REACTIONS OF HYDRAZIDOYL HALIDES WITH SULFUR COMPOUNDS

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SYMBOLS AND ABBREVIATIONS USED

Ph = C_6H_5	TEA = Triethylamine	s = second
X = Cl, Br	Nu = Nucleophile	min = minute

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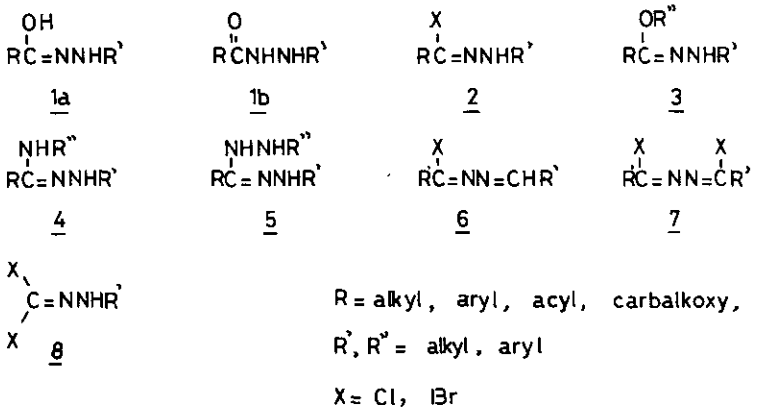
I. INTRODUCTION

Hydrazidic acids 1a are the enol tautomers of carboxylic acid hydrazides 1b. Although the free acids are not known, their halides usually referred to as hydrazidoyl halides 2; their esters, alkyl and aryl hydrazidates 3; their amides, the amidrazones 4; and their hydrazides, the hydrazidines 5 are well known for over 45 years.



The chemistry of hydrazidoyl halides 2 together with the related halides 6 - 8 has attracted the interest of many investigators within the past 75 years because they prove to be versatile intermediates in many organic syntheses. The aim of the present review is to survey only the reactions of these halides with sulfur compounds in order to provide guide-lines for future investigators. There seems no comprehensive review on this subject although several summaries have been published.[1-3] No attempt will be made here to discuss in detail the mechanisms of the reactions reported; the brief account which follows seems to be sufficient. This is because, this review is intended to consider the hydrazidoyl halides from a practical point of view and to deal with the general aspects of their reactions and the reader should refer to original references for further details.
The literature was surveyed up to the end of 1982. Some additional material originating from the author's laboratory and presently in the course of publication has also been included.

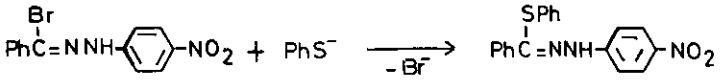
II. GENERAL REMARKS ON REACTION MECHANISMS

The reactions of hydrazidoyl halides with sulfur compounds outlined in this review fall under one of the following two headings:

1. Displacement reactions, and

2. 1,3-Cycloaddition reactions

The *displacement process* may be subdivided into (a) intermolecular (Eq. 1) and (b) intramolecular (Eq. 2)



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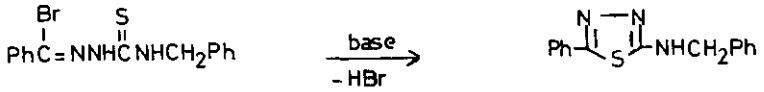
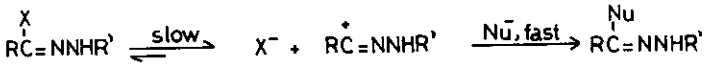


(2)

Furthermore, the displacement of the halogen atom from hydrazidoyl halides can proceed either by unimolecular (Eq. 3) or bimolecular (Eq. 4) mechanisms by analogy with acyl halides.[2] Evidence for the involvement of the SN1 and SN2 mechanisms, which has been reported, includes Hammett parameters, salt and common ion effects, and solvent variation studies.[4,5] Regardless the mechanism operating, the displacement reactions of hydrazidoyl halides have proved to be useful and convenient routes to a wide variety of chemical systems.



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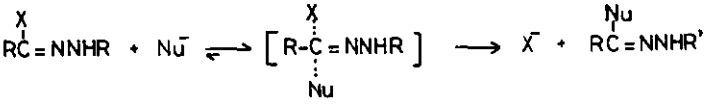

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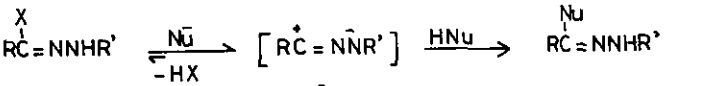

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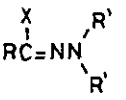
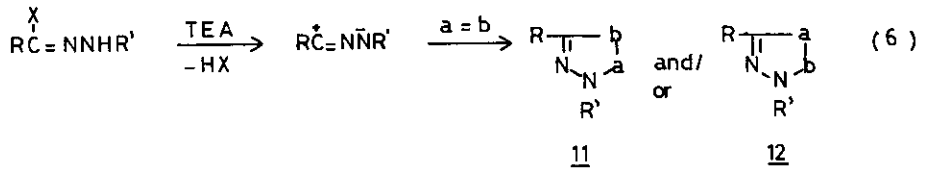


10

Another alternative pathway for displacement reactions involves the dehydrohalogenation of the hydrazidoyl halide to give the corresponding nitrile imine intermediate 9 which then adds to nucleophile to give the corresponding substitution product (Eq. 5). This elimination-addition sequence is excluded for the reactions of N,N-disubstituted hydrazidoyl halides of type 6, 7 and 10 as these halides cannot form nitrile imine intermediates.

The 1,3-cycloaddition reactions of hydrazidoyl halides lead in most cases to 5-membered heterocyclic systems. As already mentioned, the N-monosubstituted hydrazidoyl halides 2 generate the corresponding nitrile imines 9 upon treatment with a base. These dipolar ions cannot be isolated, however, if a dipolarophile is present in the reaction mixture, it will add to it and give the corresponding cycloadducts 11 and/or 12 (Eq. 6).



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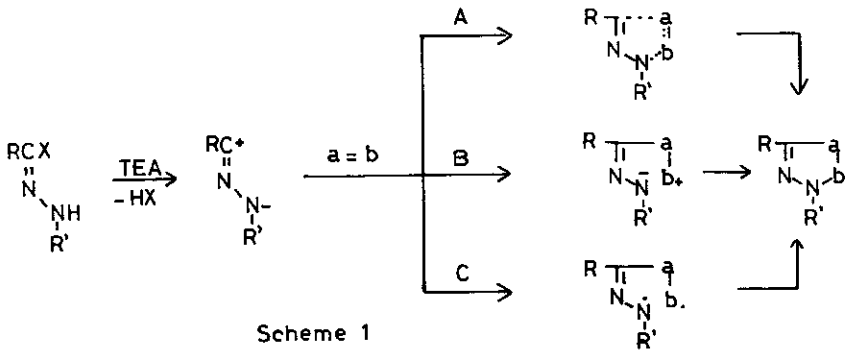


Scheme 1

As shown in equation 6, the cycloaddition of an unsaturated compound a - b to nitrile imine involves the formation of two sigma bonds (namely C-a and N-b or C-b and N-a) at the expense of two pi bonds. Theoretically there are three possible pathways for such a process (Scheme 1). These are :

1. One step concerted mechanism (route A) involving simultaneous formation of both new sigma bonds.

2. Two step mechanism (route B) involving a zwitterionic intermediate.

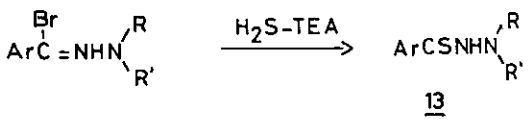
3. Two step mechanism (route C) involving a diradical intermediate.

The concerted mechanism (route A) was first postulated by Huisgen in 1960 on the basis of many experimental tests.[6-8] It has been accepted by many investigators.[9,10] It is an orbital symmetry allowed ($\pi^4 - \pi^2$) cycloaddition wherein the nitrile imine with its allyl type molecular orbitals functions as π^4 reactant and the dipolarophile as π^2 reactant.[9] The molecular orbital correlation diagram of 1,3-dipolar cycloaddition reaction bears a more than superfacial resemblance to that of Diels-Alder reaction.[11,12] Another description attributes the concertedness to a Hückel aromatic type molecular orbital of the transition state.[13-16]
Firestone proposed the two step diradical mechanism (route C) in 1968.[17] This hypothesis was also refurbished on the basis of bond energy consideration[18] and orientation phenomena[19] so that it is not considered as a viable alternative to the concerted mechanism.
The unlikelihood of the two step mechanism involving dipolar ion intermediate (route B) has been evidenced by Huisgen.[7,20]
Details of these mechanisms may be sought elsewhere[21] since further discussion is inappropriate for the purpose of this review.

III. REACTIONS

1. Reaction with hydrogen sulfide and its salts

Hydrazidoyl halides react with hydrogen sulfide in the presence of triethylamine and yield the corresponding thiohydrazides. For example, addition of one equivalent of TEA to N,N-disubstituted hydrazidoyl bromides in chloroform followed by treatment with a solution of H_2S-TEA in the same solvent yielded after acidification the thiohydrazides 13 in 15-80% yields (Eq. 7).[22]



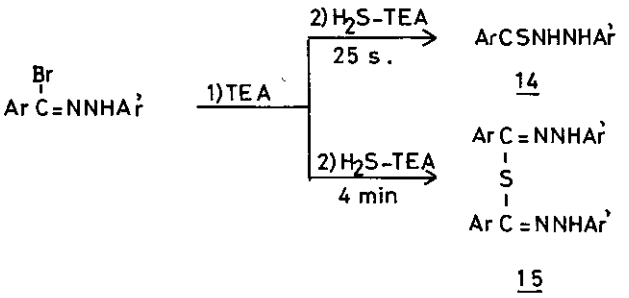
13

(7)

(R and R' usually alkyl)

Similar treatment of N-monosubstituted hydrazidoyl halides was reported to give N-aryl-N'-thioaroylhydrazines 14 and/or hydrazidoyl sulfides 15 depending on the reaction conditions.[23] For example, the thiohydrazide 14 was obtained in 82% yield when the interval between the addition of the TEA and H_2S-TEA solutions is 25 s, whereas when this interval was extended to 4 min, the product isolated was the

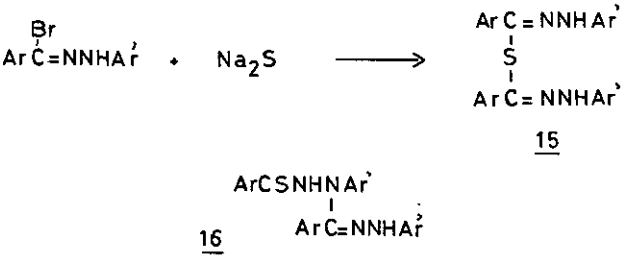
hydrazidoyl sulfide 15 (93%) (Eq. 8). Mixtures of 14 and 15 were obtained after intermediate intervals. On the other hand, treatment of hydrazidoyl halides with H_2S-TEA solution followed by TEA was reported to give 14 in 92% yield.



(8)

15

Barnish and Gibson reported that treatment of hydrazidoyl bromides with sodium sulfide monohydrate in acetonitrile gives the corresponding sulfides 15 in 40-50% yield (Eq. 9).[24,35] X-Ray crystallographic studies of one of the hydrazidoyl sulfides prepared (15, Ar = C_6H_5, Ar' = 2,6-$Br_2C_6H_3$) confirmed the symmetrical structure 15 and ruled out the isomeric unsymmetrical structure 16 formally derivable by rearrangement of 15.[25]



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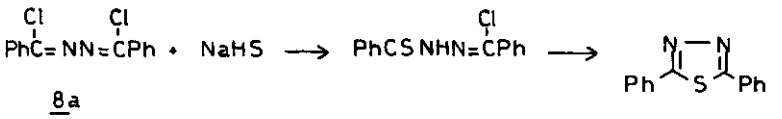
16

Also, it was reported that treatment of the dichloride 8a with sodium hydrosulfide in refluxing ethanol rapidly affords 2,5-diphenyl-1,3,4-thiadiazole in excellent yield (84%).[111]

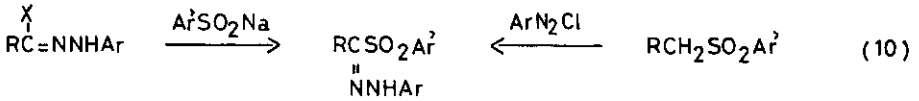


8a

2. Reaction with sodium arenesulfinate

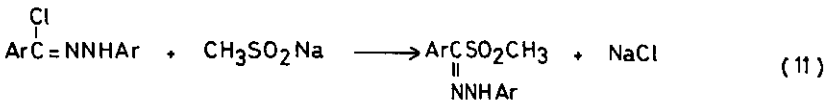
The reaction of hydrazidoyl halides with sodium arenesulfinate in ethanol was reported to give arylhydrazone derivatives of α-ketosulfones 17 (Eq. 10).[26-30] The structures of some of these products were confirmed by their alternate synthesis from coupling of active methylene sulfones with diazotized arylamines in ethanol in the presence of sodium acetate (Eq. 10).[26]

Sodium methanesulfinate reacts similarly with hydrazidoyl chlorides and gives the corresponding arylhydrazones of methanesulfonyl ketones 18 (Eq. 11).[30]



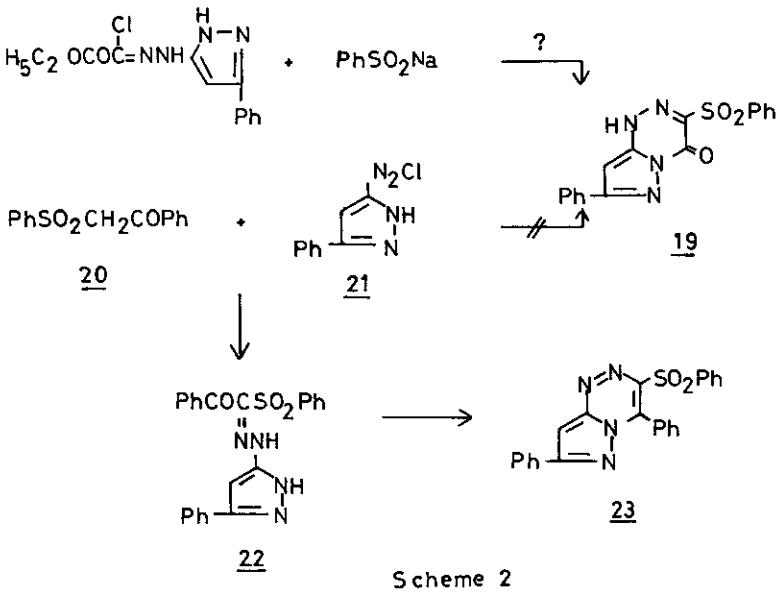
17

(R usually acyl, carbalkoxy, carbamoyl)



