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IMIDAZOLE-2-THIONES: SYNTHESIS, STRUCTURE, PROPERTIES

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The literature data concerning the methods for preparing imidazole-2-thiones and their benzo analogs have been systematized, and the structure, physico-chemical properties and chemical conversions of these compounds have been considered.

The methods for the synthesis of imidazole-2-thiones are classified according to reaction types including cyclization, reactions of halo- and oxoimidazole derivatives with sulfur-containing nucleophiles, and direct insertion of sulfur into position 2 of the imidazole ring.

The structure of imidazole-2-thiones is discussed in terms of quantum-chemical calculations, X-ray diffraction data, dipole moments, UV, and IR as well as ^{1}H and ^{15}N NMR spectroscopy.

Much attention has been given to nucleophilic addition of imidazole-2-thiones to acetylene and its derivatives as well as to alkenes with an activated double bond. The reactions of imidazole-2-thiones as nucleophilic agents, including alkylation, acylation, and interaction with carbonyl halides are discussed.

Some data concerning the use of imidazole-2-thiones are presented.

Key words: Acylation, alkylation, benzimidazole-2-thiones, imidazole-2-thiones, isothiocyanates, nucleophilic addition, *o*-phenylenediamine, thiocyanates.

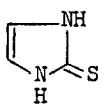
CONTENTS

I. INTRODUCTION

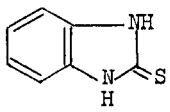
The chemistry of imidazole-2-thiones has developed for about 100 years. At the end of the last century Marckwald[1-3] synthesized for the first time "imidazolylmercaptan" and a series of substituted derivatives. In 1883 Lellmann[4] synthesized benzimidazole-2-thione called *o*-phenylenethiourea. Since the early fifties the intensive development of the chemistry of imidazole-2-thiones has been associated with the use of these compounds in medicine and industry. As early as 1927 the gold salt of 4(7)-carboxybenzimidazole-2-thione (crysolgan) was used in the treatment of tuberculosis;[5] 1-methylimidazole-2-thione (mercazolyl) is an efficient antithyroid drug.[6] Benzimidazole-2-thione and its derivatives have found many uses in industry, mainly as accelerators of rubber vulcanization and as rubber antioxidants.[7-10] Besides, imidazole-2-thiones are convenient synthons for the synthesis of imidazoles, since they are readily desulfurated by oxidants.[11,12]

Imidazole-2-thione **1** and benzimidazole-2-thione **2** are ambident compounds containing a thioureide moiety.

Scheme 1



1



2

These compounds are convenient objects for the investigation of thione-thiol tautomerism, intermolecular hydrogen bonds, acid-base properties, and of spectral features. The ability of imidazole-2-thiones and their benzo analogs to take part in nucleophilic additions to multiple bonds and in nucleophilic substitution, and to form the products of oxidation of the sulfur atom in diverse oxidation states holds great promise for the modification of these compounds and the creation of products of great practical value.

The present authors wish to review all literature data concerning the preparation of imidazole-2-thiones. We have systematized the information reported during the last 25–30 years and present the most developed and convenient reactions leading to imidazole-2-thiones and their benzo analogs. The presence of several heteroatoms (N, S) in imidazole-2-thiones suggests that they should act as polydentate ligands. The vast literature on coordination compounds of imidazole-2-thione has not been covered in the present review, since this material is of independent interest and should be considered separately.

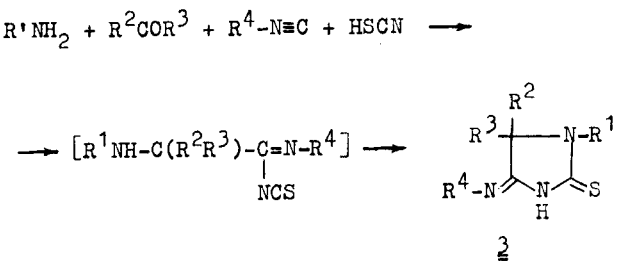
II. THE SYNTHESIS OF IMIDAZOLE-2-THIONES

It is reasonable to classify the methods for the preparation of imidazole- and benzimidazole-2-thiones according to the reaction types employed: (i) cyclizations, (ii) reactions of halo and oxo derivatives of imidazole with sulfur-containing nucleophiles, (iii) direct insertion of sulfur into the ring position 2 of imidazole.

1. Cyclizations

Imidazole-2-thiones with their five-membered ring and an exocyclic sulfur atom can be formed by nucleophilic addition to the C≡N triple or C=N double bond of thiocyanates and isothiocyanates, respectively, of various amino compounds. Due to the fact that the cyclization to imidazole-2-thiones requires heating, thiocyanates are likely to react in the isomeric form. In the synthesis of 2-thiohydantoin-2-imines **3**, one of the components being thiocyanic acid, an isothiocyanate is an intermediate which furnishes the final product by intramolecular cyclization.[13]

Scheme 2

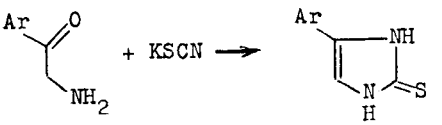


In the synthesis of substituted imidazole-2-thiones amino ketones, amino acetals and amino acids have been used as the amine component.

The most important methods for the preparation of benzimidazole-2-thiones are based on the cyclization of *o*-phenylenediamine and its derivatives with sulfur-containing compounds such as carbon disulfide, xanthates, thiourea and its derivatives, thiocyanates, and thiophosgene.

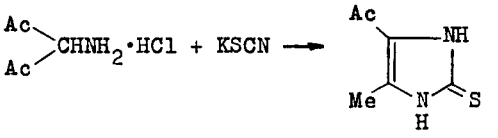
1.1. With amino ketones The reaction of amino ketones with thiocyanates and isothiocyanates constitutes a well-understood and widely accepted method for preparing substituted imidazole-2-thiones with thiocyanic acid or its potassium salt as the source of the thione function. From aromatic amino ketones and their nitro and halo derivatives a series of 4(5)-aryl substituted imidazole-2-thiones have been synthesized by condensation with potassium thiocyanate.[14–20]

Scheme 3



The condensation of α-amino ketone hydrochlorides with potassium thiocyanate is preferably carried out in dry solvents since in aqueous media pyrazine derivatives are formed as well due to hydrolysis of the α-amino ketones.[14] However, the acyl substituted imidazole-2-thiones **4** could be obtained in high yield by heating an aqueous solution of diacylmethylamine hydrochlorides and potassium thiocyanate.[21]

Scheme 4

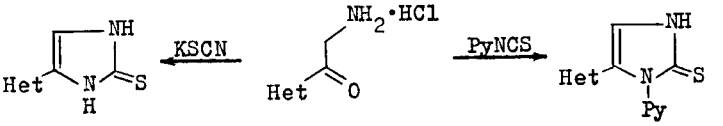


4

A convenient synthetic route to 1,5-dialkyl- and -isoalkylimidazolethiones is the reaction of α-amino ketones with alkyl thiocyanates.[22,23]

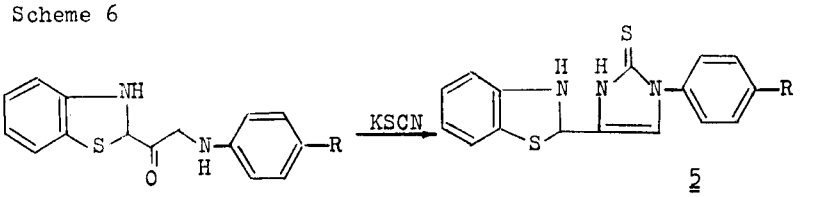
Owing to an extensive search for new drugs some efficient syntheses of hetaryl substituted imidazole-2-thiones were developed during the last years. 5-Hetarylimidazole-2-thiones have been synthesized by reaction of 3-aminoacetylindole[24,25] and 3(4)-aminoacetylpyridines[12,26] with potassium thiocyanate. The use of isothiocyanates, in particular pyridyl isothiocyanates,[27] allowed the preparation of imidazole-2-thiones substituted at the nitrogen atoms.

