
Scheme 13

\[
\begin{align*}
\text{9} & \quad \text{Ar} = \text{XC}_6\text{H}_4 \\
\text{X / n: a, H / 3; b, 4-Cl / 3; c, H / 4; d, 4-Cl / 4} \\
\end{align*}
\]

Scheme 14

\[
\begin{align*}
\text{方案 14} & \\
\text{方案 14} & \\
\text{方案 14} & \\
\text{方案 14} & \\
\end{align*}
\]

Scheme 15

\[
\begin{align*}
\text{方案 15} & \\
\text{方案 15} & \\
\text{方案 15} & \\
\text{方案 15} & \\
\end{align*}
\]
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-hydrazonoyl chlorides IXa-d in 51–83% yield (Scheme 11) [38].

The bis-hydrazonoyl 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-hydrazonoyl bromides VIIa-d in 60–75% yields (Scheme 13) [39].
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 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-1H-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-diphenyl pyrazol-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 afforded the corresponding bis-cycloadducts 24 and 25 (Scheme 19).

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-phenylethanimidothioate 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].
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-hydrazonoyl 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-hydrazonoyl chloride I with the potassium salt each of the acyl-substituted thioanilides 29 furnish the corresponding bis-thiadiazole derivatives 30 (Scheme 23) [40].

Treatment of the bis-hydrazonoyl 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'-bis-(biphenyl-4,4'-diyl)bis(2-oxopropanehydrazonoyl chloride) VI (1 mol) with 2-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-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(3H)-yl]-2(3H)-ylidene]bis[2-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-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 thiocarbamides 34a,b each with the bis-hydrazonoyl 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-hydrazonoyl chlorides IV in DMF in the presence of
Ar / Het : a, Ph / Benzothiazol-2-yl; b, 4-ClPh / Benzothiazol-2-yl

Scheme 22

Ar / X : a, Ph / EtOOC; b, Ph / CN; c, 2-furyl / CN; d, 2-benzothiazolyl / CN

Scheme 23

R / Ar : a, CN / Ph; b, PhCO / Ph; c, EtOOC / Ph; d, 2-Thenoyl / Ph;
e, EtOOC / 4-ClC6H4
Scheme 24

Scheme 25

Scheme 26
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-hydrazonoyl chloride IV with 2-(phenylmethylene)cumaronothioic dihydrazide 39 in ethanolic triethylamine (Scheme 26) [45].

Reactions with enones
Reactions of the bis-hydrazonoyl 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 hydrazonoyl 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 via 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-hydrazonoyl 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-diarylspiropyrazoline-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 hydrazonoyl
Scheme 29

\[
\text{Ar-NHN} = \text{C(Cl)-C(Cl)=NNHar}
\]

\[
\begin{array}{c}
\text{I} \\
\text{i} \\
\text{Ar-N-N} = \text{C-C=N-N-Ar} + 2 \text{PhH} \\
\text{Ar} = \text{XCH}_2 \text{H}_2 \text{X} : \text{a, H; b, 4-Cl} \\
\text{i = TEA / PhH / heat} \\
\end{array}
\]

\[
\text{45 (68-75%)}
\]

Scheme 30

\[
\text{Ar-NHN} = \text{C(Cl)-C(Cl)=NNHar}
\]

\[
\begin{array}{c}
\text{I} \\
\text{i} \\
\text{Ar-N-N} = \text{C-C=N-N-Ar} + 2 \text{PhH} \\
\text{Ar} = \text{XCH}_2 \text{H}_2 \text{X} : \text{a, H; b, 4-Cl} \\
\text{i = TEA / PhH / heat} \\
\end{array}
\]

\[
\text{47 (62-71%)}
\]

