s-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLE DERIVATIVES

Zi-Yi Zhang* and Xiao-Wen Sun

National Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, P.R. China

Abstract — This review surveys syntheses, reactivities, spectroscopic properties and biological activities of s-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives.

CONTENTS

I. INTRODUCTION

The biological high and broad spectrum activities[1-20] of s-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives obtained by coupling the biolabile 1,2,4-triazole and 1,3,4-thiadiazole rings together have stimulated much interest in the chemistry of this class of compounds and a large number of papers have been written. This review is intended to survey the chemistry and the biological activities of this important group of heterocyclic compounds.

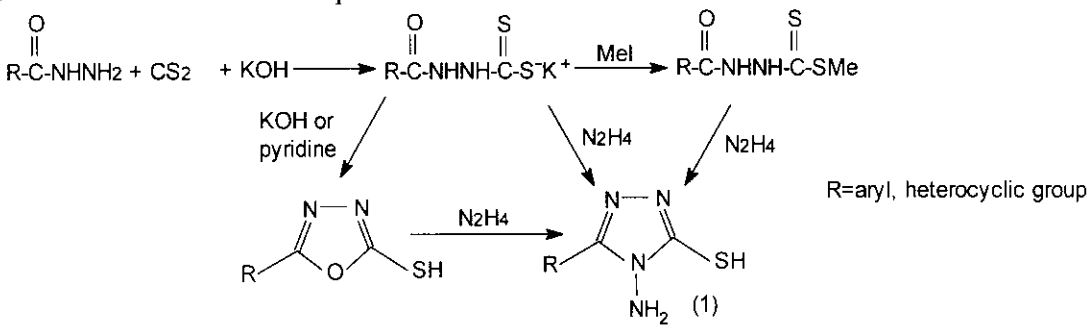
II. SYNTHETIC APPROACHES TO s-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLE DERIVATIVES

1. SYNTHESIS OF s-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLES

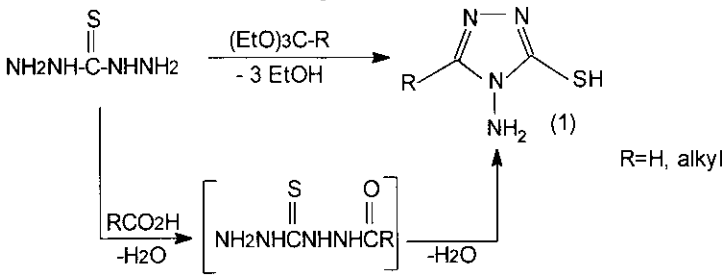
Various methods have been reported for the synthesis of s-triazolo[3,4-*b*]-1,3,4-thiadiazoles either from 1,2,4-triazoles or 1,3,4-thiadiazoles. Other routes were also known.

1.1 From 1,2,4-triazole derivatives

4-Amino-5-mercapto-3-substituted s-triazoles (**1**) were reported as excellent precursors for s-triazolo[3,4-*b*]-1,3,4-thiadiazoles. The Hoggarth synthesis[21] was once utilized as the method of choice for preparation of this useful class of heterocyclic compounds, which involved *S*-alkylation of potassium 3-aroyldithiocarbazates with methyl iodide and the subsequent hydrazinolysis. But later Reid and Heindel[22] developed two improved methods and they have been widely applied in the preparation of 4-amino-3-aryl/heterocyclyl-5-mercapto-s-triazoles. One involved the direct hydrazinolysis of potassium 3-aroyldithiocarbazates and the other involved the ring-opening and reclosure of 2-mercapto-5-substituted 1,3,4-oxadiazoles to the aminomercaptotriazoles.

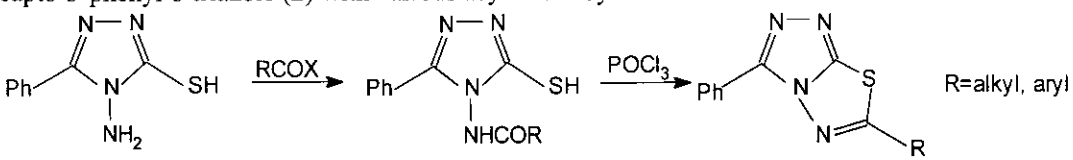


3-Alkyl-4-amino-5-mercapto-s-triazoles were first prepared starting from thiocarbohydrazide and ethyl esters of *ortho*-acids.[23] Afterward, Beyer and Kroger[24] advanced the extensively-used method by refluxing thiocarbohydrazide with excess of the suitable aliphatic monocarboxylic acids.



1.1.1 By reaction with acyl/aroyl halides

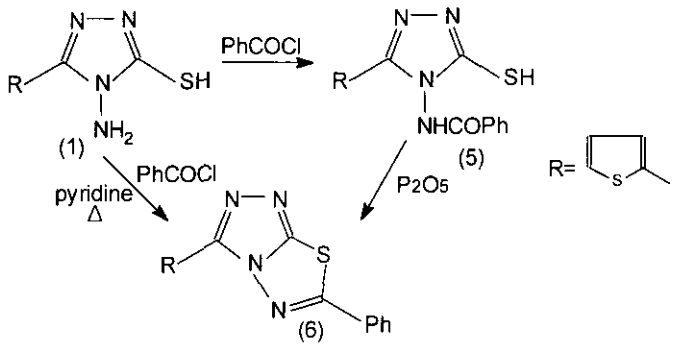
The s-triazolo[3,4-*b*]-1,3,4-thiadiazole ring system was first described by Kanaoka[25] who synthesized 6-alkyl and 6-aryl derivatives (**4**) of the system by dehydrative ring closure of 4-acylamino-5-mercapto-3-phenyl-s-triazoles (**3**) with phosphoryl chloride. The compounds (**3**) were obtained by heating 4-amino-5-mercapto-3-phenyl-s-triazole (**2**) with various acyl and aroyl halides.



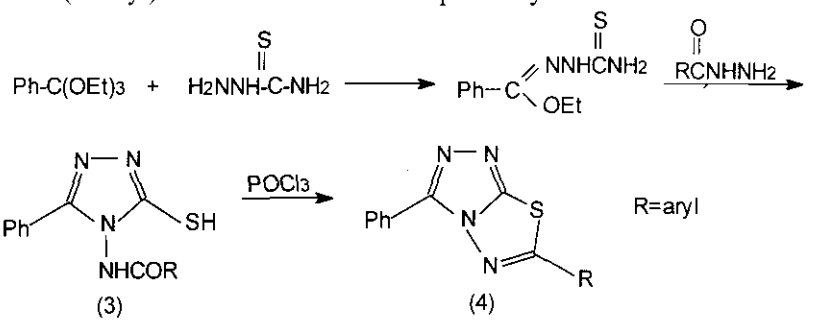
(2) (3) (4)

Similarly, 6-phenyl derivative (**6**) could be obtained either by the reaction of the 4-benzamido compound

(**5**) using phosphorus pentoxide as a cyclizing agent or by the reaction of **1** with benzoyl chloride in pyridine under reflux.[26]

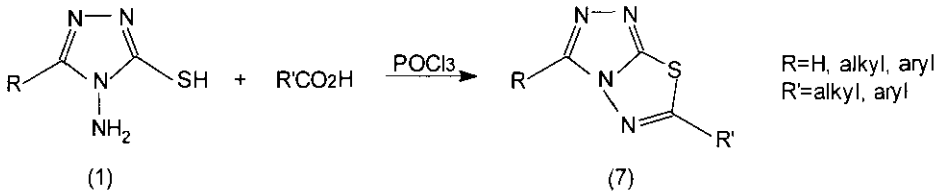


A different route to **3** (R=aryl) shown below has been reported by Malbec *et al.*[27]



1.1.2 By cyclocondensation with carboxylic acids

A one-step preparation of 3,6-disubstituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**7**) from the corresponding 4-aminotriazoles and carboxylic acids by prolonged heating with phosphoryl chloride was described by Golgolab *et al.*,[28] and most carboxylic acids gave good yields.

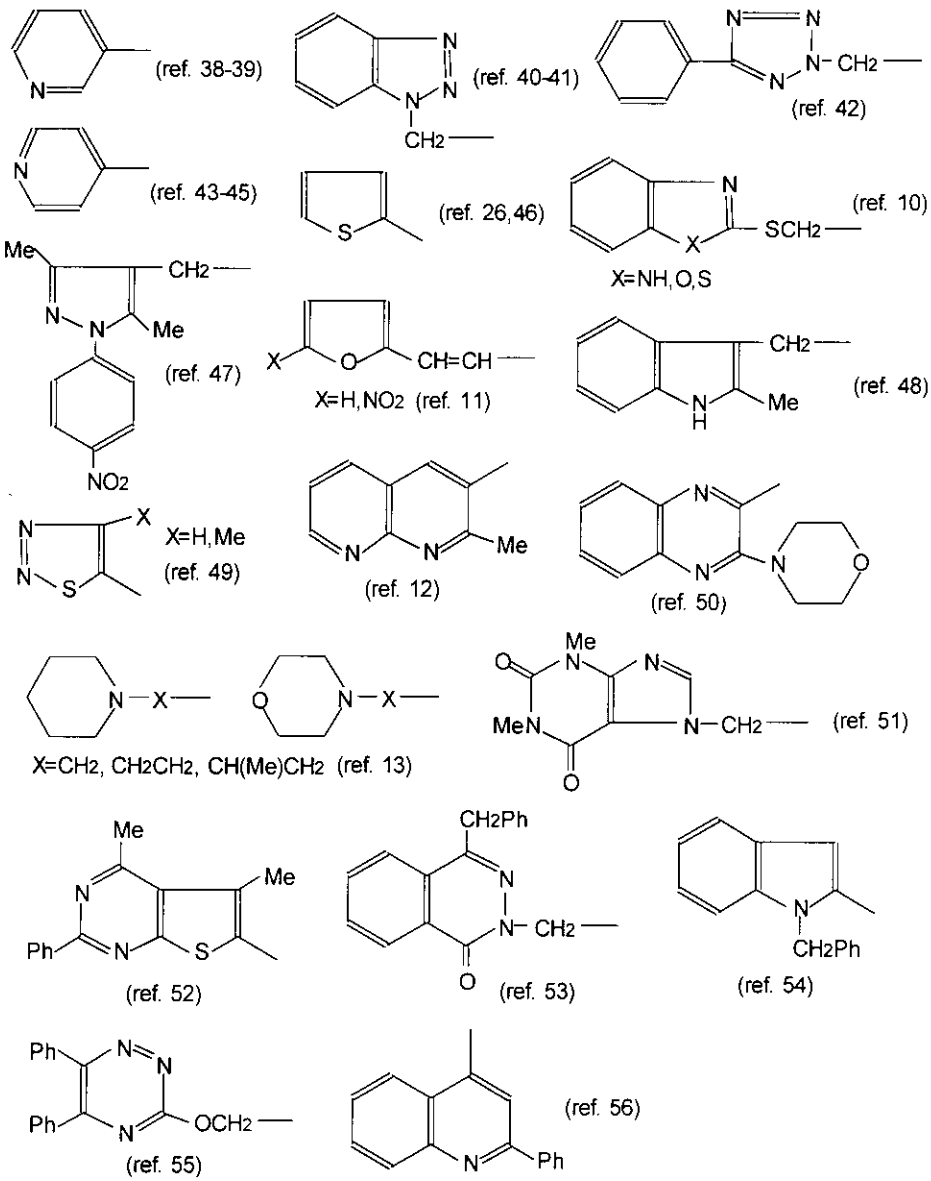


This has become the most common method for the construction of the s-triazolo[3,4-*b*]-1,3,4-thiadiazole ring system. Substituents at the 3- and 6-positions of the ring system mostly include alkyls, cycloalkyls, aryls, aryloxyalkyls, aralkyls and diaralkyls.[1-9,29-37] In recent years, various heterocyclic nuclei have been incorporated into the ring system to obtain compounds with better biological activities (Tables 1 and 2).

