APPROACHES TO THE SYNTHESIS OF SOME BENZODIISOTHIAZOLES

by

Hong Yao

A Thesis submitted to
The Faculty of Graduate Studies
of the University of Manitoba
in partial fulfilment of
the requirements of the degree of
Master of Science

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I would like to express my deepest gratitude to my supervisor, Dr. David M. McKinnon for his patient guidance, stimulating suggestions and encouragement throughout the course of this work.

A very special note of thanks goes to my family for their support and understanding. Without these, it is doubtful that I would have ever had this opportunity to achieve my Master's thesis.

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Abstract

The preparations of some isomeric benzo[c,d']diisothiazole derivatives had not previously synthesized were investigated.

The approach to the benzo[1,2-c:5,4-d]diisothiazole system gave 4,8-dimethylbenzisothiazolo-[3,4-d:1,2-d]benzothiadiazole **(159)** as the major product when 5-amino-3,6-dimethyl-1,2-benzisothiazole was treated with N-sulfinylmethanesulfonamide in pyridine. The possible mechanism of this reaction was suggested and discussed.

Several approaches toward the synthesis of the other benzo[c,d']diisothiazole derivatives **(145), (146), (147)** were also attempted, but none of them were successful.

The nucleophilic displacement of the nitro group on some aromatic systems by methanethiolate ion was observed and under some cases **(190)** and **(220)**, the relative rate of nitro displacement was much faster than that of chlorine, which was consistent with the previous observations <78JOC2048>.

Some modifications and other routes which might lead to these systems were also suggested and discussed.

FOREWORD

The following abbreviations are used throughout this text:

Alk	alkyl
Ar	aryl
B^-	base
DEM	diethyl malonate
DMAD	dimethyl acetylenedicarboxylate
DMF	N, N-dimethyl formamide
EWG	electron withdrawing group
ERG	electron releasing group
IR	infrared
^1H NMR	proton nuclear magnetic resonance
py	pyridine

THE REFERENCE SYSTEM

The reference system used throughout this thesis is based on that used previously in the series "Comprehensive Heterocyclic Chemistry" (A. R. Katritzky, C. W. Rees, Editors, Pergamon Press Ltd. Oxford, 1984)

Under this system, the references are designated by codes consisting of letters and digits. The first two characters of the code denote the last two digits of the year of publication of the reference. Following this is a one to three letter code denoting the name of the journal and finally a series of digits denoting the page of the reference.

A list of journals (in alphabetical order) and the code assigned to each is given on the next page. All reference cited in this thesis are listed on page in full and are arranged in the following order:

a) year

b) journal in alphabetical order of journal code

c) page number

For non-twentieth century references, the four digits of the year are given. Less common journals and books are given the code "MI" for miscellaneous.

Journals	Codes
Ann.	A
Antimicrob. Ag. Chemother.	AAC
Ann. Chim. (Paris)	AC(P)
Ann. Chim. (Rome)	AC(R)
Acta. Chem. Scand.	ACS
Angew. Chem. Int. Ed. Engl.	AG(E)
Aust. J. Chem.	AJC
Bull. Chem. Soc. Jpn.	BCJ
Bull. Soc. Chim. Fr.	BSF
Chem. Ber.	CB
Chem. Commun.	CC
Chem. Ind.	CI
Can. J. Chem.	CJC
Chem. Pharm. Bull	CPB
Gazz. Chim. Ital.	G
Helv. Chim. Acta	HCA
Heterocycl. Chem. (London)	HC(L)
J. Am. Chem. Soc. (C)	JAS
J. Chem. Phys.	JCP
J. Chem. Res. Synop.	JCR(S)
J. Chem. Soc.	JCS
J. Chem. Soc. (C)	JCS(C)
J. Chem. Soc. Perkin Tran. I	JCS(PI)
J. Heterocycl. Chem.	JHC

J. Med. Chem.	JMC
J. Mol. Structure	JMS
J. Org. Chem.	JOC
J. Phys. Chem.	JPC
J. Mol. Spec.	JS
Liegigs Ann. Chem.	LA
Proc. Chem. Soc.	PCS
C. R. Acad. Sci. C	RAS(C)
Russ. Chem. Rev. (Engl. Trans.)	RCR
Recl. Trav. Chim. Pays-Bas	RTC
Synthesis	S
Tetrahedron	T
Tetrahedron Lett.	TL
Z. Chem.	ZC

Book Series

"Advances in Heterocyclic Chemistry"	AHC
"Chemistry of Heterocyclic Compounds"	HC
"Comprehensive Heterocyclic Chemistry"	CHC
"Organic Reactions"	OR
"Organic Synth. Coll"	OS(C)
"Practical Organic Chemistry, Third Edition"	POC(III)
"Organic compounds of sulphur, selenium and tellurium"	SST

Patent

Rohm & Hass Co. Fr. Patent	FRP
U. S. Patent	USP

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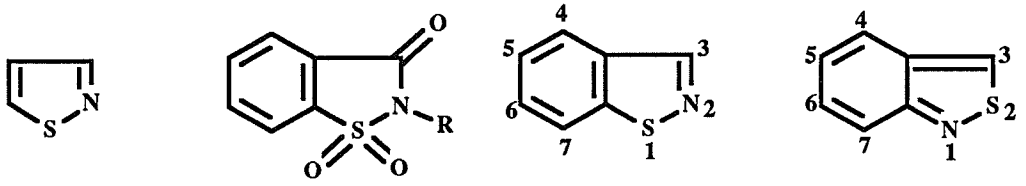
Figure 5. ^{1}H NMR spectrum of 4,8-dimethylbenzisothiazolo-[3,4-d:1,2-d]benzothiadiazole **(159)**

1. INTRODUCTION

1.1. STRUCTURE AND REACTIVITY OF ISOTHIAZOLES

Isothiazole **(1)** is a five membered ring system, containing three carbon atoms, and adjacent sulfur and nitrogen atoms. The monocyclic system and various benzo- derivatives are known, e.g., as the aromatic (6π) system, various salts, and in different oxidation levels.

First prepared in 1956, the chemical and physical properties of isothiazole have been extensively studied. The benzisothiazoles, on the other hand, have been known for much longer. The most widely known member of this family, saccharin **(2)**, was first prepared in 1879. There are two isomeric benzisothiazole systems, 1,2-benzisothiazole **(3)** and 2,1-benzisothiazole **(4)**. The numbering system is shown in **(3)** and **(4)**.



(1) **(2)** **(3)** **(4)**

Isothiazoles and benzo derivatives have been extensively reviewed <65 AHC(4)107, 72AHC(14)1, 72AHC(14)43, 73SST(2)556, 75SST(3)541, 77SST(4)339, 79SST(5)345, 80HC(L)109, 85AHC(38)105>, and this introduction will cover only a few of the most important data.

The isothiazole ring possesses a system of six delocalized π electrons, and is therefore a heteroaromatic system. Various MO investigations have been performed, including CNDO/2 and CNDO/S. They agree that most of the charge density lies on the isothiazole nitrogen atom, with the sulfur atom bearing a small net positive charge <65AHC(4)107, 74CJC596,

79RCR289>. In general, C(4) is calculated to have the highest electron density and C(3) the least among carbon atoms of the heterocyclic ring, although the calculation depends on the approximation used.

Table 1. Calculated π-Bond Orders of Isothiazole

Ref.	Isothiazole Substituent	Bond S-N	N-C(3)	C(3)-C(4)	C(4)-C(5)	C-S	Caln. Method
AHC(4)107	None	0.502	0.705	0.634	0.707	0.594	HMO
72T637	None	0.474	0.707	-	-	-	PPP
74CJC833	None	0.227	0.870	0.410	0.850	0.302	CNDO/2
73BSF1743	3-Ph	0.34	0.82	0.43	0.86	0.37	PPP

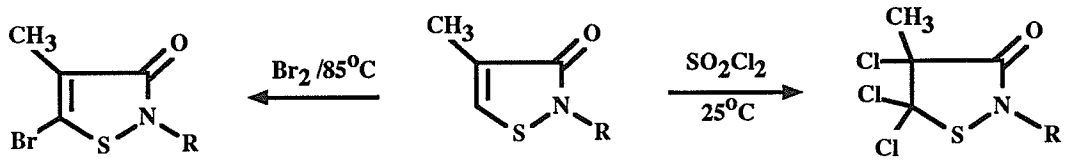
The highest bond orders have been found for the C(3)-N and C(4)-(5), and the lowest order for the bond between S-N (Table 1), which is consistent with the chemical evidence that the S-N bond is the one most easily cleaved.

1.1.1. Electrophilic Substitution

Electrophilic substitution is a very characteristic property of aromatic and heteroaromatic compounds. For the mononuclear isothiazole system, it occurs at the 4-position. Although nitration of simple isothiazole needs more vigorous conditions than that of benzene, halogenation is easier <65AHC(4)107, 72AHC(14)1, 69FRP1555414, 79SST(5)345>. Yields are often poor, possibly because of the formation of perhalogeno compounds. Isothiazoles with

electron-releasing substituents, however, undergo facile bromination and high yields have been reported <59JCS3061, 68CPB(16)148, 63CB(96)944>.

If the 4-position is occupied, bromination will occur at the 5-position in low yield, while reaction with sulfuryl chloride gives compound (7) in acceptable yield <76JHC1321>.



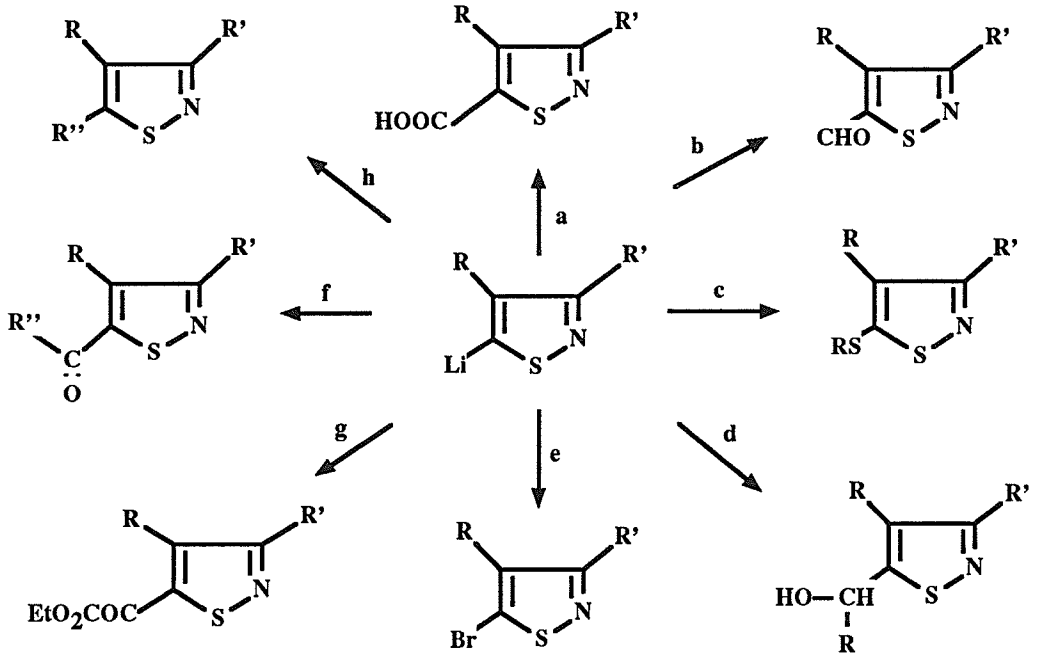
(5) (6) (7)

Nitration occurs exclusively at the 4-position in good yield <65AHC(4)107, 72AHC(14)1>. 5-Halogeno <80JHC385> and 3-alkoxy <76USP3957808> groups do not interfere. Kinetic studies have shown that isothiazole and monomethyl derivatives are much more reactive than 3,5-dimethylisothiazole <72BSF162>, because isothiazole and the monomethyl compounds are nitrated solely as free base, whereas 3,5-dimethylisothiazole is nitrated as the conjugate acid <71JCS(B)2365, 75JCS(P2)1620>.

Although isothiazoles are sulfonated at the 4-position using either oleum or sulfur trioxide <72AHC(14)1>, formylation with dimethylformamide and phosphorus oxychloride and acylation under Friedel-Crafts conditions failed <63JCS2032>.

The ring nitrogen atom is readily alkylated in all compounds bearing a 3- or 5- substituent which allows tautomerism to a ring NH structure, e.g., an OH group. Alkylating agents include diazomethane <72AHC(14)1, 76ACS(B)781>, dimethyl sulfate <75SST(3)541, 79SST(5)345>, Meerwein's reagent <79CB1288> and alkyl halides <79JMC237>.

A study of hydrogen-deuterium exchange rates showed that the 5-position exchanges very rapidly under basic conditions, indicating the formation of a relatively stable anion <69JHC(6)199>. Therefore, under the appropriate conditions, isothiazole forms a lithium derivative by the action of butyllithium or other organolithium compounds. These lithiated compounds are of considerable preparative value as they can lead to a wide variety of substituents in the 5-position, and usually in good yield, as described in Scheme 1.

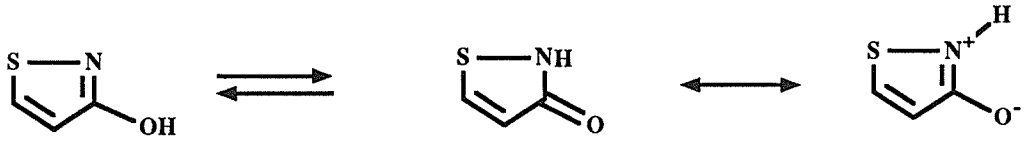


a) CO_2
b) DMF
c) 1. S
2. RX
d) R"CHO
e) Br_2
f) $(R"CO)_2O$
g) $(CO_2Et)_2$
h) R"Br

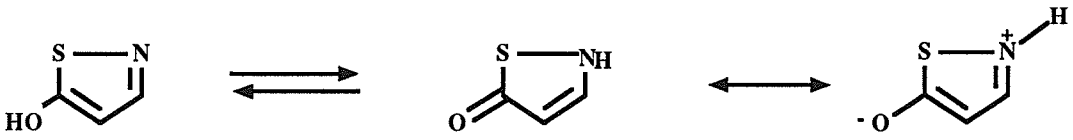
Scheme 1

Annular tautomerism does not occur in isothiazoles or benzisothiazoles. Substituent tautomers can sometimes be distinguished by either chemical methods or physical methods <76AHC(S1)1>.

3-Hydroxyisothiazole exists in the hydroxy form in non-polar solvents such as cyclohexane or ether. In polar solvents such as DMSO or methanol, more keto tautomer is present in the equilibrium mixture, indicated by the coupling value of ^1H NMR spectrum. 3-Hydroxyisothiazoles with substituents in the 4-, or 5- position also exist in the hydroxy form, even in polar solvents.



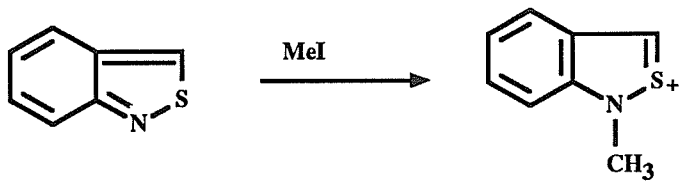
In contrast, 5-hydroxyisothiazole appears to exist predominately in the keto form in both polar and nonpolar solvents, with considerable contributions form the zwitterionic isomer in the solid state.



In general, for the potentially tautomeric 3-hydroxyisothiazole and 5-hydroxyisothiazole, the position of equilibrium is largely dependent on substituents and solvent used.

Early reports suggested that quaternary salts were formed only slowly <72AHC(14)1> at low temperature and decomposed on heating. The quantitative measurements showed that isothiazole reacted less rapidly than 1-methylpyrazole, but more rapidly than isoxazole, in line with the relative basicities of the rings <73AJC1949, 77SST(4)339>. The rate of quaternization with alkyl iodides falls somewhat with increasing size of alkyl group

<76AJC1745, 74AJC1221>. Benzofusion has very little effect on rate of alkylation in the isothiazole series, possibly because of the aromatization of the benzenoid ring during the quaternization process **(8)-(9).**



(8) **(9)**

This would provide a stimulus for reaction to compensate for any withdrawing effect of the benzo group. 2,1-Benzisothiazole is a stronger base (pK_a=-0.052±0.1) than isothiazole (pK_a=-0.51). The observation that reaction with ethyl iodide does not produce a significant increase in rate ratio to that of reaction with methyl iodide in the isothiazole series demonstrates that steric effects are relatively unimportant in the quaternization reaction. Alkyl halides, sulfates, tosylates and fluorosulfonates have been used for quaternization, as well as triethyloxonium fluoroborate.

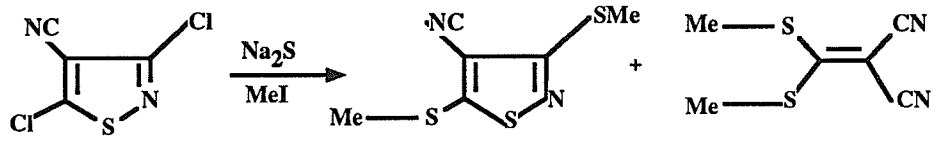
1.1.2. Nucleophilic Reactions

Usually, nucleophilic reaction can be divided into two categories, nucleophilic substitution and nucleophilic ring cleavage.

Halogen atoms in various positions on the isothiazole ring show interesting differences in reactivity and this is of considerable synthetic value. Thus, the 5-halogen, particularly when activated by an electron-withdrawing group in the 4-position, readily undergoes nucleophilic displacement to give isothiazoles with hydroxy <71JCS(C)1314>, alkoxy <64JOC(29)660,

68JMC(11)159>, alkylthio <68CPB(16)148, 64JOC(29)660>, amino <64JOC(29)660>, cyano <65JOC7277> and hydrazino substituents <71JCS(C)776>. Disulfides <71JCS(C)776, 63JOC(28)2163>, sulfides <71JCS(C)776, 68JCS(C)1402> and thiols <64JOC(29)660> have also been prepared this way.

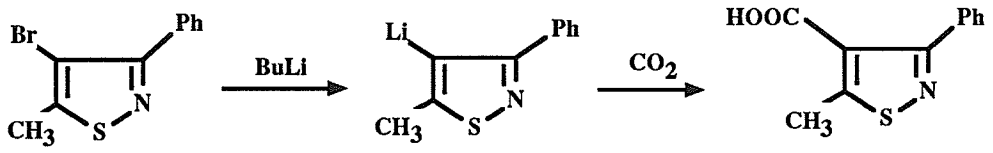
A 3-halogen, however, even when activated, is less reactive than a 5-halogen, and replacement may be accompanied by ring cleavage (Scheme 2) <64JOC(29)660>.



