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The chemistry of isothiazoles

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Contents

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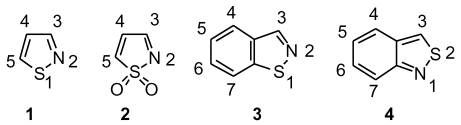
1. Introduction

A series of reviews have been published in the literature regarding the chemistry of isothiazoles and their fused derivatives.[1,2] Comprehensive reviews[3] and other recent articles on the synthesis and chemistry of isothiazoles have been reported.[4–10] There is also a dissertation about selected features of the chemistry of these compounds.[11,12] A literature[3] survey revealed that isothiazole **1** was first prepared in 1956 and since then its chemical and physical properties have been extensively studied. Due to their peculiar reactivity, isothiazoles have recently emerged as useful synthetic compounds and their applications in the search for alternative synthetic strategies and the development of novel molecular structures have been steadily growing. The synthetic versatility of isothiazole has stemmed also from the interest in the biological and pharmacological properties of its derivatives. Isothiazoles **1** (1,2-thiazole), isothiazole 1,1-dioxides (sultams) **2** and the two classes of 1,2-benzisothiazole **3** and 2,1-benzisothiazole **4** are numbered as shown below.



1 **2** **3** **4**

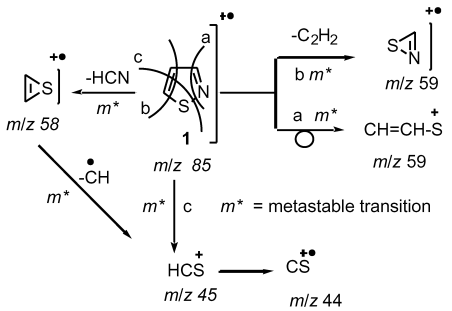
2. Structural features of isothiazoles

2.1. X-Ray diffraction

X-Ray diffraction and crystallography studies have been carried out on some derivatives of isothiazole.[13,14] The dimensions of the heterocyclic ring of some typical crystalline derivatives of isothiazole and 1,2- and 2,1-benzisothiazole are available.[4] Bond lengths should be compared with those of single and double bonds. The S–N bonds are significantly shorter than the single bond values, confirming the molecular orbital (MO) predictions of π-electron delocalisation. In addition, the short N–C, C–S and S–N bonds confirm that π-delocalisation occurs in these molecules. Coordinates are given for the isothiazole 1,1-dioxide ring, which is nearly planar with the flat endocyclic nitrogen atom attached to the SO_2 group (planar apart from the S=O bonds) and this delocalisation must involve the empty sulfur 3d-orbitals. The deviation values of each atom from the plane with the other atoms have been calculated. Hydrogen bonding is given and discussed and the five-membered 2,3-dihydro-isothiazole ring is practically planar. Several sulfonium salts and analogous derivatives have been prepared and their molecular structures determined by X-ray diffraction.[15]

2.2. Mass spectrometry

Gas phase structural characterisation data obtained by mass spectrometry and tandem mass spectrometry of fused isothiazoles, have been published in the literature and reviewed.[4–7] The influence exerted by the fused ring with different substituents as well as by the mutual position of heteroatoms in the gas phase was discussed.[16] Mass spectrometry[4,7] and tandem mass spectrometry (MS/MS) have been extensively and successfully used for the identification of unknown compounds, to confirm the identity of newly-synthesised derivatives, as well as for their structural characterisation. In addition, MS and MS/MS have been used to differentiate isothiazole isomers differing in the position of the endocyclic groups and exocyclic substituents and for studying their gas phase properties. The electron impact mass spectra of isothiazole **1** are dominated by the molecular ion, which corresponds to the base peak, reflecting the high relative stability typical of aromatic compounds. The fragmentation of many substituted isothiazoles can be related to that of isothiazole and is also detected in the decomposition of metastable ions $m^* = (m_2)^2/m_1$), as summarised diagrammatically in Scheme 1.



Scheme 1.

2.3. Stability and aromaticity of isothiazoles

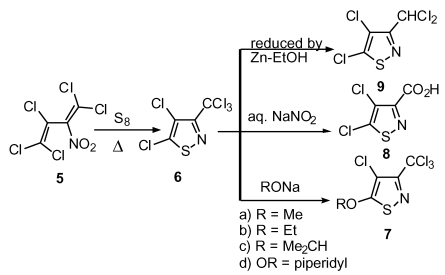
Isothiazole behaves as a typical stable aromatic molecule. The stability of isothiazole derivatives arises from the fact that it has an aromatic delocalised π-electron system. The degree of bond fixation in isothiazole and its 3- and 5-methyl derivatives has been investigated by measurements of the ring-hydrogen exchange rates under acidic conditions.[3a] The results suggest that the degree of bond

fixation in isothiazole is small, and the aromaticity of the series of heterocycles increases in the order: isothiazole> pyrazole>isoxazole. Another measure of aromaticity is the non-local diamagnetic susceptibility perpendicular to the plane of the molecule[3b] This parameter is measured from the rotational Zeeman effect and offers some advantages over NMR measurements as the non-local contributions are directly related to the ring current and the molecules are examined in the gas phase, so that the intermolecular interactions are reduced. Saccharin and other derivatives of isothiazole-1,1-dioxide do not comply with the normal $(4n+2)\pi$-electron rule for aromaticity, but in view of the fact that they have been shown earlier to have a degree of π-electron delocalisation through the sulfur atom, and for convenience of classification of their chemical reactions, they are considered to be aromatic in the subsequent sections dealing with their chemistry. The aromaticity of the heterorings containing N, S and/or O was studied from crystallographic structure data (CSD) of some isothiazole derivatives.[17,18]

3. Synthesis of isothiazoles

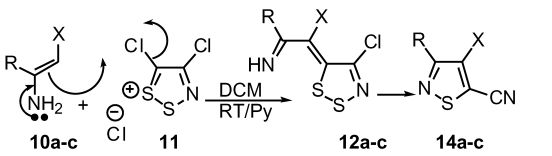
3.1. From non-heterocyclic compounds

3.1.1. From diene derivatives. The polychloronitrodiene **5** gave 3-trichloromethyl-4,5-dichloroisothiazole **6** on heating strongly with neat sulphur. The dichloroisothiazole **6** was alkoxylated by sodium alkoxides (RONa) to give the 3-trichloromethyl-4-chloro-5-alkoxy isothiazoles **7** and treated with sodium piperidide to give an 85% yield of **7d** (RO=piperidyl), which proved that C-5 is more active towards nucleophiles than C-4. When treated with aqueous $NaNO_2$, **6** gave 4,5-dichloroisothiazole-3-carboxylic acid **8** in 92% yield. Reduction by Zn–EtOH gave 3-dichloromethyl-4,5-dichloroisothiazole **9** in 53% yield, as outlined in Scheme 2[19]

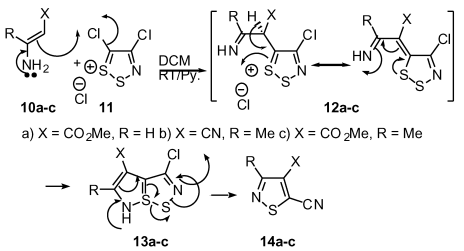


Scheme 2.

3.1.2. From enamine derivatives. A one step route to the 5-cyanoisothiazoles **14a–c** with a range of 3-and 4-substituents has been achieved by the reaction of the enamines **10a–c** with the reagent 4,5-dichloro-1,2,3-dithiazolium chloride **11** in dichloromethane at room temperature (Scheme 3). The nucleophilic adduct induces cyclisation onto the dithiazole ring to provide a new route to isothiazole, presumably via the intermediate **12a–c**, by collapsing to the hypervalent sulphur species **13a–c** (see Scheme 4) followed by elimination of hydrogen chloride and sulphur.[20]



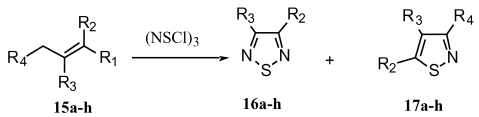
Scheme 3.



Scheme 4.

The conversion of the enamines **10a–c** by the reagent **11** into 5-cyanoisothiazoles **14a–c** involves a [3+2] atom construction of the ring with the enamine providing $N-C_3-C_4$ and the reagent **11** providing $S-C_5-CN$. The proposed mechanism is demonstrated in Scheme 4.

3.1.3. From allylic derivatives. The 1,2,5-thiadiazoles **16a–h** and isothiazoles **17a–h** have been prepared by the reaction of the activated allylic precursors **15a–h** with trithiazyl trichloride $(NSCl)_3$.[21] Simple allylic derivatives are not very reactive towards trithiazyl trichloride $(NSCl)_3$, but a terminal electron-withdrawing group (CO_2Et) will enhance their reactivity. The precursors could react with $(NSCl)_3$ either as a two-carbon unit, giving the 1,2,5-thiadiazoles **16a–h**, or as a three-carbon unit, providing the isothiazoles **17a–h** regiospecifically (Scheme 5).

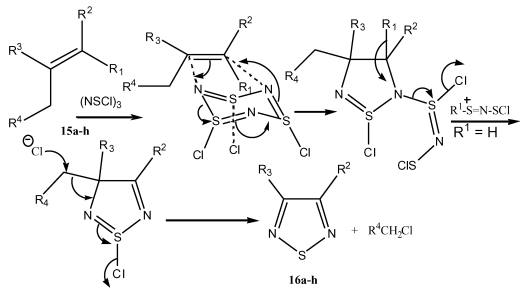


a) R^1 = H, R^2 = Ph, R^3 = H, R^4 = Ph
b) R^1 = H, R^2 = Ph, R^3 = H, R^4 = Cl
c) R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Ph
d) R^1 = CO_2Et, R^2 = H, R^3 = R^4 = CH_2Ph
e) R^1 = Ph, R^2 = Ph, R^3 = R^4 = -$(CH_2)_4$-
f) R^1 = CO_2Et, R^2 = H, R^3 = R^4 = Indnyl
g) R^1 = CO_2Et, R^2 = H, R^3 = Ph, R^4 = Ph
h) R^1 = H, R^2 = CO_2Et, R^3 = Ph, R^4 = Ph

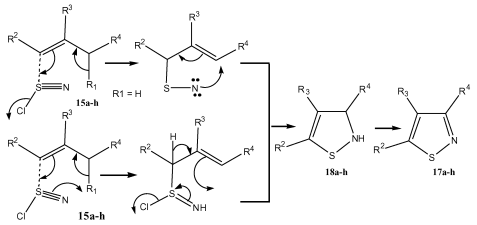
Scheme 5.

A possible mechanism for the conversion of the 2-substituted allyl derivatives **15a–h** into the 1,2,5-thiadiazoles **16a–h** by trithiazyl trichloride $(NSCl)_3$ based upon electrophilic attack on, or cycloaddition to, the double bond is outlined in Scheme 6.

When converted into the isothiazoles **17a–h** by the highly reactive monomer thiazyl chloride (N≡S–Cl) (freely available in solution at the reaction temperature), an S–N unit will be transferred to **15a–h** to give the dihydroisothiazoles **18a–h**, which were aromatised via dehydrochlorination (Scheme 7).