Furthermore, 6,6'-bis(s-triazolo[3,4-*b*]-1,3,4-thiadiazoles) (**8**) were formed when the same reaction was repeated with dicarboxylic acids such as oxalic acid and hexanedioic acid.[8,13,31,43] On the other hand, 3,3'-(phenylene)bis(s-triazolo[3,4-*b*]-1,3,4-thiadiazoles) (**9**) were prepared by utilizing benzenedicarboxylic acids to connect the starting material (**1**).[61-62]

It is worth noticing that s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**10**), in which the two substituents were identical, were also obtained by a one-step synthesis through heating excess of the appropriate carboxylic acids with thiocarbohydrazide in the presence of phosphoryl chloride.[28] This method saved trouble since

Table 1 3-Heterocyclic groups in s-triazolo[3,4-*b*]-1,3,4-thiadiazoles



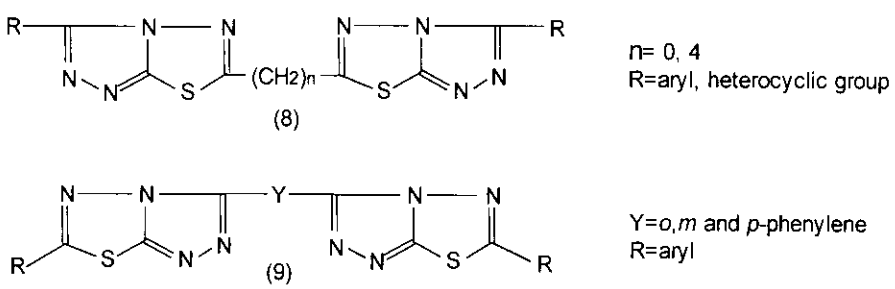
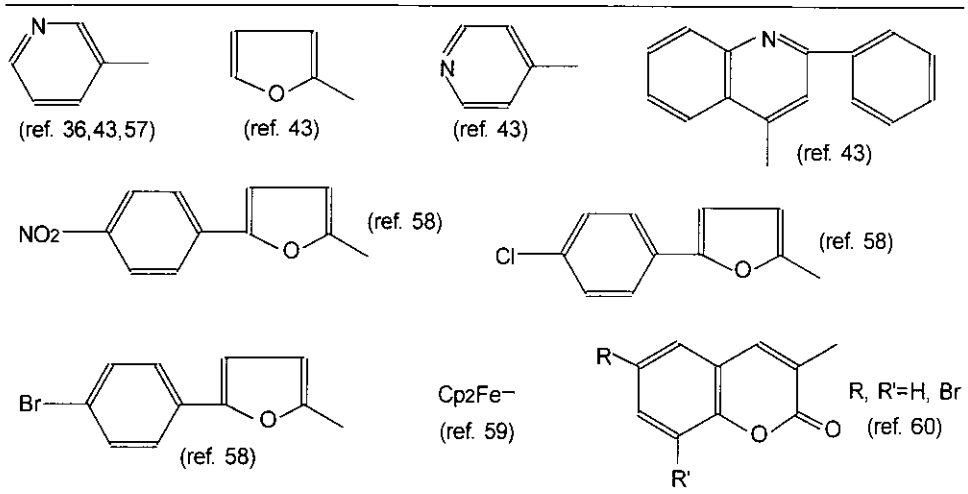
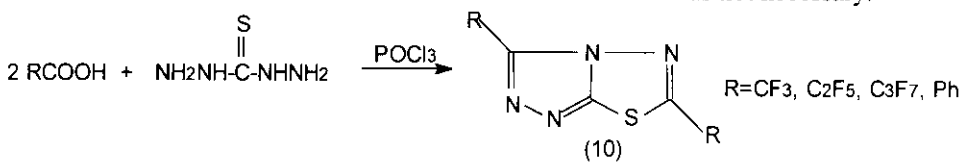


Table 2 6-Heterocyclic groups in s-triazolo[3,4-*b*]-1,3,4-thiadiazoles

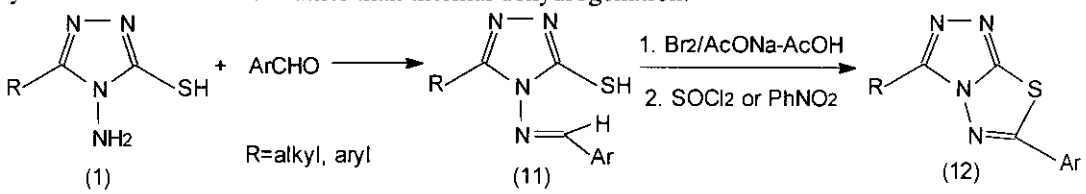


the separation of the intermediate s-triazole from the reaction mixture was not necessary.



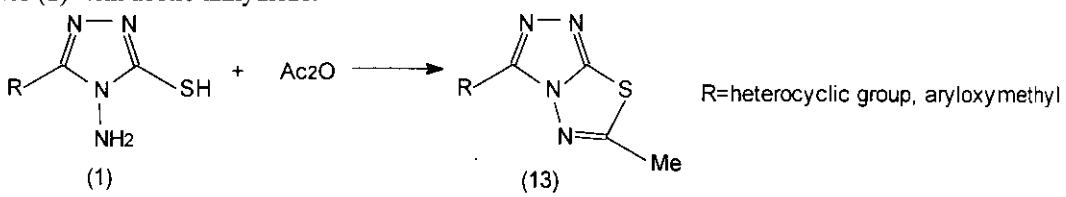
1.1.3 By reaction with aromatic aldehydes

A new indirect method for preparation of s-triazolo[3,4-*b*]-1,3,4-thiadiazoles has been developed.[47,58,63] The method is based on the cyclization of Schiff bases (**11**), which are easily accessible from s-triazoles (**1**) and a variety of aromatic aldehydes. The cyclizing agents were reported to be bromine, thionyl chloride or nitrobenzene. El-Emam *et al.*[63] furnished evidences confirming that the role of nitrobenzene in the cyclization was oxidation rather than thermal dehydrogenation.

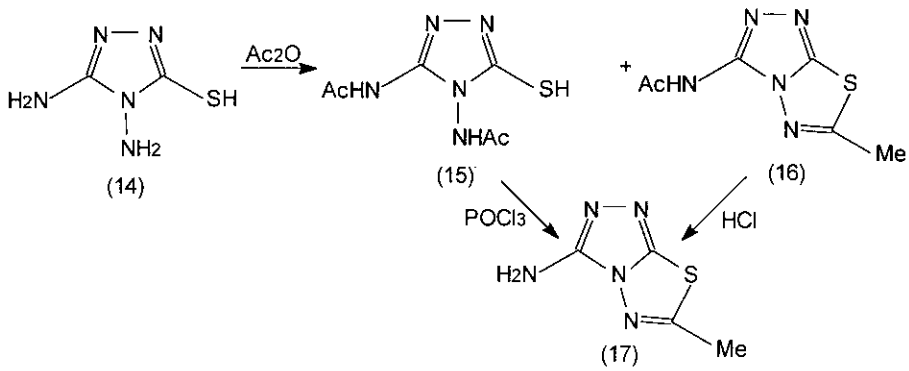


1.1.4 By reaction with acetic anhydride

An alternative approach[54,64] to the condensed triazolothiadiazoles was the reaction of substituted s-triazoles (**1**) with acetic anhydride.

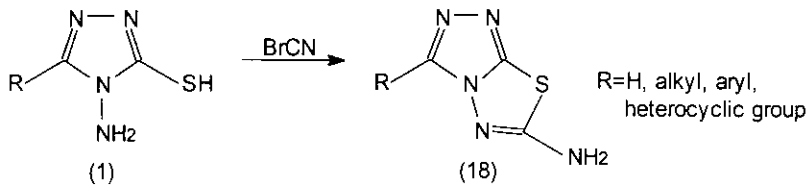


It was reported previously[65] that excessive acetic anhydride and 3,4-diamino-5-mercapto-s-triazole (**14**) in glacial acetic acid gave a mixture of **15** and **16**. **15** was treated with phosphoryl chloride under reflux to yield the condensed compound (**17**), which was also obtained by acid hydrolysis of **16**.



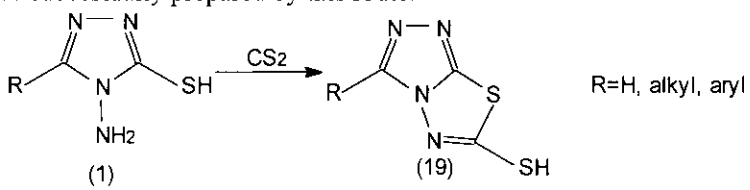
1.1.5 By cyclocondensation with cyanogen bromide

Cyanogen bromide is an excellent cyclization reagent in the formation of amino-substituted heterocyclic systems. Treatment of substituted s-triazoles (**1**) with cyanogen bromide in boiling methanol or ethanol readily afforded 6-amino-3-substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**18**) in good yields.[8,13,37,66-71] This method is suitable for the synthesis of s-triazolo[3,4-*b*]-1,3,4-thiadiazoles carrying 6-amino groups.



