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SYNTHESIS AND REACTIONS OF 1,2,3-DITHIAZOLES

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The synthesis and the reactions of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles, 4-chloro-1,2,3-dithiazole-5-thione, 4-chloro-1,2,3-dithiazol-5-one, 4-chloro-5,5-difluoro-5*H*-1,2,3-dithiazole, 5-alkylidene-5*H*-1,2,3-dithiazoles, 4,5-dialkyl-5*H*-1,2,3-dithiazoles, some 1,2,3-dithiazolium ions and 1,2,3-dithiazolyl radicals are critically discussed. Emphasis has been placed on the mechanistic interpretation of these reactions. Applications of 1,2,3-dithiazoles are also included.

Keywords: Appel's salt; 5-Arylimino-4-chloro-5*H*-1,2,3-dithiazoles; 5-Alkylidene-5*H*-1,2,3-dithiazoles; 4,5-Dialkyl-5*H*-1,2,3-dithiazoles; 1,2,3-Dithiazolium ions

CONTENTS

1. INTRODUCTION

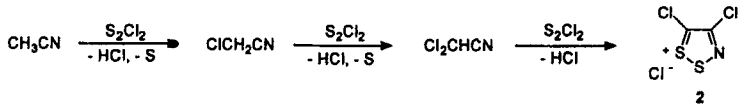
An abundance of new chemistry research has revealed much for 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) during the last decade since the structure of Appel's salt was established and its synthetic potential demonstrated by Appel *et al.* in 1985.[1] The present review outlines the synthesis, the reactions, and biological applications of

1,2,3-dithiazoles, mostly prepared by utilizing Appel's salt. The theoretical aspects and experimental structural methods of 1,2,3-dithiazoles are not covered here except for ^{15}N NMR spectroscopic data of some 1,2,3-dithiazoles because they have been included in extensive recent reviews.[2,3] A general review of 1,2,3-benzodithiazolium (Herz) salts has previously been written.[4] Only recent results relevant to Herz salts are included.

2. SYNTHESIS

2.1. 5-Arylimino-4-chloro-5*H*-1,2,3-dithiazoles, 1

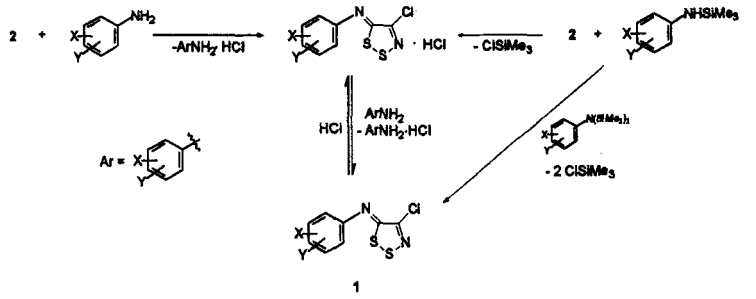
It was reported that the action of disulfur dichloride on acetonitrile gave a green substance, $C_2H_3NS_2Cl_3$, which was thought to be the labile 2,3,4-trichloro-1,2,3-dithiazole.[5] Later Appel and coworkers[1,6] isolated green crystals which were identified as 4,5-dichloro-1,2,3-dithiazolium chloride, **2**, by treatment of acetonitrile with disulfur dichloride in dichloromethane at room temperature (Scheme 1).



SCHEME 1

Compound **2** was thought to be formed by a series of reactions. That is, disulfur dichloride reacts with acetonitrile to give chloroacetonitrile together with loss of hydrogen chloride and sulfur. Further reaction of chloroacetonitrile with disulfur dichloride leads to dichloroacetonitrile which reacts with one more molecule of disulfur dichloride to give **2** with loss of hydrogen chloride. By using commercial chloroacetonitrile,[1] **2** could be obtained in 85% yield.

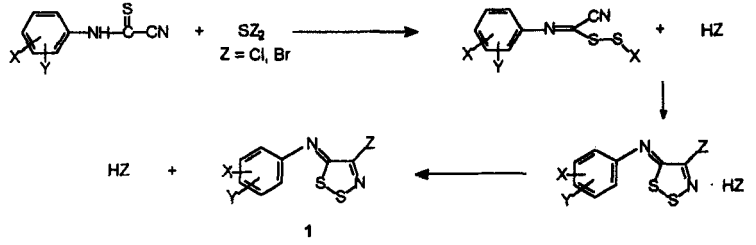
With primary arylamines, **2** reacted to form 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles **1**. The hydrogen chloride released was trapped with excess arylamine or pyridine. So compounds **1** are formed by use of two moles of amine or a mole of one second base (Scheme 2). Compounds **1** were also obtained by treatment of **2** with the less basic *N*-arylsilylamines.



SCHEME 2

Although aliphatic amines react with **2** no pure products have been isolated. The analogous imines **1** were prepared from **2** by use of the corresponding bis(trimethylsilyl)amines. Rees and coworkers prepared *N*-Me, *N*-Pr^i and *N*-CH(Me)Ph imines in this way in 48%, 38%, and 30% yield, respectively.[7]

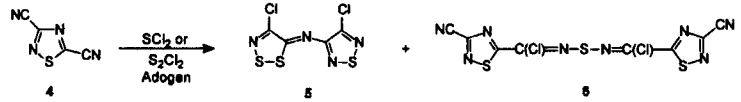
Alternatively compounds **1** were synthesized by the reaction of equimolar amounts of an *N*-arylcyanothioformamide **3** and a sulfur dihalide in the presence of a catalytic amount of a formamide or quaternary ammonium salt in various solvents, i.e. hexane, isooctane, dichloromethane, benzene, toluene, chlorobenzene, dimethoxyethane, dibutyl ether, dioxane, tetrahydrofuran, or tetrahydropyran, at 30–100°C[8] (Scheme 3).



SCHEME 3

Suitable formamide compounds include *N*-methylformamide, *N*,*N*-dimethylformamide, and *N*,*N*-diethylformamide. Tetrabutylammonium bromide and tetramethylammonium chloride were used as quaternary ammonium salts.

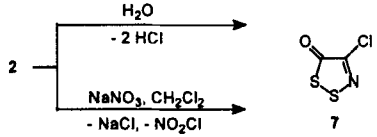
The reactions between 1,2,4-thiadiazole-3,5-dicarbonitrile, **4**, and sulfur chlorides (SCl_2 and S_2Cl_2) in the presence of a catalytic amount of Adogen®464 (Aldrich) proceeded with formation of the 1,2,3-dithiazoles **5** (34% yield) and **6** (29% yield)[9] (Scheme 4).



SCHEME 4

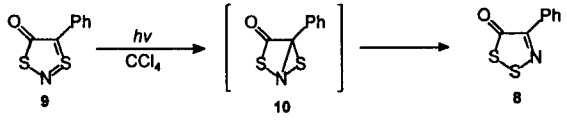
2.2. 1,2,3-Dithiazol-5-ones

Compound **2** undergoes decomposition rapidly in moist conditions with the evolution of hydrogen chloride to give a brown mass from which **7** can be isolated by sublimation.[1] Treatment of **2** with sodium nitrate in dichloromethane at reflux gives **7** in 72% yield.[1,6] (Scheme 5).



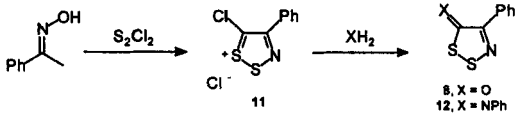
SCHEME 5

4-Phenyl-1,2,3-dithiazol-5-one, **8**, was obtained from photoisomerization of 5-phenyl-1,3,2-dithiazol-4-one, **9**, in either dichloromethane[10] or carbon tetrachloride by laboratory light in 43% and 40% yield,[11] respectively. Compound **8** was assumed to be formed via the bicyclic intermediate **10** (Scheme 6).



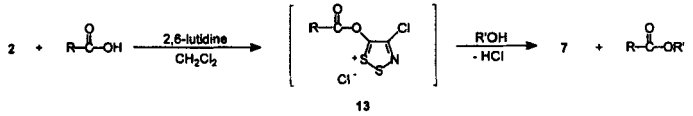
SCHEME 6

An alternative synthesis of **8** involved the reaction of acetophenone oxime with an excess of disulfur dichloride, and then reaction of the solid formed with water gave **8** in 33% overall yield, presumably via the intermediate salt **11**[11] (Scheme 7). Analogous treatment of the solid intermediate **11** with aniline gave the imine **12** in 24% overall yield.



SCHEME 7

The reactions of **2** with carboxylic acids (1 equiv.) in the presence of 2,6-lutidine at −78°C in dichloromethane, followed by warming to room temperature gave **7** and an ester[12] (39–84%) (Scheme 8).



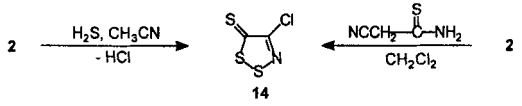
SCHEME 8

The formation of these products was rationalized by the formation of an activated intermediate **13**, which was quenched with an alcohol to give **7** and an ester. The reaction requires two equivalents of base, one to initially deprotonate the acid and one to scavenge hydrogen chloride.

The reaction was found to work best when the acid, alcohol, base and **2** were mixed at −78°C in dichloromethane and allowed to slowly warm to room temperature over 5–12 h. It was found that primary alcohols gave the best yields of esters, followed by secondary and then tertiary, probably due to the steric interactions in the attack of the alcohol on the intermediate **13**. This reaction is an alternative reaction for the synthesis of an ester.

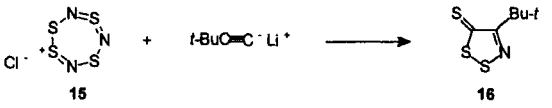
2.3. 1,2,3-Dithiazole-5-thiones

Treatment of **2** with hydrogen sulfide in acetonitrile at room temperature gave **14** in 69% yield[1] (Scheme 9). The same compound can be obtained from **2** and 2-cyanothioacetamide in dichloromethane at room temperature in 89% yield.[13]



SCHEME 9

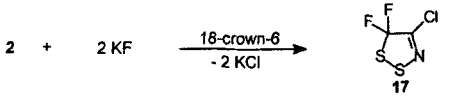
4-(*t*-Butyl)-1,2,3-dithiazole-5-thione, **16**, was isolated in 2% yield from the reaction of lithium *t*-butylacetylide and tetrathiatriazepinium chloride (S_4N_3Cl) **15**[10] (Scheme 10).



SCHEME 10

2.4. 4-Chloro-5,5-difluoro-5*H*-1,2,3-dithiazole, 17

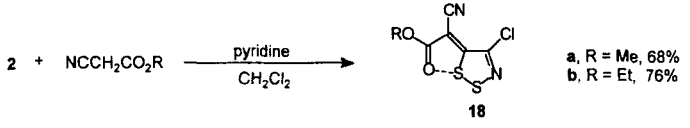
The reaction of **2** with excess potassium fluoride in the presence of 18-crown-6 in acetonitrile at room temperature gave the liquid **17** in 71% yield[1] (Scheme 11).



SCHEME 11

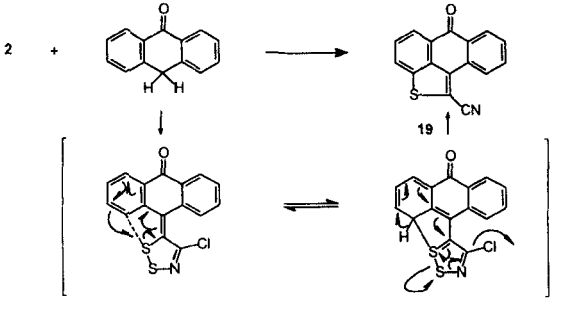
2.5. 5-Alkylidene-5*H*-1,2,3-dithiazoles

Cyanoacetic acid esters reacted with **2** in the presence of pyridine (2 equiv.) at room temperature to give dithiazol-5-ylidenes **18**[1] (Scheme 12).



SCHEME 12

Similarly anthrone reacted with **2** to give the tetracyclic compound **19** (60% yield). The formation of compound **19** was rationalized by intramolecular cyclization, followed by extrusion of sulfur and hydrogen chloride[14] (Scheme 13).

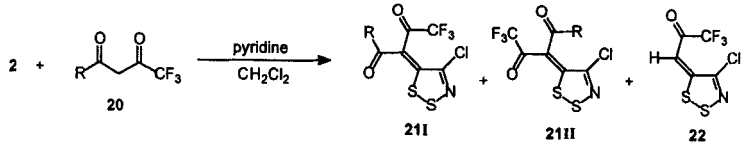


SCHEME 13

The analogous reactions with compounds having readily enolizable methylene hydrogens such as diethyl malonate, 2,4-pentanedione, and dibenzoylsulfonylmethane were reported to proceed very slowly to give low yields of the corresponding dithiazol-5-ylidenes.[14]

The reactions of 1,3-dicarbonyl compounds **20** having a trifluoromethyl group bonded to a carbonyl carbon proceeded smoothly to give a new type of 5-alkylidene-1,2,3-dithiazoles **21** and **22**[15] (Scheme 14) (see Table I).

Compounds **21** were mixtures of the stereoisomers which were inseparable by either column chromatography or HPLC.



SCHEME 14

The ratio of the stereoisomers in one compound were determined by ^{19}F NMR spectroscopy. The ^{19}F NMR spectrum of **21c** exhibited two quartets at -69.2 ($J = 5.5$ Hz) ppm and -76.2 ($J = 5.5$ Hz) ppm (Figure 1). Since the carbonyl oxygen close to S-1 would be expected to interact with S-1, this carbonyl carbon would be more electron deficient than the other carbonyl carbon. Consequently the ^{19}F NMR signal of CF_3 bonded to the electron deficient carbonyl carbon would appear more downfield. The stereochemistry is supported by an X-ray crystallographic analysis of **21bII** (Figure 2).

Unlike diphenylmethane, the reaction of diphenyldiazomethane with 1,2,3-dithiazole-5-thione, **14**, at room temperature gave the 5-alkylidene-1,2,3-dithiazole **23** in 83% yield. Similarly, the reactions

TABLE I Yields of 5-alkylidene-1,2,3-dithiazoles **21** and **22**

Entry	*R*	*Yield*[a] (%)	
		21 (21I:21II)	**22**
a	Me	21 (15:85)	
b	Ph	34 (0:100)	
c	CF_3	18	44
d	EtO	52 (10:90)	
e	2-Naphthyl	18 (0:100)	

[a] Isolated yields.

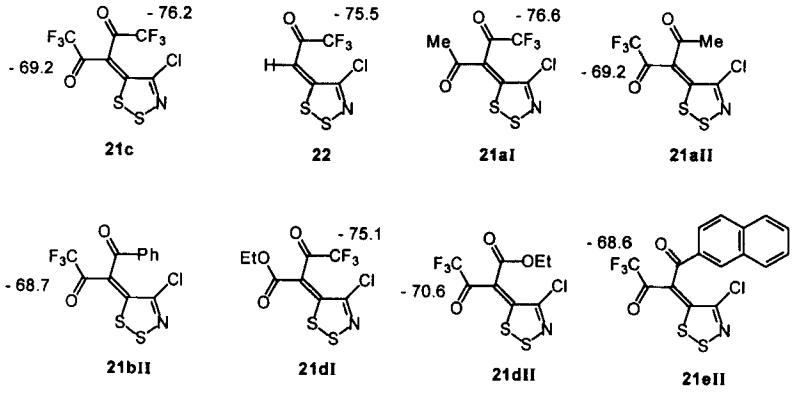


FIGURE 1

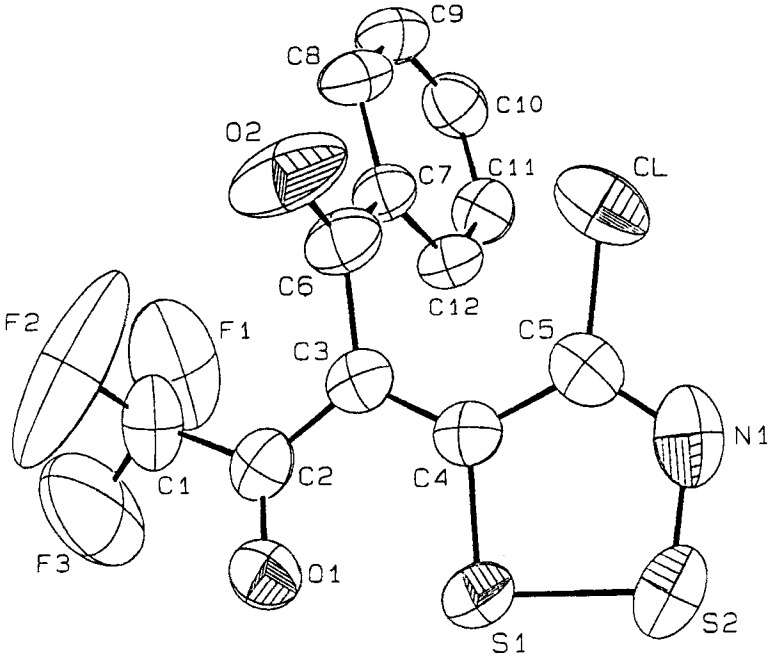
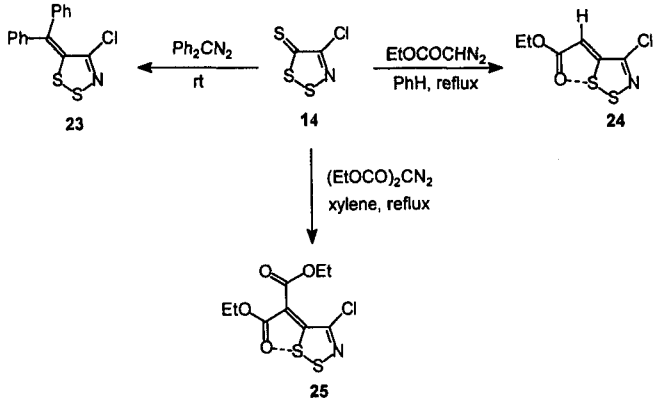


FIGURE 2 ORTEP drawing of **21bII**.

with ethyl diazoacetate in benzene and diethyl diazomalonate in xylene at reflux temperature afforded the corresponding 1,2,3-dithiazoles **24** and **25** in 63% and 37% yield, respectively[14] (Scheme 15).

