Reactions of hydrazonoyl halides with heterocyclic thiones. Convenient methodology for heteroannulation, synthesis of spiroheterocycles and heterocyclic ring transformation

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Abstract
This review summarizes research results concerning the reactions of hydrazonoyl halides with heterocyclic thiones reported by us and other research groups from 1991 to mid 2007. It outlines the utility of such reactions in various aspects of heterocyclic chemistry.

Keywords: Nitrilimines, 1,3-dipolar cycloaddition, azolethiones, azinethiones

Contents
1. Introduction
2. Heteroannulation
2.1 Heteroannulation of monoheterocycles
2.1.1. Imidazolethiones
2.1.2. 1,2,4-Triazolethiones
2.1.3. Pyrimidinethiones
2.1.4. 1,2,4-Triazinethiones
2.1.5. 1,2,4-Triazepinethiones
2.2. Heteroannulation of biheterocycles
2.2.1. Benzimidazolethiones
2.2.2. Purinethiones
2.2.3. Pyrazolo[3,4-d]pyrimidinethiones
2.2.4. Quinazolinethiones
2.2.5. Pyrido[2,3-d]thiouracils
2.2.6. Pteridinethiones
2.2.7. Quinoxalinethiones
2.3. Heteroannulation of triheterocycles
2.3.1. Benzothieno[2,3-d]pyrimidinethiones
2.3.2. Pyrido[3′,2′ : 4,5]thieno[2,3-d]pyrimidinethiones
2.3.3. Cyclohepta[4,5]thieno[2,3-d]pyrimidinethiones
2.3.4. Pyrido[2,3-d : 6,5-d′]dipyrimidinethiones
2.4. Heteroannulation of tetraheterocycles
2.4.1. Naphtho[2,1-e]pyrido[2,3-c]pyrimidinethiones
3. Synthesis of spiroheterocycles
4. Heterocyclic ring transformations
4.1 Transformation of azetine-2-thiones into 1,3,4-triazoles
4.2 Transformation of 1,3,4-oxadiazole-2(3H)-thiones into 1,3,4-thiadiazoles
4.3 Transformation of 1,4,2-dithiazole-5-thiones into 1,3,4-thiadiazoles
4.4 Transformation of tetrazole-5-(1H)-thiones into 1,3,4-thiadiazoles
4.5 Transformation of tetrazole into 1,2,4,5-tetrazines
5. Functional group transformations
6. Conclusions
7. References

1. Introduction

Hydrazonoyl halides are a class of compounds with the general formula 1 where X represents a chlorine or bromine group. These compounds are the acyl halides of the so-called hydrazonoic acids 2 as the imidoyl chlorides 3 are the chloride derivatives of imidoic acids 4 (Chart 1). Since work concerning hydrazonoyl halides 1 as synthetic auxiliaries commenced in 1970 in our group, many papers and patents have been published including some reviews by Shawali et al. 1-9 and by others 10 concerning their reactions and biological activities. Such reviews have been useful for the chemists and biologists engaged in the development of synthesis of new heterocyclic systems, new drugs or in other important works. The intention of the present review is to cover research results concerning the title reactions reported by us and by other research groups from 1991 to mid 2007 and which have not been reviewed hitheto. The coverage was made through Chemical Abstracts Vols. 114 - 145.

![Chart 1]
Reactions of hydrazonoyl halides 1 are usually carried out in the presence of a base catalyst. The function of the latter is to convert 1 into the respective 1,3-diropes 5 which are called nitrilimines or nitrilium imides via 1,3-elimination reaction. The mechanism of this dehydrohalogenation reaction has been studied by Shawali et al.\textsuperscript{11-13} and was shown to be as depicted in Scheme 1.

\[
\begin{align*}
\text{R-} & \quad \text{X} \quad \text{N-NHR'} \\
\text{1} & \quad \text{B} & \quad \text{fast} \quad \text{N-N-R'} \quad \text{+} \quad \text{HB}^+ \\
& \quad \text{slow} \quad \text{N-N-R'} \quad \text{+} \quad \text{X}^-
\end{align*}
\]

Scheme 1

Reactions of nitrilimines, derived from hydrazonoyl halides, with heterocyclic thiones may proceed via a 1,3-addition or 1,3-dipolar cycloaddition pathway depending on whether the reacting heterocyclic thiones act as protic nucleophiles or dipolarophiles, respectively. This is because thiones of type 6 that have ω-hydrogen can exist in either the tautomeric thione form 6A or the thiol form 6B. Generally, reactions of nitrilimines with heterocyclic thiones, having the thiol form 6B, start with the formation of the 1,3-adducts to give the respective thiohydrazonate esters 7 as intermediates, whereas reactions of such 1,3-dipoles with true heterocyclic thiones having the thione form 6A proceed via 1,3-dipolar cycloaddition to the C=S double bond to form the spirocycloadducts namely spirothiadiazoles 8 (Scheme 2). Both types of intermediates 7 and 8 usually undergo further in situ reactions according to their structures and the reaction conditions leading thus to either formation of new aneled heterocycles, spiro heterocycles, heterocyclic ring transformation or functional group modification as outlined in the following sections.
In this review, the heterocyclic thiones, whose reactions with hydrazonoyl halides are covered, are presented in order of their increasing ring size, the number of rings and in order of increasing number of heteroatoms. The heteroatoms have been arranged in the following sequence N, O, S and other elements. The overall style of heterocycles arrangement follows that used in *Chemical Abstracts*. Also, the naming of the heterocycles follows generally the practices of *IUPAC* and *Chemical Abstracts*.