Scheme 2

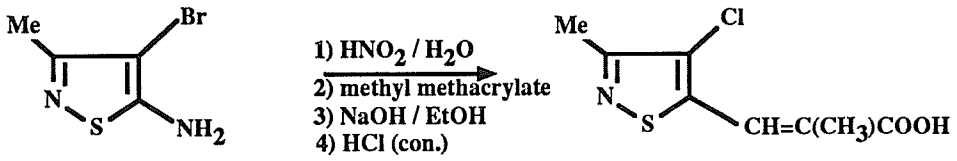
4- Halogens by contrast, resist nucleophilic attack with the exception of the formation of nitriles by reaction with copper(I) cyanides <68JMC(11)159>.

Lithiation occurs exclusively in the 5-position, and no evidence of halogen displacement has been obtained. In one case, it was reported that a 4-lithio derivative was formed by transmetalation when the 3-, and 5-positions were blocked <68CPB(16)148>. (Scheme 3)



Scheme 3

Halogen exchange has been observed during the diazotization of a 5-amino-4-bromoisothiazole in the presence of concentrated hydrochloric acid <65JCS3834>, as an intermediate in the preparation of the unsaturated acid.

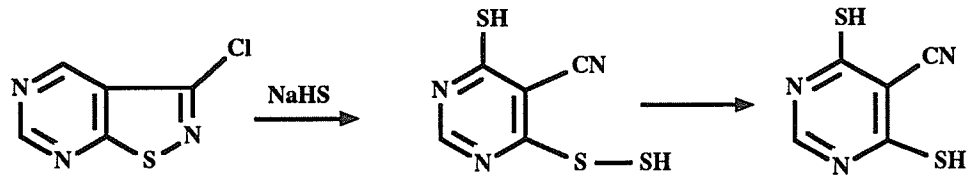


3-, 4-, And 5- Aminoisothiazoles have pK_a's of 2.49, 3.58 and 2.70 respectively. Thus, in general, aminoisothiazoles behave as weak amines. They may be diazotized, and the diazonium salts undergo Sandmeyer and Gomberg-Hey reactions.

5-Aminoisothiazoles with electron-withdrawing substituents in the 4- position gave, with a few exceptions, N-nitroso compounds on diazotization <70CB(103)112>. 5-Cyano compounds and 4-hydroxy compounds cannot be obtained from the diazonium salts, but 3- and 5- hydroxy compounds are available by this means, although the conditions are critical in the 5- series <72AHC(14)1>.

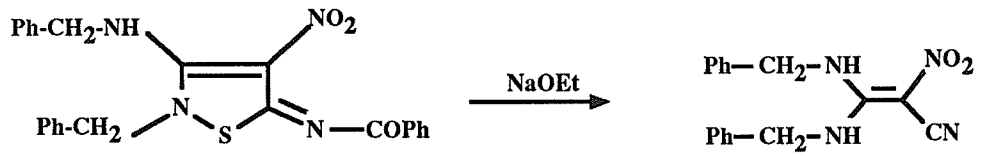
Generally, the carbonyl derivatives of isothiazole behave normally and form derivatives with oximes, hydrazines, semicarbazide and thiosemicarbazide.

A few examples of ring cleavage at the N-S bond by nucleophilic agents are known <79CB1288, 80JCS(P1)2693>. 3-Chloroisothiazoles with blocked 4- and 5- positions undergo attack on the ring sulfur by nucleophiles leading to ring opened products <72AHC(14)1>. (Scheme 4)



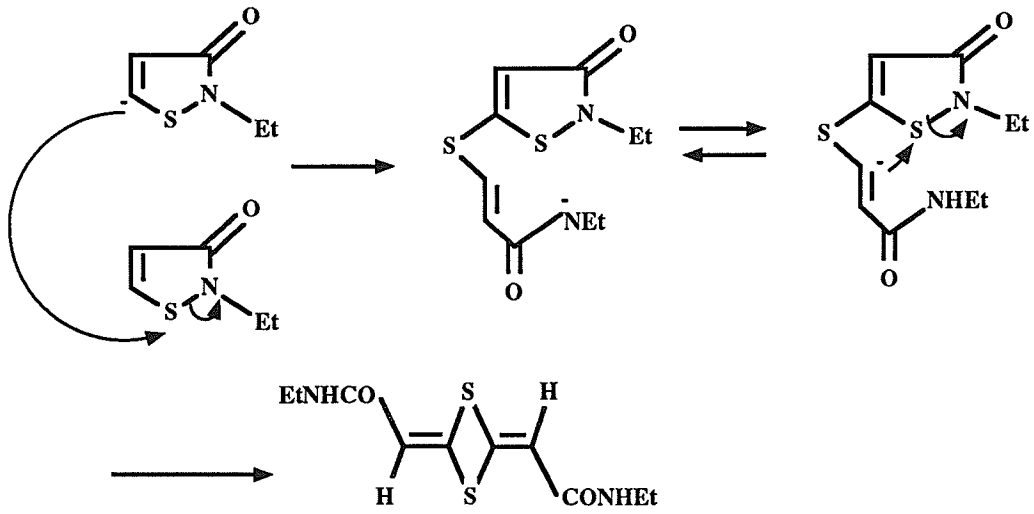
Scheme 4

By refluxing the nitroisothiazoline **(10)** with sodium ethoxide in ethanol, the product **(11)** was obtained in 75% yield <77T1057>.

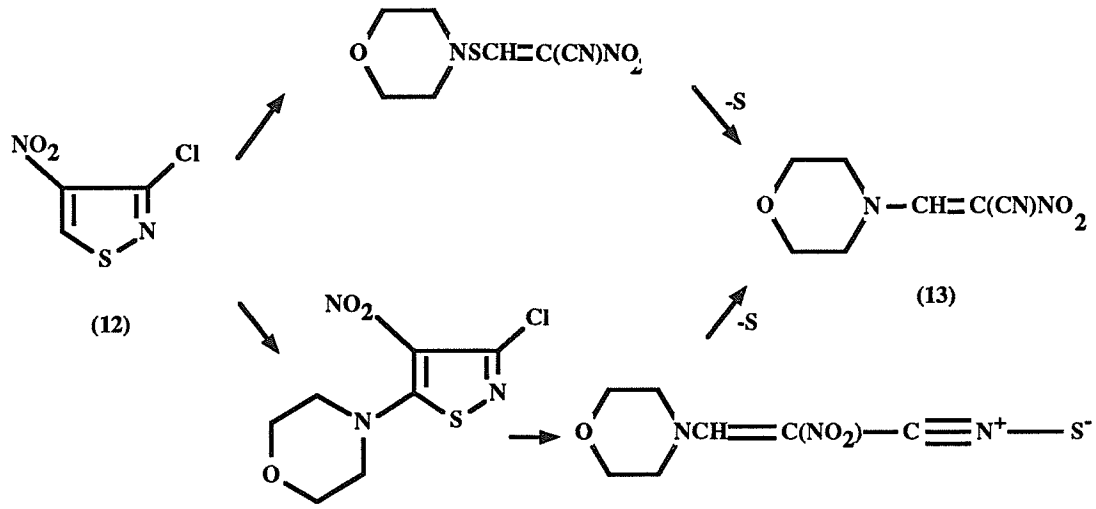


(10) (11)

In the absence of an added nucleophile, 2-alkyl-3-isothiazolones dimerize under basic conditions to give 2,4-bismethylene-1,3- dithietanes <70T(26)1493>. The mechanism below was suggested.



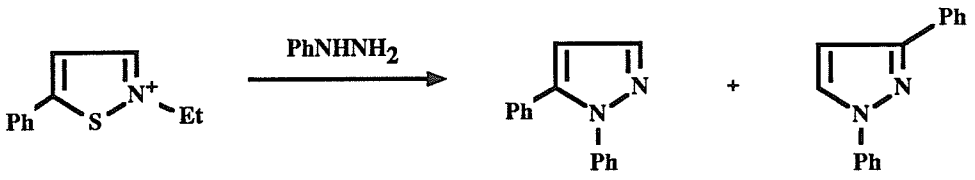
Usually, amines have no effect on the isothiazole ring, except that 3-chloro-4-nitroisothiazole (**12**) can react with cyclic amines such as morpholine at 0°C to give the enamine (**13**) <75JOC955> by attack either at the sulfur or 5-position with sulfur extrusion from either a morpholinothio alkene, or from a "nitrile sulfide" respectively.



1.1.3. Quaternary Isothiazoles

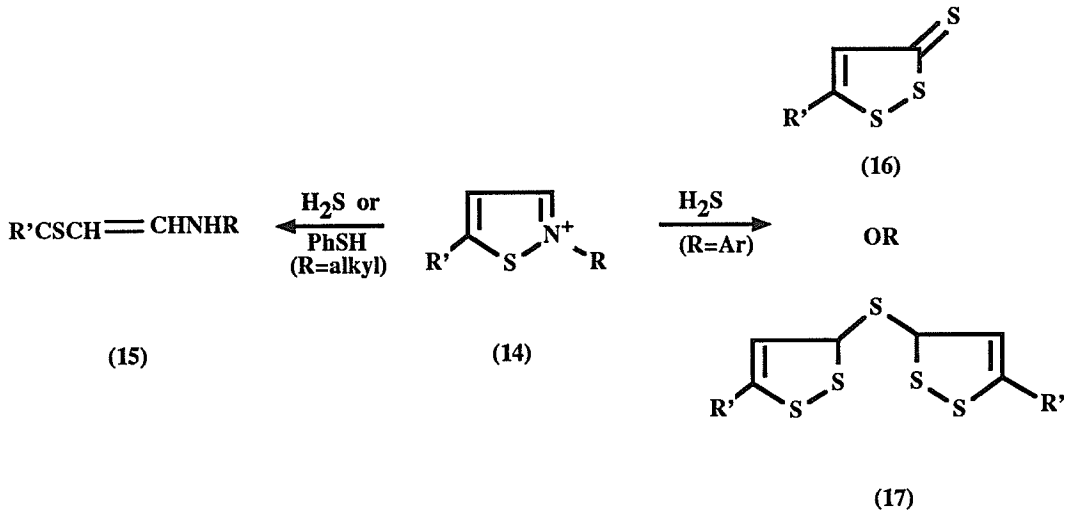
Quaternary isothiazoles are cleaved by hydroxide ions <72AHC(14)1>. Sodium alkoxides behave similarly to the hydroxides in that they occasionally cause ring cleavage at the N-S bond.

Quaternary isothiazoles give 3-phenylpyrazole on treatment with hydrazine or mixture of 1,3-diphenylpyrazole and 1,5-diphenylpyrazole on treatment with phenylhydrazine (Scheme 5) by initial attack at C-3 or C-5 <66T(22)2135>.



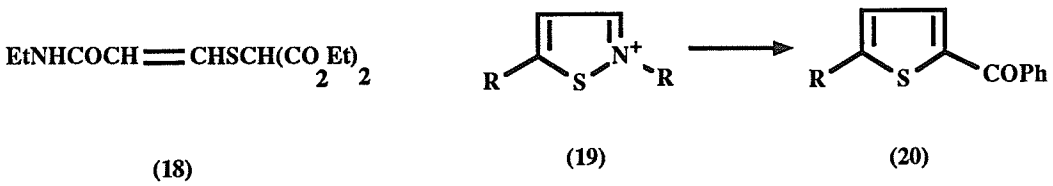
Scheme 5

2-Alkylisothiazolium salts **(14)** undergo N-S bond cleavage when treated with hydrogen sulfide or thiophenol to form acyclic products **(15)**, but 2-aryl compounds give 1,2-dithioles, **(16)** or **(17)** (Scheme 6) <75SST(3)541, 77SST(4)339>.

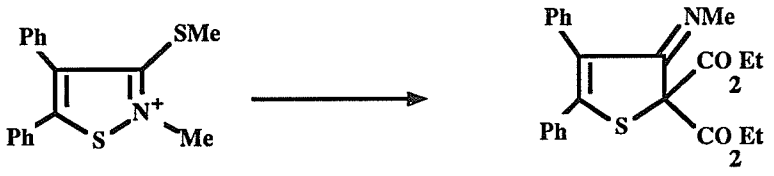


Scheme 6

Active methylene compounds react at sulfur, causing cleavage of the N-S bond, and in many cases recyclization produces thiophene compounds. For example, N-ethylisothiazoline-3-one with diethyl malonate in the presence of sodium ethoxide gives an acyclic compound **(18)** <72AHC(14)1>.

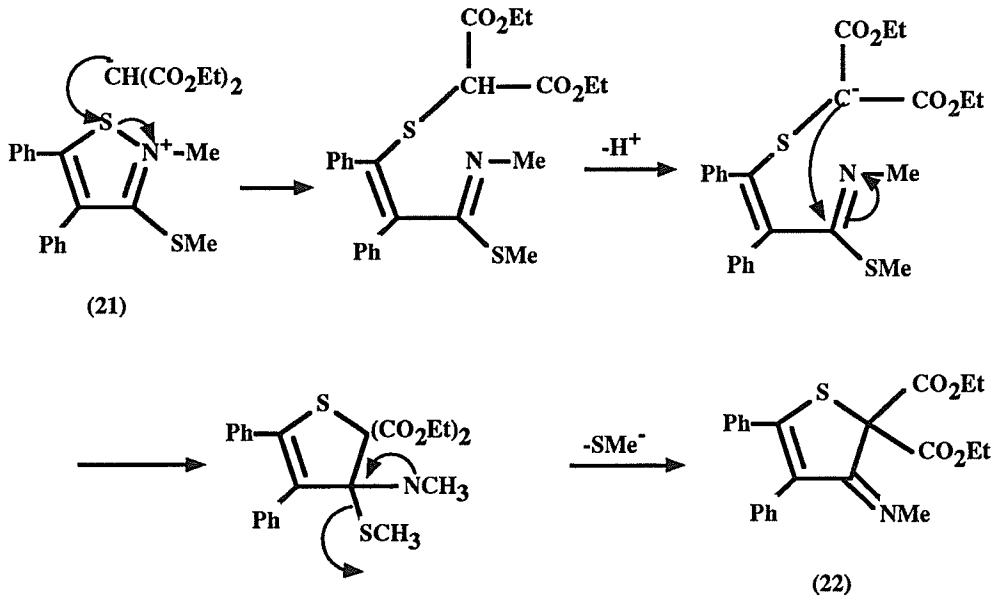


(18) (19) (20)



(21) (22)

Isothiazolium salts (**19**) react with sodium benzoylacetate to give a 2-benzoylthiophenes (**20**) <75SST(3)541>. Reaction of diethyl malonate on the isothiazolium salts (**21**) produces a different type of thiophene compound (**22**). A possible mechanism is shown in Scheme 7.

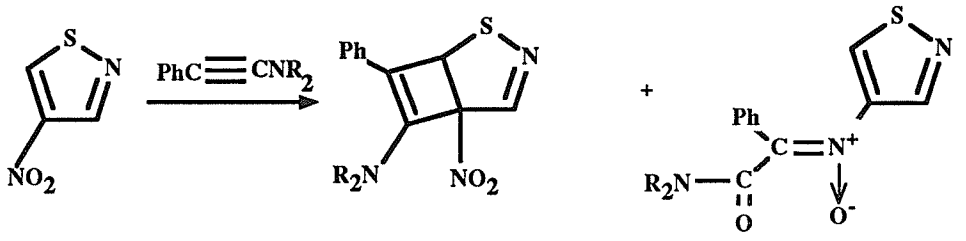


(21) (22)

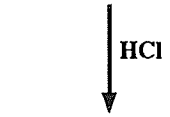
Scheme 7

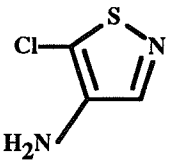
1.1.4. Miscellaneous Reactions

Few isothiazoles undergo simple cycloaddition reactions. 4-Nitroisothiazole (**23**) reacted with some yaeamines at room temperature to give both cycloaddition (**24**) and open chain products (**25**), the proportion of the two products is dependent on the polarity of the solvent. When treated with hydrochloric acid, the open chain product gave 4-amino-5-chloroisothiazole (**27**) (Scheme 7) <76RTC67, 77SST(4)339>.



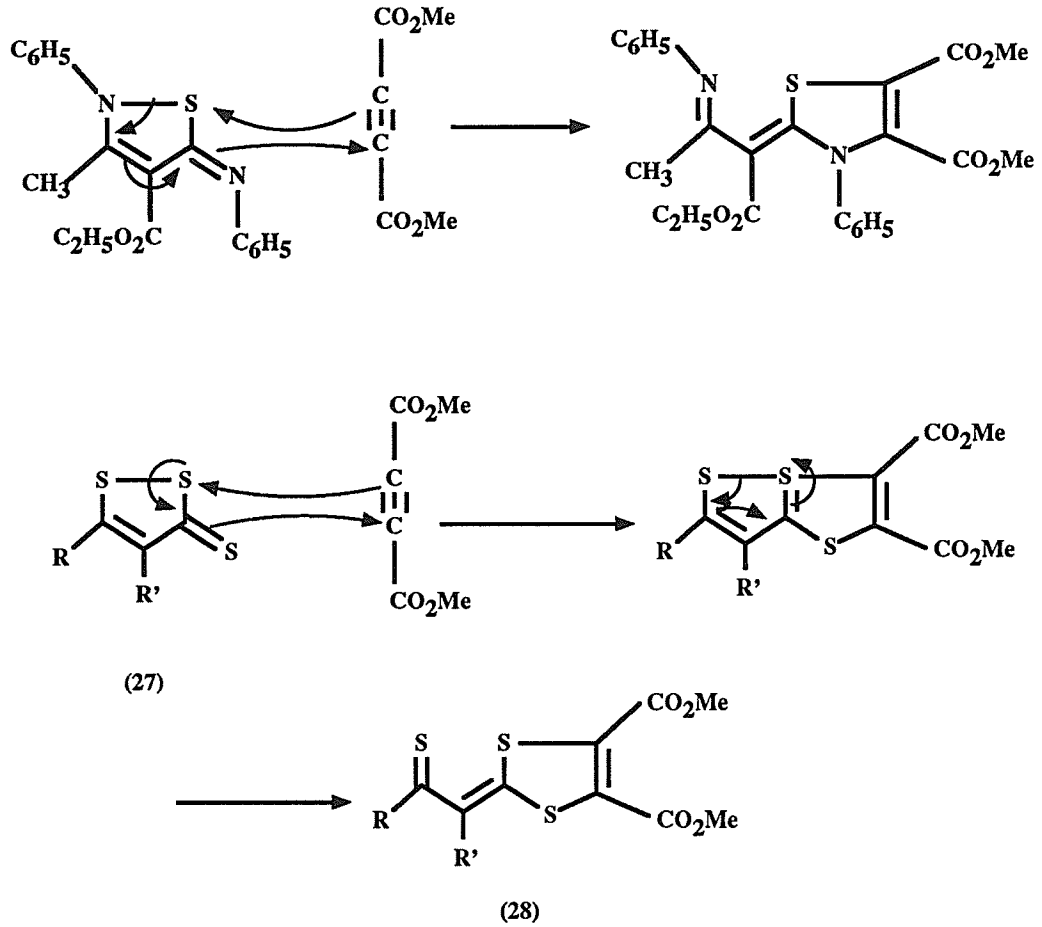
(23) (24) (25)





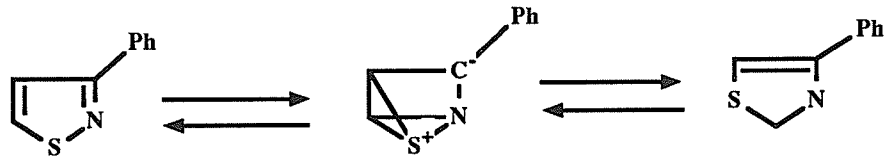
(26)

Behringer reported that treatment of an iminoisothiazole with an acetylenic diester gave a thiazole as the product (Scheme 8) <68TL1185>. The reaction involved a 1,3-dipolar cyclo-addition with cleavage at the N-S bond. This probably follows a course analogous to the reaction of 1,2-dithiole-3-thiones (**27**) with acetylene reagents to give compounds of type (**28**).



