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

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 auxilliaries 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.

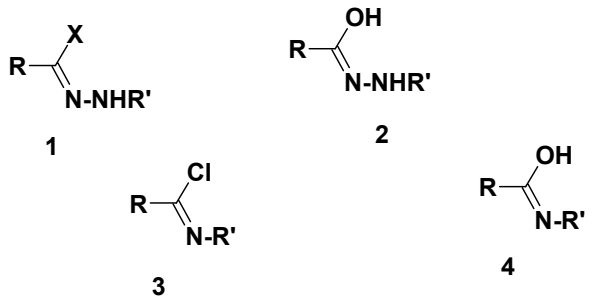
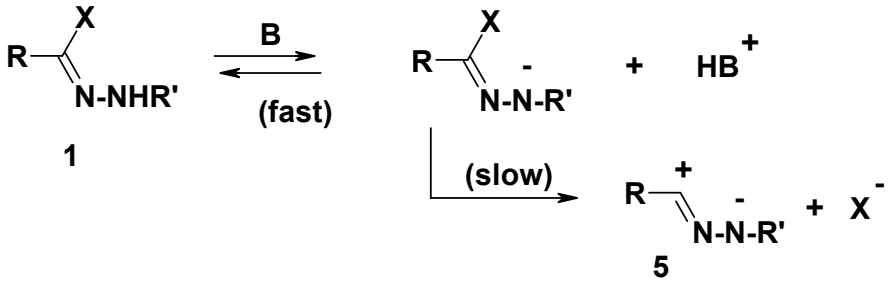


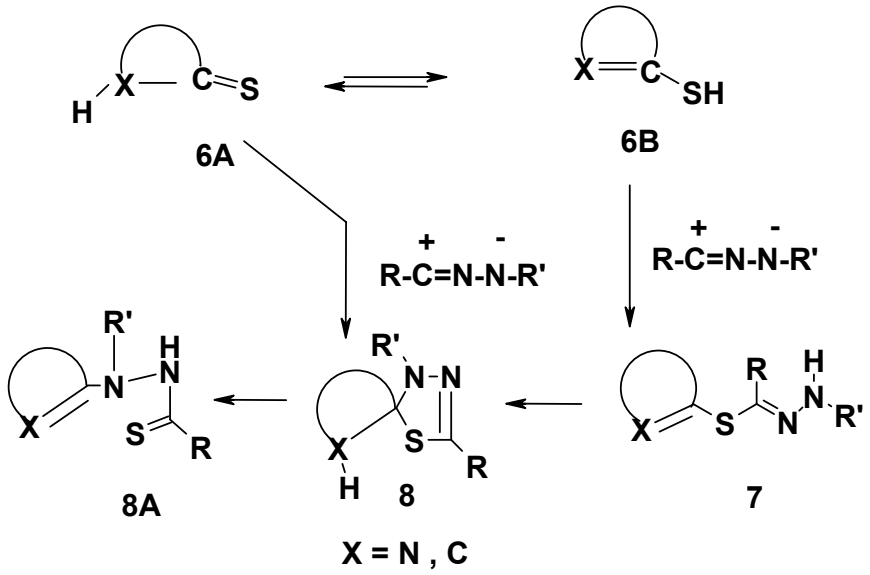
Chart 1

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- dipoles **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.*[11-13] and was shown to be as depicted in Scheme 1.



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 α-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 annelated heterocycles, spiro heterocycles, heterocyclic ring transformation or functional group modification as outlined in the following sections.



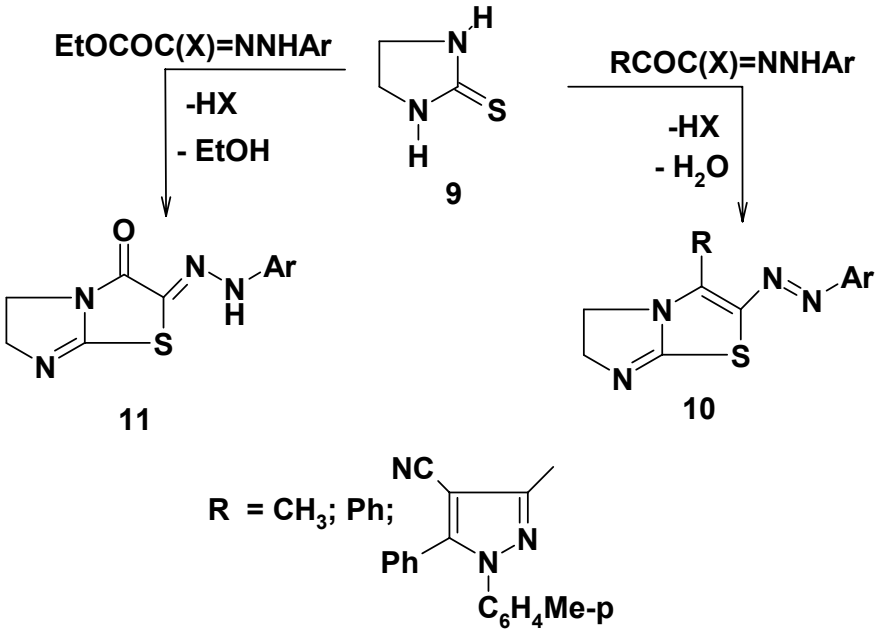
Scheme 2

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

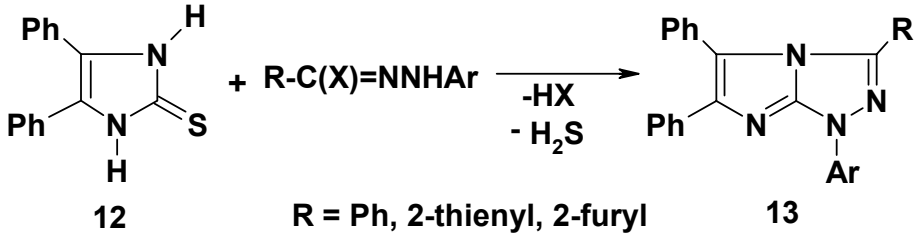
2.1. Heteroannulation of monoheterocycles

2.1.1. Imidazolethiones. Reaction of N-aryl 2-oxo-alkanehydrazonoyl halides with imidazoline-2(1*H*)-thione **9** in ethanolic triethylamine solution yielded the arylazo derivatives of imidazo[2,1-*b*]thiazole **10** *via* the thiohydrazonate (Scheme 3).[14] Similar reaction of **9** with ethyl (*N*-arylhydrazono) chloroacetate yielded the hydrazone derivative **11** (Scheme 3).[14]



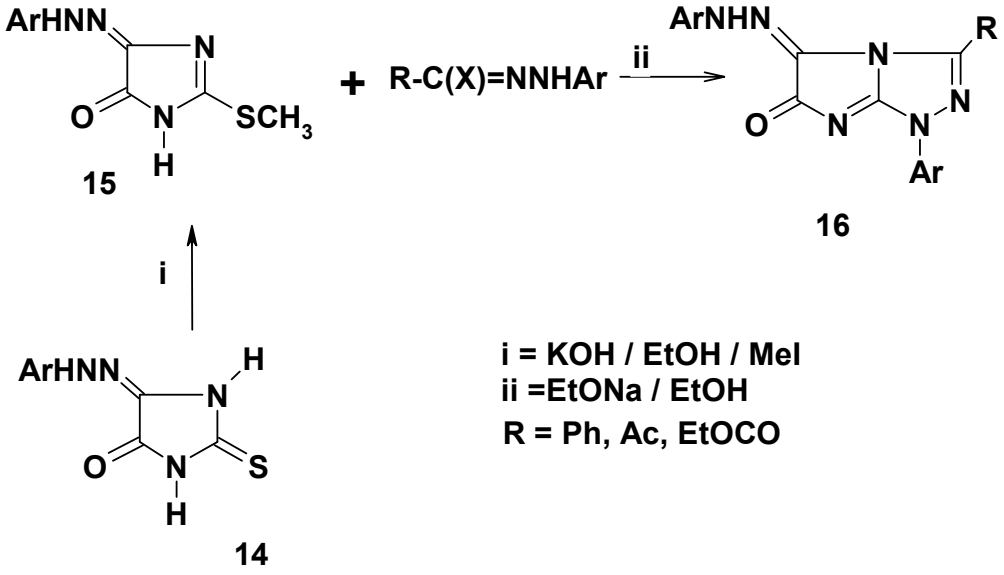
Scheme 3

Treatment of 4,5-diphenyl imidazoline-2(3*H*)-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]



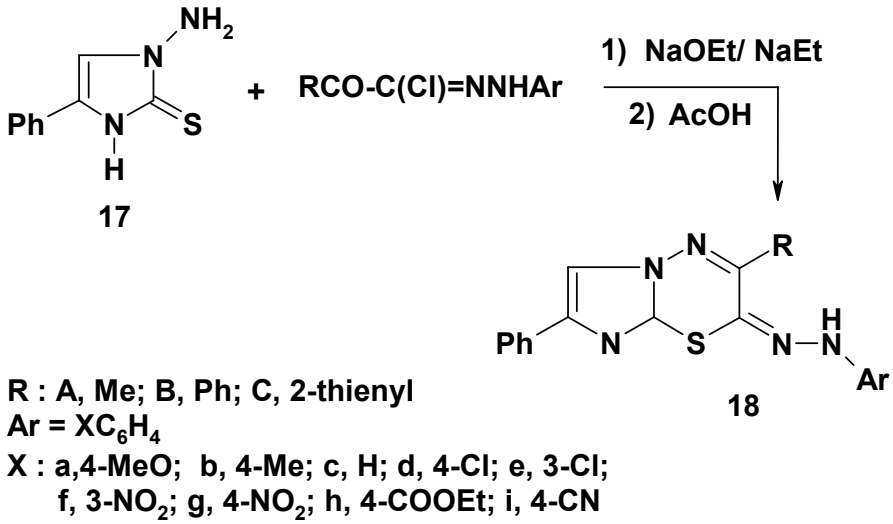
Scheme 4

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



Scheme 5

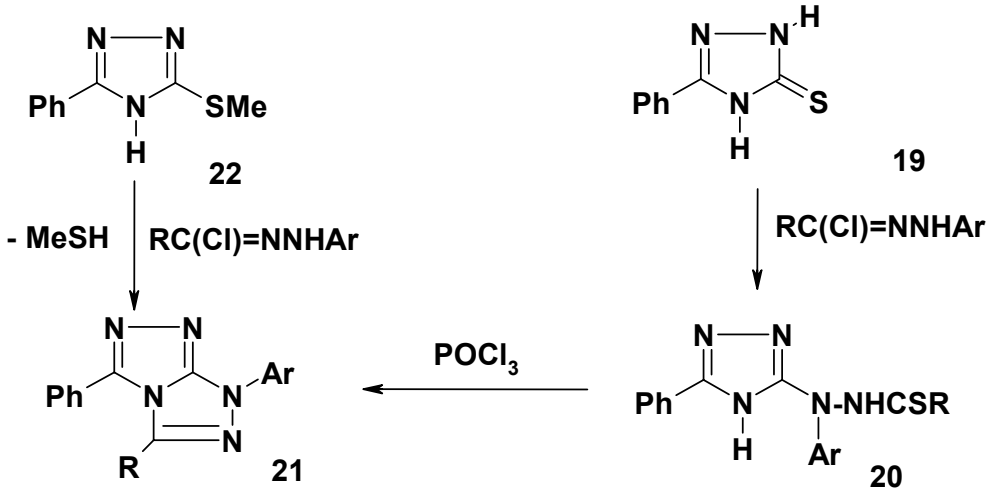
Very recently, it was reported that reaction of N-aryl-2-oxohydrazonoyl chlorides with 1-amino-4-phenylimidazoline-2-thione **17** in ethanol in the presence of sodium ethoxide at room temperature afforded the respective 2-arylazo-4*H*-imidazo[2,1-*b*][1,3,4]thiadiazines **18** (Scheme 6).[17] This finding 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

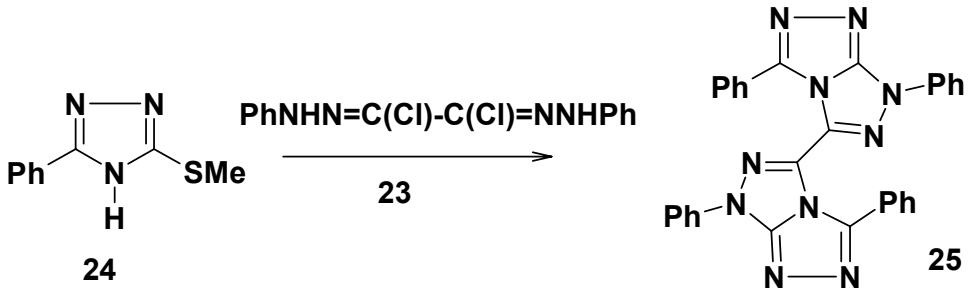
2.1.2. 1,2,4-Triazolethiones. Reaction of 5-phenyl-1,2,4-triazole-3(2*H*)-thione **19** with various hydrazonoyl chlorides gave the thiohydrazides **20**, which were converted into 1,3,5-

trisubstituted-1,2,4-triazolo[3,4-*c*][1,2,4]triazoles **21** by treatment with phosphorus oxychloride.[18-20] The latter products **21** were also prepared by reaction of 5-methylthio-3-phenyl-4*H*-1,2,4-triazole **22** with hydrazonoyl chloride (Scheme 7).[18-20]



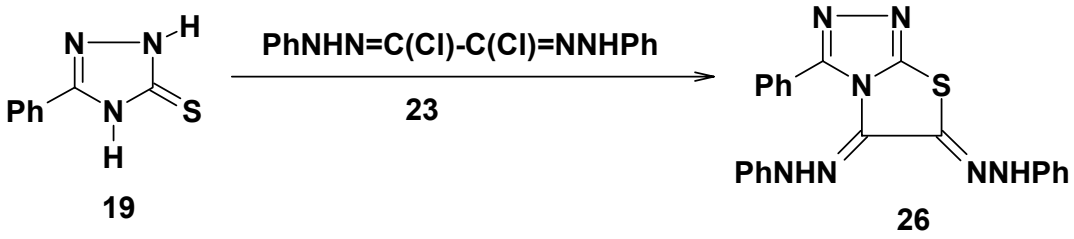
Scheme 7

Similar reaction of bis-hydrazonoyl chloride **23** with 3-methylthio-5-phenyl-4*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).[21]