Scheme 5



By reaction of (benzothiazol-2-yl)-(4-R-anilinomethyl)-ketones with potassium thiocyanate in acetic acid the 1-(4-R-phenyl)-4-(benzothiazol-2-yl)imidazole-2-thiones **5** have been synthesized.[28]

Scheme 6

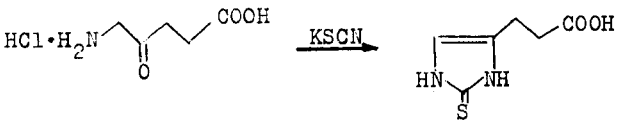


5

R = H, Me, Hal, COOH, CH_2COOH, COOEt, CH_2COOEt

The imidazole-2-thione **6** with an acid function in a side chain has been prepared by reaction of aminolevulinic acid hydrochloride with potassium thiocyanate.[29]

Scheme 7

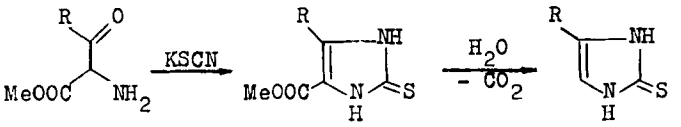


6

The methyl esters of the 4-R-imidazole-5-carboxylic acids **7** have been obtained from

the corresponding methyl esters of α-amino keto carboxylic acids and potassium thiocyanate;[30] subsequent hydrolysis and decarboxylation of **7** lead to the 4-R-imidazole-2-thiones **8**.

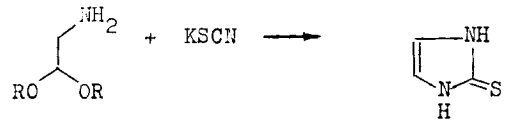
Scheme 8



R = aryl, hetaryl

1.2. With amino acetals The synthesis of imidazole-2-thione **1** has been achieved by reaction of the dimethyl or diethyl acetal of aminoacetaldehyde with potassium thiocyanate.[31,32]

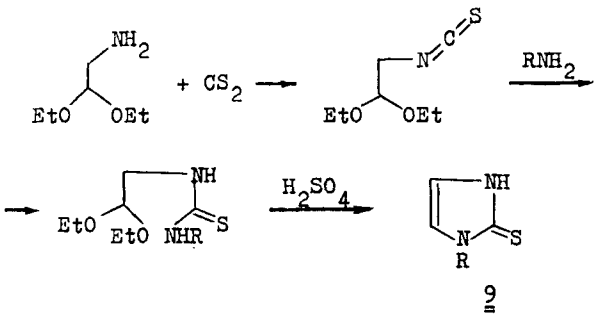
Scheme 9



R = Me, Et

This is also a convenient synthetic route to 1(3)-substituted imidazole-2-thiones, since the corresponding use of *N*-alkyl(aryl)amino acetals[33-39] or isothiocyanates[40,41] in the reaction gives the corresponding *N*-substituted imidazole-2-thiones. Imidazole-2-thiones **9** with alkyl, aralkyl, aryl, and 2-thiazolyl substituents in position 1 have been synthesized.[42] The thione group is introduced by means of carbon disulfide, followed by addition of amine and H_2SO_4-induced intramolecular cyclization.

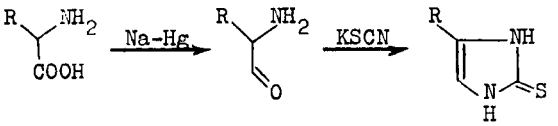
Scheme 10



R = alkyl, aryl, 2-thiazolyl

1.3. With amino acids and their esters Some methods for the preparation of 4(5)-substituted imidazole-2-thiones **10** by reduction of α-amino acids or their esters, followed by reaction of the aldehydes formed with thiocyanates are known.[43,46] Cystine, threonine, tryptophane, valine,[45] and alanine[43] have been used as amino acid components. The reduction of the acids or their esters was preferably performed with sodium amalgam.

Scheme 11

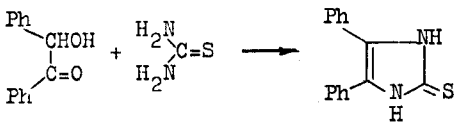


10

R = H, Me

1.4. With hydroxy ketones Several long known procedures for the preparation of alkyl and aryl substituted imidazole-2-thiones,[47,48] based on the condensation of α-hydroxy ketones with ammonium thiocyanate, thiourea, and its derivatives, require drastic conditions such as the use of an autoclave or a sealed ampoule. A method developed by Kochergin[49] avoids these difficulties. The reaction of benzoin with thiourea in hexanol solution leads to 4,5-diphenylimdazole-2-thione **11**.

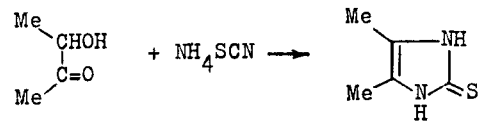
Scheme 12



11

Other substituted imidazole-2-thiones have been synthesized in a similar way.[23,50] The 4,5-disubstituted imidazole-2-thiones **12** are also formed by reaction of α-hydroxy ketones with ammonium thiocyanate.[23]

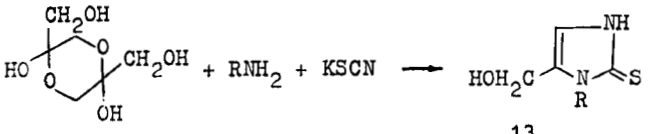
Scheme 13



12

The 1-alkyl(aralkyl)-5-(hydroxymethyl)imidazole-2-thiones[51] **13** useful as intermediates in drug synthesis have been obtained by reaction of dihydroxyacetone dimer with potassium thiocyanate and a primary amine.

Scheme 14

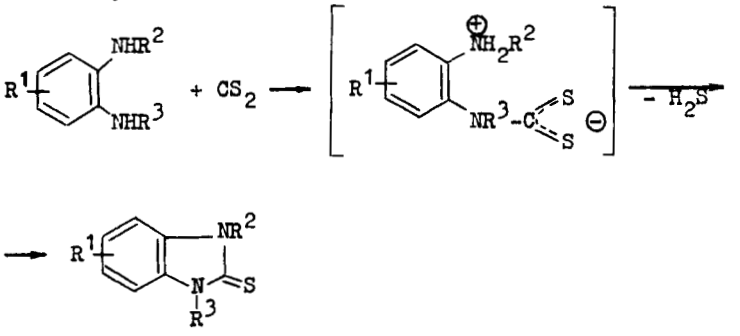


13

R = alkyl, $PhCH_2$, PhHal, $PyCH_2$

1.5. From o-phenylenediamine and its derivatives Condensation of *o*-phenylenediamine and ring substituted *o*-phenylenediamines as well as that of *N*-alkyl(aryl)- and *N,N'*-dialkyl-*o*-phenylenediamines with carbon disulfide provides the most widely accepted method for the preparation of the benzimidazole-2-thiones **14**.[52-71]

Scheme 15

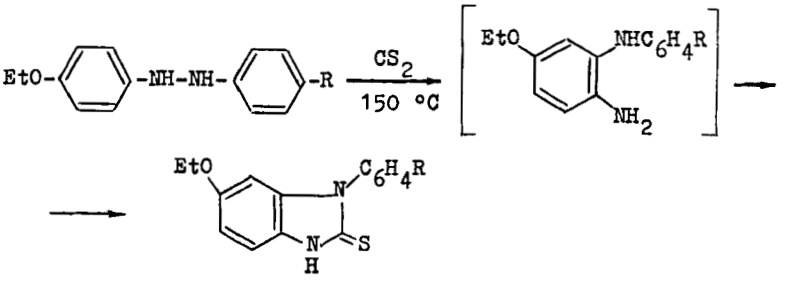


14

R^1 = H, alkyl, aryl, NO_2, Hal; R^2 = H, alkyl, aryl; R^3 = H, alkyl, aryl, $C_2H_4NEt_2$

The reaction is carried out in excess carbon disulfide,[57,59] alcohol,[53,55,60-62,64,70,71] benzene,[63,69] pyridine,[56,63,68] piperidine,[67] or benzothiazole.[58] Triethylamine,[56] alkali metal hydroxides,[53,58-62,64,70,71] or barium hydroxide[69] serve as catalysts.