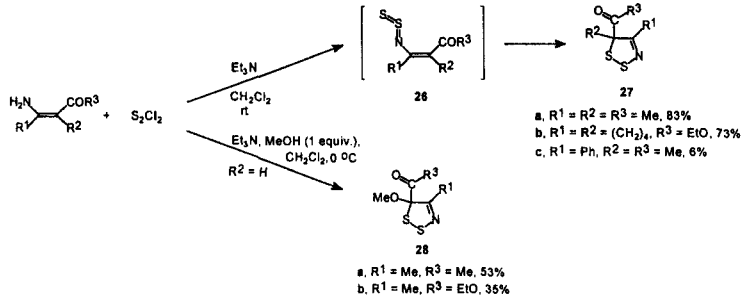
Compound **24** was obtained as a single geometrical isomer only, presumably because of the attractive O···S interaction.



SCHEME 15

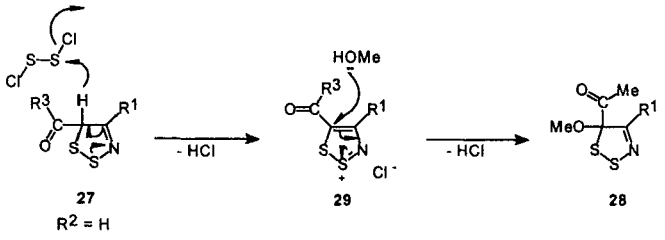
2.6. 4,5-Dialkyl-5*H*-1,2,3-dithiazoles

The reactions of β-keto enamines with disulfur dichloride in the presence of triethylamine in dichloromethane at room temperature gave 1,2,3-dithiazoles **27** via cyclization of an intermediate *N*-thiosulfinylamine **26**[16] (Scheme 16).



SCHEME 16

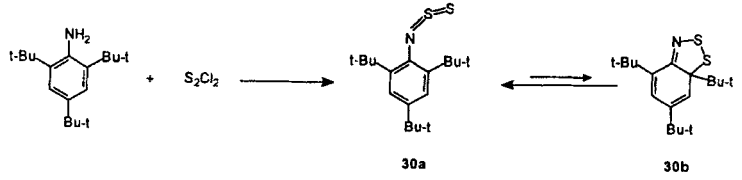
Similar reactions with β-keto enamines bearing β-hydrogen ($R^2 = H$) in methanol at 0°C gave methoxy substituted 1,2,3-dithiazoles **28**. The formation of **28** was explained by a nucleophilic attack of methanol on the dithiazolium ion **29**, which was assumed to be formed by a hydride transfer from **27** to a sulfur atom of disulfur dichloride[17] (Scheme 17).



27 $R^2 = H$ **29** **28**

SCHEME 17

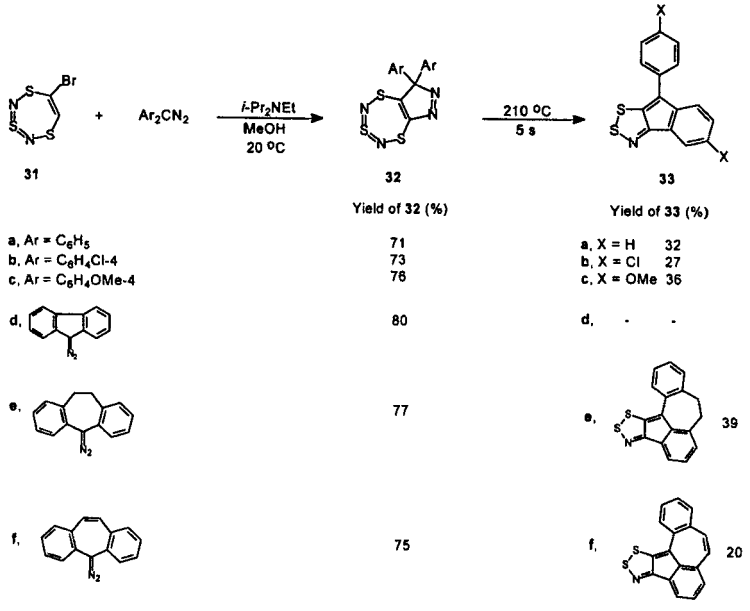
The reaction of aniline derivatives with disulfur dichloride gave *N*-thiosulfinylanilines such as **30a** which was in equilibrium with its tautomer **30b** in solution, while only **30b** existed in the solid state (Scheme 18). The conversion of **30a** to **30b** is regarded as an intermolecular 1,3-dipolar cycloaddition of the *N*-thiosulfinyl group or electrocyclization of a 1,5-dipole.[18] The equilibrium ratio, **[30a]**/**[30b]**, studied by NMR spectroscopy was subject to a considerable solvent effect, polar solvents favoring the cyclic form **30b**.[19]



30a **30b**

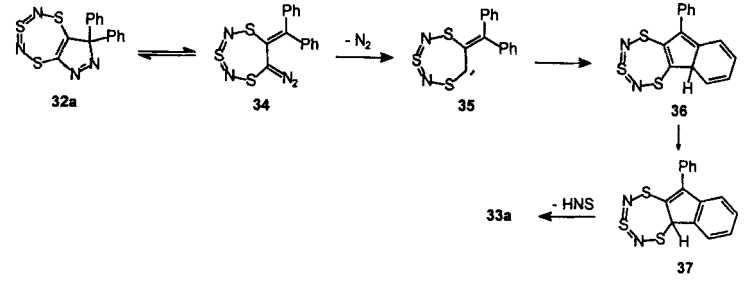
SCHEME 18

When 6-bromotrithiadiazepine, **31**, and diazo compounds were treated with *N*-ethyldiisopropylamine (Hünig's base) in methanol at room temperature the cycloadducts **32** were rapidly formed in 71–80% yield. Neat thermolysis of **32** at 210°C resulted in very rapid loss of N_2 and HNS to give the new 1,2,3-dithiazoles **33** (21–39%)[20] (Scheme 19).



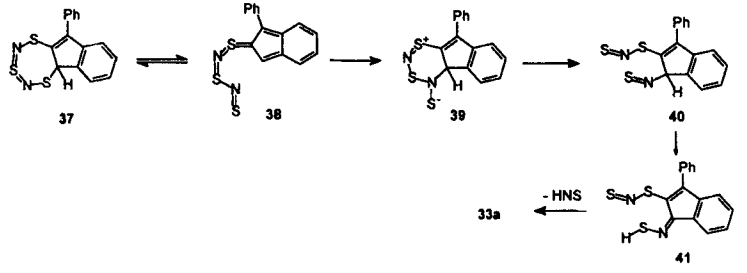
SCHEME 19

A possible mechanism for this molecular rearrangement involved reversible electrocyclic ring opening to the diazo compound **34**, followed by loss of nitrogen to form a carbene **35**, which would cyclize onto one of the benzene rings of **36**. Intermediate **36** has a stable trithiadiazepine ring which could be disrupted by a [1,5] hydrogen shift to give an aromatic benzene ring in **37**. Loss of HNS gives **33a** (Scheme 20).



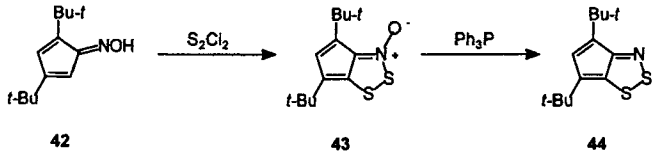
SCHEME 20

The involvement of an intermediate **37** was confirmed by its isolation and the thermolysis of **37** in a more concentrated xylene solution which gave **33a** in 36% yield.[21] A mechanism for the rearrangement of **37** to **33a** was proposed as in Scheme 21.[22] A reversible ring opening of **37** to the intermediate **38**, followed by a nucleophilic attack of the indene ring on the terminal thionitroso group to give **39**, which rapidly undergoes bond cleavage between the S and N atoms to give **40** and a proton transfer to give the thiooxime **41**. Cyclization of **41** concomitant with loss of HNS gives **33a**.



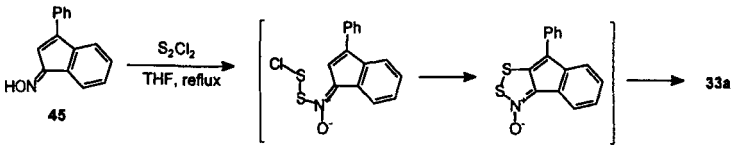
SCHEME 21

Hafner and coworkers prepared the cyclopenta-1,2,3-dithiazole **44** by treatment of cyclopentadienone oxime **42**, stabilized by two *t*-butyl groups, with disulfur dichloride in tetrahydrofuran at room temperature. The cyclized *N*-oxide **43** so formed was deoxygenated with triphenylphosphine to give the 1,2,3-dithiazole **44**[23] (Scheme 22).



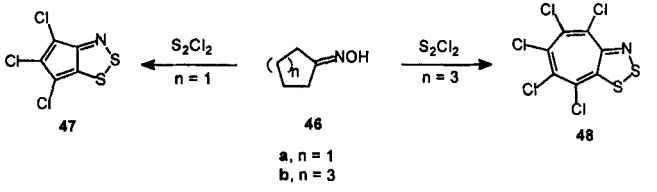
SCHEME 22

Based upon a reaction described by Hafner and coworkers, compound **33a** was independently synthesized from the oxime **45** of 3-phenylinden-1-one[24] in 58% yield[21] (Scheme 23). In the presence of *N*-ethyldiisopropylamine (Hünig's base) in tetrahydrofuran at 4°C the yield of **33a** increased to 90%.



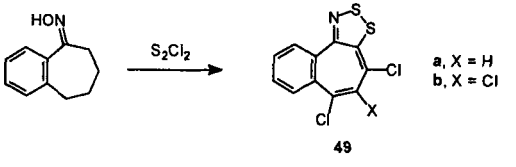
SCHEME 23

The reaction of cyclopentanone oxime **46a** with disulfur dichloride in the presence of Hünig's base in tetrahydrofuran at 4°C gave 4,5,6-trichlorocyclopenta-1,2,3-dithiazole **47** (Ca. 25%)[21] (Scheme 24). Similarly, cycloheptanone oxime (**46b**) under the same conditions gave di-, tri-, tetra- and the red pentachloro cycloheptadithiazoles (2–5%). In the presence of *N*-chlorosuccinimide (NCS) compound **48** was isolated in 14% yield, together with 7% of the tetrachloro derivative.



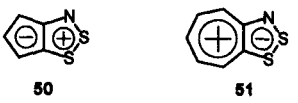
SCHEME 24

When two of the cycloheptanone ring positions were blocked by benzofusion, the oxime–S_2Cl_2 reaction gave the orange-red dichloro product **49a** (35%) and, in the presence of excess NCS the red trichloro derivatives **49b** (29%)[21] (Scheme 25).



SCHEME 25

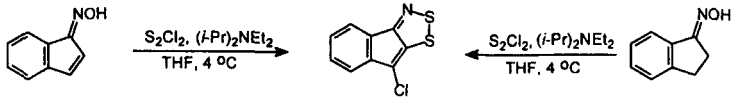
It has been proposed that polarization of the cyclopentadithiazole as shown in **50** favors complete chlorination of the election-rich ring without isolation of less chlorinated species. The reverse polarization of the cycloheptadithiazole **51** retards electrophilic substitution (Figure 3).



50 **51**

FIGURE 3

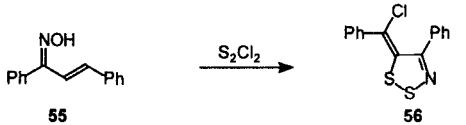
In tetrahydrofuran at 4°C in the presence of Hünig's base indenone oxime **52** gave the chloroindenodithiazole **53** (60% yield) with an excess of disulfur dichloride.[21] The same compound **53** was obtained in even higher yield (80%) from benzoindenone oxime **54** under the same conditions (Scheme 26).



52 **53** **54**

SCHEME 26

The reaction of benzylideneacetophenone oxime **55** in 1,2-dimethoxyethane or in tetrahydrofuran with Hünig's base gave the monocyclic dithiazole **56** (22–23%)[21] (Scheme 27).



55 **56**

SCHEME 27

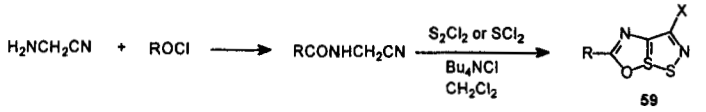
1,2,7,9-Tetrathia-3,6,8,10-tetraazacyclohept[*e*]indene, **58**, was prepared by treatment of the bifunctional sulfur diimide **57** with sulfur dichloride in dichloromethane (1% yield)[25] (Scheme 28).

57 **58**

SCHEME 28

As compounds having a skeleton of dithiazole, oxadithiadiazapentalenes **59** were prepared from sulfur dichloride or disulfur

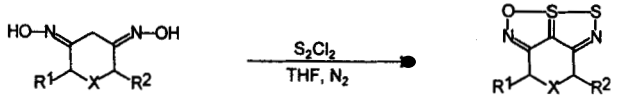
dichloride and a *N*-cyanomethylcarboxamide in the presence of tetrabutylammonium chloride[26] (Scheme 29).



X = halogen
R = alkyl, haloalkyl, halovinyl, cycloalkyl, thiocyanatoalkyl, aryloxy, arylthiomethyl, aryloxymethyl, benzylthiomethyl, benzyloxymethyl, heterocyclic.

SCHEME 29

The reactions of 1,3-dioximes with disulfur dichloride (2.2 molar equiv.) in tetrahydrofuran at −65 to −78°C under nitrogen atmosphere gave the 1-oxa-6,6aλ^4-dithia-2,5-diazapentalenes **60**[27] (Scheme 30).



X = CH_2, CHMe, CMe_2, CHPh, CH(2-furyl), CH(2-thienyl), S, SO, SO_2
R^1 = H, Me, Ph; R^2 = H, Me, Ph, 2-pyridyl

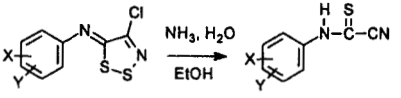
SCHEME 30

3. REACTIONS

3.1. Reactions of 5-Arylimino-4-chloro-5*H*-1,2,3-dithiazoles with Nucleophiles

3.1.1. Hydroxide

Treatment of **1** with 25% aqueous ammonia in ethanol at reflux was reported to give *N*-arylcyanothioformamides **3** in 14–86% yield[28] (Scheme 31). A mixture of compound **3** and some unidentified



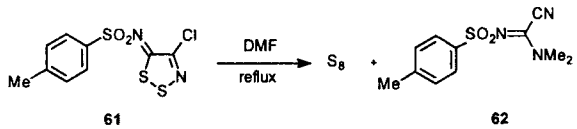
1 3

SCHEME 31

compounds were also obtained by treatment of **1** with aqueous sodium hydroxide.[1] However, it was found that separation of **3** from the mixture was very tedious. New methods for the synthesis of **3** have been developed (cf. Sections 3.1.7 and 3.4.1) although compounds **3** have been prepared by the reaction of aryl isothiocyanates with cyanides[29] along with nucleophilic displacement of C-benzenesulfonylthioformamide by cyanides.[30] However, no *N*-(aminoaryl)cyanothioformamides have been reported except for *N*-(*N*,*N*-dialkylaminoaryl)-cyanothioformamides.[29a,31]

3.1.2. Alkylamines

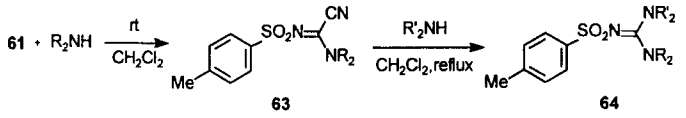
Heating of 4-chloro-5-(4-tolylsulfonylimino)-5*H*-1,2,3-dithiazole, **61**, in *N*,*N*-dimethylformamide at reflux gave sulfur (19%) and *N'*-(4-tolylsulfonyl)-*N*,*N*-dimethylcyanoformamidine **62** (64%)[32] (Scheme 32).