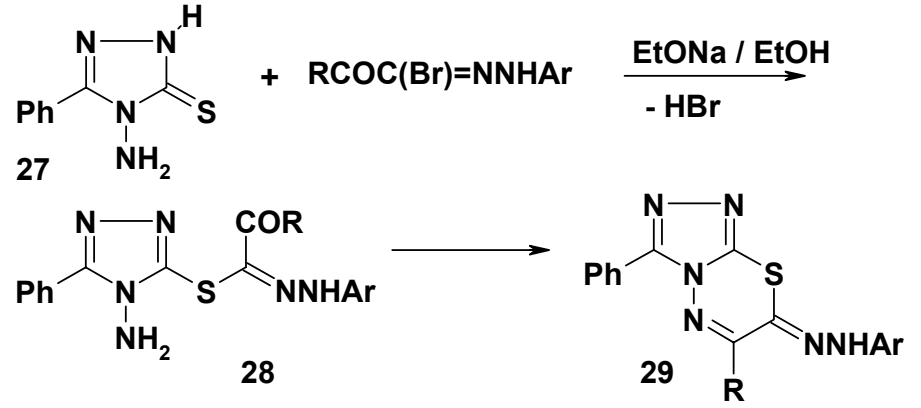
Scheme 8

However, reaction of the same bis-hydrazonoyl chloride **23** with 5-phenyl-1,2,4-triazole-3(2*H*)-thione **19** was reported to give 5,6-bis(phenylhydrazono)-2-phenylthiazolo[3,2-*b*][1,2,4]triazole **26** (Scheme 9).[21]



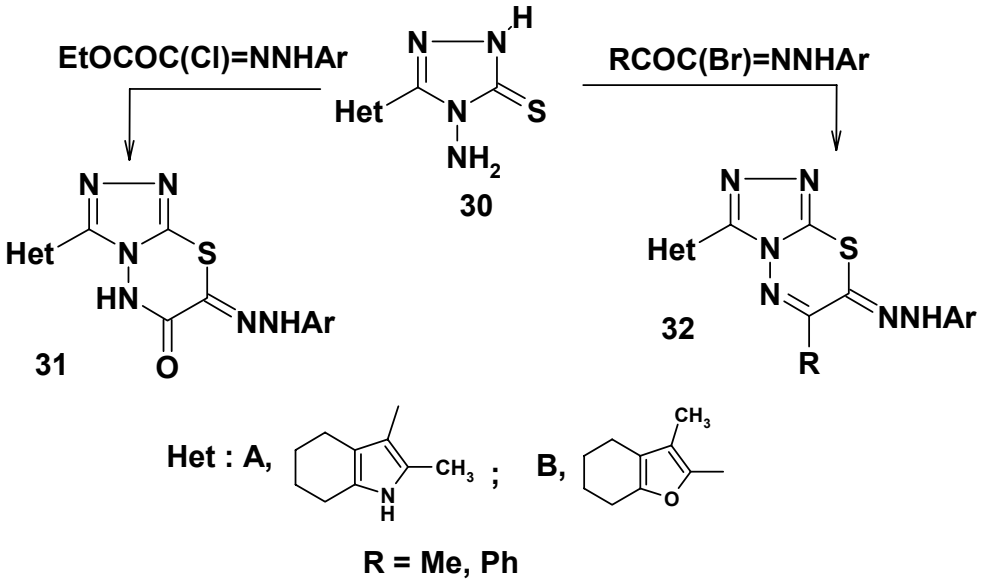
Scheme 9

Reaction of 4-amino-5-phenyl-1,2,4-triazole-3(2*H*)-thione **27** with 2-aryl-2-oxoethanehydrazonoyl bromides in ethanol in the presence of sodium ethoxide was reported by Shawali *et al*.[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 *via in situ* dehydrative cyclization of the initially formed thiohydrazonates **28h-j**.[22,23] The thiohydrazonates **28a-g** were converted into the respective triazolothiadiazines **29a-g** by treatment with acetic acid (Scheme 10). [22]



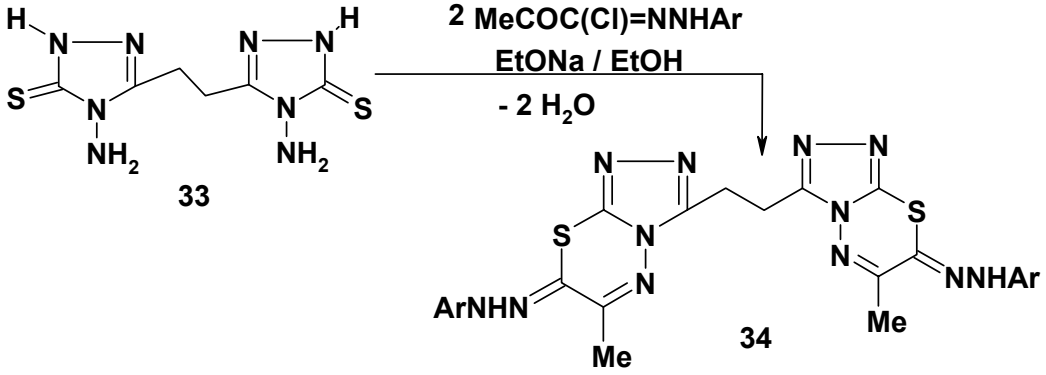
Scheme 10

Similarly, several other series of 7-arylhydrazono-7*H*-3-heteroaryl-triazolo[3,4-*b*][1,3,4]thiadiazin-6(5*H*)-ones **31** and **32** were prepared *via* reaction of 4-amino-5-heteroaryl-[1,2,4]-triazole-3(2*H*)-thiones **30** with ethyl arylhydrazonochloroacetate and *N*-aryl-2-oxoalkane hydrazonoyl halides, respectively (Scheme 11). [24,25]



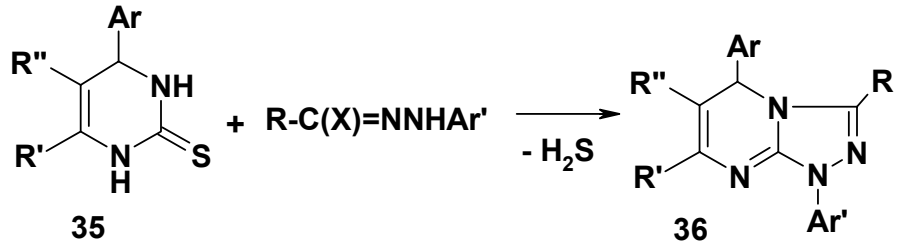
Scheme 11

Furthermore, 1,2-bis(7-arylhydrazono-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]-thiadi- azin-3-yl)ethanes **34** were prepared by reaction of 1,2-bis(4-amino-3-thioxo-2*H*-[1,2,4]triazol-5-yl)ethane **33** with *N*-aryl 2-oxopropanehydrazonoyl chlorides (Scheme 12). [26]

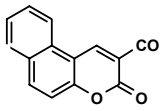
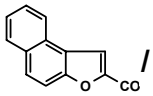


Scheme 12

2.1.3. Pyrmidinethiones. Hydrazonoyl halides reacted with 2-pyrimidinethione **35** in chloroform in the presence of triethylamine and yielded the corresponding 1*H*,5*H*-[1,2,4]triazolo[4,3-a]pyrimidine derivatives **36** (Scheme 13). [27-32]



R / X : Ph / Cl; MeOCO / Cl; EtOCO / Cl; PhNHCO / Cl; Ac / Cl;

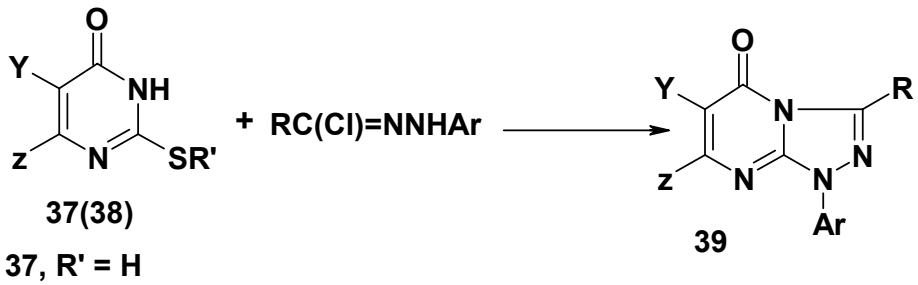
PhCO / Br; 2-thenoyl / Br;  **/Br;**  **/ Br**

Ar' = C_6H_5; 4-MeC_6H_4; 4-$MeOC_6H_4$

Ar = XC_6H_4 / MeOCO, EtOCO, 1-naphthyl, 2-naphthyl
R' = Me, 2-thienyl, Ph, 2-naphthyl
R'' = EtOCO, MeOCO, Me, H

Scheme 13

Reactions of hydrazonoyl halides with 6-substituted-2-thiouracils **37A**[33-37] and 5,6-disubstituted-2-thiouracils **37B**[29,34,38-40] 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).



37, R' = H
38, R' = Me

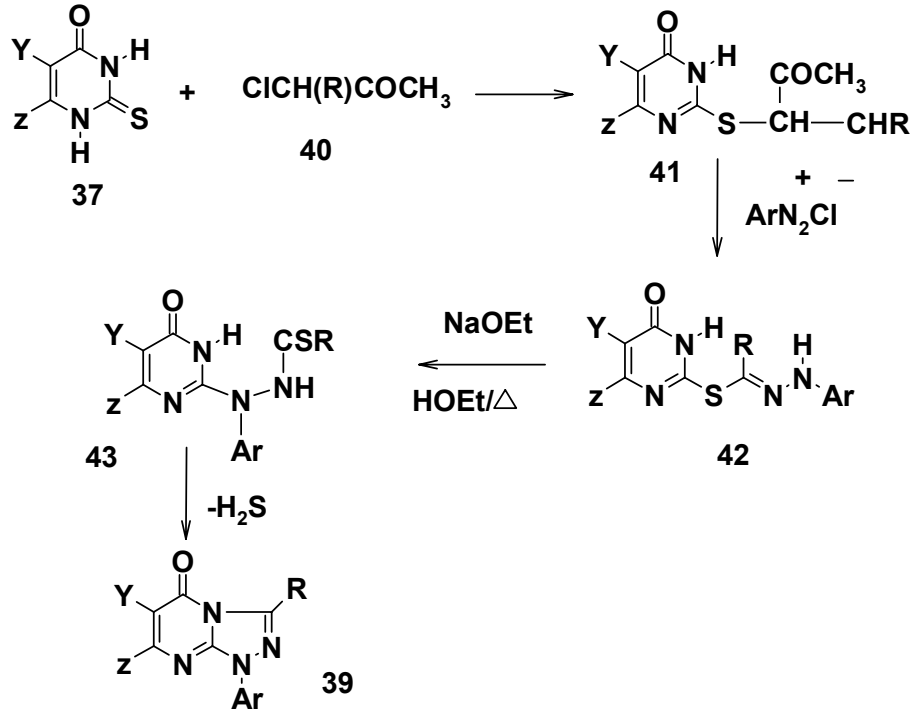
R = Ph, PhNHCO, EtOCO,PhCO,MeOCO, AC, 2-Thenoyl, 2-Naphthoyl, Ar-N=N-

Y = H, NC, EtOCO, MeOCO, PhN=N

Z = Me, Ph, 2-thienyl, H_2N, HO

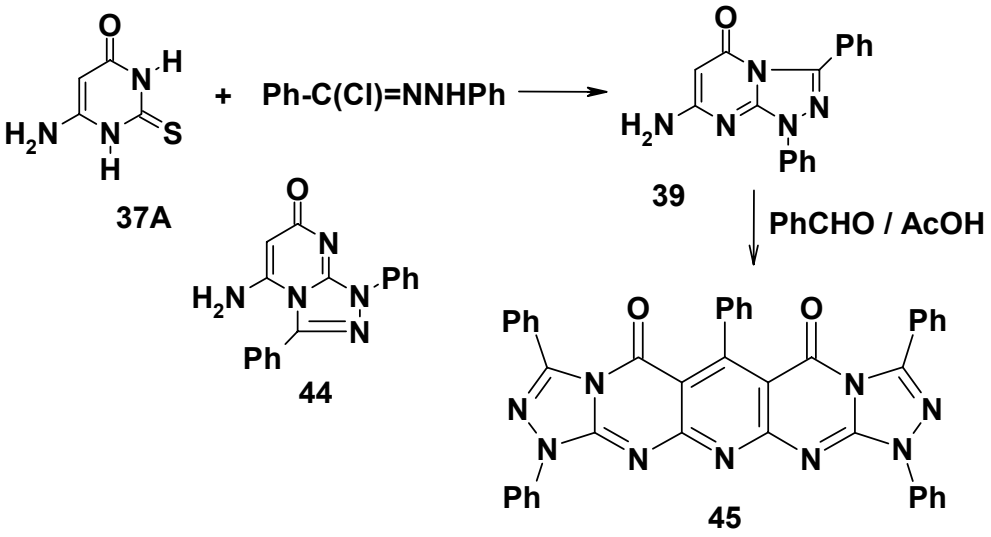
Scheme 14

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-Klingeman[34] reaction. The latter esters, upon treatment with sodium ethoxide in ethanol underwent Chapman-like rearrangement[7,9] 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).