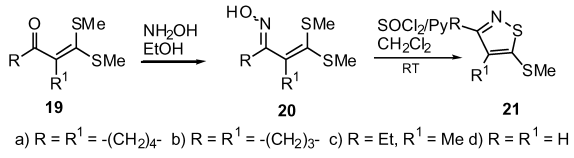


Scheme 6.



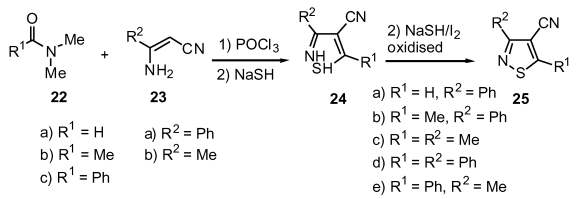
Scheme 7.

3.1.4. From α,β-unsaturated ketones and enaminonitriles via Vilsmeier salts. Treatment of the α-oxoketene dithioacetals **19** with hydroxylamine in aqueous ethanol gave the oximes **20** in the appropiate yields. This methodology required the conversion of an oxime hydroxyl moiety into a good leaving group that had to be displaced by the sulphur substituent. This oxime was treated with thionyl chloride in pyridine to give the isothiazole (Scheme 8). The formation of isothiazoles **21** from the corresponding oximes was unanticipated and was initially considered as an anomalous reaction.[22]



Scheme 8.

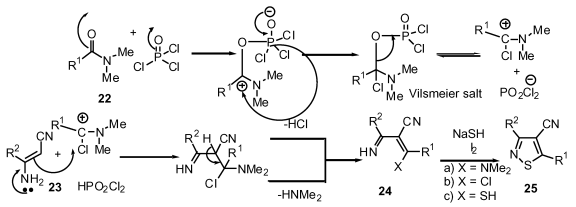
Crenshaw and co-workers reported[23] that the 4-isothiazole carbonitriles **25** could be derived from the reaction of the Vilsmeier salts of the *N*,*N*-dimethylamides **22** with enaminonitriles and treatment of the intermediate **24** with sodium hydrosulphide (NaSH)/iodine (Scheme 9).



Scheme 9.

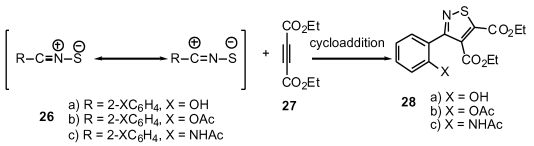
A possible mechanism for the formation of the Vilsmeier salts, which were converted into the 4-isothiazole carbonitriles **25** is demonstrated in Scheme 10.

3.1.5. From nitrile sulphides by phase transfer (1,3-dipolar cycloaddition reactions). The 1,3-dipolar cycloaddition reactions of nitrile sulphides **26** are of particular



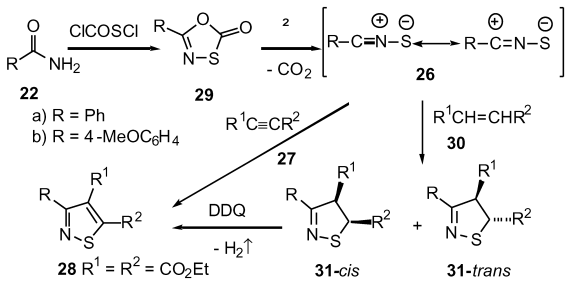
Scheme 10.

value for the synthesis of five-membered heterocycles incorporating the C=N–S unit. Cycloaddition to alkynes, nitriles, alkenes and carbonyl compounds will afford the isothiazoles. Paton and co-workers have explored[24] a unique method for the synthesis of the isothiazoles **28** starting from **27** and the *o*-substituted benzonitrile sulphides **26** (Scheme 11).



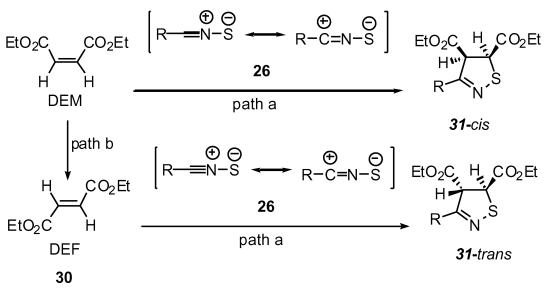
Scheme 11.

Recently, some groups have developed a method for the synthesis of isothiazole 4- and 5-dicarboxylate esters **28a–c** (more than 20 derivatives).[25] The isothiazole 4- and 5-dicarboxylate esters were prepared by the 1,3-dipolar cycloaddition of nitrile sulphides, generated by thermal decarboxylation of the corresponding 1,3,4-oxathiazole-2-ones **29**, to acrylate, fumarate and maleate esters. Dehydrogenation of the resulting 4,5-dihydroisothiazoles (2-isothiazolines) **31** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave **28** as shown in Scheme 12.



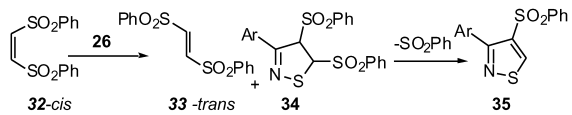
Scheme 12.

Reactions with olefins have established that diethyl fumarate (DEF) is an efficient dipolarophile for trapping a range of nitrile sulphides. The corresponding reaction with diethyl maleate (DEM) **30** has been examined with 4-methoxyphenyloxathiazolone **29b** and the only product detected and isolated was the *trans*-isothiazoline **31b** (HPLC). Two possibilities for the formation of the *trans* adduct can be considered. Either the nitrile sulphide will react with the *cis*-alkene and the resulting *cis* adduct rearranges to the thermodynamically more stable *trans* products, possibly via enolisation of the 4-carboxyl group (path a), or the dipolarophile undergoes *cis* to *trans* isomerisation under the reaction conditions prior to cycloaddition (path b), as shown in Scheme 13.



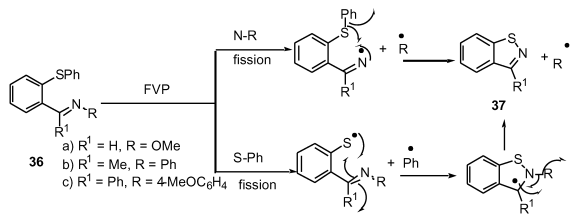
Scheme 13.

cis–trans Dipolarophile isomerisation has been observed during the reaction of nitrile sulphides with *cis*-1,2-bis(phenylsulphonyl)ethene (**32**-*cis*-PSE). Thermolysis of **32**-*cis*-PSE (1:2.5) afforded 4-(phenylsulphonyl)isothiazoles **35** rather than the expected 4,5-dihydroisothiazoles (2-isothiazolines) **34** (Scheme 14). Presumably, the initially formed 4,5-dihydroisothiazoles (2-isothiazolines) **34** undergoes spontaneous elimination of phenyl-sulphonic acid under the reaction conditions. 4-Methylbenzonitrile and sulphur were formed as byproducts.



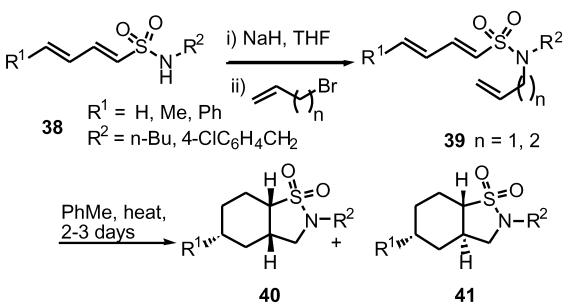
Scheme 14.

3.1.6. From iminyl radicals by gas phase cyclisation (via FVP). The benz[*d*]isothiazoles **37a–c** were formed via flash vacuum pyrolysis (FVP) of **36** in solution at 650°C[26] and the yield appears to be greatest when the thioethers **36a**,**b** are used. The formation of the benz[*d*]isothiazoles **37** involved the creation of an N–S bond with the expulsion of an aryl radical.[27] The iminyls cyclise directly by an intramolecular homolytic substitution (S_H^i) mechanism, although an addition–elimination route was possible for the thiophenoxyls (Scheme 15).



Scheme 15.

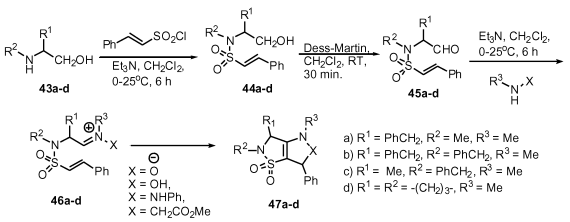
3.1.7. From sulphonamides via thermal intramolecular Diels–Alder reactions. The intramolecular Diels–Alder reaction is an attractive option for constructing rigid cyclic systems and sulphonamides have been incorporated in the dienophile component as vinyl sulphonamides.[28] Substituted 2,3,3a,4,5,7a-hexahydrobenzo[*d*] isothiazole 1,1-dioxides **40** and **41** are novel cyclic sulphonamides which were synthesised by a thermal intramolecular Diels–Alder reaction of buta-1,3-diene-1-sulphonic acid amides **38** (Scheme 16). The intramolecular Diels–Alder reactions of **39** have been performed at 145°C in toluene, in a sealed screw-cap vessel under argon to give the [4.3.0] of **40** and **41**. The relative stereochemistries of **40** and **41** were



Scheme 16.

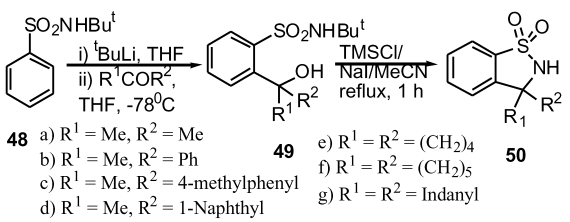
confirmed by X-ray crystallography and nuclear Overhauser effect (NOE).

A comparable investigation for the stereoselective synthesis of homochiral annulated sultams via intramolecular cycloaddition reactions has been reported.[29] Different homochiral dipoles containing a sulphonamido group were prepared starting from the L-amino acids and used for the construction of functionalised and enantiomerically pure derivatives (Scheme 17). Amino alcohols **43a–d** were treated with *trans*-2-phenylethenesulphonyl chloride to give the corresponding sulphonamido alcohols **44a–d** and converted into the α-sulphonamido aldehydes **45a–d** by oxidation with Dess–Martin periodinane. Subsequent treatment with *N*-substituted hydroxylamines, phenylhydrazines or α-amino acid esters is furnished the nitrone, oxime, hydrazone or imino derivatives **46a–d**, which spontaneously underwent intramolecular cycloaddition to the bicyclo compounds **47a–d**.



Scheme 17.

