Synthesis of 1, 2, 4-Triazoles and Thiazoles from Thiosemicarbazide and its Derivatives

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Abstract: The use of thiosemicarbazide in organic synthesis has become a classical strategy for the synthesis of several heterocycles. Their reactions with compounds containing C=O and C=N groups is an elegant method for the preparation of biologically active compounds viz. triazoles and thiazoles. The ease of forming C-N and C=N bonds as opposed to N-N bond formation is reflected in their extensive use for the preparation of these heterocycles. As the internal nitrogen atom of the hydrazine fragment is a softer nucleophilic centre than the more powerful terminal nitrogen, reagents susceptible to nucleophilic attack by the terminal nitrogen undergo cyclisation to afford the aforesaid heterocycles in excellent yields, even under mild reaction conditions. The present review attempts to summarise the cyclisation reactions of thiosemicarbazide derivatives yielding 1, 2, 4-triazoles and thiazoles.

Keywords: Thiosemicarbazides, triazoles, thiazoles, cyclisation, α-haloketones, thiobiureas.

INTRODUCTION

The chemistry of heterocyclic compounds has evoked keen interest and considerable attention owing to the wide spread applications they possess. More than half of the compounds produced by nature have heterocyclic rings incorporated in their structures. A large number of alkaloids derived from heterocyclic molecules are used as drugs. Moreover, pharmaceutical and agrochemical industries have made rapid and significant progresses to quench the quest of organic chemists in discovering and developing suitable heterocyclic compounds for the benefits of mankind. The influence of these heterocycles in day-to-day life has been convincingly established [1]. Among them, the chemistry of nitrogen-sulphur containing heterocycles has undergone remarkable advances in the last couple of decades, ever since their initial use in agriculture commenced nearly a century ago. The pesticidal [2, 3], potential chemotherapeutic [4-7], fungicidal [8-11] and antiviral [12] properties have been the reasons for the upsurge in interest and development of these heterocyclic systems in general and, triazoles and thiazoles in particular.

The term triazole is generally extended to triazolines and triazolidines also. A 1, 2, 4-triazoline formation was first observed by Pinner [13-16] during the synthesis of amidrazones [17-19] from an imidate and hydrazine. The observation that certain triazole derivatives are capable of inhibiting fog formation in photographic emulsions and that some derivatives are very effective as herbicides and convulsants led to renewed interests in this field [20]. Quite interestingly, it has been reported that inks having smooth writing properties contain 3-amino-5-mercapto-1, 2, 4-triazole derivatives [21]. The reported antidepressant [22], antihypertensive [23], anticorrosion [24, 25] and analgesic [26] properties also led chemists to continue research in this field. The concept of 1, 3-dipolar cycloadditions [27] along with the discovery of several new classes of 1, 3-dipoles has contributed greatly to the development of 1, 2, 4-triazoline chemistry.

On November 18, 1887, Arthur Rudolf Hantzsch with his collaborator, J.H. Weber signed the birth certificate of thiazole [28]. They proved the existence of both thiazole and isothiazole, compared them to glyoxaline and pyrazole respectively and proposed to name benzothiazole the "Methenylamidophenylmercaptan" just discovered by A.W. Hofmann [29]. The discovery of the fusion reaction between *p*-toluidine and sulphur to give dehydrothio-*p*-toluidine in 1887 constituted the beginning of thiazole dyestuff technology. Later 2-aminothiazole derivatives were widely employed as heterocyclic diazo components for disperse dyes [30, 31]. In addition to that, many thiazole derivatives possess biological activity [32-39] and a number of medicaments contain a thiazole ring in their structure [40-43]. As do, numerous natural aromas contain thiazole derivatives: tomato [44], roasted coffee [45, 46], the basic fraction of Scotch whisky and Jamaica rum [47] and so on. The use of a thiazole derivative in the treatment of AIDS [48] shows that among the pentaatomic heterocyclic rings, thiazole is one of the most intensively investigated and its chemistry maintains steadily its intensive development.

A. 1, 2, 4-TRIAZOLES

The name triazole was first given to the carbon-nitrogen ring system $C_2H_3N_3$ by Bladin [49, 50]. The numbering of the ring system as given in The Ring Index [51] is depicted

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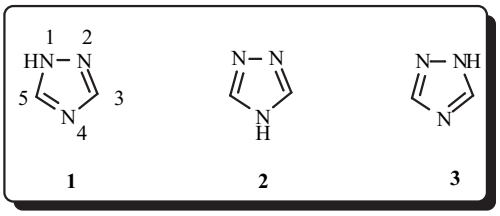
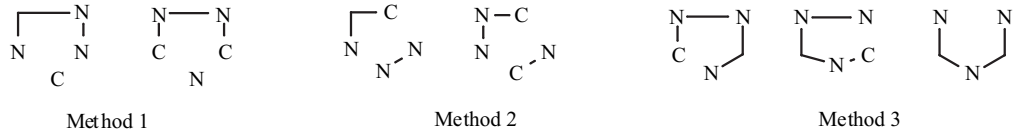
below; (**1**) is called the 1, 2, 4-triazole. Structures (**2**) and (**3**) represent the tautomeric forms. Ring systems in which there is only one double bond are called triazolines. The location of the double bond is indicated by the symbol Δ^2, Δ^3 and Δ^4. Those ring systems which do not contain any double bond in the ring are called triazolidines. Triazolines bearing the ring linked functions such as =O, =S, =NR and =CRR^1 are potentially aromatic [52].



1 **2** **3**

Synthesis

Several methods available for the triazole synthesis are depicted in Scheme **1**.

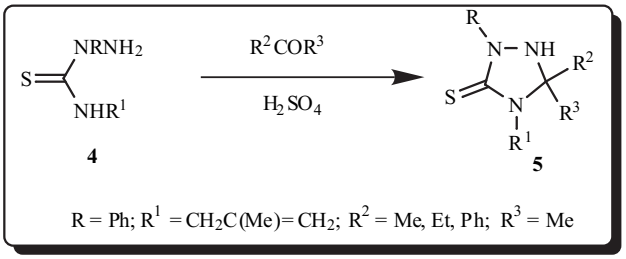


Method 1 Method 2 Method 3

Scheme 1.