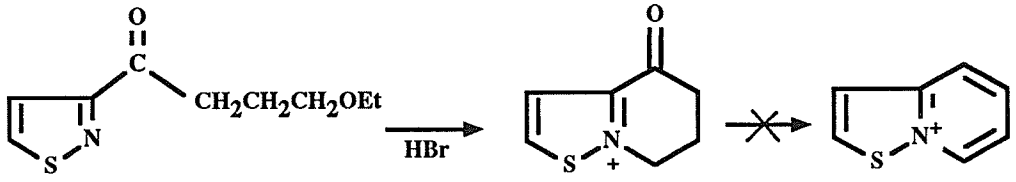
Scheme 8

Isothiazole is converted to thiazole in low yield when irradiated in propylamine. Phenyl- and diphenylisothiazoles also gave thiazoles on irradiation. It appears that isothiazole-thiazole photorearrangement may proceed through a common intermediate, possibly a tricyclic species in which the negative charge is stabilized by resonance with the phenyl group. (Scheme 9)

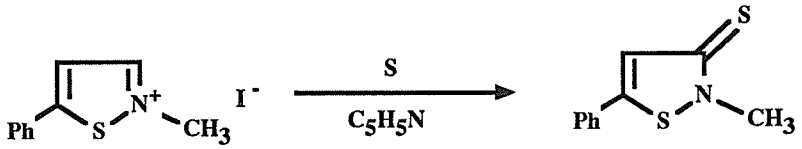


Scheme 9

An intramolecular quaternization has been reported for simple isothiazoles, but it was also reported that the product could not be aromatized to an isothiazolo[2,3-a]pyridinium system (Scheme 9) <69JCS(C)707>. This could be attributed to instability of the isothiazole ring as here the ring bears an electron withdrawing group.

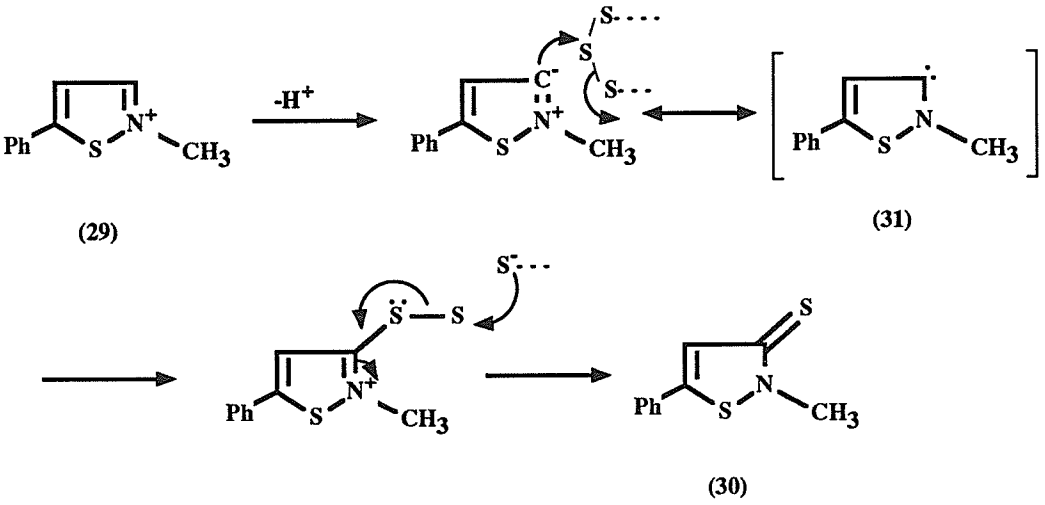


Treatment of isothiazolium salt **(29)**, unsubstituted in the 3-position, with sulfur in pyridine produced the isothiazoline-3-thione **(30)** <68CJC(46)1855> (Scheme 10). One possible mechanism may involve a carbene **(31)** as an intermediate by deprotonation of the isothiazolium cation with possibly further reaction with sulfur, and conversion to the thione **(30)**. (Scheme 11)



(29) (30)

Scheme 10

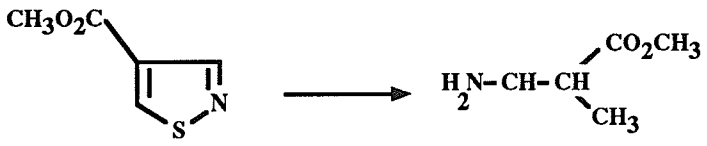


(29) (31) (30)

Scheme 11

Alternatively, the reaction may involve a thioketimine <68CJC(46)1855>.

Isothiazoles are reductively desulfurized by Raney nickel, and this appears to be a useful method to confirm structures <59JCS3061, 64JOC(29)660>. In the reductive desulfurization of the isothiazole ester **(32)**, an amino ester **(33)** will be obtained. (Scheme 12)

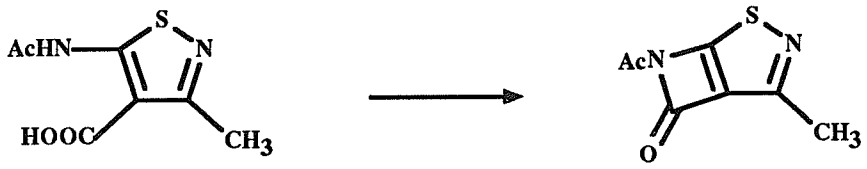


(32) (33)

Scheme 12

There are remarkable difference in the thermal stability of isothiazole having carbonyl groups at different positions on the ring. While isothiazole-5-carboxylic acids are decarboxylated relatively easily <65AHC(4)107, 72AHC(14)1>, the 3-carboxylic acids are less easily decarboxylated, and 4-carboxylic acids require high temperatures <71TL1281, 72AHC(14)1>. All acids can be converted to acid chlorides and esters by standard methods <65AHC(4)107,

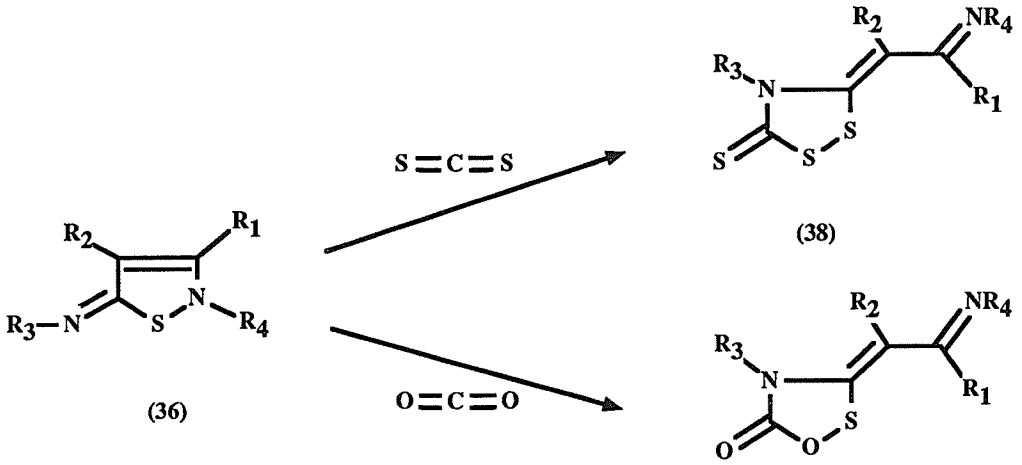
72AHC(14)1>, but it was reported that 5-acetamido-3-methylisothiazole-4-carboxylic acid (**34**) cyclized by the action of thionyl chloride to give 4-membered fused lactam (**35**).



(34) (35)

Scheme 13

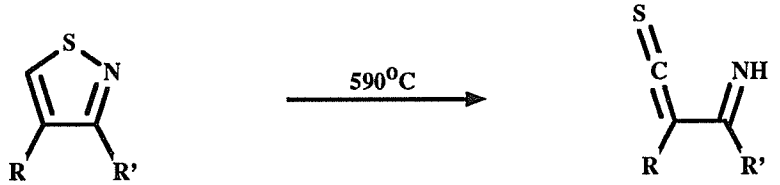
5-Iminoisothiazoles (**36**) react with carbon dioxide and carbon disulfide to give oxathiazoles (**37**) and dithiazoles (**38**), respectively <79SST(5)345>.



(36) (38) (37)

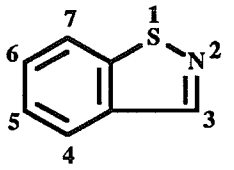
Scheme 14

Isothiazole compounds are very stable to moderate heat, but very strong heating can cause breakdown to thioketenes <80MI41700>.

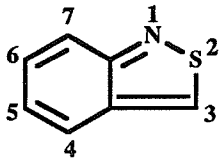


1.2. BENZO-FUSED ISOTHIAZOLES

An isothiazole and benzene ring can be incorporated in two ways to form two series of fused bicyclic compounds, which are known as 1,2- benzisothiazole and 2,1-benzisothiazole.



1.2-Benzisothiazole

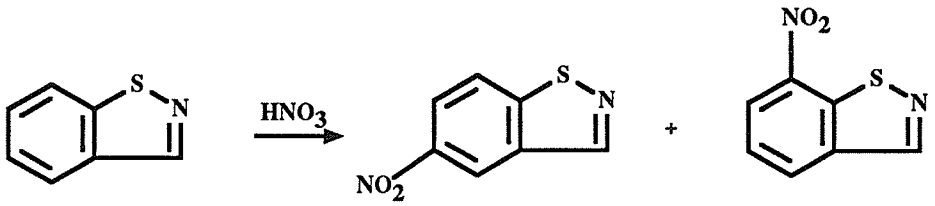


2.1-Benzisothiazole

In general, the isothiazole ring has little effect on the properties of the benzene ring, and reactions at positions 4 to 7 tend to be directed by any substituents on the benzene ring. On the other hand, reactions at positions 1 to 3 tend to be similar to the mononuclear isothiazole, indicating that benzo-fusion does not has much influence on the isothiazole ring.

1.2.1. 1.2-Benzisothiazole

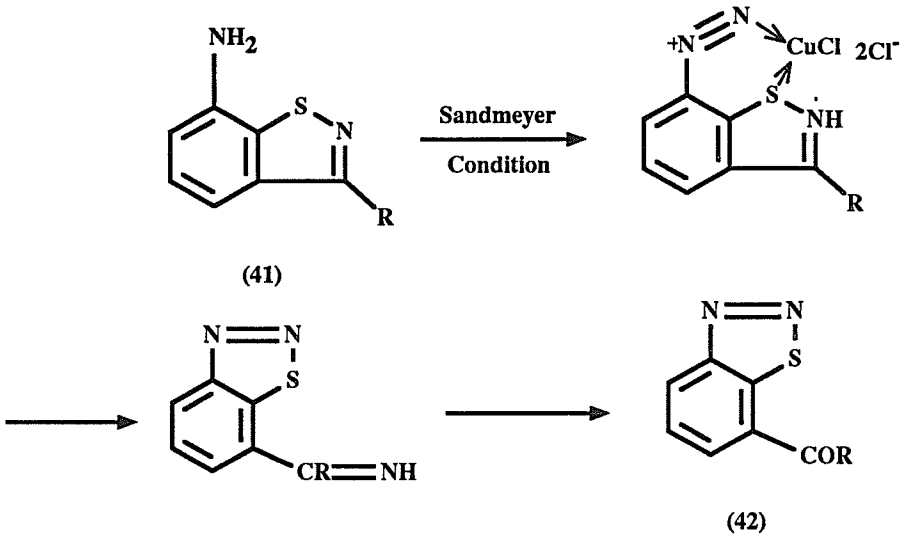
1,2-Benzisothiazole undergoes electrophilic substitution at the 5- and 7- positions <72AHC(14)43>. It was reported by Ricci and co-workers that nitration of 1,2-benzisothiazole with potassium nitrate and sulfuric acid at 0°C afforded a mixture of the 5-nitro **(39)** and 7-nitro derivatives **(40)** in equal amounts <63AC(53)1860>. 4-Chloro-1,2-benzisothiazole, surprisingly, gave only the 7-nitro compound <71JCS(C)3994, 80MI41700>.



(39) (40)

Bromination follows a similar pattern, except that 3,5-disubstituted-1,2-benzisothiazoles give 4-bromo derivatives, and 7-amino-4-chloro-1,2-benzisothiazole is brominated at the 6-position <71JCS(C)3994>.

Amino derivatives of 1,2-benzisothiazole can be easily obtained by reduction of the corresponding nitro compound using either catalytic hydrogenation or dissolving metal methods <65AHC(4)107, 72AHC(14)1>. Although almost all the amino derivatives of 1,2-benzisothiazole can be diazotized and undergo normal Sandmeyer conversion, poor yields are obtained from 7-amino derivatives (**41**). Instead, 1,2,3-benzothiadiazoles (**42**) are found to be the major products formed by some rearrangement mechanism. (Scheme 15)

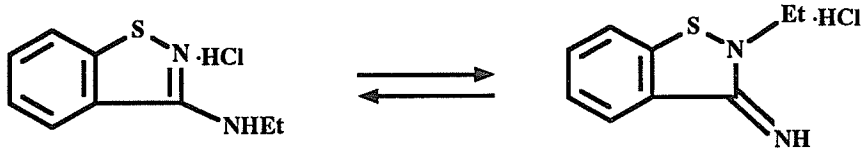


Scheme 15

3-Amino-1,2-benzisothiazole and its derivatives exist mainly in the 3-amino form. Thus, on treatment of 3-amino-1,2-benzisothiazole with nitrous acid, 3,3'-bis(1,2-benzisothiazoline) is obtained <72AHC(14)43>.

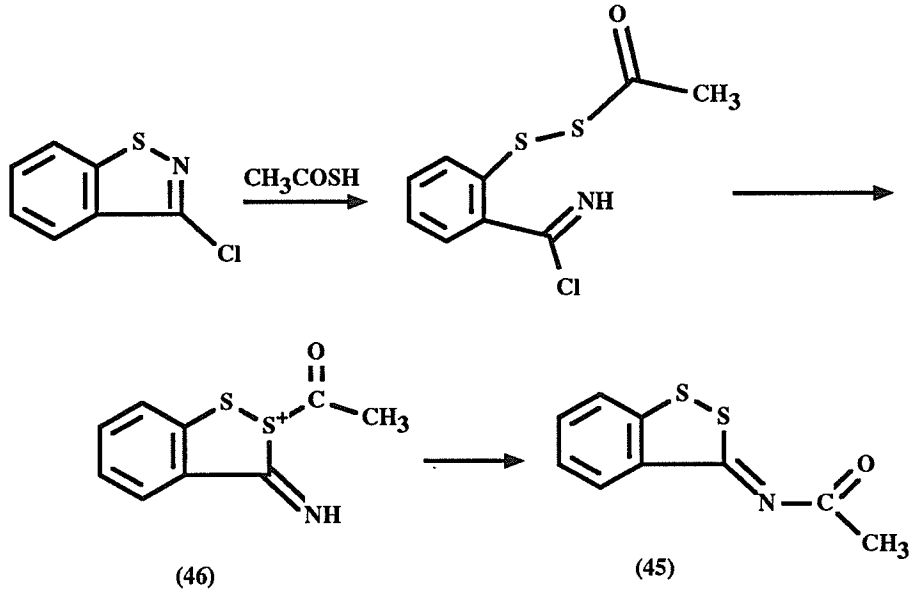
A number of interesting reactions have been observed by Boshagen and co-workers on 3-amino-1,2-benzisothiazole group compounds. For example, in aqueous solution, the

hydrochloride salt of 3-ethylamino-1,2-benzisothiazole **(43)** is in equilibrium with 2-ethyl-3-amino-1,2-benzisothiazole hydrochloride **(44)** <69CB1961>.



(43) **(44)**

It will be noted later that the N-oxide derivatives **(57)** are in equilibrium with 2-ethyl-3-oximino-1,2-benzisothiazolium compounds **(58)**, involving an ethyl-hydroxy shift. The same type of rearrangement occurs when 3-chloro-1,2-benzisothiazole is treated with thioacetic acid to afford an N- acyl-3H-1,2-benzodithiole **(45)** via an intermediate like **(46)** <68CB2472>.