2. Heteroannulation

2.1. Heteroannulation of monoheterocycles

2.1.1. Imidazolethiones. Reaction of N-aryl 2-oxo-alkanehydrazonoyl halides with imidazoline-2(1H)-thione 9 in ethanolic triethylamine solution yielded the arylazo derivatives of imidazo[2,1-b]thiazole 10 via the thiohydrazonate (Scheme 3). Similar reaction of 9 with ethyl (N-arylhydrazono) chloroacetate yielded the hydrazone derivative 11 (Scheme 3).
Treatment of 4,5-diphenyl imidazoline-2(3H)-thione 12 with hydrazonoyl halides having no α-oxo group in chloroform in the presence of triethylamine was reported to give the respective imidazo[2,1-c][1,2,4]triazole derivatives 13 directly (Scheme 4).\(^7,15\)

Also, imidazo[2,1-c][1,2,4]triazole derivatives 16 were obtained via reaction of 4-arylhydrazono-2-methylthio-imidazolin-5(1H)-one 15 with various hydrazonoyl halide in ethanol in the presence of sodium ethoxide at room temperature (Scheme 5).\(^16\)
Scheme 5

Very recently, it was reported that reaction of N-aryl-2-oxohydrazonoyl chlorides with 1-amino-4-phenylimidazoline-2-thione 17 in ethanol in the presence of sodium ethoxide at room temperature afforded the respective 2-arylazo-4H-imidazo[2,1-b][1,3,4]thiadiazines 18 (Scheme 6).17 This finding indicates that the initially formed thiohydrazonates undergo in situ dehydrative cyclization as soon as they are formed to give 18 as end products.

Scheme 6

2.1.2. 1,2,4-Triazolethiones. Reaction of 5-phenyl-1,2,4-triazole-3(2H)-thione 19 with various hydrazonoyl chlorides gave the thiohydrazides 20, which were converted into 1,3,5-
trisubstituted-1,2,4-triazolo[3,4-c][1,2,4]triazoles 21 by treatment with phosphorus oxychloride.\textsuperscript{18-20} The latter products 21 were also prepared by reaction of 5-methylthio-3-phenyl-4\textit{H}-1,2,4-triazole 22 with hydrazonoyl chloride (Scheme 7).\textsuperscript{18-20}

\textbf{Scheme 7}

Similar reaction of bis-hydrazonoyl chloride 23 with 3-methylthio-5-phenyl-4\textit{H}-1,2,4-triazole 24 was reported to give 3,3’-bis(1,2,4-triazolo[3,4-c][1,2,4]triazole derivative 25 (Scheme 8).\textsuperscript{21}

\textbf{Scheme 8}

However, reaction of the same bis-hydrazonoyl chloride 23 with 5-phenyl-1,2,4-triazole-3(2\textit{H})-thione 19 was reported to give 5,6-bis(phenylhydrazono)-2-phenylthiazolo[3,2-b][1,2,4]triazole 26 (Scheme 9).\textsuperscript{21}
Reaction of 4-amino-5-phenyl-1,2,4-triazole-3(2H)-thione 27 with 2-aryl-2-oxoethanehydrazonoyl bromides in ethanol in the presence of sodium ethoxide was reported by Shawali et al.\textsuperscript{22,23} to afford the respective thiohydrazonates 28a-g (Scheme 10). Similar reaction of 27 with the hydrazonoyl bromide having electron-withdrawing substituents in the N-aryl moiety directly afforded, however, the respective 7-arylhydrazono-3,6-diaryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines 29h-j, probably \textit{via in situ} dehydrative cyclization of the initially formed thiohydrazonates 28h-j.\textsuperscript{22,23} The thiohydrazonates 28a-g were converted into the respective triazolothiadiazines 29a-g by treatment with acetic acid (Scheme 10).\textsuperscript{22}

Similarly, several other series of 7-arylhydrazono-7H-3-heteroaryl-triazolo[3,4-b][1,3,4]thiadiazin-6(5H)-ones 31 and 32 were prepared \textit{via} reaction of 4-amino-5-heteroaryl-[1,2,4]-triazole-3(2H)-thiones 30 with ethyl arylhydrazonochloroacetate and N-aryl-2-oxoalkane hydrazonoyl halides, respectively (Scheme 11).\textsuperscript{24,25}
Furthermore, 1,2-bis(7-arylhydrazono-7\textsubscript{H}-[1,2,4]triazolo-[3,4-b][1,3,4]-thiadiazin-3-yl)ethanes \textsuperscript{34} were prepared by reaction of 1,2-bis(4-amino-3-thioxo-2\textsubscript{H}-[1,2,4]triazol-5-yl)ethane \textsuperscript{33} with \textit{N}-aryl 2-oxopropanehydrzonoyl chlorides (Scheme 12). \textsuperscript{26}

\textbf{Scheme 12}

\textbf{2.1.3. Pyrimidinethiones.} Hydrazonoyl halides reacted with 2-pyrimidinethione \textsuperscript{35} in chloroform in the presence of triethylamine and yielded the corresponding 1\textsubscript{H},5\textsubscript{H}-[1,2,4]triazolo[4,3-a]pyrimidine derivatives \textsuperscript{36} (Scheme 13). \textsuperscript{27-32}
Reactions of hydrazonoyl halides with 6-substituted-2-thiouracils $37^A$ and $37^B$ as well as their 2-methylthio derivatives $38$ were reported to be regioselective and afforded the respective 1,2,4-triazolo[4,3-$a$]pyrimidinone derivatives $39$ (Scheme 14).
The involvement of the thiohydrazonates and thiohydrazides as intermediate in the reactions of hydrazonoyl halides with 2-thiouracils 37 was evidenced by alternate synthesis of 39.37 Thus, treatment of 2-thiouracil derivative 37 with active 3-chloromethylene compounds 40 afforded the S-alkylated products 41, which yielded upon coupling with diazonium salts the thiohydrazonates 42 via Japp-Klingeman34 reaction. The latter esters, upon treatment with sodium ethoxide in ethanol underwent Chapman-like rearrangement7,9 to give the corresponding thiohydrazides 43 which cyclized in situ to yield the respective 1,2,4-triazolo[4,3-a]pyrimidinones 39 (Scheme 15).