The synthesis of these heterocycles can easily be achieved from thiosemicarbazide derivatives as they are versatile building blocks and known to chemists for a long time. Among the numerous methods employed for the synthesis of triazoles, considerable attention has been devoted to the cyclocondensation of 2, 4-disubstituted thiosemicarbazides with carbonyl functions. The cyclocondensation of 2, 4-disubstituted thiosemicarbazide derivatives with ketones in the presence of catalytic amount of sulphuric acid is known to afford triazolidinethione derivatives [53]. Thus the reactions of 4-(2-methylallyl)-2-phenyl thiosemicarbazide (**4**) with ketones afforded 3, 3-dimethyl-4-(2-methylallyl)-1-phenyl-1, 2, 4-triazolidine-5-thiones (**5**) [54].

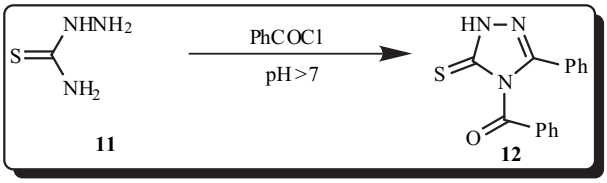
Similar results were observed in the cyclocondensation of substituted thiosemicarbazides with formic [55, 56], acetic [55] and trifluoroacetic acids [57]. On successive lines, the condensation of thiocarbohydrazides with aliphatic and aromatic carboxylic acids led to one of the choicest methods for the preparation of 3-alkyl/aryl-4-amino-Δ^2-1, 2, 4-triazoline-5-thiones [58-62]. Improvements have been made by carrying out the reactions with carboxylic acids at their melting points, affording 3-alkyl/aryl-4-amino-5-mercapto-1, 2, 4-triazole (**7**) which easily reacts with carboxylic acids or acid chlorides affording the 1, 2, 4-triazolo[3, 4-b][1, 3, 4]thiadiazole ring system (**8**) [63]. With carbohydrazide (**9**), 4-amino-3-methyl-Δ^2-1, 2, 4-triazolin-5-one was obtained (**10**) [64].



4 **5**

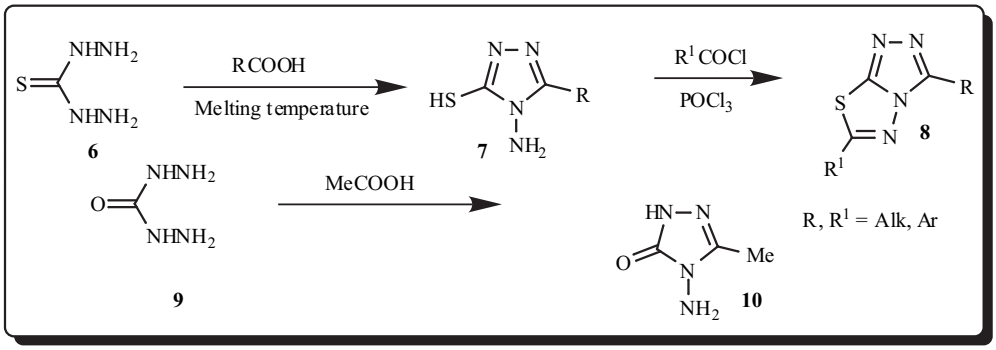
R = Ph; R^1 = $CH_2C(Me)=CH_2$; R^2 = Me, Et, Ph; R^3 = Me

Thiosemicarbazides on the treatment with acid chlorides followed by cyclisation in aqueous sodium hydroxide are found to yield triazolinethione derivatives [3]. Thus, refluxing a mixture of *p*-chlorobenzoyl chloride and 1-*p*-chlorophenyl thiosemicarbazide in benzene followed by the treatment of the product with sodium hydroxide in methanol-water mixture yielded the triazolinethione derivative [65-67]. On the other hand, thiosemicarbazide (**11**) on the treatment with benzoyl chloride in boiling pyridine or alkali is reported to undergo in situ benzoylation and cyclisation resulting in the formation of 4-benzoyl-3-phenyl-Δ^2-1, 2, 4-triazoline-5-thione (**12**) [68]. Analogously, reactions of thiocarbohydrazide with formamide and acetic anhydride afforded Δ^2-1, 2, 4-triazoline-5-thiones [62].



11 **12**

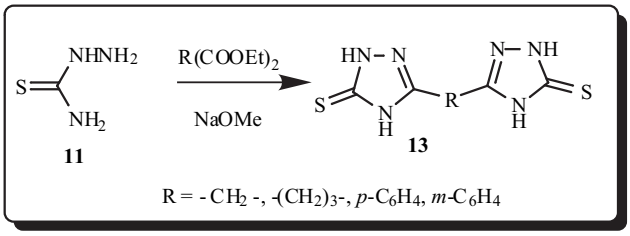
Another method of synthesis of 1, 2, 4-triazoline-5-thiones is by the reaction of aliphatic as well as aromatic esters with 4-alkyl/aryl thiosemicarbazides in the presence of sodium alkoxide [69-71]. Accordingly 1, 2, 4-triazoline-5-thiones were prepared by the reactions of thiosemicarbazide



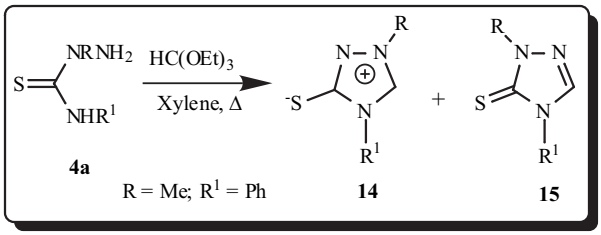
6 **7** **8** **9** **10**

R, R^1 = Alk, Ar

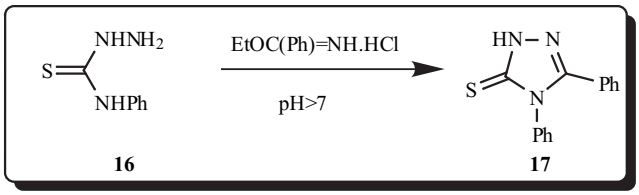
derivatives with ethyl formate in the presence of sodium methoxide [72-75]. The base catalysed condensation of thiosemicarbazide (**11**) with alkyl or aryl dicarboxylic acid esters afforded compounds containing two 1, 2, 4-triazoline-5-thione moieties linked through the 3-position by an alkyl or aryl chain (**13**) [72, 76].