Scheme 16



15

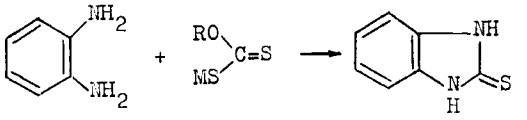
R = H, alkyl, Hal

This classical synthesis from *o*-phenylenediamine has been modified and simplified by the use of the more readily accessible *o*-nitroanilines.[53,68,72-76] In these cases the nitro group is reduced with zinc in alkaline medium,[72] with hydrogen[73] or hydrazine hydrate[73,76,77] in the presence of Raney nickel, with hydrogen sulfide[53,75] or its salts,[75] or tin (II) chloride in hydrochloric acid,[68] the *o*-phenylenediamines formed being subjected to cyclization with carbon disulfide without isolation.

Hydrazobenzenes are likely to be the original source of the 1-aryl-6-ethoxybenzimidazole-2-thiones[78] **15**. The process seems to involve rearrangement of hydrazobenzenes to substituted *o*-phenylenediamines.

For the synthesis of benzimidazole-2-thione **2** it is, in some cases, convenient to use the method of Van Allan and Deacon, based on the reaction of *o*-phenylenediamine with alkali metal xanthates in ethanol.[65,79-82]

Scheme 17



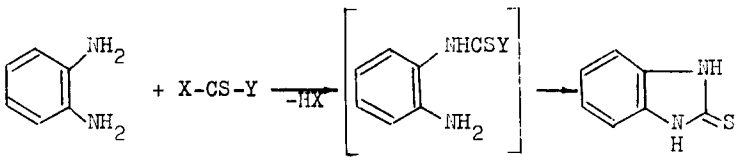
2

R = Et; M = K, Na

The ethyl ester of ethylxanthoformic acid gave 1-carboethoxybenzimidazole-2-thione which, when treated with alkali, hydrolyzes to benzimidazole-2-thione.[83] This reaction is of no preparative value.

Benzimidazole-2-thione can be prepared in high yield by reaction of *o*-phenylenediamine with thiophosgene in chloroform[84] or by fusion with thiourea.[85] In addition to the standard methods, some novel approaches employing sulfur-containing synthons such as *N*,*N*′-thiocarbonyldiimidazole[84] and 1,3-dithiolane-2-thione[86] have been presented.

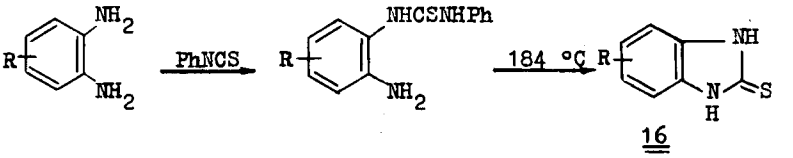
Scheme 18



X = Y = Cl, NH_2, 1-imidazolyl

For the synthesis of benzimidazole-2-thiones **16** use can be made of the condensation of *o*-phenylenediamines with ammonium thiocyanate[4,87] or isothiocyanates.[88] This pro-

Scheme 19



16

R = H, Cl, Me, OMe, NO_2

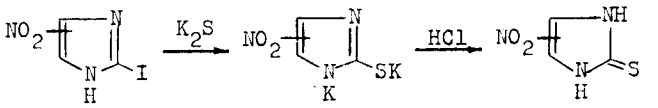
cess involves the isolation of the intermediate *o*-aminophenylthioureas which, when subjected to thermal cyclization, give the end products.

In spite of the high yields of benzimidazole-2-thiones (up to 94%) this method is not much employed which seems to be due to the necessity to synthesize the starting isothiocyanates. A simple transformation of *N'*-substituted *N*-(2-aminophenyl)-thioureas to benzimidazole-2-thiones with loss of the corresponding amine upon heating to the melting point has been reported.[89]

2. *Substitution Reactions*

The reactions of halo- and oxoimidazoles and their benzo analogs with sulfur-containing nucleophiles are of great preparative importance. Upon treatment of 2-bromo- and 2-iodimidazole with thiourea[90] or potassium sulfide[91] in ethanol the corresponding imidazole-2-thiones are obtained.

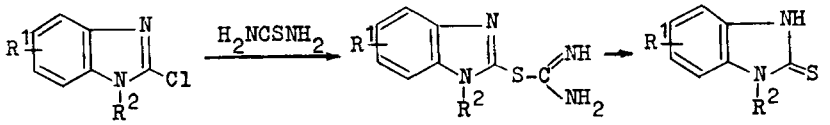
Scheme 20



It should be noted that under analogous conditions 2-chloro-4(5)-nitroimidazole forms bis[4(5)-nitro-2-imidazolyl] disulfide.[89]

2-Chlorobenzimidazoles are converted to benzimidazole-2-thiones **17** upon heating with thiourea in ethanol.[92-96]

Scheme 21



17

R^1 = H, alkyl, NO_2; R^2 = H, alkyl, $CH_2CHAlk(Ar)OH$

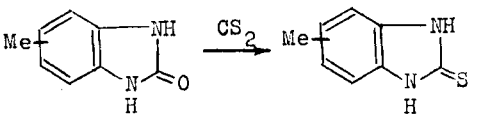
In this reaction the substitution of thiourea by thiophenol or benzimidazole-2-thione leads to phenyl(benzimidazolyl)thiobenzimidazoles. The substitution of the chlorine also takes place with sodium hydrosulfide.[94] It is of interest that the latter reaction occurs only with 1-alkyl substituted 2-chlorobenzimidazoles. The authors explain this by the fact that sodium hydrosulfide transforms 2-chlorobenzimidazole to an anion stable to nucleophilic attack.

In the nucleophilic substitution with sodium thiosulfate[95,97] and *p*-(ethoxy)thiophenol only the salts of the 2-chlorobenzimidazoles are involved.

During the last years some syntheses of benzimidazole-2-thiones from their oxygen analogs have been reported. Thus, 1,3-diarylbenzimidazol-2-ones[99] are transformed to the corresponding benzimidazole-2-thiones by P_2S_5 treatment in hot xylene or pyridine.

The 4(5)-methylbenzimidazole-2-thione **18** can also be obtained in high yield by reaction of 4(5)-methylbenzimidazol-2-one[100] in excess carbon disulfide in the presence of basic catalyst.

Scheme 22

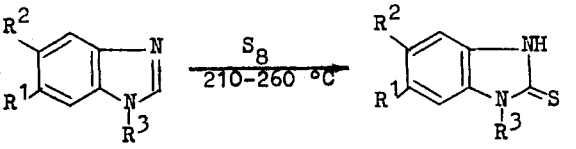


18

3. Reactions of Imidazoles with Elemental Sulfur

Sometimes the introduction of the exocyclic sulfur atom into the imidazole ring is performed by direct reaction with elemental sulfur. Fusion of benzimidazoles with sulfur provides a convenient and efficient route to the benzimidazole-2-thiones **19**.[101-107] Its use is, however, limited by the severe conditions required. 1,3-Dimethylbenzimidazolines react with sulfur under mild conditions.[108,109]

Scheme 23

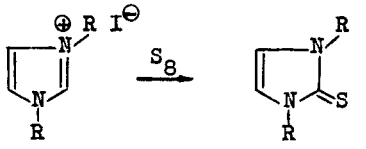


19

$R^1 = R^2 = H$, Me; $R^3 = H$, Me, CH_2Ph

No reactions of this kind are known for imidazole. Dialkylimidazolium iodides readily react with sulfur to form 1,3-dialkylimidazole-2-thiones **20**.[110,111]

Scheme 24



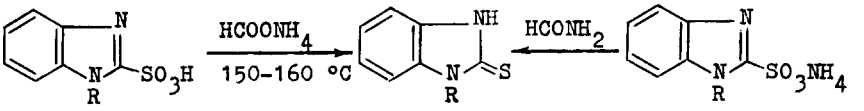
20

R = Me, Et

By heating (up to 200 °C) of sulfur and 4,5-di(2-thienyl)imidazole or 4-[4-fluoro(chloro)phenyl]-5-(2-thienyl)-imidazole in tetramethylene sulfone the corresponding imidazole-2-thiones have been obtained.[112]

Reduction of benzimidazolesulfonic acids can be mentioned as an alternative method for the preparation of benzimidazole-2-thiones **21**.[113]

Scheme 25

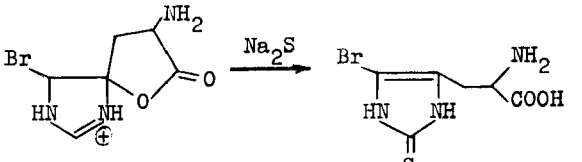


21

R = H, Me, Et, CH_2Ph

For the direct introduction of sulfur use is also made of sodium sulfide. Thus, 2-mercaptohistidine **22**, a component of natural compounds, is obtained by reaction of histidine bromolactone with $Na_2S \cdot 9H_2O$.[114]