Recently, a simple procedure for the synthesis of 3,3-disubstituted and *spiro*-2,3-dihydrobenzo[*d*]isothiazole 1,1-diones (benzosultams) **50** from benzenesulphonamides such as **48** has been developed.[30] The regiospecific *o*-lithiation of *N*-*t*-butylbenzenesulphonamide **48** followed by reaction with ketones afforded the carbinol sulphonamides **49**, which underwent TMSCl–NaI–MeCN reagent mediated cyclisation, as outlined in Scheme 18.

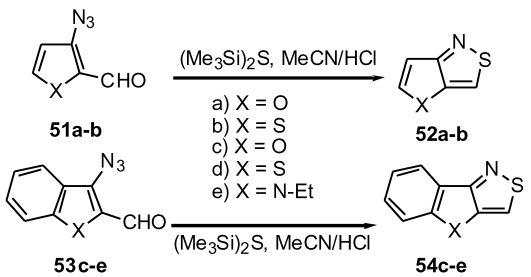


Scheme 18.

3.2. From other heterocyclic compounds

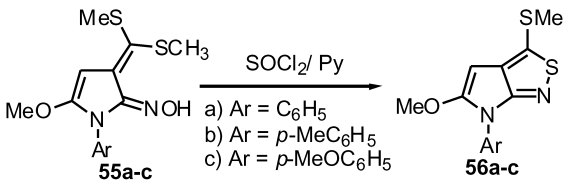
3.2.1. From other five-membered heterocycles.

3.2.1.1. From five-membered heterocycles having one heteroatom. Degl'Innocenti et al. have reported[31,12] a novel route to fused isothiazole ring systems through intramolecular trapping of o-azidoaldehydes such as **51** and/or **53** through thionation by the highly chemoselective reagent hexamethyl-disilathiane (HMDST) in the presence of HCl. The azido group seemingly represents a good trapping agent for the thioaldehydes, giving direct access to the fused isothiazoles **52a**,**b** and **54c**–**e** (Scheme 19).[32]



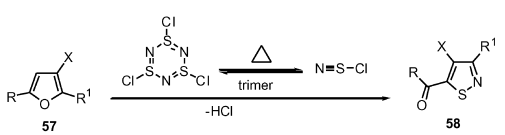
Scheme 19.

Pyrrolo[2,3-c]isothiazoles **56a**–**c** have been prepared from the highly functional oximes **55a**–**c** by the action of thionyl chloride in pyridine, as shown in Scheme 20.[33]



Scheme 20.

Rees et al. have achieved a one-step synthesis of 5-acylisothiazoles from the 2,5-disubstituted furans.[34] The reaction of the 2,5-disubstituted furans **57** with trithiazyl trichloride $(NSCl)_3$ resulted in the 5-acyl-3-substituted-isothiazoles **58**. It was not clear at this stage whether the furan ring cleavage or insertion of the S–N was regiospecific. It has been shown that fully substituted furans did not react with trithiazyl trichloride $(NSCl)_3$, the furan hydrogen in the β-position clearly being required for the elimination of hydrogen chloride that was evolved in all of these reactions (Scheme 21).

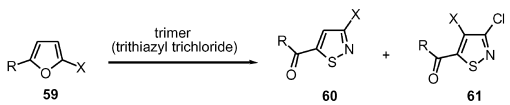


a) R = R^1 = C_6H_5, X = H b) R = R^1 = *p*-Me C_6H_4, X = H c) R = R^1 = *t*-Bu, X = H d) R = R^1 = C_6H_5, X = H e) R = R^1 = *p*-$MeOC_6H_4$, R^1 = *p*-NO_2 C_6H_4, X = H f) R = R^1 = C_6H_5, X = Br g) R = R^1 = C_6H_5, X = Ph

Scheme 21.

Recently, Rees and co-workers[35] have developed their method by preparing a new reagent from premixed ethyl carbamate, thionyl chloride and pyridine, which will generate monomeric thiazyl chloride (NSCl) (known as the Katz reagent). This reagent behaved exactly like trithiazyl trichloride $(NSCl)_3$, and transferred the 2,5-diaryl- and 2,5-di-*t*-butylfurans **57** into the 5-acyl-3-substituted isothiazoles **58**.

The deactivated furan **59** bearing an electron-withdrawing group X at position C-2 (X=CO_2H, CO_2Et, CH=NOH, CH=NOMe, CN, COMe, COPh and SO_2Ph) reacted with the monomer to give the isothiazoles **60** and **61** in low yield (Scheme 22).

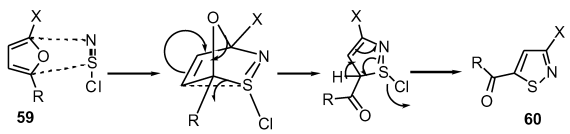


a) R = C_6H_5, X = CO_2H b) R = *p*-Me C_6H_4, X = CO_2Et c) R = *t*-Bu,X = CN d) R = C_6H_5, X = CH=NOMe e) R = *p*-$MeOC_6H_4$, X = COMe f) R = C_6H_5, X = COPh g) R = $_6H_5$, X = SO_2Ph h) R = $_6H_5$, X = $SiMe_3$ i) R = $_6H_5$, X = $SiMe_2hex^t$ i) R = $_6H_5$, X = $SiPr^i_3$ k) R = $_6H_5$, X = Cl m) R = $_6H_5$, X = H

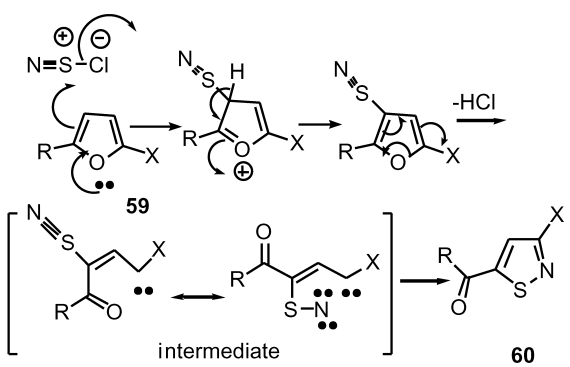
Scheme 22.

Rees et al. overcame the type of problems witnessed in the reactions of 2,5-disubstituted furans with trithiazyl trichloride and provided two possible mechanisms.

(i) Diels–Alder cycloaddition of N≡S–Cl across the furan 2,5-positions, as shown in Scheme 23.
(ii) The regiochemistry of these reactions was as expected for the initial substitution of the polarised furan ring at the more nucleophilic β-position (electrophilic substitution by sulphur at an unsubstituted β-position) via intermediates and rearrangement via ring opening and spontaneous closure to give the 5-benzoylisothiazoles, as demonstrated in Scheme 24.



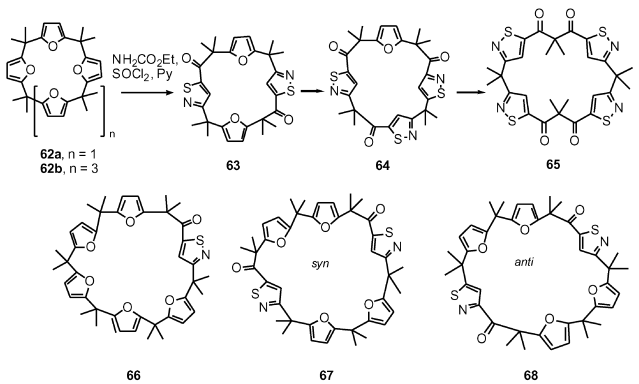
Scheme 23.



Scheme 24.

Recently, Rees et al. have applied the Katz reagent to the conversion of macrocyclic furans into a series of novel macrocyclic isothiazoles, depending upon the conditions and the amounts of reagent used.[36] Calixhetarenes of bis-**63**, tris-**64** or tetrakis-isothiazole **65** with more than one heteroatom in the constituent rings were prepared in one

step by treatment of calix[4]furan **62a** with ethyl carbamate, thionyl chloride and pyridine, as shown in Scheme 25.



Scheme 25.

It is assumed that heating calix[6]furan **62b** for 2 h at 80°C with urethane/thionyl chloride ($SOCl_2$) in a molar ratio of 4.3:8.6 yielded the mono-isothiazole **66**. Doubling the reagent amounts with added 4 Å molecular sieves and 1 h heating at the same temperature yielded an inseparable mixture of the *syn* and *anti* isomers of the bis-isothiazoles **67** and **68**.

The structures of the products **63**, **65** and **66** have been confirmed by X-ray crystallography as shown in Figures 1–3.

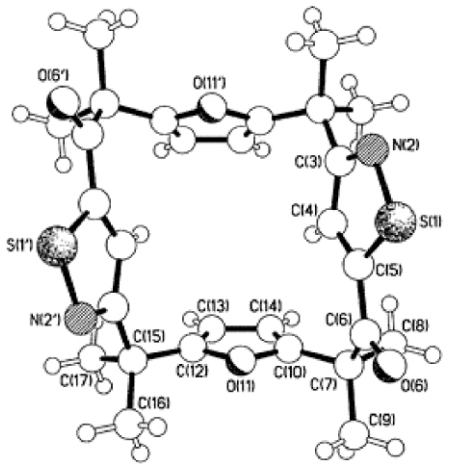


Figure 1. Molecular structure of **63**. Selected bond lengths (Å); S(1)–N(2) 1.653(3), N(2)–C(3) 1.313(4), C(3)–C(4) 1.420(4), C(4)–C(5) 1.354(4), C(5)–S(1) 1.714(3).

Recently, the author of the present review and his co-workers have developed a simple procedure for the conversion of 3-aryl-5-phenyl-2(3*H*)-furanones **69a–c** into 2-benzyl-4-aryl-5-benzoylisothiazole-3-ones **71a–c**. This occurred via ring opening of the furan-2(3*H*)-ones **69a–c** through thermal heating with neat benzylamine to give the *N*-benzyl-α-aryl-β-benzoylpropionamides **70a–c**, which were reacted with thionyl chloride at room temperature to give the corresponding isothiazoles **71a–c** in good (80–90%) yields (Scheme 26).[37]

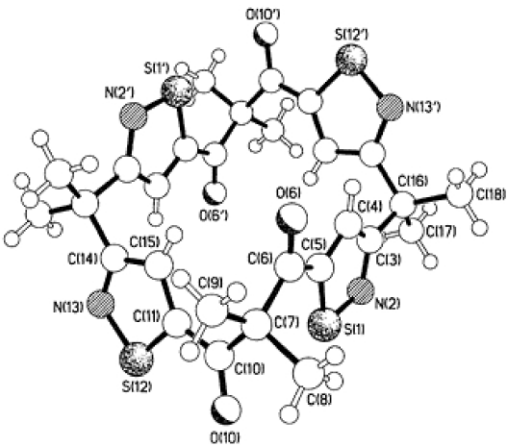


Figure 2. Molecular structure of the major isomer present in the crystals of 65. Selected bond lengths (Å); S(1)–N(2) 1.644(8), N(2)–C(3) 1.329(11), C(3)–C(4) 1.397(13), C(4)–C(5) 1.342(12), C(5)–S(1) 1.707(9), S(12)–N(13) 1.652(8), N(13)–C(14) 1.312(10), C(14)–C(15) 1.443(11), C(15)–C(11) 1.373(11), C(11)–S(12) 1.710(8).