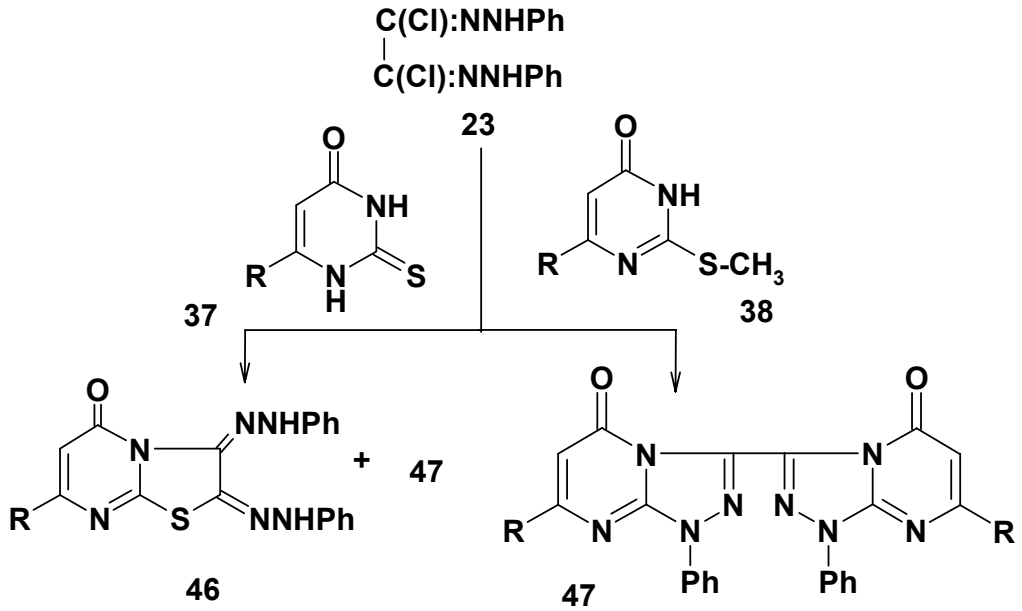
Scheme 15

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 ^{13}C NMR evidences.[35] When compound **39** was refluxed with benzaldehyde in acetic acid, it yielded **44** (Scheme 16).[36]



Scheme 16

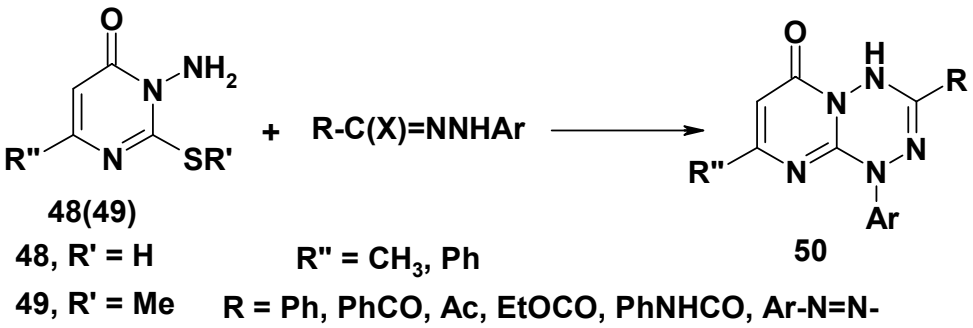
Bishydrazonoyl chloride **23** was reported to react regioselectively with 2-thiouracil **37A** to give a mixture of 2,3-bis-(arylhydrazono)-thiazolo[3,2-*a*]pyrimidine-5-one **46** and 3,3'-bis-1,2,4-triazolo[4,3-a]pyrimidin-5-one **47**. However, reaction of the same bis-hydrazonoyl chloride with 2-methylthiouracil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



Scheme 17

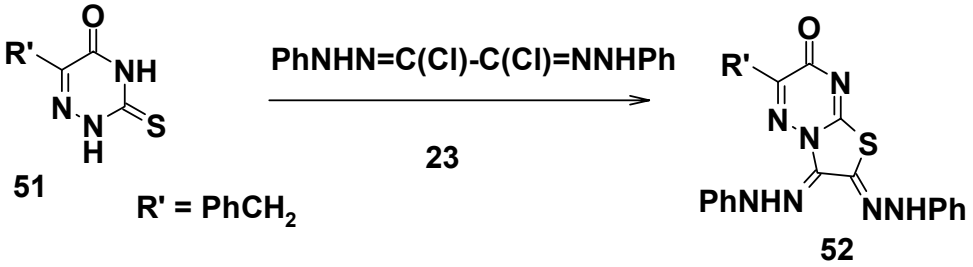
Reactions of hydrazonoyl halides with either 3-amino-2,3-Dihydro-6-substituted-2-thioxopyrimidin-4(3*H*)-ones **48** or 3-amino-6-substituted -2,3-dihydro-2-methylthio-4(3*H*)-

pyrimidinone **49** were recently reported by Shawali *et al.*[42-44] to give the respective 4H-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-ones **50** (Scheme 18).

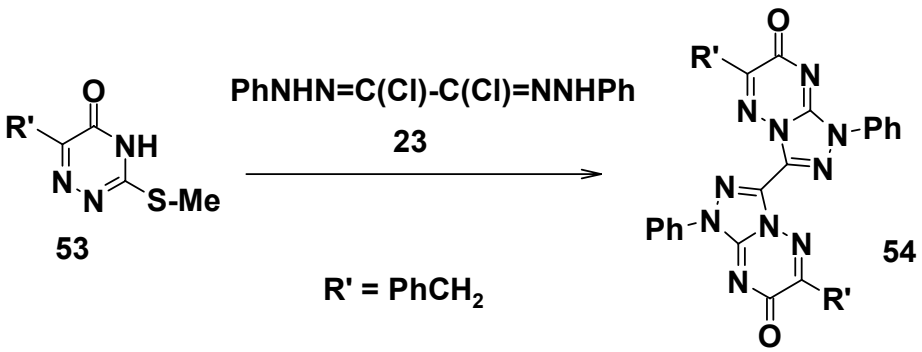


Scheme 18

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.[21]

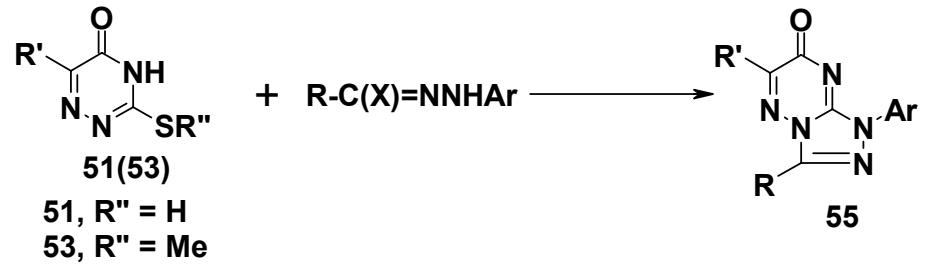


Scheme 19

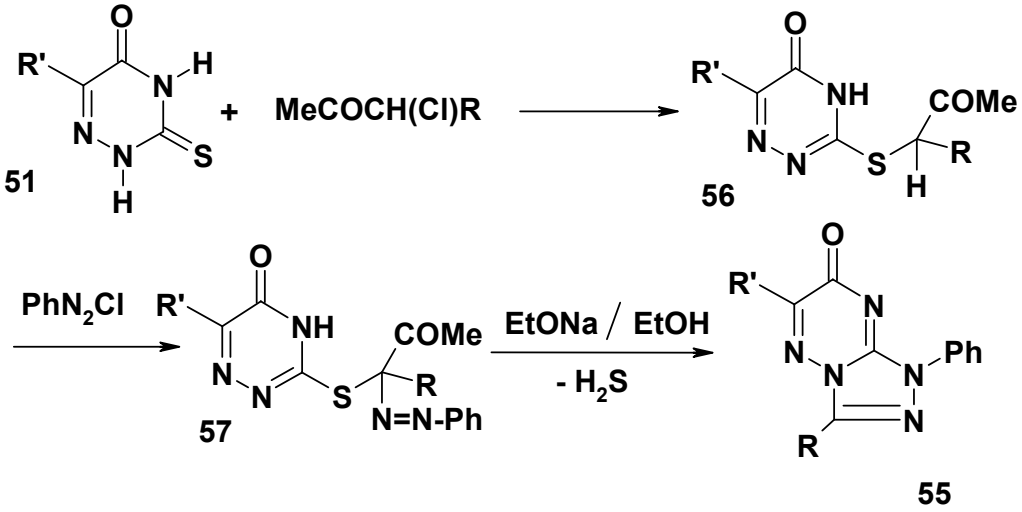


Scheme 20

Reactions of hydrazonoyl halides with either 6-substituted 3-thioxo-1,2,4-triazin-5(2*H*)-ones **51**[45] or 6-substituted-3-methylthio-1,2,4-triazin-5(4*H*)-one **53**[46] were reported to give in both cases the respective 1,2,4-triazolo[4,3-**b**][1,2,4]triazin-7(1*H*)-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(4*H*)-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(1*H*)-ones **55** (Ar = Ph) upon treatment with sodium ethoxide in ethanol (Scheme 22). [46]

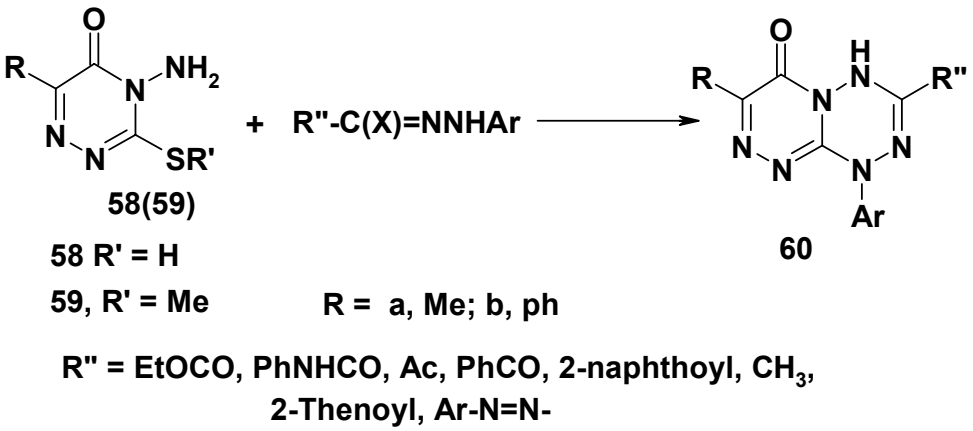


Scheme 21



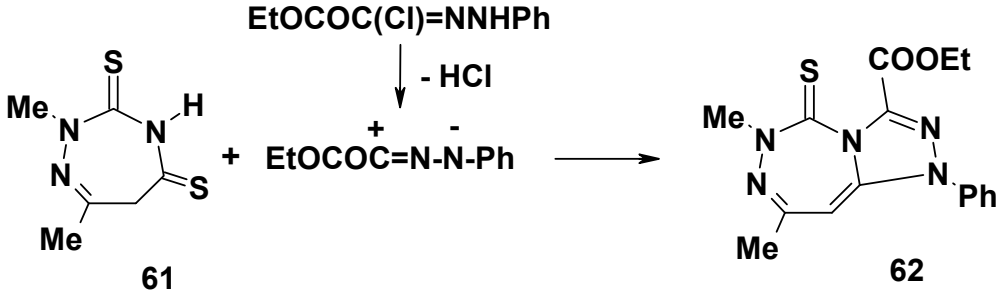
Scheme 22

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" = Ar-N=N-)[44] (Scheme 23).



Scheme 23

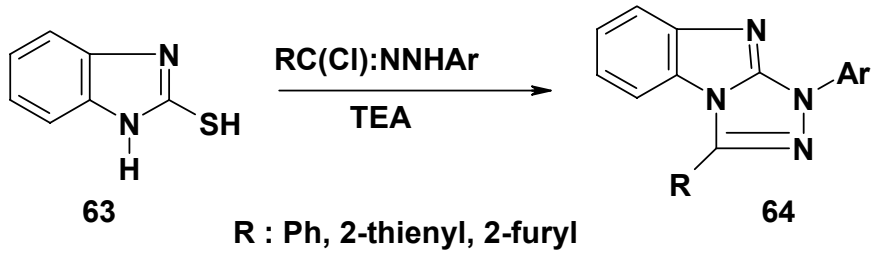
2.1.5. 1,2,4-Triazepinethiones. The reaction of *N*-aryl-*C*-ethoxycarbonylnitrilimines with [1,2,4]triazepine-3,5-dithiones **61** was reported to yield the respective [1,2,4]-triazolo[4,3-*d*][1,2,4]triazepines **62** (Scheme 24).[48] The reaction was said to be completely peri and regioselective.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



Scheme 24

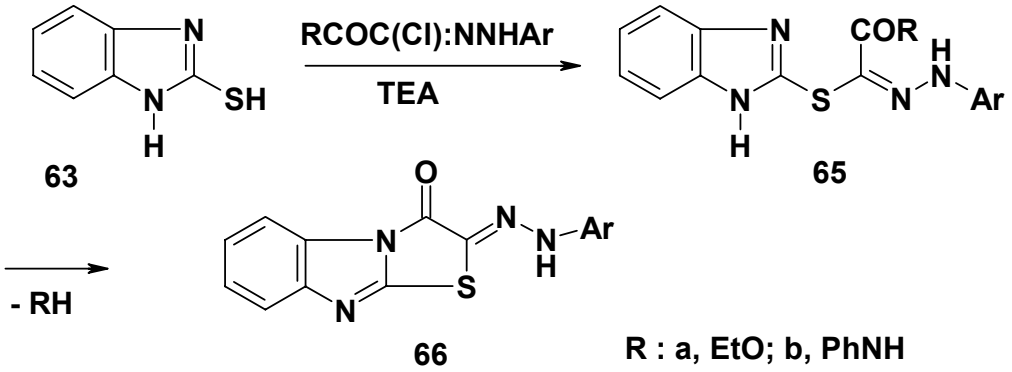
2.2. Heteroannulation of biheterocycles

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]



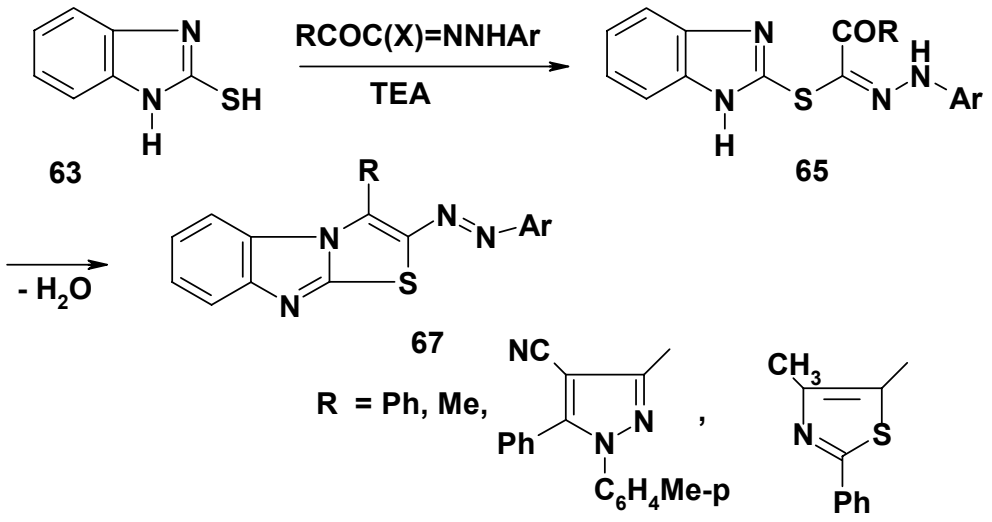
Scheme 25

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]



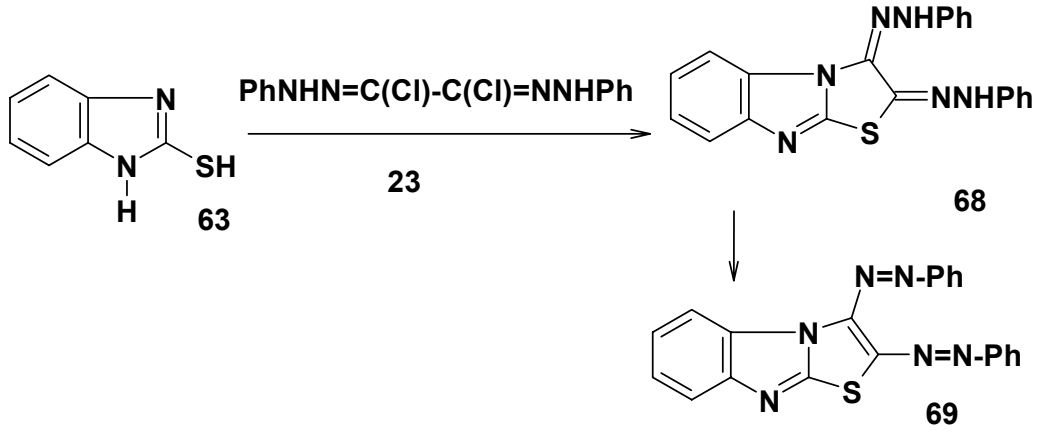
Scheme 26

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).