1.1.6 By cyclocondensation with carbon disulfide

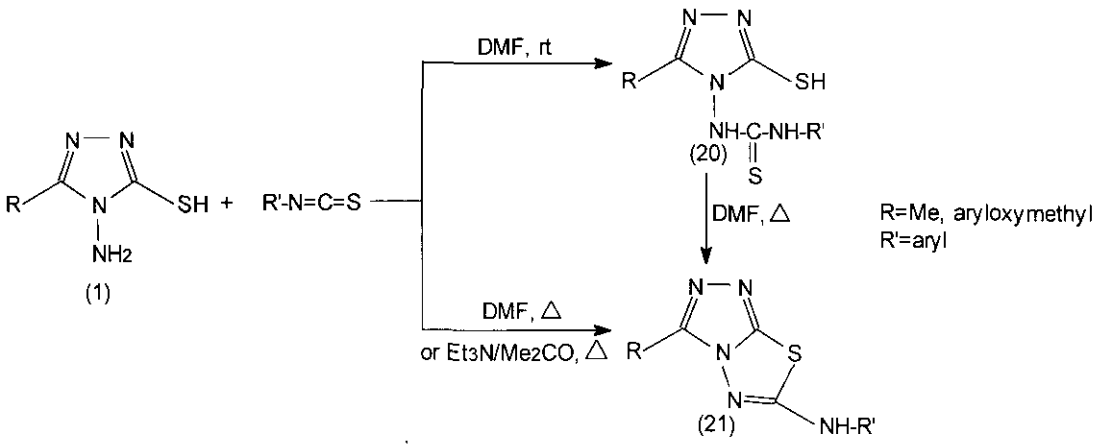
The ring closure of substituted s-triazoles (**1**) with carbon disulfide in methanolic potassium hydroxide formed 6-mercapto-3-substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**19**).[66] s-Triazolo[3,4-*b*]-1,3,4-thiadiazoles bearing 6-mercapto groups, which existed preferably in the thione forms rather than in the thiol forms, could be successfully prepared by this route.[13-15,36,47,68]



Kanaoka *et al.*[72] claimed that only the starting material was recovered when **1** was treated with carbon disulfide in pyridine, which was consistent with the report by Eweiss and Bahajaj.[8] However, the expected products (**19**) were obtained when the reaction under the same conditions was repeated by some chemists.[7,50,73-75]

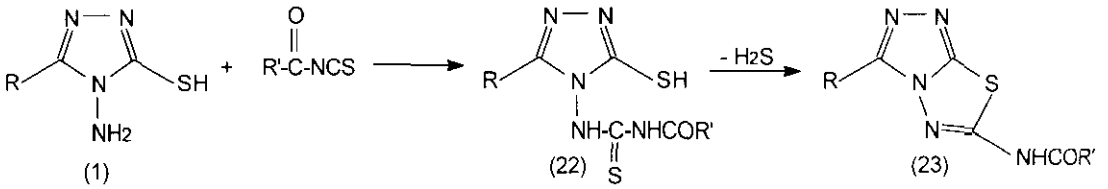
1.1.7 By reaction with aryl/aroyl isothiocyanates

The reaction between s-triazoles (**1**) and aryl isothiocyanates at room temperature in dry dimethylformamide afforded smoothly the uncyclized substituted thiourea derivatives (**20**) which upon refluxing cyclized into 6-arylamino-3-substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**21**).[14,16,71,76-78] These compounds were also prepared in one-step under reflux without isolating **20**. This method appeared to be quite suitable for the aromatic isothiocyanates, however, attempts with aliphatic isothiocyanates failed.[76]



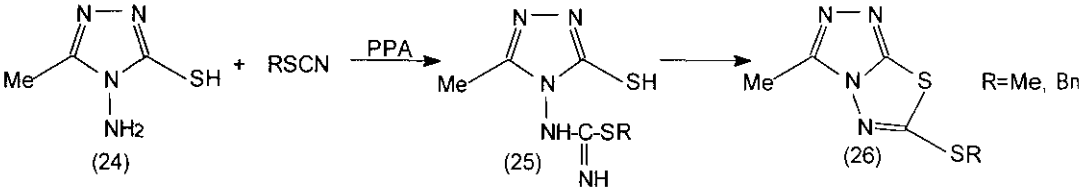
The reaction carried out in refluxing ethanol in the presence of DCC could give the fused compounds as well.[8,71] In our attempt[79] the product (**21**) (R=4-pyridyl; R'=Ph) could be formed only by means of refluxing **1** (R=4-pyridyl) with phenyl isothiocyanate in dry acetone in the presence of excessive triethylamine which improved the electrophilic activity of NCS group probably due to the formation of the complex isothiocyanate-triethylamine.

Refluxing s-triazoles (**1**) with aroyl isothiocyanates in dry acetone yielded 6-aroylamino-3-substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**23**) *via* the ring closure of acylthiosemicarbazides (**22**) which were possible intermediates of the process.[50,71,80]



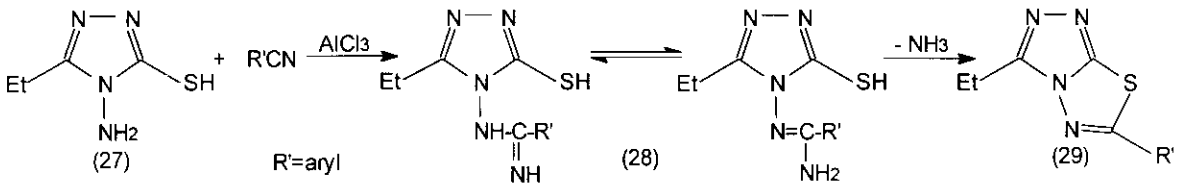
1.1.8 By reaction with alkyl/aryl thiocyanates

A simple method, recently reported by Shukurov and Kukaniev,[81] has been applied in the preparation of 3-methyl-6-methylthio/benzylthio-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**26**) which could be obtained generally by *S*-alkylation of **19**. The synthesis was accomplished in good yields by the condensation of 1,2,4-triazole (**24**) with methyl/benzyl thiocyanates in the presence of PPA, in which **25** were assumed as possible intermediates.



1.1.9 By condensation with nitriles

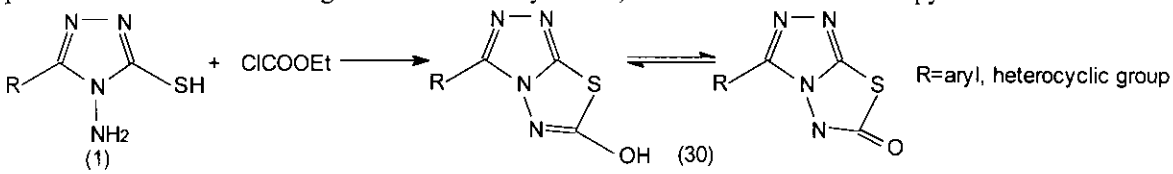
The synthetic route which utilized nitriles was first described by George *et al.*,[69] who treated s-triazole (**27**) with aromatic nitriles in the presence of anhydrous aluminium chloride to afford 6-aryl-3-ethyl-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**29**) and envisaged the course of the reaction as the formation of the amidines (**28**) followed by elimination of ammonia.



Shukurov *et al.*[82] reported the reaction procedure above in the presence of PPA and obtained the compounds (**7**) (R=Me; R'=aryl). On the other hand, triazolothiadiazoles (**7**) (R=Me,Et; R'=CH_2CO_2Et) were given in 50-62% yields when ethyl cyanoacetate was allowed to react with s-triazoles (**24**,**27**).[83]

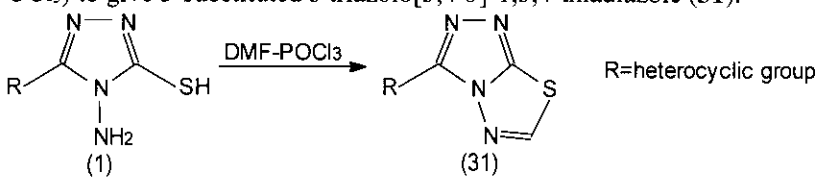
1.1.10 By reaction with ethyl chloroformate

A particular approach to synthesize 6-hydroxy substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**30**), existing in tautomeric forms, has been developed by heating s-triazoles (**1**) with ethyl chloroformate in the presence of various basic reagents such as triethylamine, fused sodium acetate and pyridine.[9,47]



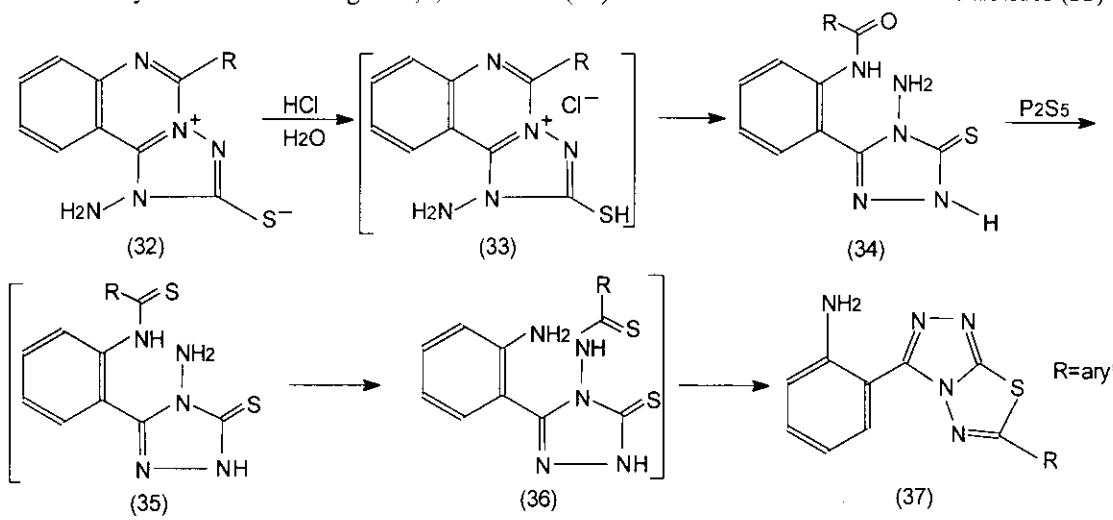
1.1.11 By reaction with the Vilsmeier reagent

An interesting study examined by Patel *et al.*[47] showed that 1,2,4-triazole (**1**) reacted with the Vilsmeier reagent (DMF-$POCl_3$) to give 3-substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazole (**31**).