Scheme 15

Reaction of 6-amino-2-thiouracil 37A with N-phenyl benzenecarbohydrazonoyl chloride in dioxane in the presence of triethylamine under reflux yielded 39 (Scheme 16). The other isomeric structure 44 was discarded on the basis of the IR and 13C NMR evidences.35 When compound 39 was refluxed with benzaldehyde in acetic acid, it yielded 44 (Scheme 16).36
Scheme 16

Bishydrazonoyl chloride 23 was reported to react regioselectively with 2-thiouracil 37A to give a mixture of 2,3-bis-(arylhydrazono)-thiazolo[3,2-α]pyrimidine-5-one 46 and 3,3'-bis-1,2,4-triazolo[4,3-a]pyrimidin-5-one 47. However, reaction of the same bis-hydrazonoyl chloride with 2-methylthiouracil 38 afforded only 47 (Scheme 17). 41

Scheme 17

Reactions of hydrazonoyl halides with either 3-amino-2,3-Dihydro-6-substituted-2-thioxopyrimidin-4(3H)-ones 48 or 3-amino-6-substituted -2,3-dihydro-2-methylthio-4(3H)-
pyrimidinone 49 were recently reported by Shawali et al.\textsuperscript{42-44} to give the respective 4H-
pyrimido[1,2-\(b\)][1,2,4,5]tetrazin-6-ones 50 (Scheme 18).

![Scheme 18](image)

**Scheme 18**

2.1.4. 1,2,4-Triazine-5(4\(H\))-thiones. \(N,N\)-Diphenyl ethane-bishydrazonoyl chloride 23 was
reported to react with 2,3-dihydro-3-thioxo-1,2,4-triazin-5(4\(H\))-one 51 and its 3-methylthio
derivative 52 to give 2,3-bis(phenylhydrazono)thiazolo-[3,2-b][1,2,4]triazin-7-one 52 and 3,3’-
bis(1,2,4-triazolo[4,3-b][1,2,4] triazines) 54 (Schemes 19 and 20) respectively.\textsuperscript{21}

![Scheme 19](image)

**Scheme 19**

![Scheme 20](image)

**Scheme 20**
Reactions of hydrazonoyl halides with either 6-substituted 3-thioxo-1,2,4-triazin-5(2H)-ones \(51\) \(45\) or 6-substituted-3-methylthio-1,2,4-triazin-5(4H)-one \(53\) \(46\) were reported to give in both cases the respective 1,2,4-triazolo[4,3-b][1,2,4]triazin-7(1H)-ones \(55\) (Scheme 21). The structure of the latter products and the regiochemistry leading to them was confirmed by Shawali et al. \(46\) via their alternate synthesis. \(46\) Thus, treatment of 2-chloro-3-oxobutanilide and ethyl 2-chloro-3-oxobutanoate each with 2,3-dihydro-3-thioxo-1,2,4-triazin-5(4H)-one \(51\) afforded the respective active (1,2,4-triazin-3-yl)thio methylene compounds \(56\). Reaction of the latter with benzenediazonium chloride in ethanol in the presence of sodium acetate furnished the azo compounds \(57\), which yielded [1,2,4]triazolo[4,3-b][1,2,4]triazin-7(1H)-ones \(55\) (\(Ar = \text{Ph}\)) upon treatment with sodium ethoxide in ethanol (Scheme 22). \(46\)

\[\text{R-C(X)=NNHAr} \quad + \quad \text{R-C(X)=NNHAr} \quad \rightarrow \quad \text{R-C(X)=NNHAr} \]

\[\text{R' = PhCH}_2, \quad 4\text{-ClC}_6\text{H}_4\text{CH}_2, \quad 4\text{-MeC}_6\text{H}_4\text{CH}_2, \quad 4\text{-MeOC}_6\text{H}_4\text{CH}_2, \quad \text{piperonyl-CH}=\text{CH, 4-ClC}_6\text{H}_4\text{CH}=\text{CH} \]

Scheme 21

\[\text{R = Ph, PhCH}=\text{CH-; 2-Furyl; 2-Thienyl; EtOCO-; PhNHCO-; MeCO-; PhCO-; 2-Thenoyl} \]

\[\text{PhN}_2\text{Cl} \quad \rightarrow \quad \text{R' = PhCH}_2, \quad 4\text{-ClC}_6\text{H}_4\text{CH}_2, \quad 4\text{-MeC}_6\text{H}_4\text{CH}_2, \quad 4\text{-MeOC}_6\text{H}_4\text{CH}_2, \quad \text{piperonyl-CH}=\text{CH, 4-ClC}_6\text{H}_4\text{CH}=\text{CH} \]

Scheme 22
Very recently Shawali et al. \(^{47}\) reported that reaction of hydrazonoyl halides with either 4-amino-2,3-dihydro-6-substituted-3-thioxo-[1,2,4]triazin-5(2\(H\))-ones \(^{58a,b}\) or 4-amino-2,3-dihydro-3-methylthio-6-substituted-[1,2,4]triazin-5(4\(H\))-ones \(^{59a,b}\) gave the respective \([1,2,4]\)triazino[4,3-\(b\)][1,2,4,5]tetrazine derivatives \(^{60}\) (Scheme 23). Similar reactions of \(^{58}\) and \(^{59}\) each with 3-chloroformazans were also found to give the respective 3-arylazo derivatives \(^{60}\) (\(R'' = \text{Ar-N=N-}\))\(^{44}\) (Scheme 23).

\[
\begin{align*}
\text{R} & = \text{a, Me; b, ph} \\
58 & \text{R'} = \text{H} \\
59 & \text{R'} = \text{Me} \\
\text{R''} & = \text{EtOCO, PhNHCO, Ac, PhCO, 2-naphthoyl, CH}_3, \\
& \text{2-Thenoyl, Ar-N=N-}
\end{align*}
\]

Scheme 23

2.1.5. 1,2,4-Triazepinethiones. The reaction of \(N\)-aryl-C-ethoxycarbonylnitrilimines with \([1,2,4]\)triazepine-3,5-dithiones \(^{61}\) was reported to yield the respective \([1,2,4]\)-triazolo[4,3-\(d\)][1,2,4]triazepines \(^{62}\) (Scheme 24).\(^{48}\) The reaction was said to be completely peri and regioselective. The preferred orientation was predicted correctly by AM1 calculations.

\[
\begin{align*}
\text{EtOCOC(Cl)=NNHPh} & \quad - \text{HCl} \\
\text{Me} & \quad \text{EtOCOC=NN-Ph} \\
61 & \quad \text{COOEt}
\end{align*}
\]