18

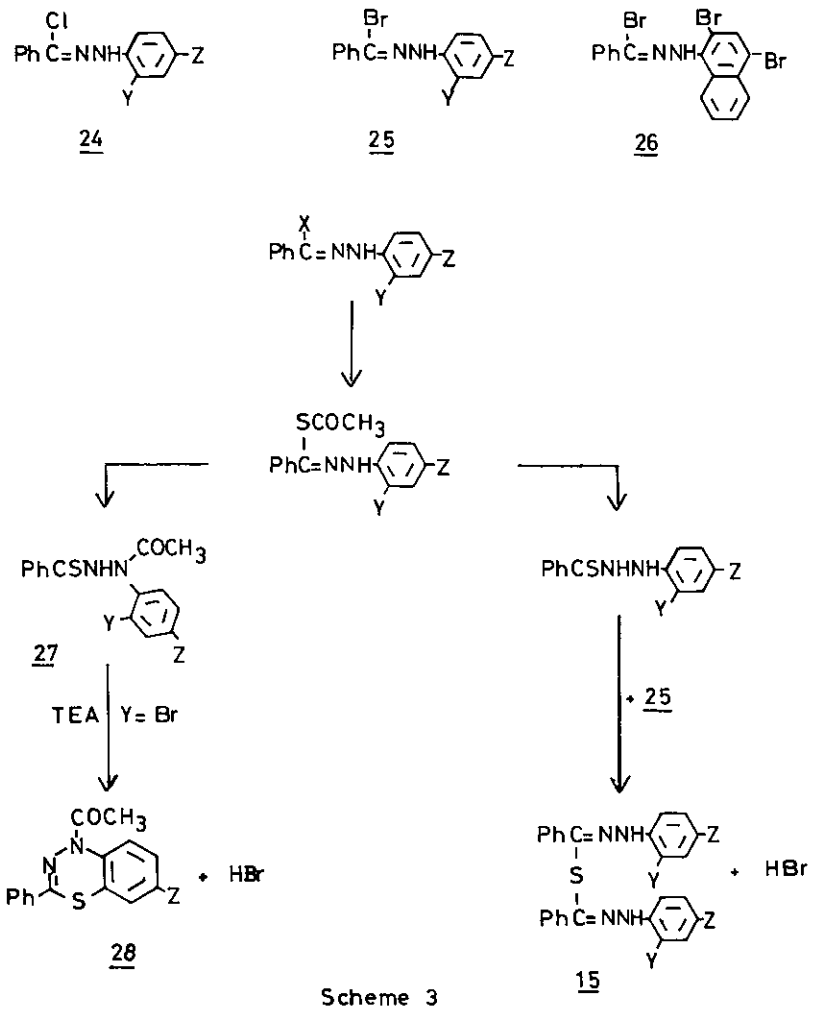
Recently an ambiguous product was reported to be obtained from the reaction of N-[5-(3-phenyl)pyrazolyl]hydrazidoyl chloride with sodium benzenesulfinate in ethanol at room temperature.[31] It was claimed that this reaction gave the pyrazolotriazine derivative 19 and that the same product was also obtained in 75% yield via coupling of ω-benzenesulfonylacetophenone 20 with diazotized 3-phenyl-5-aminopyrazole 21 (Scheme 2). As coupling of 20 with 21 would yield 22 which upon cyclization (by loss of elements of water) would yield 23,[32] the identity of the product 19 has to be reinvestigated.



Scheme 2

3. Reaction with potassium thioacetate

The reaction of hydrazidoyl halides 24-26 (Y = halogen atom) with thioacetate anion has been extensively studied by Gibson and coworkers.[24,25,33-35] This reaction was reported to give, according to reaction conditions and nature of substituents on the N-aryl moiety, one or more of the following: (i) the N-acetyl-N-aryl-N'-thiobenzoylhydrazine 27, (ii) the bis-hydrazidoyl sulfide 15, (iii) 4-acetyl-7-Z-phenyl-4H-1,3,4-benzothiadiazine 28, by a process involving displacement of the ortho halogen atom Y (Scheme 3). For example, treatment of hydrazidoyl halides 24 (Y = Z = Br) and 25 (Y = Z = Br) with potassium thioacetate in acetonitrile at room temperature afforded 27 (Y = Z = Br) in good yield together with some of 15 (Y = Z = Br). Compounds of type 27 were converted into the corresponding benzothiadiazines 28 (Z = Br) when refluxed with TEA in acetonitrile.[25]



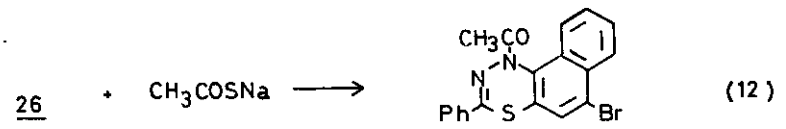
Scheme 3

Similar treatment of 24 (Y = Z = Br) and 25 (Y = Z = Br) with potassium thioacetate in boiling acetonitrile gave 28 (Z = Br) and 15 (Y = Z = Br) in virtually the same yields, indicating no significant difference between the labilities of bromine and chlorine atoms in the starting halide.

The ease of displacement of the ortho halogen atom Y in the ring closure leading

to 28 was found to be in the order F) Br= I) Cl. For example, compound 25 (Y = F, Z = Br) was found to undergo conversion into the corresponding 28 (Z = Br) in good yield, by contrast 25 (Y = Cl, Z = Br) afforded the hydrazidoyl sulfide 15 (Y = Cl, Z = Br) with no detectable amount of 28 (Z = Br). Also, compound 24 (Y = F, Z = I) gives the thiadiazine 28 (Z = I) in 67% yield, whereas compound 24 (Y = Cl, Z = Br) gives only the sulfide 15 (Y = Cl, Z = Br). The yield of 28 (Z = I) from 24 (Y = Br, Z = I) was moderate (38%) and that from 24 (Y = Z = I) was rather small (14%).[34]

The reported results also indicate that the nature of the Z substituent influences the formation of 28 from 24 or 25. For example, treatment of 25 (Y = Br, Z = CN) and 24 (Y = Br, Z = CF_3) with potassium thioacetate in boiling acetonitrile gave the corresponding benzothiadiazine derivatives 28 (Z = CN) and 28 (Z = CF_3) in 7% and 12% yields respectively.[35] Similar treatment of 25 (Y = Z = F) and 24 (Y = F, Z = H) gave the thiadiazines 28 (Z = F), and 28 (Z = H) in 67% and 13% yields, respectively. Compound 24 (Y = Br, Z = CH_3) afforded the sulfide 15 (Y = Br, Z = CH_3) in 11% yield and no thiadiazine. Also, from the hydrazidoyl halides 24 (Y = I, Z = Br) and 24 (Y = I, Z = Cl), 24 (Y = I, Z = F) the yields of 28 (Z = Br), 28 (Z = Cl) and 28 (Z = F) were 25, 31, and 40% yield respectively. The hydrazidoyl bromide 26 gave naphthothiadiazine 29 in 76% yield upon treatment with potassium thioacetate in boiling acetonitrile (Eq. 12). This presumably reflects the stabilization of the transition state, in which one of the naphthalene rings remains benzenoid, relative to the cases of ring closure to form benzothiadiazines 28 (Eq. 10).[35]



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29

4. Reaction with thioalcohols and thiophenols

Treatment of hydrazidoyl halides with thiophenols in ethanol in the presence of sodium ethoxide or in benzene in the presence of TEA was reported to give the corresponding aryl thiohydrazidates 30 (Eq. 13).[36] Thioalcohols react similarly with hydrazidoyl halides and give the corresponding alkyl thiohydrazidates 31 (Eq. 14).[30]

$$Ar'SH + RC(X)=NNHAr \xrightarrow{\text{base}} RC(SAr')=NNHAr \quad (13)$$

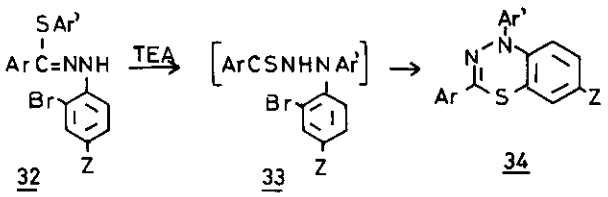
30

$$R'SH + RC(X)=NNHAr \xrightarrow{\text{base}} RC(SR')=NNHAr \quad (14)$$

31

R' = alkyl

The thiohydrazidate 32 with ortho bromine atom on the N-aryl moiety was reported to give the thiadiazine derivative 34 upon heating with TEA in ethanol presumably through the thiohydrazide 33 (Eq. 15).[37]



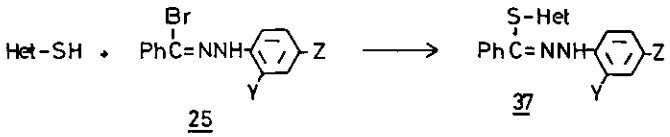
32 33 34 (15)

$$RC(OAr')=NNHAr \xrightarrow{\text{heat}} RCONHN(Ar')Ar \quad (16)$$

35 36

The conversion of 32 into 34 can be effected also with sodium hydroxide and TEA in dimethylformamide at reflux.[37,38] These reactions of aryl thiohydrazidates differ from the rearrangement of aryl hydrazidates 35 which were reported to rearrange into N,N-diarylhydrazides 36 (Eq. 16).[36,39-44] and resemble rather those of hydrazidoyl halides with thioacetate anion (see the following section), in which a hydrazidoyl thioacetate, presumed as intermediate, undergoes rearrangement and cyclization by displacement of the transiently activated o-halogen atom to a 4-acetyl-4H-1,3,4-benzothiadiazine 28.[24] As there was no definite evidence for the involvement of 33 in the conversion of 32 into 34, it was assumed that 33 is consumed as it is formed.[37]

Elliott et al. have also prepared a group of heteroaryl thiohydrazidates 37a-h through the reaction of 25 with either the appropriate thiol in ethanol-TEA mixture or the sodium salt of the thiol (Eq. 17).[37]



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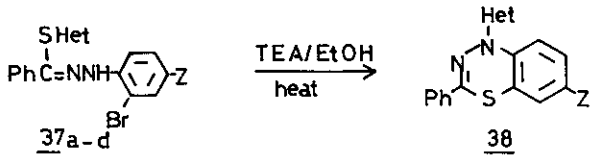

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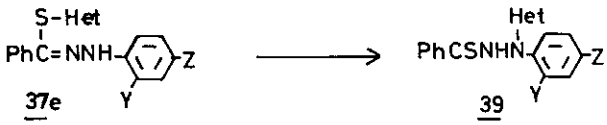
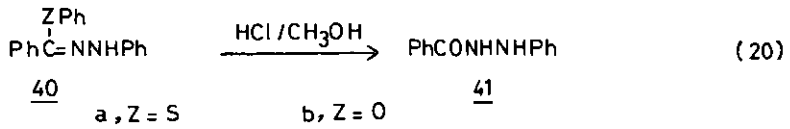


(19)

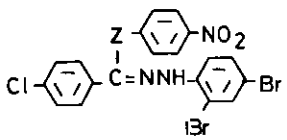
37a, Het = 2-quinoxalyl
37b, Het = 5-nitro-2-pyridyl
37c, Het = 4-methyl-2-quinolyl
37d, Het = 2-benzothiazolyl
37e, Het = 4,6-dimethyl-2-pyrimidyl
37f, Het = 1-phenyl-5-tetrazolyl
37g, Het = 2-pyridyl
37h, Het = 2-benzoxazolyl

When such heteroaryl thiohydrazidates were treated with ethanol-TEA mixture at reflux, the corresponding thiadiazines 38 were obtained in the cases of 37a-d (Eq. 18).[37] Under these conditions the ester 37e rearranged into the thiohydrazide 39 (Eq. 19), whereas 37f decomposed extensively. No reaction was observed with 37g and 37h.

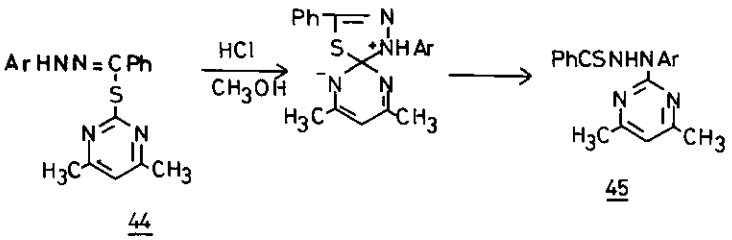
The thiohydrazidate 40a was reported to undergo hydrolysis to hydrazide 41a in concentrated hydrochloric acid-methanol[45] and the analogous hydrazidate 40b behaves similarly (Eq. 20).[36] The hydrazidates 42 and 43 were stable, however, in concentrated hydrochloric acid-benzene mixture.[37] When the pyrimidyl thiohydrazidate ester 44 (Ar = p-BrC_6H_4) was so treated, the thiohydrazide 45 (Ar = p-BrC_6H_4) was obtained in 55% yield. This was the only thiohydrazidate ⟶ thiohydrazide rearrangement which has been reported so far.