61 62

SCHEME 32

The isolation of compound **62** indicated that *N*,*N*-dimethylamine, possibly produced by decomposition of *N*,*N*-dimethylformamide at high temperature,[33] had participated in the reaction of **61** leading to cyanoformamidine **62**.[32] Indeed, the reactions of **61** with primary and secondary alkylamines (3 equiv.) in dichloromethane at room temperature gave *N'*-(4-tolylsulfonyl)-*N*-alkyl- and *N*,*N*-dialkylcyanoformamidines **63**, respectively (Scheme 33). On the other hand, refluxing of **63** with secondary alkylamines in dichloromethane gave 1,3-dialkyl-2-(4-tolylsulfonyl)guanidines **64**. The results are summarized in Table II. These reactions were the first examples with a sulfonyl group at the imino nitrogen atom of cyanoformamidines and guanidines.



63 64

R_2NH: 1° and 2° alkylamines, R'_2NH: 2° alkylamines

SCHEME 33

TABLE II Yields and melting points of *N'*-(4-tolylsulfonyl)-*N*-alkyl- and *N,N*-dialkylcyanoformamidines **63** and 1,3-dialkyl-2-(4-tolylsulfonyl)guanidines **64**

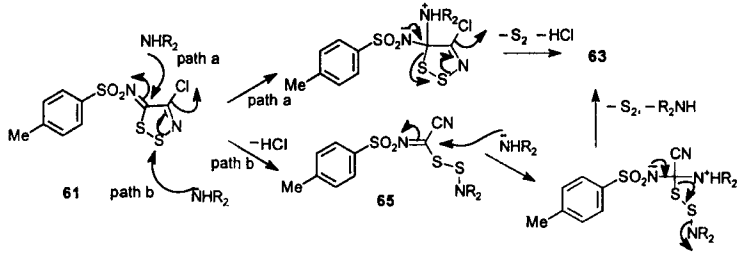
R_2NH	$R'NH$	*Yield*[a] (%) **63**	*mp*[b] °C	*Yield*[a] (%) **64**	*mp*[b] °C
		**b** 79	126–127	**a** 81(65)[c]	144–145.5
				**b** 99	179–180
				**c** 50	103–104
	Et_2NH			**d** 51	63–64
		**c** 77	128–129.5	**e** 83(53)[c]	106–107
				**f** 40	116–117.5
Et_2NH		**d** 53(18)[c]	100–101	**g** 57	48–49
		**e** 63	97–97.5	**h** 70	
i-$PrNH_2$		**f** 55	105–109		
t-$BuNH_2$		**g** 68	132–133		
n-$PentNH_2$		**h** 74	43–44		

[a] Isolated yields.
[b] Compounds **63**, **64a** and **64e** were recrystallized from a mixture of *n*-hexane and dichloromethane and other compounds **63** from a mixture of *n*-hexane and ethyl acetate.
[c] Numbers in parentheses represent the yields of **64a**, **64e**, **63d** obtained by treatment of **63** (3 mmol) in morpholine (10 ml), pyrrolidine (10 ml), and diethylamine (10 ml), respectively, without solvent.

Interestingly, reaction of **63c** with piperidine in dichloromethane gave **64f** in 40% yield whereas that of **63e** with pyrroline under the same conditions gave **64f** in 70%. This result suggests that better yields of **64** can be obtained when the sterically less hindered of two different amines to be involved in the conversion of **61**–**64** via the formation of **62** is used for the second step. There is only one report in which various sulfonyl guanidines were prepared by aminolysis of *N,N*-dialkyl-*N*-chlorosulfonylchloroformamidines with primary or secondary amines.[34] In addition compound **64** could be prepared directly by stirring the solution of **61** in a large excess of amine for 2 h at room temperature. Thus **64a** and **64e** were isolated in 65% and 53% yield, respectively, by treatments of **61** with morpholine and pyrroline, respectively. However, the same treatment of **61** in diethylamine gave only **63d** in 18% yield.

The mechanism for the formation of the cyanoformamidines **63** was explained as a nucleophilic attack of an amine on the imino carbon atom of **61** (path a, Scheme 34), followed by elimination of disulfur along with hydrogen chloride to give the cyanoformamidine **63**. On the

other hand, nucleophilic attack of an amine on S-2 to give (4-tolylimino)cyanomethyl alkylamino disulfides **65** (path b), followed by nucleophilic attack of another molecule of the amine on the imino carbon of **65** would also give **63** after elimination of disulfur and of the amine bonded to sulfur.

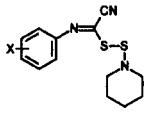


SCHEME 34

The intermediacy of the disulfides **65** was proven by isolation of the corresponding disulfides from the reations of 1,2,3-dithiazoles **1** with various alkylamines. The reaction of 5-(4-anisylimino)-4-chloro-5*H*-1,2,3-dithiazole **1a** with 2 equivalents of piperidine in dichloromethane at room temperature afforded (4-anisylimino)cyanomethyl(pentane-1,5-diyl)amino disulfide **66a** and *N'*-(4-anisyl)-*N*,*N*-(pentane-1,5-diyl)-cyanoformamidine **70a** in 53% and 32% yield, respectively. Similarly the reactions of 4-chloro-5-(4-tolylimino) **1b**, 4-chloro-5-[(4-nitrophenyl)imino], **1c**, and 4-chloro-5-[(3-nitrophenyl)imino]-5*H*-1,2,3-dithiazole **1d** with primary and secondary alkylamines were carried out under the same conditions (see Figure 4). Reaction conditions and yields are summarized in Tables III–VI.[35]

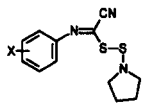
The amino iminomethyl disulfides **66–69** were first isolated from these reactions. Moreover, the isolation of the compounds **66–69** was the first evidence for the mechanistic suggestion that nucleophiles might attack S-2 among the possible nucleophilic centers, S-1, S-2, C-4, and C-5 of the aromatic 1,2,3-dithiazole derivatives **1**.

The reactions are sensitive to steric hindrance as shown by the recovery of approximately half of the starting material from the reaction of **1a** with isopropylamine (Table III, entry 4) and no formation of the amino iminomethyl disulfide from the reaction of **1c** with *t*-butylamine (Table V, entry 7). The failure for even the detection of the corresponding amino iminomethyl disulfides in the reactions of **1a** and **1b** with morpholine or in the reaction with ethylamine is due to the rapid transformation of the disulfides into the cyanoformamidines.



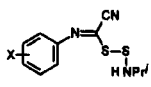
66

a, X = 4-MeO
b, X = 4-MeO
c, X = 4-NO_2
d, X = 3-NO_2



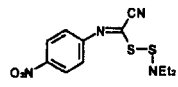
67

a, X = 4-MeO
b, X = 4-Me
c, X = 4-NO_2

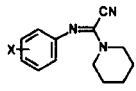


68

a, X = 4-MeO
b, X = 4-Me

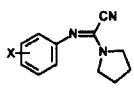


69



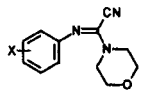
70

a, X = 4-MeO
b, X = 4-Me
c, X = 4-NO_2
d, X = 3-NO_2



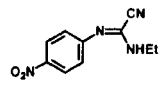
71

a, X = 4-MeO
b, X = 4-Me
c, X = 4-NO_2

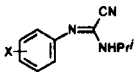


72

a, X = 4-MeO
b, X = 4-Me
c, X = 4-NO_2

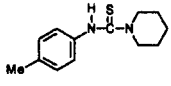


73

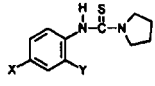


74

a, X = 4-MeO
b, X = 4-NO_2

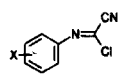


75



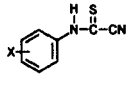
76

a, X = Me , Y = H
b, X = NO_2, Y = H
c, X = H, Y = CO_2Et



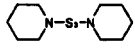
77

a, X = 4-MeO
b, X = 3-MeO



3

a, X = 4-MeO
b, X = 4-Me
c, X = 4-NO_2
d, X = 3-NO_2
e, X = 2-CO_2Et
f, X = 2-F
g, X = 4-F



78

FIGURE 4

This view is supported by the results in which the yields of cyanoformamidines increase at the expense of those of the corresponding amino iminomethyl disulfides. The involvement of the intermediacy of the amino iminomethyl disulfides during the course of the formation of cyanoformamidines was confirmed by the reactions of the selected

TABLE III Reactions of **1a** with primary and secondary alkylamines

Entry	**1a** (mM)	*Amine* (mM)	*Reaction time* (h)	*Yield*[a] (%)		
				1a	*Disulfide*	*Amidine*
1	1.95	Piperidine (4.0)	1.5		**66a** (53)	**70a** (32)
2	2.08	Pyrrolidine (4.2)	1.5		**67a** (65)	
3	1.25	Pyrrolidine (4.8)	1.0			**70a** (88)
4	3.86	Isopropylamine (7.8)	1.5	55	**68a** (14)	
5	1.97	Morpholine (4.0)	1.5	50		**71a** (23)
6	1.02	Morpholine (4.6)	1.0			**71a** (87)

[a] Isolated yields.

TABLE IV Reactions of **1b** with primary and secondary alkylamines

Entry	**1b** (mM)	*Amine* (mM)	*Reaction time* (h)	*Yield*[a] (%)		
				1b	*Disulfide*	*Amidine*
1	1.08	Piperidine (2.4)	1.0		**66b** (64)	
2	2.06	Piperidine (6.1)	1.0			**70b** (49)[b]
3	0.869	Pyrrolidine (1.8)	1.5	8	**67b** (56)	**71b** (18)
4	2.07	Pyrrolidine (6.0)	0.5			**71b** (84)[c]
5	1.31	Isopropylamine (2.9)	1.5	49	**68b** (23)	
6	2.31	Morpholine (6.8)	2.5			**72b** (77)

[a] Isolated yields.
[b] *N,N*-(Pentane-1,5-diyl)-*N'*-(4-tolyl)thiourea **75** (9%) and an unknown compound were isolated.
[c] *N,N*-(Butane-1,4-diyl)-*N'*-(4-tolyl)thiourea **76a** (12%) was isolated.

TABLE V Reactions of **1c** with primary and secondary alkylamines

Entry	**1c** (mM)	*Amine* (mM)	*Reaction time* (h)	*Yield*[a] (%)		
				1c	*Disulfide*	*Amidine*
1	1.97	Piperidine (4.0)	0.5	15	**66c** (83)	
2	1.85	Piperidine (7.6)	12			**70c** (47)
3	0.902	Pyrrolidine (2.0)	0.5		**67c** (47)	**71c** (18)
4	1.87	Diethylamine (3.8)	1.0		**69** (36)	
5	2.02	Ethylamine (16)	15			**73** (48)
6	1.08	Isopropylamine (2.3)	1.5	47		
7	3.57	*t*-Butylamine (14)	2.0	14		

[a] Isolated yields.

TABLE VI Reactions of **1d** with piperidine

Entry	**1d** (mM)	*Piperidine* (mM)	*Reaction time* (h)	*Yield*[a] (%)		
				1d	*Disulfide*	*Amidine*
1	0.773	1.7	0.5	16	**66d** (80)	
2	2.19	8.7	4.0			**70d** (14)
3	1.71	10	30			**70d** (26)

[a] Isolated yields.

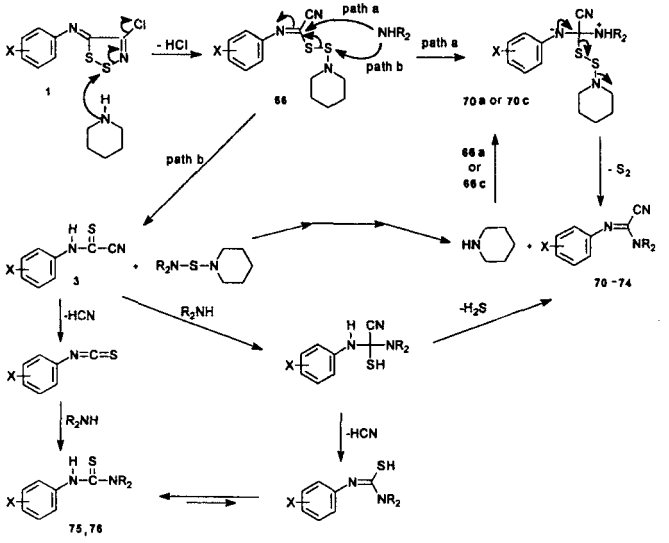
TABLE VII Preparation of *N'*-aryl-*N*-alkylcyanoformamidines from (arylimino)-cyanomethyl *N,N*-(pentane-1,5-diyl)amino disulfides **66a**, **66c**, and **66d**

Entry	*Compound* (mM)	*Amine* (mM)	*Reaction time* (h)	*Reaction temp.*	*Yield*[a] (%) *Amidine*
1	**66a** (0.163)	Pyrrolidine (1.2)	1.5	RT	**71a** (97)
2	**66a** (0.621)	Isopropylamine (4.7)	3.0	Reflux	**70a** (26)
3	**66c** (1.80)	Piperidine (5.6)	12	RT	**70c** (43)
4	**66c** (0.822)	Pyrrolidine (6.0)	1.5	RT	**71c** (24)[b]
5	**66c** (1.12)	Ethylamine (13)	15	RT	**73** (25), **70c** (5)
6	**66c** (0.372)	Isopropylamine (4.7)	5.0	Reflux	**74b** (45), **70c** (44)
7	**66c** (0.828)	*t*-Butylamine (7.5)	5.0	Reflux	**70c** (49)
8	**66c** (1.52)	Diethylamine (5.8)	24	RT	**70c** (22)
9	**66d** (0.599)	Piperidine (3.0)	30	RT	**70d** (22)
10	**66d** (1.46)	Morpholine (8.1)	0.5	RT	**72c** (77)

[a] Isolated yields.
[b] *N,N*-(Butane-1,4-diyl)-*N*-(4-nitrophenyl)thiourea **76b** was isolated in 48% yield.

compounds **66a**, **66c**, and **66d** with primary and secondary alkylamines in dichloromethane at room or reflux temperature. From the reactions were isolated the expected cyanoformamidines. The results are summarized in Table VII.

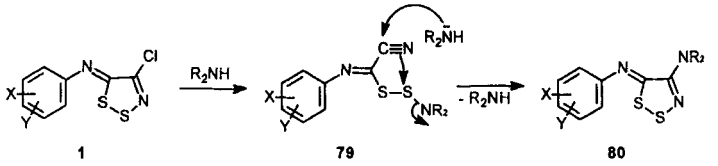
A noteworthy observation was the isolation of a thiourea derivative **76b** from the reaction with pyrrolidine (Table VII, entry 4). This result offers a clue for the mechanism of the reactions which is outlined in Scheme 35.



SCHEME 35

N-Arylcyanothioformamides **3** are good dipolarophiles,[36] and useful for the synthesis of variety of heterocyclic compounds.[29b,36e,37] Attempts to isolate bisamino sulfides failed. Instead, bis(piperidino) trisulfide **78** was isolated in 62%, 43%, 61% and 26% yield from the reactions of **1c**, **1d**, **66c**, and **66d** with piperidine, respectively.[38]

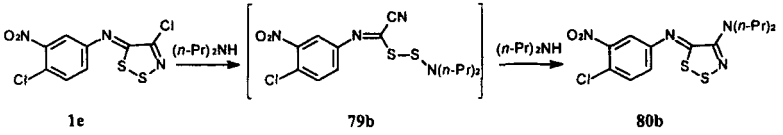
The reaction of **1** with excess bulky dialkylamines in dichloromethane at room temperature gave the 4-dialkylamino-5-arylimino-5*H*-1,2,3-dithiazoles **80**[39] (Scheme 36).