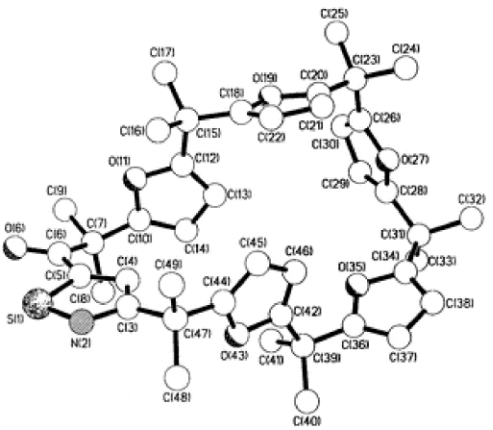
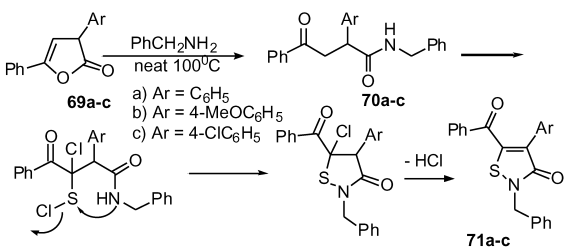


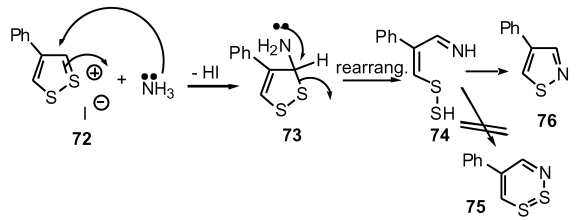
Figure 3. Molecular structure of **66**. Selected bond lengths (Å); S(1)–N(2) 1.647(4), N(2)–C(3) 1.325(5), C(3)–C(4) 1.421(5), C(4)–C(5) 1.374(5), C(5)–S(1) 1.707(3).



Scheme 26.

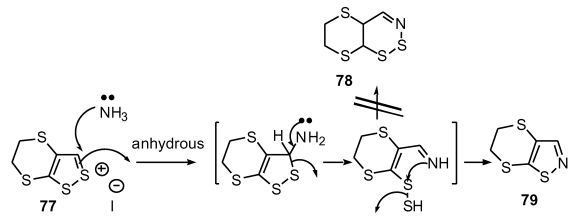
3.2.2. From five-membered heterocycles having two heteroatoms.

3.2.2.1. From 1,2-dithiole derivatives. The conversion of the1,2-dithiolium cation **72** into the isothiazoles **76** via the action of ammonia has been demonstrated.[38] The amine adduct **73** ring opened into the imine **74**, which underwent ring closure with rearrangement to form 4-phenylisothiazole **76** with no dithiazine **75** detected during the reaction conditions (Scheme 27).



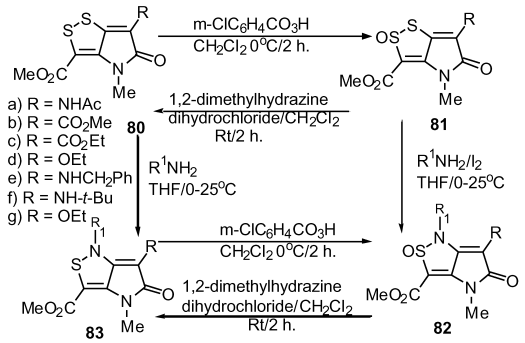
Scheme 27.

The results described by Bryce and co-workers[38] indicated that the 1,2-dithiolium cation **77** yielded the isothiazole **79** without conversion to the 1,2,3-dithiazine **78** (undetected during the transformation, as shown in Scheme 28).



Scheme 28.

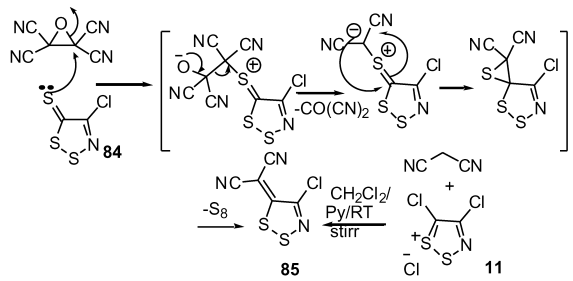
The oxidation of *S*(2) and *S*(1) of the 1,2-dithiolopyrrolones **80a–g** by organic peracids has been examined depending on the substituents. The 1,2-dithiolopyrrolones **80a–g** reacted with *m*-chloroperbenzoic acid in dichloromethane at 0°C to give the corresponding *S*(2)-oxides **81a–g**, which showed a proclivity to disproportionation and were easily reduced to the dithioles **80a–g** with symmetrical dimethylhydrazine. From the *S*(2)-oxides **81a–g** and several primary amines, the bicyclic isothiazole-*S*-oxides (sultims) **82a–d** were obtained by (S/N-exchange reaction). It is noteworthy that the S/N-exchange reaction was performed with the poorly nucleophilic ammonia to produce isothiazole oxide **82d**. The compound **82d** could not be obtained by the alternative debutylation of **82c** with trifluoroacetic acid. Obviously, the conversion of the intermediate **82d** into **83a–c** by induced of trifluoroacetic acid, which occurred via a Pummerer-type rearrangement (Scheme 29).[39]



Scheme 29.

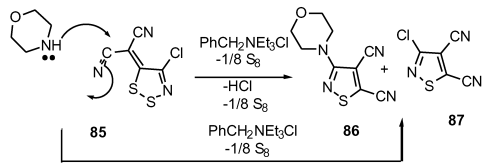
3.2.3. From five-membered heterocycles having three heteroatoms.

3.2.3.1. From 1,2,3-dithiazole derivatives. Rees et al. have exploited 4,5-dichloro-1,2,3-dithiazolium chloride **11** to prepare the dicyanomethylene dithiazole **85**, through the reaction with active methylene compounds such as malononitrile. Condensation reactions of 4-chloro-5*H*-1,2,3-dithiazole-5-thione **84** with tetracycanoethylene oxide (TCNEO) likewise gave **85** via nucleophilic attack on the epoxide ring by the thione sulphur, followed by fragmentation to give carbonyl cyanide and a thiocarbonyl ylide. These ylides could be isolated when strongly electron-releasing groups are presented to stabilise the positive charge, but otherwise they collapse to the thiirane, which will lose sulphur to give the dicyanomethylene dithiazole **85**. This latter method gave a better yield of the dicyanomethylene compound **85**, as shown in Scheme 30.[40]



Scheme 30.

The dicyanomethylene dithiazole **85** reacted with morpholine in the presence of a catalytic source of chloride ions (from anhydrous benzyltriethyl-ammonium chloride) to give 3-morpholino-isothiazole-4,5-dicarbonitrile **86** and 3-chloro-isothiazole-4,5-dicarbonitrile **87**. In view of the formation of 3-chloro-4,5-dicyanoisothiazole **87** in trace amounts in the morpholine reaction, the isolation of this compound revealed that the chloride ion could compete with morpholine in the initial addition. In addition, the chlorine in **87** was shown to be displaced by morpholine to give the major product **86** in high yield and this possibility was confirmed by the reaction of **85** with a catalytic source of chloride ions to give 3-chloro-4,5-dicyanoisothiazole **87**, as shown in Scheme 31.



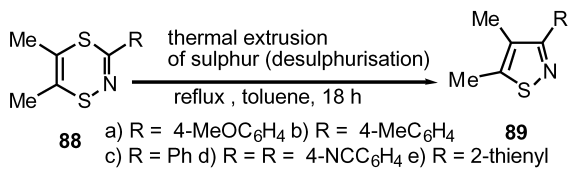
Scheme 31.

3.2.4. From six-membered heterocycles.

3.2.4.1. From 1,4,2-dithiazine derivatives. The conversion of thiophene-1,4,2-dithiazine derivatives **88** into the isothiazoles **89** has been studied by Bryce and co-workers,[38,41] the most widely documented reaction being thermal extrusion of sulphur (desulphurisation) from position 4 of the 1,4,2-dithiazine derivatives **88** to afford the isothiazoles **89**, as shown in Scheme 32.

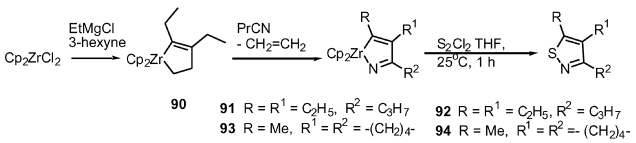
3.3. From azametallacycle derivatives

A series of $Ag^{(I)}$ complexes of some isothiazole-based ligands has been studied.[42] Interestingly, however, all of these complexes, characterized crystallographically,



Scheme 32.

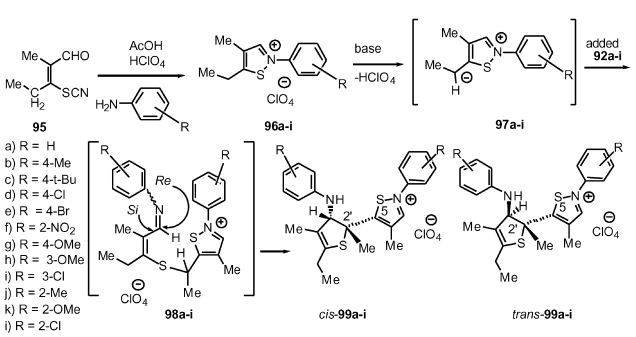
featured dimeric units of the form $L_2Ag_2^{2+}$ (L= isothiazole) in the solid state involving additional donor sites within the ligand side chains. Recently, the synthesis of isothiazoles via metallacycle transfer was reported.[43] 3-Hexyne has been reacted with Grignard reagents (ethylmagnesium halides) in the presence of zirconocene dichloride to give the metallacyclopentene **90**. Addition of butyronitrile resulted in the loss of ethylene and formation of the azametallacycle **91**, which was converted into the isothiazoles **92** via the addition of sulphur monochloride or the metallacycle transfer reaction. In a similar manner, the isothiazole **94** was prepared from the azametallacycle **93** with sulphur monochloride in THF (Scheme 33).



Scheme 33.