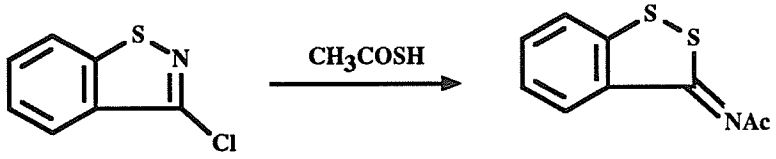


(46) **(45)**

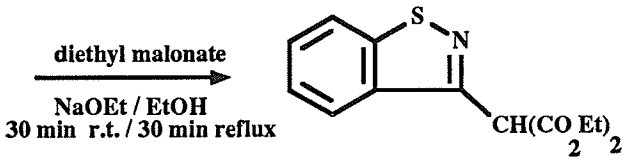
Scheme 16

Halogen atoms at different positions of 1,2-benzisothiazole show different reactivity. Also, in some cases, the products depend on the reaction conditions. Thus, the chlorine atom of 4-chloro-1,2-benzisothiazole is inert to nucleophilic attack, except when activated by a electron withdrawing group at the 7-position. Otherwise, the more vigorous conditions

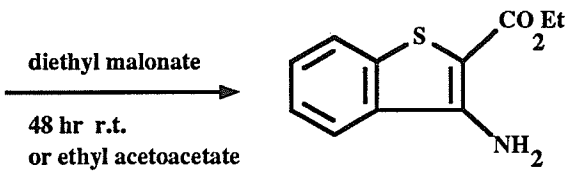
necessary for the replacement often cause ring cleavage <71JCS(C)3994, 75LA1994>. 3-Halogeno-1,2-benzisothiazoles also suffer ring cleavage when treated with nucleophiles <72AHC(14)43, 73SST(2)556>. The treatment of 3-chloro-1,2-benzisothiazole **(47)** with thioacetic acid, followed by rearrangement, affords an N-acyl-3H-1,2-benzodithiole **(48)** <68CB2472>. It reacts with malonic ester and sodium ethoxide to give either the expected product **(49)** or the benzothiophene **(50),** depending on the reaction conditions. Ethyl cyanoacetate gives only the benzisothiazole **(51)**, but the benzothiophenes **(52)** and **(50)** were isolated as the only products by reaction with acetylacetone or ethyl acetoacetate, respectively.



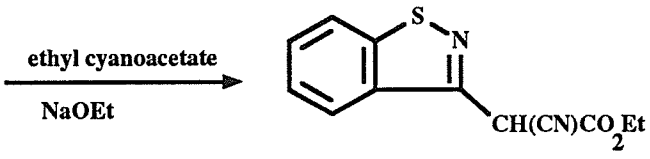
(47) (48)



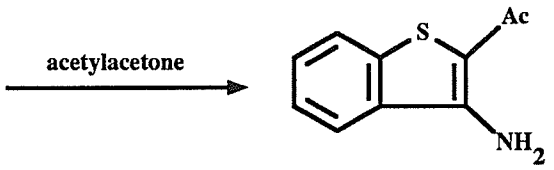
(49)



(50)



(51)

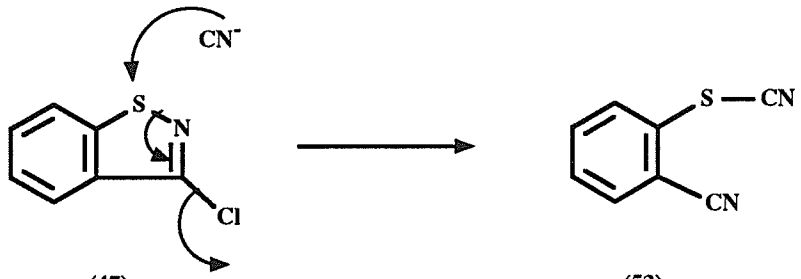


(52)

Scheme 17

The various products obtained from the reaction of 3-chloro-1,2-benzisothiazole can be explained by nucleophilic attack at C(3) or sulfur, depending upon the carbanion used and the reaction conditions <71TL1075, 71JCS(C)3262, 71JCS(C)3903>.

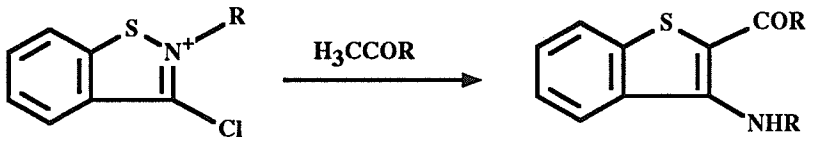
All the halogenoisothiazoles react with copper(I) cyanide to give the corresponding nitriles. However, with sodium cyanide, 3-chloro-1,2-benzisothiazole **(47)** suffers ring cleavage, giving o-cyanophenyl thiocyanate **(53)** as the major product <71TL1075>. The mechanism involves the nucleophilic attack at sulfur with cleavage of the S-N bond and loss of the chlorine atom. (Scheme 18)



(47) (53)

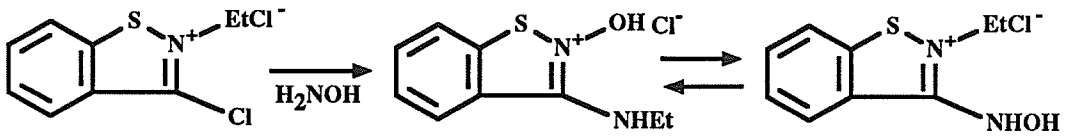
Scheme 18

The quaternized 3-chloro-1,2-benzisothiazole **(54)** also reacted with methyl ketones to yield 2-acyl-3-amino-benzo[b]thiophenes **(55)** <72LA(764)58>.



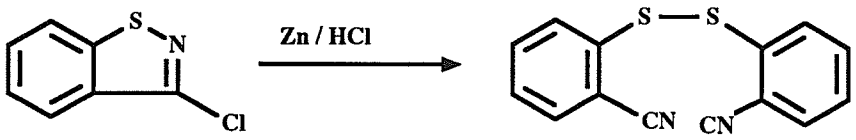
(54) (55)

When heated with hydroxylamine, the salt **(56)** gives an N-oxide derivative **(57)**, which can be reversibly converted into the isomeric 2-ethyl-3-oximino-1,2-benzisothiazolium compound **(58)**.

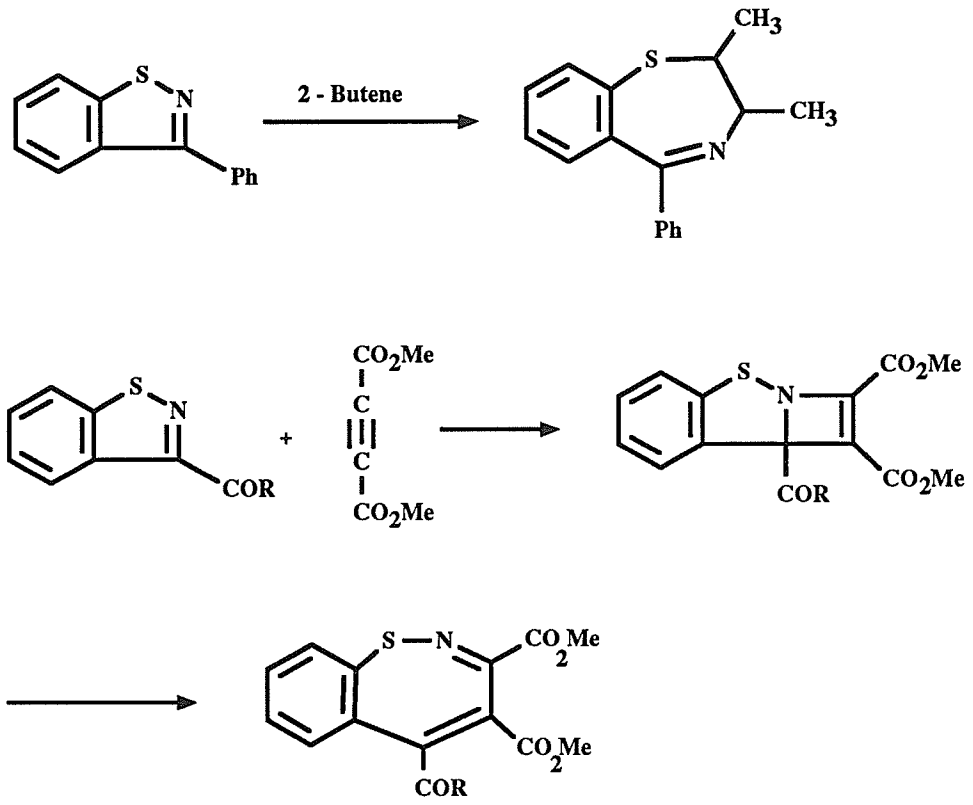


(56) (57) (58)

With zinc and hydrochloric acid, 3-chloro-1,2-benzisothiazole gives di-(o-cyanophenyl)disulfide <73SST(2)556>.



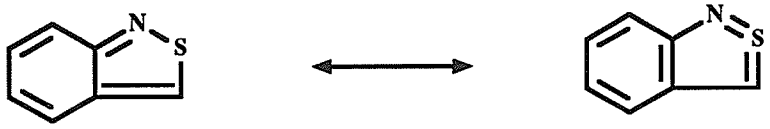
1,2-Benzisothiazole undergoes a variety of photochemical additions (Scheme 19) <81T3377, 81TL525, 81TL529>.



Scheme 19

1.2.2. 2,1-Benzisothiazole

While the chemistry of 2,1-benzisothiazole is similar to the 1,2-series in many ways, there are several differences. Although drawing 2,1-benzisothiazole as the o-quinonoid structure is now generally accepted, the compound displays none of the reactivity or instability generally associated with an o-quinonoid system. The contribution of sulfur 3d-orbital to the ground electronic state is considered to be important and chemical reactivity suggest that resonance forms such as **(59)**, in which sulfur is tetravalent, contribute significantly.



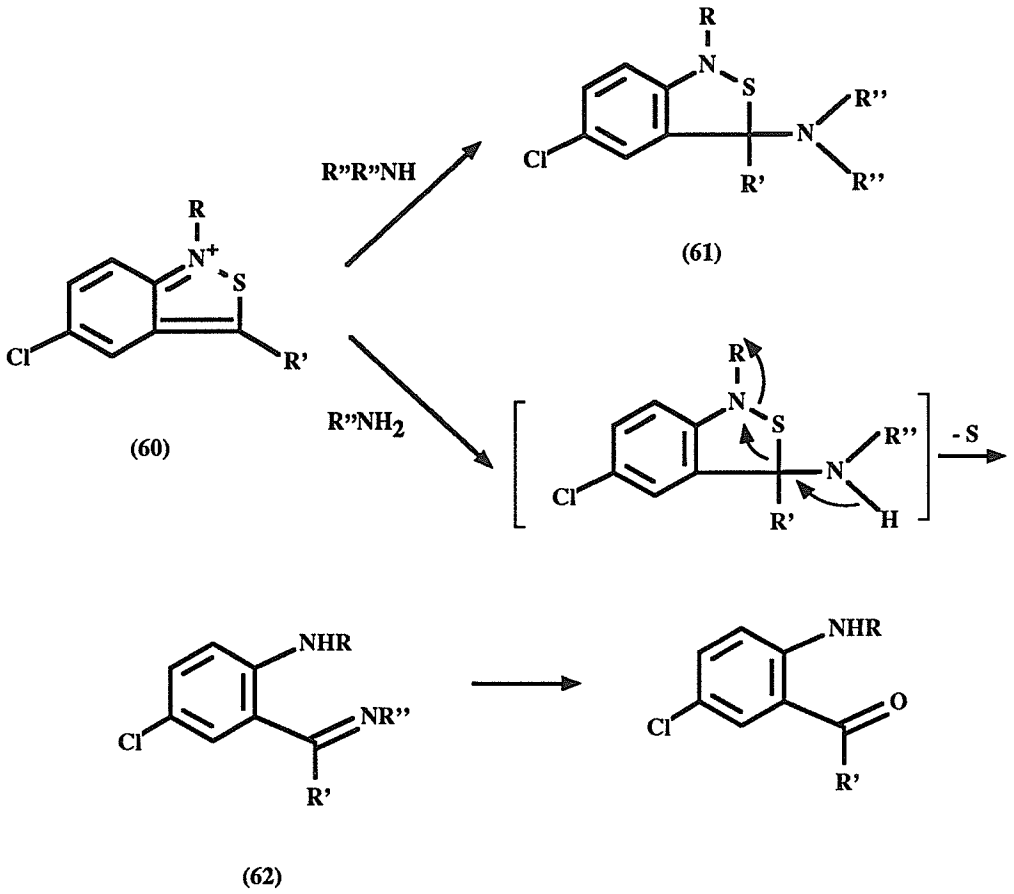
(59)

2,1-Benzisothiazoles form predominantly 5-nitro derivatives upon nitration, with minor amounts of 7- and 4- nitro compounds. On bromination, equal amount of 5-bromo- and 7-bromo-2,1-benzisothiazole are obtained, together with a lesser amount of 4,7-dibromo-2,1-benzisothiazole and a trace of 4-bromo-2,1-benzisothiazole. 4,5,7-Tribromo-2,1-benzisothiazole is formed on treatment with brominating reagents in excess <72AHC(14)43>. As in its 1,2- analogue, the direction of further substitution is governed by existing substituents on the benzene ring.

Friedel-Crafts or Vilsmeier-Haack acylation reactions on the parent compound were unsuccessful <72AHC(14)43>, but it is reported that 3-substituted 1-methyl-2,1-benzisothiazole-2,2-dioxides could be acetylated at the 5- position <73JHC249> and 1-methyl-2,1-benzisothiazole-3-one could be chlorosulfonated at the 5- position <78JHC529>. Vilsmeier-Haack conditions usually cause isothiazole ring cleavage.

2,1-Benzisothiazole is stable to hot alkali, although 3-amino-2,1-benzisothiazole derivatives derived from the quaternary salts are much more sensitive to acid and alkali, and give a wide variety of products. For example, 1-alkyl-3-aryl-2,1-benzisothiazolium salts **(60)** can be converted smoothly into 1-alkyl-3-aryl-3-dialkylamino-2,1-benzisothiazoline derivatives **(61)** upon treatment with secondary amines. On the other hand, the reaction of a primary amine

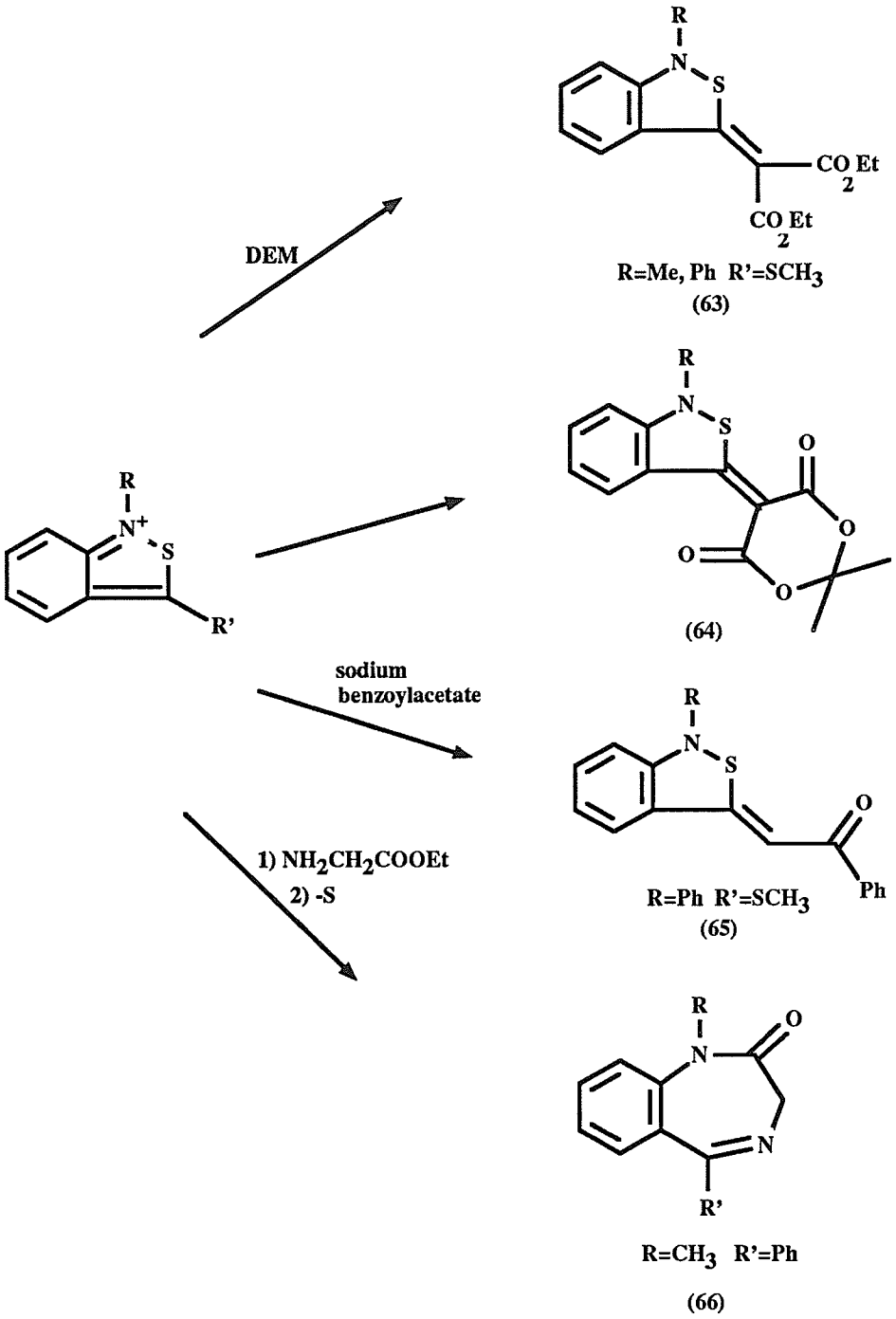
with **(60)** gives the unexpected compound **(62)** by ring opening.



Scheme 20

The formation of compound **(62)** may involve the initial nucleophilic attack at C(3) followed by the extrusion of the sulfur atom, as depicted in scheme 20 <72CPB2372>. In some cases in which R' is a good leaving group, the initial nucleophilic attack at C(3) is followed by the loss of the R' group to afford N-substituted 2,1-benzisothiazolylidenes, e.g. **(63)**, **(64)**, **(65)** <82CJC440>.

Sometimes, subsequent recyclization may lead to other benzo-fused ring systems such as benzoquinolones **(66)** <72CPB2372> (Scheme 21).