1.1.12 By a translocative rearrangement

Molina *et al.*[84] reported the ring-opening reaction of mesoionic 1,2,4-triazolo[1,5-*c*]quinazolines (**32**) by the action of hydrochloric acid to give 1,2,4-triazoles (**34**) *via* the initial formation of the chlorides (**33**) in

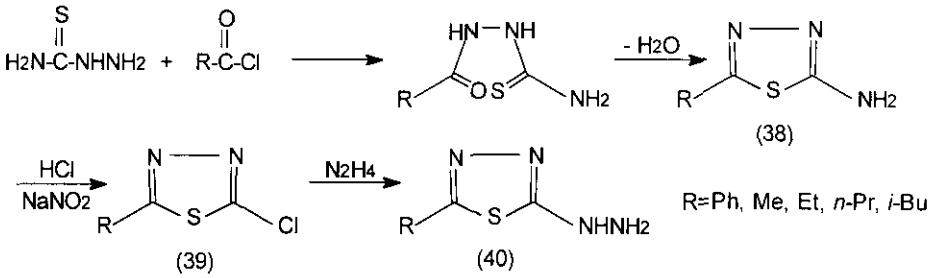


fair yields due to the high reactivity at the position 2 of the pyrimidine ring. However, on treatment with

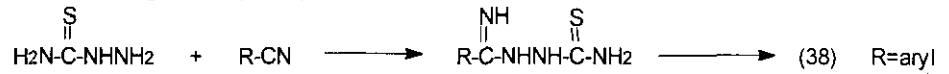
phosphorus pentasulfide in refluxing pyridine, compounds (**34**) were transformed into triazolothiadiazoles (**37**) rather than the expected 1,2,4-triazoles (**35**). This remarkable conversion presumably involved a rearrangement that a thioaroyl group attached to the phenylamino side chain in **35**, formed by thionation of the amide group of **34**, was translocated to the amino group in **35**. The thus obtained **36** finally gave the bicyclic compounds (**37**) by cyclodehydrosulfurization.

1.2 From 1,3,4-thiadiazole derivatives

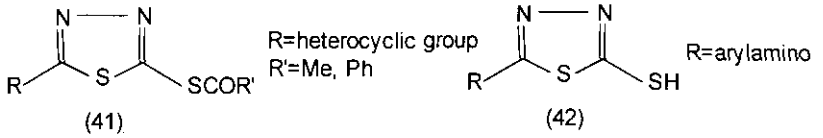
The method for preparation of 2-hydrazino-5-substituted 1,3,4-thiadiazoles (**40**), which were reported as the other important precursors for s-triazolo[3,4-*b*]-1,3,4-thiadiazoles, was based on the acylation of thiosemicarbazide followed by dehydration to afford 2-amino-5-substituted 1,3,4-thiadiazoles (**38**). The common dehydrating reagents have been neat sulfuric acid, neat polyphosphoric acid or their mixture, and especially 1.5 molar equivalent of methanesulfonic acid.[85] **38** could be transformed into 2-chloro-5-substituted 1,3,4-thiadiazoles (**39**) by diazo-reaction and subsequent hydrazinolysis of **39** under mild conditions provided **40**.[86]



Recently aromatic nitriles have been found to readily react with thiosemicarbazide in a solution of polyphosphoric acid to give **38** (R=aryl).[82]



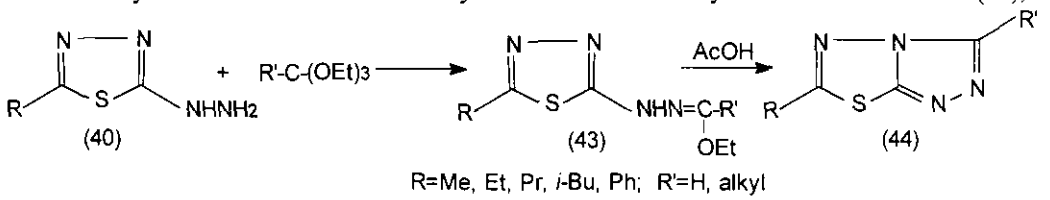
Other reported approaches to **40** involved hydrazinolysis of 2-acylthio-1,3,4-thiadiazoles (**41**) at room temperature and 2-mercapto-1,3,4-thiadiazoles (**42**) under reflux, respectively.[17,47]



Only a few methods for construction of s-triazolo[3,4-*b*]-1,3,4-thiadiazoles from hydrazinothiadiazoles (**40**) were reported in the past years[37,59,67,77,83-86] because of the many steps for preparing the starting materials and the poor overall yields. The products had similar substituents in alternative positions to those obtained from the 1,2,4-triazole derivatives.

1.2.1 By reaction with *ortho*-esters

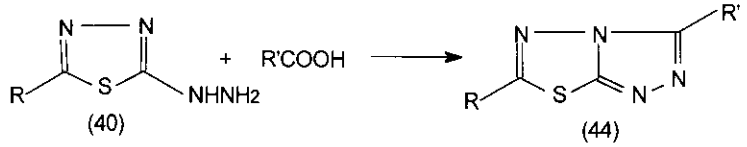
Kanaoka[87] initially described that the acid-catalyzed intramolecular cyclization of imidoates (**43**), which



were prepared by the interaction of 2-hydrazino-5-substituted 1,3,4-thiadiazoles (**40**) with ethyl esters of *ortho*-acids, gave 3,6-disubstituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**44**).

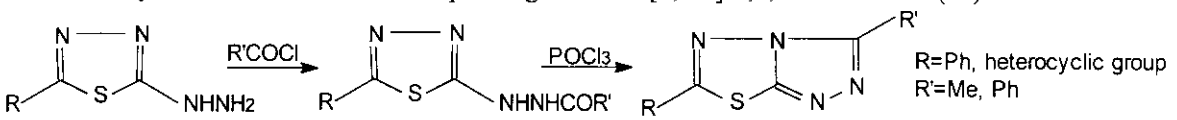
1.2.2 By reaction with carboxylic acid derivatives

As would be anticipated, treatment of hydrazinothiadiazoles (**40**) with carboxylic acids in refluxing methanol resulted in cyclocondensation to give 3,6-disubstituted derivatives (**44**).[17,81]



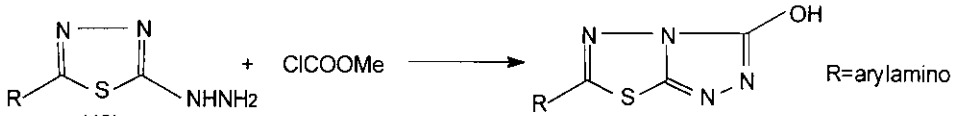
(40) (44)

Moreover, hydrazinothiadiazoles (**40**) reacted with acyl chlorides in the presence of pyridine to give the corresponding substituted hydrazides (**45**), which on treatment with phosphorus oxychloride in xylene underwent cyclization to form the corresponding s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**44**).[47,66]



(40) (45) (44)

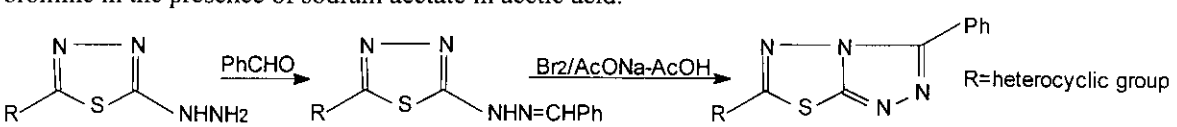
It was reported by Bano *et al.*[17] that the reaction between 1,3,4-thiadiazoles (**40**) and methyl chloroformate in refluxing methanol could furnish 3-hydroxy substituted derivatives (**46**).



(40) (46)

1.2.3 By reaction with benzaldehyde

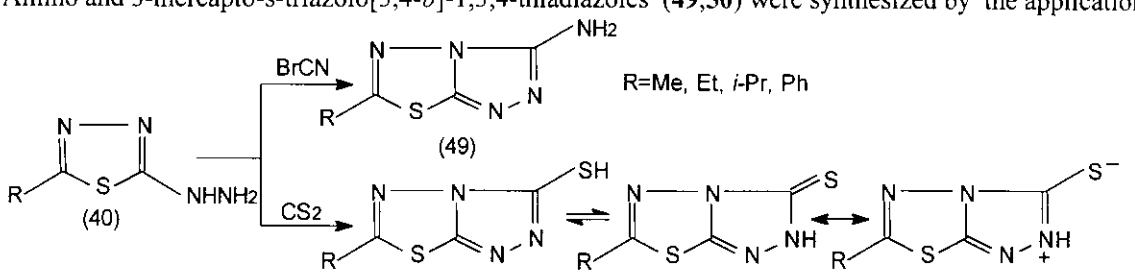
In addition to the route above using benzoyl chloride as reacting reagent, 3-phenyl-6-substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**48**) were also obtained by treating hydrazinothiadiazoles (**40**) with benzaldehyde to give hydrazones (**47**), which were successively subjected to cyclization on treatment with bromine in the presence of sodium acetate in acetic acid.[47]



(40) (47) (48)

1.2.4 By cyclocondensation with cyanogen bromide or carbon disulfide

3-Amino and 3-mercapto-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**49**,**50**) were synthesized by the application



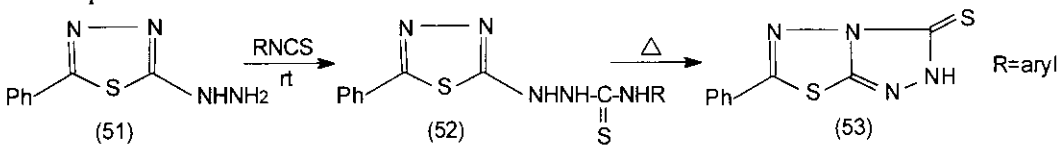
(40) (49) (50)

R=Me, Et, *i*-Pr, Ph, arylamino

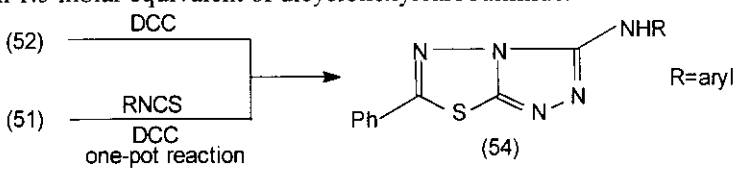
of cyanogen bromide and carbon disulfide, respectively, to hydrazinothiadiazoles (**40**) as reported.[17,66,72] The latter approach was achieved in the presence of alkali, which was not necessary in some cases, and the expected products (**50**) existed in prototropic tautomers.