SCHEME 36

In order to determine whether the disulfides **79** act as intermediates for the formation of **80**, the disulfide **79a** (X = 5-NO_2, Y = 2-Cl, R = Et) was treated with diethylamine (8 equiv.) in dichloromethane at room temperature for 6 h to give **80a** in 26% yield. The structure of **80a** was confirmed by X-ray crystallography. This result indicates that **80** are indeed formed via the intermediacy of the disulfides **79**.

Figure 5 shows the absorption spectra of the reaction mixture after 2 min, 4.2 and 89.3 h. Figure 6 contains the absorption spectra of **1e**, **79b** (X = 3-NO_2, Y = 4-Cl, R = *n*-Pr) and **80b** in dichloromethane. Comparing Figures 5 and 6, one can recognize the rapid transformation of **1e** to disulfide **79b**, followed by a slow conversion of **79b** to **80b**. Therefore, ring opening and subsequent recyclization was proposed for the mechanism for the formation of **80b** from **1e** (Scheme 37).



SCHEME 37

3.1.3. Hydrazines

It was reported that reactions of Appel's salt **2** with hydrazines in the presence of base, i.e. triethylamine, Hünig's base, pyridine, and

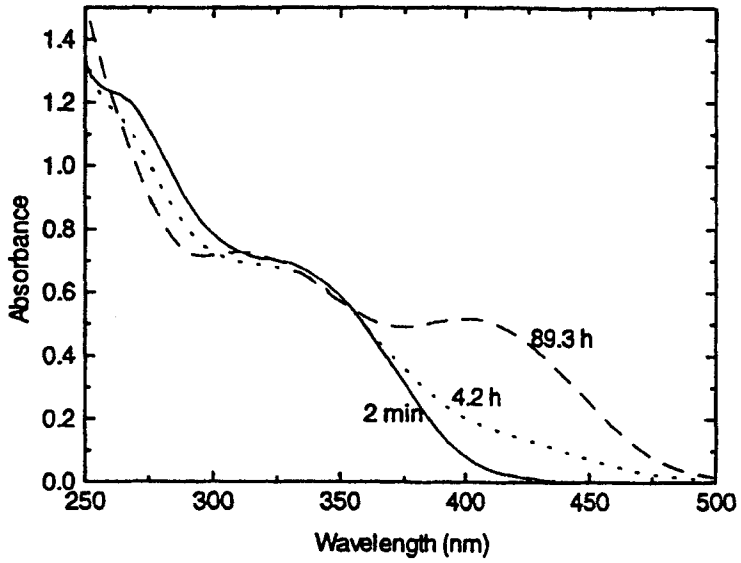


FIGURE 5 Absorption spectra of a reaction mixture obtained from the reaction of **1e** with $(n\text{-Pr})_2NH$ in CH_2Cl_2 at 2 min, 4.2 h, and 89.3 h.

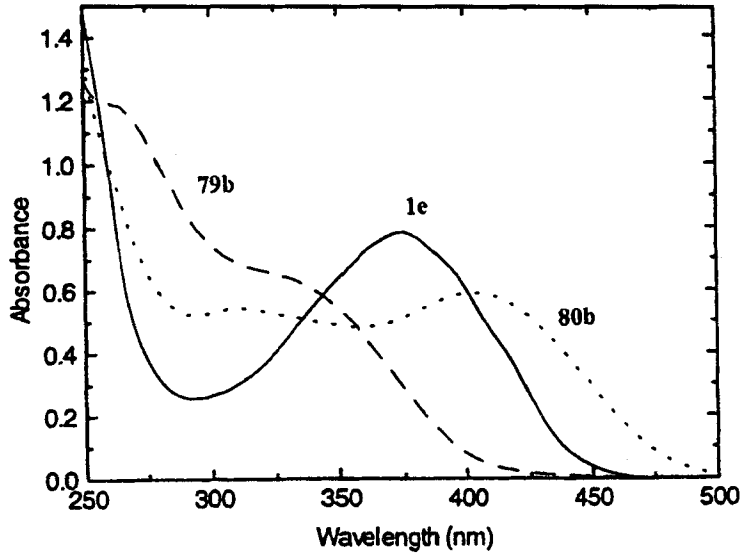
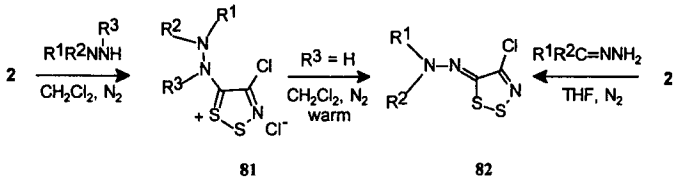


FIGURE 6 Absorption spectra of **1e**, **79b**, and **80b** in CH_2Cl_2. **1e**: λ_{max} 376 (ε 7850) nm; **79b**: λ_{max} 326 (ε 6500) nm; **80b**: λ_{max} 403 (ε 5930) nm.

lutidine at low temperature gave a complex mixture, from which the only product characterized was the dithiazole-5-thione **14**.[40] However, the same reaction with slow addition of hydrazines without base at room temperature under nitrogen in dichloromethane or tetrahydrofuran gave 5-(*N*-acetyl-*N'*-aryl- and *N*,*N*-diarylhydrazino)-4-chloro-1,2,3-dithiazolium chlorides **81** (Scheme 38). On the other hand, the reaction with benzoylhydrazine, 4-toluenesulfonylhydrazine and *N*-aminophthalimide gave directly (4-chloro-1,2,3-dithiazol-5-ylidene)hydrazines **82**. The yields of dithiazolium chlorides **81** and 5-ylidene dithiazoles **82** are summarized in Table VIII.



81 **82**

SCHEME 38

The compounds **81a–c** were reported to be light sensitive and gradually decomposed by loss of hydrogen chloride. Treatment of **81b** with dipolarophiles, i.e. dimethyl acetylenedicarboxylate in the presence of aqueous potassium carbonate or *N*-methylmaleimide in the presence of pyridine at room temperature, did not give [2 + 3] cyclized products. Instead, **1f** (X = Y = H) was the only identifiable product. Treatment of **2** with hydrazones in dry tetrahydrofuran under nitrogen atmosphere gave the corresponding derivatives **82d–e** without added base.

TABLE VIII Yields of dithiazolium chlorides **81** and 5-ylidenedithiazoles **82**

Compound	R^1	R^2	R^3	*Yield* (%)
81a	C_6H_5	C_6H_5	H	40
81b	C_6H_5	H	C_6H_5	49[a]
81c	C_6H_5	H	COMe	70
82a	C_6H_5CO	H	H	93
82b	4-$MeC_6H_4SO_2$	H	H	78
82c			H	80
82d	C_6H_5	C_6H_5		75
82e	Me	$-O_2NC_6H_4$		82

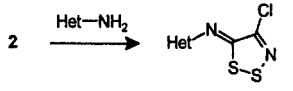
[a] Isolated as hydrochloride.

TABLE IX Yields of 5-heteroimino-dithiazoles **83**

Compound	*Amino heterocycle*	*Yield* (%)
83a	3-Aminopyrazole	67
83b	5-Amino-3,4-diphenyl-1-(4-tolyl)pyrazole	85
83c	2-Amino-1,3,4-thiadiazole	70
83d	3-Amino-2-phenylindazole	78
83e	1-Aminobenzotriazole	69
83f	2-Aminobenzotriazole	87

3.1.4. Amino Heterocycles

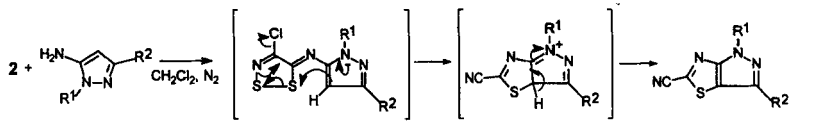
Appel's salt **2** reacted with amino heterocycles under the same conditions as for compounds **1** to give the expected 5-heteroiminodithiazoles **83** as yellow/orange crystalline solids[40] (Scheme 39).



83

SCHEME 39

Selected examples are shown in Table IX. However, the reaction with 5-aminopyrazoles **84** under the same conditions as for compounds **1** gave 1*H*-pyrazolo[3,4-*d*]thiazoles **85**.[40b] (Scheme 40). Compounds **85** were proposed to be formed by a spontaneous intramolecular cyclization of the imines **86** to give the intermediates **87**, which lost sulfur and hydrogen chloride to yield **85**. The enamine moiety in pyrazoles



84

a, $R^1 = R^2 = Me$

b, $R^1 = R^2 = Ph$

c, $R^1 = Ph$, $R^2 = Me$

86

87

85

a, $R^1 = R^2 = Me$, 81%

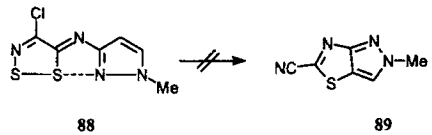
b, $R^1 = R^2 = Ph$, 52%

c, $R^1 = Ph$, $R^2 = Me$, 40%

SCHEME 40

86 must be responsible for this facile intramolecular cyclization because product **88** derived from 3-amino-1-methylpyrazole was unable to give 2*H*-pyrazolo-[3,4-*d*]thiazole **89** by a similar mechanism. The thermal stability of **88** is attributed to the lower nucleophilicity of

the C-4 position compared with **86**, and also to the attractive S···N interaction[41] (Scheme 41).

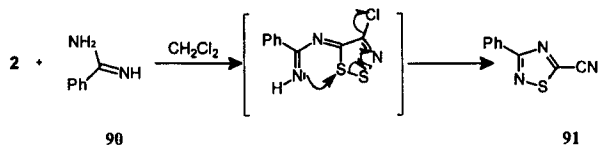


88 **89**

SCHEME 41

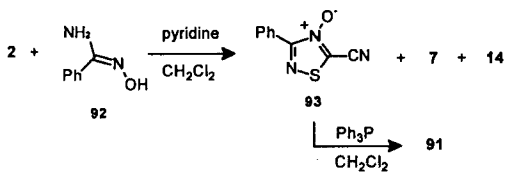
3.1.5. Benzamidoximes

The reaction of **2** with benzamidine **90** in dichloromethane at room temperature was reported to give 5-cyano-3-phenyl-1,2,4-thiadiazole **91**[42] (Scheme 42). Similar treatment of benzamidoxime **92** with **2** in dichloromethane at room temperature, followed by addition of pyridine, gave the 4-oxide **93** (8%) together with dithiazol-5-one **7** (32%) and dithiazole-5-thione **14** (15%). Deoxygenation of the *N*-oxide **93** with triphenylphosphine in dichloromethane at room temperature for three days gave **91** (89%) (Scheme 43).



90 **91**

SCHEME 42

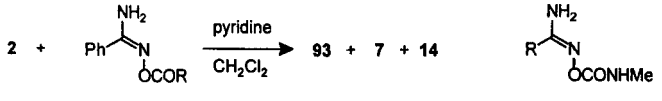


92 **93**

SCHEME 43

The reactions with various *O*-substituted benzamidoximes **94** gave **93** in somewhat higher yields, together with comparable amounts of **7** and **14** (Scheme 44). From the reactions with the alkyl amidoximes **95** (R = Me, *t*-Bu, $PhCH_2$) and aryl amidoximes **95** (R = 4-ClC_6H_4,

4-BrC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2,4-$Cl_2C_6H_3$) were obtained only **7** (up to 38%) and **14** (up to 60%), often in high combined yield. With **95** (R = 4-MeC_6H_4 and 4-$Me_2NC_6H_4$), the corresponding *N*-oxides, analogous to **93**, were isolated in 16% and 11% yield, together with **7** (15% and 20%) and **14** (25% and 28%), respectively.



94

95

a, R = Me, 22%

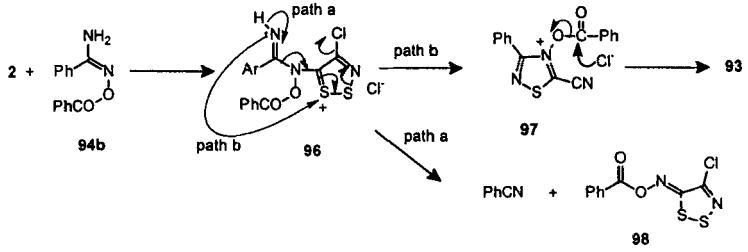
b, R = Ph, 20%

c, R = NHMe, 30%

d, R = NHC_6H_4Cl-4 25%

SCHEME 44

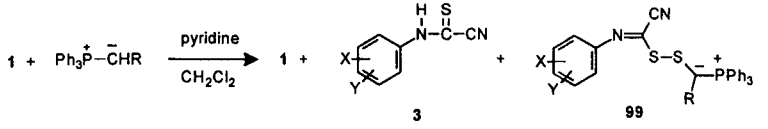
The formation of **93** from **2** and **94** was explained by initial attack by the amidoxime **94b** upon Appel's salt **2** through the oxime nitrogen atom to give an intermediate **96**, which undergoes further reaction via two pathways. Nucleophilic attack of an imine nitrogen S-2 concomitant with extrusion of S_8 and hydrogen chloride gives a new intermediate **97** (path b), which undergoes bond cleavage between a carbonyl carbon and an oxygen atom to give **93**. Cleavage of a bond between the amino carbon and nitrogen atom (path a) gives benzonitrile (23%) and benzoyloxy imine **98** (15%) (Scheme 45). The structure of the latter was established by comparison with that of an authentic sample which was prepared independently (34%) from *O*-benzoylhydroxylamine and **2** in dichloromethane in the presence of pyridine.



SCHEME 45

3.1.6. Phosphoranes

The reactions of **1** with stable phosphoranes (2 equiv.) such as carboethoxymethylene-, acetylmethylene-, 4-chlorobenzoylmethylene-, and cyanomethylenetriphenylphosphoranes in the presence of pyridine (1 equiv.) in dichloromethane at room temperature gave the (arylimino)-cyanomethyldithiomethylenephosphoranes **99** as the major product along with **3** as the minor product[43] (Scheme 46). Some examples are shown in Table X.



SCHEME 46

The structures of **99** were determined unambiguously on the basis of the X-ray crystallographic analysis of **99i** (Figure 7). Without pyridine, the yields of **3b**, **3c**, and **3a** increase at the expense of the yields of **99b**, **99f**, and **99h**, respectively with out appreciable change in the amount of the recovered starting materials. These results indicate that compounds **3** are formed by reaction of compounds **99** with the hydrogen chloride generated. The major role of pyridine may be to trap hydrogen chloride formed.

The mechanism for the formation of **3** and **99** was formulated as a nucleophilic attack of the phosphorane to S-2 to form a phosphonium

TABLE X Reactions of 1,2,3-dithiazoles **1** with some stable phosphoranes

X	*Y*	*R*	*Yield*[a] (%)					
			1		**3**		**99**	
4-MeO	H	CO_2Et	**a**	7	**a**	11	**a**	69
4-Me	H	CO_2Et	**b**	8 (11)	**b**	7 (32)	**b**	81 (38)
2-Cl	H	CO_2Et	**g**	9	**h**	28	**c**	41
4-Cl	H	CO_2Et	**h**	6	**i**	14	**d**	75
4-Br	H	CO_2Et	**i**	7	**j**	7	**e**	78
4-NO_2	H	CO_2Et	**c**	15 (17)	**c**	8 (38)	**f**	70 (32)
2-Me	4-NO_2	CO_2Et	**m**	9	**m**	12	**g**	74
4-MeO	H	COMe	**a**	7 (6)	**a**	9 (38)	**h**	79 (39)
2-CN	H	COMe	**j**	8	**l**	8	**i**	68
2-Me	H	4-ClC_6H_4CO	**k**	16	**k**	11	**j**	48
4-MeO	H	CN	**a**	15	**a**	16	**k**	53

[a] Isolated yields. Numbers in parentheses represent the yield in the absence of pyridine.