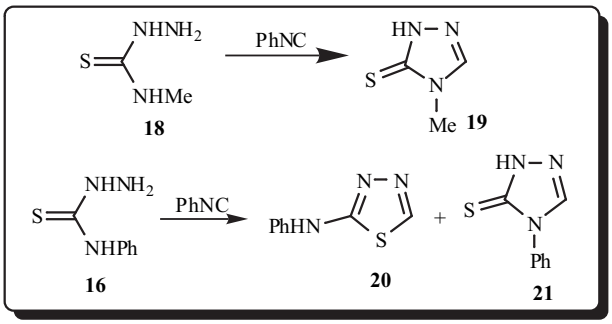
Based on the report of Stolle and Bowles [77] that thiocarbohydrazide on reaction with ethyl orthoformate afforded 4-amino-1, 2, 4-triazole-3-thiol, further investigations were carried out on similar lines [78]. However the products formed in the reactions between thiosemicarbazide or 4-substituted thiosemicarbazides with aliphatic orthoesters were found to depend on the experimental conditions adopted and the orthoesters employed [79-81]. In the mean time the reactions of 2-methyl-4-phenyl thiosemicarbazide with ethyl orthoformate [82] and ethyl orthoacetate [83] were reported to afford compounds having a thiadiazoline structure. A true identity of this compound was reported by Werber *et al.* [84]. Later a re-examination of the reactions of 2-methyl-4-phenylthiosemicarbazide (**4a**) with ethyl orthoformate in boiling xylene led to the formation of 2-methyl-4-phenyl-1, 2, 4-triazolium-5-thiolate (**14**) and 1-methyl-4-phenyl-1, 2, 4-triazoline-5-thione (**15**). The formation of these mesoionic compounds resulted from the rearrangements of 2, 4-disubstituted thiosemicarbazides to 1, 4-derivatives, which helped to depict the structure quite convincingly [85].



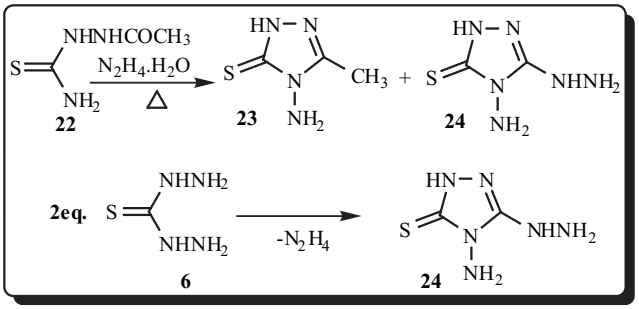
The reactions involving alkyl imidates also proceeded in a like-wise manner. Subsequent reactions of 4-phenyl thiosemicarbazide (**16**) with ethylphenylimidate hydrochloride at pH > 7 illustrated the formation of 3, 4-bis(phenyl)-Δ^2-1, 2, 4-triazoline-5-thione (**17**) [86]. Extension of this approach on substituted ethylimidate hydrochloride in the presence of hydrazine yielded 3-alkyl/aryl-Δ^2-1, 2, 4-triazoline-5-thiones [87, 88].



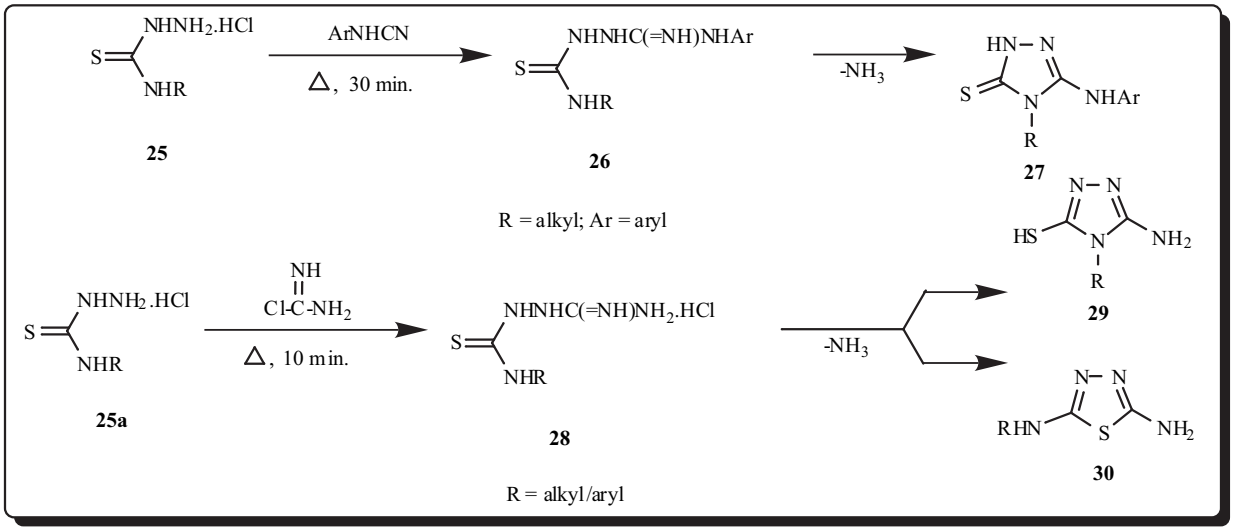
Reactants like triformylaminomethane are also capable of contributing a C- atom to an -N-C-N-N- skeleton and yield triazole ring [89]. In the reactions of thiosemicarbazides with phenyl isocyanide, it was shown that the substituents in the 4-position of the thiosemicarbazide play a major role. Thus 4-methyl thiosemicarbazide (**18**) reacts with phenyl isocyanide to yield only the 4-methyl-Δ^2-1, 2, 4-triazoline-5-thione (**19**) whereas 4-phenyl thiosemicarbazide (**16**) afforded a 2-phenylamino-1, 3, 4-thiadiazole derivative (**20**) in addition to 4-phenyl-Δ^2-1, 2, 4-triazoline-5-thione (**21**) [90].



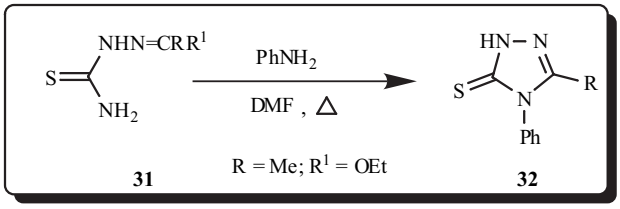
The cyclisation reactions of 1-acetyl thiosemicarbazide (**22**) and thiocarbohydrazide (**6**) in the presence of hydrazine hydrate were reported by Saikachi *et al*. In both the cases the products were found to be triazole derivatives. It was observed that in the former case hydrazine reacts with thiosemicarbazide (**22**) to afford 4-amino-3-methyl-Δ^2-1, 2, 4-triazoline-5-thione (**23**) and 4-amino-3-hydrazino-Δ^2-1, 2, 4-triazoline-5-thione (**24**) whereas in the second case two molecules of thiocarbohydrazide (**6**) reacted together to form 4-amino-3-hydrazino-Δ^2-1, 2, 4-triazoline-5-thione (**24**) [91].