40 a, Z = S b, Z = O 41 (20)

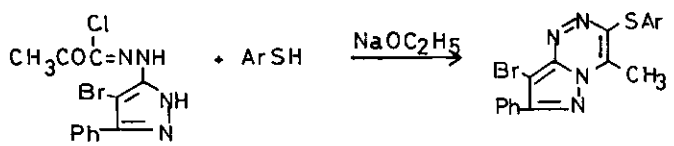


42, Z = S
43, Z = O

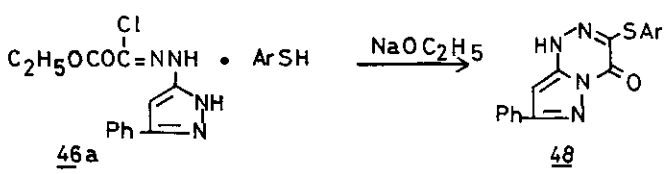


44 45 (21)

N-Heteroarylhydrazidoyl chlorides 46 and 46a were reported to react with sodium thiophenolates in ethanol to give products identified as pyrazolo[1,5-c]-as-triazine derivatives 47 and 48 respectively (Eqs. ?? and ?3).[31,46]

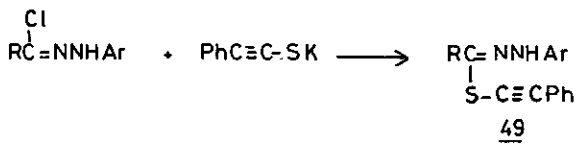


46 47 (22)



46a 48 (23)

Potassium 2-phenylethynethiolate reacts with N-arylhydrazidoyl chlorides in the absence of bases to give the corresponding 2-phenylethynyl-N-arylthiohydrazidates 49 in quantitative yields (Eq. 24).[47] When compounds 49 were treated with bases such as sodium hydroxide in methanol, intramolecular cyclization occurs readily with quantitative formation of the corresponding 4H-1,3,4-thiadiazine 50 (Eq. 25).



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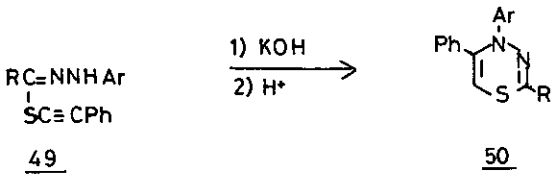
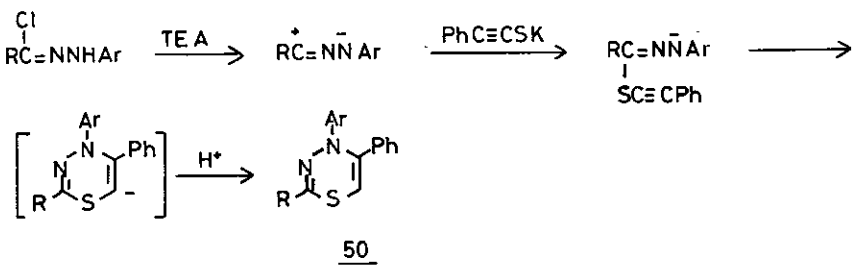


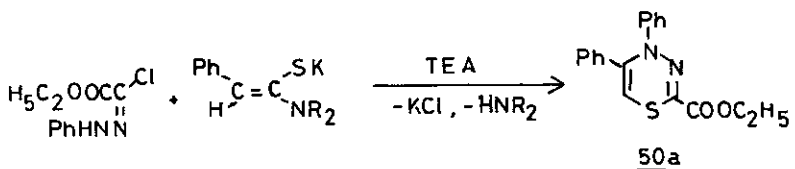
(25)

When the reaction between 2-phenylethynethiolate and hydrazidoyl chlorides was carried out in aprotic solvent in the presence of TEA, the [3 + 3] cycloadduct 50 was obtained in good yields. Attempts to cyclize 49 by heating it with TEA for several hours met with failure. These results were considered to indicate that 50 results from [3 + 3] cycloaddition of nitrile imine to 2-phenylethynethiolate and exclude the involvement of 49 (Eq. 26) as intermediate.

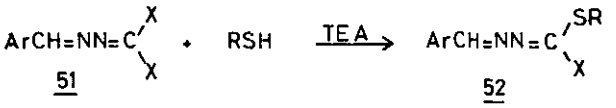


(26)

Also, it was reported that potassium 1-N,N-dialkylamino-2-phenylethenethiolates react with N-phenyl-C-carbethoxyhydrazidoyl chloride in the presence of TEA and give the thiadiazine 50a in 30-71% yield.[112]



Hydrazidoyl halides of type 51 react with thioalcohols and thiophenols in the presence of TEA and yield the corresponding substitution products 52 (Eq. 27).[48,49] Alternatively, the products 52 were found to be obtained by treating 51 with sodium thiolate. Compound 52 can react with thiophenols or thioalcohols and give the corresponding disulfides 53 (Eq. 28). The latter can be obtained directly from 51 by treating them with excess thiol in refluxing benzene in the presence of TEA.[48]



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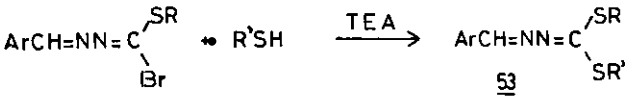
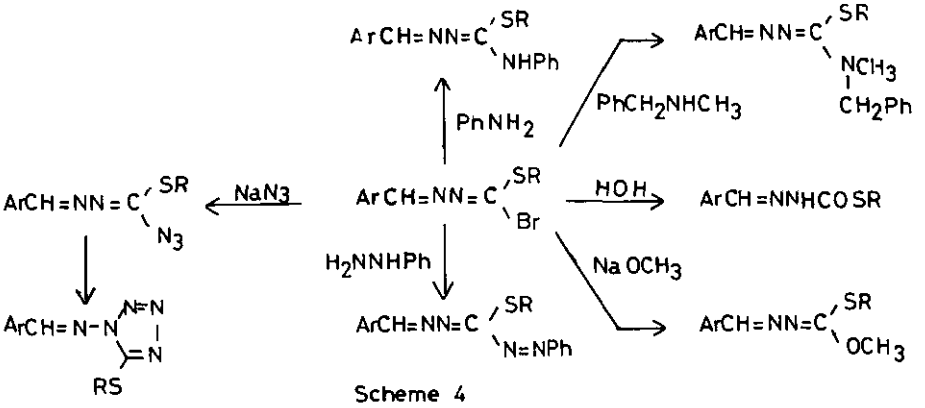


(28)

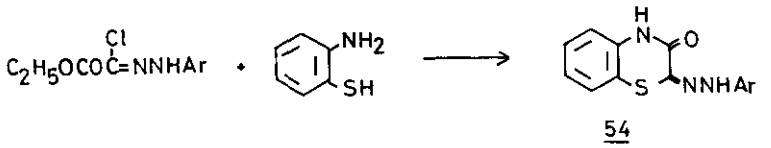
The halogen atom in 52 (X = Br) was reported to be readily displaced by nitrogen and oxygen nucleophiles too (Scheme 4).[48] The kinetics of hydrolysis of 52 (X = Br) and the effects of substituents in the Ar and R groups have been studied.



Scheme 4

5. Reaction with o-aminothiophenol

Ketohydrazidoyl halides react readily with o-aminothiophenol and yield benzo-1,4-thiazine derivatives. For example, when C-carbethoxyhydrazidoyl chlorides were refluxed with o-aminothiophenol in ethanol, they yield benzo-1,4-thiazine derivatives 54 (Eq. 29).[50] Similar reaction of C-acylhydrazidoyl halides with o-aminothiophenol yielded products that could be formulated as 55 or 56.[50,51]



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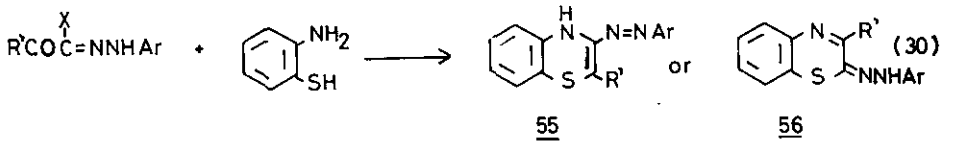
54



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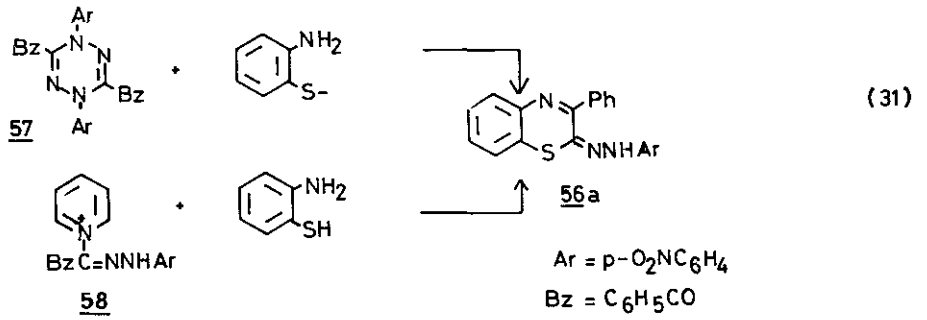
55 56

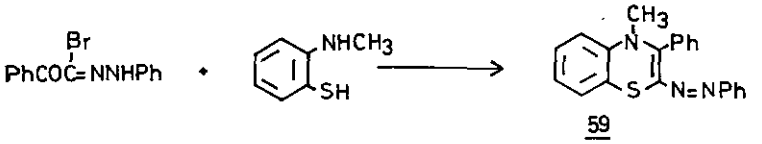


(31)

57 58 56a

Ar = p-$O_2NC_6H_4$

Bz = C_6H_5CO



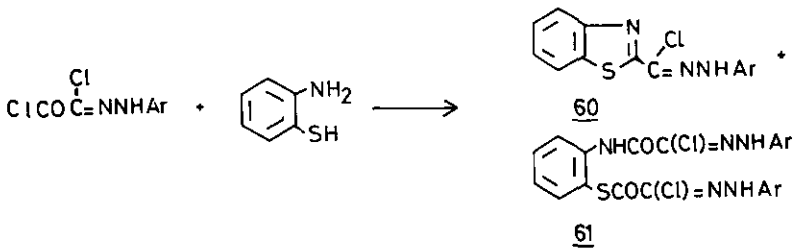
(32)

59

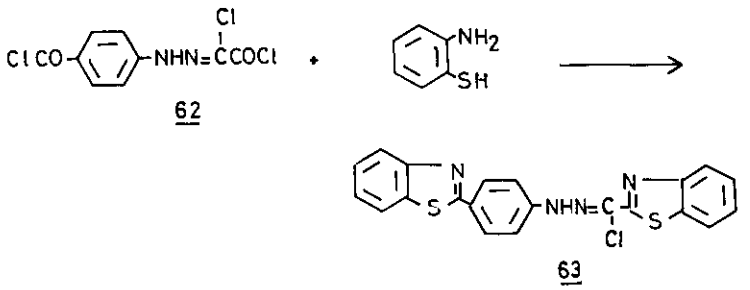
Structure 55 was excluded on the basis of alternate synthesis of 56a (R' = C_6H_5,

Ar = p-$O_2NC_6H_4$) from refluxing 58 with o-aminothiophenol or from condensation of the tetrazine 57 with the sodium salt of o-aminothiophenol (Eq. 31).[51] Condensation of o-N-methylaminothiophenol with C-benzoyl-N-phenylhydrazidoyl bromide yielded the azo derivative 59.[51]

C-Chlorocarbonylhydrazidoyl chlorides were reported to react with o-aminothiophenol and give benzothiazole derivatives 60 and some of 61 (Eq. 33).[52] Similar reaction of 62 with o-aminothiophenol was reported to give 63 (Eq. 34).[52] However, reaction

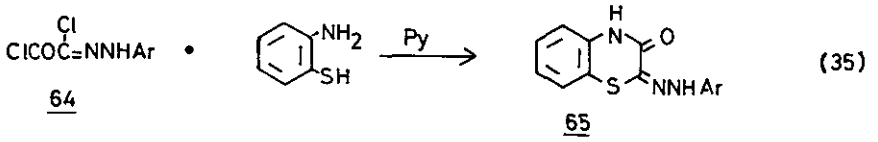


60 61 (33)



62 63 (34)

of C-chlorocarbonylhydrazidoyl chlorides with o-aminothiophenol in pyridine gave benzo-1,4-thiazine derivatives 65 (Eq. 35). On the other hand, similar reaction of 64 (Ar = o-$CH_3OC_6H_4$, p-BrC_6H_4) with o-aminothiophenol in pyridine at 50° was reported to give the disulfides 66 (Eq. 36).[52]



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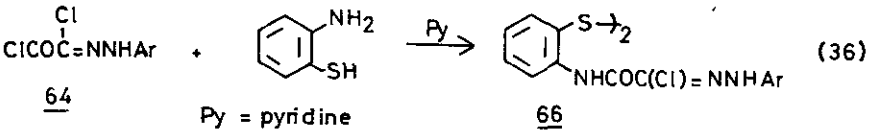
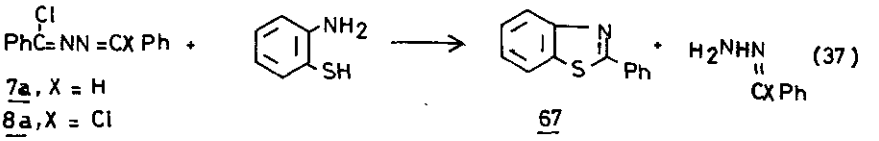


(36)

Py = pyridine

N-Benzylidenebenzohydrazidoyl chloride 7a gives 2-phenylbenzothiazole 67 in 81% yield when it is treated with o-aminothiophenol (Eq. 37).[53] Also, the dichloride 8a yields 67 in 67% yield when it is treated with four-fold excess of o-aminothiophenol.[111]

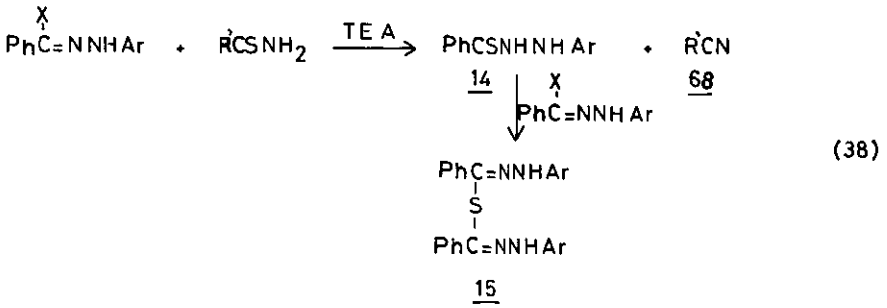


(37)

6. Reaction with thioamides

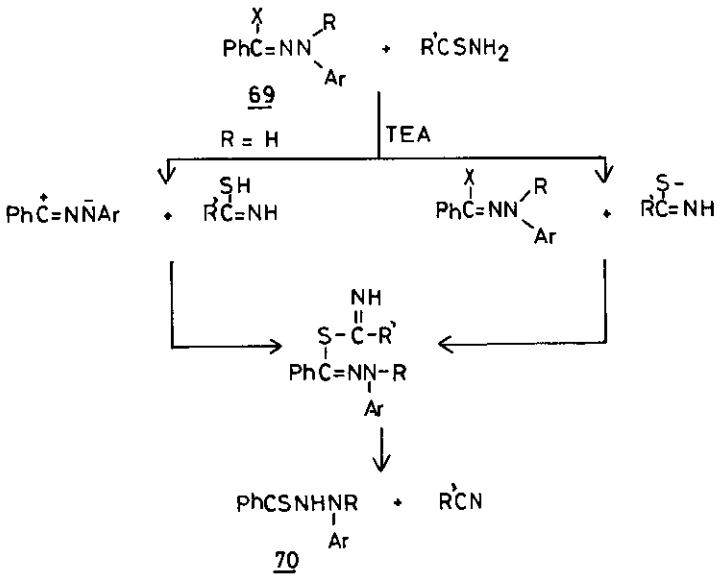
a. Primary thioamides

Primary thioamides react with hydrazidoyl halides in the presence of TEA to form thiohydrazides 14, hydrazidoyl sulfides 15 and nitriles 68 (Eq. 38).[54] The reaction was found to provide an easy route to 14 as well as 15 and compares favourably with previously reported syntheses of such compounds.[23] The yield ratio 14:15 was found to depend on the relative concentrations of the halide to the thioamide. For example, when the halide and the thioamide are present in equimolar amounts the thiohydrazide 14 is the main product (80-90%), whereas 15 predominates (89-90%) when an excess of the halide is employed. The formation of 14 in preference to 15 when equimolar amounts of thioacetamide and the halide are used also indicates that the thioacetyl group of thioacetamide is more reactive towards the halide than is the thiobenzoyl group of 14. This was confirmed by the observation that 14 rather than 15 is formed when TEA is added to a mixture of equimolar amounts of a hydrazidoyl halide, thioacetamide and thiohydrazide 14.