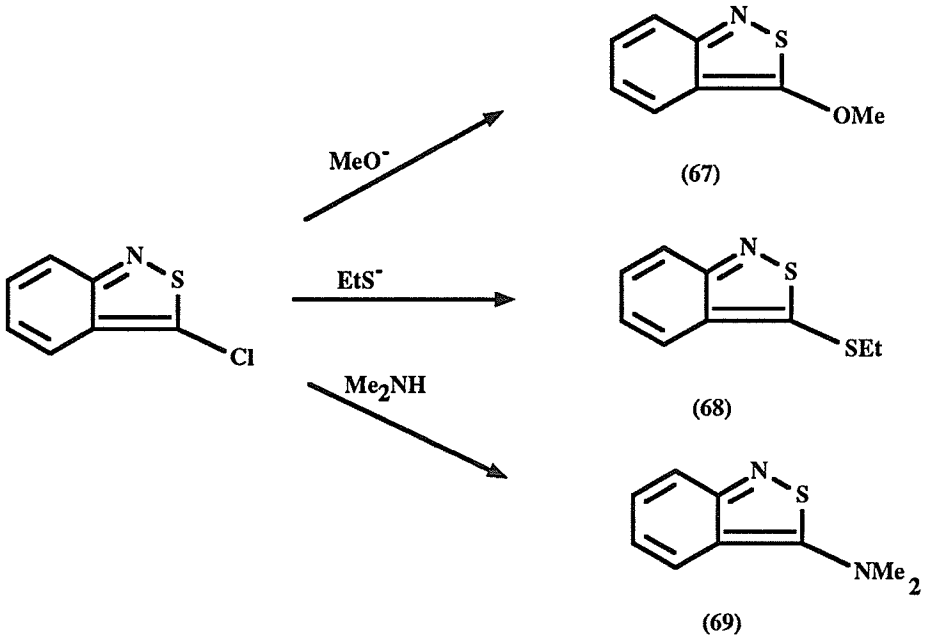

R
N
S
CO Et
2
CO Et
2
DEM
R=Me, Ph R'=SCH3
(63)
R
N+
S
R'
O
O
O
O
(64)
sodium
benzoylacetate
R
N
S
O
Ph
R=Ph R'=SCH3
(65)
1) NH2CH2COOEt
2) -S
R
N
O
N
R'
R=CH3 R'=Ph
(66)

Scheme 21

3-Amino-2,1-benzisothiazole gives diacyl derivatives upon acylation, indicating that it has a great tendency to exist in the imino form <72AHC(14)43>. Unlike 3-amino-1,2-benzisothiazole, it also can be diazotized, undergoing Sandmeyer reactions to give halogen compounds or coupling with tertiary aromatic amine to form azo dyes <72AHC(14)43, 84CHC(6)131>. The 3-cyano compounds can be also prepared in this way.

2,1-Benzisothiazole is lithiated at the 3-position which corresponds to the 5-position in the mononuclear series <75JHC877>.

Unlike 3-halogeno-1,2-benzisothiazoles, 3-halogeno-2,1-benzisothiazoles undergo normal nucleophilic substitution, and various 3-substituted derivatives **(67), (68), (69)** can be obtained <75AJC129, 75AJC2051, 78JHC529>.

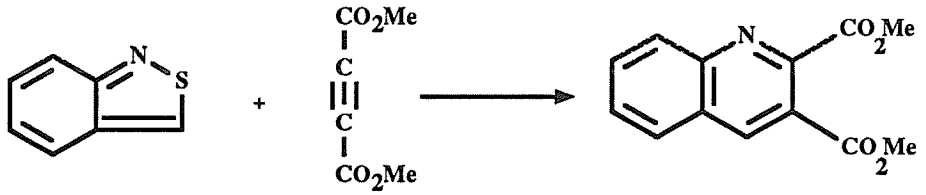


(67)

(68)

(69)

2,1-Benzisothiazoles are not good Diels-Alder substrates. Only a prolonged reaction (10 days, 90°C) of 2,1-benzisothiazole with dimethyl acetylenedicarboxylate yielded substituted quinolines **(70)**.



(70)

1.3. SPECTROSCOPIC DATA

1.3.1. ^{1}H NMR Spectroscopy

The ^{1}H NMR spectroscopy of isothiazole has been extensively studied. Some of the available data are listed in Table 3.

Table 3. ^{1}H NMR Chemical Shifts of Isothiazoles

Substituent			Solvent	Isothiazole			Ref.
				Chemical shifts δ(ppm)			
3	4	5		3	4	5	
H	H	H	CCl_4	8.54	7.26	8.72	65CB1111
Me	H	H	CCl_4	-	7.00	8.54	65CB1111
H	Me	H	CCl_4	8.24	-	8.21	65CB1111
H	H	Me	CCl_4	8.24	6.92	-	65CB1111
H	H	Br	CCl_4	8.32	7.40	-	75CJC1642
H	H	Cl	CCl_4	8.37	7.35	-	75CJC1642
H	Br	H	CCl_4	8.33	-	8.57	75CJC1642
H	NH_2	H	$CDCl_3$	7.43	-	8.06	76MI141701
H	CN	H	CCl_4	8.69	-	9.17	75CJC596
H	NO_2	H	CCl_4	9.00	-	9.42	75CJC596
OH	H	H	$CDCl_3$	-	6.48	8.28	71JHC571

From the data, we can see that the proton on C(4) is most benzene-like and that 3-H and 5-H appear at much lower field, the order being determined by the substituents on the isothiazole ring. For the benzo-fused series, 1,2-benzisothiazole shows a singlet at 8.73 ppm (CCl_4), attributed to H(3) and a multiplet between 7.12-8.00 ppm (CCl_4), attributed to the proton on the benzenoid ring. On the other hand, the H(3) of 2,1-benzisothiazole appears at 9.06 ppm (CCl_4) <72AHC(14)43>. The H(3) signal of the mononuclear isothiazoles is broadened due to the ^{14}N-H(3) spin coupling by quadrupolar relaxation of the nitrogen atom <68MI41701>. This broadening can be used to distinguish H(3) from other proton signals.

1.3.2. UV Spectroscopy

Isothiazole has a maximum absorption at 244 nm with a molar absorptivity of 5200, which results from a π-π^* electronic transition. For substituted systems, bathochromic or hypsochromic shifts have been observed and are related to the nature of substituents and their positions on the ring.

The spectra of 1,2- and 2,1-benzisothiazole are much more complex with as many as six maxima above 200nm.

1.3.3. IR Spectroscopy

The bands characteristic of the isothiazole ring usually appear at 1510, 1400 and 1340 cm^{-1}, although, in some cases, they may be weak and unobservable. While ring vibrations give rise to one or more fundamental bands between 1300-900 cm^{-1}, they are quite sensitive to substitution effects. The strongest band is found around 820 cm^{-1} and 750 cm^{-1}, attributable to C-S and S-N stretching.

1.4. SYNTHESIS OF ISOTHIAZOLES

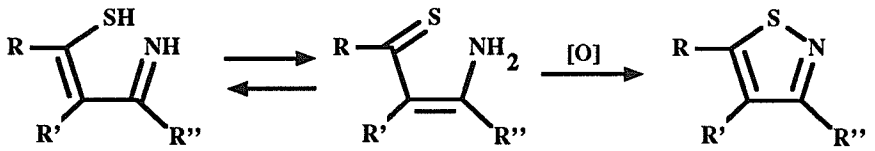
The synthesis of isothiazoles can be divided into two categories, either starting from a acyclic system or from some other heterocyclic systems.

1.4.1. SYNTHESIS OF MONONUCLEAR ISOTHIAZOLES

1.4.1.1. FORMATION FROM AN ACYCLIC SYSTEM

1.4.1.1.1. Isothiazole Synthesis Involving the Formation of One Bond

Since the S-N bond of isothiazoles is the one most easily cleaved, it is interesting to note that most of the commonly used syntheses of isothiazole from acyclic precursor involves the formation of this bond. Thus, one of the best methods of synthesis of isothiazoles is by direct oxidation of γ-iminothiols **(71)** or their tautomers. The general equation is shown in Scheme 22.

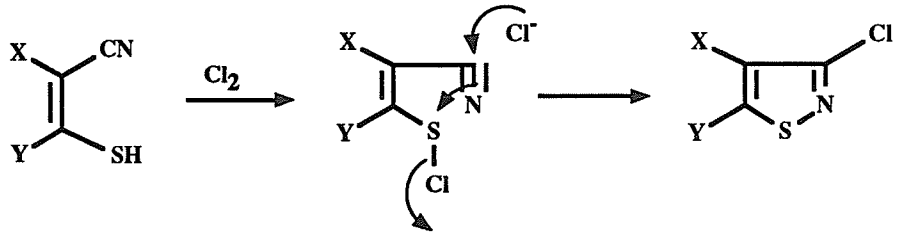


(71) (72) (73)

Scheme 22

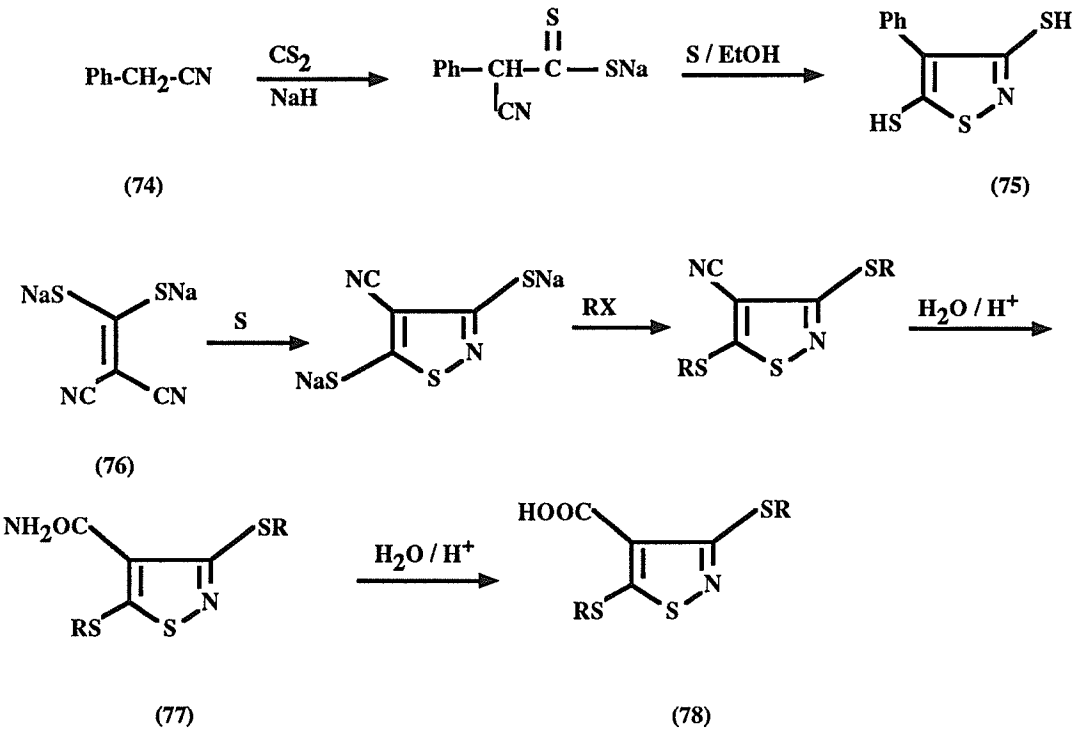
This method can lead to the synthesis of a wide variety isothiazoles by choice of suitable substituents R_1, R_2, R_3 <65AHC(4)107, 72AHC(14)1, 84CHC(6)131>. The most commonly used oxidizing agents are halogens or hydrogen peroxide.

Oxidation of substituted β-mercaptoacrylonitriles using chlorine as the oxidizing agent is one important method for synthesis of isothiazoles. A possible mechanism is shown in Scheme 23.



Scheme 23

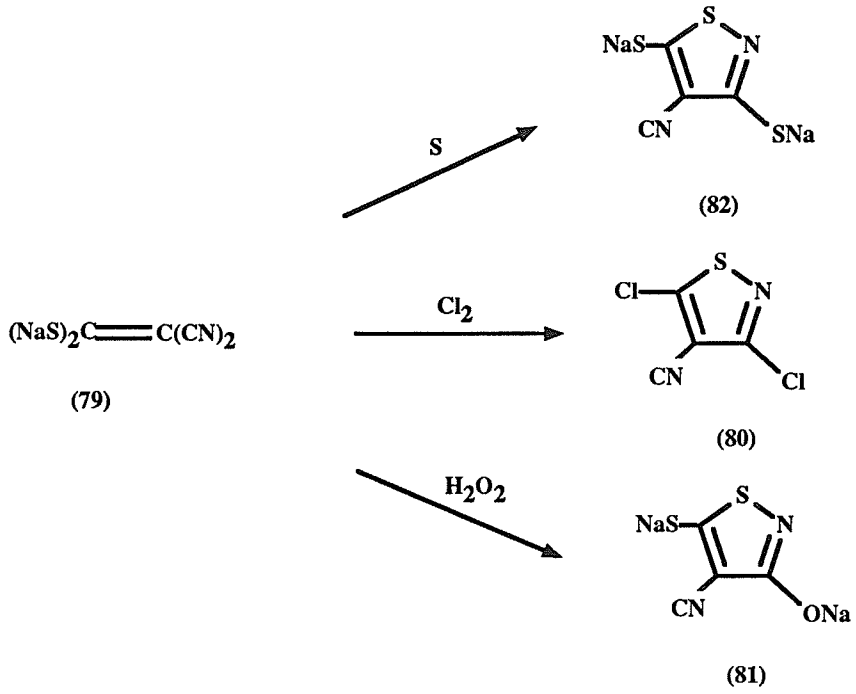
Using analogous starting compounds, such as ethylene-dithiolates, 4-phenyl <67JCS(C)124>, 4-ethoxycarbonyl <65ACS(19)549> and carboxamidoisothiazole derivatives <64JOC(29)665>, **(75)** and **(78)** have been made. (Scheme 24)



Scheme 24

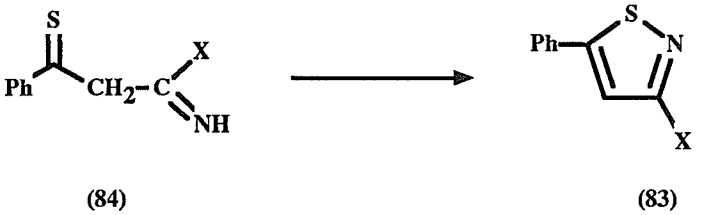
Sometimes, the oxidizing agent may also cause further reaction after the ring closure. Thus, compound **(79)** can be both oxidized and chlorinated by chlorine to give 3,5-dichloro-4-cyanoisothiazole **(80)**. When hydrogen peroxide is used, compound **(81)** is

obtained. On the other hand, ring closure using sulfur affords compound **(82)** as shown in Scheme 25 <65AHC(4)107, 72AHC(14)1>. The use of chloramine as oxidizing agent can produce a 3-amino compound <75SST(3)541>.



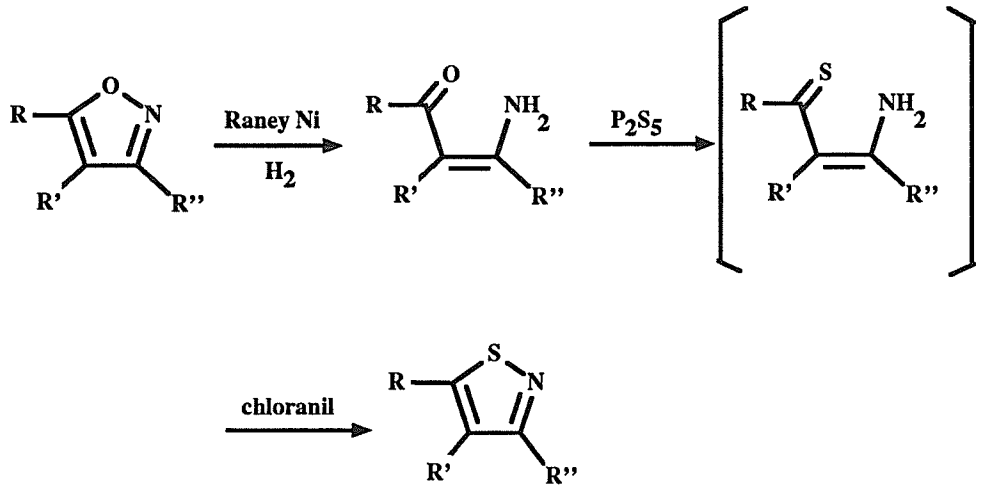
Scheme 25

By modification of the above method, the 3-hydroxy,-methoxy, and -aminoisothiazoles **(84)** were first prepared starting from appropriate thioketone **(83)**.

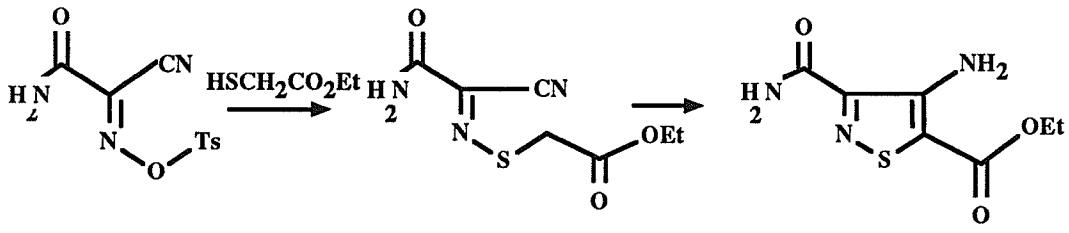


X= OH, OMe, NH_2

An analogous reaction uses the readily available substituted isoxazoles to give isothiazoles with the same substitution pattern. Treating the intermediate enaminoketones with phosphorus pentasulfide and chloranil or sulfur, isothiazoles are obtained in moderate yield <69T(25)389>.