On heating 4-alkyl thiosemicarbazides (**25**) with aryl cyanamides, 4-alkyl-3-arylamino-Δ^2-1, 2, 4-triazoline-5-thiones (**27**) were formed; the observation being supported by the assumption that the 1-(N-arylamidino)-4-alkyl thiosemicarbazide (**26**) initially formed underwent in situ cyclisation by the attack of the alkyl-substituted nitrogen on the arylamidino carbon with the elimination of ammonia [92]. On the other hand, the reaction of 4-alkyl/aryl thiosemicarbazides (**25a**) with cyanamide in the presence of an acid afforded 2-alkyl/arylamino-5-amino-1, 3, 4-thiadiazoles (**30**) and 3-amino-4-alkyl/aryl-5-mercapto-1, 2, 4-triazoles (**29**). The formation of both these products was explained by the nucleophilic displacement of ammonia from the intermediate (**28**) either by the attack of sulphur or the nitrogen atom carrying the alkyl/aryl substituent. The chloroamidine formed by the addition of HCl to cyanamide undergoes a nucleophilic displacement of chlorine by the attack of amino group of the hydrazino nitrogen of (**25a**) resulting in the formation of the intermediate 1-amidino-4-phenylthiosemicarbazide (**28**) [93].



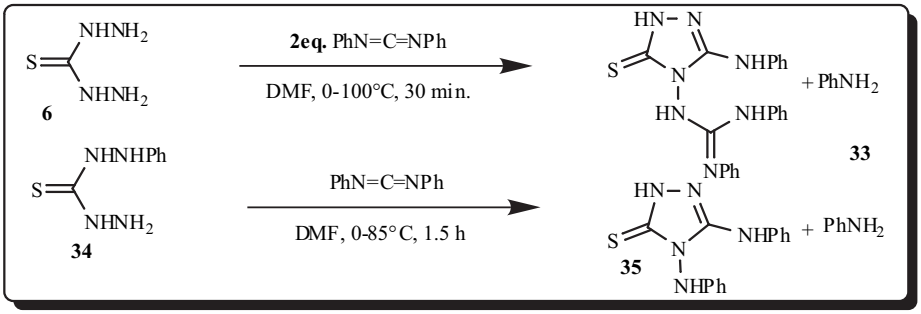
Alternatively an elegant route for the preparation of 3-methyl-4-phenyl-Δ^2-1, 2, 4-triazoline-5-thione (**32**) was obtained by refluxing a mixture of 1-(2-ethoxyacetyl) thiosemicarbazone (**31**) and aniline in DMF [94].



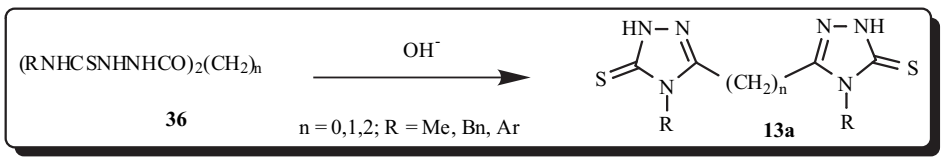
However the reactions of thiocarbohydrazide with diphenylcarbodiimide depend on the reaction conditions. Thus thiocarbohydrazide (**6**) is known to react with two equivalents of diphenylcarbodiimide in DMF and yield a 3-anilino-4-(N, N'-diphenylguanidino)-Δ^2-1, 2, 4-triazoline-5-thione (**33**) [95]. On the contrary, 1-phenyl thiocarbohydrazide (**34**) reacts with one equivalent of diphenylcarbodiimide in DMF and yields 3, 4-bis(phenylamino)-Δ^2-1, 2, 4-triazoline-5-thione (**35**) [96].

their fusion [112]. A comprehensive extension of this approach was illustrated in the cyclisation reaction of 1-(N-benzyloxycarbonylglycyl) thiosemicarbazide with sodium carbonate [113]. However, the cyclisation of 1, 4-disubstituted thiosemicarbazides in acidic medium has also been a concept of overwhelming interest. In this case the product was found to be a thiadiazole derivative instead of the triazole derivative [114, 115]. Successive developments witnessed the incorporation of microwave irradiation in alkaline medium [116]. Various bis(1, 2, 4-triazolyl) derivatives (**13a**) were prepared by the base catalysed cyclodehydration of bis(thiosemicarbazide) derivatives (**36**) [117-119]. A few 1, 2, 4-triazoline-5-thiones having long alkyl chains at 3-position were prepared by cyclodehydration of acyl thiosemicarbazide using ethanolic sodium hydroxide [120].

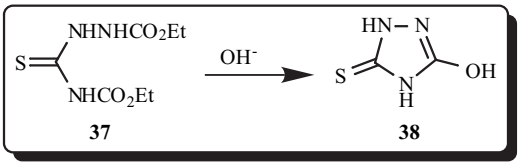
Herbst and Klingbeil [121] observed that the cyclisation of 1-acetyl-4-phenyl thiosemicarbazide in the presence of lead oxide results in the formation of 3-methyl-4-phenyl-Δ^2-1, 2, 4-triazoline-5-thione. Later, oxidative cyclisation of substituted aldehyde thiosemicarbazones induced by different



A perusal of literature reveals that the cyclisation of substituted thiosemicarbazides occurs when they are reacted with sodium carbonate [55, 97-99], alkoxides [100-102] or sodium hydroxide [11, 103-110], triethylamine [111] and by metallic salts also led to 1, 2, 4-triazoline derivatives. The method of cyclisation was determined by the structure of the substrate and the nature of the cyclizing agent [122-127].

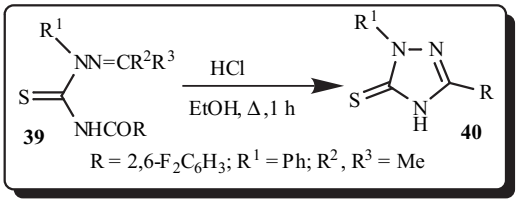


Another attempted synthesis of thiosemicarbazide by Ohshiro *et al.* [128] resulted in its in situ cyclisation to the triazolinethione. A similar reaction was reported by Elmoghayar *et al.* also [129]. Diacyl and diaroyl derivatives also are known to undergo cyclisation under alkaline condition [99, 101]. The ring closure of 4-benzoyl-1-carbamoyl/ethoxycarbonyl thiosemicarbazide in alkaline medium has been demonstrated independently by Sugii and Kurzer *et al.* [130-132]. In continuation, Kurzer *et al.* depicted the formation of 3-hydroxy-Δ^2-1, 2, 4-triazoline-5-thione (**38**) from 1, 4-diethoxycarbonyl thiosemicarbazide (**37**) under alkaline condition [133].