(38)

Primary thioamides do not react with hydrazidoyl halides in the absence of a base catalyst. This together with the observation that N,N-disubstituted hydrazidoyl halides 69 react with thioacetamide in the presence of TEA and give the thiohydrazides 70 indicates that these reactions proceed through nucleophilic displacement mechanism rather than 1,3-dipolar addition sequence. The latter path is excluded by the presence of two substituents on the terminal nitrogen atom as in 69. The base catalyst would serve to convert the thioamide to thioamide anion prior to displacement (Scheme 5).

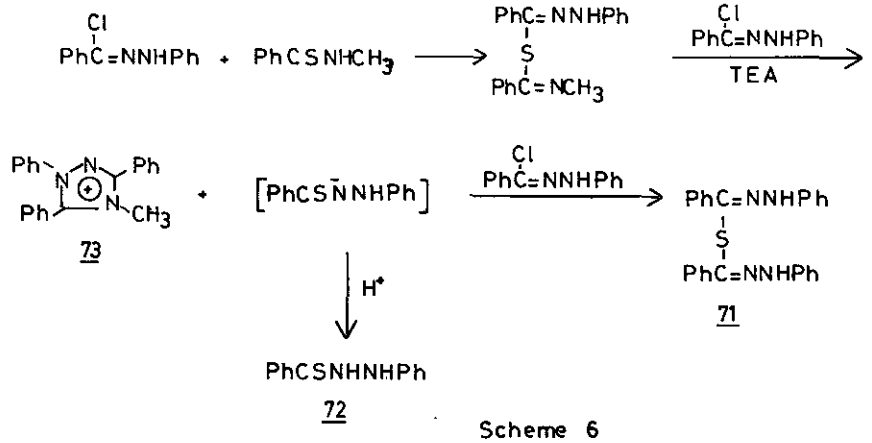


Scheme 5

In these reactions it was found that the relative yields of 14 and 15 vary somewhat with the solvent employed. For example, the ratio of 14:15 from N-phenylbenzohydrazidoyl chloride and thioacetamide is 13 and 2 respectively in chloroform and benzene.[54] The reason for this may be that the acidity of thioamides exhibits a significant solvent dependence.

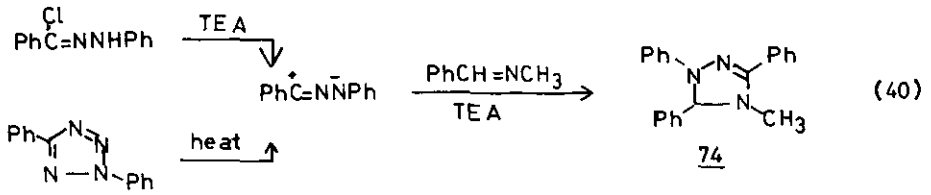
b. Secondary thioamides

The reactions of secondary thioamides with hydrazidoyl halides were found to be remarkably different, and the reactivity of the hydrazidoyl halides was very dependent on the nature of the halogen atom. The reaction of N-alkylthioamides with hydrazidoyl bromides proceeds readily, whereas with hydrazidoyl chlorides a base catalyst (TEA) is required for reaction to take place; base is necessary for N-arylthiobenzamides to react in either case. It is not clear whether this difference is due to higher relative reactivity of bromides, or if the two types of halides react in part by different mechanisms. For example, N-methylthiobenzamide reacts with N-phenylbenzohydrazidoyl chloride under a variety of conditions and gives a mixture of thiohydrazide 72 (detected by TLC); hydrazidoyl sulfide 71 in yields varying from 20-60%, and 4-methyl-1,3,5-triphenyl-1,2,4-triazolium chloride 73 (Scheme 6).[55] The possibility of the above sequence of reactions is supported by the observation that imidoyl halides react with hydrazidoyl halides and give 1,2,4-triazolium halides (Eq. 39). This reaction is analogous to the formation of 1,2,4-triazolines from nitrile imines and Schiff bases (Eq. 40).[56,57]

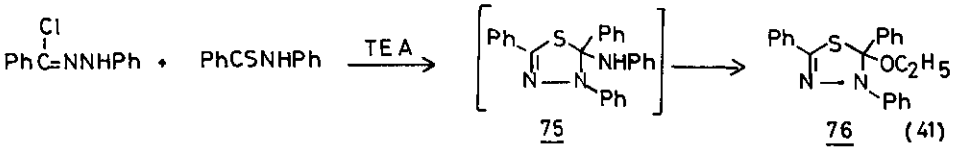


Scheme 6

(39)



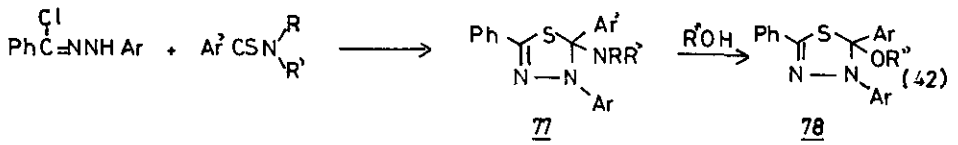
Thiobenzanilide was found to react with hydrazidoyl halides in a manner similar to that of tertiary thioamides. For example, treatment of N-phenylbenzohydrazidoyl chloride with thiobenzanilide in the presence of TEA in benzene gave the thiadiazoline derivative 75, which upon boiling in ethanol gave 5-ethoxy-2,4,5-triphenyl-1,3,4-thiadiazoline 76 in 91% yield (Eq. 41). Attempts to isolate 75 yielded



small amount of N'-thiobenzoyl-N-benzoylphenylhydrazine. The latter compound is presumably formed from 75 by elimination of aniline and ring opening. It has been found that the ring of 2,4,5-triaryl-1,3,4-thiadiazolinium chlorides is opened by bases to give thiohydrazides of the general formula ArCSNHN(COAr)Ph.[55]

c. Tertiary thioamides

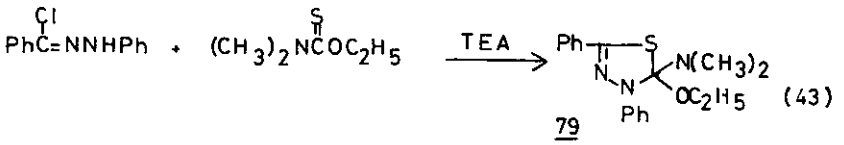
Tertiary thioamides react with hydrazidoyl halides in the presence of TEA to give 5-disubstituted amino-2,4,5-triaryl-1,3,4-thiadiazolines 77, which upon alcoholysis produce the corresponding 5-alkoxy-1,3,4-thiadiazolines 78 (Eq. 42).[55,59] Neither thiohydrazides nor hydrazidoyl sulfides were formed in these reactions.



N,N-Dimethylthiobenzamide displaces the bromine atom of hydrazidoyl bromides, even in the absence of TEA and yields the corresponding thiadiazolines 77. It was noticed that the latter compounds decompose by liberation of dimethylammonium bromides in the reaction mixture, decreasing thus the yield of 77 or after alcoholysis 78.

7. Reaction with thiocarbamates

Treatment of N-phenylbenzohydrazidoyl chloride with ethyl N,N-dimethylthiocarbamate in benzene in the presence of TEA was reported to give 3,5-diphenyl-2-dimethylamino-2-ethoxy-2,3-dihydro-1,3,4-thiadiazole 79 (Eq. 43).[59] However, O-alkylthiocarbamates react with the same halide in benzene in the presence of TEA and give 82% yield of the sulfide 71 (Eq. 44).[54]



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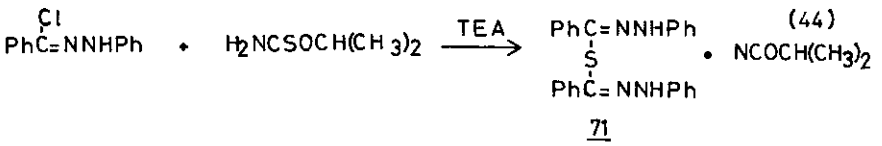
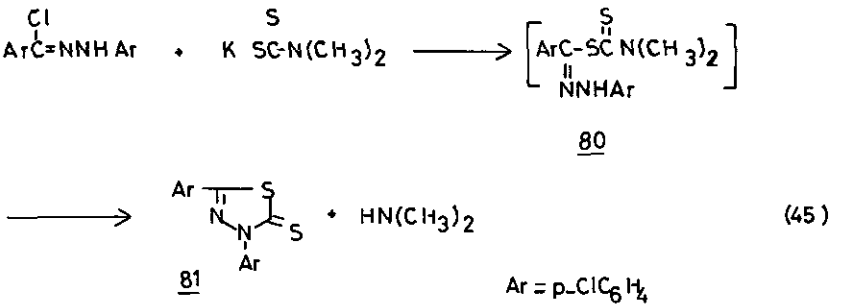


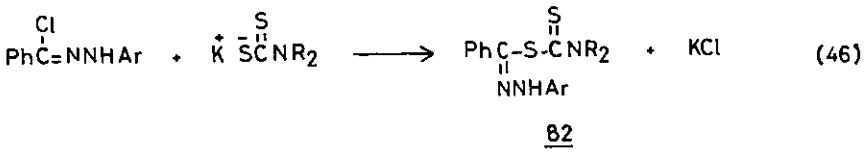
(44)

N-p-Chlorophenyl-p-chlorobenzohydrazidoyl chloride reacts with potassium N,N-dimethyldithiocarbamate in acetone at room temperature and affords ?,3-dihydro-1,3,4-thiadiazole-2-thione derivative 81 (Eq. 45).[30] The involvement of the hydrazone intermediate 80 in this reaction was confirmed by Kaugars and Rizzo.[60] The latter authors indicated that the stability of 80 is determined by branching of the alkyl groups in the dithiocarbamate fragment and by the ortho-substituents in the hydrazonoaryl group. Thus treatment of N-?,4,6-trichlorophenylbenzohydrazidoyl chloride with N,N-diethyl- and N,N-di-n-propyl-dithiocarbamates yields the corresponding stable hydrazones 82 (Eq. 46). Also, the reaction of N-?,6-dimethylphenylbenzohydrazidoyl chloride with N,N-di-n-propyldithiocarbamate yields the hydrazone 82 (Ar = ?,6-$(CH_3)_2C_6H_3$, R = $CH_3CH_2CH_2$). However, in the reaction of N-phenylbenzohydrazidoyl chloride with potassium N,N-dimethyl-, N,N-di-n-propyl- or N,N-di-i-propyl-dithiocarbamates, the intermediate hydrazones could not be isolated as they undergo cyclization to give 3,5-diphenyl-1,3,4-thiadiazole-2-thione. These results show that steric crowding about the reaction site in 82 inhibits its cyclization to form the corresponding 1,3,4-thiadiazole-?-thione derivative.



(45)

Ar = p-ClC_6H_4

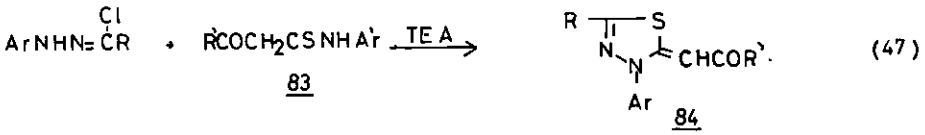


82

8. Reaction with β-ketothioanilides

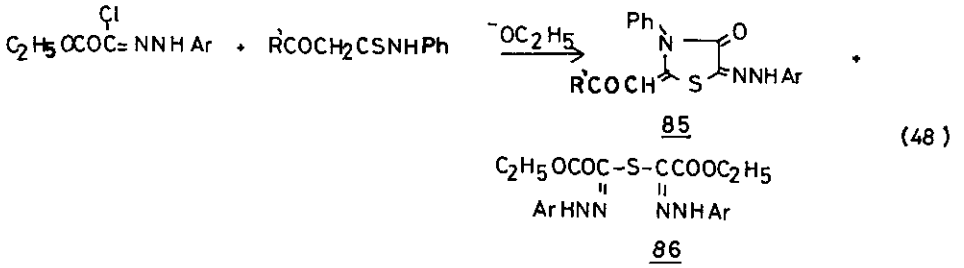
By reacting the thioanilides 83 with hydrazidoyl halides in the presence of TEA or sodium acetate, the corresponding 5-ketonylidene-2,4-disubstituted 1,3,4-thiadiazoline derivatives 84 (Eq. 47) were easily obtained through nucleophilic attack of the thiolate group followed by ring closure and arylamine elimination.[61]

The elimination of the amine moiety was confirmed by the isolation of the product 84 (R = $COOC_2H_5$, Ar' ≠ R' = C_6H_5) by using N-phenyl-C-ethoxycarbonylhydrazidoyl chloride with either 83 (R' = C_6H_5, Ar' = p-$CH_3C_6H_4$) or 83 (R' = Ar' = C_6H_5) as starting materials.