Scheme 26



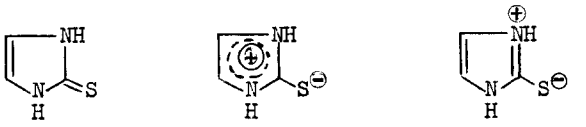
22

III. STRUCTURE AND PROPERTIES OF IMIDAZOLE-2-THIONES

1. Structure and Physico-Chemical Properties of Imidazole-2-thiones

The main structural feature of imidazole-2-thiones is the presence of a thioureide moiety. Quantum-chemical calculations show a non-uniform distribution of π-electron density in imidazole-2-thione with the largest negative charge on the exocyclic sulfur atom.[115] The molecular structure of imidazole-2-thione[116] and 1,3-dimethylimidazole-2-thione[117] has been studied by X-ray diffraction. Imidazole-2-thione is planar. A strong mesomeric shift of the nitrogen electron pairs toward the sulfur atom leads to partial double-bonding in the N–C–N system. The C–N bond length is 1.345 Å which is very close to that of the partially double-bonded C–N bond in aromatic nitrogen-containing heterocyclic systems (1.352 Å). According to a calculation[115] the C–S bond order in imidazole-2-thione is less than 2, its length being 1.70 Å[116] which is longer than that of the C=S bond (1.61 Å). Thus, imidazole-2-thione can most conveniently be represented by the resonance hybrid A. The bond lengths and bond orders[115–117] provide evidence for the dipolar form B to be prevailing in the resonance hybrid A.

Scheme 27



A B

Benzimidazole-2-thione is planar and aromatic.[118] The bond lengths in the condensed imidazole ring are longer than those in a monocyclic imidazole system. There are no essential differences between the lengths of the two C–N bonds (1.362 and 1.383 Å). The C–S bond has 80% double bond character, the bond length being 1.671 Å. The angles between the bonds are in good agreement with these data.[116]

The high contribution from the canonical dipolar form to the molecular structure can account for the high dipole moments of imidazole-2-thione and benzimidazole-2-thione (5.67 and 4.14 D, respectively, in dioxane).[119] Condensation with a benzene ring considerably decreases the dipole moment due to π-conjugation between the imidazole and the benzene ring.

CNDO calculations of the ionization potentials of imidazole-2-thiones and PES band assignments for 1-methyl- and 1,3-dimethylimidazole-2-thione[120] as well as 1,3-dimethylbenzimidazole-2-thione[121] have been carried out. The bonding π-MO is shown to be the HOMO, the non-bonding nσ-MO firmly localized on the thiocarbonyl sulfur atom being the next occupied.

Imidazole-2-thiones are weak organic bases protonated in acids. The imidazole-2-thione pK_{BH^+} values range from -1.1 to -2.2.[115] Imidazole-2-thiones are also NH acids. Measurements revealed two acid dissociation constants of imidazole-thiones in water, $pK_1 = 9.18$ and $pK_2 = 10.98$ which characterize, in the authors' opinion,[122] dissociation of the NH and the SH group. In studies of the pH effect of medium and solvent on the UV spectra of benzimidazole-2-thione derivatives it has been established that the deprotonation in alkaline medium involves the NH group whereas the protonation in strongly acidic medium occurs at the thione moiety.[123]

The UV spectrum of imidazole-2-thione shows two absorption maxima at 217 and 270 nm.[124] The introduction of alkyl substituents into positions 1 and 3 does not displace the long-wavelength absorption maximum much. The effect of bulky substituents on the spectra makes itself felt from the *t*-butyl group on. The presence of aromatic substituents on the nitrogen atoms causes an 18–20 nm bathochromic shift of the maximum. Going from imidazole-2-thione to benzimidazole-2-thione a considerable bathochromic shift is observed, the absorption maxima of benzimidazole-2-thione in ethanol occurring at 246 and 304 nm.[125] Quantum-chemical calculations of the electronic spectra of imidazole-2-thiones allowed the assignment of nearly all transitions observed to the π-π^* type.[124]

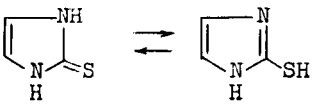
The most comprehensive analysis of the IR spectra of imidazole-2-thione and its alkyl derivatives has been carried out in.[16,126–131] Comparison of the spectra of imidazole-2-thione, its *N*,*N*′-deuterated, its oxygen- and selenium-containing analogs, and an *S*-derivative as well as calculations of the observed bands according to symmetry type and

approximate shape of internal vibrations allow the 520 cm^{-1} band to be assigned to the C=S group vibration.[126] Band assignments for other bonds have been performed, too. For 1-alkylimidazole-2-thiones the thiocarbonyl group vibrations correspond to the bands in the region 1220–1150 ($\nu_{C=S}$) and 550–515 cm^{-1} ($\delta_{C=S}$ or ring + $\nu_{C=S}$).[127] Some authors[128-130] consider a number of bands in the IR spectra of imidazole-2-thiones as HN–C=S vibrations. In the spectrum of imidazole-2-thione four bands at 1480, 1228, 1070, and 740 cm^{-1} have been assigned to thioamide vibrations. For benzimidazole-2-thione the following thioamide bands have been assigned: 1508 ($\nu_{N-C=S}$), 1270 (δ_{N-H}), and 1180 ($\nu_{C=S}$).[132] Comparison of the IR spectra of benzimidazole-2-thione and -2-selenone permits the 598 cm^{-1} band to be assigned to the C=S vibrations.[133]

Imidazole-2-thiones are associated via intermolecular hydrogen bonds of the type N–H . . . S.[74,134,135] This is indicated by the rather high melting points of imidazole-2-thiones and considerably lowered ones for *N*- and *S*-substituted derivatives. The IR spectra of imidazole-2-thiones in CCl_4 show two absorption bands: a narrow one at 3470 cm^{-1} corresponds to the vibrations of free NH groups, whereas a broad 3200–2900 cm^{-1} band arises from H-bonded NH group vibrations.[134] As established by X-ray diffraction each sulfur atom in benzimidazole-2-thione is bound by a hydrogen bond to two NH groups of neighboring molecules (N . . . S 3.336 Å, S . . . H 2.42Å).[118] The HN . . . S angle (22°) indicates a slight deviation from linearity.

Imidazole-2-thiones can exist in two tautomeric forms, a thione and a thiol.

Scheme 28



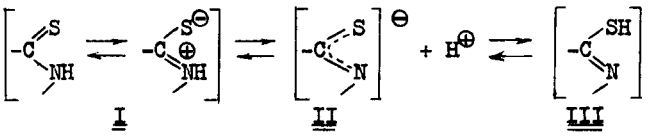
As proved by dipole moments,[119] IR,[126-133,136] UV,[124,126,136] ^1H,[117] ^{13}C,[137,138] and ^{15}N NMR spectroscopy,[138,139] as well as X-ray diffraction,[116,118] imidazole-2-thiones exist in the thione form both in the crystalline state and in solution. According to ^{15}N NMR data 1-methylimidazole-2-thione in DMSO exists exclusively as the thione tautomer, whereas for benzimidazole-2-thione the equilibrium concentration of the latter is 92%.[139] The ionization constants of tautomeric and methylated model compounds have been used to examine the tautomeric equilibrium of imidazole-2-thione.[115] The equilibrium constant of the tautomeric thiol-thione mixture proved to be 10^8.

2. Chemical Properties

Imidazole-2-thiones belong to the so-called "ambifunctional nucleophilic compounds" and are readily involved in reactions with electrophilic agents. The ambident anion of compounds with a thioamide group, generated by proton abstraction, represents a triatomic moiety **II** the negative charge being unevenly distributed between the two end points.[140]

The interaction of imidazole-2-thione with electrophilic reagents normally involves

Scheme 29



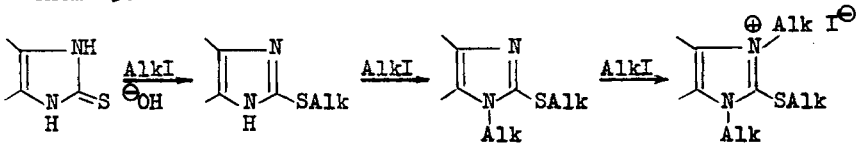
I II III

the readily polarized and highly nucleophilic sulfur atom. In the case of polar electrophiles, however, the new bond is formed with the more electronegative nitrogen atom.