Scheme 24
2.2. Heteroannulation of biheterocycles

2.2.1. Benzimidazolethiones. When benzimidazole-2-thiol \(63\) was refluxed with hydrazonoyl halides in chloroform in the presence of triethylamine, it afforded the respective 1,2,4-triazolo[4,3-a]benzimidazoles \(64\) (Scheme 25).\(^{15}\)

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{S} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
R : & \text{ Ph, 2-thienyl, 2-furyl}
\end{align*}
\]

Scheme 25

The reaction of benzimidazole-2-thiol \(63\) with ethyl (N-arylhydrazono)chloroacetate and 2-phenylamino-2-oxoethane-hydrazonoyl chloride in the presence of base catalyst yielded the corresponding thiohydrazonate esters \(65a\) and \(65b\), respectively.\(^{14}\) Acid treatment of the latter products resulted in their cyclization to give thiazolo[3,2-a]benzimidazol-3-one \(66\) (Scheme 26).\(^{14}\)

\[
\begin{align*}
\text{H} & \quad \text{S} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
R : & \text{ a, EtO; b, PhNH}
\end{align*}
\]

Scheme 26

Similar reaction of 2-oxopropanehydrazonoyl chloride,\(^{14}\) 2-oxo-2-(pyrazol-3-yl)ethanehydrazonoyl bromide,\(^{14}\) and \(N\)-phenyl 2-(2-phenyl-4-methylthiazol-5-yl)-2-oxoethanehydrazonoyl bromide\(^{50}\) each with benzimidazole-2-thione \(63\) afforded the respective thiohydrazonate esters \(65\) that cyclized upon heating to give the corresponding 2-arylazothiazolo[3,2-a]benzimidazoles \(67\) (Scheme 27).
Scheme 27

2,3-Bis(phenylhydrazono)thiazolo[3,2-α]benzimidazoles 68 were obtained by reaction of bishydrazonoyl chloride 23 with benzimidazole-2-thiol 63 (Scheme 28). Treatment of bis(phenylhydrazone) 68 with lead(IV) tetracetate in DMF-acetonitrile mixture afforded the respective bis(phenylazo) derivative 69.

Scheme 28

Treatment of benzimidazole-2-thiol 63 with hydrazonoyl halides in refluxing chloroform in the presence of triethylamine was reported to give the respective 1,2,4-triazolo[4,3-α]benzimidazole derivatives 71. The latter product were also obtained by refluxing 2-methylthiobenzimidazole 70 with hydrazonoyl halides in chloroform in the presence of triethylamine (Scheme 29).
The reaction of bishydrazonoyl chloride 23 with 2-methylthio-benzimidazole 70 was reported recently to give 3,3'-bis(1,2,4-triazolobenzimidazole) 72 (Scheme 30). 21

2.2.2. Purinethiones. Recently Shawali et al. 54 reported that reactions of hydrazonoyl halides with theophylline-8-thione 73 and 8-methylthiotheophylline 74 in refluxing pyridine yielded in both cases 1,3-disubstituted [1,2,4] triazolo[3,4-f]purine derivatives 75 (Scheme 31). The formation of the latter from 74 and hydrazonoyl halides was proposed to proceed via 1,3-dipolar cycloaddition of nitrilimines, derived by the action of pyridine on hydrazonoyl halides used, on the C=N double bond to give the cycloadducts as intermediates which undergo in situ elimination of methanethiol to give 75 as end products (Scheme 31). However, the formation of 75 from 73 and hydrazonoyl halides was supposed to proceed via the formation of the thiohydrazonate esters which then undergo in situ two tandem reactions namely rearrangement
into the thiohydrazides followed by cyclization of the latter with concurrent elimination of H₂S to afford 75 (Scheme 31). ⁵⁴

![Scheme 31](image)

### 2.2.3. Pyrazolo[3,4-d]pyrimidinethiones.

Reaction of hydrazonoyl halides with 5-amino-1-phenyl-6-thioxopyrazolo[3,4-d]pyrimidin-4-one 76A and its methylthio derivative 77B in refluxing dioxane in the presence of triethylamine was also reported by Shawali et al. ⁵⁵ to afford pyrazolo[3,4-d]pyrimido[1,2-b][1,2,4,5]tetrazine derivatives 78. The mechanism of the studied reaction was discussed and the structures of the isolated products were evidenced by alternate synthesis depicted in Scheme 32. ⁵⁵

![Scheme 32](image)
2.2.4. Quinazolinethiones. Reaction of bis-hydrazonoyl chloride 23 with 2-thioxoquinazolin-4(1H)-one 80 afforded the bis-(phenylhydrazono)-thiazoloquinazoline derivative 81 (Scheme 33). 41

![Scheme 33](image)

Similar reaction of 80 with various hydrazonoyl halides in refluxing chloroform in the presence of triethylamine yielded 1,3-disubstituted 1,2,4-triazolo[4,3-a]quinazolin-5-one derivatives 82. The other regioisomers 83 were not produced (Scheme 34). 56

![Scheme 34](image)

R/ X : Me / Br; Et / Br; Ph / Cl; PhCH=CH- / Cl; 2-thienyl / Br; Ac / Cl; EtOCC / Cl; PhCO / Br; 2-thenoyl / Br; Ph / Br; 2-naphthoyl / Br; 2-furyl / Br; PhNHCO / Cl