1.2.5 By reaction with aryl isothiocyanates

When **51** was allowed to treat with aryl isothiocyanates in ethanol at room temperature, the reaction afforded 2-arylthiocarbamoylhydrazino-5-phenyl-1,3,4-thiadiazoles (**52**) in good yields. The cyclization of **52** yielded **53**, which was identical with the product prepared by utilizing carbon disulfide when heated to elevated temperature.[88]

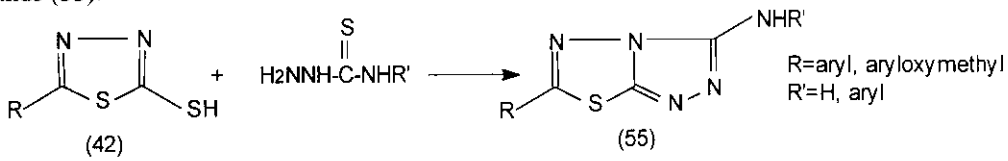


The cyclodehydrosulfurization of **52** in the presence of dicyclohexylcarbodiimide in a boiling mixture of ethanol and benzene gave 3-arylamino-6-phenyl-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**54**) in high yields, which were also produced according to the one-pot cyclodehydrosulfurization reaction of **51** and aryl isothiocyanates with 1.5 molar equivalent of dicyclohexylcarbodiimide.[88]



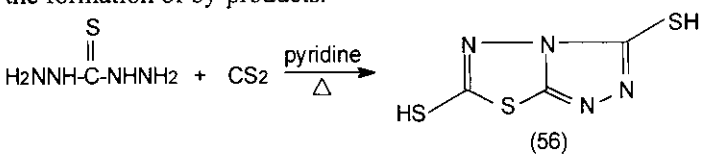
1.2.6 By reaction of thiadiazolethiols with thiosemicarbazides

Only one example of synthesis starting from 2-mercapto-5-substituted 1,3,4-thiadiazoles (**42**) was reported.[89] The reaction with thiosemicarbazides also yielded 3-amino/arylamino substituted condensed compounds (**55**).

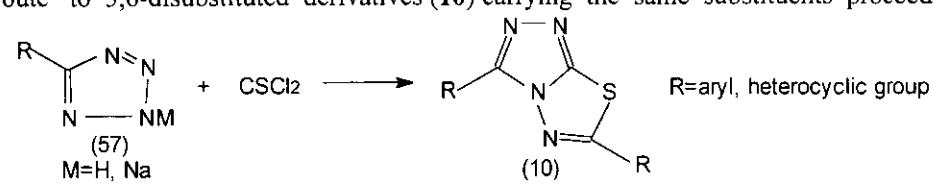


1.3 Other methods

The fused ring system was synthesized by Sandstrom[90] who obtained 3,6-dimercapto-s-triazolo[3,4-*b*]-1,3,4-thiadiazole (**56**) from a refluxing pyridine solution of thiocarbohydrazide and carbon disulfide in poor yield because of the formation of by-products.



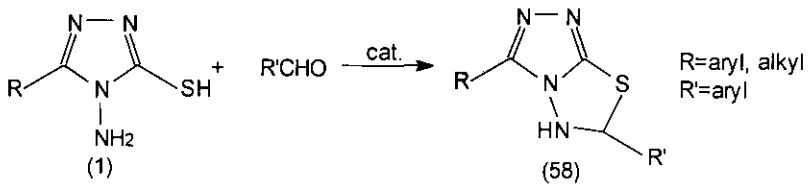
Another route to 3,6-disubstituted derivatives (**10**) carrying the same substituents proceeded *via* the



condensation of tetrazoles (**57**) with thiocarbonyl chloride in dioxane.[91] Compounds (**57**) were obtained by cyclization of aldehydes RCHO with NH_2OH, NaN_3 and NH_4Cl in dimethylformamide.

2. SYNTHESIS OF 5,6-DIHYDRO-s-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLES

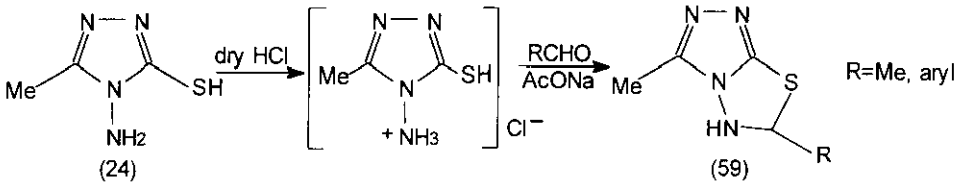
The traditional synthetic route to 5,6-dihydro-3,6-disubstituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**58**) involved the cyclization of 4-amino-5-mercapto-3-substituted s-triazoles (**1**) with various aromatic aldehydes under reflux in the presence of a catalytic amount of *p*-toluenesulphonic acid, acetic anhydride or piperidine.[15,18-20,29,33,47,92]



(1) (58)

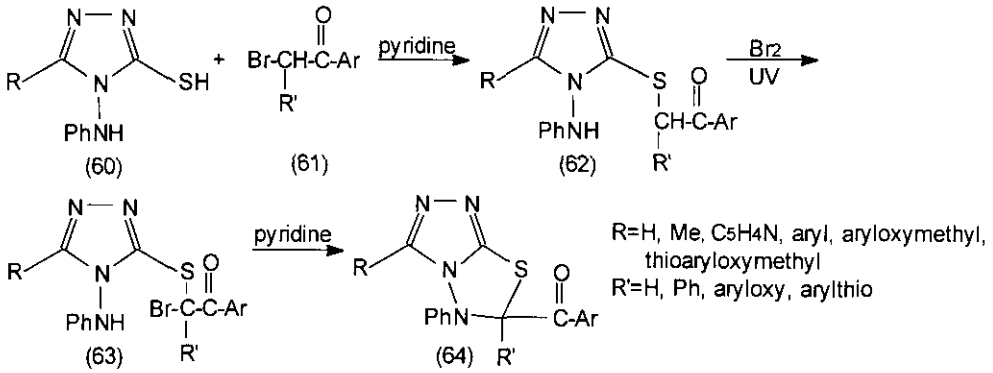
Gupta *et al.*[93] utilized the concept of "Microwave-induced Organic Reaction Enhancement"(MORE) chemistry by carrying out the same reaction in unsealed vessels under microwave irradiation using DMF as energy transfer medium and successfully made the synthesis rapid and efficient by cutting down the reaction time from hours to minutes with improved yields. The condensation of s-triazoles (**1**) with some aliphatic aldehydes was accomplished in boiling absolute ethanol to furnish the desired 5,6-dihydro derivatives (**58**) (R=aryl; R'=H, Me).[9]

In the earlier report,[94] a stream of dry hydrogen chloride gas was passed through a suspension of s-triazole (**24**) and hydrochloric salt of **24** was formed, which was refluxed with various aldehydes in the presence of sodium acetate under nitrogen atmosphere to afford the required products (**59**).



(24) (59)

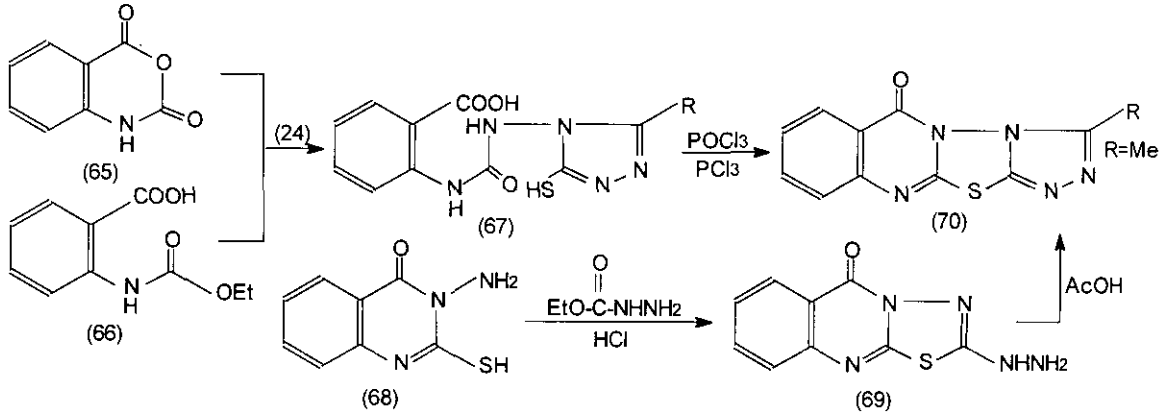
Multisubstituted 5,6-dihydro-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**64**) have been synthesized recently by several steps rather than one step reaction. 4-Anilino-5-mercapto-3-substituted s-triazoles (**60**) on interaction with bromides (**61**) in ethanol containing pyridine gave **62**, which upon bromination with bromine in acetic acid in the presence of UV light afforded **63**. The cyclized compounds (**64**) were eventually obtained by refluxing **63** in ethanol containing pyridine. Furthermore, alternative unambiguous approaches have also been described.[95-96]



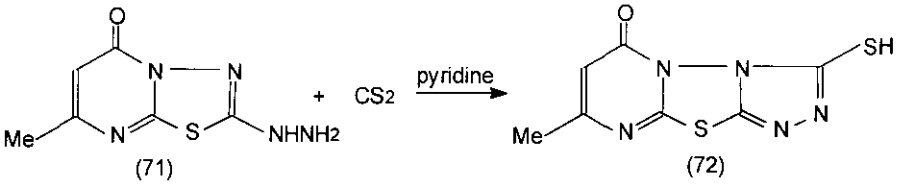
(60) (61) (62) (63) (64)

3. SYNTHESIS OF s-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLES FUSED WITH ADDITIONAL HETEROCYCLIC NUCLEI

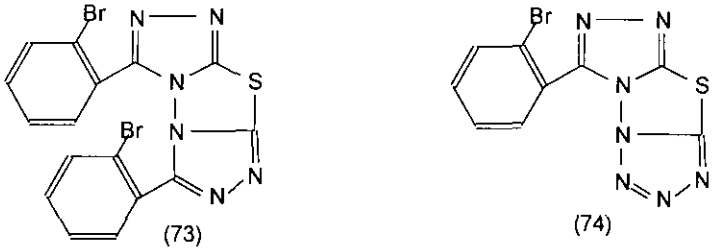
Prompted by the physiological importance of some heterocyclic compounds including quinazolines, pyrimidines, triazoles and tetrazoles, some s-triazolo[3,4-*b*]-1,3,4-thiadiazoles fused with these additional heterocyclic nuclei were prepared. Gakhar *et al.*[97] reported the synthesis of s-triazolo[4',3':4,5]-1,3,4-thiadiazolo[2,3-*b*]quinazolin-6-one (**70**) by two approaches. The first one was based on the cyclization of the intermediate (**67**) with phosphorus oxychloride and phosphorus trichloride, which were available from the condensation of s-triazole (**24**) with isatoic anhydride (**65**) or *N*-carbethoxyanthranilic acid (**66**). The second one involved the condensation of 3-amino-2-mercapto-3*H*-quinazolin-4-one (**68**) with *N*-carbethoxyhydrazine in the presence of hydrochloric acid and the final cyclization of the intermediate (**69**) with acetic acid.