2.1. Imidazole-2-thiones as nucleophiles

2.1.1. Alkylation and arylation Much attention has been given to the alkylation of imidazole-2-thiones with alkyl halides,[15,72,141–148] dialkyl sulfates,[15,23,146–151] esters of phosphoric and phosphorous acid,[150–152] and with diazomethane.[23,149] The alkylation is usually carried out in an alcoholic, aqueous alcoholic or aqueous medium in the presence of alkali metal hydroxides or carbonates for the removal of the hydrogen halide formed. The more nucleophilic sulfur atom is the first to be alkylated which leads to the formation of 2-(alkylthio)imidazoles **23**. Treatment of the latter with excess alkyl halide gives the dialkyl substituted derivatives **24** and the quaternary salts **25**.

Scheme 30



23 24 25

1-Methylbenzimidazole-2-thione has been obtained in good yield by refluxing the corresponding quaternary salt in pyridine.[141]

The rate of the reaction of 1-methylimidazole-2-thione and of 1-methylbenzimidazole-2-thione with methyl and isopropyl iodide is described by a second-order equation, benzimidazole-2-thione reacting by a factor of 10–20 more slowly than imidazole-2-thione.[153]

During the last decade, phase-transfer catalysis has been employed[154] in the exhaustive alkylation of imidazole-2-thiones, which makes it possible to use in this reaction not only alkyl iodides, but alkyl bromides and chlorides as well.[155]

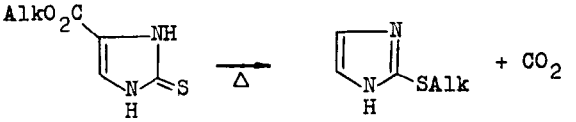
In dimethyl sulfate alkylation, along with exhaustive methylation,[146,148] the formation of a mixture of mono- and disubstituted imidazoles is observed.[23]

A simple and efficient route to the (alkylthio)imidazoles **23** is the reaction of imidazole-2-thiones with alcohols in a medium saturated with gaseous hydrogen chloride.[156]

Of interest is the use of *N,N*-dimethylformamide dimethyl acetal as alkylating agent.[157] Depending on the reaction time it is possible to obtain either mono- or disubstituted benzimidazoles in high yields.

Heating of alkyl-2-thioxoimidazole-4(5)-carboxylates gives 2-(alkylthio)imidazole and carbon dioxide.[158] The authors suggest intermolecular alkylation by the ester group, followed by CO_2 elimination of the acid formed.

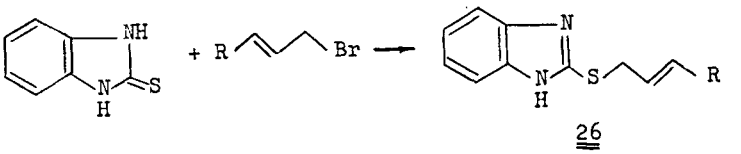
Scheme 31



This is confirmed by the reaction of imidazole-2-thione with alkyl benzoates which leads to (alkylthio)imidazoles and benzoic acid.[31]

The reaction of benzimidazole-2-thione with allyl bromides is completed in a few minutes and yields *S*-allylation products **26**.[159,160]

Scheme 32

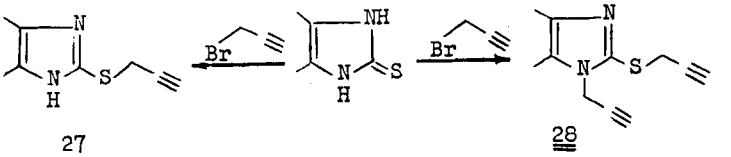


26

R = H, Ph

Imidazole-2-thiones react with propargyl bromide to give 2-(propargylthio)imidazole **27**.[161-166] With excess propargyl bromide in acetone in the presence of potassium carbonate 1-propargyl-2-(propargylthio)imidazole **28** is formed.[163]

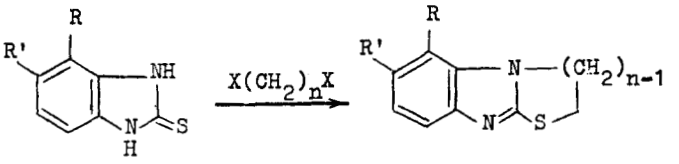
Scheme 33



27 **28**

The interaction of benzimidazole-2-thione with dihaloalkanes occurs simultaneously both at the sulfur and the nitrogen to lead to thiazole and thiazine derivatives, depending on the structure of the starting dihaloalkane.[167-175]

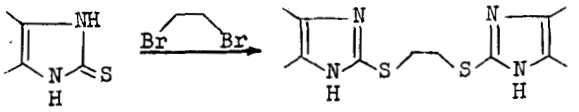
Scheme 34



R = H, NO_2, Me; R'= H, Br, NO_2; X = Cl, Br; n = 2, 3

At the same time, the 1,2-di[(2-imidazolyl)thio]ethanes **29** were isolated by refluxing **1** with excess dibromoethane in toluene or by heating two moles of imidazole-2-thione with one mole of dibromoethane in ethanol in the presence of alkali.[159,168,176]

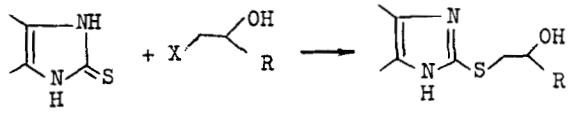
Scheme 35



29

S-Alkylation with β- and γ-halo substituted alcohols in the presence of alkali has been reported.[64,168,177-179]

Scheme 36

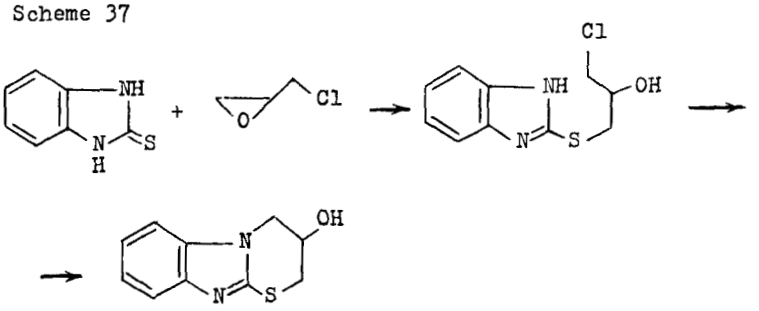


30

R = H, CH_3, Cl, Br; X = Cl, Br

The 2-[(2-hydroxyethyl)thio]imidazoles **30** can also be obtained from imidazole-2-thione and ethylene oxide.[81,180] The reaction with halo substituted epoxy compounds is

Scheme 37

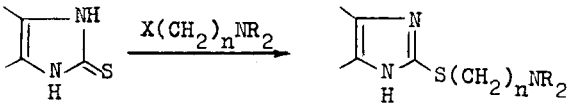


31

accompanied by intramolecular cyclization.[177,181-183] By reaction of benzimidazole-2-thione with epichlorohydrin it was possible to isolate the hydroxy substituted 1,3-thiazinobenzimidazole **31** formed by intramolecular cyclization of the alkylated intermediate.[177,181]

The introduction of an amino function into a side chain of an imidazole-2-thione is accomplished by reaction with haloalkylamines.[64,184-187]

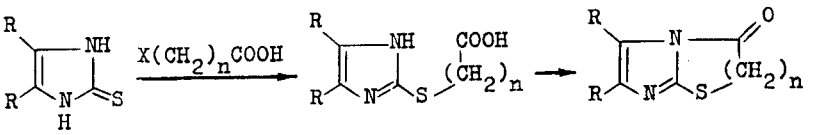
Scheme 38



R = alkyl; X = Cl, Br

The reaction of imidazole-2-thiones with bifunctional compounds such as halo substituted carboxylic acid and their derivatives are synthetically attractive for the preparation of reactive synthons,[55,71,72,143,175,177,188-197] since further modification of the latter can lead, in particular, to condensed imidazothiazoles and imidazothiazines.[65,71,143,167,168,173,175,190,193,194,197-205]