37 **38**

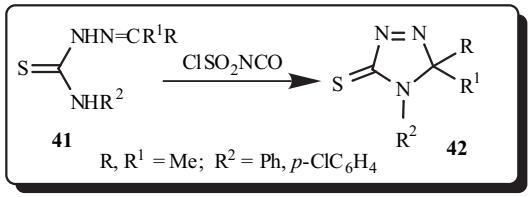
Thermal [134] and acetic anhydride [106, 135] catalysed cyclisations of 4-alkyl/aryl-1-oxamoyl/carbamoyl thiosemicarbazides are known to yield 1, 2, 4-triazoline-5-thione derivatives in reasonable yield. Cyclisations were also carried out with sulphur monochloride. Apparently its reaction with 1-benzylidene-4-methyl thiosemicarbazone at 115°C in acetic acid gave 4-methyl-3-phenyl-Δ^2-1, 2, 4-triazoline-5-thione [136]. Novel compounds like 3-(2, 6-difluorophenyl)-1-phenyl-Δ^2-1, 2, 4-triazoline-5-thione (**40**) having insecticidal properties were prepared by heating thiosemicarbazone (**39**) in ethanolic hydrochloric acid [137].



39 **40**

R = 2,6-$F_2C_6H_3$; R^1 = Ph; R^2, R^3 = Me

An exquisite exposition of the synthesis of 3, 3-disubstituted-4-substituted-Δ^1-1, 2, 4-triazoline-5-thiones (**42**) by the reaction of 4-aryl thiosemicarbazones (**41**) with chlorosulphonyl isocyanate provided a novel route with good yield [138].



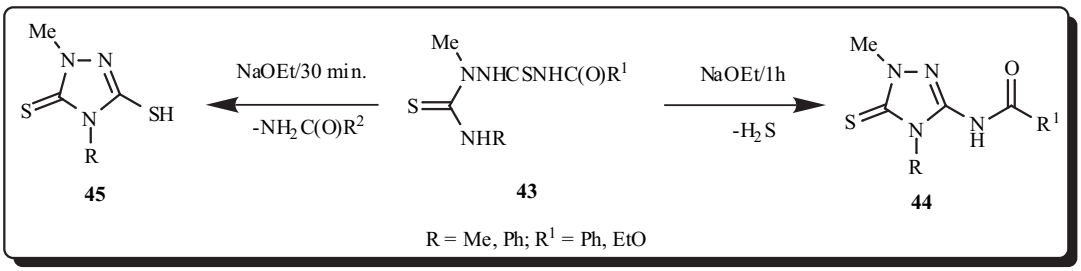
41 **42**

R, R^1 = Me; R^2 = Ph, *p*-ClC_6H_4

It was reported that addition of benzyl chloride to a refluxed mixture of 1-benzylidene thiocarbohydrazone and triethylamine in acetonitrile, afforded 4-amino-3-phenyl-Δ^2-1, 2, 4-triazoline-5-thione in good yield [139]. Furthermore, the thermal decomposition of 1-thiobenzoylthiocarbohydrazide afforded 4-amino-3-phenyl-Δ^2-1, 2, 4-triazoline-5-thiol as a by-product. It was isolated from the filtrate as its benzyl derivative [140].

Thiosemicarbazides offer the possibility of undergoing reactions like condensations, as the terminal nitrogen atom of the hydrazino fragment is more nucleophilic in nature. Accordingly, their condensation with isothiocyanates and isocyanates gave extended urea type chain compounds [141], which can be easily cyclised to form several heterocycles like 1, 3, 4-thiadiazoles, 1, 2, 4-triazoles and 1, 3, 5-triazines. Isothiocyanates are electrophilic compounds, which are able to react with different types of nucleophiles [142, 143] and this synthetic utility was detailed by Hartmann *et al.* [144]. Since thiobiureas are considered as 1, 4-disubstituted thiosemicarbazide derivatives, their cyclisations leading to 1, 2, 4-triazoles are also taken into account. Thus when phosgene reacts with 1, 6-diaryl-2, 5-dithiobiurea, 4-aryl-3-arylamino-Δ^2-1, 2, 4-triazoline-5-thione is formed [145]. Heating 1-phenyl-2, 5-dithiobiurea with hydrazine on the other hand results in a mixture of 3-amino-4-phenyl-Δ^2-1, 2, 4-triazoline-5-thione and 4-phenyl-1, 2, 4-triazolidine-3, 5-dithione [146]. Guha [147], who investigated the action of acetic anhydride on various 1-alkyl/aryl-2, 5-dithiobiureas, observed that the product formed in each case was 3, 4-diacetyl-2, 5-diimino-1, 3, 4-thiadiazole. Moreover, the cyclisation [148] and the phase transfer catalysed cyclisation [149] of 1-acyl dithiobiurea resulted in the formation of 1, 2, 4-triazole, 1, 3, 4-thiadiazole [148] and 1, 2, 4-triazoline-5-thione derivatives [149]. However, the reaction of these acyl dithiobiureas (**43**) with sodium ethoxide afforded 3-mercapto-1-methyl-4-alkyl/aryl-Δ^2-1, 2, 4-triazoline-5-thione (**45**) and 1-methyl-3-substituted-4-alkyl/aryl-Δ^2-1, 2, 4-triazoline-5-thione (**44**) derivatives. The formation of the products depends upon the reaction conditions employed [150].