Also, it was reported that reaction of hydrazonoyl halides with 3-amino-2-thioxoquinazolin-4(1H)-one 84 afforded 4H-[1,2,4,5]-tetrazino[3,2-b]quinazolin-6-ones 86 (Scheme 35). 57 The latter products 86 were also obtained by reaction of 3-amino-2-methylthioquinazolin-4(3H)-one 85 with the same series of hydrazonoyl halides (Scheme 35). 57, 58
2.2.5. **Pyrido[2,3-d]thiouracils.** Recently, it was reported that treatment of pyridino[2,3-d]-2-thiouracil 87 with hydrazonoyl chlorides in boiling chloroform in the presence of triethylamine yielded the corresponding pyridino[2,3-d]triazolo[4,3-a]pyrimidin-5-one derivatives 88. The structure of the latter products 88 were established by their alternate synthesis via reaction of formamidine 89 with acetophenone in boiling acetic acid (Scheme 36). The involvement of the thiohydrazonate esters as intermediates in the studied reactions of 87 with hydrazonoyl halides was evidenced by alternate synthesis of 88 via reaction of 87 with the appropriate active α-chloromethylene compounds followed by coupling with diazotized aniline to give the respective coupling products. Treatment of the latter with ethanolic sodium ethoxide resulted in its Chapman-rearrangement to yield the respective thiohydrazides which cyclized in situ to give 88 as end products (Scheme 36).
2.2.6. Pteridinethiones. Reaction of 2-thioxopteridine-4(3H)-one derivatives 90 with hydrazonoyl halides in tetrahydrofuran in the presence of triethylamine under reflux afforded the respective 1,2,4-triazolo[3,4-b]pteridine derivatives 91 (Scheme 37). The structure of the latter products was established by X-ray analysis.
2.2.7. **Quinoxalinethiones.** Various 2,4-disubstituted-4H-1,3,4-thiadiazino[5,6-b] quinoxalines 93 were obtained by reaction of hydrazonoyl halides with 2-amino-3-quinoxalinethiol 92 in ethanol in the presence of sodium ethoxide (Scheme 38). The structure of the isolated products was evidenced by alternate synthesis of 93 (R = PhN=N-, X = H). Thus reaction of 1,5-diphenyl-3-mercaptopformazan 95 with either 2,3-dichloroquinoxaline 94a or 2-amino-3-chloroquinoxaline 94b in ethanol in the presence of triethylamine afforded in each case a product that proved identical in all respects with the one obtained above from reaction of 92 with 1,5-diphenyl-3-chloroformazan (Scheme 38).

![Scheme 38](image)

**Scheme 38**

2.3. **Heteroannulation of triheterocycles**

2.3.1. **Benzothieno[2,3-d]pyrimidinethiones.** Reactions of 3-amino-2,3,5,6,7,8-hexahydro-2-thioxo[1]benzo-thieno [2,3-d]pyrimidin-4(3H)-one 96a and its 2-methylthio derivative 96b with hydrazonoyl halides in ethanol in the presence of triethylamine afforded the fused tetrazine derivatives 97 as end products (Scheme 39).
2.3.2. Pyrido[3',2':4,5]thieno[2,3-b]pyrimidinethiones. Reaction of hydrazonoyl halides with 98 in dioxane in refluxing dioxane in the presence of triethylamine gave pyrido[3',2':4,5]thieno[3,2-d][1,2,4]triazolo[5,4-a]pyrimidin-5-one 99. The mechanism of the studied reactions and the structure of the products were evidenced by spectral data and alternate synthesis (Scheme 40).

Similar reaction of hydrazonoyl halides with each of 3-amino-2,3-dihydro-7,9-dimethyl-2-thioxo-pyrido[3',2':4,5]-thieno[2,3-d]pyrimidin-4(3H)-one 100a and its 2-methyl derivative 100b in ethanol in the presence of triethylamine afforded the fused tetrazine derivatives 101 as end products (Scheme 41).
Scheme 41

However, reaction of the thione 100a with hydrazonoyl halides in ethanol in the presence of sodium ethoxide at room temperature led to the formation of the thiohydrazonate ester. Treatment of the latter with glacial acetic acid produced the respective 2-arylhydrazonopyrido[3",2":4',5']thieno[3',2':4,5]pyrimido[2,1-b][1,2,4]thiadiazinones 102 and 103. The structure of 102 was evidenced by alternate synthesis via coupling of 104 with the appropriate diazotized anilines (Scheme 42). 65

Scheme 42
2.3.3. Cyclohepta [4,5]-thieno[2,3-d]pyrimidinthiones. Recently various functionalized derivatives of 5H-cyclohepta[4,5]-thino[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one 106 were synthesized via reaction of hydrazonoyl halides with either 2,3,5,6,7,8,9-heptahydro-2-thioxo-4H-cyclohepta[4,5]thino[2,3-d] pyrimidin-4-one 105a or its methylthio derivative 105b. The mechanism and the regioselectivity of these reactions were investigated and discussed (Scheme 43).

![Scheme 43](image)

Treatment of the thione 107a or its methylthio derivative 107b each with hydrazonoyl halides in ethanol in the presence of sodium ethoxide at room temperature gave the respective 1,3-disubstituted 1,7,8,9,10,11-hexahydro-4H,6H-cyclohepta[4',5']thieno[2',3':4,5]pyrimido[1,2-b][1,2,4,5]tetrazin-6-one 108 (Scheme 44).

![Scheme 44](image)

2.3.4. Pyrido[2,3-d : 6,5-d']dipyrimidinethione. Reaction of 2,8-dihydropyrido[2,3-d:6,5-d']dipyrimidine-4,6(1H,7H)- dione 109 with hydrazonoyl chlorides in ethanol in the presence of triethylamine at room temperature was found to give products identified as the bis-thiohydrazonate esters 110 (Scheme 45). Treatment of 110 with sodium ethoxide in refluxing ethanol gave the products 111 via in situ Smiles rearrangement \(^{34}\) of 110 followed by cyclization with concurrent elimination of hydrogen sulfide (Scheme 45). \(^{36}\) That the isolated products from the latter treatment have the structure 111 and not its isomer 112, was confirmed by their alternate synthesis. Thus, treatment of the dithione 109 with two molar equivalents of ethyl 2-
chloro-3-oxobutanoate in ethanol in the presence of potassium hydroxide at room temperature yielded the substitution product 113 (Scheme 46). Treatment of 113 with p-chlorobenzenediazonium chloride in ethanol in the presence of sodium acetate at low temperature (0-5°C) yielded product identical in all respects with the product 110Cc isolated from reaction of 109 with N-(p-chlorophenyl)-C-ethoxycarbonylnitritlimine (Scheme 45). Treatment of the 110Cc with sodium ethoxide in ethanol in attempt to get the respective bis-thiohydrazide, was found to give 111Cc directly as end product (Scheme 46).
2.4. Heteroannulation of tetraheterocycles


Scheme 47
3. Synthesis of spiroheterocycles

The reaction of heterocyclic thiones 116 with nitrilimines, generated in situ by base-catalyzed dehydrohalogenation of hydrazonoyl halides, has been described for synthesis of various derivatives of spiro[heterocycle-n,2'-3H-1,3,4-thiadiazole] 117 (Fig. 1).