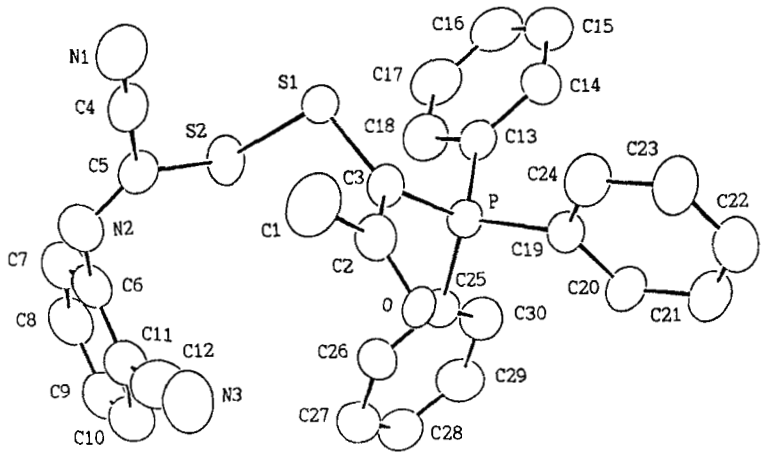
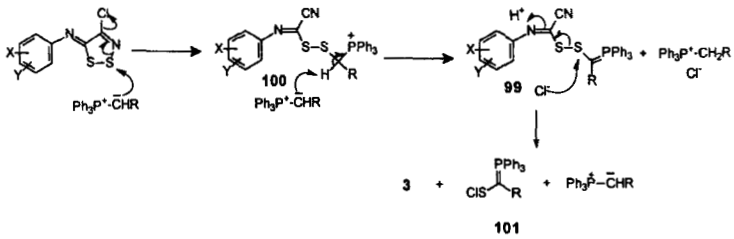


FIGURE 7 ORTEP drawing of compound **99i**.

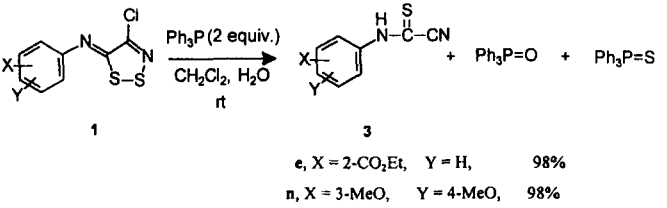
chloride **100**, which lost hydrogen chloride in the presence of another molecule of phosphorane to form the dithiomethylenephosphorane **99**. Compounds **99** react with hydrogen chloride to form cyanothioformamides **3**. The fate of the new phosphoranes **101** which are conceived to be generated with **3** during the reaction is uncertain (Scheme 47).



SCHEME 47

3.1.7. Triphenylphosphine

Treatment of **1** with triphenylphosphine (2 equiv.) in moist dichloromethane at room temperature gave **3** together with triphenylphosphine oxide and sulfide[44a] (Scheme 48). However, the reaction with anthranilic acid (1 equiv.) in dichloromethane at room temperature, followed by the addition of pyridine (2 equiv.), gave 2-cyano-3,1-benzoxazin-4-one **102** (46%) and with triphenylphosphine gave 2-cyano-3,1-benzothiazin-4-one **103** (69%) (Scheme 49). When an excess of

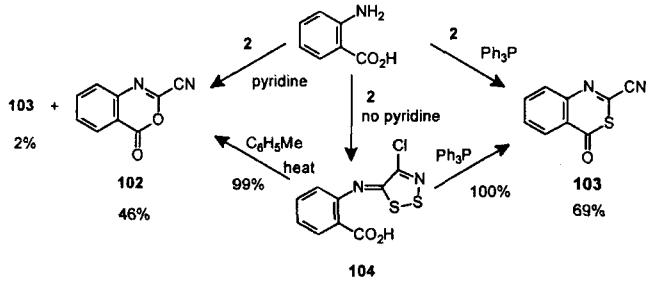


1 3

e, X = 2-CO_2Et, Y = H, 98%

n, X = 3-MeO, Y = 4-MeO, 98%

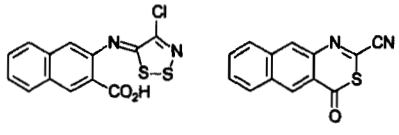
SCHEME 48



SCHEME 49

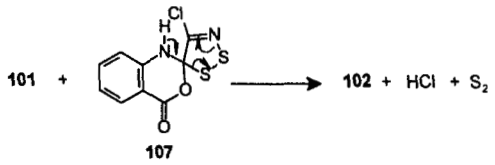
anthranilic acid (4 equiv.) was treated with **2** without the addition of pyridine, the imino derivative **104** of the free carboxylic acid was isolated in 60% yield, whereas when 3 and 5 equivalents of anthranilic acid were used, the yield of **104** decreased to 52% and 22%, respectively. When **104** was heated in boiling toluene, the benzoxazinone **102** was formed in 99% yield and when heated with triphenylphosphine (2 equiv.) in dichloromethane it gave the benzothiazinone **103** quantitatively. Similarly, the reaction with 3-amino-2-naphthoic acid under the same conditions without base gave the imino carboxylic acid **105** (72%) analogous to **104** (Figure 8). In contrast, the imino carboxylic acid reacted with triphenylphosphine under the same conditions to give only the naphthothiazinone **106** (24%). The same acid gave in the presence of pyridine under the same conditions the thiazinone **106** (48%).[44b]

It has been proposed that thermolysis of the imino carboxylic acid **104** proceeds by cyclization to the spiro intermediate **107** and elimination from this of hydrogen chloride and disulfur to give **102**[44a] (Scheme 50). The triphenylphosphine induced conversion of imines **1** into the cyanothioformamides **3** may be explained by nucleophilic attack of the phosphine on S-2 of **1** with formation of the thioamide



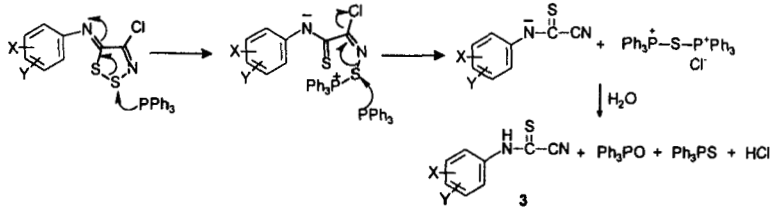
105 106

FIGURE 8



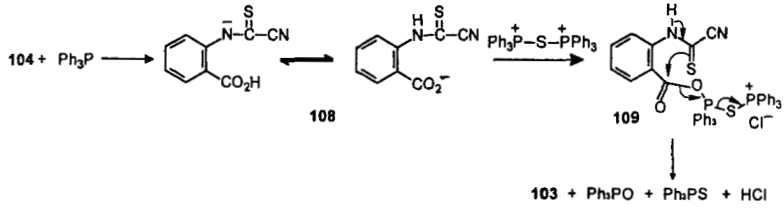
SCHEME 50

anion, followed by attack of the second phosphine on the same sulfur to give the stabilized cyanothioformamide anion and $Ph_3P^+-S-P^+Ph_3$, hydrolysis of which would give all the observed products (Scheme 51).



SCHEME 51

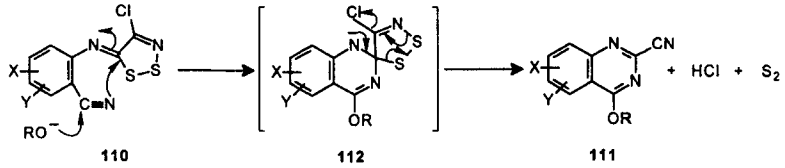
The imine **104** would give the ionic species **108**, which could collapse to give **109**, in which the carboxylic acid is now activated by the phosphonium salt; this then acts as a good leaving group to give the benzothiazonine **103** and the other observed products[44a] (Scheme 52).



SCHEME 52

3.1.8. Alcohols

Long heating of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilonitrile **110** (X = Y = H) in alcohols at reflux gave the corresponding quinazolines **111** in low to modest yields[45] (Scheme 53). The yields were increased when the alcohol was first treated with one equivalent of base (NaH or KF), sodium hydride generally being superior. Typical examples are shown in Table XI.



SCHEME 53

The formation of the quinazolines **111** was explained by addition of the alkoxide ion to the cyano group, followed by cyclization to give the spiro intermediate **112** or its *N*-protonated form, which rapidly fragmented to give **111**, together with disulfur and hydrogen chloride (Scheme 53). Interestingly the yield of **111** was much improved, in a short reaction time, by microwave irradiation of the reaction mixture. 4-Alkoxyquinazoline-2-carbonitriles have been prepared in a Reissert type reaction by treatment of the 4-alkoxyquinazoline 1-oxide with potassium cyanide and benzoyl chloride.[46]

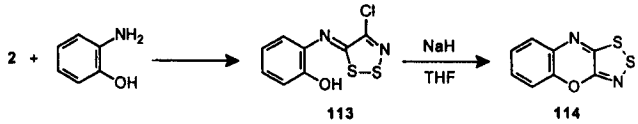
o-Aminophenol condenses with **2** to give the iminodithiazole **113** in 95% yield (Scheme 54). When the iminodithiazole is converted to the

TABLE XI Yields of quinazoline-2-carbonitriles **111**

X	*Y*	*R*	*Reaction conditions*	*Yield* (%)
4-MeO	5-MeO	Me	MeOH, NaH (1.1 equiv.), reflux, 40 h	77
4-MeO	5-MeO	Et	EtOH, NaH (1.1 equiv.), reflux, 40 h	77
5-MeO	5-MeO	Et	EtOH, KF 10%, reflux, 40 h	74
5-MeO	5-MeO	Bu	BuOH, NaH (1.1 equiv.), reflux, 40 h	82
4-MeO	5-MeO	Bu	BuOH, KF 10%, reflux, 40 h	72
H	H	Et	EtOH, NaH (1.1 equiv.), reflux, 40 h, Microwave irradiation	29
4-MeO	5-MeO	Et	EtOH, NaH (1.1 equiv.), reflux, 2 h [a,b]	80
H	H	Et	EtOH, NaH (1.1 equiv.), reflux, 2 h	80

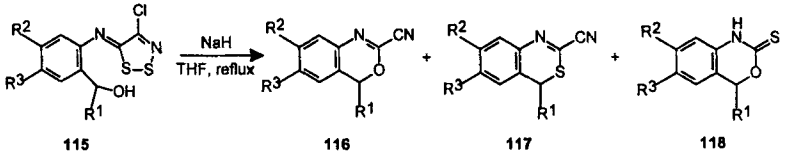
[a] Incomplete reaction after 1 h (yield 50%).
[b] Incomplete reaction without NaH after 5 h of irradiation.

corresponding phenoxide ion it cyclizes readily to give the dithiazolobenzoxazine **114** (68%). The intermolecular equivalent of this cyclization did not proceed with sodium phenoxide and **1f** (X = Y = H) under vigorous conditions.[14]



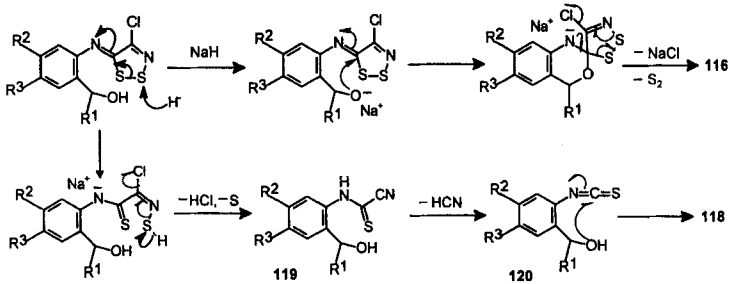
SCHEME 54

On the other hand, refluxing of 4-chloro-5-(2-hydroxymethylarylamino)-5*H*-1,2,3-dithiazoles **115** with sodium hydride in tetrahydrofuran led to benzoxazine **116** (29–71%), benzothiazine **117** (5–10%), and benzoxazine-2-thiones **118**[47] (Scheme 55).

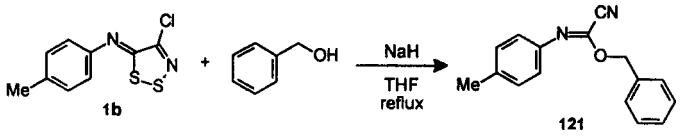


SCHEME 55

The formation of **116** was rationalized by nucleophilic attack of alkoxide ion on the imino carbon, followed by extrusion of sulfur (Scheme 56). On the other hand, nucleophilic attack of hydride ion at S-2, followed by ring opening gave *N*-(2-hydroxymethylaryl)cyanothioformamides **119**, which then lose hydrogen cyanide, yielding 2-(hydroxymethyl)aryl isothiocyanates **120**. Intramolecular cyclization of **120** gives **118**. However, the intermolecular reaction of **1b** (X = 4-Me, Y = H) with benzyl alcohol under the same conditions gave only a 17% yield of [*N*-(4-tolyl)imino]cyanomethyl benzyl ether **121**, which is the acyclic analog of **116**[47] (Scheme 57).

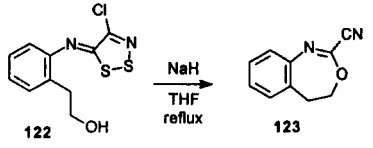


SCHEME 56



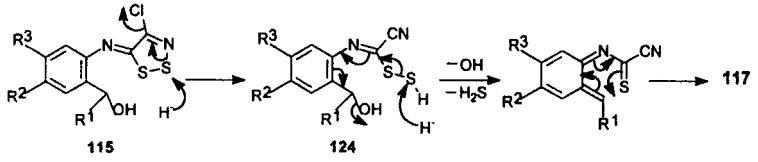
SCHEME 57

The dihydro-3,1-benzoxazepine **123** was also prepared in two steps in 71% yield from 2-amino-phenethyl alcohol **122**[48] (Scheme 58).

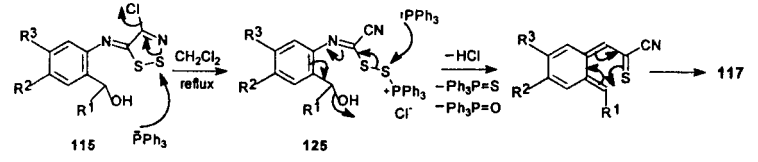


SCHEME 58

The formation of the benzothiazines **117** may involve opening of the dithiazole ring by hydride, followed by elimination of hydrogen sulfide and water to give the reactive intermediate **124** which cyclizes to the stable product **117**[48] (Scheme 59). The benzothiazine ring was obtained in much better yield by heating of **1** in dichloromethane at reflux in the presence of 2 equivalents of triphenylphosphine.[48] It was envisaged that initial attack of phosphorus on S-2 would open the dithiazole ring with the formation of the intermediate **125**, which cyclized to give **117** (Scheme 60). The yields of benzoxazines **116** and benzothiazines **117** obtained by using sodium hydride and triphenylphosphine are given in Table XII.



SCHEME 59



SCHEME 60

TABLE XII Synthesis of benzoxazines **116** and benzothiazines **117** from imines **115**

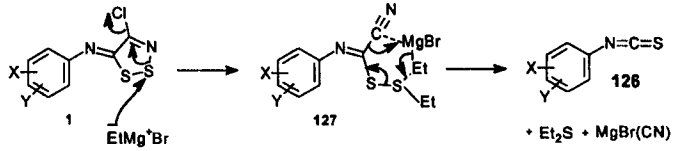
Imines **115**			*Method*[a]	*Product*	*Yield of product*[b] (%)
R^1	R^2	R^3			
H	H	H	A	**116a**	44 (55:5)
H	H	H	B	**117a**	58
H	Me	H	A	**116b**	54 (60:10)
H	Me	H	B	**117b**	65
H	H	Cl	A	**116c**	30 (44:6)
H	H	Cl	B	**117c**	80

[a] Method A: NaH (2 equiv.), THF, reflux; method B: PPh_3 (2 equiv.), CH_2Cl_2, reflux.
[b] In brackets: yields of compounds (**116**:**117**) after a rapid separation by column chromatography.

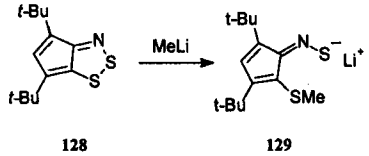
3.1.9. Organometallic Bases

A commercial solution of ethylmagnesium bromide (2 equiv.) in tetrahydrofuran was added dropwise to a heated solution of **1** in tetrahydrofuran under argon and heated at reflux to give the isothiocyanates **126** in 45–65% yield[49] (Scheme 61). Similar yields were obtained under mild conditions (room temperature, overnight) and by microwave irradiation. The results are summarized in Table XIII.

The mechanism for the formation of **126** was explained by nucleophilic attack of the Grignard reagent at S-2, followed by generation of the cyano group. Attack by a second molecule of the Grignard reagent on the same sulfur could result in formation of the isothiocyanate, dialkyl sulfide and cyanide anion, possibly assisted by electrophilic catalysis in a cyclic transition state **127**. Cyclopenta-1,2,3-dithiazole **128** undergoes cleavage at the S–S bond to give a salt **129** on reaction with methyllithium at −80°C[23] (Scheme 62).