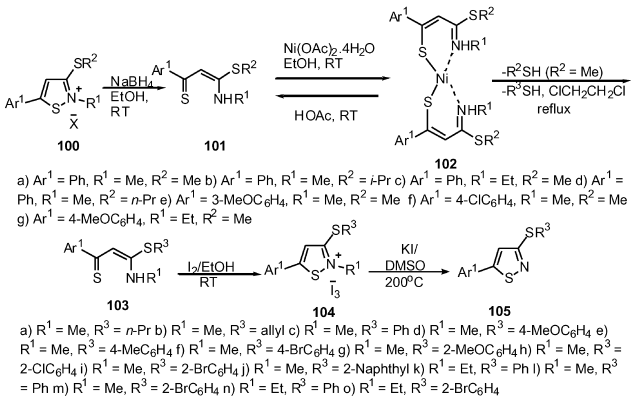
4. Conversion into other heterocyclic compounds

It has been reported that the base-catalysed rearrangement of 5-ethyl-4-methylisothiazolium salts **96a–i** will yield the 2,3-dihydrothiophene derivatives.[44] The substituted isothiazolium salts **96a–i** were prepared by the reaction of (*Z*/*E*)-2-methyl-3-thiocyanatopent-2-enal **95** with substituted anilines in an acidic medium (Scheme 34). In order to explain the observed transformation of the salts **96**, one could invoke the following model. Nucleophilic attack of the carbanion of the deprotonated salt **97** at the sulphur atom of a second salt **96** leads, after ring opening at the S–N bond, to the non-isolable intermediate **98**. Ring closure between the active methylene group and the azomethine carbon atom in **98** is possible from the *re*- or *si*-side to form the diastereomeric 2,3-dihydrothiophenes **99**.



Scheme 34.

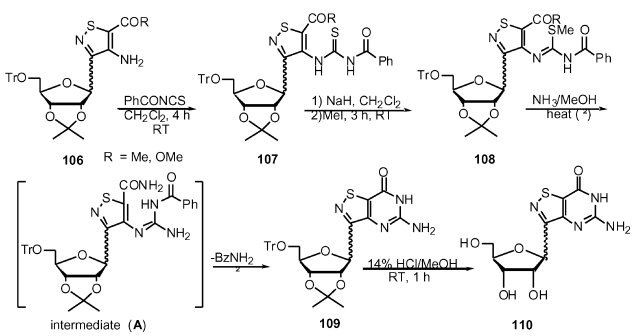
The stereoselective influence of different bases and solvents on the intramolecular cyclisation from **98** to the 2,3-dihydrothiophenes **99** has been studied. In the presence of dicyclohexylamine and piperidine basic/catalysts, the *p*- and *m*-substituted salts **96a–e,g–i** reacted to give a mixture of the diastereomeric compounds *rac–cis* **99** and *rac–trans* **99** with a selectivity *cis*>*trans* in 34–79% yield. The chloro-substituted salts had the highest selectivity *rac–cis*-**99d,i** / *rac–trans*-**99d,i**=89:11. It was found that the reaction of the salts **96a–e,h** in a mixture of ethanol/water (1:1) in the presence of sodium acetate as base proceeds in a diastereoselective fashion to the 2,3-dihydrothiophene *rac–cis*-**99**<*rac–trans*-**99**. Recently, a convenient procedure has been developed for the synthesis of *cis*-Ni(II)-3-alkylimino-3-alkylthio-1-arylpropenethiolates **102** based on the reaction of the 2-alkyl-alkylthio-5-phenylisothiazolium salts **100** with sodium borohydride in ethanol, followed by the reaction of the (*E*)-3-alkylimino-3-alkylthio-1-(thioaryl)-propenes **101** with $Ni(OAc)2{\cdot}4H_2O$.[45] The complexes **102** converted into the ketene S,N-acetals **103** by the reaction with alkyl and/or aryl thiols, which were transformed into the 5-aryl-3-(arylthio)isothiazoles **105** through the intermediate **104**, as shown in Scheme 35.



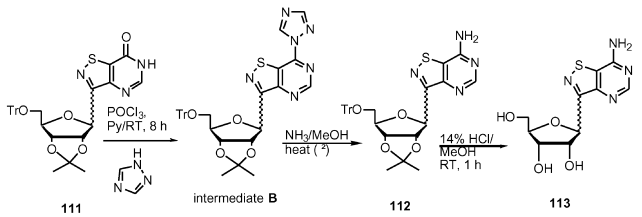
Scheme 35.

5. Analogues of isothiazoles

It has been reported[46] that the C-nucleosides **110** and **113** (Schemes 36 and 37) are related to guanosine and adenosine, respectively. The synthesis of the analogue of guanosine **110** has been achieved via a procedure starting from isothiazole C-nucleoside **106**, which was treated with benzoyl isothiocyanate, followed by methylation of the



Scheme 36.

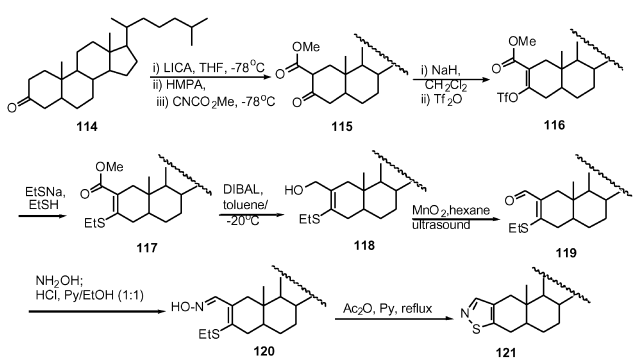


Scheme 37.

resulting thioureido derivative **107**, to give the protected S-methylthioureido compound **108** and cyclised to the more polar 5-amino-C-nucleoside **109**. The cyclisation of the S-methylthioureido compound occurred **108** via direct nucleophilic attack of the amide (NH_2) group on the carbamoyl C-atom with loss of benzamide. A higher ammonia concentration favoured the substitution of methylthio by $-NH_2$ and subsequent ring closure of the guanidine intermediate (A) yielded the 5-amino derivative **109**. Deprotection of the blocked C-nucleoside **109** with HCl (14%)/MeOH afforded 8-aza-7,9-deaza-7-thiaguanosine **110** as the monohydrochloride salts, as shown in Scheme 36.

The adenosine analogue **113** was prepared by treatment of the protected isothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one C-nucleoside **111** with (1,2,4-1*H*-triazolyl)phosphine oxide in pyridine at 25°C for 8 h to give the 7-triazolyl intermediate (B). Treatment of this intermediate (B) with methanolic ammonia gave the 7-amino-C-nucleoside **112**, which was deprotected by the action of 14% HCl/MeOH at 25°C to yield the desired compound, as shown in Scheme 37.

An efficient route for the synthesis of a fused steroidal isothiazole **121** has been developed recently.[47] Starting with the 5α-cholestan-3-one **114**, via treatment with LICA followed by addition of CNCOMe afforded esters **115**, which was reacted with sodium hydride in dichloromethane at room temperature and subsequent addition of triflic anhydride, produced 2-carboxymethyl-3-trifluoromethanesulpfonyloxy-5α-cholest-2-eno **116**. Mixed of the ester derivatives **116** with sodium thioethoxide in thioethanol at room temperature gave thioether **117**, which has treated by di-isobutylaluminium hydride (DIBAL) to give the corresponding allylic alcohol **118**. Oxidation of **118** by activated MnO_2 in hexane and then treated in ultrasonic irradiation afforded aldehydes **119**, which was reacted with hydroxylamine chlorohydrate in pridine/ethanol (1:1) to give oximes **120**. Ring closure of oximes **120** by refluxed with acetic anhydride in anhydrous pridine furnished steroidal isothiazole **121**, as demonstrated in Scheme 38.

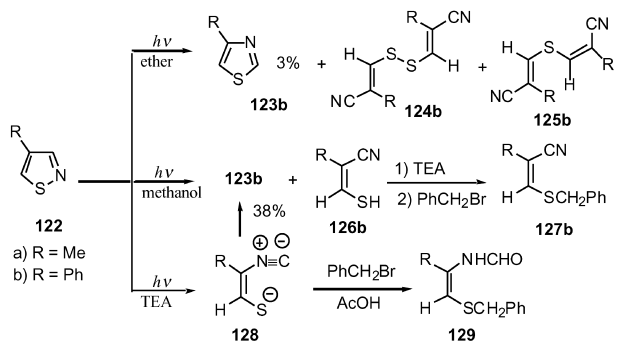


Scheme 38.

6. Reactions of isothiazoles

6.1. Photochemical reactions

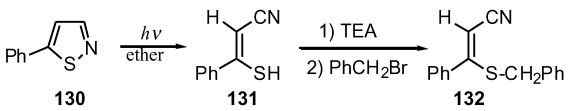
The photochemical reactions and behaviour of isothiazoles and some other five-membered heteroaromatic compounds have been reviewed in 19987 and a dissertation has been reported in 1999 or the photochemistry of some substituted isothiazoles.[48] The photochemical behaviour of 4-phenylisothiazole **122b** has been re-analyzed.[49] The authors showed that, this compound when irradiated in ether, reacted to give the ring-opened products and only a 3% yield of 4-phenylthiazole **123b**, with the sulphide **124** and disulphide **125** derivatives as byproducts. Irradation in methanol led to the formation of 4-phenylthiazol **123b** in 38% yield with the cyanothiol **126b** as byproduct, which was trapped with benzyl bromide to give the benzyl thioether derivative **127b**. Moreover, in the presence of triethylamine (TEA) the resulting yields of 4-phenylthiazole **123b** were increased. All these data can be explained by invoking the intervention of a ring-opened thiol intermediate, as described in Scheme 39. Addition of a small amount of a base such as triethylamine (TEA) to the reaction media has a profound effect on the photoreaction, the transposition occur ring by the isocyanosulfide intermediates **128**, which were trapped with benzyl bromide and acetic acid to give the *N*-formylaminobenzyl thioether derivatives **129**. In the absence of trapping agents, these isocyanosulfides **128b** were cyclised to the 4-substituted thiazoles **123b**. The changes in the yield of 4-phenyl isothiazole **122b** with the use of TEA were found to be due to the instability of **123** upon prolonged irradiation in the presence of this base.



Scheme 39.

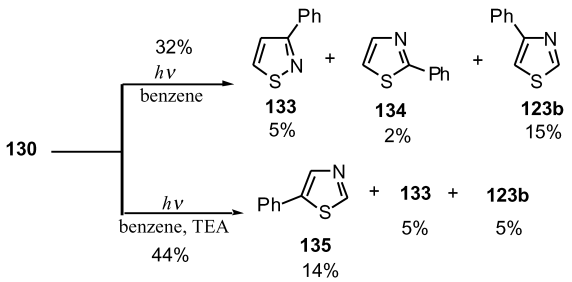
The acidity of the C-2 hydrogen of 4-phenylthiazole **123b** was enhanced upon photochemical excitation in the presence of TEA, and the excited **123b** was no doubt efficiently deprotonated, which may have enhanced its reactivity. 5-Phenylisothiazole **130** undergoes photo-transposition via an electrocyclic ring closure-heteroatom migration pathway and by the N2–C3 interchange reaction pathway. The latter route is enhanced by the addition of TEA to the reaction medium and by increasing the polarity

of the solvent. In addition to phototransposition, 5-phenylisothiazole **130** also undergoes photocleavage to 2-cyano-1-phenylethenethiol **131**, which was trapped by reaction with benzyl bromide in TEA to yield 2-cyano-1-phenylethen-1-ylbenzyl thioether **132** (Scheme 40).[50]



Scheme 40.