![Figure 1](image_url)

Thus, reaction of 2-oxoalkanehydrazonoyl halides reacted with 4-oxo-1,3-diphenylimidazole-2-thione 118 in chloroform in the presence of triethylamine gave the corresponding spiro[imidazole-2,2'-3H-1,3,4-thiadiazole] derivatives 119 in 75-77% yield (Scheme 48). This finding indicates that the dipolarophilicity of the C=S group is more than that of the C=O group.

![Scheme 48](image_url)

Similar reaction of 5-phenylmethylene-1,3-diphenyl-5-oxo-2-thioxo-tetrahydroimidazole 120 with hydrazonoyl halides in chloroform in the presence of triethylamine afforded, however, spiro[5H-pyrazolo-4,4'-imidazole] 121 in 78-80% yield via cycloaddition of the in situ generated nitrilimines on the exocyclic C=C double bond. This result indicates that the C=S, while being more reactive dipolarophile than the C=O double bond, is less reactive than the enone moiety of 120 (Scheme 49).
Scheme 49

On the other hand, the spiro[3H-thiazole-2,2'-3H-thiadiazole] derivatives 123 were formed by reaction of 3-phenyl-4-phenylmethylene-2-thioxothiazolin-5-one 122 with nitrilimines, generated in situ by the action of triethylamine on hydrazonoyl halides in refluxing chloroform (Scheme 50). In this case, the C=S double bond seems to be more dipolarophilic than both the enamine or enone C=C double bond.

Scheme 50

Various substituted derivatives of spiro[thiazole-2,2'-3H-1,3,4-thiadiazole] 125 were prepared in good yield by reaction of hydrazonoyl halides with 5-arylmethylene-3-phenyl-2-thioxothiazolidin-4-one 124 in chloroform in the presence of triethylamine (Scheme 51).
Diphenylnitrimine, derived from thermolysis of 3,5-diphenyltetrazole in mesitylene, cycloadded to 5-thioxothiazoline derivative 126 to give 83% of spiro[5H-thiazole-5,2′-3H-1,3,4-thiadiazole] 127 (Scheme 52). \(^{72}\)

![Diagram 52]

Scheme 52

Also, diphenylnitrimine, derived from N-phenylbenzencarbohydrazonoyl chloride, reacted with 3,5-diphenyl-1,3,4-thiadiazine-2-thione 128 and afforded the respective derivative of spiro[3H-1,3,4-thiadiazole-2,2′-3H-1,3,4-thiadiazole] 129 (Scheme 53). \(^{73}\)

![Diagram 53]

Scheme 53

Heating a mixture of N-phenyl benzencarbohydrazonoyl chloride and 1,2-dithioline-3-thiones 130 in chloroform in the presence of triethylamine yielded 1,2,4-thiadiazoline derivatives 132. The latter products were said to result via ring cleavage of the initially formed spiro[1,2-dithioline-3,2′-3H-1,3,4-thiadiazole] cycloadducts 131 (Scheme 54). \(^{74}\)
Reactions of the pyrimidine-2(1H)-thione 133 and its analog 4(1H)-thione 136 each with one molar equivalent of the appropriate hydrazonoyl halide in benzene in the presence of triethylamine gave under normal conditions the respective spiro cycloadducts 134 and 137, respectively. Using two mole equivalents of hydrazonoyl halide in the reaction with pyrimidine-2(1H)-thiones 133 led to the 2:1 cycloadducts 135 (Scheme 55). The structure of the latter bis-cycloadduct 135 needs further investigation as it results from $4\pi + 4\pi$ cycloaddition which is thermally forbidden.
N\N
R-C=N-N-Ph

136

+ R3

= Ph, Ac, EtOCO

R3 = 4-Me, CH2COOEt, Me,

4-ClC6H4, CH2COOMe

Ar2 = Ph, 4-ClC6H4

Scheme 55

Spiro[3H-1,3,4-thiadiazole-2,3′-2H-pyridazine] derivatives 139 were prepared by reaction of 6-thioxo-1,6-dihydropyridazines 138 with N-phenyl 2-oxopropanedithyrazonoyl chloride (Scheme 56).76-78

N\N
S

R'

R" = H, Ph

138

R' = 4-ClC6H4, CH3, Ph

Scheme 56

Also, spiro[3H-1,3,4-thiadiazole-2,6′-1,4,5,6-tetrahydro-1,2,4-triazine] 141 was said to be formed when 3-phenyl-4,5-dihydro-1,2,4-triazin-6(1H)-thione 140 with N-methyl benzeneborohydrazonoyl bromide in chloroform in the presence of triethylamine. However, this spirocycladduct 141 was said to be unstable so that full characterization could not be achieved (Scheme 57).77

N\N
S

Ph-C(Br)=NNH-Me.HBr

140

+ Et3N

Ph-C(Br)=NNH-Me.HBr

141

Scheme 57
2,3,3-Triphenyl-1-thioxophthalimidine 142 reacted with hydrazonoyl halides in boiling benzene in the presence of triethylamine afforded 2,3,3,3',5'-pentasubstituted spiro[benzopyrolidine-1,2'-(2',3'-dihydro)-[1',3',4']-thiadiazoles] 143 (Scheme 58).\(^7^9\)

\[
\begin{array}{c}
\text{S} & \text{S} \\
\text{N} & \text{N} \\
\text{R} & \text{N} \\
\text{N} & \text{Ph} \\
\text{Ph} & \text{Ph} \\
\text{Ph} & \text{Ph} \\
\text{Ph} & \text{Ph} \\
\end{array}
\xrightarrow{\text{PhH / Et}_3\text{N} / -\text{HCl}}
\begin{array}{c}
\text{S} & \text{S} \\
\text{N} & \text{N} \\
\text{N} & \text{Ph} \\
\text{R} & \text{N} \\
\text{Ph} & \text{Ph} \\
\text{Ph} & \text{Ph} \\
\text{Ph} & \text{Ph} \\
\end{array}
\]