SCHEME 61



SCHEME 62

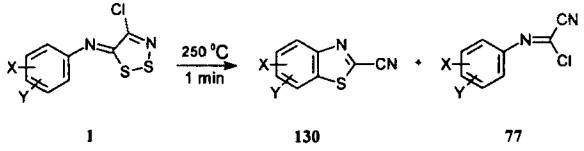
TABLE XIII Synthesis of aryl isothiocyanates, **126** from iminodithiazoles, **1**

Compound	*X*	*Y*	*Yield* (%)
126a	H	H	54
126b	2-F	H	50
126c	2-CN	H	55 (A);76 (B)
126d	4-MeO	H	44 (A);75 (B)
126e	4-CN	H	60
126f	3-MeO	4-MeO	50
126g	$3\text{-}OCH_2CH_2O\text{-}4$		47(A); 73 (B)

(A): Compounds **126** were obtained with ethylmagnesium bromide. (B): Compounds **126** were obtained *via* the formation of cyanothioformanilides.

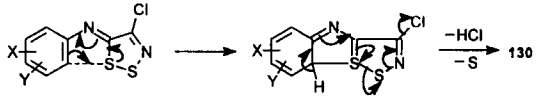
3.2. Thermolysis

Compounds **1** decomposed when vigorously heated to give sulfur, hydrogen chloride and the 2-cyanobenzothiazoles **130**[14,50] (Scheme 63). An electron-releasing group (X = 3-MeO, Y = H) favored formation of the benzothiazole **130** while a strongly electron-withdrawing group (X = 3- or $4\text{-}NO_2$, Y = H) reduced the yield of **130** dramatically, in favor of the cyanoimidoyl chloride **77**. Compound **130** was assumed to be formed by an electrocyclization and fragmentation process (Scheme 64).



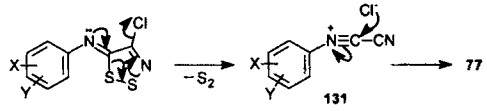
1 **130** **77**

SCHEME 63



SCHEME 64

The formation of the imidoyl chloride **77** was explained by direct loss of sulfur as S_2 to form the nitrilium chloride **131** which collapses to the observed product (Scheme 65).



SCHEME 65

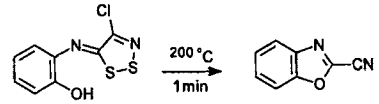
TABLE XIV Yields of cyanobenzothiazoles **130** and imidoyl chlorides 77

X	*Y*	*Yield* (%)	
		130	**77**
2-F	H	50	
3-F	H	34[a]	
4-F	H	34	10
2-F	4-F	11	2
3-F	4-F	22[b]:3[c]	20

[a] 5-Fluorobenzothiazole-2-carbonitrile.
[b] 5,6-Difluorobenzothiazole-2-carbonitrile.
[c] 6,7-Difluorobenzothiazole-2-carbonitrile.

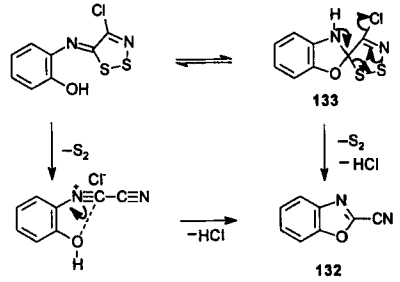
Compounds **1** having monofluoro and difluoro atoms as substituents under the same conditions gave benzothiazoles **130** but three gave some imidoyl chlorides **77**[51] (Table XIV). The fluorine atoms appeared not to be sufficiently electron-withdrawing for the imidoyl chloride to become dominant.

Thermolysis of the neutral (*o*-hydroxyphenyl)imine **113** involved loss of sulfur as well as of hydrogen chloride to give 2-cyanobenzoxazole **132** (90%)[14] (Scheme 66). A possible mechanism for the formation of **132** involved the loss of disulfur to give the nitrilium salt, followed by collapse to benzoxazole, but cyclization to the spiro compound **133** with subsequent loss of hydrogen chloride and disulfur has also been proposed (Scheme 67).



113 **132**

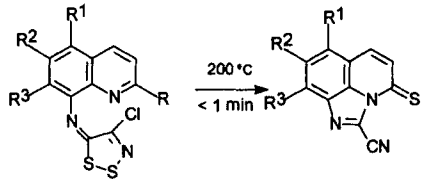
SCHEME 66



SCHEME 67

Thermolysis of the imino-1,2,3-dithiazoles **134** (R = H), prepared from 8-aminoquinolines and Appel's salt **2**, at 200°C in less than

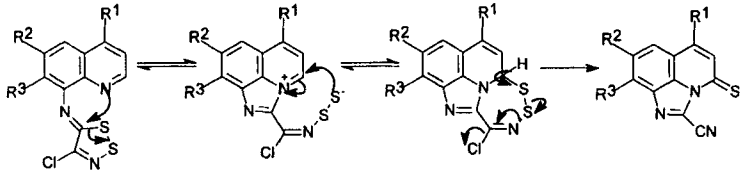
1 min gave the imidazo[5,4,1-*ij*]quinoline-4-thiones **135**[52] (25–49%) (Scheme 68).



134 **135**

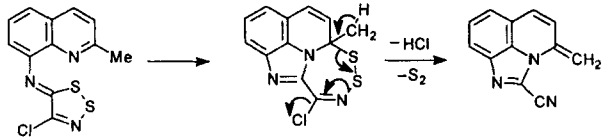
SCHEME 68

The mechanism for the formation of **135** was proposed to consist of nucleophilic attack of the quinoline nitrogen on C-5 of the 1,2,3-dithiazole moiety to give the imidazoquinoline **136** which collapsed to the tetracyclic species **137**. Elimination of hydrogen chloride and loss of one sulfur atom from the 7-membered ring in **137** possibly via the nitrile sulfide, would yield **135** (Scheme 69). When the quinoline 2-position was blocked (R = Me, Cl), no 6-thiones **135** were isolated, which indicated the involvement of intramolecular sulfur transfer. A very minor product, tentatively assigned structure **139**, was isolated from the methyl compound **138** (Scheme 70).



134 **136** **137** **135**

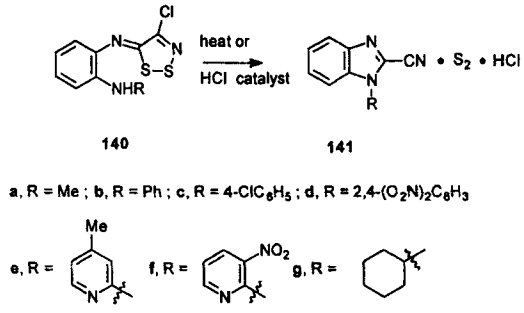
SCHEME 69



138 **139**

SCHEME 70

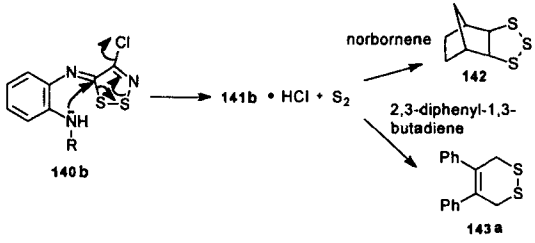
Upon thermolysis, most of the (*o*-aminophenyl)imines **140** gave the corresponding 1-substituted 2-cyanobenzimidazoles **141** in fair to good yields[50] (Scheme 71).



SCHEME 71

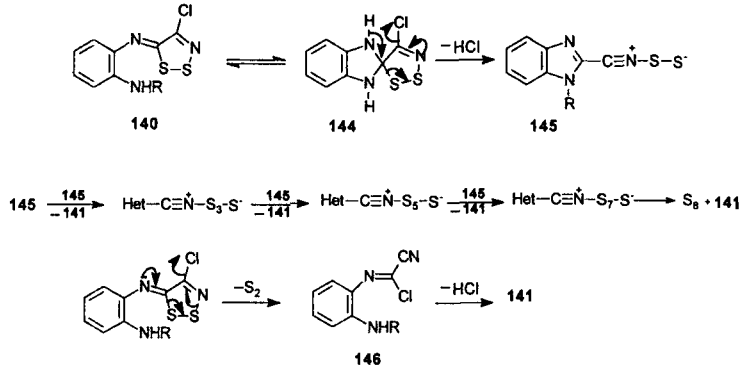
Compound **141a** was obtained from **140a** in benzene at reflux for 10 min, **141g** by heating neat at 160°C for 2 h. Compounds **140b** and **140f**, which are very poorly nucleophilic, failed to undergo rearrangement at temperature up to 180°C. Compounds **140a–c** rearranged to the corresponding **141** in dichloromethane at room temperature in yields of 31%, 93%, and 80%, respectively. Addition of pyridine (2 equiv.) to the reaction mixture, however, suppressed the spontaneous rearrangement. By omission of pyridine it was possible to convert the amines into compounds **141** in one step, without isolation of the imines **140**.

Heating of compound **140b** in norbornene at 140–150°C for 4 h in a sealed tube gave **141b** (72%) together with trisulfide **142** (78%) which indicated the formation of S_2. Similarly, in the presence of 2,3-diphenylbutadiene the S_2 Diels–Alder adduct **143a** (25%) was obtained at 140–150°C for 3 h in a sealed tube[50] (Scheme 72). However, decomposition of **140b** in the presence of norbornene at a lower temperature in boiling toluene did not give **142**, although **141b** was formed (69%). Similarly, the same treatment of **140a** in toluene (2.5 h), in xylene (4 h) or in a sealed tube at 110°C (2 h) in the presence of 2,3-diphenylbutadiene did not give **143a**. These results suggest that S_2 is generated only at the higher, and S_8 at the lower temperature.



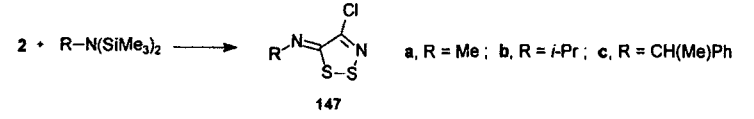
SCHEME 72

The mechanism for the formation of compounds **141**, S_2, and S_8 was proposed as the following[50] (Scheme 73). At the lower temperature, the *o*-amino group on the dithiazole **140** attacks C-5 of the 1,2,3-dithiazole moiety to give the spiro compound **144**, which loses hydrogen chloride to give the nitrile disulfide **145** which could undergo extension of the sulfur chain with final formation of S_8. At higher temperature compound **144** could fragment to compound **141**, hydrogen chloride, and disulfur, or alternatively disulfur could be extruded directly, with formation of the cyanoimidoyl chloride **146**, which then cyclizes to the benzimidazole **141**.

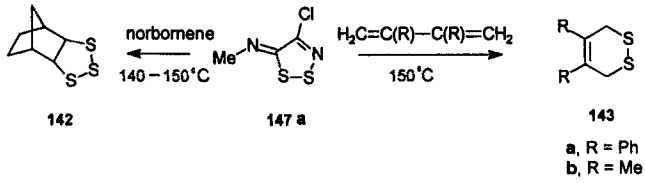


SCHEME 73

N-Alkylimines **147**, prepared from **2** by use of the corresponding bis(trimethylsilyl)amines, decomposed at lower temperature. Thus, they would be more appropriate for the generation and interception of singlet disulfur[7] (Scheme 74). Heating **147a** in sealed tubes, with 2,3-diphenylbutadiene and 2,3-dimethylbutadiene gave the known disulfur Diels–Alder adducts **143a** (29%) and **143b** (19%), respectively (Scheme 75). Under the same conditions norbornene gave the trisulfide **142** (62%). The disulfur adducts **142** and **143** were not formed from S_8 and the alkenes under the same conditions.



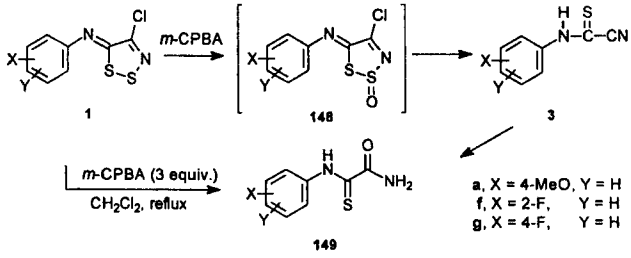
SCHEME 74



SCHEME 75

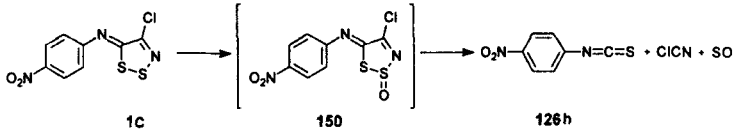
3.3. Oxidation

Compound **1a** (X = 4-MeO, Y = H) was treated with *m*-chloroperbenzoic acid (*m*-CPBA) (1.1 equiv.) in dichloromethane at −20°C and room temperature to give *N*-(4-methoxyphenyl)cyanothioformamide **3a** (X = 4-MeO, Y = H) in 32% and 65% yield, respectively[51] (Scheme 76). Compound **3a** was assumed to be formed via hydrolysis of the unstable oxide **148**. Similar oxidation of **1a** with excess *m*-CPBA (3 equiv.) in refluxing dichloromethane gave the thioamide **149** in 72% yield, presumably by oxidative hydration of the cyano group in **3a**. Similarly, the cyanothioformamides **3f** and **3g** were obtained in 59% and 37% yield, respectively.



SCHEME 76

In contrast, oxidation of **1c** (X = 4-NO_2, Y = H) with *m*-CPBA (1.1 equiv.) in dichloromethane at room temperature gave 4-nitrophenyl isothiocyanate **126h** in 90% yield.[51] It was proposed that the *S*-oxide **150** formed underwent rapid fragmentation as shown (Scheme 77). Oxidation of the heterocyclic imine **83a** with *m*-CPBA (2 equiv.) in dichloromethane at room temperature did not give the corresponding oxidation products.[40a] The imine **83a** was recovered in 82% yield. Upon treatment of **83a** with potassium permanganate in acetone at



SCHEME 77

room temperature or dinitrogen tetroxide in dichloromethane at 0°C **83a** was recovered in 62% and 80% yield, respectively. It was reported that oxidation of **83b** with *m*-CPBA (2 equiv.) in the dichloromethane at 0°C, followed by standing at room temperature, gave the *S,S*-dioxide **151** in 55% yield (Figure 9).

The reaction of tetrathiatriazepinium chloride (thiotriazyl chloride), S_4N_3Cl,[10] with phenylacetylene in toluene at reflux gave a complex mixture of products, from which the 1,2,3-dithiazolyl imine **152** was isolated in 5% yield (Figure 10). Oxidation of **152** with *m*-CPBA in dichloromethane gave the *S*-oxide **153** in 60% yield. S-1 appears to be less nucleophilic due to an electron shift towards the imino nitrogen. The 1,2,3-dithiazole ring in the fused system **33a** was oxidized to an *S*-oxide **154** by treatment with dinitrogen tetroxide in dichloromethane[20] (Figure 11). S-1 would be less nucleophilic than S-2 owing to its electron release to the imine nitrogen around the 5,5-fused ring system.

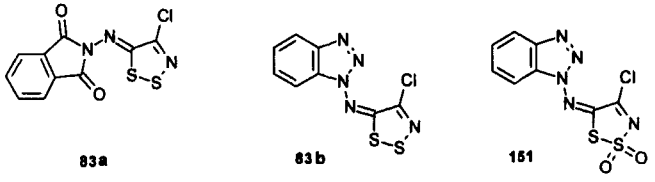


FIGURE 9

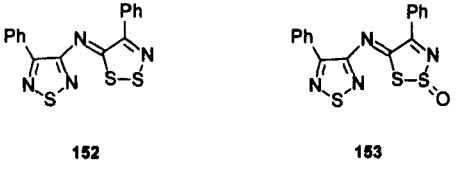


FIGURE 10

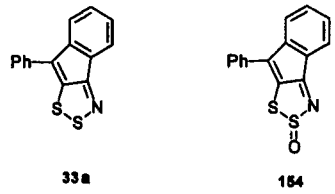
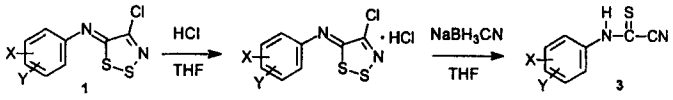


FIGURE 11

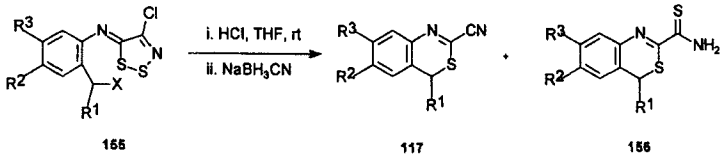
3.4. Reduction

3.4.1. Sodium Cyanoborohydride ($NaBH_3CN$)

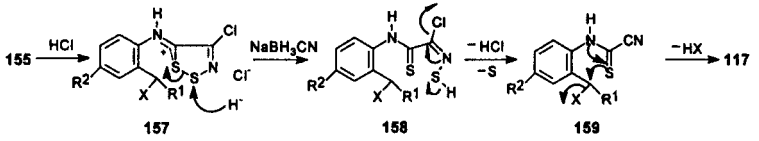
Hydrochloride salts of **1**, formed *in situ* by bubbling of hydrogen chloride into the solution of **1** in dry tetrahydrofuran, reacted with excess sodium cyanoborohydride in dry tetrahydrofuran at room temperature to give the cyanothioformamides **3** (40–100%)[53] (Scheme 78) (cf. Sections 3.1.1., 3.1.7., and 3.3.). Similarly, from the hydrochlorides of the 4-chloro-5-(2-halomethylarylimino)-5*H*-1,2,3-dithiazoles **155** and sodium cyanoborohydride were obtained the 2-cyano-4*H*-3,1-benzothiazines **117** (44–71%) and the 2-thiocarbamoyl-4*H*-3,1-benzothiazines **156** (7–13%)[47] (Scheme 79). The formation of the benzothiazines **117** was explained by nucleophilic attack of hydride ion on S-2 of the hydrochlorides **157** to form the ring-opened intermediate **158**, which rapidly lost hydrogen chloride and sulfur to give the cyanothioformamide derivative **159**. Intramolecular cyclization of **159** yielded **117** (Scheme 80).