3-Phenylisothiazole also phototransposes by both reaction pathways, but the product distribution is not affected by the addition of TEA or by changing the solvent polarity. The effect of TEA on the photochemistry of 5-phenylisothiazole **126**, was evaluated when two solutions of **130**, in benzene, with and without TEA, were simultaneously irradiated and gas liquid chromatographic (GLC) analysis of the resulting solutions showed that, in the absence of TEA, 32% of the reactant had been consumed and that 3-phenylisothiazole **133**, 2-phenylthiazole **134** and 4-phenylthiazole **123b** were formed and did not reveal the presence of any 5-phenylthiazole **130**, as shown in Scheme 41.



Scheme 41.

On addition of TEA to the solution, GLC analysis revealed several changes in the reaction. Firstly, in the presence of TEA, the consumption of **130** increased from 32 to 44% and, secondly, although 5-phenylthiazole **135** was not observed as a product in the absence of TEA, in the presence of TEA it was the major product, formed in 14% yield.

Order to determine the effect of changes in the solvent polarity, the photochemistry of 5-phenylisothiazole **130** has been investigated in methanol and 2,2,2-trifluoroethanol (TFE) solvents, with and without added TEA. Solutions of **130** in methanol, without and with TEA, were irradiated simultaneously and GLC analysis showed that, in the absence of TEA, 33% of **130** had been consumed, but, in the presence of TEA, the consumption of **130** was increased to 51%. Indeed, when **130** was irradiated in the more polar TFE solvent, the 5-phenylthiazole **135** was the only product observed (Fig. 4).

The mechanistic pathway for the photochemical reaction of 5-phenylisothiazole **130** with or without TEA can be described as shown in Scheme 42.

5-Bromo-4-dibromoamino-3-phenylisothiazole **136** when

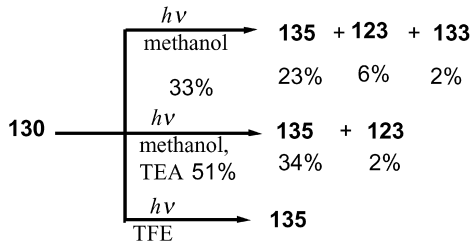
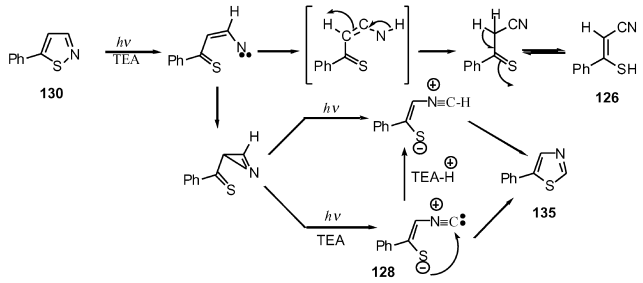
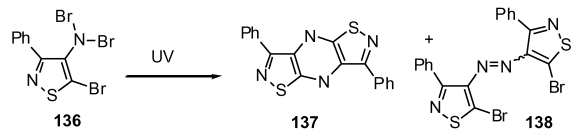


Figure 4. Irradiation of **130** with and without (TEA or TFA).



Scheme 42.

irradiated by UV light was converted into 3,7-diphenyl-bisisothiazolo[4,5-*b*:4′,5′-e]pyrazine **137** and *N*,*N*′-bis(5-bromo-3-phenylisothiazol-4-yl)diazene **138** (Scheme 43).[51]



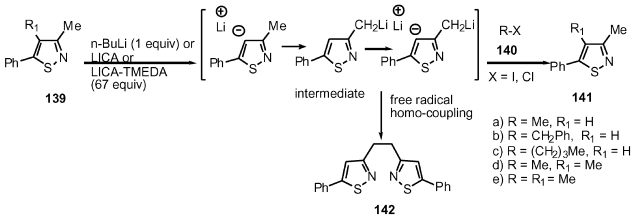
Scheme 43.

6.2. Reactions with electrophiles

There is a review[8,52] from 1997 with **165** references on the synthetic methods, reactions, and biological applications of isothiazole 1,1-dioxides. The formation of monocyclic and heterocyclic annulated isothiazole 1,1-dioxides by the oxidation of isothiazoles, cyclocondensation of sulfonamides and cycloaddition of isothiazole-3(2*H*)-one 1,1-dioxides is discussed. The preparation of the pharmacologically important *N*-substituted saccharins was reported. Saccharin-derived chiral *N*-enoyl- and *N*-acyl-2,3-dihydro-1,2-benzisothiazole 1,1,-dioxides serve as advantageous stereo face-directing dienophile and dipolarophile auxiliaries in Diels–Alder reactions and 1,3-dipolar cycloadditions. Asymmetric alkylations, acylations and aldolisations are described.

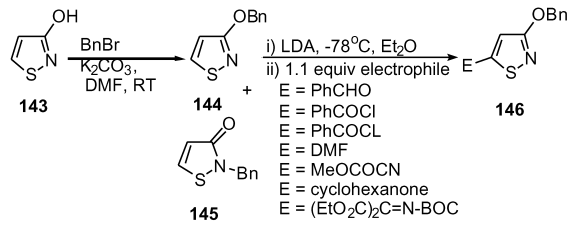
6.2.1. Reactions with alkyl halides. It was reported that the reaction of 3-methyl-5-phenylisothiazole **139** with alkyl halides 140 in the presence of bases (*n*-BuLi, LICA or LICA-TMEDA) afforded the alkylated products **141** (Scheme 44). In some cases, the free radical homo-coupling of the intermediate afforded 1,2-bis[3-(5-phenylisothiazolyl)]ethane **142**.[53]

Direct functionalisation of the 3-oxygenated isothiazole **143** protected by reaction with benzyl bromide in in K_2CO_3 provided an easily separable mixture of the *O*- and



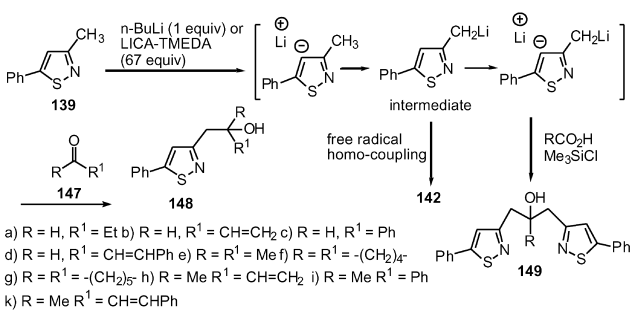
Scheme 44.

N-benzylated derivatives **144** and **145**.[54] The synthesis of the sulphur analogues **146** was achieved by regioselective lithiation of the 5-position of 3-benzyloxyisothiazole **144** using LDA in diethyl ether, followed by reaction with various electrophiles (Scheme 45).



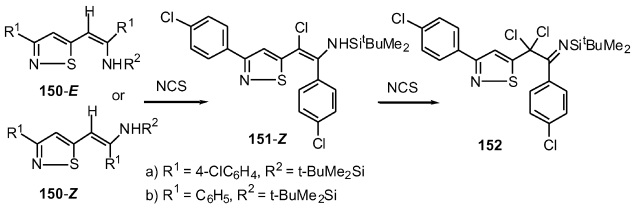
Scheme 45.

6.2.2. Reactions with carbonyl compounds. The reactivity of 3-methyl-5-phenylisothiazole **139** (R1=H) toward electrophiles such as carbonyl compounds in the presence of a base such as *n*-butyllithium and/or lithium isopropylcyclohexyl amide-*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (LICA-TMEDA) has been studied. *n*-Butyllithium led to a higher yield of the hydroxy derivatives of isothiazole than LICA-TMEDA as a deprotonating system for 3-methyl-5-phenylisothiazole.[55] 3-Methyl-5-phenylisothiazole **139** reacted with the oxo compounds **147a**–**k** on the C-3 methyl group, in the presence of *n*-butyllithium and/or LICA-TMEDA, and afforded the hydroxy isothiazoles **148a**–**k** (Scheme 46). When the reaction with alkyl halides was repeated with chlorotrimethylsilane and/or a carboxylic acid in the presence of the aforementionated bases, it afforded the 1,3-bis[3-(5-phenylisothiazolyl)] alkylisopropyl alcohols 149. The formation of 1,2-bis[3-(5-phenylisothiazolyl)] ethane **142** was observed in all cases, when either *n*-butyllithium or LICA-TMEDA were used.



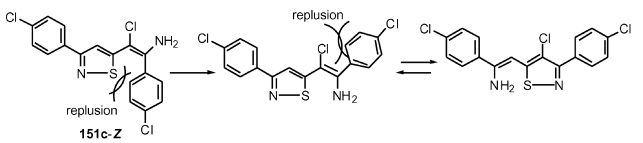
Scheme 46.

6.2.3. Chlorination by *N*-chlorosuccinimide (NCS). These reactions proved to be considerably more stereoselective, Katsuo et al. demonstrated that they are highly stereoselective through all derivatives.[56] The selective monochlorination of the 5-[2-(*N*-silylamino)vinyl]isothiazoles **150a**,**b** with *N*-chlorosuccinimide at the vinyl carbon gave the *Z*-isomer of **151a**,**b**, but with two equivalents of NCS afforded a dichlorinated derivative **152** in 91% yield without the removal of the silyl group, as outlined in Scheme 47.

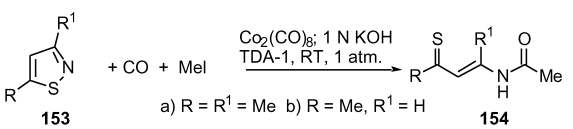


Scheme 47.

It is noteworthy that, whereas **150c** (R1=4-ClC$_6$H$_5$, R2=H) smoothly underwent as *E*–*Z* switch, **151c** did not. Steric repulsion between the benzene ring and the isothiazole rings most likely accounts for this observation.

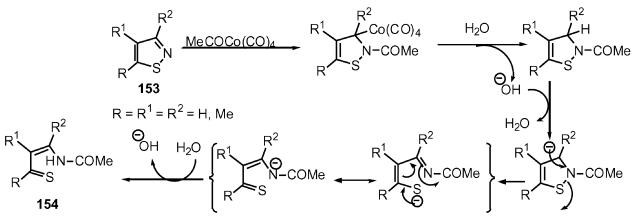


6.2.4. Ring opening and acetylation by the action of PTC. It was reported[57] that the reductive ring cleavage of isothiazoles with acylation using acetylcobalt tetracarbonyl MeCOCo(CO)$_4$ occurred in the presence of phase transfer co-catalysis (PTC). Treatment of the isothiazoles **153** with carbon monoxide, methyl iodide and cobalt carbonyl $Co_2(CO)_8$ with H_2O and TDA-1 [tris-(2,6-dioxaheptyl)-amine] as a phase transfer catalyst gave the 1-methyl-1-(*N*-acetyl)amino-2-thio-acetylethylenes **154** (Scheme 48). A variety of reaction conditions was used in order to investigate the influence of the phase transfer catalyst on the *E*:*Z* ratio of substituted α-amido-ethylenes.



Scheme 48.