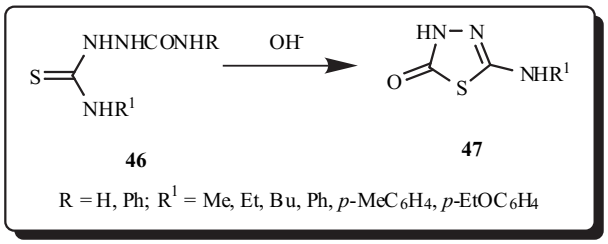
The reaction conditions accounted for the product selectivity in the cyclisation reactions of thiobiureas. Unsubstituted 2, 5-dithiobiurea on digestion with alcoholic alkali gave a triazoline-5-thione derivative [151, 152]. When 1-anilino-6-phenyl-2, 5-dithiobiurea was digested with alcoholic alkali, 2-phenylamino-5-phenylhydrazino-1, 3, 4-thiadiazole and 2-phenylhydrazino-Δ^2-1, 3, 4-thiadiazoline-5-thione are reported to be formed [153]. In the presence of a base, cyclisation to a 1, 2, 4-triazoline-5-thione occurs [154]. Heating 1, 6-diaryl-2, 5-dithiobiureas above their melting points afforded 2, 5-bis(arylamino)-1, 3, 4-thiadiazoles by the elimination of hydrogen sulphide [155]. Even when 1, 6-diphenyl-2, 5-dithiobiurea was subjected to prolonged



45 **43** **44**

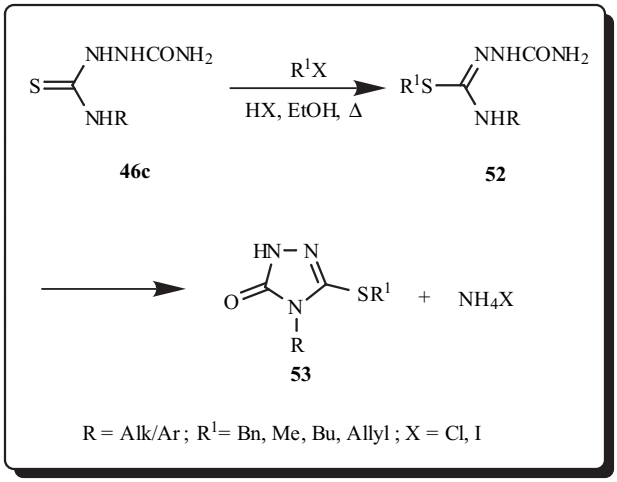
R = Me, Ph; R^1 = Ph, EtO

heating in ethanol it is known to yield 2, 5-diphenylamino-1, 3, 4-thiadiazole [156]. Similar result was reported in the case of its 1, 6-dialkyl counterpart also [157]. Thermal cyclisation of 1-aryl-2, 5-dithiobiureas on the other hand is reported to yield 3-amino-4-aryl-Δ^2-1, 2, 4-triazoline-5-thiones [158]. It has been observed that alkali catalysed thermal cyclisation of 1- and 1, 6-disubstituted-2-thiobiureas (**46**) resulted in the exclusive formation of 2-alkyl/arylamino-Δ^2-1, 3, 4-thiadiazolin-5-ones (**47**) [159].



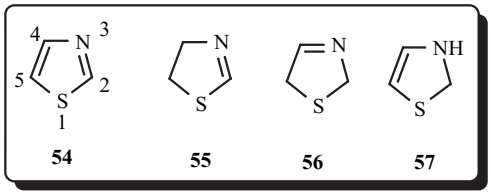
Noticeably N-substituted-2, 5-dithiobiureas in their alkali catalysed thermal cyclisation showed discrepant behaviour. The product formed has been found to depend mainly on the electronic and steric effects and the position of the substituents [155, 159-162]. The reaction of phosphorous oxychloride with thiobiurea (**48**) has also been reported by Gehlen [163]. It is found to effect cyclisation and produce 2, 5-diamino-1, 3, 4-thiadiazole (**49**). Guha and Chakraborty reported that 1, 6-diphenyl-2-thiobiurea (**46a**) on heating with acetic anhydride, 3-phenylamino-4-phenyl-Δ^2-1, 2, 4-triazoline-5-thione (**50**) is formed. In contrast, when 1-*p*-tolyl-2-thiobiurea (**46b**) was heated with acetic anhydride both 2-*p*-tolylamino-Δ^2-1, 3, 4-thiadiazolin-5-one (**47a**) and 3-*p*-tolylimino-2-acetyl-1, 2, 4-triazolidine-5-thione (**51**) were formed [135].

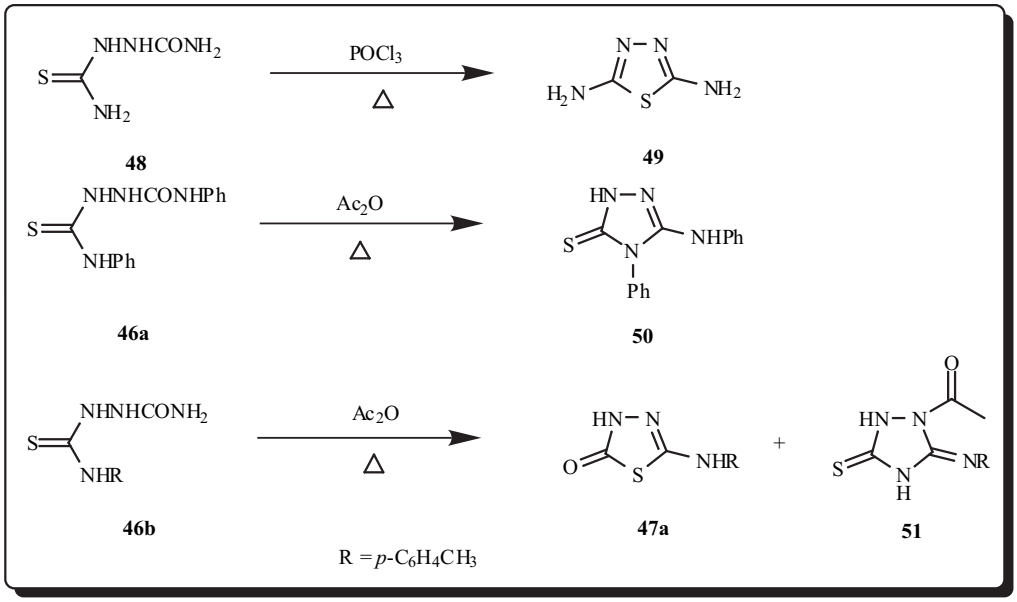
Alkylation of 1- and 1, 6-disubstituted-2, 5-dithiobiureas in neutral and alkaline media had been examined in our laboratory and it was found that the product obtained in neutral medium was a 1, 3, 4-thiadiazole derivative whereas in alkaline medium the product was a 1, 2, 4-triazole derivative [164, 165]. An overview of all the above reported reactions evoked keen interest in us to explore the chemistry of 1- and 1, 6-disubstituted-2-thiobiureas (**46c**). Cyclisation of these with alkyl halides in acidic medium confirmed the mechanistic pathway that the reaction proceeds through an intermediate formation of 1-alkyl/aryl-2-S-alkylisothiobiurea derivatives (**52**) since it contains only one enolisable thione group. Here the product was found to be a 4-alkyl/aryl-3-alkylthio-Δ^2-1, 2, 4-triazolin-5-one (**53**) [166, 167].