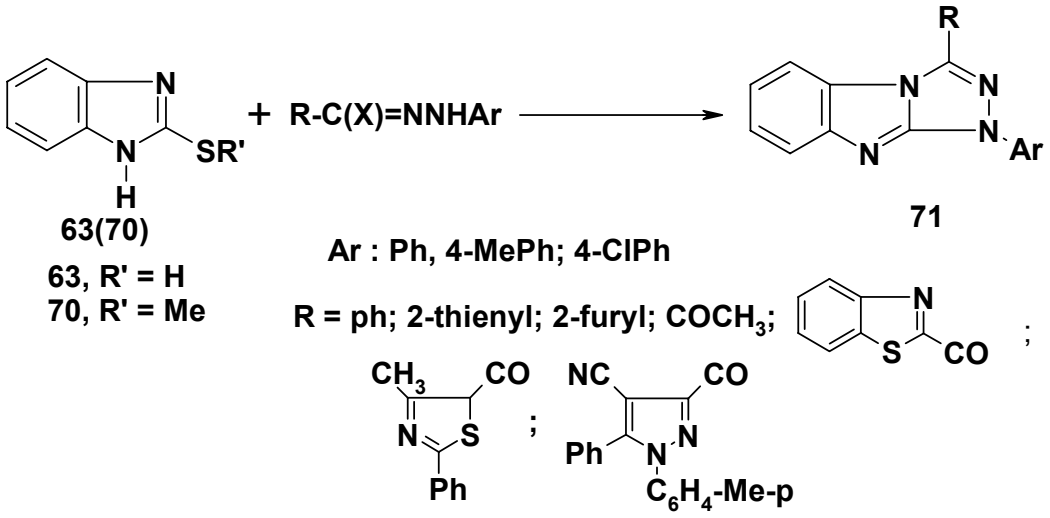
Scheme 27

2,3-Bis(phenylhydrazono)thiazolo[3,2-*a*]benzimidazoles **68** were obtained by reaction of bishydrazonoyl chloride **23** with benzimidazole-2-thiol **63** (Scheme 28).[21] Treatment of bis(phenylhydrazone) **68** with lead(IV) tetracetate in DMF-acetonitrile mixture afforded the respective bis(phenylazo) derivative **69**.[21]



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-*a*]benzimidazole derivatives **71**.[15,51,52] The latter product were also obtained by refluxing 2-methylthiobenzimidazole **70** with hydrazonoyl halides in chloroform in the presence of triethylamine (Scheme 29).[15,49,50,51,53]



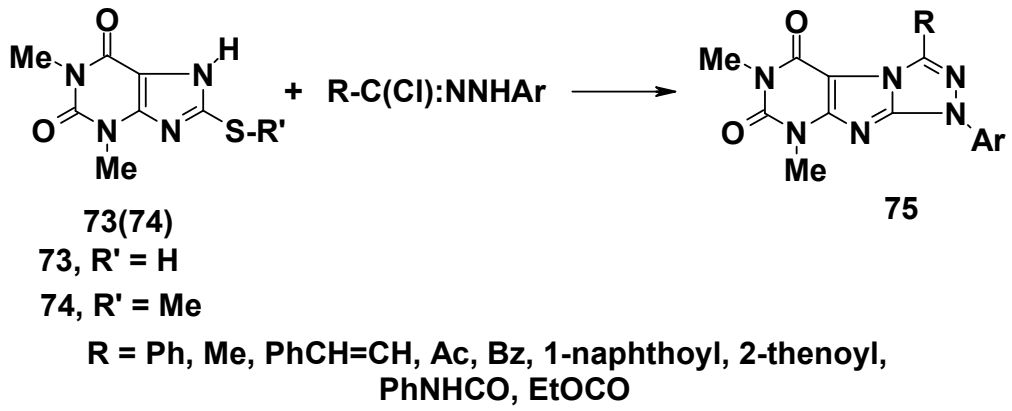
Scheme 29

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]

Scheme 30

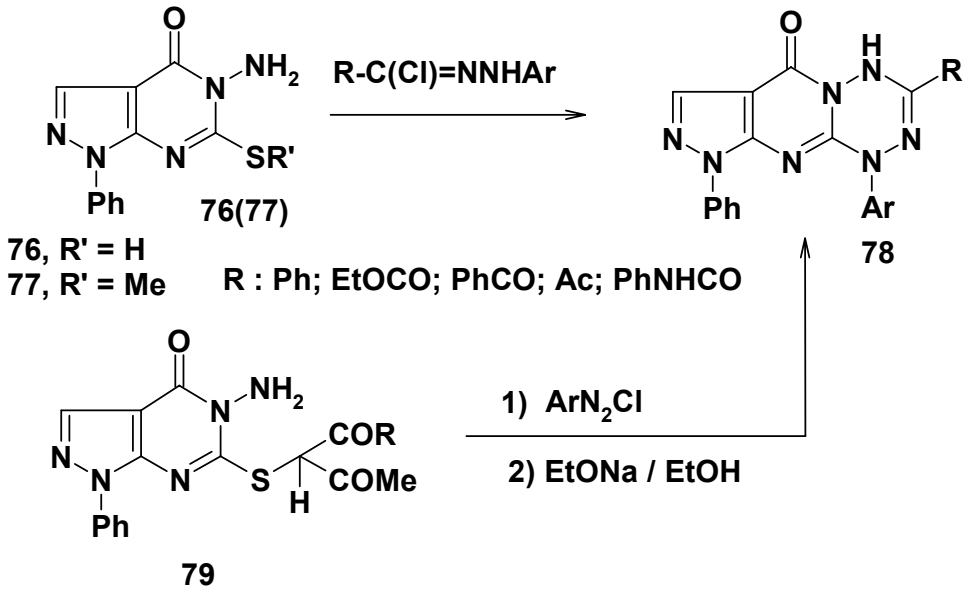
2.2.2. Purinethiones. Recently Shawali *et al.* [54] reported that reactions of hydrazonoyl halides with theophylline-8-thione **73** and 8-methylthiotheophylline **74** in refluxing pyridine yielded in both cases 1,3-disubstituted [1,2,4] triazolo[3,4-*f*]purine derivatives **75** (Scheme 31). The formation 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 H_2S to afford **75** (Scheme 31). [54]



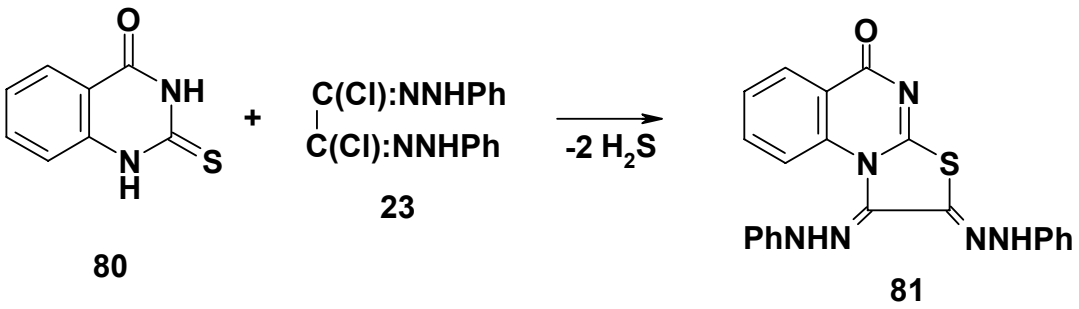
Scheme 31

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]



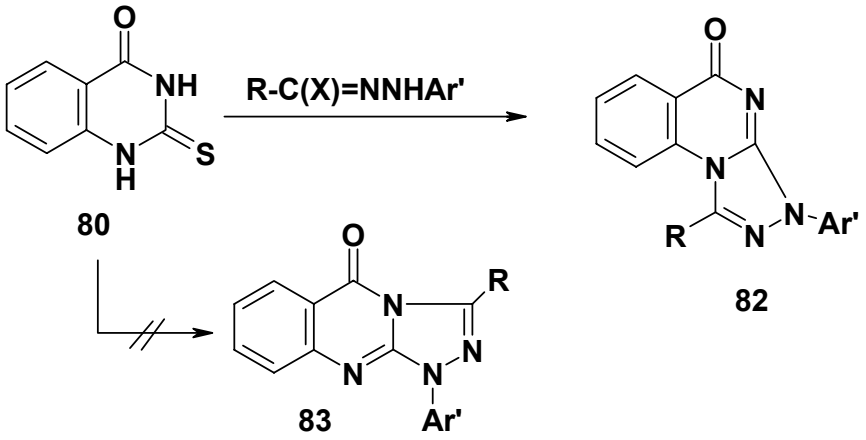
Scheme 32

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



Scheme 33

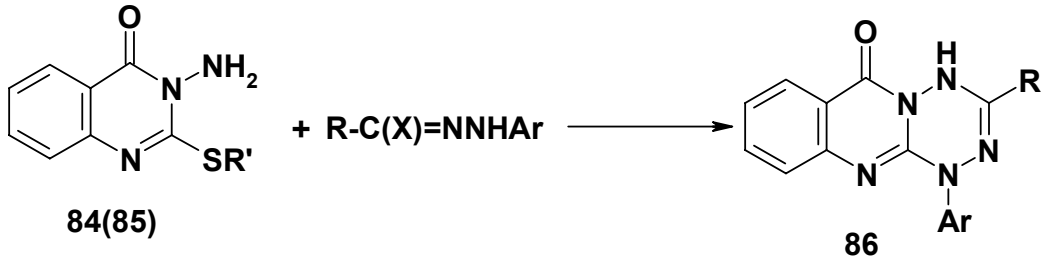
Similar reaction of **80** with various hydrazonoyl halides in refluxing chloroform in the presence of triethylamine yielded 1,3-disubstituted 1,2,4-triazolo[4,3-*a*]quinazolin-5-one derivatives **82**. The other regioisomers **83** were not produced (Scheme 34). [56]



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

Scheme 34

Also, it was reported that reaction of hydrazonoyl halides with 3-amino-2-thioxoquinazolin-4(1*H*)-one **84** afforded 4*H*-[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(3*H*)-one **85** with the same series of hydrazonoyl halides (Scheme 35).[57,58]



84(85)

84, R' = H

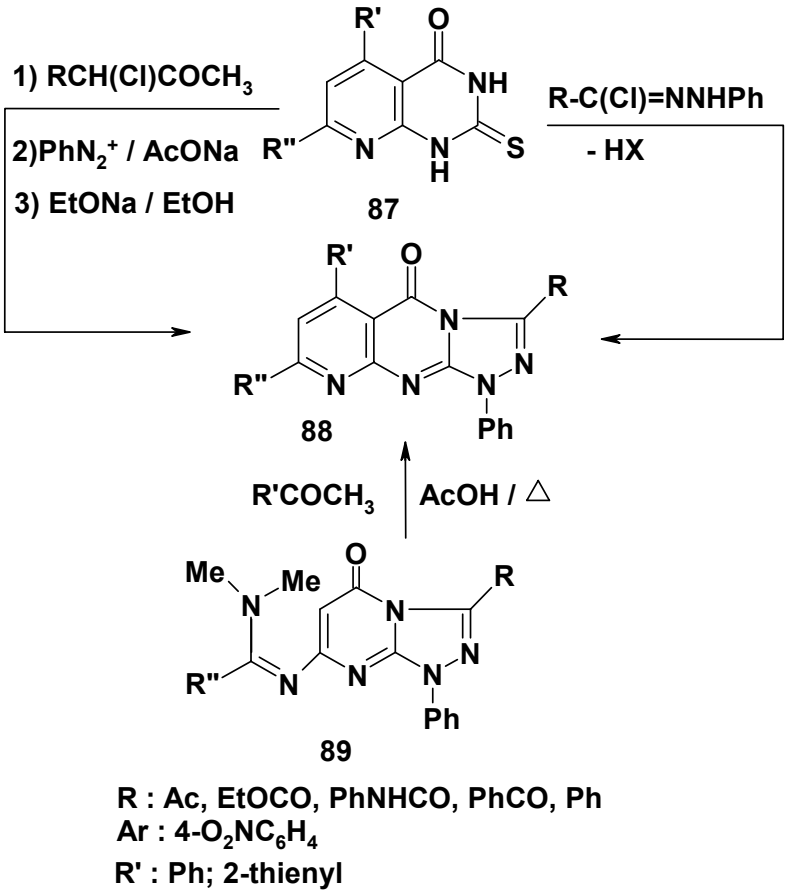
85, R' = Me

86

R = Ph, PhNHCO, EtOCO, Ac, POhCO, 2-naphthoyl,2-thenoyl, Me, ArN=N-, (2-phenyl-4-methylthiazol-5-yl)CO