83 84

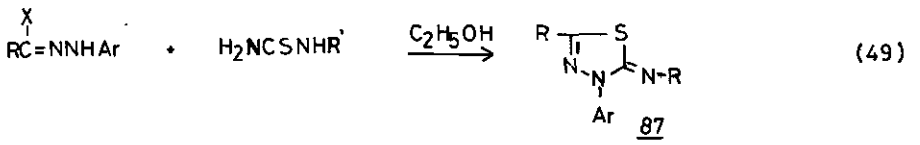
A different reaction pathway was observed when the anilides 83 react with C-ethoxycarbonylhydrazidoyl chlorides in the presence of bases such as sodium ethoxide. For example, by reacting benzoylthioacetanilide with N-phenyl- and N-p-chlorophenyl derivatives of C-ethoxycarbonylhydrazidoyl chloride, the thiadiazolidinones 85 (R' = Ar = C_6H_5) and 85 (R' = C_6H_5, Ar = p-ClC_6H_4) were obtained respectively in moderate yields as the main products and the corresponding sulfides 86 were formed as by-products (Eq. 48).[59] Obviously the strength of the base used can influence the reaction path. The thiohydrazide is most likely formed first by formal abstraction of hydrogen sulfide from 83; further reaction with hydrazidoyl halide leads to the sulfide 86. However, the product 85 (R' = C_6H_5, Ar = p-ClC_6H_4) was obtained in practically quantitative yield by reaction of benzoylthioacetanilide with N-p-chlorophenyl-C-chlorocarbonylhydrazidoyl chloride. Analogously, the product 85 (R' = CH_3, Ar = p-ClC_6H_4) was obtained from the reaction of the latter hydrazidoyl chloride with acetothioacetanilide.[61]



(48)

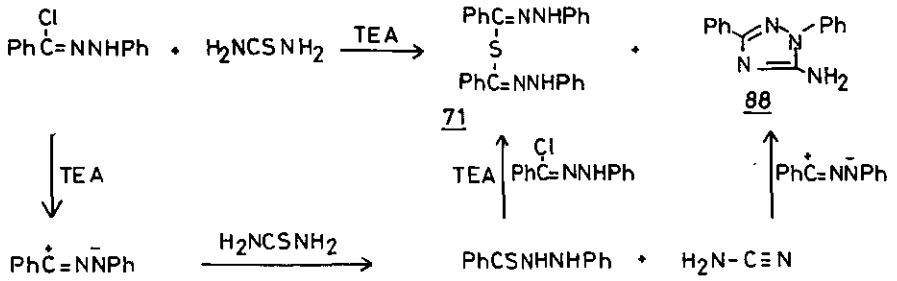
9. Reaction with thiourea and its derivatives

Reaction of hydrazidoyl halides with thiourea and its derivatives leads to products that depend on the reaction conditions and the structure of the hydrazidoyl halide used. Thus, treatment of C-aryl- and C-alkyl-hydrazidoyl halides with thiourea, and its N-phenyl- or N-acetyl derivatives in ethanol afforded the corresponding derivatives of 2,3-dihydro-2-imino-1,3,4-thiadiazoles 87 (Eq. 49).[58,62-64]



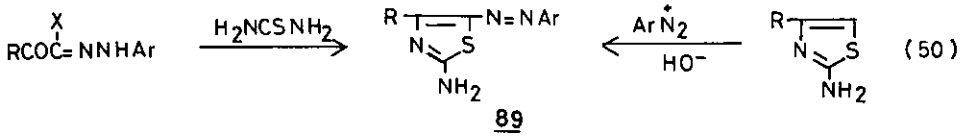
(49)

When the reactions between hydrazidoyl halides and thiourea were conducted in the presence of excess TEA, several products were formed namely, the hydrazidoyl sulfide 71 and 1,2,4-triazole derivative 88. For example, reaction of N-phenylbenzohydrazidoyl chloride with thiourea in ethanol in the presence of TEA in molar ratio 2:1:4 gave 71 (21%) and 5-amino-1,3-diphenyl-1,2,4-triazole 88 (59%) (Scheme 7).[65] The competition between the reactions shown in Scheme 7 was reported to be very favourable to triazole formation with thiourea, but so unfavourable with phenylthiourea that no triazole was obtained in the cases examined.[65] In the latter cases hydrazidoyl sulfide 71 was the major product.



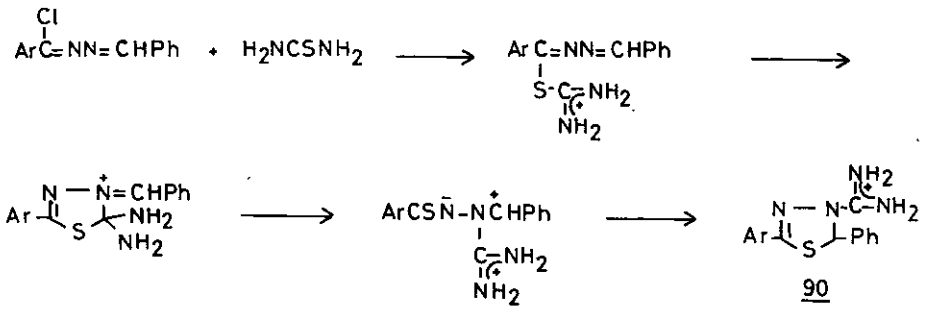
Scheme 7

α-Ketohydrazidoyl bromides react with thiourea in refluxing ethanol and yield 5-arylazo-4-substituted 2-aminothiazoles 89 (Eq. 50).[66-68] The structures of the latter products were confirmed by comparison with authentic samples prepared by coupling 2-amino-4-substituted thiazoles with diazotized arylamine.

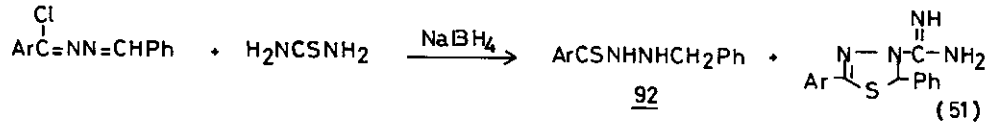


(50)

N-Benzylidenebenzohydrazidoyl chlorides react with thiourea quite readily at ambient temperature in dry ethanol to give the hydrochloride salts of 4-amidino-2,5-diphenyl- Δ^2-1,3,4-thiadiazolines 90 from which the corresponding free bases 91 were obtained in 68% yield by treatment with cold alkali (Scheme 8).[69,70] In the presence of excess sodium borohydride, the reaction of such chlorides with thiourea was reported to yield some N'-benzylthiobenzoylhydrazine 92 (20%) (Eq. 91) compatible with the capture of an intermediate iminium ion as postulated in the mechanism shown in Scheme 8. It was shown in a separate experiment that sodium borohydride does not react under the same conditions with thiourea or with 91 although a slow reaction does occur with these chlorides.[69]

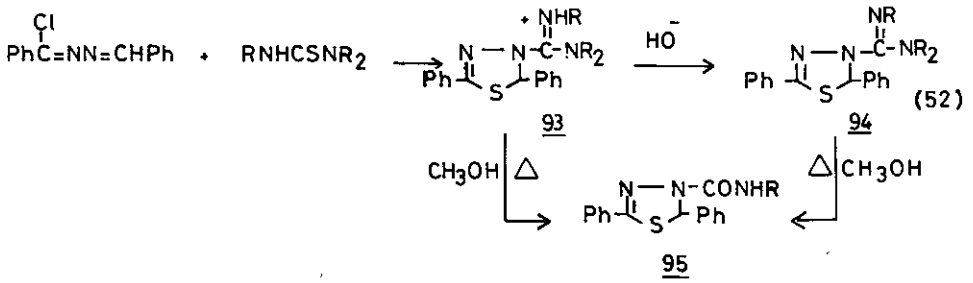


Scheme 8



(51)

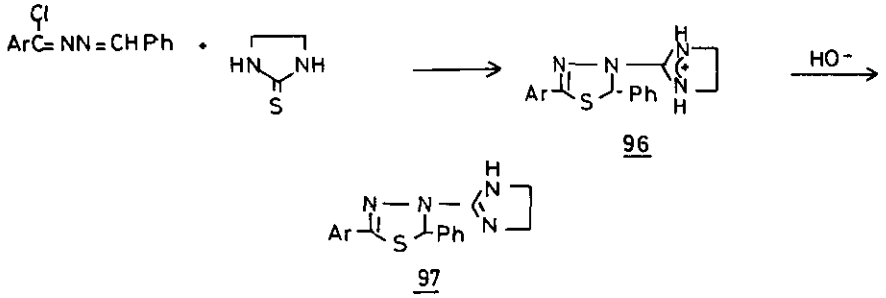
Reactions of methylthiourea, dimethylthiourea and trimethylthiourea with N-benzylidenebenzohydrazidoyl chloride were also reported to give the corresponding substituted 4-amidino-2,5-diphenyl-Δ^2-1,3,4-thiadiazoline 94.[70] Prolonged hydrolysis of 93 and 94 in refluxing methanol yields moderate yield of the corresponding amidothiadiazoline 95 (Eq. 52).[70]



(52)

10. Reaction with imidazoline-2-thione

Imidazoline-2-thione reacts rapidly with N-benzylidenehydrazidoyl chlorides at ambient temperature and gives the corresponding hydrochloride salts 96 which can be converted into the free bases 97 with aqueous alkali in 70% overall yield (Eq. 53).[69]

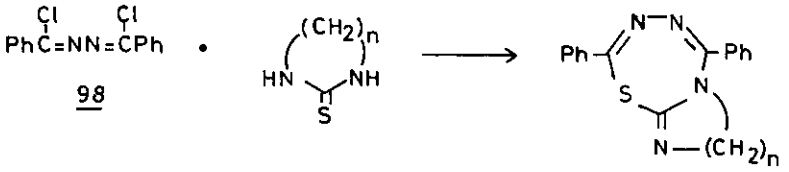


96

97

(53)

Also the dichloride 98 has been found to react with imidazoline-2-thione and propylenethiourea to give the annelated 1,3,4,6-thiatriazepines 99 (Eq. 54).[71]



98

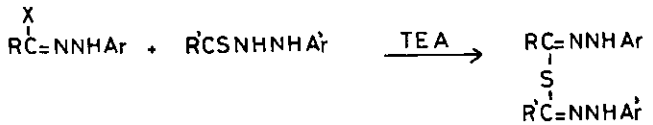
n = 2, 3

99

(54)

11. Reaction with thiohydrazides

Treatment of hydrazidoyl halides with thiohydrazides in chloroform or acetonitrile in the presence of TEA was reported to give the sulfides 100 in 40-80% yield (Eq. 55).[23] The reaction was found to be useful in synthesis of both sym- and unsym-hydrazidoyl sulfides.

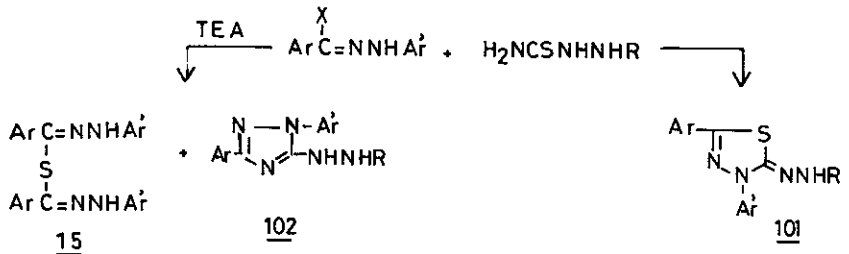


100

(55)

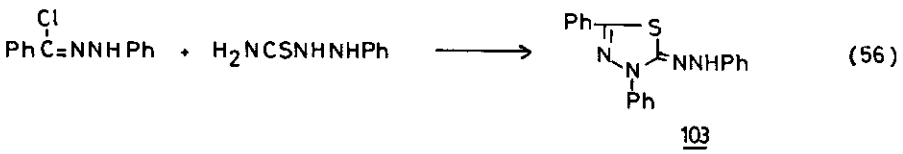
12. Reaction with thiosemicarbazide and its derivatives

Thiosemicarbazide and its aryl derivatives react readily with hydrazidoyl halides in refluxing ethanol and give the corresponding thiadiazoline derivatives 101 (Scheme 9).[63] In the presence of TEA the reaction gives a mixture of the triazole 102 (30%) and the sulfide 15 (44%) (Scheme 9).[65]

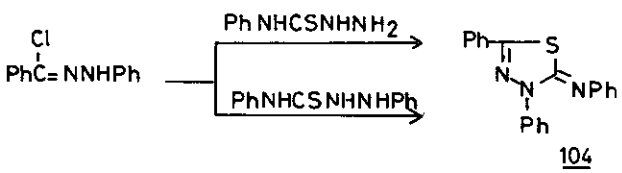


Scheme 9

Similar reaction of N-phenylbenzohydrazidoyl chloride with 1-phenylthiosemicarbazide gave 103 (Eq. 56), whereas with 4-phenylthiosemicarbazide and 1,4-diphenylthiosemicarbazide in refluxing ethanol yielded in both cases the thiadiazoline derivative 104 (Eq. 57).[65]

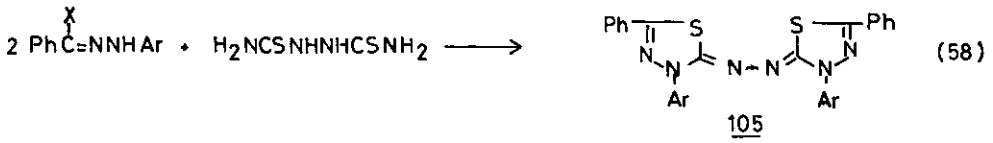


(56)



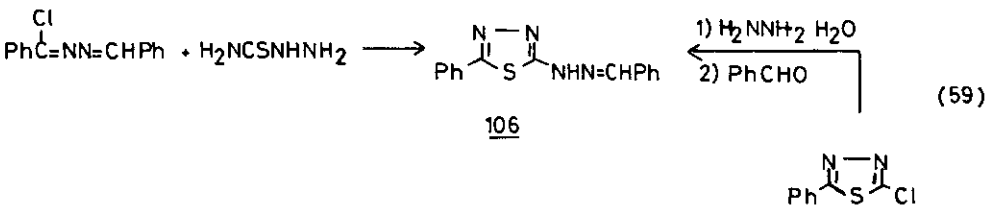
(57)

1-Thiocarbamoylthiosemicarbazide reacts also with hydrazidoyl halides and gives the azine 105 (Eq. 58).