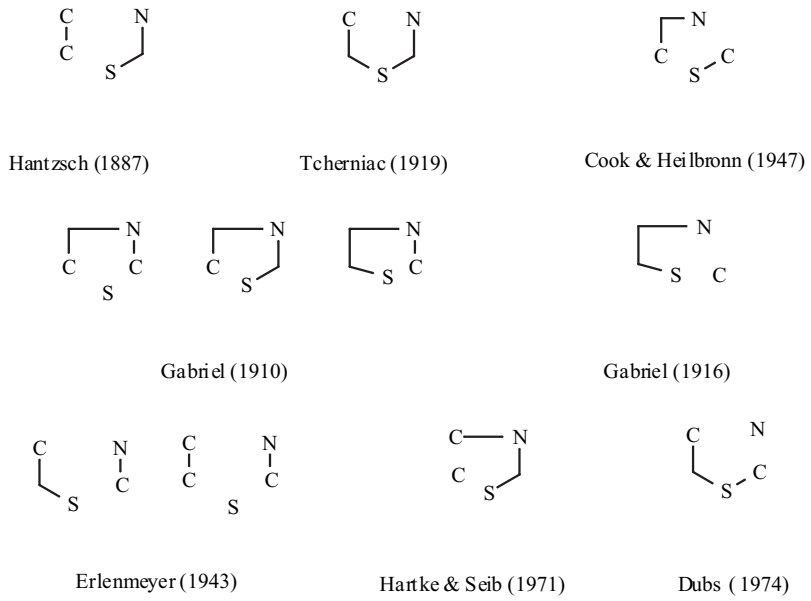


B. THIAZOLES

Thiazole ring was first described by Hantzsch and Weber [28] as "the pyridine of the thiophene series". The correct numbering is that given by The Ring Index [168] and corresponds to (**54**). As previously mentioned, the position of the double bond is indicated by Δ^2 (**55**), Δ^3 (**56**) and Δ^4 (**57**).







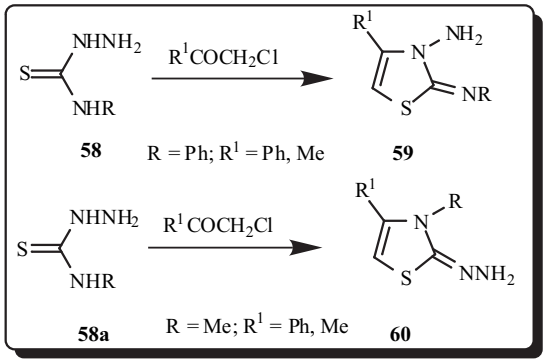
Scheme 2.

Synthesis

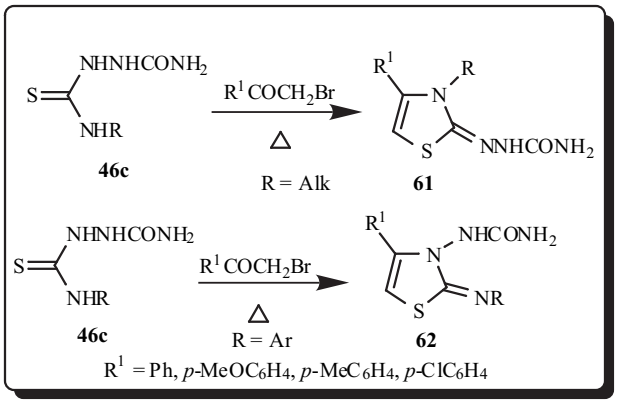
Several methods available for the thiazole synthesis are depicted in Scheme **2**.

Discovered a century ago, Hantzsch thiazole synthesis using α-haloketones and thiourea derivatives is still in vogue [169]. α-Haloketones have proved to be valuable reagents and literature continuously reports the progress in their utilisation for the synthesis of a variety of target molecules [170-174]. Generally these compounds were prepared by direct side chain halogenation of corresponding ketones [175]. Later in order to encounter the difficulties of halogenation, new synthetic protocols using inorganic supports in solvent free condition [176], sodium halide in the presence of oxone® [177] were explored.

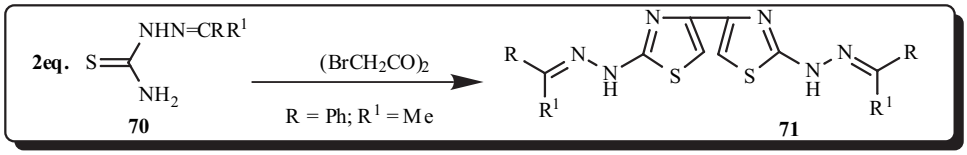
The significance of Hantzsch's methodology inspired chemists in recent years to implement its synthetic utility to thiosemicarbazides as well. Thus reaction of thiosemicarbazide with chloroacetone was found to result in the formation of 2-hydrazinothiazole [178]. Similar reaction of 4-substituted thiosemicarbazides is found to be governed by the nature of the substituent at the 4-position. Thus 4-phenyl thiosemicarbazide (**58**) reacts with α-haloketones and yield 3-amino-2-phenylimino-4-substituted-Δ^4-thiazolines (**59**), whereas 4-methyl thiosemicarbazide (**58a**) afforded 2-hydrazono-4-substituted-3-methyl-Δ^4-thiazolines (**60**). An extension of this approach was reported by Rafat *et al.* [8].



In this connection, it was worthwhile to examine the cyclocondensation of 1-alkyl/aryl-2-thiobiureas with α-haloketones. Our investigations in this direction led to the synthesis of 3-alkyl-4-aryl-2-semicarbazono-Δ^4-thiazolines (**61**) and 4-aryl-2-arylimino-3-ureido-Δ^4-thiazolines (**62**) from 2-thiobiureas (**46c**) in a single step, thereby confirming the fact that the reaction is governed by the nature of the substituent on the nitrogen atom at position-1 of 1-alkyl/aryl-2-thiobiureas [179, 180].