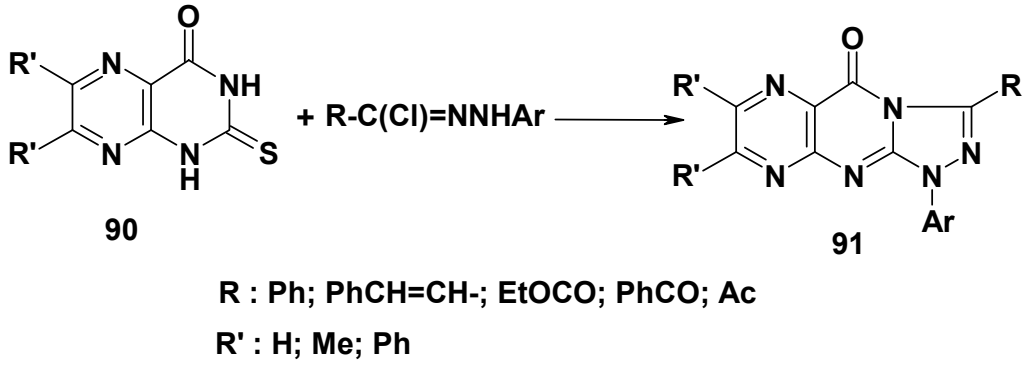
Scheme 35

2.2.5. Pyrido[2,3-*d*]thiouracils. Recently, it was reported that treatment of pyridino[2,3-*d*]-2-thiouracil **87** with hydarzonoyl 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).[59,60] The involvement of the thiohydrazonate esters as intermediates in the studied reactions of **87** with hydrazonoyl halides was evidenced by alterenate 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-rearrangment[7,9] to yield the respective thiohydrazides which cyclized in *situ* to give **88** as end products (Scheme 36). [60]



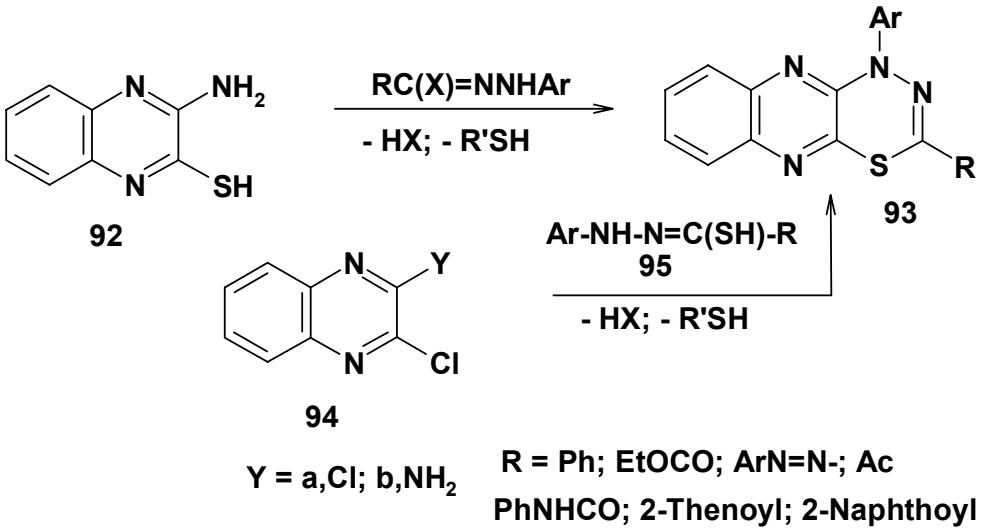
Scheme 36

2.2.6. Pteridinethiones. Reaction of 2-thioxopteridine-4(3*H*)-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).[61] The structure of the latter products was established by X-ray analysis.



Scheme 37

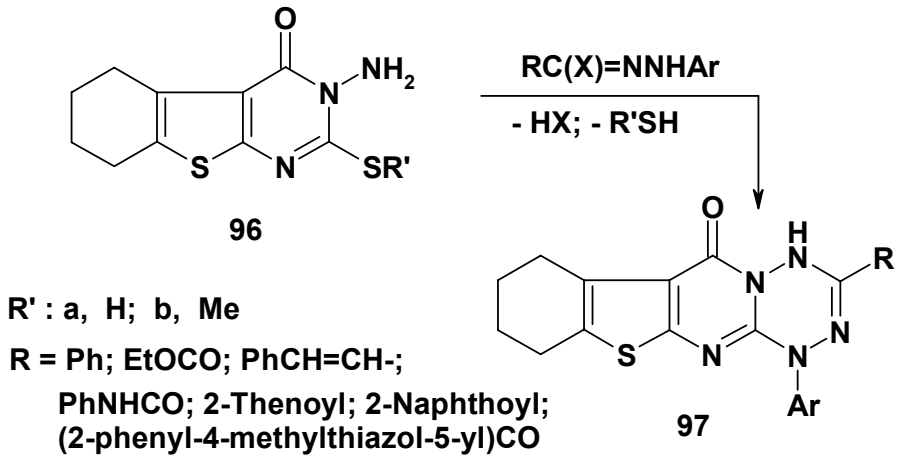
2.2.7.Quinoxalinethiones. Various 2,4-disubstituted-4*H*-1,3,4-thiadiazino[5,6-*b*] quinoxalines **93** were obtained by reaction of hydrazonoyl halides with 2-amino-3-quinoxalinethiol **92** in ethanol in the presence of sodium ethoxide (Scheme 38).[62] The structure of the isolated products was evidenced by alternate synthesis of **93** (R = PhN=N-, X = H). Thus reaction of 1,5-diphenyl-3-mercaptoformazan **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). [62]



Scheme 38

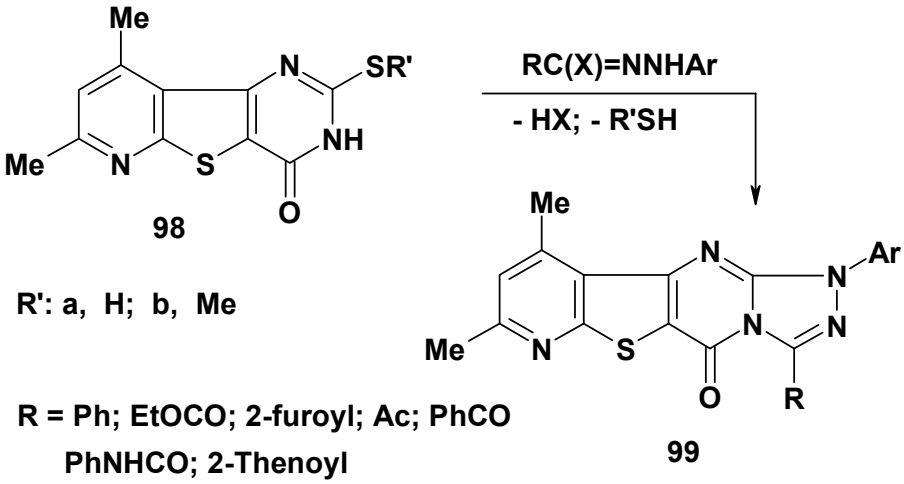
2.3. Heteroannulation of triheterocycles

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(3*H*)-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).[58,63]



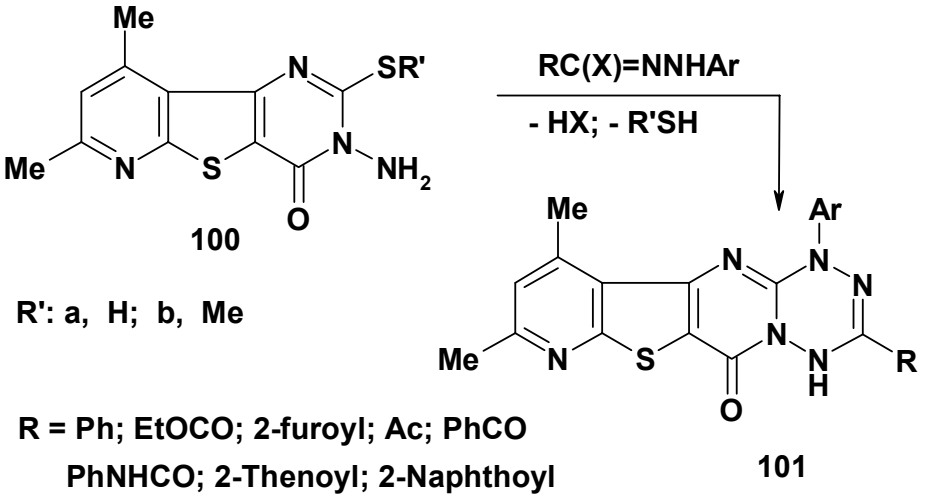
Scheme 39

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**.[64] The mechanism of the studied reactions and the structure of the products were evidenced by spectral data and alternate synthesis (Scheme 40).[64]



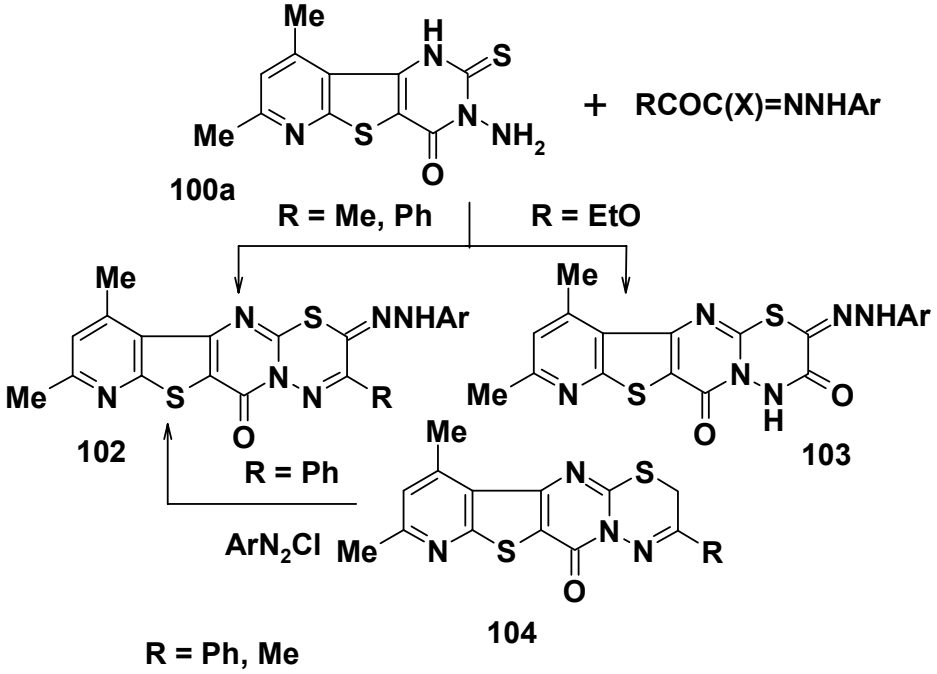
Scheme 40

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).[65]



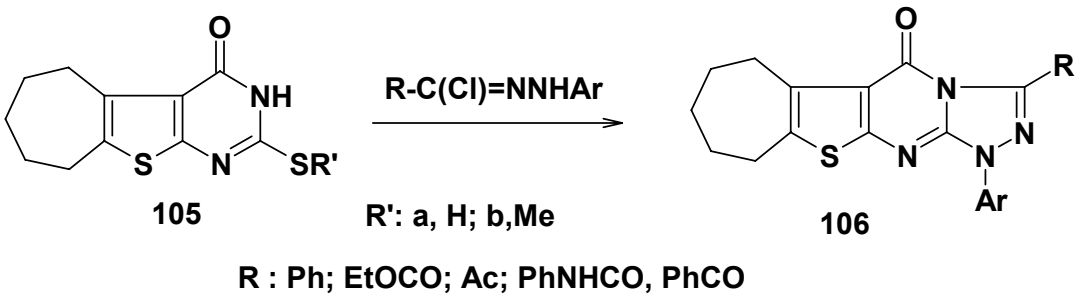
Scheme 41

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]



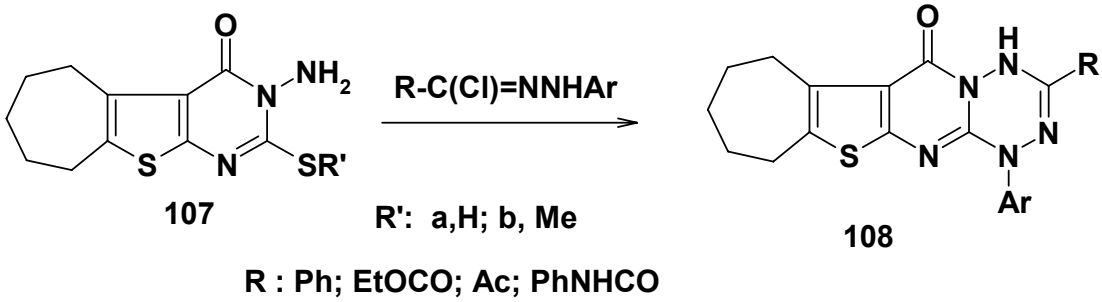
Scheme 42

2.3.3. Cyclohepta [4,5]-thieno[2,3-*d*]pyrimidinthiones. Recently various functionalized derivatives of 5*H*-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-4*H*-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 inviestigated and discussed (Scheme 43).[66]



Scheme 43

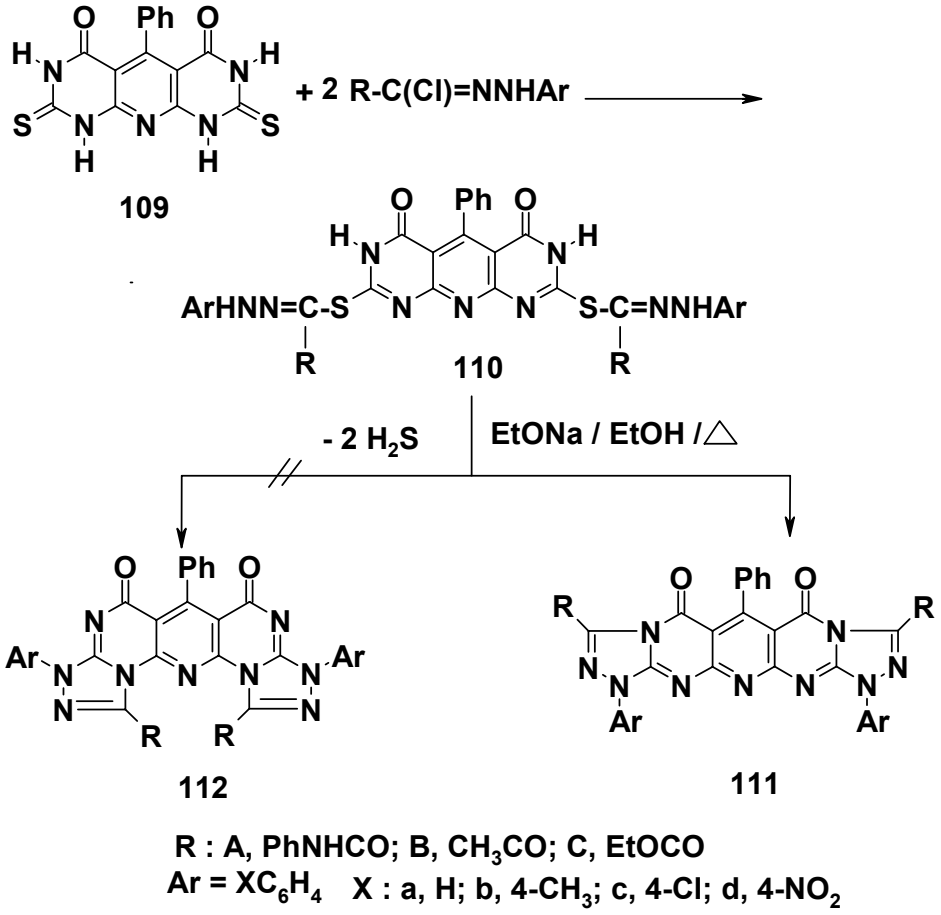
Treatment of the thione **107a** or its methylthio derivative **107b** each with hydrazonoyl halides in ethanol in the presence of sodium ethoxide at room temperature gave the respective 1,3-disubstituted 1,7,8,9,10,11-hexahydro-4*H*,6*H*-cyclohepta[4',5']thieno[2',3':4,5]pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one **108** (Scheme 44).[67]