Scheme 39



R + R = (-CH=CH-)$_2$, R = aryl; X = Cl, Br; n = 1-3

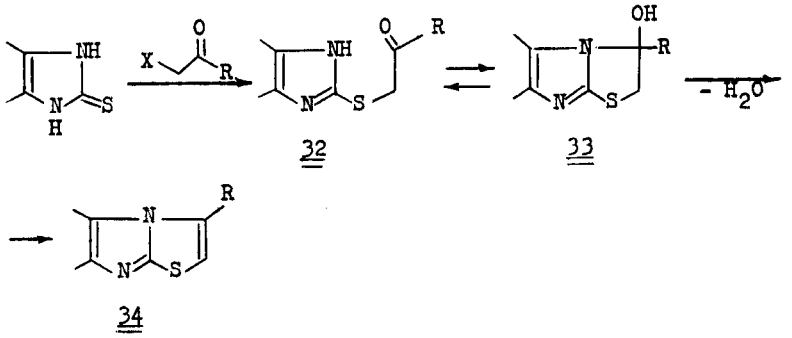
The reaction of benzimidazole-2-thione with 2-bromopropanoic acid gave 2-(benzimidazolylthio)propionic acid which could be separated into the enantiomers.[191]

Nucleophilic substitution of *cis*- and *trans*-β-chloroacrylic acid by benzimidazole-2-thione proceeds with complete retention of configuration.[190]

To extend the series of bioactive compounds in the reaction with imidazole-2-thiones it is possible to use, apart from halo substituted carboxylic acids, their derivatives such as amides,[145,185,206] esters,[71,148,183,206-210] and nitriles.[164,206,211,212] In all cases, the corresponding 2-thio derivatives have been obtained.

The reaction of imidazole-2-thiones with α-halo ketones is widely used[173,213-218] because of possible further intramolecular cyclization of the 2-[β-ketoalkyl(aryl)]thioimidazoles **32** formed.[94,219-224] According to the data reported[213,216,217,219-221,223] the latter are in equilibrium with the tautomeric cyclic form **33**.

Scheme 40



32 33 34

R = alkyl, aryl; X = Cl, Br

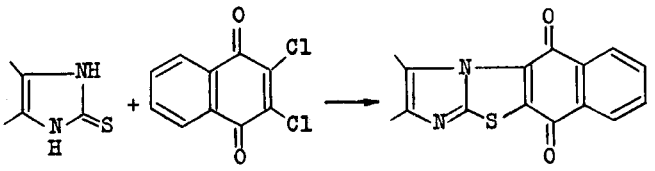
With acidic catalysts elimination of water from the cyclic imidazolethiazoline intermediate and formation of the imidazothiazoles **34** take place. Thus, imidazolyl thioketones should be regarded as intermediates in the synthesis of thiazoles according to Hantzsch.[219] The equilibrium shift to either side depends on the structure of the starting components and the reaction conditions.[213,216,223] In alkaline medium the equilibrium is completely shifted towards the open form, whereas in acid medium a shift toward the cyclic isomer is observed.

Thiazolo[3,2-*a*]benzimidazoles and the intermediate acyclic products have been synthesized from benzimidazole-2-thione and ketones in the presence of iodine.[195] This methods is of preparative value since it allows ketones instead of the sometimes difficultly accessible α-halo ketones to be employed.

In the reaction of 4(5)-substituted imidazole-2-thiones with bromoacetaldehyde it was not possible to isolate (imidazolylthio)acetaldehydes. Instead, the corresponding 3-hydroxyimidazo[2,1-*b*]thiazolines were obtained.[225,226] However, in the reaction with acetals (imidazolylthio)acetaldehyde dialkyl acetals have been synthesized. Some simple preparative routes to (benzimidazolylthio)acetaldehydes and acetals thereof, as well as 3-hydroxythiazolino[3,2-*a*]benzimidazole and its derivatives by the reaction of benzimidazole-2-thione with α-halo aldehydes and their acetals have been developed.[227]

Some reactions with aromatic halo derivatives[55,159,188] which extend the synthetic potential of imidazole-2-thiones should be mentioned. Imidazole-2-thiones react with 2,3-dichloro-1,4-naphthoquinone to form dioxo derivatives of condensed azole systems **35**.[228]

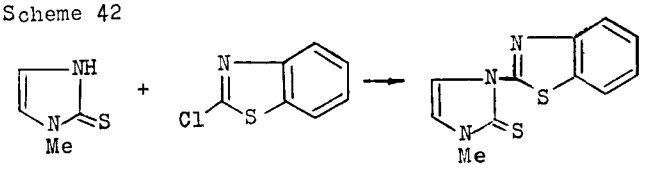
Scheme 41



35

The interaction of imidazole-2-thiones with halo substituted heterocycles[92,229-233] leads to (hetarylthio)imidazoles among which interesting pharmacological effects have been found.[230,231] However, by fusion of 1-methylimidazole-2-thione with 2-chlorobenzothiazole it was possible to isolate 1-methyl-3-(2-benzothiazolyl)imidazole-2-thione **36**.[232]

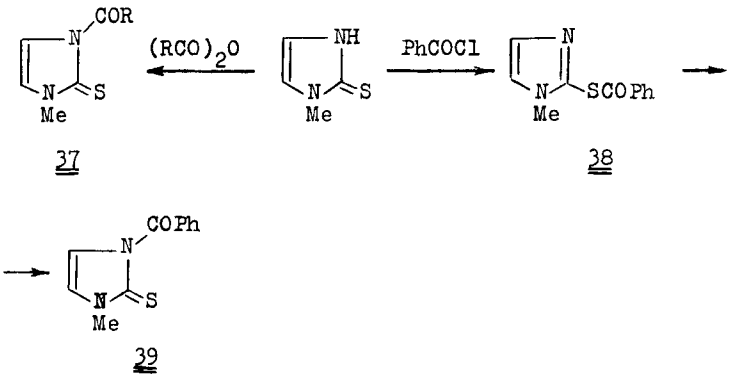
Scheme 42



36

2.1.2. Acylation In the acylation of imidazole-2-thiones the medium and the reaction conditions are of great importance.[234-238] The imidazole-2-thione *N*-acyl derivatives **37** have been synthesized by reaction of imidazole-2-thione and its derivatives with benzoyl

Scheme 43



37 **38** **39**

chloride and aliphatic carboxylic acid anhydrides in pyridine.[236] The (benzoylthio)imidazoles **38** have been prepared in dry ethanol.

It has been established that the acyl substituent is able to migrate from the sulfur to the nitrogen atom to form the more stable *N*-acylimidazole-2-thione **39**.

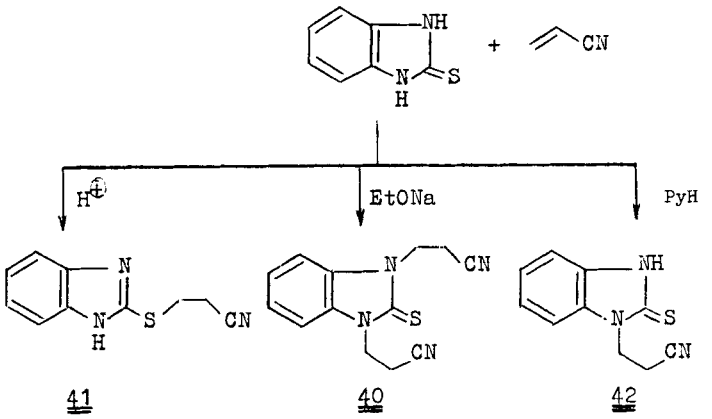
N-Acylbenzimidazole-2-thiones have been synthesized with acyl chlorides and anhydrides as acylating agents, as well as with isocyanates in the absence of base.[239-242] With oxalyl chloride in neutral medium benzimidazole-2-thione forms *S*,*S*′-bis(2-benzimidazolyl) 1,2-dithioxalate.[243]

2.1.3. Addition to activated double bonds In the reaction of benzimidazole-2-thione with acrylic acid and acryloyl chloride under mild conditions addition products, rather than acylation products, are formed, the reaction involving the sulfur atom.[244]

The addition of benzimidazole-2-thione to α,β-unsaturated aldehydes and ketones in the presence of HCl also leads to *S*-adducts.[245,246]

The cyanoethylation of imidazole-2-thione has only been mentioned in a patent.[247] The behavior of benzimidazole-2-thione in this reaction has been studied in more detail. The reaction of benzimidazole-2-thione with acrylonitrile gave the diadduct 1,3-bis(2-cyanoethyl)benzimidazole-2-thione **40**.[248] It has been stated, however,[249,250] that, depending on the catalyst, the reaction can proceed via one of the nucleophilic centers. In an acidic medium the selective cyanoethylation involves the sulfur atom to form the adduct **41**, whereas in the presence of a basic catalyst the reaction takes place at the nitrogen atoms.