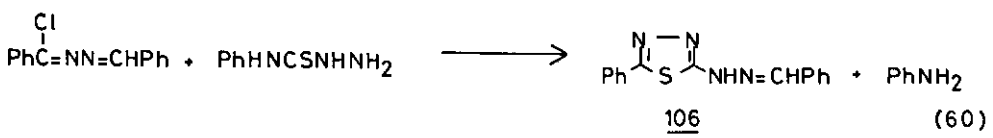


105 (58)

N-Benzylidenebenzohydrazidoyl chloride was reported to react quite readily with thiosemicarbazide and gives the hydrazone derivative 106 (66%) (Eq. 59).[53] The structure of the latter product was confirmed by its alternate synthesis as shown in Eq. 59. The reaction between N-benzylidenebenzohydrazidoyl chloride and 4-phenylthiosemicarbazide also was reported to give 106 with liberation of aniline (Eq. 60).



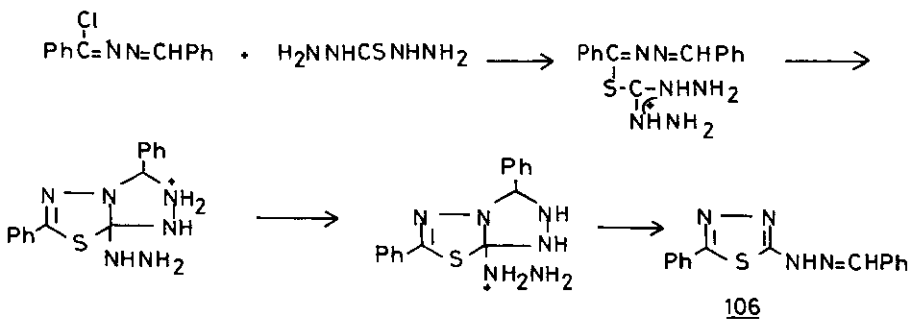
106 (59)



106 (60)

13. Reaction with thiocarbohydrazide

The interaction between N-benzylidenebenzohydrazidoyl chloride with thiocarbohydrazide has recently been reported by Taylor et al.[53] It was shown that such interaction leads to 2-benzylidenehydrazino-5-phenyl-1,3,4-thiadiazole 106 in 77% yield (Scheme 10). The formation of the latter indicates that the mechanism involved is similar to that of the reaction between thiosemicarbazide and N-benzylidenebenzohydrazidoyl chloride.

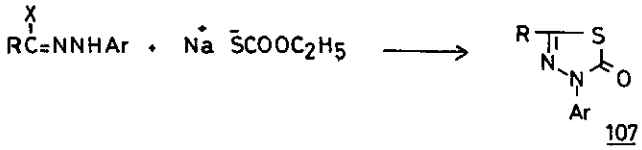


106

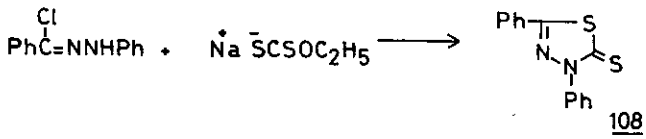
Scheme 10

14. Reaction with O-ethyl thiocarbonate and ethyl xanthate

Hydrazidoyl halides were reported to react with sodium O-ethyl thiocarbonate at room temperature in ethanol or ethanol-ether mixture and give the corresponding 3,5-disubstituted 1,3,4-thiadiazole-2-ones 107 in good yields (Eq. 61).[59,72] Similar reaction of N-phenylbenzohydrazidoyl chloride with sodium ethyl xanthate afforded 3,5-diphenyl-1,3,4-thiadiazole-2-thione 108 in almost quantitative yield (Eq. 62).[72]

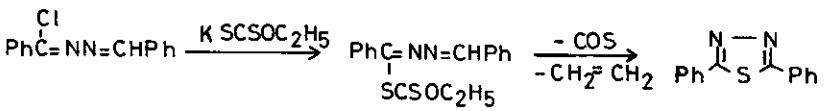


(61)

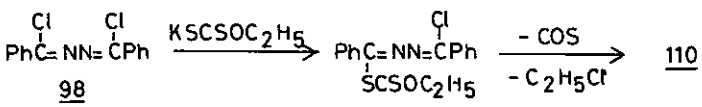


(62)

The reaction between N-benzylidenebenzohydrazidoyl chloride and potassium ethyl xanthate gives 1-ethylxanthyl-2,3-diazabutadiene 109 (Eq. 63).[53,73] Pyrolysis of the latter yielded 69% of 2,5-diphenyl-1,3,4-thiadiazole 110. Compound 110 was also obtained in 79% yield from reaction of the dichloride 98 with potassium ethyl xanthate in refluxing ethanol.[111]

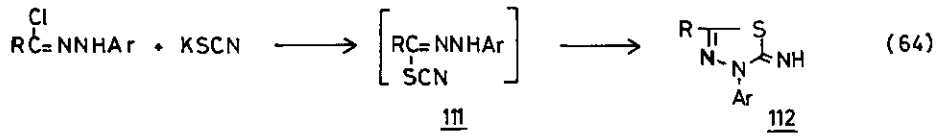


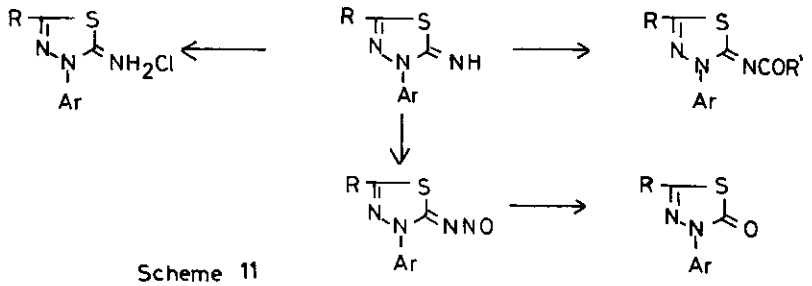
(63)



15. Reaction with potassium thiocyanate

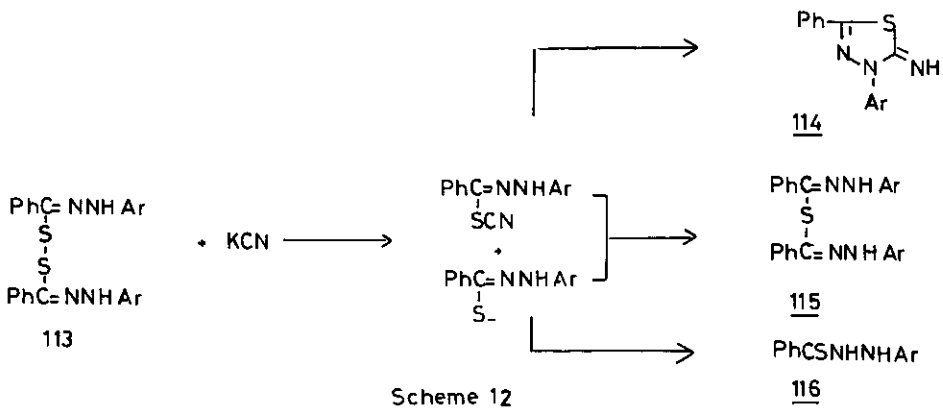
Reaction of hydrazidoyl halides with potassium thiocyanate in ethanol at room temperature produces the corresponding thiadiazoline derivatives 112 in good yields.[28,29,65-68,74-76] The structures of these products were confirmed by their chemical reactions which are summarized in Scheme 11. In the cases examined no detection of the intermediate thiocyanate 111 was reported. Indirect evidence for 111 was found when the hydrazidoyl sulfide 115 was isolated as a by-product from treatment of the disulfide 113 with potassium cyanide at room temperature in chloroform, the major products being the thiohydrazide 116 and the thiadiazoline 114 (Scheme 12).[65,78] The isolation of 115 may be rationalized in terms





Scheme 11

of heterolytic cleavage of the S-S bond by the action of the cyanide ion, in similar manner to that known for ordinary disulfide, to give the thiohydrazidate anion and hydrazidoyl thiocyanate 111 (R = C_6H_5).[79] Nucleophilic displacement of the thiocyanato group from 111 before cyclization to 114 by the thiohydrazidate anion would yield 115. Compound 113 was also found to very easily cleaved by potassium cyanide in refluxing acetonitrile to give approximately equal amounts of 114 and 116.

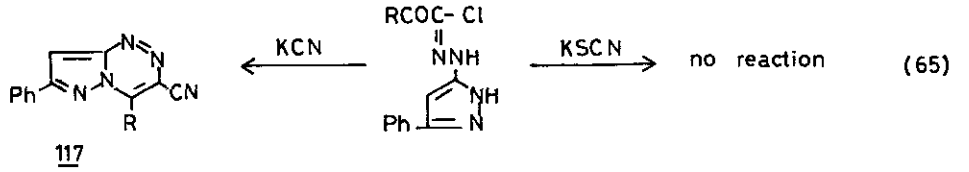


Scheme 12

The regiochemistry of the reaction between nitrile imines and thiocyanate anion was rationalized in terms of the frontier orbital treatment.[76] The thiocyanate

anion being electron rich dipolarophile, its reaction with nitrile imine is expected to be controlled by the LUMO and HOMO of nitrile imine and the thiocyanate anion respectively. As the HOMO of the thiocyanate anion has larger orbital coefficient on the sulfur atom,[80,81] it was concluded that the larger coefficient in the LUMO of the nitrile imine is on the carbon atom.

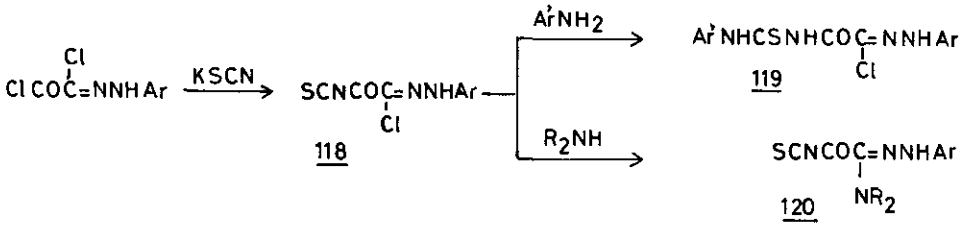
It was reported that N-(5-(3-phenyl)pyrazolyl)hydrazidoyl chlorides do not react with potassium thiocyanate in refluxing acetone, although they react readily with potassium cyanide to give 117 (Eq. 65).[82]



(65)

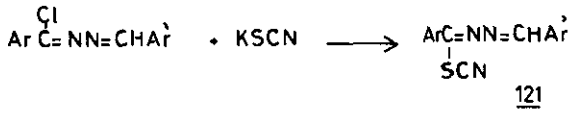
117

C-Chlorocarbonylhydrazidoyl chlorides react with potassium thiocyanate in acetone at room temperature and give the products 118 in 70-90% yields.[83] The latter products add primary amines to yield 119. However, they react with secondary amines and yield the amidrazones 120 (Scheme 13).[84]

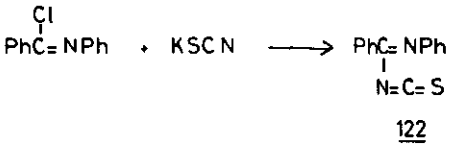


Scheme 13

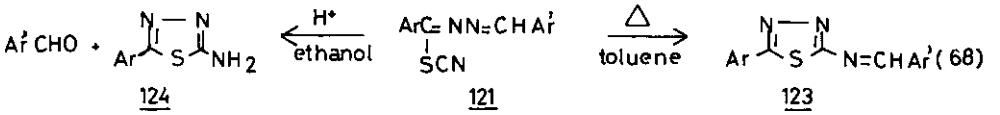
N-Benzylidenehydrazidoyl chlorides react with potassium thiocyanate in ethanol and give the thiocyanate substitution products 121 (Eq. 66).[53,70,85] In contrast to this the related imidoyl chlorides were reported to react with potassium thiocyanate and yield the isothiocyanates of type 122 (Eq. 67).[86] When the hydrazidoyl thiocyanates 121 were heated in toluene, they were converted into the thiadiazole derivatives 123 (47%). Also acid hydrolysis of 121 in refluxing ethanol gave aldehyde and the aminothiadiazole derivatives 124 (94%) which were isolated as



(66)

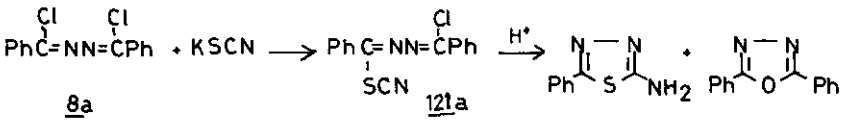


(67)

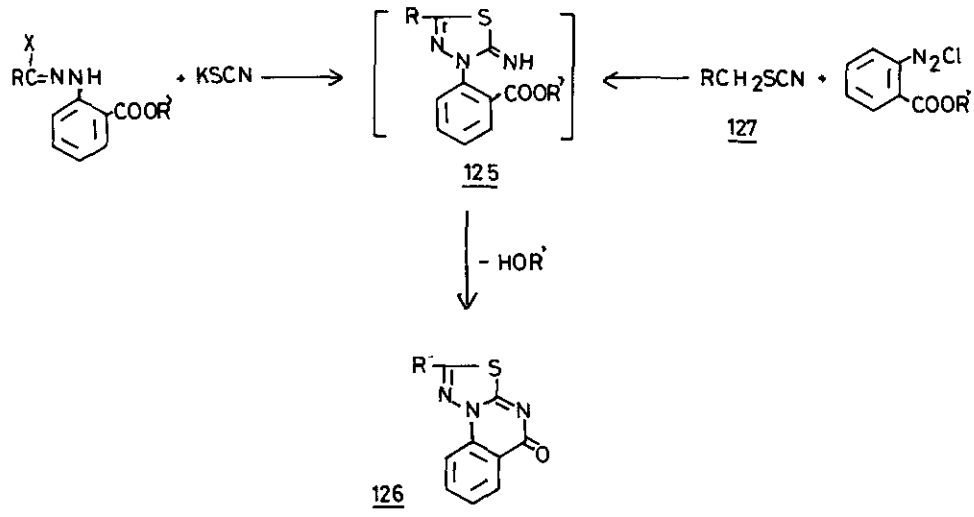


(68)

When either of the aromatic rings in N-benzylidenebenzohydrazidoyl chloride is substituted by p-nitro group, the reaction with potassium thiocyanate yields only amorphous brown solids which resisted purification and none of the desired thiocyanates of type 121 can be isolated even after prolonged reaction time.[53,85] This was considered to suggest that the SN1 mechanism proposed for replacement of chlorine group in dilute alkaline solution also holds for substitution by thiocyanate anion. When an ortho-methyl substituent is present in the aromatic ring next to the site of substitution, the yield of 121 was reported to be slightly reduced.
On treatment with an equimolar proportion of potassium thiocyanate in refluxing ethanol, the dichloride 8a was converted into 1-chloro-4-thiocyanato-2,3-diazabutadiene 121a (84%).[111] This product is not isomerized by heat, but is hydrolyzed by acid to a mixture of 2,5-diphenyl-1,3,4-oxadiazole and 2-amino-5-phenyl-1,3,4-thiadiazole.