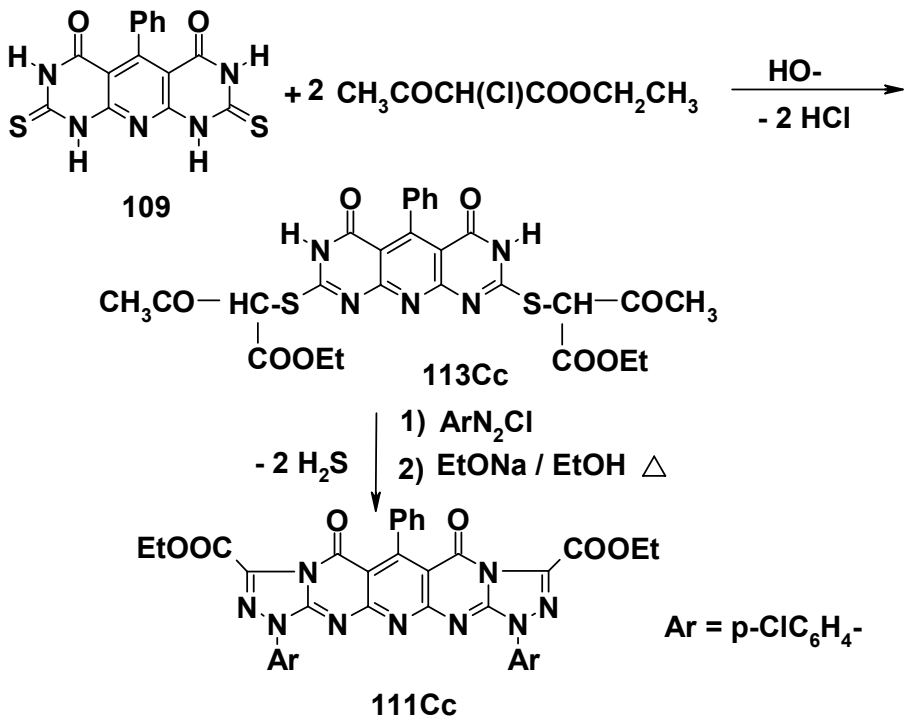
Scheme 44

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(1*H*,7*H*)- 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). [36] 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-ethoxycarbonylnitrilimine (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). [36]



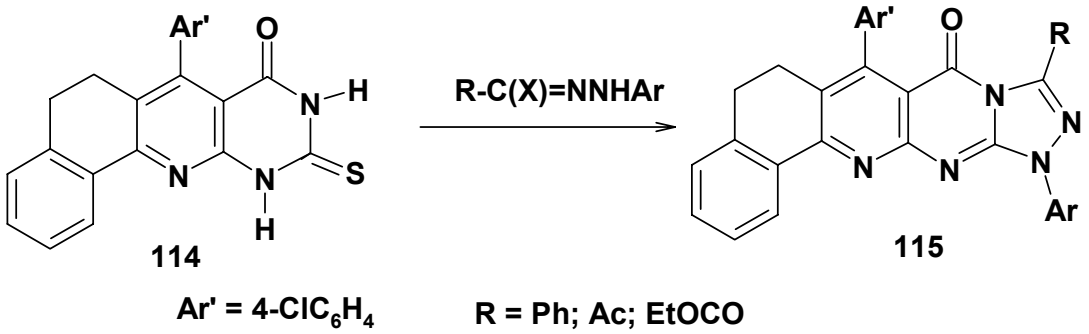
Scheme 45



Scheme 46

2.4. Heteroannulation of tetraheterocycles

2.4.1. Naphtho[2,1-*e*]pyrido[2,3-*c*]pyrimidinethiones. Naphtho[2,1-*e*]pyrido[2,3-*c*]pyrimidinethione derivatives **114** reacted with hydrazonoyl halides and yielded the respective fused naphthotriazolopyridopyrimidines **115** (Scheme 47). [68]



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'-3*H*-1,3,4-thiadiazole] **117** (Fig. 1).

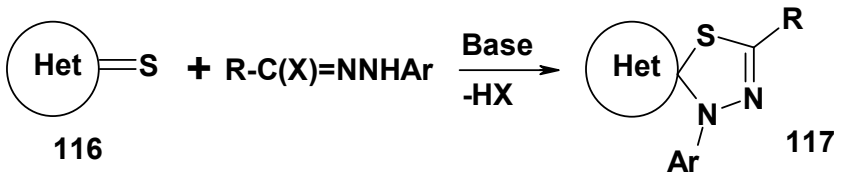
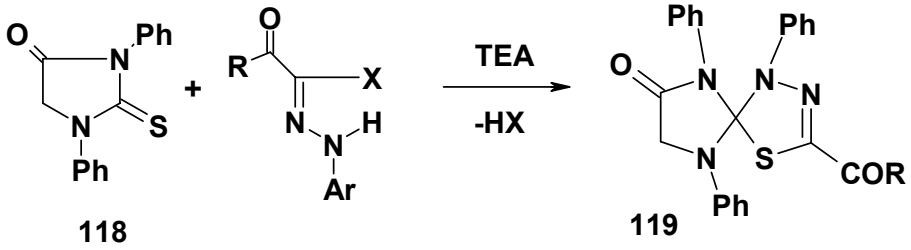


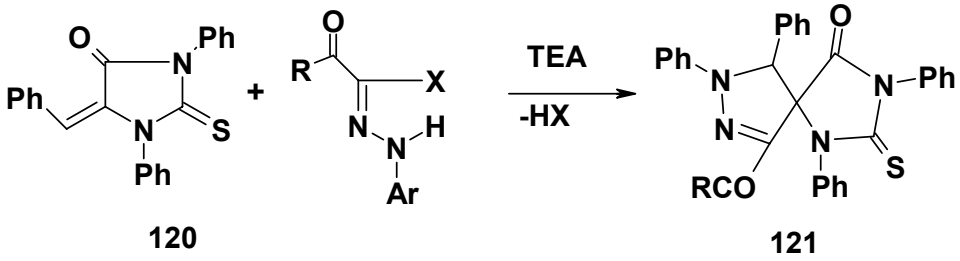
Figure 1

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'-3*H*-1,3,4-thiadiazole] derivatives **119** in 75-77% yield (Scheme 48). [69] This finding indicates that the dipolarophilicity of the C=S group is more than that of the C=O group.



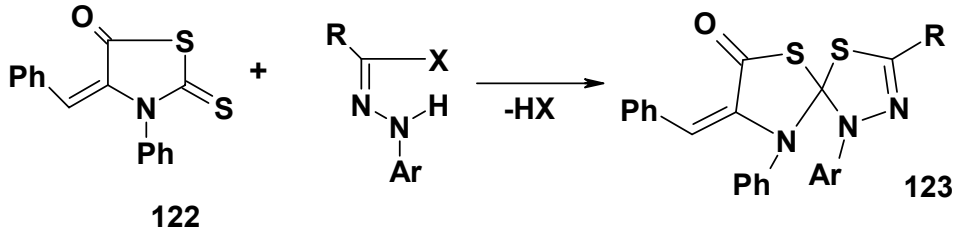
Scheme 48

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[5*H*-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). [69]



Scheme 49

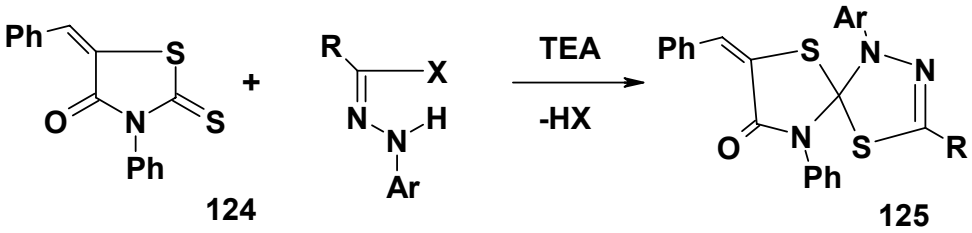
On the other hand, the spiro[3*H*-thiazole-2,2'-3*H*-thiadiazole] derivatives **123** were formed by reaction of 3-phenyl-4-phenylmethylene-2-thioxothiazolin-5-one **122** with nitrilimines, generated *in situ* by the action of triethylamine on hydrazonoyl halides in refluxing chloroform (Scheme 50).[70] In this case, the C=S double bond seems to be more dipolarophilic than both the enamine or enone C=C double bond.



R = EtOCO, Ph, PhCO, 2-thenoyl, PhNHCO, Ac, PhCH=CH, 2-naphthoyl, 2-furyl

Scheme 50

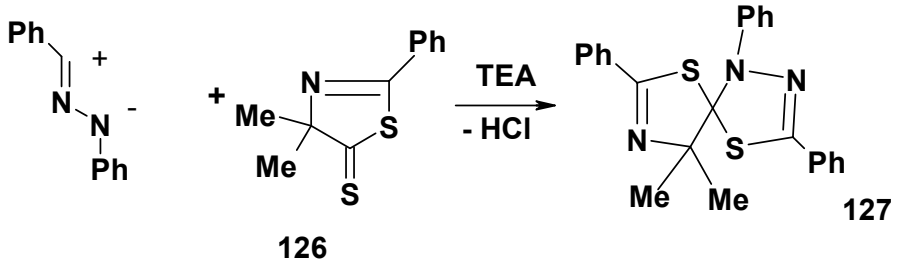
Various substituted derivatives of spiro[thiazole-2,2'-3*H*-1,3,4-thiadiazole] **125** were prepared in good yield by reaction of hydrazonoyl halides with 5-arylmethylene-3-phenyl-2-thioxothiazolidin-4-one **124** in chloroform in the presence of triethylamine (Scheme 51). [71]



R = Ph, PhCH=CH, PhCO, 2-thenoyl, 2-naphthoyl, Ac, EtOCO, PhNHCO

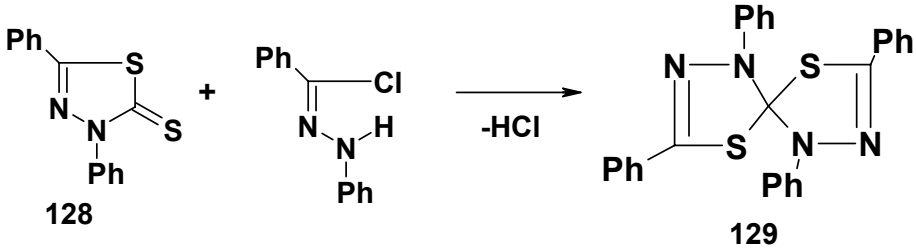
Scheme 51

Diphenylnitrilimine, derived from thermolysis of 3,5-diphenyltetrazole in mesitylene, cycloadded to 5-thioxothiazoline derivative **126** to give 83% of spiro[5*H*-thiazole-5,2'-3*H*-1,3,4-thiadiazole] **127** (Scheme 52). [72]



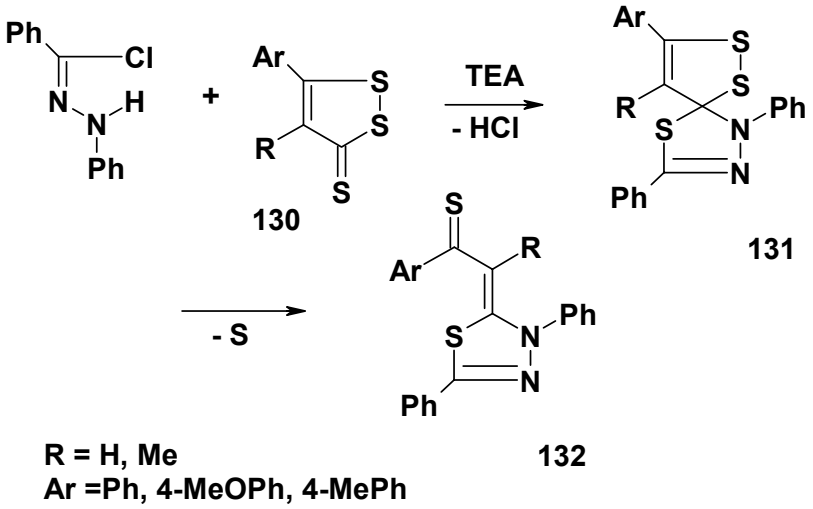
Scheme 52

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



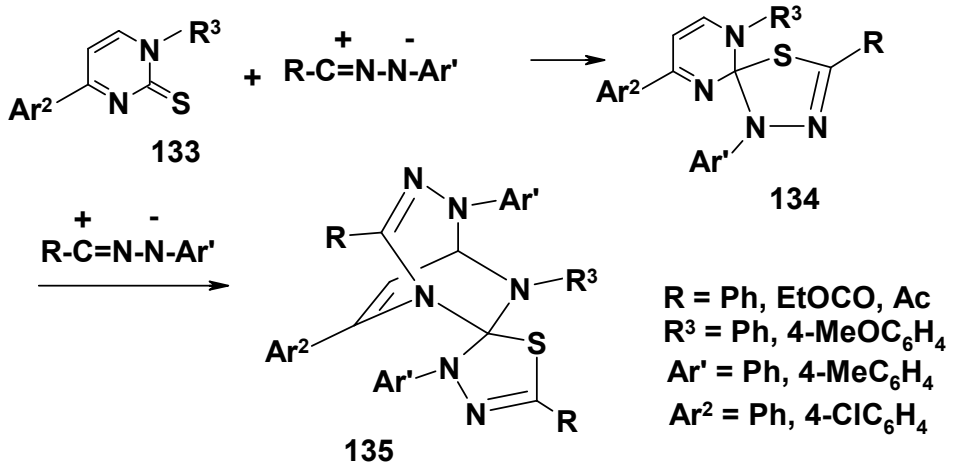
Scheme 53

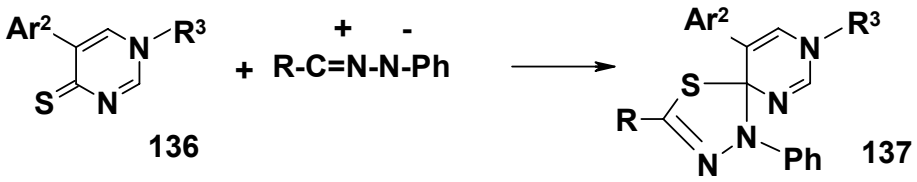
Heating a mixture of *N*-phenyl benzenecarbohydrazonoyl chloride and 1,2 –dithioline-3-thiones **130** in chloroform in the presence of triethylamine yielded 1,2,4-thiadiazoline derivatives **132**. The latter products were said to result *via* ring cleavage of the initially formed spiro[1,2-dithioline-3,2'-3*H*-1,3,4-thiadiazole] cycloadducts **131** (Scheme 54).[74]



Scheme 54

Reactions of the pyrimidine-2(1*H*)-thione **133** and its analog 4(1*H*)-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(1*H*)-thiones **133** led to the 2:1 cycloadducts **135** (Scheme 55).[75] The structure of the latter bis-cycloadduct **135** needs further investigation as it results from 4π + 4 π cycloaddition which is thermally forbidden.