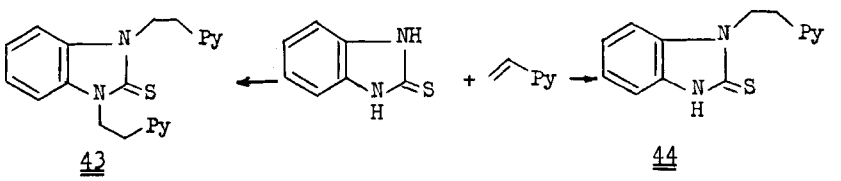
Scheme 44



The possibility for the synthesis of 1-(cyanoethyl)benzimidazole-2-thione **42** has been established.[251] The *N*-monoadduct has also been obtained in the reaction of benzimidazole-2-thione with methyl methacrylate.[159]

N,*N*′-Di- and *N*-[2-(2-pyridylethyl)]benzimidazole-2-thione **43** and **44** have been obtained by heating of benzimidazole-2-thione with 2-vinylpyridine in glacial acetic acid.[104]

Scheme 45

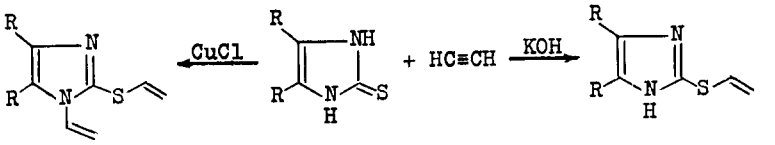


2.1.4. Reactions with alkynes

One of the most interesting chemical properties of imidazole-2-thiones is their nucleophilic addition to the carbon-carbon triple bond leading to the formation of *S*- or *N*-derivatives depending upon the reaction conditions and the nature of the reagent.

Benzimidazole-2-thione and 4,5-diphenylimidazole-2-thione react with acetylene at elevated temperature and pressure in dioxane in the presence of potassium hydroxide or metal salts (copper(I) chloride, cadmium acetate).[252-254] Depending on the catalyst nature *S*-vinyl and *N*,*S*-divinyl derivatives can be prepared.

Scheme 46

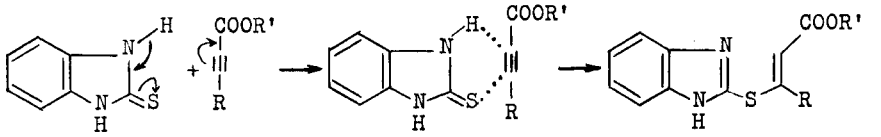


R = Ph; R + R = $(-CH{=}CH-)_2$

Activating groups (COOH, COOR, COR, CN) directly attached to the alkyne triple bond enhance the electrophilicity of the latter and permit the addition of imidazole-2-thione under milder conditions, on one hand, and expand the synthetic potential of this reaction at the expense of intramolecular cyclization, on the other hand.

The reaction of benzimidazole-2-thione with acetylenecarboxylic acids and their esters has been fairly well studied.[255-265] Benzimidazole-2-thione reacts smoothly with propiolic acid and its esters upon heating in ethyl acetate[255,256] or benzene in the presence of base or acid catalysts[257] to give unsaturated sulfides. In the authors' opinion,[255,256] the reaction proceeds via an intermediate cyclic complex.

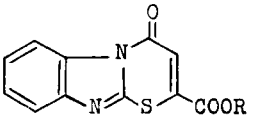
Scheme 47



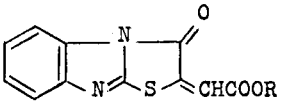
R = H, COOH, COOMe, COOEt; R'= H, Me, Et

By reaction of benzimidazole-2-thione with the ethyl ester of phenylpropiolic acid (200 °C, 12 h) 2-phenyl-4*H*-1,3-thiazino-[3,2-*a*]benzimidazol-4-one[261] has been prepared. The addition of benzimidazole-2-thione to acetylenedicarboxylic acid esters is carried

Scheme 48



45



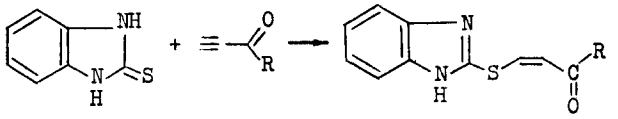
46

R = H, Me, Et

out in methanol or acetic acid to give a 1:1 mixture of the 1-3-thiazino[3,2-*a*]-benzimidazol-4-one **45** and 1,3-thiazolo[3,2-*a*]benzimidazol-3-one derivatives **46**,[259,260,262] prone to interconversion when boiled in methanol in the presence of sulfuric acid. When the reaction is performed in dry methanol or dry acetonitrile only the thiazinone **45** or the thiazolone **46**, respectively, is obtained.[263]

The reaction of benzimidazole-2-thione and 4,5-diphenylimidazole-2-thione with α-acetylenic ketones and with dibenzoylacetylene in hot methanol or acetonitrile leads to acylvinyl sulfides or *N*,*S*-diadducts, depending on the ratio of reactants.[266,267] With an equimolar ratio the reaction of terminal α-acetylenic ketones with benzimidazole-2-thione proceeds stereospecifically to give benzimidazolylacyl sulfides **47** with a *cis*-

Scheme 49



47

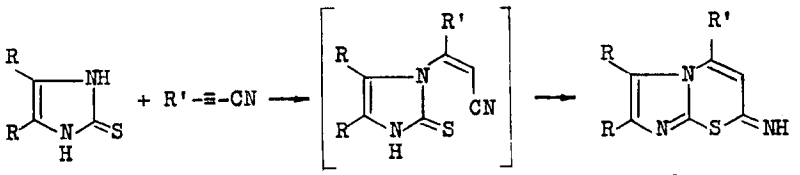
R = Ph, thienyl

configuration. With substituted acetylenic ketones such as 1-benzoyl-2-phenylacetylene and 1-thenoyl-2-phenylacetylene, a mixture of *Z*- and *E*-isomers is formed.

A route to unsaturated sulfides from imidazole- and benzimidazole-2-thiones and ethynylchlorobenzenes has been reported.[268]

Imidazole-2-thiones react with phenylcyanoacetylene[269,270] and tertiary cyanoacetylenic alcohols.[271-273] The activating effect of the cyano group and base catalysis facilitate the addition of the thione **2** and of 4,5-diphenylimidazole-2-thione to the triple bond via the hard center of the ambident anion, i.e., the nitrogen atom. The reaction is highly stereospecific under mild conditions and is followed by intramolecular cyclization to

Scheme 50



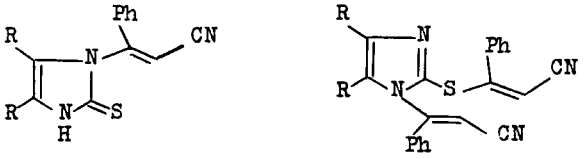
48

R = Ph, R + R = $(-CH{=}CH-)_2$; R' = Ph, $C(Alk)_2OH$

yield the substituted 2-iminoimidazo[2,3-*b*]-1,3-thiazines **48**.

The addition of imidazole-2-thiones to phenylcyanoacetylene is catalyzed by potassium hydroxide. It should be noted that in the presence of 5–10% KOH the substituted 2-iminoimidazo[2,3-*b*]thiazines **48** are formed whereas the presence of 20% KOH leads

Scheme 51



49 50

R = Ph, R + R = $(-CH{=}CH-)_2$

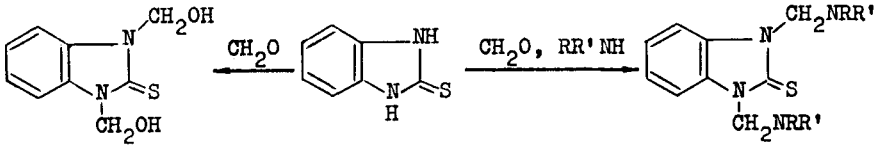
to the 1(3)-(1-phenyl-2-cyanovinyl)imidazole-2-thiones **49**. Use of excess phenylcyanoacetylene gives the corresponding dicyanovinyl derivatives **50**.[270]

The reaction of imidazole-2-thiones with tertiary cyanoacetylenic alcohols proceeds readily in the presence of lithium hydroxide to form only the 2-iminoimidazothiazines **48**.[273] The mechanism of the formation of the latter has been examined by ^{1}H NMR and IR spectroscopy.[274] The reaction of imidazole-2-thiones with substituted cyanoacetylenes has been shown to involve intermediate unstable *N*-adducts with following intramolecular cyclization to iminoimidazothiazines.