Ring formation by methods other than formation of an S-N bond is not common, and only a few cases are reported. Reaction of α-cyanooximes **(85)** with ethyl mercaptoacetate gives a compound **(86)**, which cyclizes to give the isothiazole derivative **(87)**. (Scheme 26)

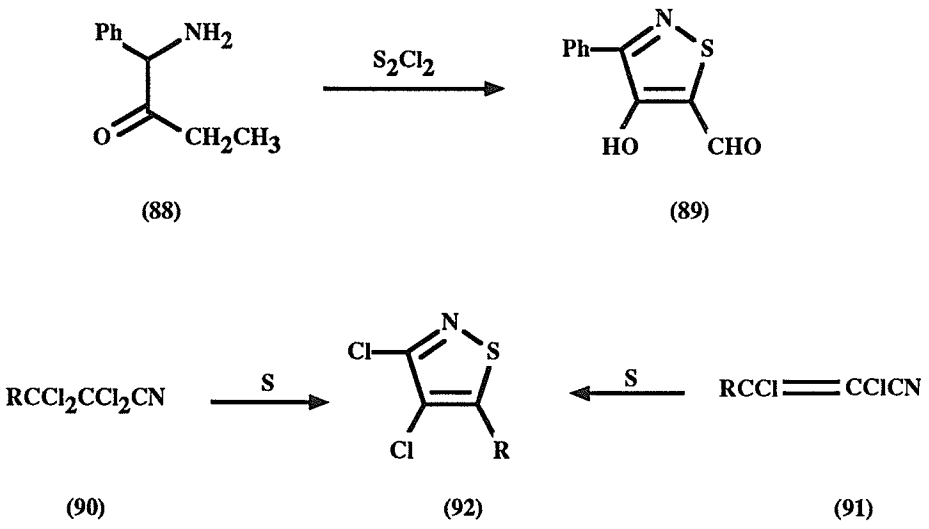


(85) **(86)** **(87)**

Scheme 26

1.4.1.1.2. Isothiazole Synthesis Involving the Formation of Two Bonds

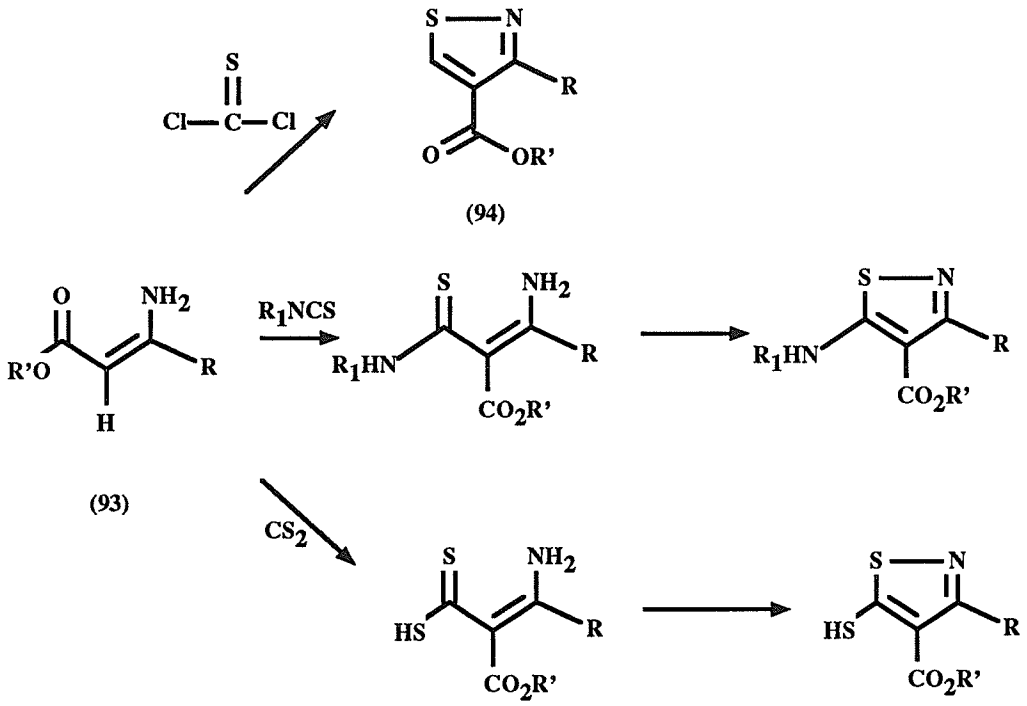
Insertion of sulfur into an appropriate 4-atom fragment is one of the popular methods of isothiazole synthesis involving the formation of two bonds. Thus, the α-acylbenzylamine **(88)** reacts with sulfur monochloride to give 5-formylisothiazole **(89)**. Obviously the sulfur halide is also acting as an oxidant. A large number of substituted isothiazoles can be obtained this way by starting from appropriate α-imino ketones, α-iminonitriles, and other compound bearing an active methylene or methylidyne group. Both of the polychloronitriles **(90)** and **(91)** give the 3.4-dichloroisothiazole **(92)** on heating strongly with sulfur in the absence of solvent. (Scheme 27)



Scheme 27

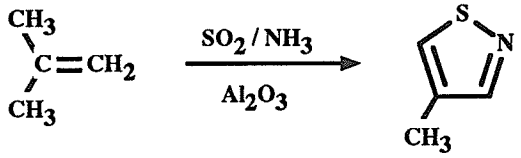
The other common method for a two bond formation of an isothiazole ring is the insertion of a nitrogen atom. α,β-Unsaturated aldehydes having a thiocyanato or thiolsulfonate substituent at the β-position cyclize in liquid ammonia or react with amines to afford isothiazoles with a free 3-position. The use of a corresponding ketone gives a 3-substituted derivative <65AHC(4)107,79SST(5)345>.

Another synthesis involves the reaction of 3-aminocrotonic esters with various sulfur reagents. The enamines **(93)** condense with thiophosgene to give isothiazoles **(94)**, which has a free 5-position <72AHC(14)1>. If thiocyanates or carbon disulfide are used, compounds with 5-amino and 5-mercapto functions respectively are obtained <75SST(3)541, 78JCS(P1)1017>.



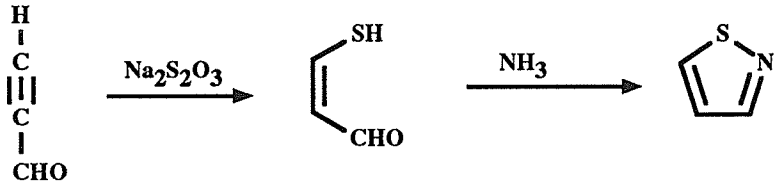
1.4.1.1.3. Isothiazole Synthesis Involving the Formation of Three Bonds

A mixture of an alkene, sulfur dioxide, and ammonia in the presence of a catalyst at 200°C will give an isothiazole in moderate yield. This method can also be used to prepare phenyl and lower alkyl derivatives. Higher alkenes give low yields and increasing amounts of thiophene compounds <62AG(E)508, 63AG(E)714>.



Thus, isobutene will give 4-methyl-isothiazole, which is difficult to obtain by other methods. Both 1-, and 2-butene give mixture of 3- and 5-methylisothiazole due to isomerization of the alkene.

The best laboratory method for preparing isothiazole itself is the reaction between propynal, sodium thiosulfate, and ammonia <72AHC(14)1>. It involves an intermediate like **(95)** followed by the cis-addition with ammonia to afford the isothiazole. (Scheme 28)



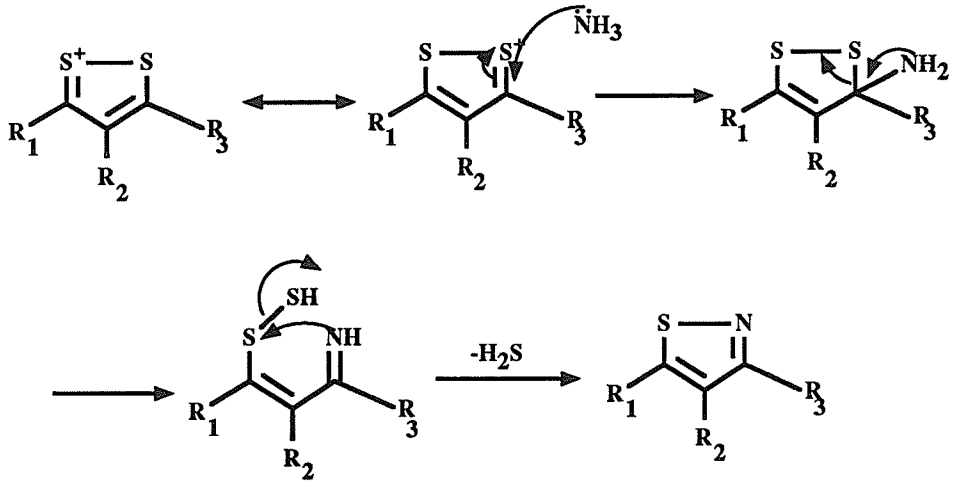
(95)

Scheme 28

1.4.1.2. SYNTHESIS FROM OTHER HETEROCYCLIC SYSTEMS

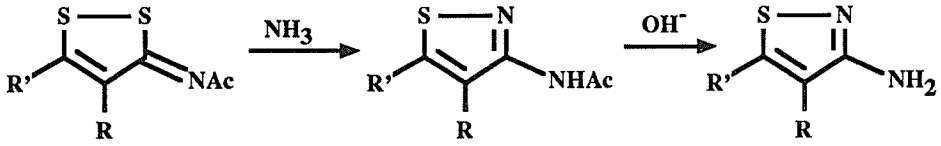
1.4.1.2.1. From Five-membered Heterocycles

In the past years, 1,2-dithiolium salts have received great attention and found various applications in isothiazole synthesis. 1,2-Dithiolium salts, particularly with aromatic substituents, readily form isothiazoles on treatment with ammonia <60PCS252, 65JCS32, 66T2119, 67CC353, 66G(96)1000>. Nucleophilic attack at either C(3) or C(5), depending on relative steric hindrance of the two carbons, followed by the cleavage of the C-S bond, gives an acyclic intermediate which recyclizes to give the isothiazole. (Scheme 29)



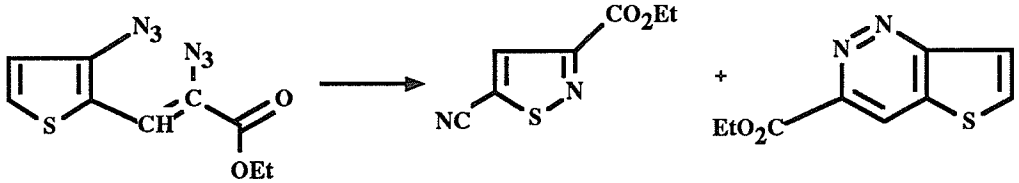
Scheme 29

Some unquaternized dithiole compounds also produce isothiazole. 3-Aminoisothiazoles have been prepared from acyliminodisulfides. (Scheme 30)



Scheme 30

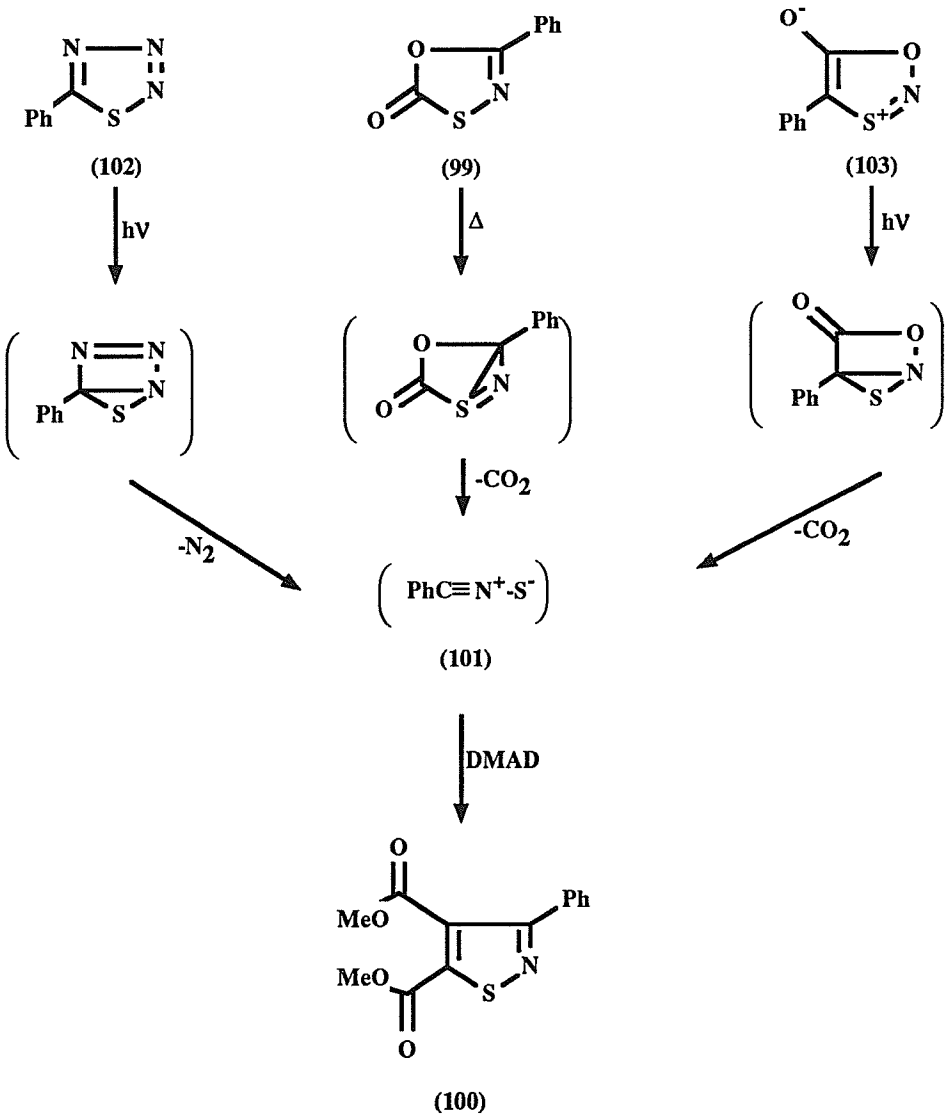
Certain thiophene compounds having nitrogen substituents can be converted into isothiazoles. Thus, heating an azidothiophene **(96)** in xylene affords a mixture of the isothiazole **(97)** and the thienopyridazine **(98)** (Scheme 31) <81CC550>.



(96) (97) (98)

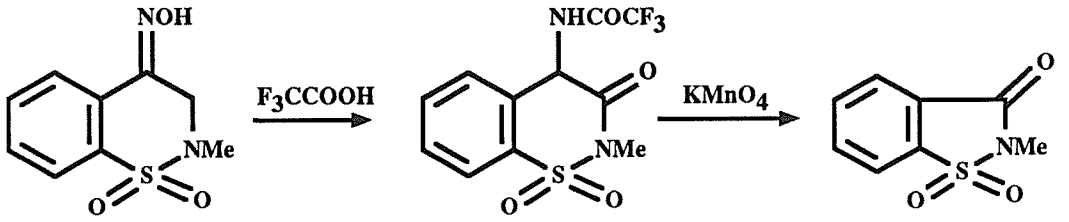
Scheme 31

On heating with alkenic or alkynic esters, 1,3,4-oxathiazol-2-ones **(99)** will give the isothiazoles **(100)**, via an intermediate nitrile sulfide **(101)** <72AHC(14)1, 75SST(3)541, 80MI41700>. The same isothiazole derivatives are produced by photolysis of 1,2,3,4-thiatriazoles and 1,3.2-oxathiazolium-5-olate **(102)** and dimethyl acetylenedicarboxylate via the same intermediate <75JA6197>.



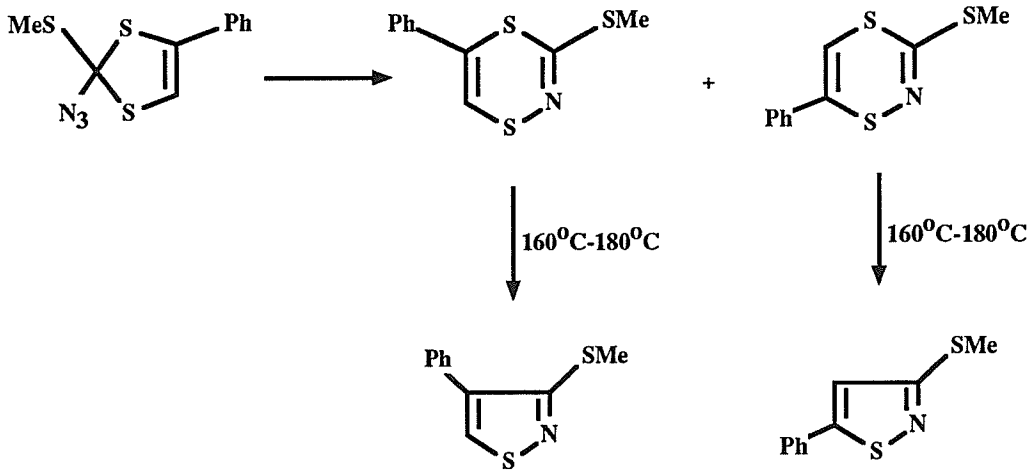
1.4.1.2.2. From Six-membered Heterocycles

Isothiazoles can be obtained by appropriate ring contraction of thiazines. For example, when treated with trifluoroacetic acid, the 1,2-benzothiazine-1,1-dioxide **(104)** forms compound **(105)**, which gives N-methylsaccharin on oxidation with permanganate <77JHC1063>.



(104) **(105)**

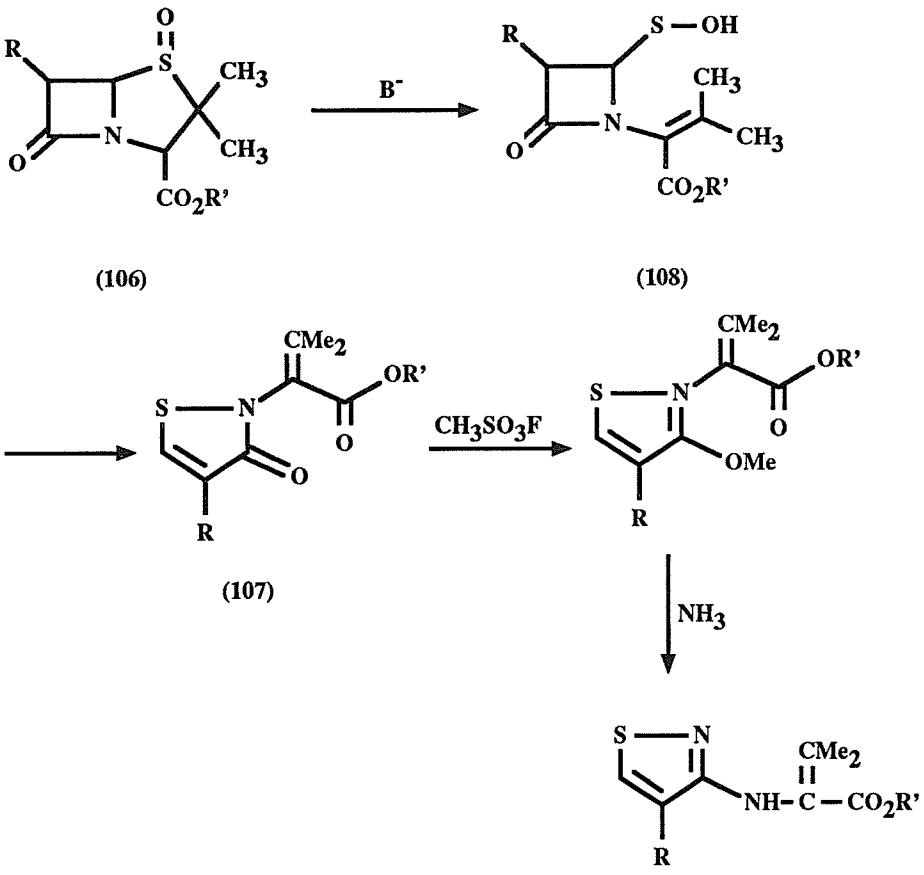
It was reported that a thermal elimination of sulfur from 1,4,2-dithiazines gives 3-methylthioisothiazole (Scheme 32) <65ZC(5)386>.