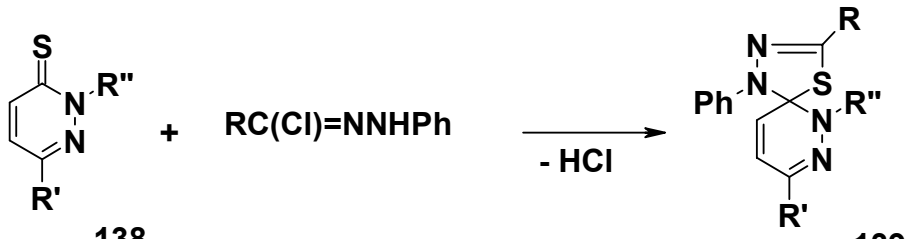




R = Ph, Ac, EtOCO
R^3 = 4-Me, CH_2COOEt, Me,
4-ClC_6H_4, CH_2COOMe
Ar^2 = Ph, 4-ClC_6H_4

Scheme 55

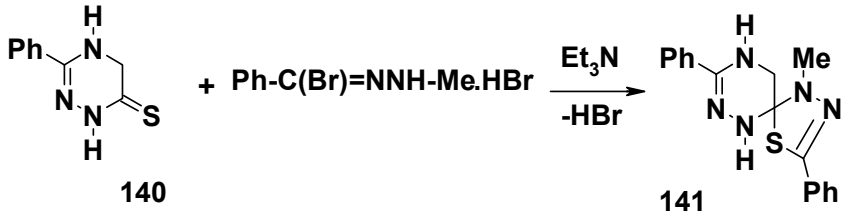
Spiro[3*H*-1,3,4-thiadiazole-2,3'-2*H*-pyridazine] derivatives **139** were prepared by reaction of 6-thioxo-1,6-dihydropyridazines **138** with N-phenyl 2-oxopropanehydrazonoyl chloride (Scheme 56).[76-78]



R = Ac, EtOCO
R' = 4-ClC_6H_4, CH_3, Ph
R'' = H, Ph

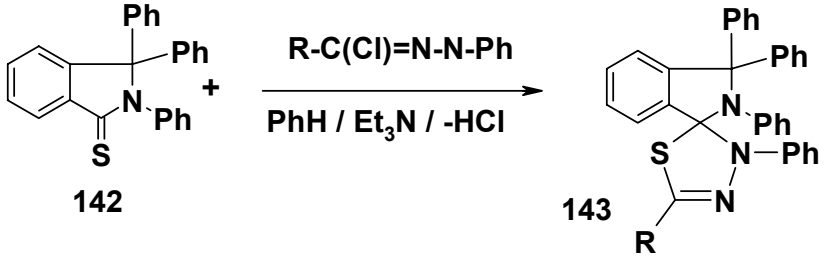
Scheme 56

Also, spiro[3*H*-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(1*H*)-thione **140** with N-methyl benzenecarbohydrazonoyl bromide in chloroform in the presence of triethylamine. However, this spirocycloadduct **141** was said to be unstable so that full characterization could not be achieved (Scheme 57).[77]



Scheme 57

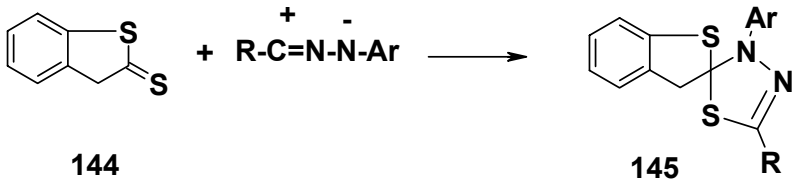
2,3,3-Triphenyl-1-thioxophthalimidine **142** reacted with hydrazonoyl halides in boiling benzene in the presence of triethylamine afforded 2,3,3,3',5'-pentasubstituted spiro[benzopyrolidine-1,2'-(2',3'-dihydro)-[1',3'4']-thiadiazoles] **143** (Scheme 58).[79]



R = Ph, 4-$NO_2C_6H_4$, Ac, PhCO, EtOCO

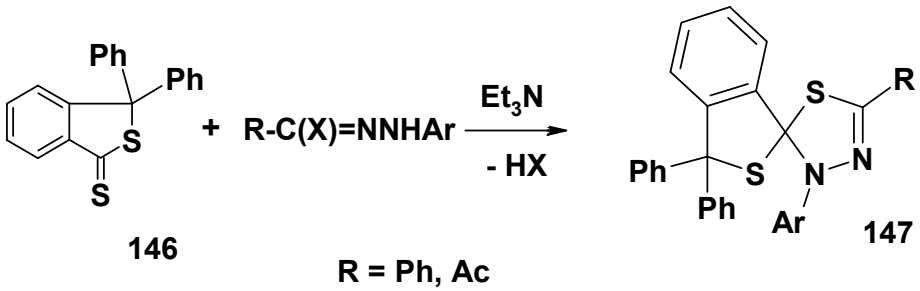
Scheme 58

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).[80]



Scheme 59

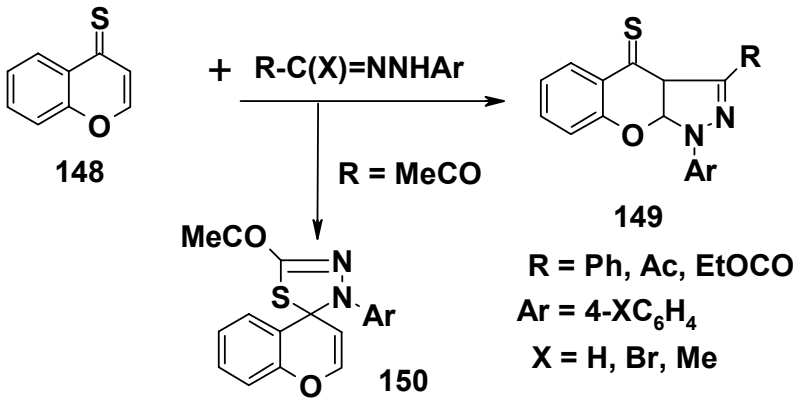
Similarly, reaction of hydrazonoyl halides with 1-thioxo-3,3-diphenyl-isobenzothiophene **146** yielded 80% of the respective spiro[3*H*-1,2,4-triazole-2,1'-1*H*,3*H*-isobenzothiophenes] **147** (Scheme 60).[81]



R = Ph, Ac

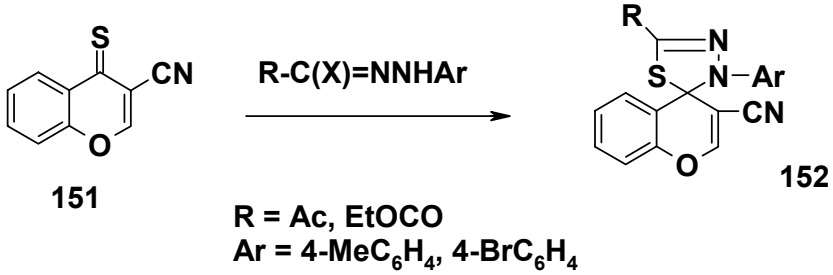
Scheme 60

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,[82] such a reaction was reported to proceed smoothly and gave the cycloadduct **149** (Scheme 61). In another report, [83] 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).



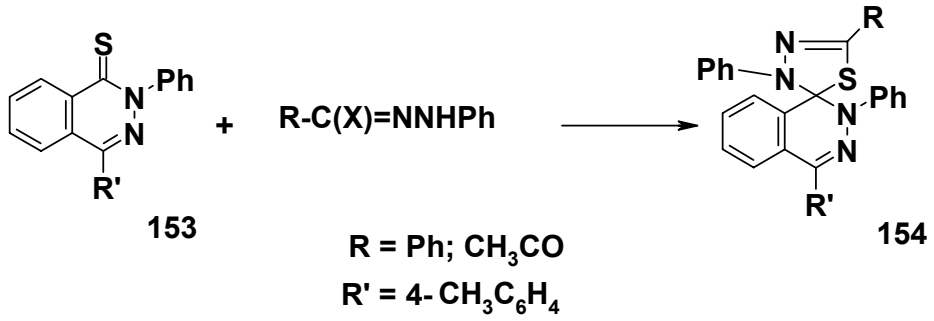
Scheme 61

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). [84]



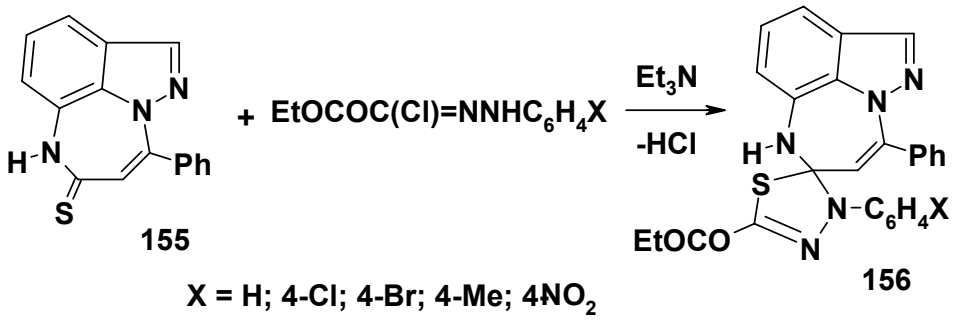
Scheme 62

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-thiadiaole-2,4'-3*H*-quinazoline] derivatives **154** in 75-80% yield (Scheme 63).[85]



Scheme 63

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[4*H*-1,4-diazepin-6-ene[1,2,3-hi]imidazole-2,2'-2*H*-1,3,4-thiadiazole] **156** (Scheme 64).[86]



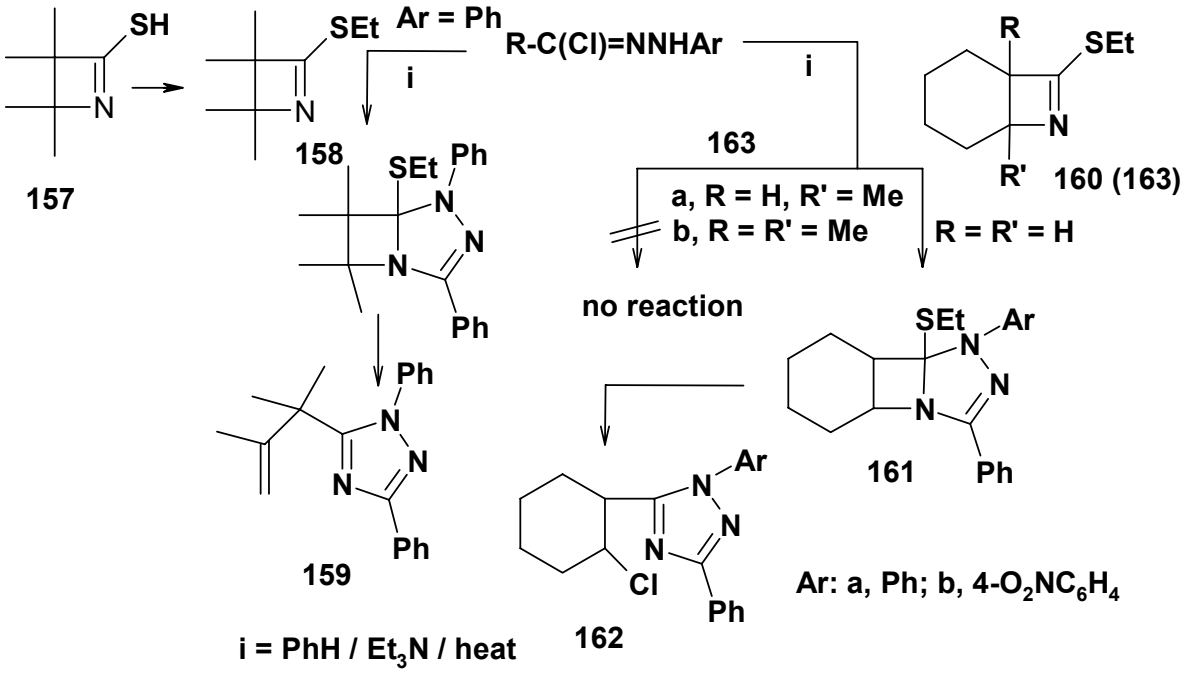
Scheme 64

4. Heterocyclic ring transformations

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

Reactions of 2-ethylthio-3,3,4,4-tetreamethyl-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 ^{1}H 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