2.2. *Other reactions*

Hydroxy- and aminomethylations have been studied mainly with benzimidazole-2-thione. Thus, the condensation of the latter with formaldehyde gave the *N,N'*-

Scheme 52



51 52

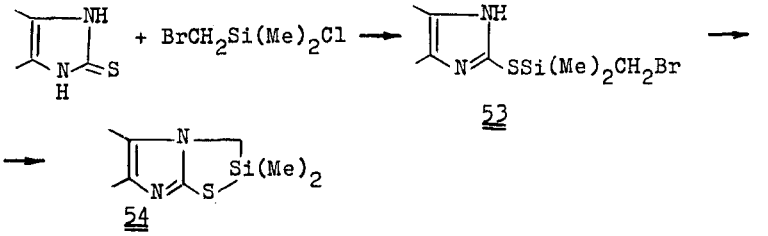
R, R' = alkyl, aryl, hetaryl

bis(hydroxymethyl)benzimidazole-2-thione **51**[149,275,276] whereas the reaction with formaldehyde and primary or secondary amines according to Mannich leads to the *N,N'*-bis[alkyl(aryl,hetaryl)aminomethyl]benzimidazole-2-thiones **52**.[148,149,275,277-279]

Due to the known cytostatic effects of some hydroxy- and aminomethyl derivatives[277,280] a vast number of imidazole-2-thione 1,3-bis(aminomethyl) derivatives have been synthesized.[148]

Also the silylation of benzimidazole-2-thione involves the nitrogen atoms.[281,282] The reaction of imidazole-2-thiones and benzimidazole-2-thiones with (bromomethyl)-dimethylchlorosilane in tetrahydrofuran, however, yields the corresponding *S*-silyl derivatives **53** which can be converted to the silaazoles **54**.[283]

Scheme 53



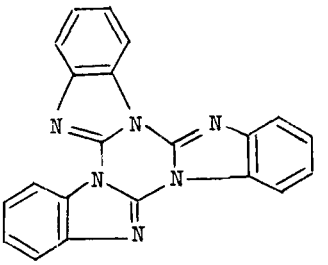
53

54

By oxidation of imidazole-2-thiones it is possible to obtain the corresponding disulfides, sulfinic, or sulfonic acids, depending on the nature of the oxidant and the reaction conditions. Air oxygen,[284] halogens,[275,285] hydrogen peroxide,[285-289] potassium permanganate,[53,105,285,290] as well as *t*-butylhydroperoxide,[291] diacetyl,[289] and dibenzoyl peroxide[292] have been used as oxidants. In some cases the oxidation of imidazole-2-thiones is of preparative value in the synthesis of the corresponding imidazoles formed by elimination of the sulfur in the course of the oxidation.[11,12,20,72]

Some unexpected results have been obtained upon heating benzimidazole-2-thione with phosphoryl chloride[293] and DMSO,[294] the tris(benzimidazo)-*s*-triazine **55** being the major reaction product in both cases.

Scheme 54



55

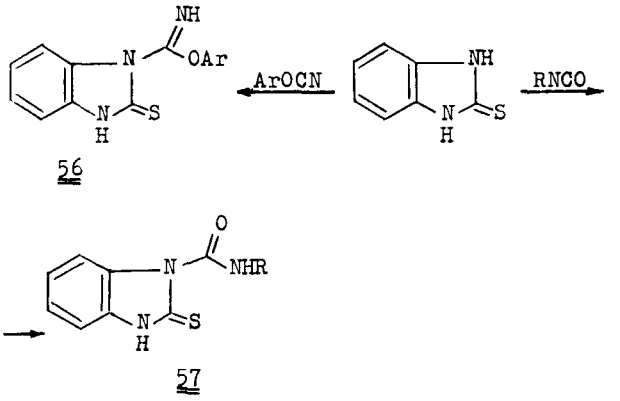
The reaction of cyanates[295] and isocyanates[296] proceeds via the nitrogen atom of benzimidazole-2-thione to form substituted imino ethers **56** and amides **57**, respectively.

Further transformations of these compounds could lead to the corresponding benzimidazothiadiazoles. Under mild conditions, 1-carbamoylbenzimidazole-2-thione with cyanogen bromide forms the corresponding 2-thiocyanatobenzimidazole.[297]

A new reaction, the substitution of the mercapto group by chlorine under the action of thionyl chloride on substituted benzimidazole-2-thiones has been found.[298]

Heating of benzimidazole-2-thione with Raney nickel in butanol gives benzimidazole in high yield.[299] Desulfurization also takes place when elemental sulfur,[101] nickel, cobalt, or their salts[299] are used as catalysts.

Scheme 55



R = Me, n-Bu, cyclohexyl, Ph

IV. USES OF IMIDAZOLE-2-THIONES

Benzimidazole-2-thione and its derivatives have found many uses, mainly in industry, which seems to be due to their ready availability. Benzimidazole-2-thione and some of its salts are used as rubber antioxidants,[8-10,300-304] antiagers, rubber vulcanization inhibitors,[7,305-307] and polymer stabilizers,[308-316] Benzimidazole-2-thione and its *N*-substituted derivatives have been reported to be efficient collectors of copper and zinc from minerals.[317-319] Benzimidazole-2-thione serves as an analytical reagent in the quantitative determination of a number of elements.[320-327]

Being biological toxicants, benzimidazole-2-thione derivatives find wide application in agriculture as insecticides,[187,328,329] fungicides,[82,187,328,329] herbicides,[187,328-330] and acaricides.[268]

The action of benzimidazole-2-thione on the human organism has been studied and found to produce a strong goitrogenic effect[331] and to affect the nervous system and the blood.[66] Among benzimidazole-2-thione derivatives compounds with neuroleptic,[332] antithyroid,[81,331] analgesic,[55,98,333-335] anticonvulsive,[181,336,337] antifungal,[195] antiulcerous, antisecretory,[99] and bactericidal[40,174,338] activity have been found.

Imidazole-2-thione derivatives are most widely employed in medicine as drugs or synthons for drugs. During many years mercazolyl (1-methylimidazole-2-thione) has been used for the treatment of thyroid gland disorders.[6] Some imidazole-2-thione based drugs possessing therapeutic action against arthritis have been developed as reported in patents.[176,180,339] In some cases, an antiinflammatory activity is accompanied by an analgesic action.[112] (Alkylthio)imidazoles and their salts substituted at the nitrogen atom are used in the form of pills and capsules as dopamine β-hydroxylase inhibitors.[39] Compounds exhibiting diuretic, hypotensive, and cardiotonic activity as well as formulations efficient for curing ulcers and Parkinson's disease have been found in the same series.[244,340]

V. CONCLUSION

By the present time a number of convenient and efficient procedures for the preparation of substituted imidazole-2-thiones and their benzo analogs have been developed. The direct reaction of benzimidazole with elemental sulfur is, in our opinion, the most promising synthetic route to benzimidazole-2-thione. However, the parent imidazole-2-thione remains to be difficultly accessible. The known method for its preparation is limited by the fact that the starting amino acetals are of limited availability.

It is beyond any doubt that imidazole-2-thiones exist in the thione form with their thioureide group prone to act in its bipolar form. Depending on the nature of the reagent, imidazole-2-thiones yield derivatives of both the thiol and the thione form.

A number of promising heterocyclic vinyl monomers have been synthesized by the reaction of imidazole-2-thiones with acetylene. The reactions of imidazole-2-thiones with substituted acetylenes and with acyl halides involving intramolecular heterocyclization are of great interest. The functionally substituted condensed heterocyclic systems obtained may serve as synthons for the preparation of bioactive compounds.

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