Scheme 32

1.4.1.2.3. From Other Heterocycles

Cephalosporin 5-oxides and penicillin S-oxides **(106)** can be converted to isothiazoles **(107)** by the action of bases via an intermediate of azetidinonesulfenic acid **(108)**. Compound **(107)** can be further treated with methyl fluorosulfonate followed by ammonia, to form 3-alkyl or 3-arylaminoisothiazoles **(109)** in high yield <79JOC1118, 81SST(6)271>.



(106) **(108)**

(107)

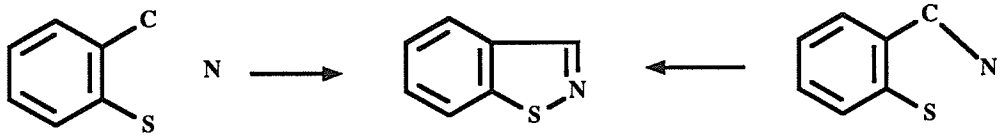
(109)

1.4.2. SYNTHESIS OF BENZO-FUSED ISOTHIAZOLES

The syntheses of 1,2- and 2,1-benzisothiazoles and their derivatives have been reviewed <72AHC(14)43, 73SST(2)556, 75SST(3)541, 77SST(4)339, 79SST(5)345, 80HC(L)109, 85AHC(38)105>.

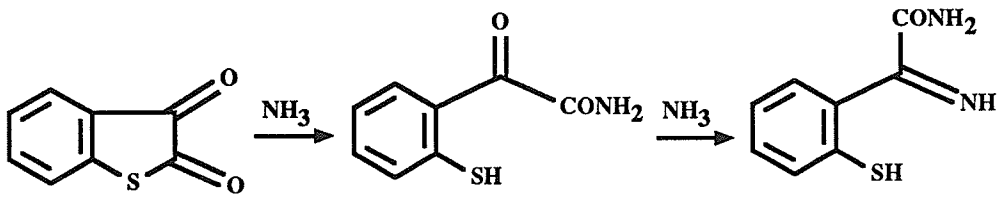
1.4.2.1. Synthesis of 1,2-Benzisothiazoles

Most of the syntheses of 1,2-benzisothiazoles involve the reaction of either structures like **(110)** or **(111)** as precursors. These are usually aromatic sulfur containing compounds with a functionalized carbon atom adjacent to the sulfur. 1,2-Benzisothiazole can be obtained from either **(110)** or **(111)** by using appropriate reagents.

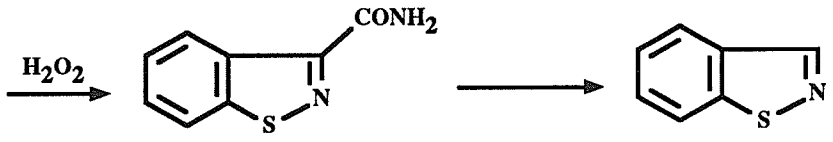


(110) **(111)**

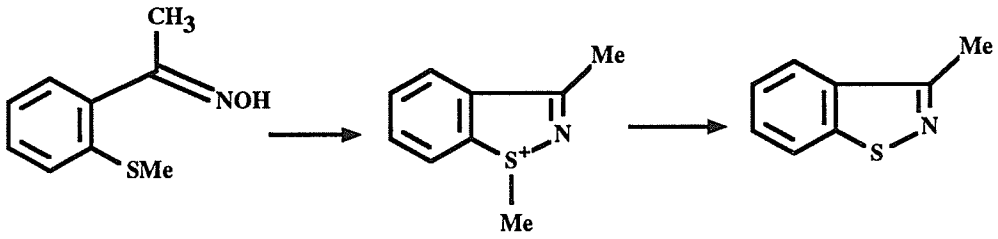
The first preparation of the parent 1,2-benzisothiazole itself was made by Stolle in 1923 by using thianaphthenequinone as the starting material. The treatment of thianaphthenequinone **(112)** with aqueous ammonia followed by hydrogen peroxide afforded 1,2-benzisothiazole-3-carboxamide **(113)**, which was then hydrolyzed and decarboxylated to form the parent system.



(112) (115)



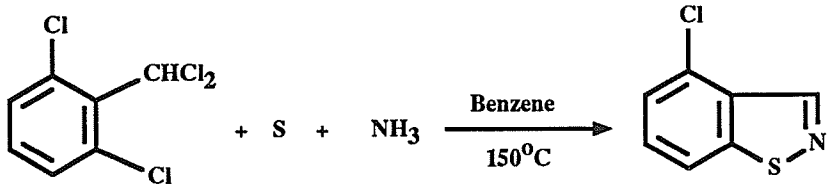
(113) (114)



(116)

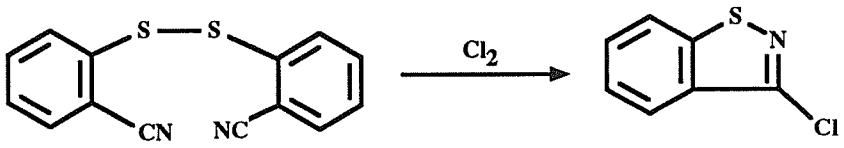
The isothiazole ring is formed via cleavage of the S-carbonyl bond and addition of ammonia to the second carbonyl group, giving an imine **(115)**, which is then cyclized by oxidation. Sulfur-nitrogen bonds are easily formed by oxidation of imino-thiols, such as **(115)**, or elimination from 2-methylthio groups, such as ketoximes **(116)**. The latter has been developed into a general synthesis of 1,2-benzisothiazoles, as the alkyl-substituted thioethers, such as **(116)**, are much easier to handle than the corresponding air-sensitive thiols <66JOC1655>.

It is reported that on heating 2,6-dichlorobenzylidene dichloride **(117)**, sulfur, ammonia and benzene together will afford 4-chloro-1,2-benzisothiazole **(118)** in good yield <69A(729)146>. The limitation of this reaction is that only 4-chloro substituted products can be obtained.



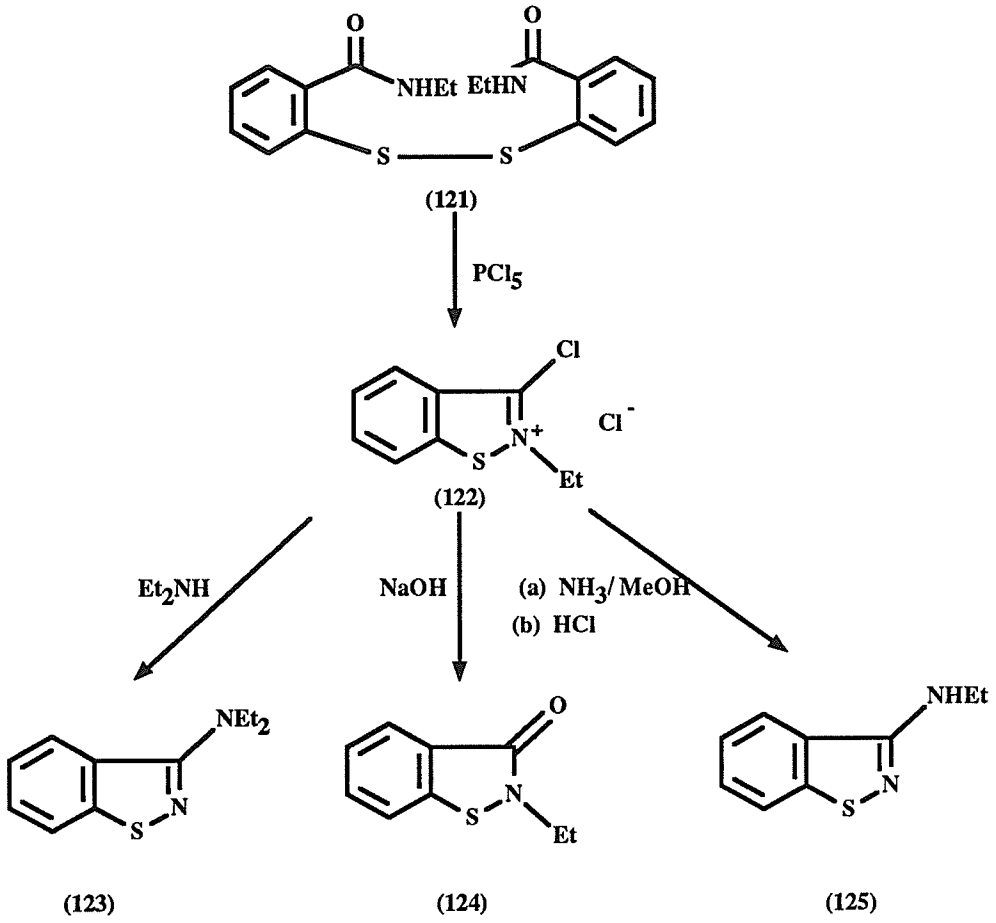
(117) (118)

Oxidation of 2,2'-dicyanodiphenyl disulfide **(119)** with chlorine can produce 3-chloro-1,2-benzisothiazole **(120)**, a very useful intermediate for other substituted derivatives <78JOC(43)1604>.



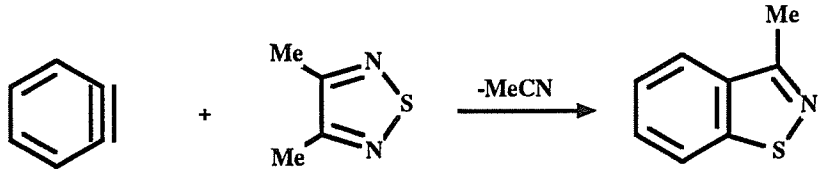
(119) (120)

A similar synthetically useful reaction occurs between dithiosalicylamide or its N-substituted derivatives and phosphorus pentachloride to yield a synthetically useful benzisothiazolium salt. For example, N,N-diethyldithiosalicylamide **(121)** yields 3-chloro-2-ethyl-1,2-benzisothiazolium chloride **(122)**, which can be converted into various 1,2-benzisothiazole derivatives under different reaction conditions as listed in Scheme 33.



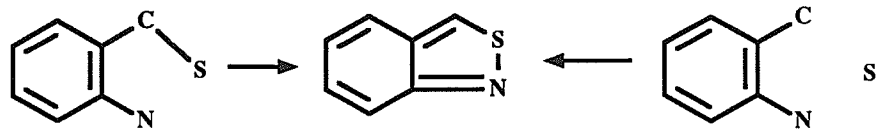
Scheme 33

The addition of benzyne to the 1,2,5-thiadiazole ring will yield a 1,2-benzisothiazole <82CC299>.



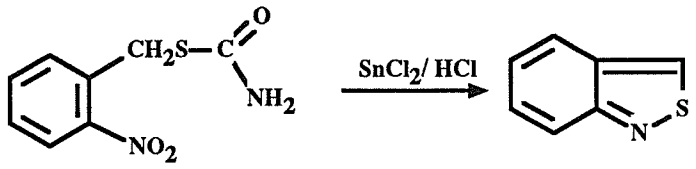
1.4.2.2. Formation of 2,1-Benzisothiazoles

For the 2,1-benzisothiazole, there are two basic methods for the construction of the ring. The first involves a precursor of type **(126)**, in which cyclization can be achieved by either oxidation or reduction. The second route is from type **(127)**, in which a sulfur atom is introduced during the reaction.



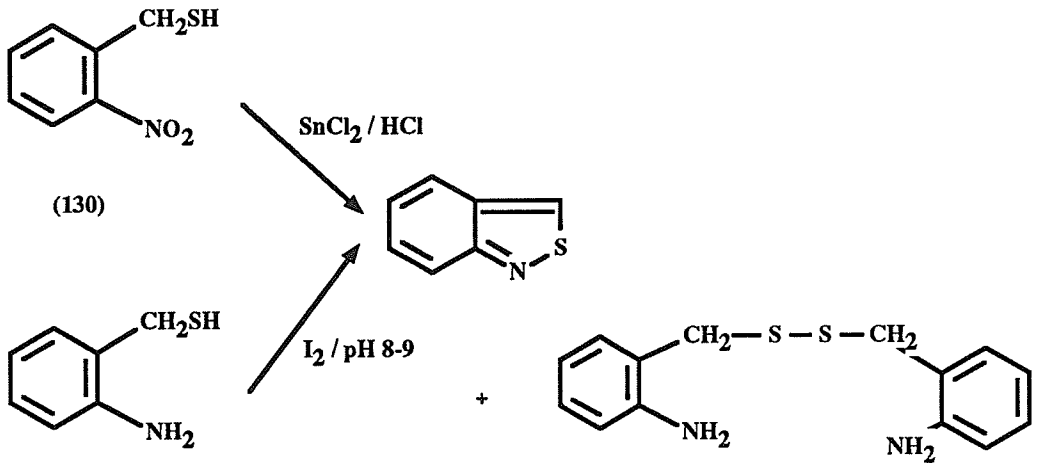
(126) **(127)**

The first preparation of 2,1-benzisothiazole was accomplished by Gabriel and co-workers by the reduction of o-nitro-α-toluenethiolcarbamate **(128)** with stannous chloride and hydrochloric acid <1895CB(28)1025, 1896CB(29)160>.

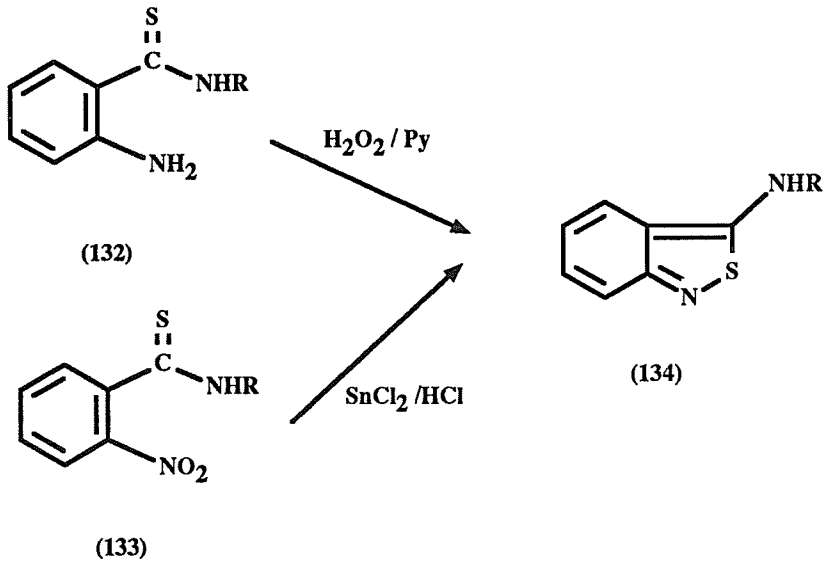


(128)

Another useful method for preparation of the parent 2,1-benzisothiazole involves oxidation of *o*-amino-α-toluenethiol **(129)**, or the reduction of *o*-nitro-α-toluenethiol **(130)**. During the oxidation of **(129)**, the disulfide **(131)** is also formed. The relative yields of **(131)** and 2,1-benzisothiazole depend on the pH conditions of the reaction <59CB1679>.



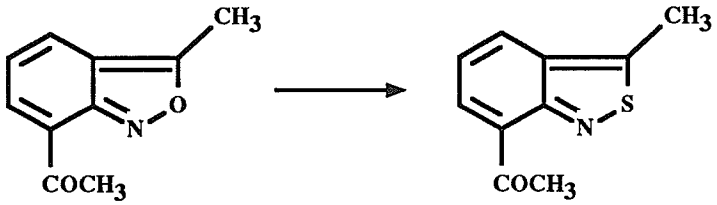
In a similar reaction, *o*-aminothiobenzamides **(132)** could be oxidized, and *o*-nitrothiobenzamides **(133)** reduced, with ring closure to give 3-amino-2,1-benzisothiazoles **(134)**. Since 3-amino-2,1-benzisothiazoles can be diazotized, they act as useful intermediates for other 3-substituted-2,1-benzisothiazole derivatives <65JMC(8)515>.



One of the most useful methods for the formation of 2,1-benzisothiazoles is the cyclization of appropriate *o*-toluidines. While thionyl chloride was initially used, it was not that satisfactory

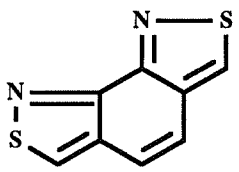
since the yields were usually low and chlorinated by-products were often found <68CC1547, 69JOC2985>. Singerman made a significant advance in the usefulness of this reaction by replacing thionyl chloride with N-sulfinylmethanesulfonamide. This reagent is easily obtained from methanesulfonamide and thionyl chloride. By using this method, better yields are usually obtained and chlorinated by-products are not formed <75JHC877>.

2,1-Benzisothiazoles can also be obtained from the corresponding 2,1-benzisoxazoles by treatment with phosphorus pentasulfide <71CJC(49)2018, 75CJC(53)1336>.

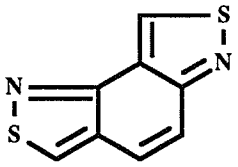


This may represent a direct displacement (ring opening, displacement, ring closure), or a pericyclic process.

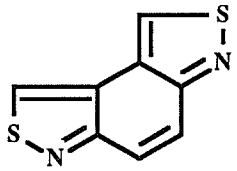
Some angular benzo[c]diisothiazoles **(135), (136), (137)** have been successfully made by Davis and co-workers <80JHC533>.



(135)

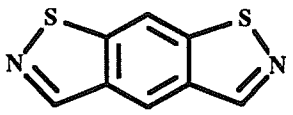


(136)

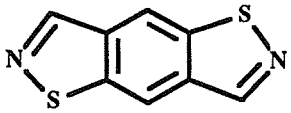


(137)

Also, two linear **(138), (139)** (made by N-sulfinylmethanesulfonamide method) and two angular **(140), (141)** (made by variations of oxime methods) benzo[d,d']diisothiazoles have been successfully synthesized <91JHC(28)445>.



(138)



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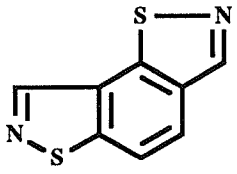

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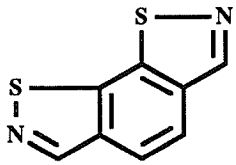


(141)

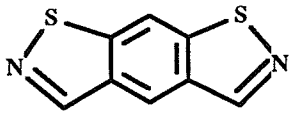
2. OBJECT OF RESEARCH

In 1979, Davis and co-workers made all the possible angular benzo[c,c']diisothiazoles by repeated use of N-sulfinylmethanesulfonamide, e.g. by initial synthesis of 2,1-benzisothiazole from an appropriate amino methyl precursor, then further substitution in the carbocyclic ring and elaboration to a precursor suitable for further cyclization <80JHC(17)533>.