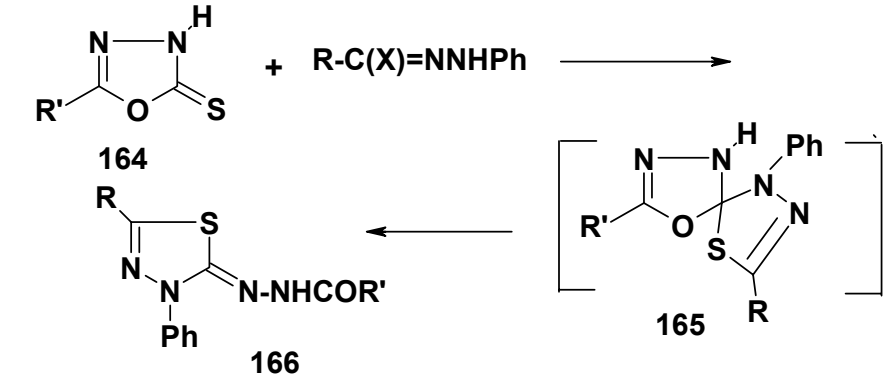
hydrazonoyl chloride and each of 8-(ethylthio-6-methyl-7-azabicyclo[4.2.0]oct-3,7-diene **163a** and its 1,6-dimethyl analog **163**.[87]



Scheme 65

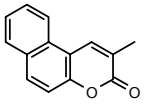
4.2 Transformation of 1,3,4-Oxadiazole-2(3*H*)-thiones into 1,3,4-thiadiazoles

In recent reports, Shawali *et al.* [88-90] and others[91-93] indicated that reactions of hydrazonoyl halides with 1,3,4-oxadiazole-2(3*H*)-thiones **164** afforded 1,3,4-thiadiazol-2(3*H*)-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(3*H*)-thione with hydrazonoyl halides in refluxing ethanol in the presence of triethylamine afforded also the corresponding **166** (Scheme 66).[25]

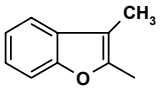


R = Ph, Ac, EtOCO, PhNHCO, 2-thenoyl, 2,3-$(Me)_2C_6H_3$;

2,4-dimethylthiazol-5-yl-CO;



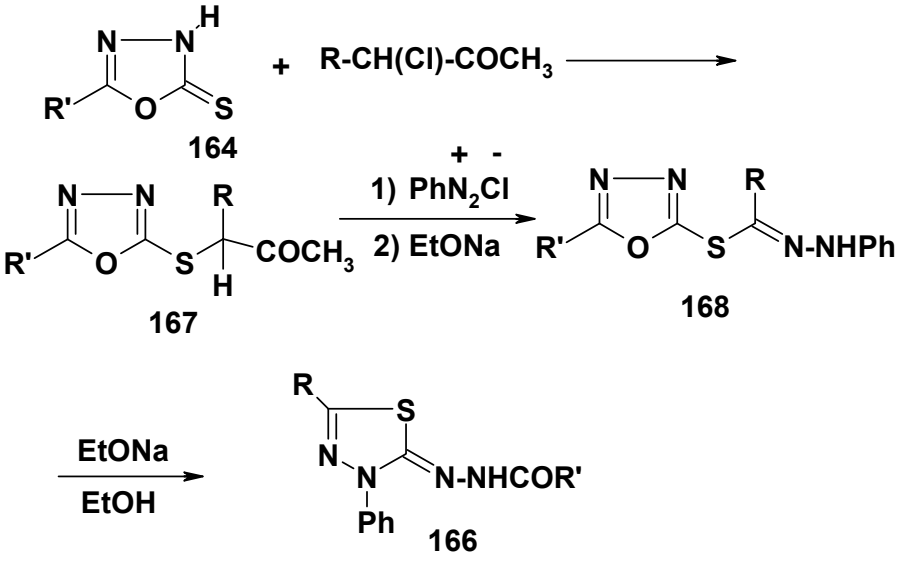
R' = X C_6H_4,



X = H, 4-Me, 4-MeO, 4-Br, 3-NO_2, 4-NO_2

Scheme 66

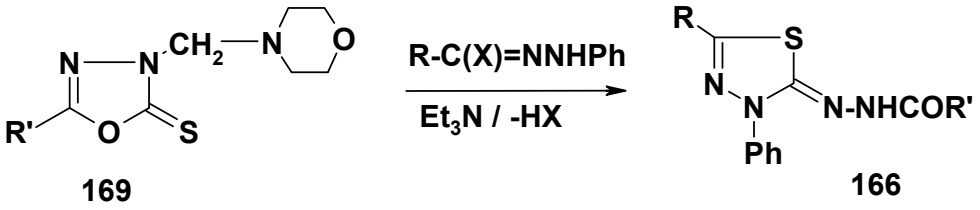
The involvement of thiohydrazonate **168** as intermediates in the studied reactions was confirmed by alternate synthesis of **166** as depicted in Scheme 67. [89,90]



R' = aryl, 3-Me-benzofuran-2-yl

Scheme 67

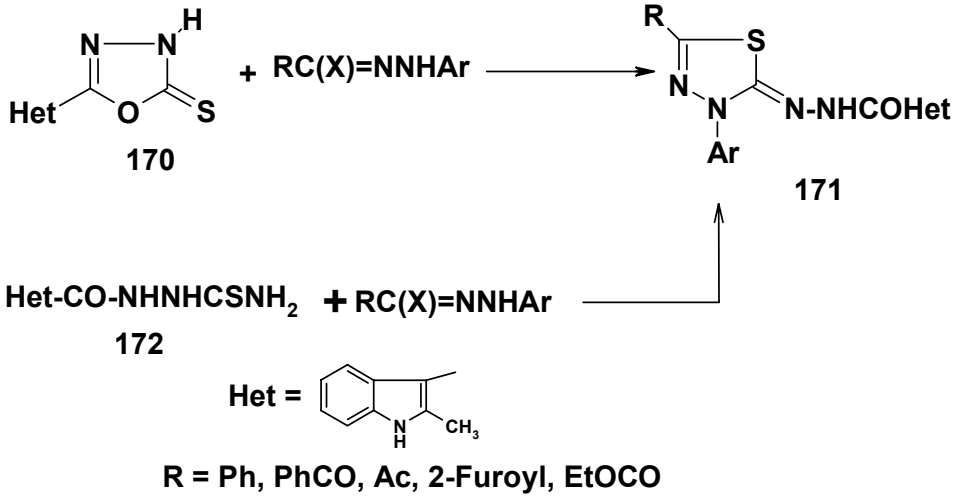
Also, reactions of the Mannich bases **169** with hydrazonoyl halides in benzene or ethanol in the presence of triethylamine at room temperature was reported to afford the respective thiadiazoline derivatives **166** (Scheme 68).[89]



169 166

Scheme 68

Reaction of 5-heteroaryl 1,3,4-oxadiazole-2(3*H*)-thione **170** with hydrazonoyl halides in ethanol in the presence of triethylamine under reflux gave the respective 1,3,4-thiadiazole derivatives **171**.[94] The structure of the latter was confirmed by its alternate synthesis *via* reaction of hydrazonoyl halides with *N*-acylthiocarbohydrazide **172** (Scheme 69).[94]

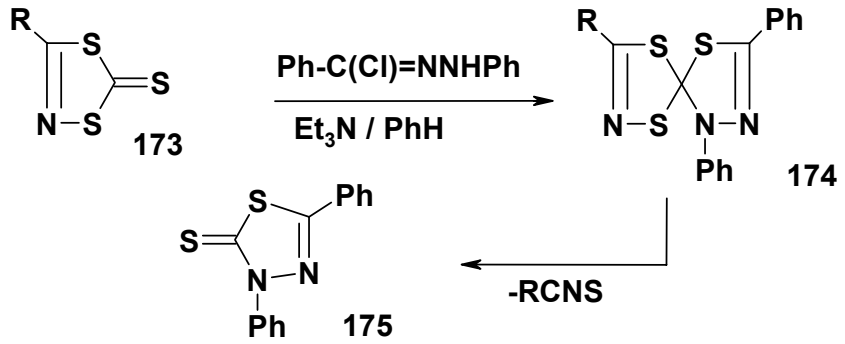


170 171 172

Scheme 69

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

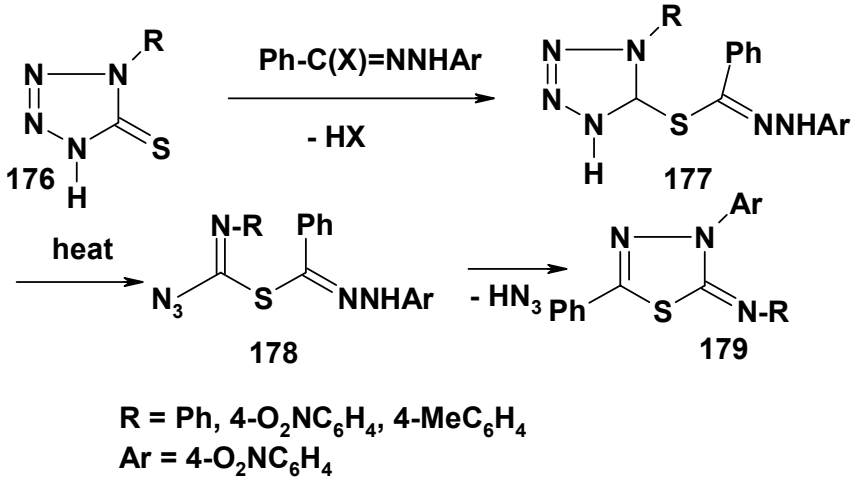
Reaction of benzenecarbohydrazonoyl chloride with 3-substituted 1,4,2-dithiazole-5-thione **173** in benzene in the presence of triethylamine was reported to yield 3,5-diphenylthiadiazole-2-thione **175** [95] The latter products were considered to result *via* ring cleavage of the initially formed spiro intermediate **174** (Scheme 70).[95]



Scheme 70

4.4. Transformation of tetrazole-5(1*H*)-thiones into 1,3,4-thiadiazoles

Treatment of hydrazonoyl halides with tetrazole-5(1*H*)-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]

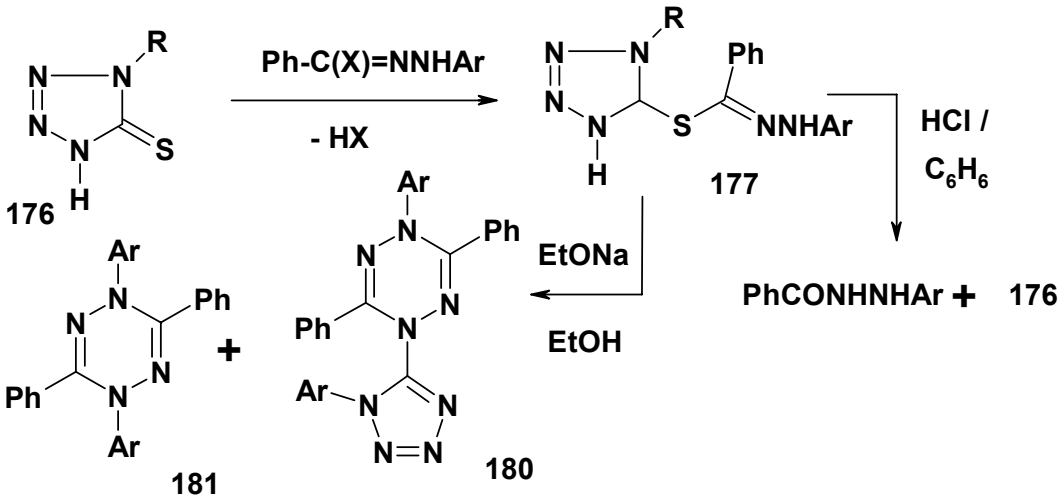


Scheme 71

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-dibromo-phenyl)hydrazide and 1-phenyltetrazole-5-thione **176** (Scheme 72).[96,97] When the

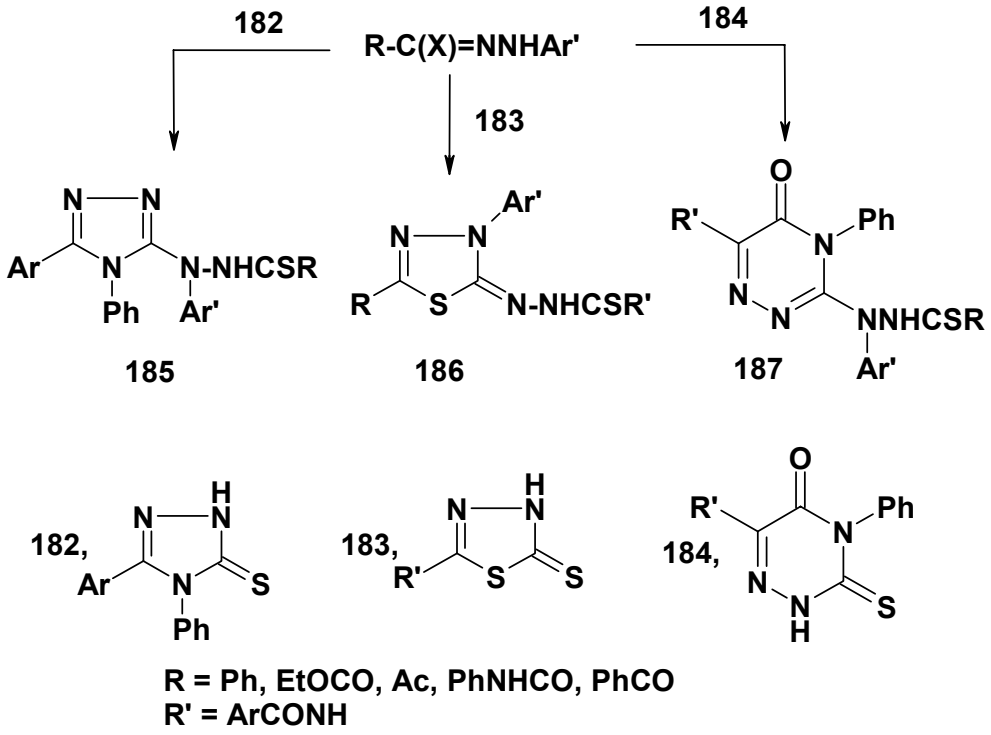
thiohydrazonate esters **177** were heated with sodium ethoxide in ethanol under reflux, they were reported to give the substituted dihydrotetrazines derivatives **180**. In each case, the latter products were accompanied by lesser yields of the symmetrical tetrazines **181**.[98]



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 *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**,[18,19,99] 5-substituted-1,3,4-thiadiazole-2-thiones **183**[100] and 4,6-disubstituted-3-thioxo-1,2,4-triazin-5(4*H*)-one **184**[45] afforded the thiocarbohydrazides **185-187**, respectively (Scheme 73).



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.

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