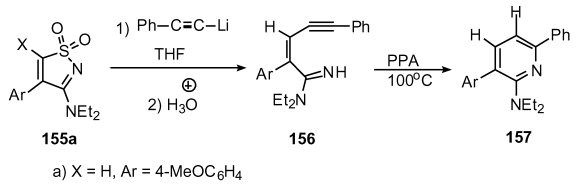
A possible mechanism for the reductive ring-cleavage acylation reaction is outlined in Scheme 49.



Scheme 49.

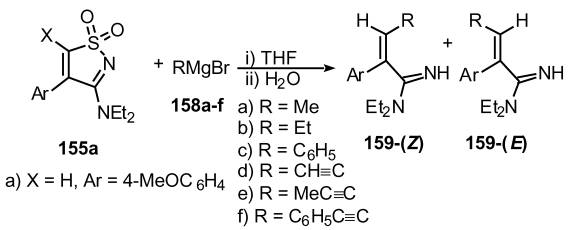
6.3. Reactions with nucleophiles

6.3.1. Reactions with carbon nucleophiles. It has been reported that base-catalysed ring opening of 3-diethylamino-4-arylisothiazole 1,1-dioxides (sultams) such as **155a** gave 2-arylpropenamidines incorporating a 1-azadiene system. Using this method, a large number of compounds with different substituents on C-3 have been obtained in good yields.[58] The reaction with electron-rich alkynes such as phenyllithium acetylide gave the amidine **156**, which was converted by heating in polyphosphoric acid (PPA) at 100°C into the pyridines **157** (Scheme 50).



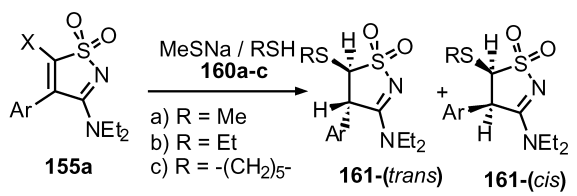
Scheme 50.

The reaction of the 3-diethylamino-4-arylisothiazole 1,1-dioxid **155a** with Grignard reagents **158** in anhydrous THF at room temperature afforded (in good yields) the expected isomeric amidines **159**. In this way, highly conjugated systems with interesting reactivity could be prepared (Scheme 51).[59]



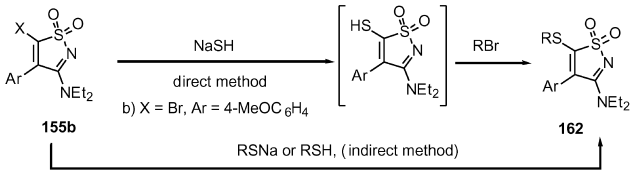
Scheme 51.

6.3.2. Reactions with sulphur nucleophiles (methyl thiolate and/or mercaptans). The reactivity of the 3-diethylamino-4-arylisothiazole 1,1-dioxide **155a** has been studied and the expected nucleophilic attack at C-5 occurred by a Michael-type reaction,[60] with the formation of the 4,5-dihydrosultams **161**. The Sultam **155a** was treated with the sulphur nucleophiles, methyl thiolate or the mercaptans **160a–c** to give the 4,5-dihydrosultams **161** in *trans*- and *cis*-forms with a ratio of 2:1 (Scheme 52).



Scheme 52.

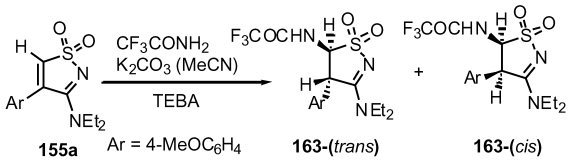
5-Bromo-3-diethylaminoisothiazole 1,1-dioxides (5-bromosultams) such as **155b** appeared to be a key starting material due to the possibility of elimination of bromide ion (Scheme 53). With regard to the sulphur nucleophiles, two different approaches have been used to synthesise the



Scheme 53.

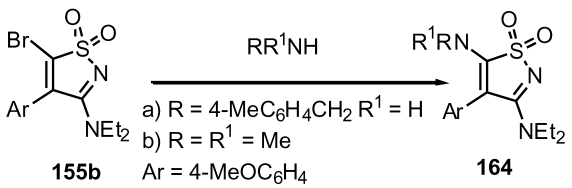
thiosultams **162**. The first studies were made using 5-bromosultam **155b** and sodium sulphide (direct method). In the second method, methyl thiolate or mercaptans are added (indirect method), which gave better yields of the 5-thioalkyl-substituted isothiazole 1,1-dioxide **162**.[60]

6.3.3. Reactions with nitrogen nucleophiles. These reactions proved to be considerably more stereoselective and general than the methods mentioned previously. 3-Diethylamino-4-arylsultam such as **155a** for example, reacted with trifluoroacetamide as the nitrogen nucleophile (using triethylbenzylammonium chloride (TEBA) as the phase transfer catalyst) to give the corresponding isomeric 4,5-dihydro-5-amidosultam **163** in *trans*- and *cis*-forms with a ratio of 2:1 (Scheme 54).[60]



Scheme 54.

5-Bromo-3-diethylamino-4-arylisothiazole 1,1-dioxides (5-bromosultams) e.g **155b** have been reacted with amine nucleophiles such as 4-methylbenzylamine and dimethylamine to give the 5-diethylamino-4-arylisothiazole 1,1-dioxides **164a**,**b** in good yields (Scheme 55).[60]

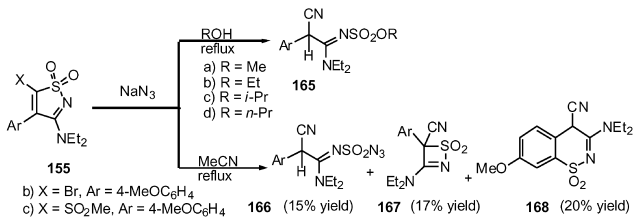


Scheme 55.

The sultams **155a** and 5-bromosultams **155b** underwent Michael addition with nucleophiles to yield the 4,5-dihydrosultams **163**, but in the case of the sultams **155b** the presence of a bromine group allowed the regeneration of the 4,5-double bond. Many attempts were made to transform the dihydrosultams into the corresponding sultams.[60]

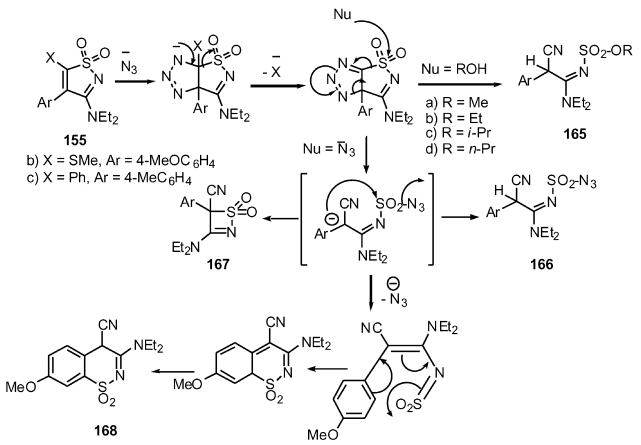
The reactivities of certain isothiazole 1,1-dioxides with sodium azide have been reviewed.[10] Recently, the reactivities of NaN3 with isothiazole 1,1-dioxides bearing different substituents at C-5 have reported.[61] It was found that 5-bromo-3-diethylamino-4-arylisothiazole 1,1-dioxides (5-bromosultams) **155b** reacted with sodium azide in different alcohols to afford the [2-cyano-1-diethylamino-2-(4-methoxylphenyl)-ethylidene]-sulphamic acid esters **165**, but in acetonitrile they furnished a mixture of **166**–**168**, as

outlined in Scheme 56. It was found that **169** could be obtained in high yield by the reaction of diethyl-[5-methanesulfonyl-4-(4-methoxyphenyl)-1,1-dioxo-isothiazol-3-yl-]amine **155c** with sodium azide in acetonitrile.



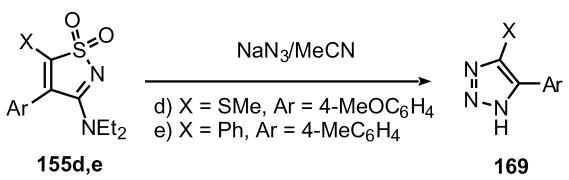
Scheme 56.

A mechanistic scheme for the synthesis of all of the desired products has been proposed in Scheme 57.



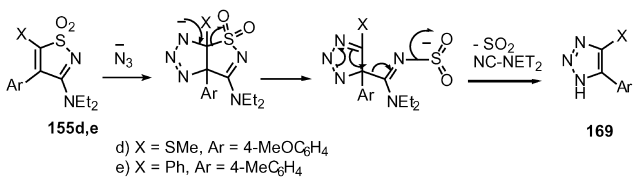
Scheme 57.

The reactions of isothiazole 1,1-dioxides bearing different substituents at C-5 **155d,e** with sodium azide in acetonitrile afforded **169** (Scheme 58).



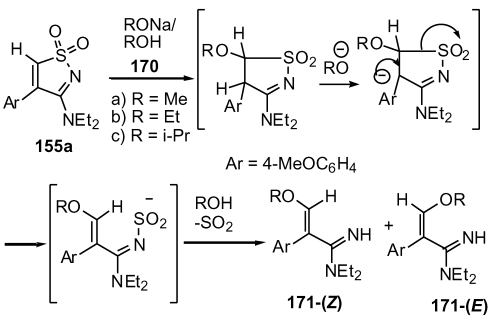
Scheme 58.

A possible mechanism for the formation of triazole **169** is demonstrated in Scheme 59.



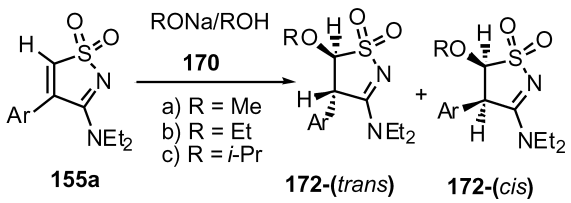
Scheme 59.

6.3.4. Reactions with oxygen nucleophiles. It was demonstrated that the C-5 in 3-diethylamino-4-aryl isothiazole 1,1-dioxide **155a** moiety is more electrophilic and nucleophilic attack occurs at this position by a Michael type reaction. The reaction of 3-diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide **155a** with a solution of two equivalents of the sodium alkoxides **170a–c** afforded the two stereomeric amidine derivatives **171a–c** in *Z*- and *E*-forms in a ratio of 3:1, as demonstrated in Scheme 60.[59]



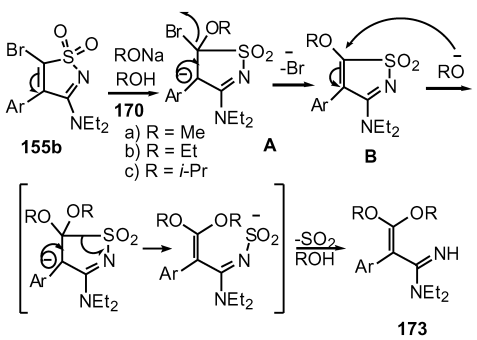
Scheme 60.