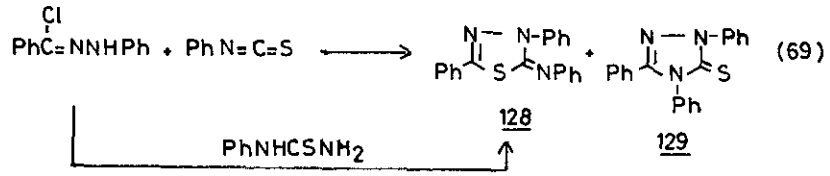
Recently it was reported that N-(o-carboxyphenyl)hydrazidoyl halides react with potassium thiocyanate in ethanol to give thiadiazolo[2,3-b]quinazoline derivatives 126 directly (Scheme 14).[74,87] N-(o-Carbomethoxyphenyl)hydrazidoyl halides react similarly with potassium thiocyanate and give 126. The latter products were also obtained by coupling the corresponding active methylene thiocyanates 127 with diazotized anthranilic acid or it methyl ester (Scheme 14).



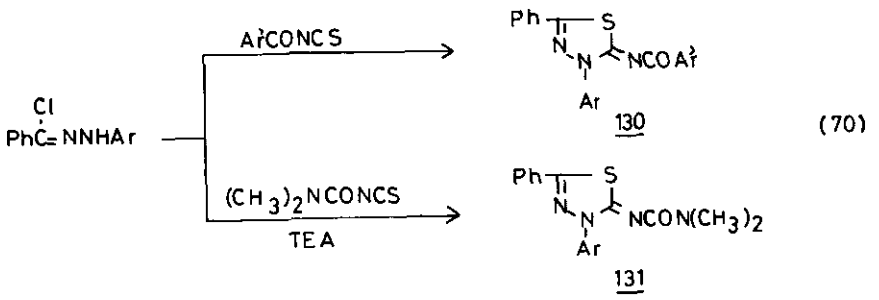
Scheme 14

16. Reaction with isothiocyanates

Only few examples for the reaction of hydrazidoyl halides with isothiocyanates have been reported. N-Phenylbenzohydrazidoyl chloride reacts with phenyl isothiocyanate in benzene in the presence of TEA to give 3,5-diphenyl-2-phenylimino-2,3-dihydro-1,3,4-thiadiazole 128 (58%) and 1,3,4-triphenyl-1,2,4-triazole-5-thione 129 (Eq. 69)[59] Product 128 was identical with that obtained from refluxing the same chloride with phenylthiourea in ethanol.[65]

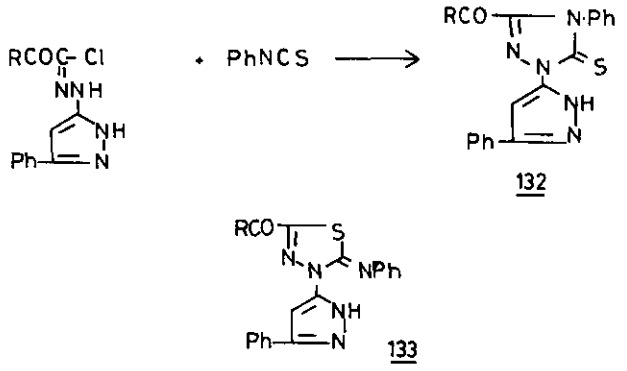


N-Acyl- and N-carbamoyl-isothiocyanates were reported to react with N-arylbenzohydrazidoyl chlorides in the presence of TEA to give only one regioisomer in each case, the products being 130 and 131 respectively (Eq. 70).[30,59] These examples indicate that the diarylnitrile imine derived from hydrazidoyl halide adds mainly to the C = S rather than the N = C double bond of isothiocyanate molecule. This regiospecifity was interepreted in terms of frontier molecular orbitals.[88]



(70)

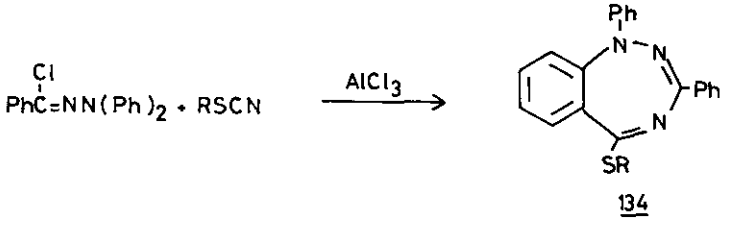
A recent report claimed that treatment of N-[5-(3-phenyl)pyrazolyl]hydrazidoyl chlorides with phenyl isothiocyanate in refluxing pyridine gave the products 132 that result from cycloaddition to the C = N double bond of the isothiocyanate (Eq. 71).[89] The possibility of the other regioisomer 133 was not discussed, however.



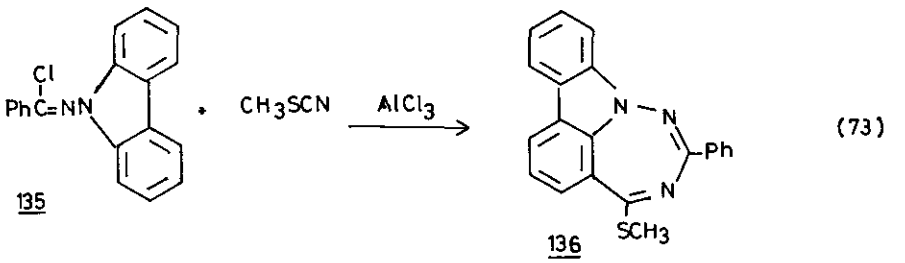
(71)

17. Reaction with alkyl and aryl thiocyanates

The reaction of alkyl and aryl thiocyanates with hydrazidoyl halides has been investigated by Corral et al.[90] N,N-Diphenylbenzohydrazidoyl chloride reacts with these thiocyanates in o-dichlorobenzene in the presence of aluminum chloride and gives the 1H-1,2,4-benzotriazepine derivatives 134 (Eq. 72). Also the hydrazidoyl chloride 135 reacts with methyl thiocyanate in the presence of aluminum chloride to give 36% yield of 136 (Eq. 73).[90]



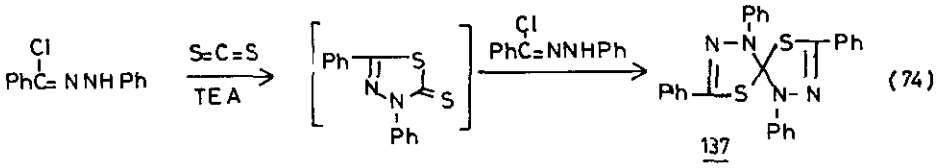
(72)



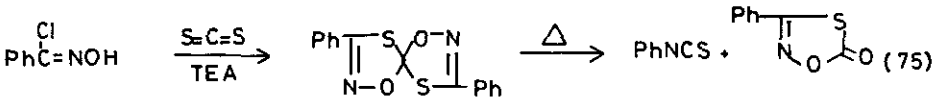
135 136 (73)

18. Reaction with carbon disulfide

Hydrazidoyl halides react with carbon disulfide in the presence of TEA and afford cycloadducts. For example, N-phenylbenzohydrazidoyl chloride yields the spiro-compound 137 when it is treated with carbon disulfide in benzene in the presence of TEA (Eq. 74).[59] The latter product was found to be more stable than the compound obtained from benzohydroximoyl chloride with carbon disulfide in the presence of TEA (Eq. 75).[91] Compound 138 was reported to decompose spontaneously to 4-phenyl-1,3,5-oxathiazolin-2-one and phenyl isothiocyanate (Eq. 75).



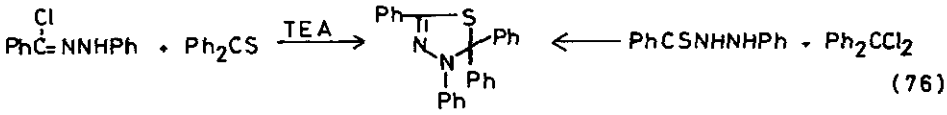
137 (74)



138 (75)

19. Reaction with thioketones

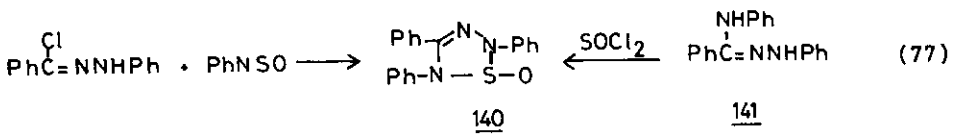
N-Phenylbenzohydrazidoyl chloride reacts with thiobenzophenone in benzene ine the presence of TEA and gives 72% yield of 2,2,3,5-tetraphenyl-2,3-dihydro-1,3,4-thiadiazole 139 (Eq. 76).[59] The structure of the latter was substantiated by its alternate synthesis from N-phenyl-N-thiobenzoylhydrazine with diphenylchloro-methane.



139 (76)

20. Reaction with sulfinylaniline

N-Phenylbenzohydrazidoyl chloride was reported to react with sulfinylaniline in the presence of TEA to yield 2,4,5-triphenyl-2,5-dihydro-1,2,3,5-thiatriazole-1-oxide 140 in 87% yield (Eq. 77).[59] The structure of this product was confirmed by its alternate synthesis from treatment of the amidrazone 141 with thionyl chloride.

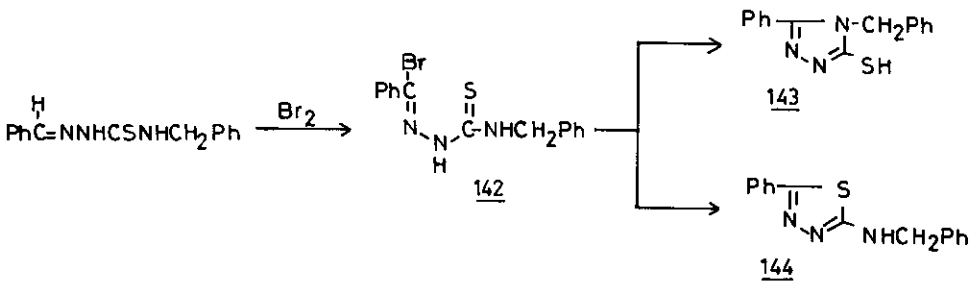


(77)

21. Intramolecular substitution by neighbouring thioacyl group

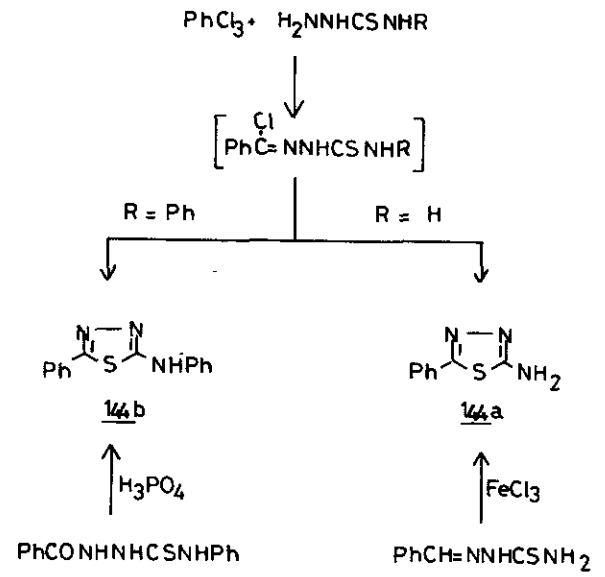
a. Thiocarbamoyl group

Bromination of aldehyde 4-benzylthiosemicarbazones was reported to yield 1-benzyl-2-aryl-5-mercapto-1,3,4-triazoles 143 and 2-aryl-5-benzylamino-1,3,4-thiadiazoles 144 (Scheme 15).[92,93] Thus treatment of the thiosemicarbazone with bromine in chloroform gave 143 and 144 in 50-80 and 10-30% yields, respectively. However, in case of bromination in carbon tetrachloride the yield of 143 decreases (1-30%) and that of 144 increases (55-80%). Bromination of the same thiosemicarbazone with bromine in acetic acid or with N-bromosuccinimide in carbon tetrachloride gave only 144 in 65-80% and 60-90% yields respectively. The reaction is considered to proceed through the hydrazidoyl bromide 142 which cyclizes by displacing the bromine atom.



Scheme 15

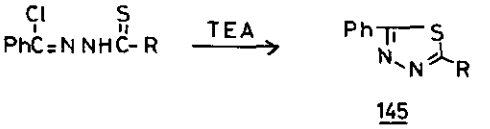
Recently, it was reported that trichlorophenylmethane reacts with thiosemicarbazide and 4-phenylthiosemicarbazide in refluxing ethanol in the presence of anhydrous sodium carbonate to afford 2-amino-5-phenyl-1,3,4-thiadiazole 144a and 2-phenylamino-5-phenyl-1,3,4-thiadiazole 144b, respectively (Scheme 16).[94] The latter products were thought to be formed by intramolecular displacement of the chlorine atom in the intermediate N-thiocarbamoylbenzohydrazidoyl chloride. The structures of the products 144a and 144b were confirmed by their alternate synthesis by oxidation of benzaldehyde thiosemicarbazone[95] and by dehydration of 1-benzoyl-4-phenylthiosemicarbazone,[96] respectively.