Scheme 31

\[
\begin{array}{c}
\text{Cl} \\
\text{ArHN-N-N-NH-Ar} \\
\text{I} \\
\text{TEA} \\
\text{-2 HCl} \\
\end{array}
\]

\[
\begin{array}{c}
\text{RO} \\
\text{Ar} \\
\text{RO} \\
\text{R'} \\
\text{49 (50)} \\
\text{+} \\
\text{Ar-N-N-N-N-Ar} \\
\text{R'} \\
\text{RO} \\
\text{RO} \\
\text{51 (52)} \\
\end{array}
\]

\[
\text{R / R': 49 (51), H / Me; 50 (52), Me / Et} \\
\text{Ar} = \text{XCH}_2 \text{H}_2 \text{X} : \text{a, H; b, 4-Me; c, 4-Cl; d, 2,4-Cl}_2; \text{e, 4-NO}_2
\]

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-alisoquinolines) 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 enamiones**

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

Shawali et al. [3] reported that treatment of the bis-hydrazonoyl 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 36

\[
\begin{align*}
H_2COCH_2\text{N} & \text{H} - \text{N} - \text{S} - \text{O} - \text{N} - \text{H} - \text{N} - \text{C} - \text{OCH}_3 \\
\text{XI} & \\
\text{R / R'}: \text{a, H / XC}_6\text{H}_4; \text{b, H / 2-furyl}; \text{c, H / 2-pyridyl}; \text{d, Me / 2-thienyl} \\
X = \text{H; 4-Me; 4-Br; 2-HO} \\
\end{align*}
\]

Scheme 37

\[
\begin{align*}
\text{H}_2\text{COCH}_2\text{N} & \text{H} - \text{N} - \text{N} - \text{Cl} \\
\text{XII} & \\
\text{R / R'}: \text{a, H / XC}_6\text{H}_4; \text{b, H / 2-furyl}; \text{c, H / 2-pyridyl}; \text{d, Me / 2-thienyl} \\
X = \text{H; 4-Me; 4-Br; 2-HO} \\
\end{align*}
\]

Scheme 38

\[
\begin{align*}
\text{Cl} & \text{N} - \text{NHAr} \\
\text{I} & \\
2 \text{NaN}_3 & \rightarrow \text{N}_2 \text{N} - \text{NHAr} \\
\text{2 Ph}_3\text{P} & \rightarrow \text{Ph}_3\text{P} = \text{N} - \text{NHAr} \\
\text{2 RCOCI} & \rightarrow \text{R} - \text{COCl} \\
\text{Ar} = \text{XC}_6\text{H}_4; \text{X} = \text{H; 4-Cl} \\
\text{R} = \text{YC}_6\text{H}_4; \text{ClCH}_2; \text{Y} = \text{a, H; b, 4-Me; c, 4-Cl; d, 3-NO}_2 \\
\end{align*}
\]
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) \( 70 \) (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) \( 72 \) (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 \( 2,2' \)-bis-(1-aryl-5-imino[1,3,4]thiadiazoles) \( 74 \) and bis-(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 chlorides \( I \) each with thiourea [4] and selenourea [5] in refluxing ethanol yielded the corresponding \( 2,2' \)-bis-(1-aryl-5-imino)[1,3,4]thiadiazoles \( 74 \) and bis-(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 aminothiophenol

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

Reactions with thioamides

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

Treatment of the bis-hydrazonoyl 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-hydrazonoyl 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-hydrazonoyl bromide IIIB with 4,4-dimethyl-2,6-dioxocyclohexane-thiocarboxanilide 87 in refluxing chloroform in the presence of triethylamine gave a single
Scheme 49

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad | \\
\text{H} & \quad \text{PhHN=C(Cl)}-\text{C(Cl)=NNPh} \\
\text{EtOH / EtONa} & \\
\end{align*}
\]

\[
\begin{align*}
\text{PhHN} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{NNPh} & \quad | \\
\text{Ph} & \quad \text{H} \\
\end{align*}
\]

\text{Scheme 49}

\[R / R': a, H / H; b, Ph / Ph\]

Scheme 50

\[\text{Scheme 50}\]

\[
\begin{align*}
\text{R} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{S} & \quad | \\
\text{R'} & \quad \text{PhHN=C(Cl)}-\text{C(Cl)=NNPh} \\
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{R'} & \quad | \\
\text{PhHN} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{NNPh} & \quad | \\
\text{Ph} & \quad \text{H} \\
\end{align*}
\]

\[\text{Scheme 51}\]

\[\text{Scheme 51}\]