Abd El-Samii *et al.*[98] described the preparation of **70** (R=CH_2OAr) in accordance with the first route above. Similarly, hydrazinothiadiazolopyrimidinone (**71**) was made to react with carbon disulfide in pyridine to give tricyclic compound (**72**).[99]



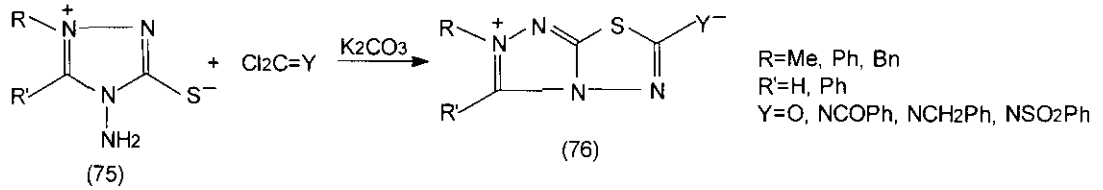
The synthesis of fused compounds (**73**) and (**74**) starting from s-triazole (**1**) (R=*o*-bromophenyl) was also reported.[100]



4. SYNTHESIS OF CATIONIC AND MESOIONIC s-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLES

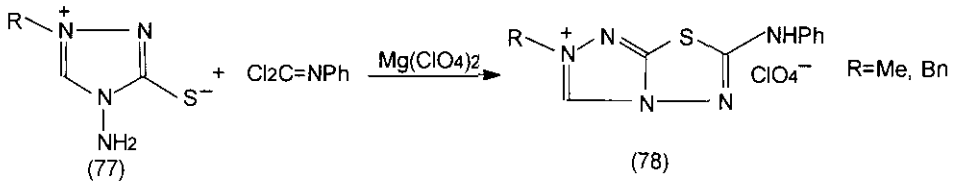
Lazaris *et al.*[101-102] synthesized a series of mesoionic s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**76**) by the cyclocondensation of 4-amino-1,5-disubstituted 1,2,4-triazolium-3-thiolates (**75**) with Cl_2C=Y in boiling

chloroform containing potassium carbonate.



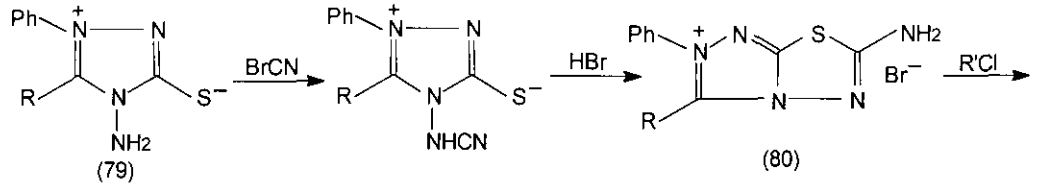
(75) (76)

On the other hand, the salts (**78**) were obtained in high yields by treatment of triazolium compounds (77) with $Cl_2C{=}NPh$ in the presence of magnesium perchlorate.[103]

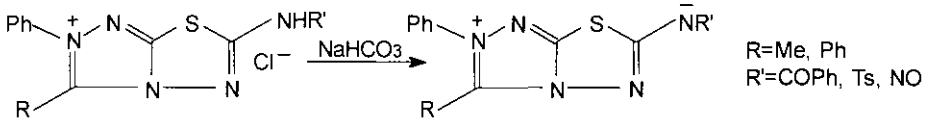


(77) (78)

An alternative approach to similar bicyclic compounds (**82**) was described by Masuda *et al.*[104] Treating **79** with cyanogen bromide gave bromides (**80**) *via* the cyclization of the intermediates nitriles with the aid of hydrogen bromide, which were benzoylated, tosylated or nitrosated at the exocyclic nitrogen to afford chlorides (**81**). The expected free mesoionic compounds (**82**) were readily given when **81** were on treatment with alkali.

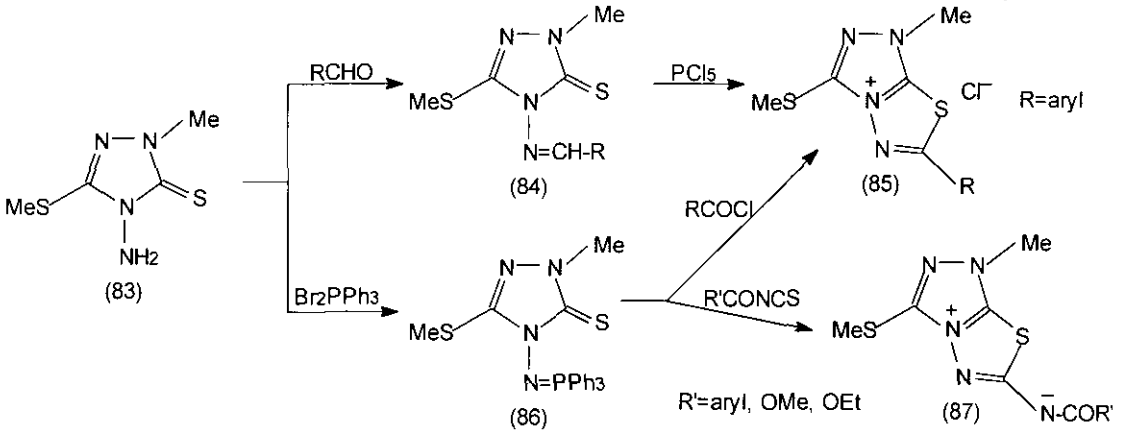


(79) (80)



(81) (82)

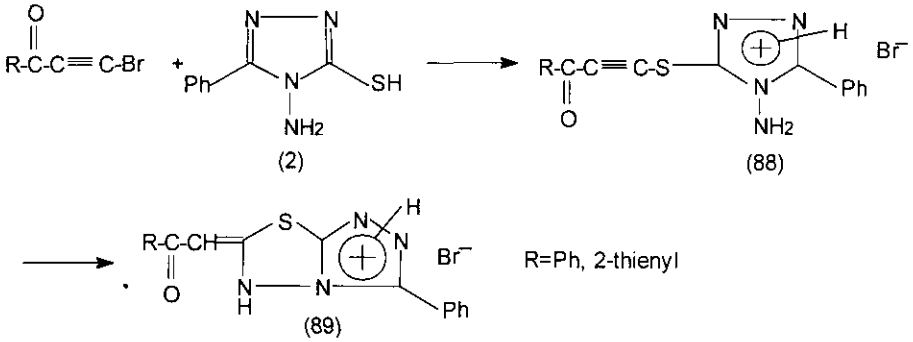
s-Triazolo[3,4-*b*]-1,3,4-thiadiazolium salts (**85**) were prepared by the initial formation of arylidene derivatives (**84**) from s-triazole (**83**) and aromatic aldehydes and the final cyclization of **84** by the action



(83) (84) (85) (86) (87)

of phosphorus pentachloride in refluxing toluene. The bicyclic cations (**85**) were also obtained by the reaction of iminophosphorane (**86**), available from **83** and triphenylphosphane dibromide, with aroyl chlorides in toluene under reflux. The reaction of **86** with acyl isothiocyanates, performed in dry benzene at room temperature, led directly to the mesoionic compounds (**87**). These methods furnished a generally useful procedure for the preparation of s-triazolo[3,4-*b*]-1,3,4-thiadiazolium cations or mesoionic derivatives.[105]

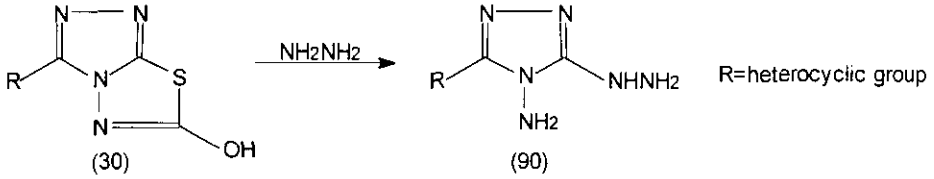
The bromides (**89**) were produced with yields of 65-69% as a result of the reaction of s-triazole (**2**) with 1-bromo-2-acylacetylenes in acetonitrile in the absence of catalysts.[106] The clearly elucidated reaction pathway involved the formation of the intermediate ethynyl sulfides (**88**) by nucleophilic substitution of the bromine atom and the successive nucleophilic attack by the amino group on the α-carbon atom of the acetylenic bond accompanied by intramolecular cyclization.



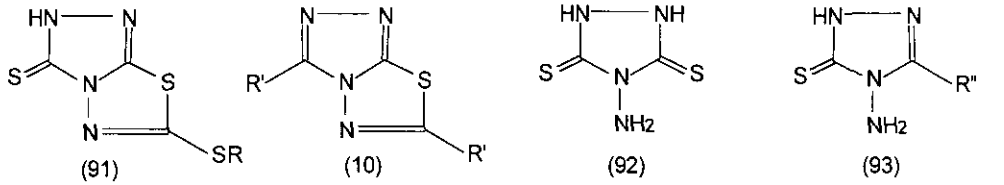
III. REACTIONS OF s-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLE DERIVATIVES

1. HYDRAZINOLYSIS REACTION

On treatment with hydrazine hydrate, 6-hydroxy-3-substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazole (**30**) underwent ring cleavage of the thiadiazole system to afford 5-hydrazino-s-triazole (**90**).[47]



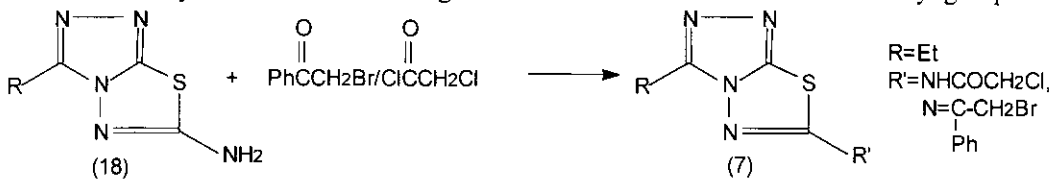
Similarly, the destructive hydrazinolysis of triazolothiadiazole derivatives (**91**) and (**10**) (R'=SMe) took place, whose mechanism involved the attack of hydrazine on C-7a and the subsequent ring cleavage, to give various triazolethiones (**92**,**93**). Hydrazinolysis of compound (**10**) (R'=Ms), however, proceeded *via* a slightly different mechanism.[107]