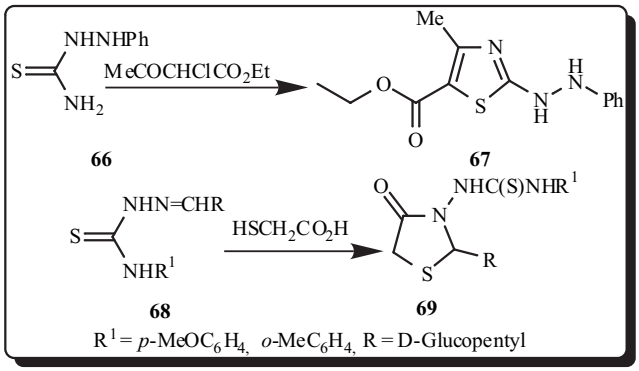
It has been reported that thiosemicarbazide derivatives undergo condensation with fluorinated phenacyl bromide to afford thiazole derivatives [2]. New and efficient procedures for thiazole synthesis were reported by Hassan *et al.* [181]. However, the reactions of haloketones with 2, 4- and 4-substituted thiosemicarbazides are known to proceed through different modes of heterocyclisation on varying the chain length between the carbonyl group and the halogen atom [182-185]. Similar results were reported with their 2, 4-disubstituted counterparts also [186]. The formation of conjugated thiazoles was reported from thiosemicarbazide and thiosemicarbazones by their reactions with α-haloketones [187, 188].



Reaction of 4-aryl thiosemicarbazide (**58**) with carbon disulfide in alkaline medium afforded a salt (**63**) which underwent cyclisation with α-halogenated compounds resulting in the formation of 1-phenyl-3-(4-phenyl-2-thioxothiazol-3-yl)thiourea (**64**) and 1-(5-oxo-2-thioxothiazolidin-3-yl)-3-phenylthiourea (**65**) [189].

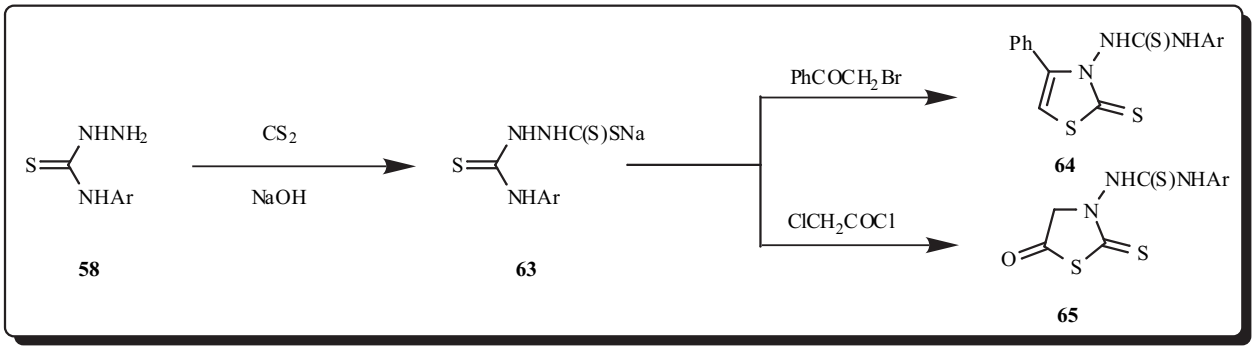
Just as in the case of thiosemicarbazides, thiosemicarbazones also are known to yield thiazole derivatives on reacting with α-haloketones [190-192]. It has been reported that 2, 4-disubstituted thiosemicarbazides react with α-bromoacetophenone to yield 1, 3, 4-thiadiazine derivatives instead of the thiazole derivatives. On the other hand, with *β*-chloropropiophenone the product was found to be a thiadiazole derivative [186].

α-Haloesters also behave in an identical manner. 5-Carbethoxy-4-methyl-2-hydrazinothiazole is reported to be formed on reacting thiosemicarbazide with ethyl α-chloroacetoacetate at 50-70°C [193]. Similar treatment of thiosemicarbazide with ethyl α-bromoacetoacetate and subsequent saponification yields 2-(1, 2-disubstituted) hydrazino-4-methylthiazole-5-carboxylic acid [194]. With 1-phenyl thiosemicarbazide (**66**), 2-phenylhydrazino-4-methyl-5-carbethoxythiazole (**67**) is reported to be formed [195].



It was observed that on heating thiosemicarbazide with α-chloroacetic acid, cyclocondensation occurs yielding a thiazolidine derivative [196]. However, when 4-phenyl thiosemicarbazide is treated with chloroacetic acid 2-hydrazono-3-phenylthiazolidin-4-one is reported to be formed [197]. The influence of substituents at the 4-position was once again revealed in these reactions. Having demonstrated the role of α-haloacids, Yadav *et al.* envisaged the effects of thioglycollic acid on 4-aryl thiosemicarbazones (**68**) to furnish 3-(3-arylthioureido)-2-(D-glucopentyl)-4-thiazolidinones (**69**) [198].

It has been reported that α-haloketoester on reaction with thiosemicarbazide affords thiadiazine or thiazole or the corresponding carboxylic acid depending upon the acidity of the medium [199]. With α, β-dichloroether, a thiazole derivative was found to be formed [195]. Just as thiosemicarbazides, the nature of the substituent at 4-position play a critical role in the reaction of thiosemicarbazones with chloroacetylchloride [200]. A hydrazino bisthiazolyl derivative (**71**) is obtained by the reaction of thiosemicarbazone (**70**) with 1, 4-dibromodiacetyl. Similar reaction of 4-phenyl thiosemicarbazide with 1, 4-dibromodiacetyl afforded a 1, 3, 4-thiadiazine derivative [201].



CONCLUSION

Among the several heterocycles studied, triazoles and thiazoles have drawn considerable attention due to their biological importance. Even though thiosemicarbazides had been extensively employed for the synthesis of these heterocyclic ring systems; its chemistry still remains significant because of its easiness to undergo cyclocondensation reactions with reagents susceptible to nucleophilic attack. The versatility of thiosemicarbazides are highlighted in the preparation of extended urea type chain compounds by their condensation with isothiocyanates and isocyanates. These urea derivatives serve as the starting materials for the synthesis of triazoles and thiazoles. The course of cyclisation reaction was found to depend upon the pH of the medium and the nature of the substituents on the terminal nitrogen atom. Their ability to undergo S-alkylation is of substantial value in the preparation of these heterocyclic ring systems.

ABBREVIATIONS

Alk = Alkyl

Ar = Aryl

Bn = Benzyl

Bu = Butyl

DMF = Dimethylformamide

Et = Ethyl

EtO = Ethoxy

Me = Methyl

Ph = Phenyl

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