Scheme 16

b. Thioacyl group

N-Thiobenzoyl- and N-thioacetyl-hydrazidoyl chlorides were reported to give 1,3,4-thiadiazole derivatives 145 upon treatment with TEA in benzene (Eq. 78).[92,93,97]

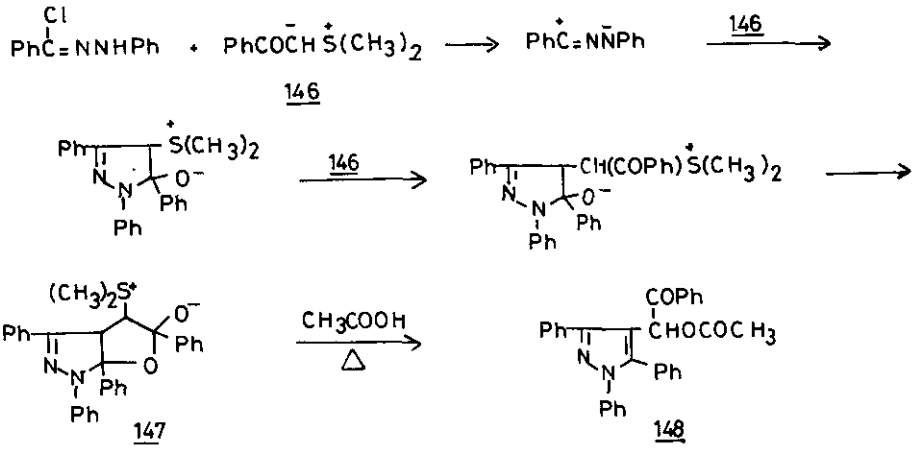


(78)

145

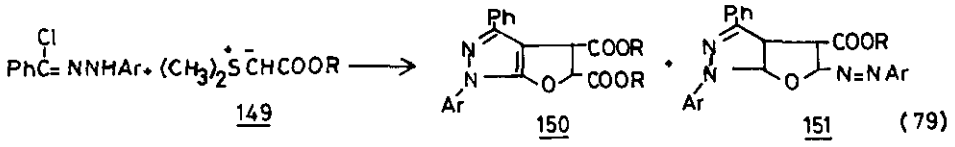
22. Reaction with sulfonium ylides

Hayashi and Oda investigated the reaction of carbonyl stabilized ylide 146 with N-phenylbenzohydrazidoyl chloride.[98] The bicyclic product 147 was obtained from this reaction. It was proposed that the ylide acted as a base to generate the nitrile imine intermediate which reacts with two molecules of the ylide to give 147 (Scheme 17). Heating the product obtained in acetic acid results in the formation of the pyrazole derivative 148.



Scheme 17

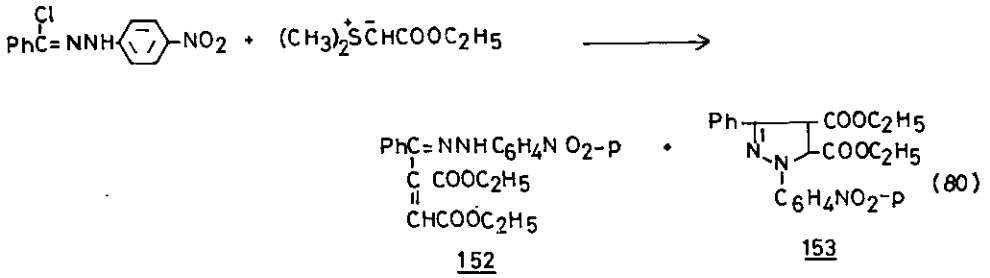
Alkoxycarbonylmethylenesulfonium ylides 149 react with hydrazidoyl halides and give interesting products of type 150 and 151 (Eq. 79).[99] The relative yields of the products were found to depend on the structures of the halide and the ylide used. For example, 149 (R = C_2H_5) reacts with N-phenylbenzohydrazidoyl chloride and gives the corresponding 150 and 151 in 62 and 36% yields respectively. However, reaction of 149 (R = CH_3) with N-p-chlorophenylbenzohydrazidoyl chloride yielded the corresponding 150 and 151 in 13 and 5% yields respectively. A variation of the reaction was observed when N-p-nitrophenylbenzohydrazidoyl chloride was used.[99] The reaction in this case was reported to give a mixture of 152 and 153 (Eq. 80).



(79)

R = CH_3 , CH_2CH_3

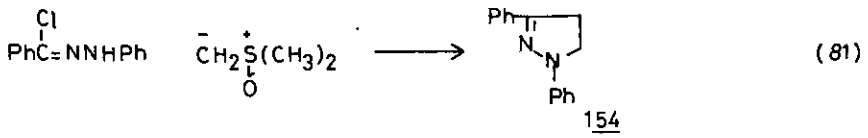
Ar = C_6H_5 , p-ClC_6H_4



(80)

152 153

1,3-Diphenylpyrazoline 154 was obtained from the reaction of N-phenylbenzohydrazidoyl chloride with dimethyloxosulfonium methylide in good yield (Eq. 81).[100]

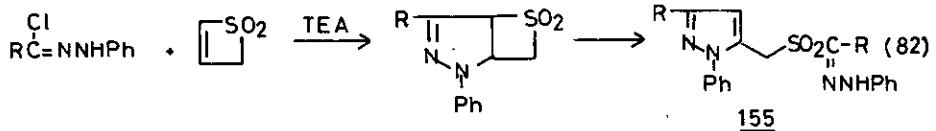


(81)

154

23. Reaction with thiete 1,1-dioxide

Thiete 1,1-dioxide reacts with two equivalents of N-phenylbenzohydrazidoyl chloride in the presence of TEA and gives the pyrazole derivative 155 (Eq. 82).[101]



(82)

155

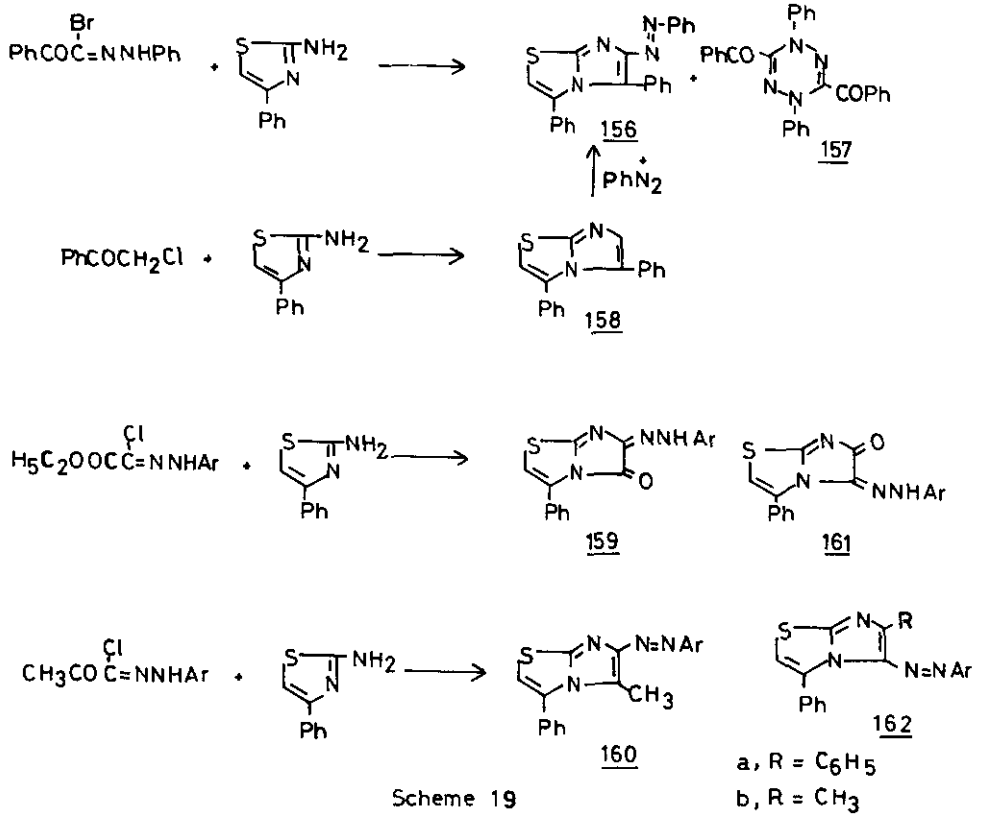
R = C_6H_5 , $COOCH_3$

Scheme 18

24. Reaction with 2-aminothiazoles

When C-benzoylhydrazidoyl bromide was refluxed in ethanol with two equivalents of 2-amino-4-phenylthiazole, three products were isolated. These were identified as the hydrobromide salt of 2-amino-4-phenylthiazole, 3,6-dibenzoyl-1,4-diphenyl-1,4-dihydrotetrazine 157 (60%) and 6-phenylazo-3,5-diphenylimidazo[2,1-b]thiazole 156 (20%).[102] However, when the reaction was carried out using two equivalent amounts

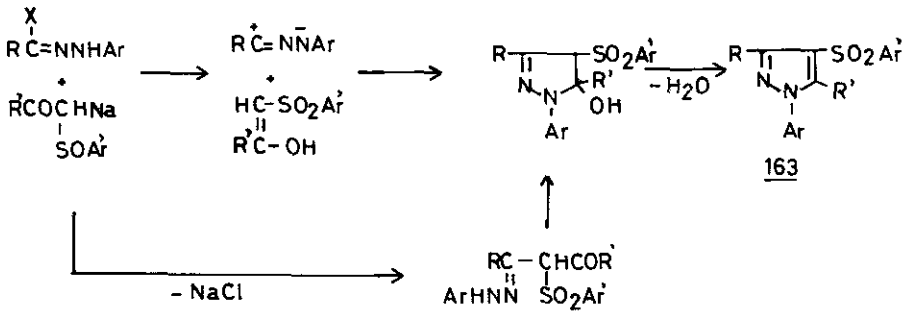
of the bromide and the thiazole and in the presence of TEA, the azo derivative 156 was obtained in 80% yield. Similar reactions of C-carbethoxy- and C-acetyl-hydrazidoyl chlorides with 2-amino-4-phenylthiazole yielded the products 159 and 160 respectively (Scheme 19). The isomeric structures 162a, 161 and 162b were excluded on the basis that 2-aminothiazole reacts with α-halo ketones and α-halo esters to give 5-substituted and 5-oxo derivatives of imidazo[2,1-b]thiazoles.[103] Furthermore, coupling of 3,5-diphenylimidazo[2,1-b]thiazole 158 with diazotized aniline or N-nitrosoacetanilide in ethanol was reported to give a product identical with 156 (Ar = C_6H_5).



Scheme 19

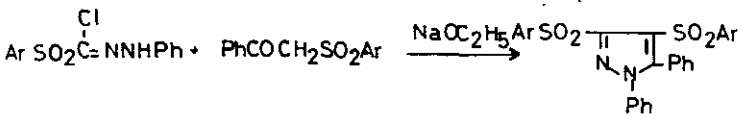
25. Reaction with β-ketosulfones

One of the more general methods for synthesis of 4-arylsulfonylpyrazole derivatives 163 utilizes the reaction of hydrazidoyl halides with β-ketosulfones in their salt form (Scheme 19). The reaction has generally been carried out in alcoholic solution, usually on standing for several hours at room temperature or by heating briefly at reflux.[104-107] The reaction mechanism probably involves 1,3-cycloaddition of the nitrile imine of the hydrazidoyl halide used to the carbon-carbon double bond of the enol of the ketosulfone and it is completed by the loss of elements of water to form the pyrazole derivative. Alternatively, the reaction may involve alkylation of the sulfone with the hydrazidoyl halide to give the acyclic hydrazone which is then cyclized to pyrazole (Scheme 20). In all cases studied neither the pyrazoline nor the acyclic hydrazone intermediate was isolated.



Scheme 20

The use of C-p-toluenesulfonyl-N-phenylhydrazidoyl chloride in this reaction yielded 3,4-diarylsulfonyl derivatives of 1,5-diarylpyrazoles 164 (Eq. 83).[97]



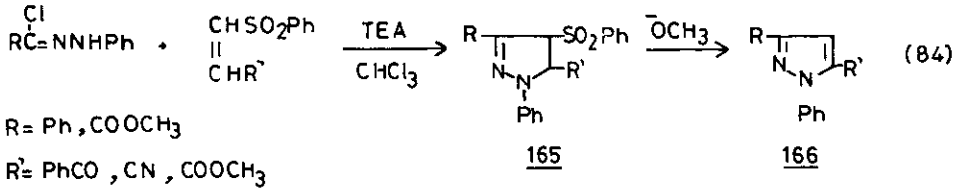
(83)

Ar = p-CH3C6H4

164

26. Reaction with 1-phenylsulfonyl-2-substituted ethylenes

The reaction of C-phenyl- and C-carbomethoxy-hydrazidoyl chlorides with 1-phenylsulfonyl-2-substituted ethylenes has been recently reported by Croce and coworkers.[108] When this reaction was carried out in chloroform in the presence of TEA, it gave one of the two possible cycloadducts 165 (Eq. 84). The high regioselectivity of this cycloaddition reaction has been interpreted in terms of the frontier orbital energies and coefficients.



(84)

165 166

Treatment of the pyrazolines 165 with sodium methoxide in methanol results in the loss of the 4-phenylsulfonyl group and the formation of the corresponding 1,3,5-trisubstituted pyrazoles 166. Such behaviour is in line with the known characteristics of 4-benzoyl- and 4-phenylsulfonyl-substituted pyrazolines that undergo an aromatization reaction in basic medium by elimination of the 4-substituent.

Conclusions

Reactions of hydrazidoyl halides with sulfur compounds have provided the organic chemist with opportunity of synthesizing numerous sulfur and nitrogen containing acyclic and cyclic compounds. The range of synthetic possibilities which these reactions open for the construction of fused heterocyclic compounds is also large. The use of new functionalized reactants together with a better understanding of some of the mechanistic features will significantly increase the scope of these reactions.

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