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{R} & \quad \text{N} \\
\text{SMe} & \quad | \\
\text{Ph} & \quad \text{H} \\
\end{align*}
\]

Scheme 52

\[
\begin{align*}
\text{R} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad | \\
\text{Ph} & \quad \text{N} \\
\text{R} & \quad | \\
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad | \\
\text{Ph} & \quad \text{N} \\
\text{R} & \quad | \\
\text{Ph} & \quad \text{N} \\
\end{align*}
\]

\[R : a, \text{Me}; b, \text{Ph}\]
product identified as 5,5′-(1,3-Phenylene)bis[2-(5,5-dimethylcyclohexane-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(3H)-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-(arylhydrazono)-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].
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(4H)-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...
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 methythio 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 methythio 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**

| Ar | a, 4-MeOC₆H₄; b, 4-ClC₆H₄; c, 2-Thienyl; d, 2,4-Cl₂C₆H₃; e, C₆H₅; f, 4-MeC₆H₄; g, C₆H₅CH=CH₂; h, 2-Furyl; i, 4-Me₂NC₆H₄; j, 4-FC₆H₄ | Ar | a, Ph; b, 4-MeOC₆H₄; c, 4-ClC₆H₄; d, 4-MeC₆H₄; e, 3,4-(MeO)₂C₆H₃; f, 4-BrC₆H₄; g, 2,4-Cl₂C₆H₃; h, 4-FC₆H₄ |
Reaction of bis-hydrazonoyl chloride I with 2-thioxoquinazolin-4(1H)-one 115 afforded the bis-(phenylhydrazono)-thiazoloquinazoline derivative 116 (Scheme 59) [54].

Recently, reaction of the bis-hydrazonoyl 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 dipolarphilic 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(4H)-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 65

Scheme 66

Scheme 67
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-hydrazonoyl chlorides Ia-e each with dibenzoylmethane in ethanolic sodium ethoxide furnished the 3,3′-bis(1-aryl)-4-benzoyl-5-phenylpyrazole derivatives 121. Similar reaction of Ia-e each with benzoylecetonitrile under the same condition yielded the bis-pyrazole derivatives 122a-e, respectively (Scheme 62) [34].

2-Cyanomethylbenzothiazole reacted with the bis-hydrazonoyl chlorides I 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-(arylazo)-3-cyanopyrrolo[2,1-b]benzothiazoles 124 (Scheme 63) [6].

Similar reaction of 2-cyanoacetylbenzothiazole 125 with each of the bis-hydrazonoyl chlorides Ia-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-hydrazonoyl chloride VI with each of malononitrile, cyanoacetamide, 2,4-pentanedione, ethyl benzoylacetaete 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-hydrazonoyl chloride I 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 1670–1676 cm⁻¹ and their ¹³C NMR spectra showed the amide carbon signals at 161–162. 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 N⁰,N⁰₀-(biphenyl-4,4₀-diyl)bis(2-oxo-propanehydrazonoyl chloride) VI with 4-aminomethylpyridine (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 N⁰,N⁰₀-(biphenyl-4,4₀-diyl)bis[2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylino)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-
ethylamine were reported to yield bis-imidazo[1,2-a]pyridine 137-139, respectively (Scheme 69) [56].

Similarly, reaction of each of the bis-hydrazonoyl 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-hydrazonoyl 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-hydrazonoyl 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-hydrazoneoyl 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-hydrazoneoyl 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].

Reactions with dithiocarbazates

Reaction of the bis-hydrazoneoyl 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].
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 polymeric 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
Also, it was reported that the polytriazole 168 was produced in 75% yield when a mixture of the bis-hydrazonoyl 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-hydrazonoyl 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-hydrazonoyl 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-hydrazonoyl 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-hydrazonoyl chloride IV and bis-maleimide 172 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-hydrazonoyl chlorides I. In this case, the bis-nitrilimine intermediates, generated in situ by the action of excess triethylamine on the bis-hydrazonoyl chlorides I, cyclode 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**

*Bi* -hydrazonoyl 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 biological activities of some of the *bi*-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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