2. REACTION ON THE PRIMARY AND SECONDARY AMINO GROUPS

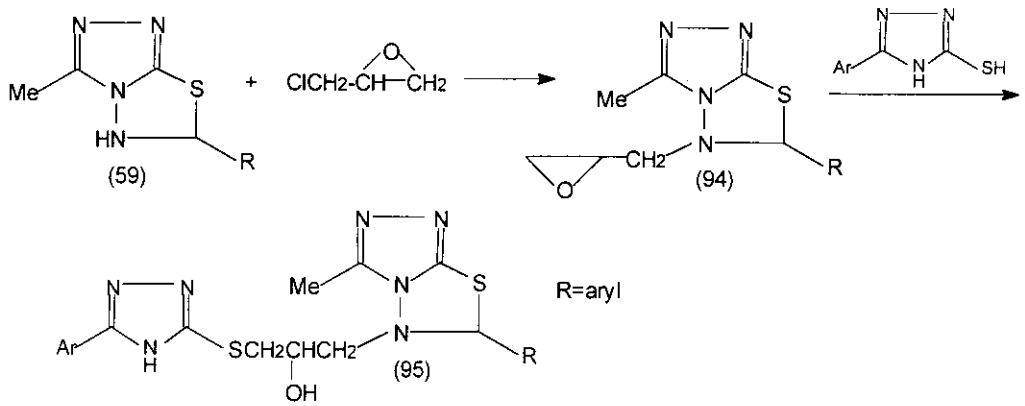
The condensed compound (**18**) (R=Et) was allowed to react with phenacyl bromide and chloroacetyl

chloride to yield 6-(α-phenyl-β-bromoethylidene)amino and 6-(α-chloroacetyl)amino derivatives (**7**), respectively. But attempts to repeat the same reactions with compound (**18**) (R=CF_3) were unsuccessful due to the low basicity of the molecule arising from the contribution of the trifluoromethyl group.[69]



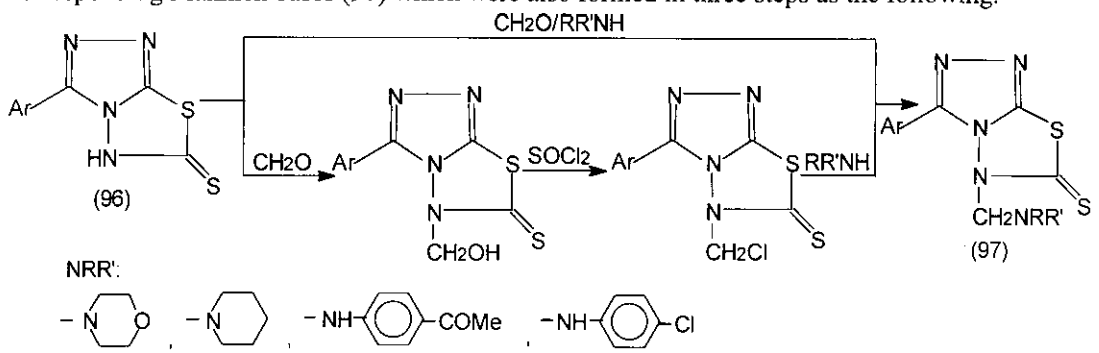
(18) (7)

5,6-Dihydro derivatives (**59**) could be alkylated with 1-chloro-2,3-epoxypropane in acetone containing potassium carbonate to give epoxy derivatives (**94**), which opened readily by refluxing with various mercaptotriazoles in methanol to yield **95**.[18]



(59) (94) (95)

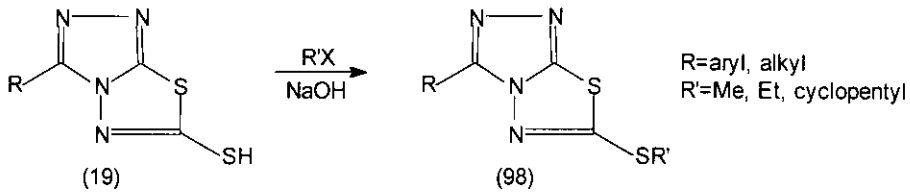
In addition, **96** reacted with formaldehyde and primary or secondary amines in absolute ethanol to afford the corresponding Mannich bases (**97**) which were also formed in three steps as the following.[15]



(96) (97)

3. *S*-ALKYLATION REACTION

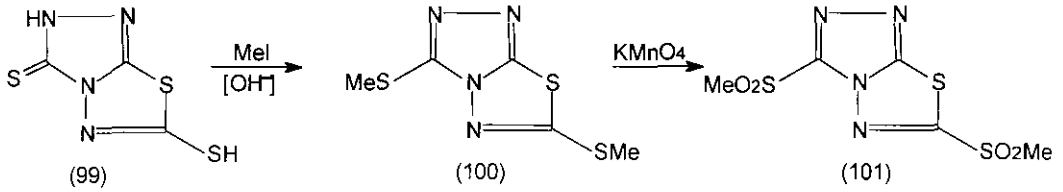
Compounds (**19**) could be transformed into their alkylthio ethers (**98**) by interaction with alkyl halides in sodium hydroxide solution.[15,66,72]



(19) (98)

Kovalev *et al.*[108] pointed out by Pariser-Parr-Pople calculations and UV experiments that 3,6-dimercapto-

s-triazolo[3,4-*b*]-1,3,4-thiadiazole (**56**) existed in the tautomeric form (**99**) in dioxane or in the crystal state. **99** exhibited considerable acidity with the result that dimethylthio substituted product (**100**) was given on alkylation with methyl iodide in alkaline medium, which was oxidized to form **101**.



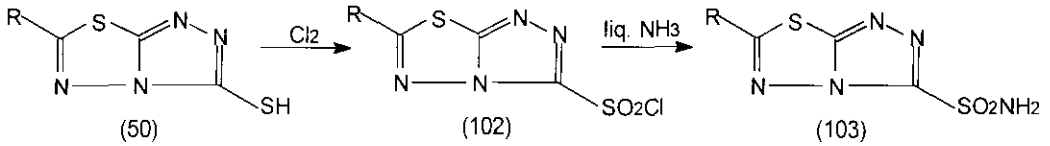
(99) (100) (101)

4. COORDINATION WITH SOME METAL IONS

3,6-Dimercapto substituted compound (**56**) (abbreviated as $DTTH_2$), as a monobasic as well as dibasic acidic chelating ligand, could coordinate mainly with bivalent metal ions such as Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Pd^{2+}, Pt^{2+} and Ru^{2+} in neutral or basic medium to form complexes including $M(DTT)\cdot nH_2O$, $M(DTTH)_2$, $M(DTT)Py\cdot nH_2O$, $M(DTTH)_2Py_2$ and so on.[109-110] It was also found that **56** could coordinate as a neutral sulphur donor as well with Pd^{2+} or Pt^{2+} in acidic solution. The fair reactivity was based on the two thioamide groups in **56** which was expected to exist in four thiol-thione tautomeric forms.

5. OTHER REACTIONS

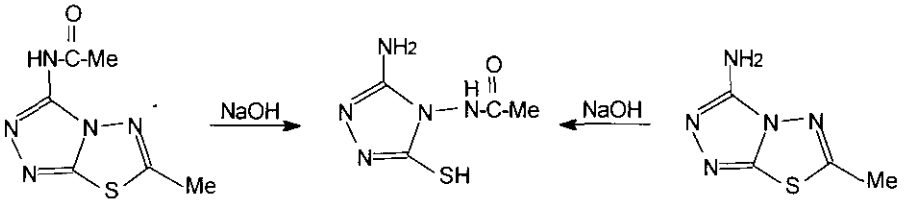
By the application of chlorine to 3-mercapto compounds (**50**) in acetic acid, oxidative chlorination took place to afford 3-chlorosulfonyl compounds (**102**) which were aminated to 3-sulfamoyl compounds (**103**).[72]



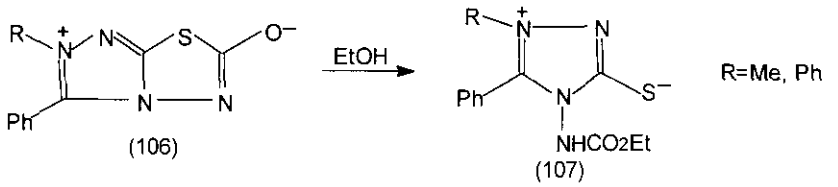
(50) (102) (103)

R=alkyl, Ph

It was reported that the ring cleavage was achieved by hydrolysis and thermolysis in addition to hydrazinolysis.[65,104] Either **104** or **17** was changed into 1,2,4-triazole (**105**) by the action of hot alkali. Moreover, the thiadiazole ring of the oxo-type compounds (**106**) easily underwent ring opening on heating in ethanol to give the monocyclic mesoionic esters (**107**).



(104) (105) (17)



(106) (107)

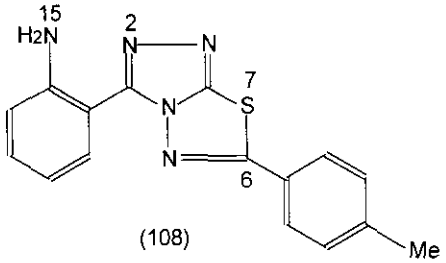
IV. SPECTROSCOPIC PROPERTIES

1. CRYSTAL STRUCTURES

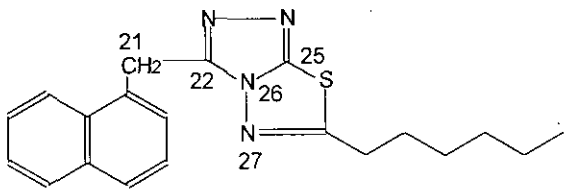
The first single-crystal structure was reported for 6-methyl-3-phenyl-s-triazolo[3,4-*b*]-1,3,4-thiadiazole in which the nucleus of the triazolothiadiazole system was planar confirming the aromatic character of the 10-π electron system. The cohesion of the crystal was due to Van der Waals and electrostatic interactions.[111]

Next, an unambiguous structural assignment for 3-(2-aminophenyl)-6-(4-tolyl)-s-triazolo[3,4-*b*]-1,3,4-thiadiazole (**108**) was achieved from an X-Ray crystallographic analysis.[84] It was found that the bond lengths of the bicycle were within the ranges reported for the s-triazole and 1,3,4-thiadiazole derivatives except the C6-S7 length and the angle between the two five-membered rings was 1.9°. The intramolecular contact between N15 and N2 might be responsible for the planarity of the molecule.

Then, the crystal structure of 6-hexyl-3-(1-naphthylmethylene)-s-triazolo[3,4-*b*]-1,3,4-thiadiazole (**109**) was determined by X-Ray diffraction by us.[112] The analysis indicated that each of the single-bond lengths of N26-N27, C22-N26 and C25-S in this compound was shorter than the normal bond length, while those for all C=N bonds were longer. It is worth noticing that the C21-C22 distance was significantly small, perhaps due to the favorable hyperconjugation effect between the triazolothiadiazole nucleus and methylene directly linked to it because C21 was at the distance of only 0.00051nm from the plane of the fused nucleus.