SCHEME 78



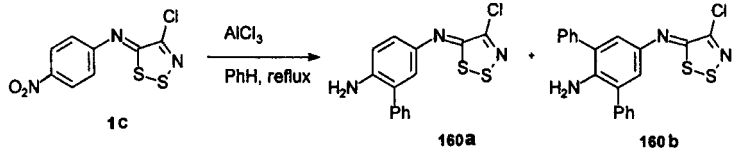
SCHEME 79



SCHEME 80

3.4.2. *Anhydrous Aluminum Chloride ($AlCl_3$)*

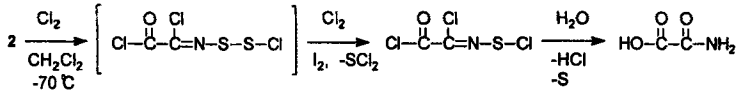
Compound **1c** in anhydrous benzene was heated in the presence of anhydrous aluminum chloride at reflux to give two compounds **160a** and **160b** bearing an amino group on the arylimino group at C-5 of compound **1c**[54] (Scheme 81). The yields of **160a** and **160b** were variable depending on the molar ratio of **1c** and $AlCl_3$. The highest yields of **160a** and **160b** were obtained when 14 equivalents of $AlCl_3$ were used. The compounds **160** prepared are summarized in Table XV. Compounds **160a–c**, **160f–h**, **160j** and **160l** are the first examples of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles having a primary amino group at the arylimino group.



SCHEME 81

3.5. Reactions of 1,2,3-Dithiazol-5-ones

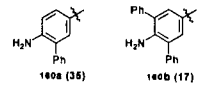
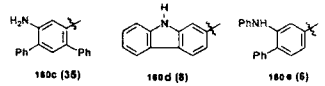
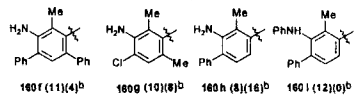
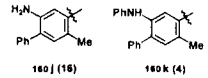
The reaction of **2** with chlorine in dichloromethane at room temperature led slowly and incompletely to a mixture of unreacted starting material, chloro disulfide **161**, and sulfenyl chloride **162**. The intermediate **161** is thermally labile and changes into the stable **162** with evolution of chlorine by gentle heating. In the presence of iodine at elevated temperature **2** was quantitatively converted to **162** which hydrolyzed slowly to give oxalic acid monoamide **163**[1] (Scheme 82).



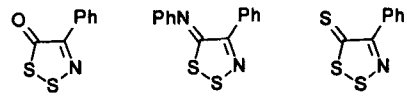
161 162 163

SCHEME 82

TABLE XV Reactions of nitroarylimines **1c–g** with anhydrous $AlCl_3$ (14 equiv.) in benzene

Compound	*X*	*Y*	*N-Ar Yield*[a] (%)
1c	4-O_2N	H	 160a (35) 160b (17)
1d	3-O_2N	H	 160c (35) 160d (8) 160e (6)
1n	3-O_2N2-Me		 160f (11)(4)[b] 160g (10)(6)[b] 160h (8)(16)[b] 160i (12)(0)[b]
1o	5-O_2N2-Me		 160j (16) 160k (4)
1p	4-O_2N2-Me		 160l (14)[c]

[a] Isolated yield.
[b] Yields when $AlCl_3$ (7 equiv.) was used. Unreacted **1n** (40%) was recovered.
[c] Unreacted **1p** (28%) was recovered.



8 **12** **164**

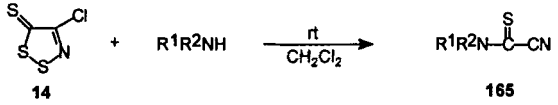
FIGURE 12

Treatment of 4-phenyl-1,2,3-dithiazol-5-one **8** with thionyl chloride or phosphorus pentachloride in refluxing dichloromethane and subsequent treatment of the resulting solid with aniline gave none of the imino compound **12**, but only recovered starting material.[11]

The reaction of **8** with Lawesson's reagent in toluene at 80°C led to destruction of the starting material and gave none of the corresponding thione **164** (Figure 12).

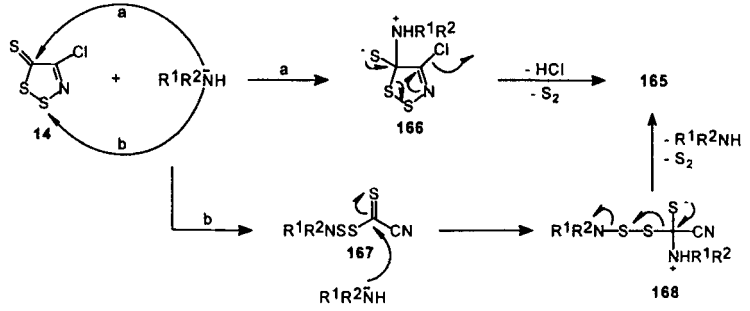
3.6. Reaction of 4-Chloro-5*H*-1,2,3-dithiazole-5-thione, 14, with Alkylamines

To a solution of **14** in dichloromethane was added primary and secondary alkylamine (2 equiv.). The mixture was stirred at room or reflux temperature. From the reactions were isolated the *N*-alkyl- and *N*,*N*-dialkylcyanothioformamides **165** (27–93%)[55] (Scheme 83).



SCHEME 83

The formation of **165** was rationalized by a nucleophilic attack of the alkylamine at C-5 to give an intermediate **166**, which loses hydrogen chloride and disulfur to yield **165**. Alternatively, a nucleophilic attack of alkylamine at S-2 concomitant with the displacement of the chlorine atom was proposed to give an intermediate **167**, which would be attacked by a second molecule of alkylamine to give **165** via an intermediate **168** (Scheme 84).



SCHEME 84

3.7. Reactions of 5-Alkylidene-5*H*-1,2,3-dithiazoles with Alkylamines

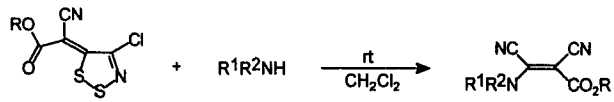
The reactions of alkyl (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)cyanoacetate **18** with primary and secondary alkylamines in dichloromethane

TABLE XVI Yields and C=O absorptions of acrylates **169**

Compound	*R*	*R'*	R^2	*Yield*[a] (%)	*C=O* (cm^{-1})
169a	Me	Me	H	68	1680
169b	Me	Et	H	64	1688
169c	Me	*i*-Pr	H	39	1690
169d	Me	*t*-Bu	H	54	1686
169e	Me	*n*-Pent	H	69	1688
169f	Me	*i*-Pr	Me	47	1712
169g	Me	*n*-Pr	*n*-Pr	55	1715
169h	Me	*n*-Bu	*n*-Bu	56	1716
169i	Et	*i*-Pr	H	72	1675
169j	Et	*t*-Bu	H	41	1680
169k	Et	Et	Et	61	1706
1691	Et	*i*-Pr	Me	55	1706

[a] Isolated yields.

at room temperature gave the 3-alkylamino-2,3-dicyanoacrylates **169** (39–72%)[15] (Scheme 85). Yields and C=O absorptions of **169** are summarized in Table XVI.



18 **169**

R^1 = alkyl; R^2 = H, alkyl

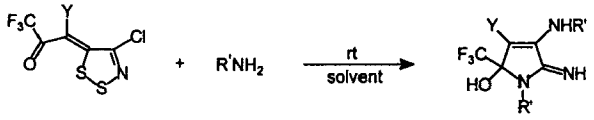
SCHEME 85

The stereochemistry of **169** was assigned based on the ester carbonyl stretching frequencies. That is, compounds **169a–e**, and **169i,j** having a secondary amino group exhibited C=O stretching absorptions at 1675–1690 cm^{-1}, while compounds **169f–h** and **169k,l** having a tertiary amino group exhibited their corresponding absorptions at 1706–1716 cm^{-1}. The lower frequencies of the former may be attributable to hydrogen bonding between an N-H hydrogen and a carbonyl oxygen, whereas the latter do not have a hydrogen atom on nitrogen for hydrogen bonding. As a result, the C=O absorptions of the latter appear at higher wave numbers.

Compounds **169** are alkenes with three electron-withdrawing and one electron-donating groups, which is seldom reported.[56]

Treatment of compounds **21** and **22** with primary alkylamines in either dichloromethane or tetrahydrofuran (aqueous methyl- or

ethylamine) at room temperature for 2–4 h gave the 2,5-dihydro-2-iminopyrroles **170** (25–55%) (Scheme 86).

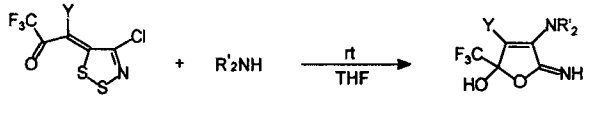


21, 22 **170**

SCHEME 86

The most diagnostic feature in the ^{13}C NMR spectrum of **170** is the carbon absorption of CF_3, appearing at 123.6–125.7 ppm, exhibiting a quartet due to splitting by three fluorine atoms with $J_{CF} = 258$ Hz and the absorption of the quaternary carbon next to the CF_3 group, appearing at 60.2–81.1 ppm, exhibiting a quartet with $J_{CCF} = 30$ Hz.[15]

Treatment of **21** with secondary alkylamines in tetrahydrofuran for 9–16 h under the same conditions as for primary alkylamines gave the 2,5-dihydro-2-iminofuranes **171** (18–62%) (Scheme 87).

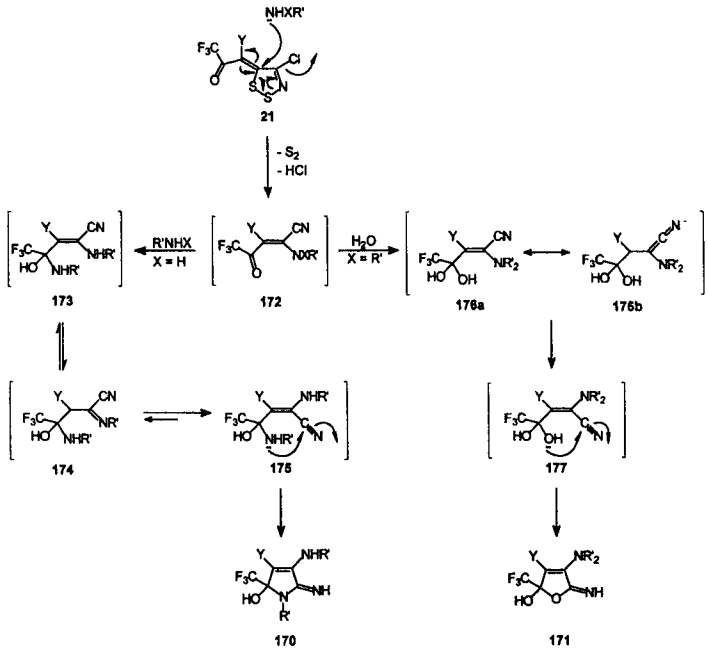


21 **171**

SCHEME 87

The ^{13}C NMR spectra of **171** exhibited two quartets at 81.3–85.1 ppm with $J_{CCF3} = 33$ Hz and at 122.5–124 ppm with $J_{CF} = 288$ Hz. The former quartet was assigned as a quaternary carbon next to the CF_3 group and the latter as the CF_3 carbon atom.

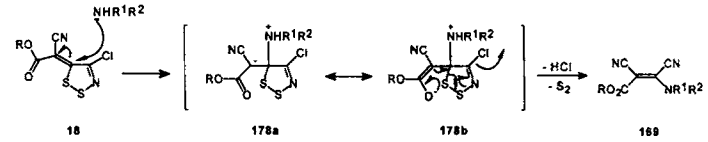
The mechanism for the formation of **170** may be explained by nucleophilic attack of a primary alkylamine on C-5 of compound **21** concomitant with extrusion of disulfur and hydrochloric acid to give a keto enamine **172** which reacts with a second molecule of the primary alkylamine to give the enamino hemiaminal **173** rather than its stereoisomer **174** (cf. Scheme 89). The intermediate **174** isomerizes to **175** via a tautomerization, followed by cyclization, to yield **170** (Scheme 88).



SCHEME 88

However, when a second molecule of a bulky secondary alkylamine attacks the carbonyl carbon of intermediate **172**, severe steric hindrance would be expected. As a result, water originating from either a wet alkylamine or the moisture in the air attacks the carbonyl carbon to form a *gem*-diol **176a**, which may be isomerized to **177** via a polar form **176b**. Intramolecular cyclization of **177** gives **171**.

When **18** were treated with primary or secondary alkylamines, compounds **169**, which are analogous to an intermediate **172** (Scheme 88) were isolated as major products. The mechanism for the formation of **169** can be explained by nucleophilic attack of an alkylamine on C-5 of **18** to give an intermediate **178a**. Electron delocalization according to resonance form **178b**, followed by extrusion of disulfur and hydrogen chloride, gives **169** (Scheme 89).



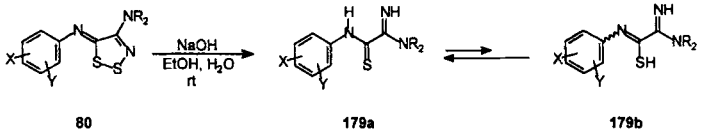
SCHEME 89

Based on the stereochemistry of **169**, the stereochemistry of the intermediate **172** is proposed as shown.

3.8. Reactions of 4-Dialkylamino-5-arylimino-5*H*-1,2,3-dithiazoles, 80

3.8.1. Hydroxide

Treatment of compounds **80** with hydroxide ions in aqueous ethanol at room temperature gave the *N*,*N*-dialkyl-*N'*-arylthiocarbamoylamidines **179** (68–99%)[57] (Scheme 90).



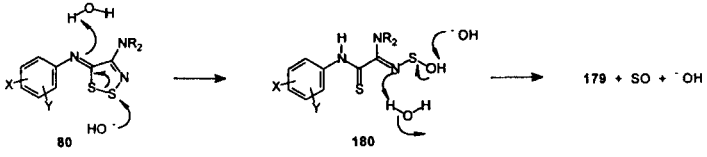
SCHEME 90

Compounds **179** are the first examples of amidines with an *N'*-arylthiocarbamoyl group, although a variety of amidines have been reported.

The ^{13}C NMR spectrum of compound **179** (X = 4-NO_2, Y = H, R = *n*-Bu) showed six peaks at 122.51, 124.17, 139.63, 158.92, 164.15, and 175.95 ppm. The last two peaks, i.e. 175.95 and 164.15 ppm, may be assignable to thione and imino carbons, respectively, in view of the literature values for thione carbon atoms[58] and imino carbon atoms of amidines in $CDCl_3$[59] around 180 and 165 ppm, respectively. One cannot rule out the possibility of an equilibrium mixture of two tautomeric forms.