\(R = \text{Ph, 4-NO}_2\text{C}_6\text{H}_4, \text{Ac, PhCO, EtOCO}\)

Scheme 58

Spiro[3\(H\)-1,3,4-thiadiazole-2,2'-benzothiophenes] 145 were also prepared from 1,2-dithiophthalides 144 and nitrilimines, derived from the respective hydrazonoyl halides (Scheme 59).\(^8^0\)

\[
\begin{array}{c}
\text{S} & \text{S} \\
\text{N} & \text{N} \\
\text{R} & \text{N} \\
\text{Ar} & \text{N} \\
\text{Ar} & \text{N} \\
\text{Ar} & \text{N} \\
\text{Ar} & \text{N} \\
\end{array}
\xrightarrow{\text{R-C(X)=NNHAr} - \text{HX}}
\begin{array}{c}
\text{S} & \text{S} \\
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{R} & \text{R} \\
\text{S} & \text{S} \\
\text{N} & \text{N} \\
\end{array}
\]

Scheme 59

Similarly, reaction of hydrazonoyl halides with 1-thioxo-3,3-diphenyl-isobenzothiophene 146 yielded 80% of the respective spiro[3\(H\)-1,2,4-triazole-2,1’-1\(H\),3\(H\)-isobenzothiophenes] 147 (Scheme 60).\(^8^1\)

\[
\begin{array}{c}
\text{S} & \text{S} \\
\text{Ph} & \text{Ph} \\
\text{Ph} & \text{Ph} \\
\end{array}
\xrightarrow{\text{R-C(X)=NNHAr} - \text{HX}, \text{Et}_3\text{N}}
\begin{array}{c}
\text{S} & \text{S} \\
\text{N} & \text{N} \\
\text{R} & \text{R} \\
\text{R} & \text{R} \\
\text{R} & \text{R} \\
\end{array}
\]

\(R = \text{Ph, Ac}\)

Scheme 60
Contradicting results regarding the site selectivity in the reaction of 4\(H\)-1-benzopyran-4-thione 148 with hydrazonoyl halides were reported. Thus, in one report,\(^8\) such a reaction was reported to proceed smoothly and gave the cycloadduct 149 (Scheme 61). In another report,\(^9\) the product isolated from the reaction of 148 with \(N\)-\(p\)-bromophenyl 2-oxopropanehydrazonoyl chloride in the presence of triethylamine was shown on the basis of X-ray analysis to be spiro[3\(H\)-1,3,4-thiadiazole-2,4'-4\(H\)-1-benzopyran] 150 (Scheme 61).

**Scheme 61**

Furthermore, spiro[3\(H\)-1,3,4-thiadiazole-2,4'-4\(H\)-benzopyran] derivatives 152 were obtained by the reaction of 3-cyano-4\(H\)-1-benzopyran-4-thione 151 with hydrazonoyl halides in chloroform in the presence of triethylamine (Scheme 62).\(^8\)

**Scheme 62**

Heating a mixture of thioxophthalazines 153 and hydrazonoyl halides in chloroform in the presence of triethylamine afforded the respective spiro[3\(H\)-1,3,4-thiadiazole-2,4'-3\(H\)-quinazoline] derivatives 154 in 75-80% yield (Scheme 63).\(^8\)
Reaction of pyrazolo[1,5,4-ef][1,5]benzodiazepine-6-thione 155 with N-aryl-C-ethoxycarbonylnitrilimines, generated in situ by the action of triethylamine on the respective ethyl N-arylhydrazonochloroacetate, yielded the respective spiro[4H-1,4-diazepin-6-ene[1,2,3-hi]imidazole-2,2′-2H-1,3,4-thiadiazole] 156 (Scheme 64). 86

4. Heterocyclic ring transformations

4.1 Transformation of azetine-2-thiones into 1,3,4-triazoles

Reactions of 2-ethylthio-3,3,4,4-tetramethyl-azetine 158, derived from the respective thione 157, with N-phenylbenzenecarbohydrazonoyl chloride in refluxing benzene in the presence of triethylamine was reported to give 5-(2,3-dimethylbuten-1-en-3-yl)-1,3-diphenyl-1,2,4-triazole 159a whose structure was evidenced by 1H NMR and X-ray analyses as well as chemical reactions (Scheme 65). 87 Similar reaction of 160 with the same hydrazonoyl chloride under the same conditions afforded 162a in 73% yield. However, reaction of 160 with N-(4-nitrophenyl) benzenecarbohydrazonoyl chloride gave a separable mixture of the tricyclic cycloadduct 161 and 162b (Scheme 65). 87 On the other hand, no reaction was observed between the latter
hydrazonoyl chloride and each of 8-(ethylthio-6-methyl-7-azabicyclo[4.2.0]oct-3,7-diene 163a and its 1,6-dimethyl analog 163.87

i = PhH / Et3N / heat

Scheme 65

4.2 Transformation of 1,3,4-Oxadiazole-2(3H)-thiones into 1,3,4-thiadiazoles

In recent reports, Shawali et al. 88-90 and others91-93 indicated that reactions of hydrazonoyl halides with 1,3,4-oxadiazole-2(3H)-thiones 164 afforded 1,3,4-thiadiazol-2(3H)-one derivatives 166. The formation of the latter was assumed to occur via the rearrangement of the initially formed thiohydrazonate esters as intermediate (Scheme 66). Similar reaction of 5-heteroaryl-1,3,4-oxadiazole-2(3H)-thione with hydrazonoyl halides in refluxing ethanol in the presence of triethylamine afforded also the corresponding 166 (Scheme 66).25
The involvement of thiohydrazonate 168 as intermediates in the studied reactions was confirmed by alternate synthesis of 166 as depicted in Scheme 67. 89,90