(108)



(109)

Afterward, we determined the structure of 6-(4-methylphenyl)-3-(1-naphthylmethylene)-s-triazolo[3,4-*b*]-1,3,4-thiadiazole (**110**) in which the phenyl substituent was almost coplanar with the central ring system but the bulky naphthyl group was twisted out of this plane (Figure 1).[113]

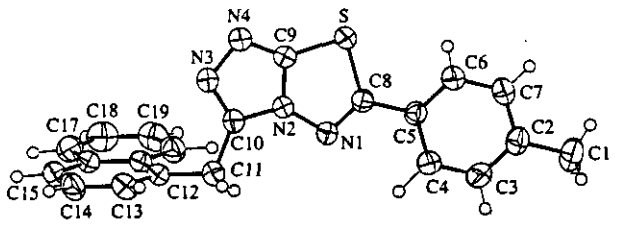


Figure 1 Molecular structure of the compound (110)

2. UV SPECTRA

The UV absorption of the s-triazolo[3,4-*b*]-1,3,4-thiadiazole nucleus, as represented by the 3,6-dimethyl product, occurred at λ_{max} 251nm (logε 3.45).[87] Some conclusions could be drawn on the basis of the experimental data reported in literature.[8,42,45,66-67,69,72]

The introduction of a 6-amino substituent resulted in a hypsochromic shift of 13 nm of the absorption maximum, whereas the introduction of a 6-thiol substituent caused a 34 nm bathochromic shift of the

absorption maximum. On the contrary, a 24 nm bathochromic shift appeared for the 3-amino group and a 8 nm hypsochromic shift arose for the 3-thiol group. The absorption maximum shifted to longer wavelength with the extension of the conjugation system resulting from the introduction of a 3- or 6-aryl/heterocyclic group. Especially, the red shift effect of the 6-nitrophenyl and 6-methoxyphenyl derivatives was more obvious than that of the others. It is worthwhile to notice that the 3- or 6-*ortho*-substituted phenyl product did not show such red shift because steric crowding inhibited the substituent from achieving complete coplanarity with the fused nucleus.

3. IR SPECTRA

The IR spectra of the reported compounds exhibited three characteristic absorption bands of the s-triazolo[3,4-*b*]-1,3,4-thiadiazole nucleus: 1590-1640 cm^{-1} for $\nu_{C=N}$, 1230-1280 cm^{-1} for $\nu_{N-N=C}$ and 680-720 cm^{-1} for ν_{C-S-C}, respectively. The tautomeric forms of the compounds carrying the mercapto or hydroxy group could be concluded from their IR spectra.[7-8,13,32,47,72-75]

4. NMR SPECTRA

The NMR spectra of the products lacked the signals for both SH and NH_2 protons in their precursors (**1**) demonstrating that the cyclization involving both functional groups occurred. Moreover, the NMR spectra of some products, like their IR spectra, could also be used to identify their tautomeric forms.[8,13,15,47,73,75]

The δ_H data for the substituents at the positions 3 and 6 in s-triazolo[3,4-*b*]-1,3,4-thiadiazole nucleus are listed in Table 3. The results indicate that the absorption peaks for these substituents have shifted to the down-field to a certain extent in comparison with their normal absorption peaks, which is mostly based on the induction effect resulting from the fused nucleus. For the aliphatic protons, the other possible reason is related to the electron transfer from the alkyl groups to the heterocyclyl nucleus *via* hyperconjugation.

Table 3 δ_H data for the substituents in s-triazolo[3,4-*b*]-1,3,4-thiadiazoles*

3-substituents		6-substituents	
RC<u>H</u>$_2$ (R=H, alkyl)	2.0-3.2ppm	RC<u>H</u>$_2$ (R=H, alkyl)	2.6-3.6ppm
RC<u>H</u>$_2$ (R=aryl)	4.4-5.2ppm	ROC<u>H</u>$_2$ (R=aryl)	5.3-5.8ppm
Ar<u>H</u>	6.6-8.1ppm	Ar<u>H</u>	6.8-8.6ppm
ROC<u>H</u>$_2$ (R=aryl)	4.2-5.2ppm	N<u>H</u>Ar	6.6-7.7ppm
RSC<u>H</u>$_2$ (R=heterocyclic group)	~4.2ppm	SC<u>H</u>$_3$	2.7-2.9ppm
O<u>H</u>	~3.5ppm	N<u>H</u>Ar	9.4-9.5ppm
S<u>H</u>	~3.5ppm	N<u>H</u>$_2$	7.7-8.1ppm
RC<u>H</u>$_2$ (R=heterocyclic group)	3.7-6.7ppm	O<u>H</u>	~5.9ppm

* Solvent: $CDCl_3$ or DMSO-d_6

The characteristic absorption peak for 5,6-dihydro-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles appeared at 4.0-5.2 ppm, which was assigned to the C-6 proton. The ^{13}C NMR spectra for some of them have also been reported.[95-96] The NMR spectra of some mesoionic compounds were examined by Lazaris and

Egorochkin[114] who discussed the deshielding action of the solvent CF_3COOH or DMSO-d_6 as well as the role of mesomeric effects.

5. MASS SPECTRA

By analyzing the mass spectra of a large number of s-triazolo[3,4-*b*]-1,3,4-thiadiazoles, it was found that the strong conjugated system tended to stablize the molecular ion under electron impact, which was reflected by the compounds carrying 3-alkyl and 3-aryl/heterocyclyl groups as reported by us.[1-2,38,45,57]

The fragmentation of this kind of fused compound, as represented by 6-(4-chlorophenyl)-3-(4-pyridyl)-s-triazolo[3,4-*b*]-1,3,4-thiadiazole, followed three different competing pathways corresponding to the rupture of the fused nucleus (Figure 2).[45] In accordance with pathway 1, the molecular ion eliminated 4-cyanopyridine, nitrogen and cyanide moieties producing ion A at m/z 155 as the base peak. In pathway 2, ion B at m/z 181 was formed by the expulsion of 4-cyanopyridine and nitrogen molecules from the molecular ion, which in turn lost carbon monosulfide and cyanide fragments to give ion C at m/z 111, or underwent further cleavage of a carbon monosulfide molecule yielding ion D at m/z 137. In alternative pathway 3, the molecular ion cleaved successively 4-chlorophenylcyanide and nitrogen molecules to furnish ion E at m/z 148, which on elimination of a carbon monosulfide molecule produced ion F at m/z 104.

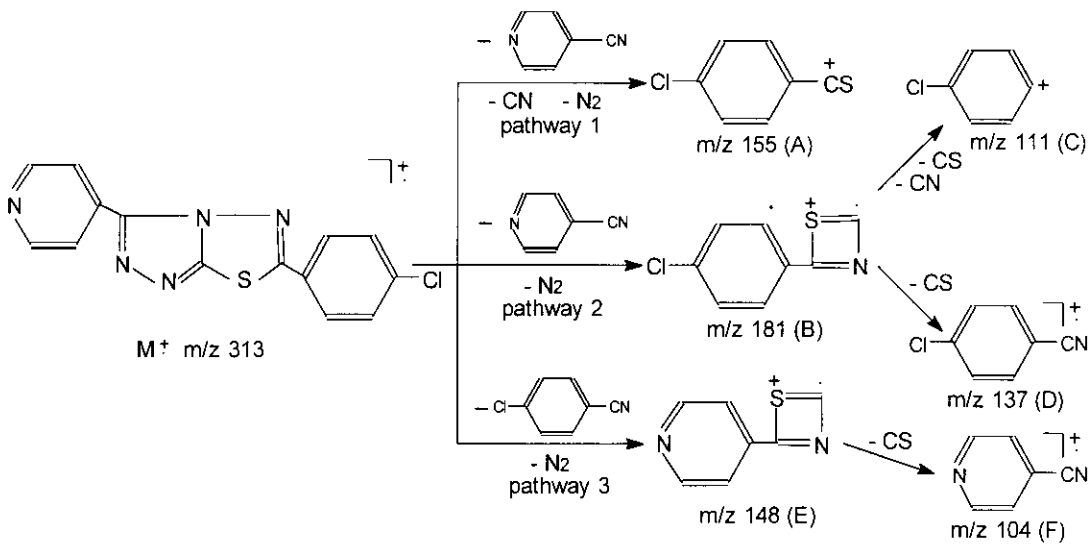
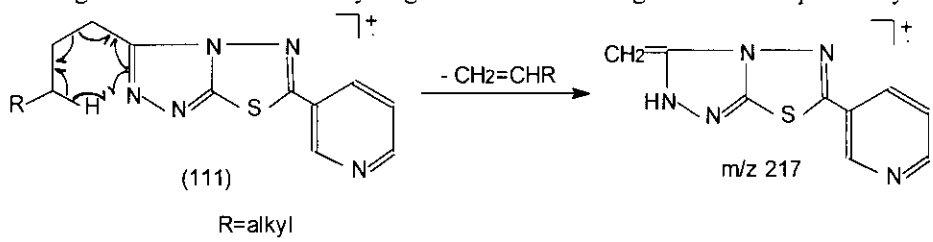


Figure 2 Fragmentation of 6-(4-chlorophenyl)-3-(4-pyridyl)-s-triazolo[3,4-*b*]-1,3,4-thiadiazole

The ion peak formed by the direct denitrogenation from the s-triazole ring in the molecular ion could be observed in some compounds.[42] In the case of 3-alkyl substituted products (carbon number >3) (**111**), the predominant fragmentation involved a hydrogen transfer rearrangement accompanied by the loss of an



olefinic molecule to give the base peak at m/z 217.[57]

V. BIOLOGICAL ACTIVITIES

Most of s-triazolo[3,4-*b*]-1,3,4-thiadiazoles have been reported to possess antibacterial and antifungal actions against various strains of bacteria and fungi.[1-2,4,7-9,11-17,38-39,41,43,45,47-48,57-58,70,73-74,77,79-80,88] They also exhibited herbicidal, antiinflammatory, CNS depressant, hypocholesteremic, hypotensive, antiviral, analgesic, anthelmintic and plant growth regulative effects.[1-3,5-6,10-11,38,57,80]

The structure and activity relationship, such as the effect of the substituents of 6-phenyl ring on the activity, was studied in order to get some meaningful results.[10-12,45] We investigated the antibacterial activity of 3-(4-pyridyl)-6-substituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles and came to the conclusion that the order of antibacterial activity was: bis(s-triazolo[3,4-*b*]-1,3,4-thiadiazol-3-yl)alkanes>>6-heterocyclyl derivatives>6-alkyl derivatives>6-aryl derivatives.[43]

With regard to 5,6-dihydro-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles, they exhibited CNS depressant and antiinflammatory activity and varying degree of fall in the blood pressure and the heart rate.[18-20,93]

In view of the diverse biological activities above, it is highly likely that the investigations concerning s-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives will be actively pursued into the future.

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