Of the two stereoisomers of **179**, the *E*-isomer, having an imino N–H bond trans to C-NR_2 group, is expected to be predominant in solution because of avoiding steric overcrowding of the N-H and N-alkyl groups in view of the results obtained with *N*,*N*-dimethylbenzamidine.[60]

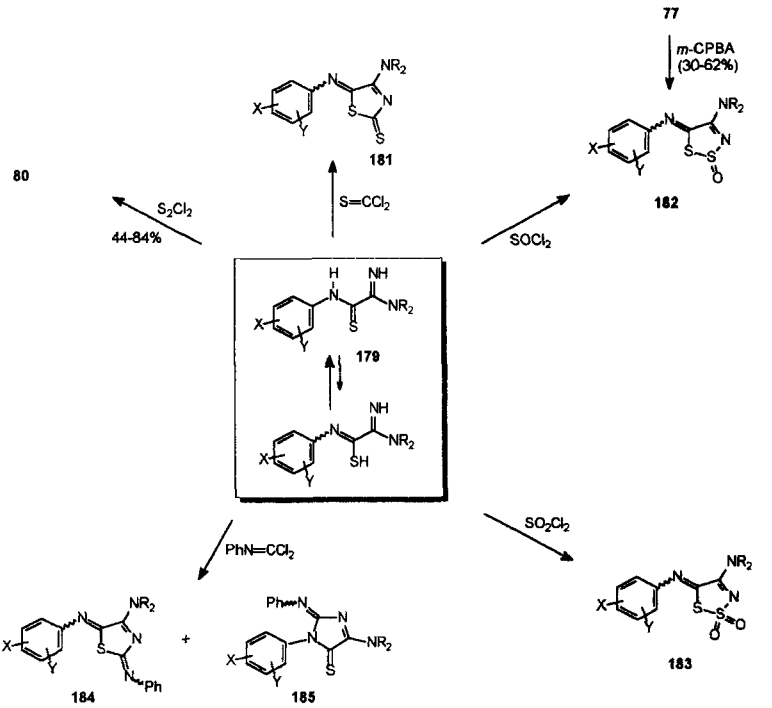
The formation of **179** was proposed to take place by nucleophilic attack of hydroxide ion on S-2 to cleave the bond between S-1 and S-2, yielding an intermediate **180** because of the presence of a dialkylamino group at C-4 which is known as a poor leaving group. Rapid extrusion of SO, followed by protonation, gives compound **179** (Scheme 91).



SCHEME 91

3.8.2. *Reactions of N,N-Dialkyl-N'-arylthiocarbamoylamidines, 179, with Electrophiles*

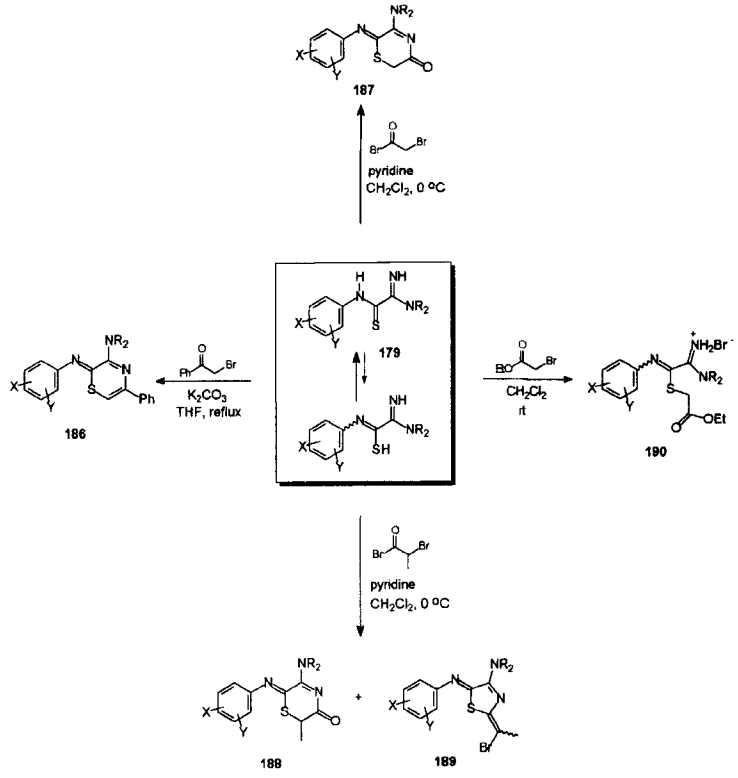
The synthetic potentialities of **179** have been demonstrated by the reactions of **179** with various electrophiles.[57] 4-Dialkylamino-5-aryliminothiazoline-2-thiones **181** (71–91%), 4-dialkylamino-5-arylimino-5*H*-2-oxo-1,2,3-dithiazoles **182** (21–78%), 4-dialkylamino-5-arylimino-5*H*-2,2-dioxo-1,2,3-dithiazoles **183** (9–14%) and 4-dialkylamino-5-arylimino-2-phenyliminothiazolines **184** (56–93%) have been prepared from compounds **179** (Scheme 92), which have a four-atom unit, as nucleophiles, reacting with one atom unit such as thiophosgene, thionyl chloride, sulfuryl chloride, and *N*-phenylimidoyl dichloride as electrophiles.



SCHEME 92

The reactions of **179** with α-bromo ketones, α-bromoacyl bromides and α-bromo esters in the presence of base at room or reflux temperature gave new compounds, i.e.

3-(di-*n*-alkylamino)-2-arylimino-5-phenyl-2*H*-1,4-thiazines **186** (32–62%), 5-(di-*n*-alkylamino)-6-arylimino-2*H*-1,4-thiazin-3-ones **187** (41–84%), 5-(di-*n*-alkylamino)-6-arylimino-2-methyl-2*H*-1,4-thiazin-3-ones **188** (45–63%), 4-(di-*n*-alkylamino)-5-arylimino-2-(1-bromoethylidene)thiazolines **189** (0–21%) and *N*,*N*-(di-*n*-alkyl)[(arylimino)-(S-ethoxycarbonylmethyl)]methylamidine hydrobromides **190** (71–88%)[61] (Scheme 93).

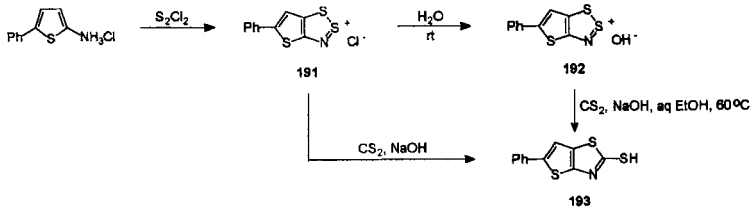


SCHEME 93

3.9. 1,2,3-Dithiazolium Ions

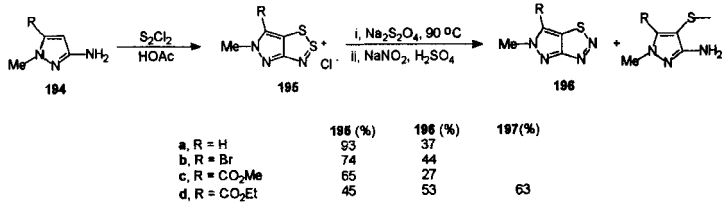
The Herz reaction of anilines with disulfur dichloride gives dithiazolium chlorides, which has been extensively explored.[4] The thiophene Herz salt **191**[62] is converted to its hydroxide salt **192** (97% yield) by treatment with water at room temperature. The hydroxide salt **192** is

transformed to a thiazole derivative **193** (15% yield) by reaction with carbon disulfide in the presence of sodium hydroxide in ethanol at 60°C (Scheme 94).



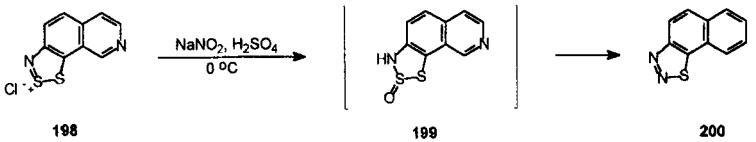
SCHEME 94

The pyrazolodithiazolium chlorides **195**, have been prepared by reaction of 5-substituted 1-methyl-3-aminopyrazoles, **194**, with disulfur dichloride in glacial acetic acid at 40–65°C[63] (Scheme 95). These Herz salts afforded pyrazolo[3,4-*d*]-1,2,3-thiazoles **196**, and, disulfides **197** when subjected to reduction with sodium dithionite, followed by nitrosation. A significant amount of **197** was formed even when the reaction was carried out under an inert atmosphere. Similarly, the reaction of isoquinolino-1,2,3-dithiazolium chloride **198** with sodium nitrite in sulfuric acid gave the 1,2,3-thiadiazole derivative **200** in 42% yield via the transient formation of *S*-oxide **199**[64] (Scheme 96).



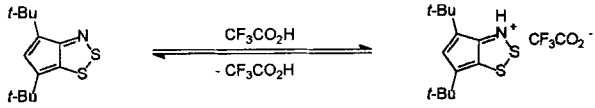
	195 (%)	196 (%)	197(%)
a, R = H	93	37	
b, R = Br	74	44	
c, R = CO_2Me	65	27	
d, R = CO_2Et	45	53	63

SCHEME 95



SCHEME 96

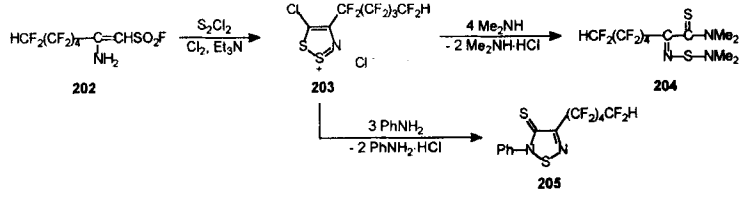
4,6-Di-*t*-butylcyclopenta-1,2,3-dithiazole **128** is protonated reversibly on nitrogen by trifluoroacetic acid in deuterochloroform to produce a violet solution of the salt **201**[23] (Scheme 97).



128 **201**

SCHEME 97

Treatment of 1,7-H_2-2-amino-1-(fluorosulfonyl)decafluoro-1-heptene **202** with disulfur dichloride in the presence of triethylamine in ether at 0°C gave the dithiazolium chloride **203** (68% yield), which reacted with *N*,*N*-diethylamine (4 molar equiv.) and aniline (3 molar equiv.) to give *N*,*N*-dimethyl-1-(dimethylaminothioimino)-6-H-decafluoroheptanethioamide **204** (79% yield) and 3-(5-H-decafluoropentyl)-5-phenyl-1,2,5-thiadiazol-2-ine-4-thione, **205**, (87% yield), respectively[65] (Scheme 98).

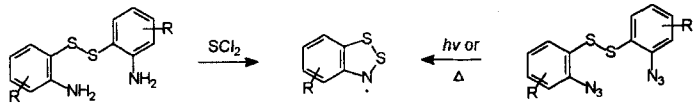


202 **203** **204** **205**

SCHEME 98

3.10. 1,2,3-Dithiazolyl Radicals

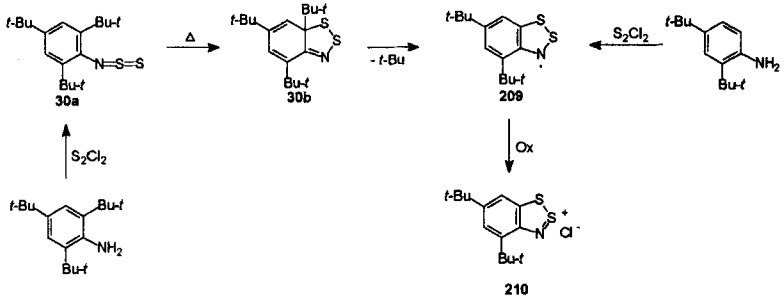
Bis(*o*-aminoaryl) disulfides **206** with sulfur dichloride afforded stable 1,2,3-dithiazolyl radicals **207** in good yields[66b] (Scheme 99). The same result was obtained by irradiation or thermolysis of bis(*o*-azidoaryl) disulfides **208**.[66b]



206 **207** **208**

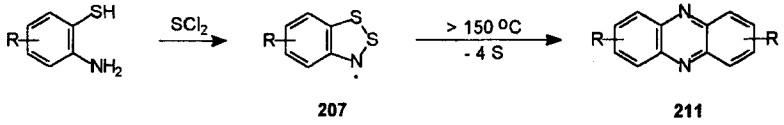
SCHEME 99

Interestingly Mayer and coworkers observed the formation of 1,2,3-dithiazolyls when arylamines and enamines in carbon tetrachloride were added to a solution of disulfur dichloride in carbon tetrachloride. For example, 4,6-di-*t*-butylbenzo[*d*]-1,2,3-dithiazolyl **209** was obtained from 2,4-di-*t*-butylaniline and disulfur dichloride[66] (Scheme 100). The same radical **209** was obtained from 2,4,6-tri-*t*-butylaniline. Further oxidation of the radical **209** gave the 1,2,3-dithiazolium salt **210**. These results indicate that the relatively drastic reaction conditions of the Herz reactions favor the formation of the dithiazolium salts.[66c]



SCHEME 100

Treatment of aminothiophenol and naphthylamines with sulfur dichloride gives stable 1,2,3-dithiazolyl radicals **207** in good yields[66b] (Scheme 101). Stable areno-1,2,3-dithiazolyl radicals decompose to give diarenopyrazines **211** on heating above 150°C.[66c]

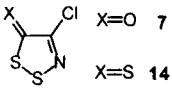
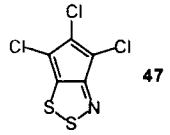
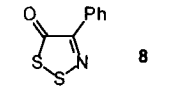


SCHEME 101

Herz salts of the type **212** (X = C, N) are reduced by zinc dust or tin in a variety of solvents to the corresponding radicals **213** which persist in solution (Figure 13). These radicals have not been isolated but can be oxidized by halogens back to the Herz salts.[66]

FIGURE 13

TABLE XVII ^{14}N NMR data of dithiazoles

Compound	*Solvent*	*Chemical shift*[a] δ (ppm)	*Linewidth at half-peak height* $\nu_{1/2}$ (Hz)
 X=O **7** X=S **14**	$CDCl_3$	319	315
 **47**	$CDCl_3$	321	365
	$CDCl_3$	320	420
 **8**	$CDCl_3$	332	487

[a] Chemical shifts are relative to anhydrous ammonia at 0°C.

3.11. ^{14}N NMR Studies of Dithiazoles

The use of the quadrupolar ^{14}N nucleus ($I = 1$, 99.6% abundant) in NMR experiments allows rapid accumulation and high signal-to-noise spectra. Although the resonances are broad they are small in comparison to the chemical shift range. It has been reported that the degree of saturation has a large effect on the chemical shifts: single bonded sulfur–nitrogen compounds such as S_7NH resonate at around 0 ppm; in contrast triply bonded NSF has δ 576 ppm. In sulfur diimides the formal N=S double bonds show signals in the range 250–400 ppm. For pseudo-aromatic compounds such as $(NSCl)_3$, chemical shifts (90–140 ppm) intermediate between those of singly and doubly bonded species are seen.[11] Some ^{14}N NMR data are summarized in Table XVII.

4. APPLICATIONS

5-Arylimino-4-halo-5*H*-1,2,3-dithiazoles **1** have been reported to be useful as fungicides, ovicides, insecticides and herbicides and useful for controlling fungi, particularly plant fungal infections caused by *Botrytis cinerea*, leaf blight caused by organisms such as *Pythium ultimum*, *Helminthosporum sativum*, *Fusarium moniliforme*, *Rhizoctonia solani*, *Monilinia fructicola* and *Uromyces phaseoli typica*.[8]

Compounds **1** were tested for their *in vitro* antibacterial activity against the following bacterial strains:[67] Gram-negative bacteria; *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* Lab. coll. *Proteus mirabilis* CIP 1031811, *Salmonella choleraesuis* ser. *typhimurium* Lab. coll. Gram-positive bacteria; *Staphylococcus aureus* ATCC 9144, *Streptococcus pyogenes* ATCC 19165, *Listeria monocytogenes* CIP 82110T, *Enterococcus faecalis* ATCC 29212. The antimicrobial assays were performed by the disk diffusion method.[68]

Compounds **1** showed significant antibacterial activity against only the Gram-positive bacteria. The unsubstituted aromatic compound **1f** (X = Y = H) and its *o*-methoxy derivative **1a** (X = 4-MeO, Y = H) appeared to be the most active of the series tested.

The antifungal activity of **1** was studied with the following pathogenic strains: *Candida albicans* ATCC 10231, *Candida glabrata* DSM 6425, *Candida tropicalis* DSM 1346, *Issatchenkia orientalis* DSM 6128, *Cryptococcus neoformans* DSM 70219.[69] A preliminary antifungal test was performed by the aga diffusion method.[70] Compounds **1** also showed significant antifungal activity against the yeasts tested. Compounds **1a** and **1l** (2-MeO, Y = H) were always the most active.

For the five yeast strains tested, the minimum fungicidal concentrations (MFC_{99}) of **1** were no more than two or three-fold greater than the MIC showing a good and significant fungicidal activity.

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