Scheme 66

Scheme 67
Also, reactions of the Mannich bases 169 with hydrazonoyl halides in benzene or ethanol in the presence of triethylamine at room temperature was reported to afford the respective thiadiazoline derivatives 166 (Scheme 68).  

\[ R-C(X)=NNHPh \rightarrow E_{t_3}N / -HX \]

**Scheme 68**

Reaction of 5-heteroaryl 1,3,4-oxadiazole-2(3H)-thione 170 with hydrazonoyl halides in ethanol in the presence of triethylamine under reflux gave the respective 1,3,4-thiadiazole derivatives 171. The structure of the latter was confirmed by its alternate synthesis via reaction of hydrazonoyl halides with N-acylthiocarbohydrazide 172 (Scheme 69).

\[ \text{Het-CO-NHNHCSNH}_2 + R-C(X)=NNHAr \rightarrow \text{Het}= \]

**Scheme 69**

**4.3. Transformation of 1,4,2-dithiazole-5-thiones into 1,3,4-thiadiazoles**

Reaction of benzenecarbohydrazonoyl chloride with 3-substituted 1,4,2-dithiazole-5-thione 173 in benzene in the presence of triethylamine was reported to yield 3,5-diphenylthiadiazole-2-thione 175. The latter products were considered to result via ring cleavage of the initially formed spiro intermediate 174 (Scheme 70).

\[ \text{Het} = \]

\[ R = \text{Ph, PhCO, Ac, 2-Furoyl, EtOCO} \]
4.4. Transformation of tetrazole-5(1H)-thiones into 1,3,4-thiadiazoles

Treatment of hydrazonoyl halides with tetrazole-5(1H)-thiones 176 in chloroform in the presence of triethylamine led to the formation of the thiohydrazonate esters 177. When the latter thiohydrazonates were heated in toluene, they were converted into 1,3,4-thiadiazoles 179 (Scheme 71). 96

\[
\begin{align*}
R = \text{Ph, 4-}O_2\text{NC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4 \\
\text{Ar} = 4-\text{O}_2\text{NC}_6\text{H}_4
\end{align*}
\]

Scheme 71

4.5 Transformation of tetrazoles into 1,2,4,5-tetrazines

Reaction of 1-phenyltetrazole-5-thione 176 with \(N\)-(2,4-dibromophenyl) benzenecarbohydrazonoyl chloride in ethanolic solution of sodium ethoxide at room temperature yielded the thiohydrazonate ester 177 in 89\% yield (Scheme 72). 97 The latter esters 177 were cleaved upon heating in benzene and hydrochloric acid to give benzoic \(N\)-(2,4-dibromophenyl)hydrazide and 1-phenyltetrazole-5-thione 176 (Scheme 72). 96,97 When the
thiohydrazonate esters 177 were heated with sodium ethoxide in ethanol under reflux, they were reported to give the substituted dihydrotetrazines derivatives 180. In each case, the latter products were accompanied by lesser yields of the symmetrical tetrazines 181.\(^9\)

\[ \text{NN} \quad \text{N} \quad \text{N} \quad \text{S} \quad \text{R} \]
\[ \begin{align*}
\text{NN} & \quad \text{N} \quad \text{N} \\
\text{S} & \quad \text{R}
\end{align*} \]

\[ \begin{align*}
\text{NN} & \quad \text{N} \\
\text{Ar} & \quad \text{N} \quad \text{N}
\end{align*} \]

\[ \text{Ph} = 2,4-\text{Br}_2\text{C}_6\text{H}_3, 4-\text{O}_2\text{NC}_6\text{H}_4 \\
\text{R} = \text{Ph, 4-} \text{O}_2\text{NC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4 \\
\]

Scheme 72

5. Functional group transformation

Literature reports indicate that in some reactions of heterocyclic thiones with hydrazonoyl halides, the initially formed spirocycloadducts are unstable so that they undergo \textit{in situ} ring-chain tautomerism to give the respective N-aryl-N-heteroaryl-thiocarbohydrazides as end products. For example, reactions of hydrazonoyl halides with each of 4,5-diaryl-1,2,4-triazole-3-thiones 182,\(^1\) 5-substituted-1,3,4-thiadiazole-2-thiones 183\(^1\) and 4,6-disubstituted-3-thioxo-1,2,4-triazin(4\(H\))-one 184\(^5\) afforded the thiocarbohydrazides 185-187, respectively (Scheme 73).
6. Conclusions

The present review has outlined the importance of the reactions of hydrazonoyl halides with heterocyclic thiones as convenient methodology for annulation of heterocycles, synthesis of spiro heterocycles and heterocyclic ring transformation. It is hoped that it will further stimulate interest in the chemistry of such halides and their use as popular synthons for other heterocycles of industrial and biological potentials. The reactions covered still require further exploration and applications.

7. References


**Biographical Sketches**

Ahmad Sami A. S. Shawali is presently Professor of Physical organic chemistry in the Chemistry Department, Faculty of Science, University of Cairo. He graduated with B.Sc. degree from the same university 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, Lowell, Massachusetts, USA. He was awarded the degree of Doctor of Science (D.Sc.) from British Royal Chemical Society and the University of Cairo in 1995. Prof. Shawali has been the recipient of the state award for science 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 visiting professor at the university of Texas, 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 was appointed Vice-Dean for student affairs in 1989, then he was elected Dean of the Faculty of Science in 1991. He published 204 papers including 8 review articles in
the fields of reaction mechanisms, applications of LFERs, chemistry of hydrazonoic acid derivatives, 1,3-dipolar cycloaddition and electrocyclization of nitrilimines. At present the average numbers of citations of his work by other authors are 50/year and 9/paper.

Thoraya Abd Elreheem Farghaly was born in Cairo, Egypt in 1974. She received her B.Sc. (1996); M.Sc. (2002) and Ph.D. (2005) degrees from University of Cairo. At present, She is Assistant Professor of organic chemistry in the Chemistry Department, Faculty of Science, University of Cairo. She joined the scientific school of Prof. A. S. Shawali in 1997 and conducted several research projects in the area of the chemistry of hydrazonoyl halides and heterocyclic chemistry.