The reaction of sultams **155a** with oxygen nucleophiles would be expected to occur with attack at C-5 by a Michael-type reaction and formation of the 4,5-dihydrosultams **172** as two isomers, (*trans* major and *cis* minor) (Scheme 61).



Scheme 61.

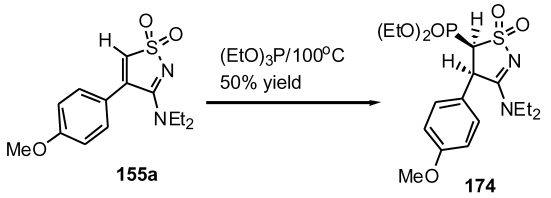
When similar reactions were performed on the 5-bromo-sultams **155b**, the 3,3-dialkoxy-substituted propenamidines **173** were formed.[60] A reasonable mechanism for the formation of **173** is depicted in Scheme 62.



Scheme 62.

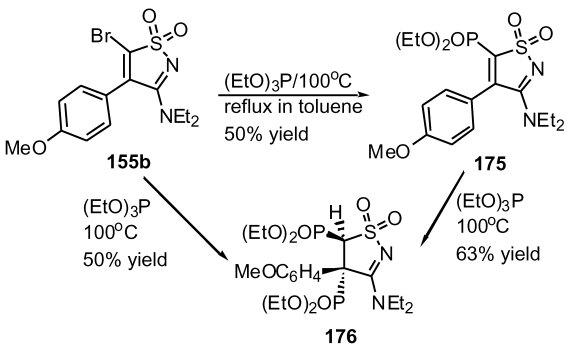
6.3.5. Reactions with phosphorus nucleophiles. Several groups have investigated the use of phosphorus activating groups in the ring-opening reactions of isothiazoles.[62] In one example, 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide **155a** reacted with triethylphosphite (TEP) at 100°C regiospecifically to give 3-diethylamino-4,5-dihydro-4-aryl-5-isothiazolyl phosphonate **174** as the sole product (Scheme 63).

The 5-bromosultams **155b** has been reacted with TEP in



Scheme 63.

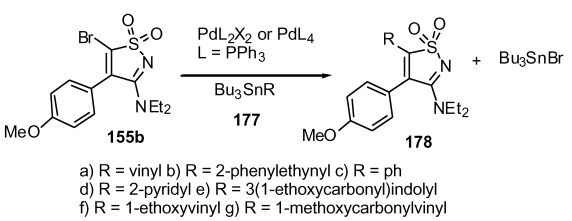
toluene to give the 3-diethylamino-4-aryl-5-isothiazolyl phosphonate **175** or the 5-diethoxyphosphoryl-4,5-dihydro-3-diethylamino-4-arylisothiazolyl phosphate **176** (Scheme 64).



Scheme 64.

6.4. Coupling reactions

6.4.1. Stille coupling reactions. The Stille coupling reaction[63] of 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide **155b** with a range of stannanes **177** provides a general and efficient method for the synthesis of 5-substituted isothiazole-1,1-dioxides **178** (Scheme 65). A general catalytic cycle for the cross-coupling reaction of organometallics, which involves oxidative addition–trans-metallation–reductive elimination sequences, is depicted in Figure 5. Although each step involves further knotty processes, including ligand exchanges, there is no doubt about the presence of the intermediates (**179** and **180**), which have been characterised by isolation or by spectroscopic analyses.[64]



Scheme 65.

It is significant that the great majority of cross-coupling reactions catalysed by Pd(0) is rationalised in terms of this common catalytic cycle. Oxidative addition of aryl halides to a palladium(0) complex affords a stable *trans*-σ-palladium(II) complex **179**. The reaction proceeds with complete retention of configuration for aryl halides. Oxidative addition is often the rate-determining step in a catalytic cycle. The relative reactivity decreases in the order I>Br. Aryl halides activated by the proximity of electron-withdrawing groups are more reactive in the oxidative addition than those with electron-donating groups. A possible mechanism for these coupling reactions is described in Figure 5.[65]

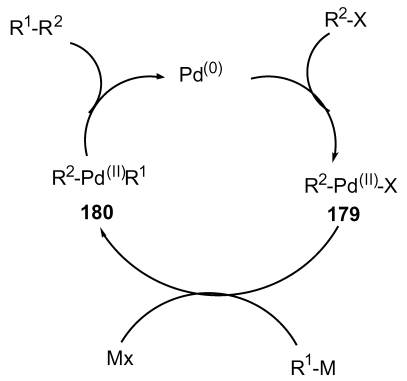
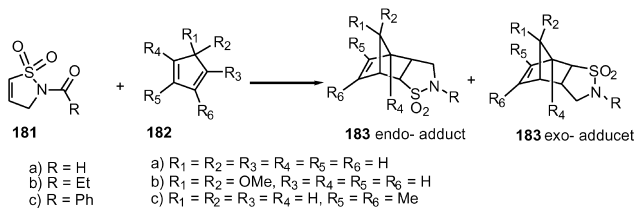


Figure 5. General catalytic cycle for cross-coupling reactions of organometallic

6.4.2. Diels–Alder reactions of α,β-unsaturated-γ-sultams. The intramolecular Diels–Alder reactions of vinylsulphonamides have been reported by Metz and co-workers.[66] The ability of the sulphonamide group to moderate the activity of the vinylic unit (as a dienophile) in intramolecular Diels–Alder reactions is comparable to that of the sulfonates. Recently, Lee and co-workers[67] reported the Diels–Alder reactions of α,β-unsaturated-γ-sultams, the prop-1-ene-1,3-sultams **181** with the dienes **182**, as shown in Scheme 66.



Scheme 66.

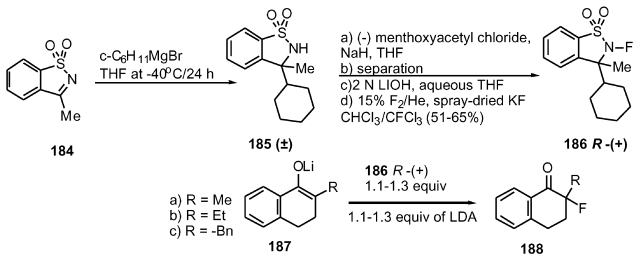
The electron-withdrawing COR group attached to the nitrogen atom moderated the reactivity or selectivity of the unsaturated sultam subjected to the Diels–Alder reactions with or without a Lewis acid catalyst. Good yields of the cycloadducts were obtained and confirmed after the separation of the *exo*/*endo* diastereomers in optically pure forms by column chromatography. The structure of one of the diastereomeric adducts **183** was determined by X-ray analysis.

7. Applications

7.1. Chemical applications

For the time, the optically pure benzosultams (+)-**50g** and (−)-**50g** could be obtained and these are useful as chiral auxiliaries for asymmetric synthesis.[30] *N*-Fluoro-isothiazoles have been used as fluorinating reagents for some organic syntheses. One such reagent, *N*-fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]isothiazole 1,1-

dioxide (CMIT-F) **186**, was found to be an efficient agent for the electrophilic asymmetric fluorination of enolates.[68] The preparation of **186** was accomplished in good yield in five steps starting with the imine **184**, which was prepared from saccharin, and was subjected to alkylation with cyclohexylmagnesium bromide to give **185**. Fluorination of **185** in $CHCl_3/CFCl_3$ with 15% F_2/He in the presence of spray-dried KF as an HF scavenger afforded (*R*)-**186** and (*S*)-**186** as stable, colorless crystalline solids. These compounds were efficient fluorinating agents in electrophilic asymmetric fluorination of enolates. Fluorination of the lithium enolate of 2-methyl-1-tetralone **187** with (*R*)-**186** in THF, furnished the (*S*)-2-fluoro-2-substituted-1-tetralone **188** in 65–79% yield with 72–88% ee, as shown in Scheme 67.



Scheme 67.

7.2. Biological applications

The isothiazole ring has been incorporated into a wide range of known biologically active compounds, either as a substitutuent group or as a replacement of another ring. A further development has been found recently. Apreliminary biological evaluation of some of the isothiazole 1,1-dioxide and 4,5-dihydroisothiazole 1,1-dioxide series has shown a promising pharmacological activity, namely their ability to inhibit arterial smooth cell (SMC) proliferation. It is well known that, in atherosclerotic plaques, SMC's are the predominant cell type and their accumulation is a key requisite leading to vascular occlusion. Accordingly, the discovery of compounds containing the isothiazole ring potentially affecting SMC proliferation is an attractive target.[60] Sulphonamides are a very common organic functional group and are well known for their wide range of biological activities such as antibacterial and antimycotic activity. Unsaturated sulphonamides were also identified as potent, irreversible inhibitors of cysteine proteases, which are essential to the life cycles of many pathogenic protozoa.[28,62] Acylated 5-aminoisothiazoles showed insecticidal, acaricidal and fungicidal activities.[69] The assumption was made that the *S*(2)-oxides may be biologically important as active metabolites of pyrrothiones and analogues of the type (**82** in Scheme 29) in their action as antibacterials and antimycobacterials.[39] 3,4,5-Trisubstituted isothiazoles are used as effective inhibitory agents of enteroviruses.[70] The synthesis and evaluation of 3,4,5-trisubstituted isothiazoles as antiviral agents led to the discovery of several compounds that were effective in vitro against enteroviruses. Some isothiazolamide urea derivatives have been used as anticancer agents.[71] Isothiazolopyridine derivatives are useful as antimycobacterial agents[72] and isothiazole-carbonitrile derivatives have shown antirhinoviral activity.[73] Considering the diverse biological profile of these sulphonamide derivatives, the benzosultams are of interest for biological evaluations and as substrates for developing sulphonamide peptidomimetics.[30]

7.3. Industrial applications

There are many references in the patent literature to azo dyes prepared from aminoisothiazole and 1,2-benzisothiazole derivatives, which are particularly useful in the dyeing of synthetic fibres. Isothiazoles have also been suggested for other industrial applications, such as corrosion inhibitors[74] and antifreeze compositions for diesel engines.[75] The 4-cyanoisothiazole derivatives are used as ink-jet inks and dyes.[76] The inks form sharp, fast-drying, wet-fast images and do not clog the printer. It was reported that the isothiazoline-type used as wood preservative,[77] comparable with some of the polyhydric alcoholic of the fatty acid ester derivatives used as agents for prevention of discoloration of wood treatment.

8. Conclusions

Isothiazoles are useful either as synthetic intermediates or in biological and industrial applications. The chemical behaviour of such compounds is dependent on the structure of isothiazole itself or isothiazole 1,1-dioxide (sultam) at position 4 and 5 towards electrophiles or nucleophiles. The reactivity of 1,2-thiazoles towards Grignard reagents and *n*-BuLi is such that derivatives with an intact ring are formed, as distinct from the isothiazole 1,1-dioxides, which undergo ring opening. The present popularity of the isothiazoles is mainly due to their close structural relationship to some clinically important inhibitors of HIV-1 and this will open the door for many organic chemists to challenges both in the areas of synthetic organic and medicinal chemistry. It is hoped that this report will further stimulate interest in the chemistry, biology and industrial potential of this class of heterocycles.

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