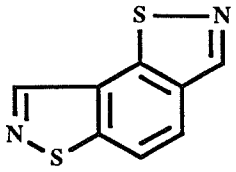
In 1990, McKinnon and Abouzeid successfully prepared four benzo[d,d']diisothiazoles **(138), (139), (140), (141)** among five possible isomeric systems. **(138), (139), (140), (141), (142)** by simultaneous formation of the two heterocyclic ring in three cases, or elaboration of a 1,2-benzisothiazole in one other case <91JHC(28)445>. The two [c,d']diisothiazoles **(143), (144)** among six possible isomeric systems **(143), (144), (145), (146), (147), (148)** were prepared by cyclization of suitably substituted methyl amino 1,2-benzisothiazoles <91JHC(28)347>.

Thus, it would be possible to compare the effects of one ring on the other with respect to the relative chemical reactivity and spectroscopic properties. Since isothiazoles themselves can be converted to other heterocyclic systems, these would also make accessible to other fused heterocycles.

The research reported in this thesis describes attempts to prepare the remaining four isomeric benzo[c,d']diisothiazoles which can be named as: benzo[1,2-c:4,3-d]diisothiazole **(145),** benzo[1,2-c:3,4-d]diisothiazole **(146),** benzo[1,2-c:4,5-d]diisothiazole **(147),** benzo-[1,2-c:5,4-d]diisothiazole **(148).**



(138)



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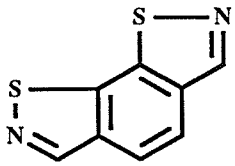
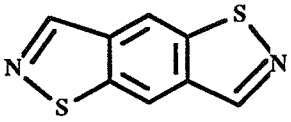


(140)



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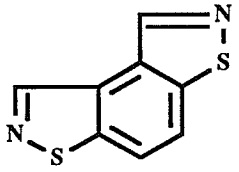
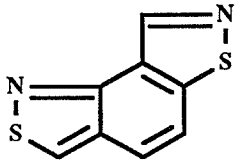
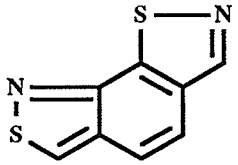


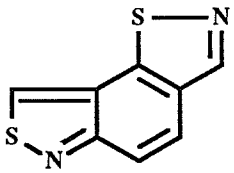
(142)



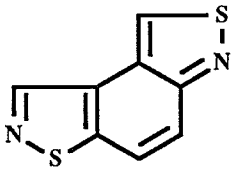
(143)



(144)



(145)



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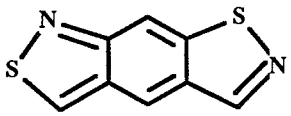
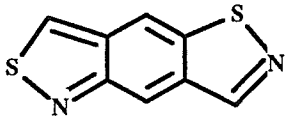


(147)

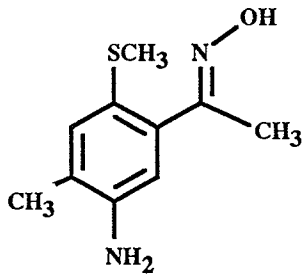


(148)

3. DISCUSSION

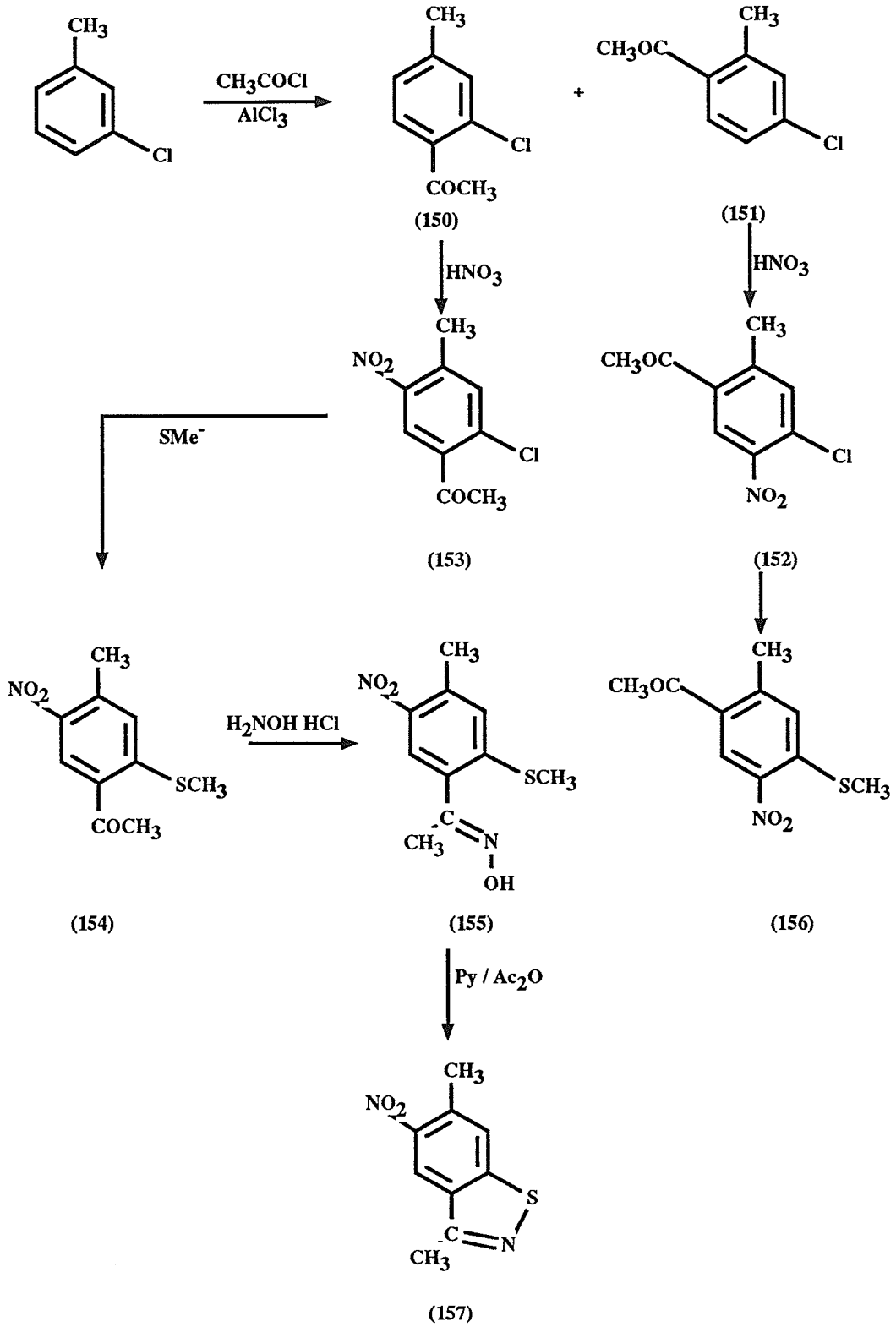
3.1. Synthesis of Benzo[1,2-c:5,4-d]diisothiazole (148)

This system can be considered as a 1,2-benzisothiazole and a 2,1-benzisothiazole incorporating a benzene ring in a linear form. If we consider the ketoxime method as modified by McKinnon and Lee for the synthesis of 1,2-benzisothiazoles, and Singerman's method for 2,1-benzisothiazoles, a retrosynthetic analysis will require precursor **(149)**, in which the adjacent methylthio and ketoxime functions can be cyclized to the 1,2-benzisothiazole ring, and the adjacent methyl and amino function can be cyclized using Singerman's reagent to give the 2,1-benzisothiazole ring.

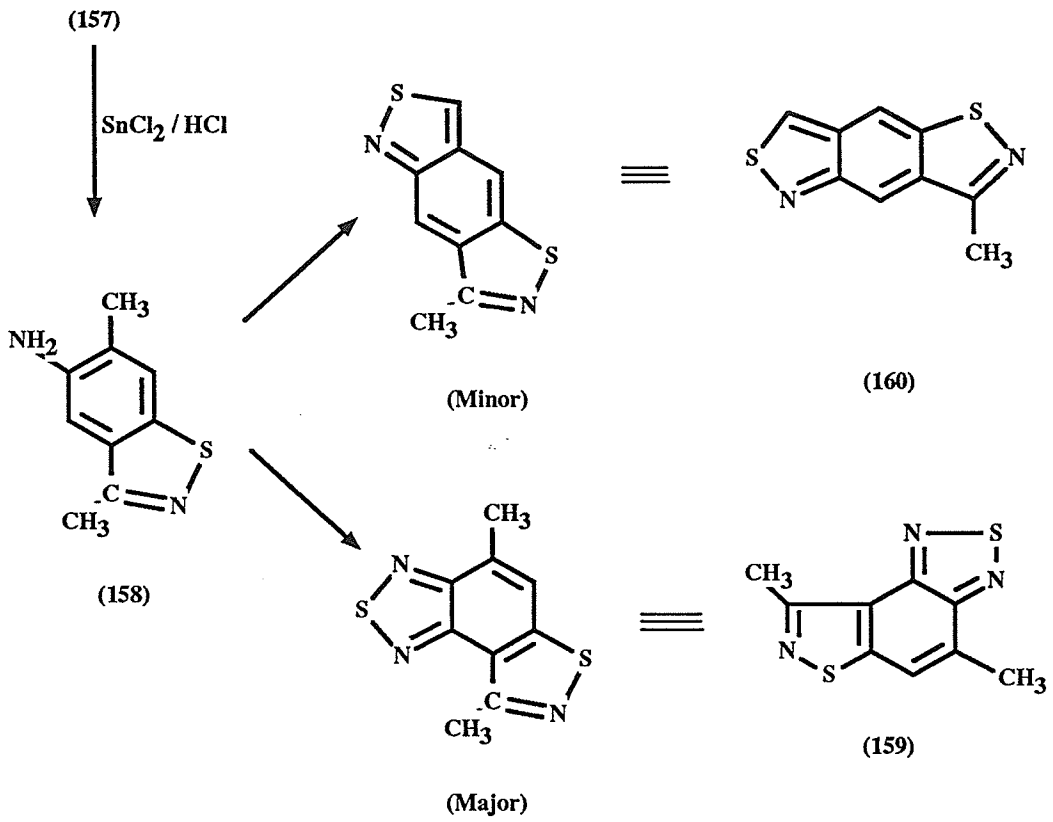


(149)

In order to make the precursor **(149)**, several approaches were investigated.


CH3
Cl
CH3COCl
AlCl3
CH3
Cl
COCH3
(150)
+
CH3
CH3OC
Cl
(151)
HNO3
HNO3
CH3
NO2
Cl
COCH3
(153)
CH3
CH3OC
Cl
NO2
(152)
SMe-
CH3
NO2
SCH3
COCH3
(154)
H2NOH HCl
CH3
NO2
SCH3
C
CH3
N
OH
(155)
CH3
CH3OC
SCH3
NO2
(156)
Py / Ac2O
CH3
NO2
S
C
N
CH3
(157)

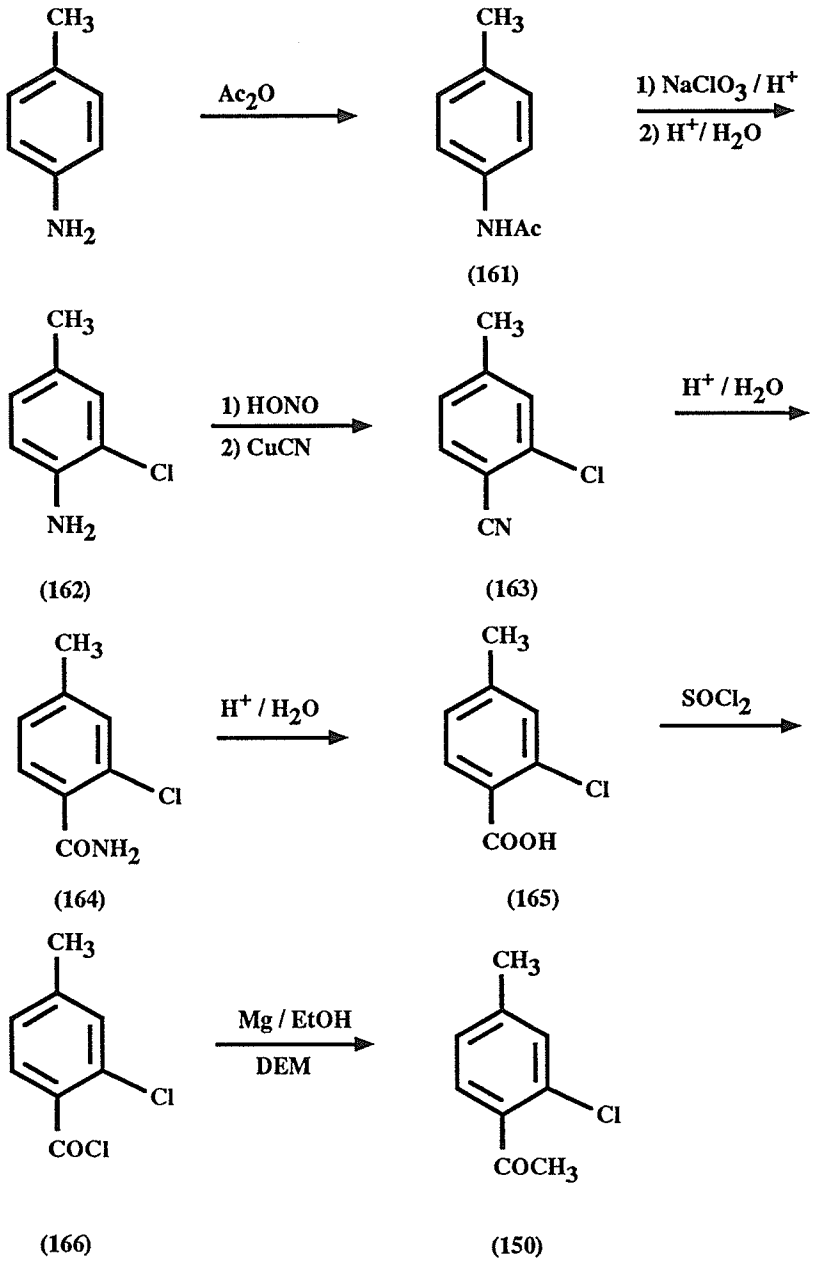
Scheme 34



Scheme 34 (Continued)

One approach started from commercially available 3-chlorotoluene. (Scheme 34) Acetylation under Friedel-Crafts condition gave a mixture of 2-chloro-4-methylacetophenone **(150)** and 4-chloro-2-methylacetophenone **(151)**. Due to their close boiling points, the mixture was further nitrated by nitric acid in concentrated sulfuric acid without isolation. A crystalline compound isolated from the nitration was originally assigned the structure **(153)**. Although this gave a crystalline methylthio compound originally assigned structure **(154)** by treatment with methanethiol, this failed to cyclize on treatment with hydroxylamine and then acetic anhydride in pyridine. We have further examined this product and found that in fact the nitration product isolated was the isomeric compound **(152)**, which could not give a 1,2-benzisothiazole. The crystalline methylthio compound thus had the structure **(156)**.

However, from the mother liquor of recrystallization of **(153)**, an oily material was isolated which on treatment with methanethiol gave the ketone **(154)** and this was converted to its oxime **(155)**, which cyclized satisfactorily to the 1,2-benzisothiazole **(157)**. However, the separation of the nitro compounds by fractional recrystallization was tedious and due to the low yield, this approach was finally abandoned and an alternative approach investigated.


CH3
NH2
Ac2O
CH3
NHAc
1) NaClO3 / H+
2) H+/ H2O
(161)
CH3
Cl
NH2
1) HONO
2) CuCN
CH3
Cl
CN
H+ / H2O
(162)
(163)
CH3
Cl
CONH2
H+ / H2O
CH3
Cl
COOH
SOCl2
(164)
(165)
CH3
Cl
COCl
Mg / EtOH
DEM
CH3
Cl
COCH3
(166)
(150)

Scheme 35

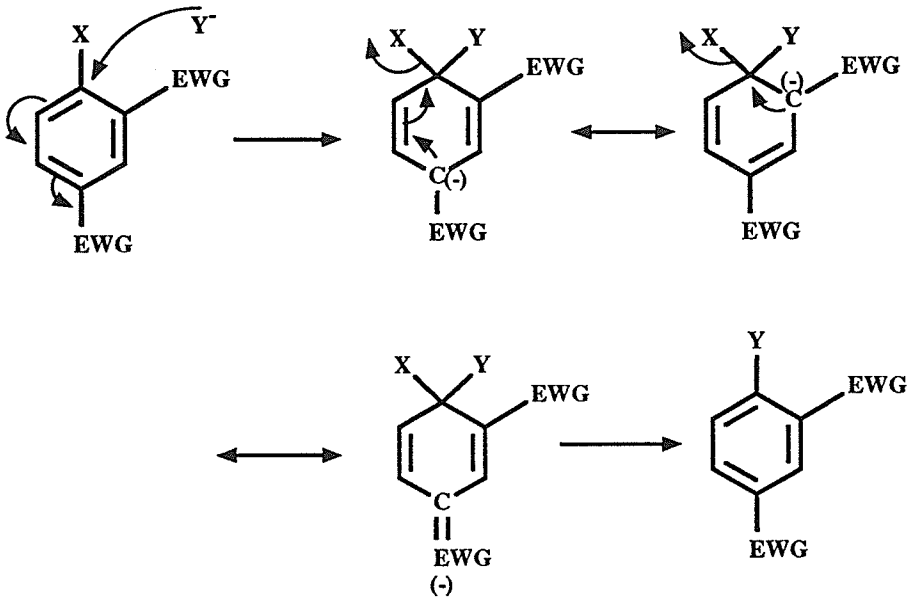
An alternative proposed approach is shown in Scheme 35. The acid **(165)** could be made by the hydrolysis of the corresponding nitrile **(163)**, and could be converted to the ketone **(150)** by reaction of its acid chloride **(166)** with diethyl ethoxymagnesium malonate and hydrolysis. This would produce an unambiguous synthesis of **(150)**.

2-Chloro-4-methylbenzonitrile **(163)**, which was prepared according to the literature procedure <40JAS2103>, was selected as a suitable precursor for the desired 2-chloro-4-methylacetophenone **(150)**. Thus, hydrolysis under acidic condition gave the corresponding 2-chloro-4-methylbenzoic acid **(165)**, which was further converted to 2-chloro-4-methylbenzoylchloride **(166)** by the action of thionyl chloride. Treatment of **(166)** with ethoxymagnesium malonic ester followed by acid hydrolysis gave 2-chloro-4-methylacetophenone **(150)**. Upon nitration in concentrated sulfuric acid, the ketone gave 2-chloro-4-methyl-5-nitroacetophenone **(153)** (see Scheme 34) in good yield with the nitro group in the less sterically hindered position. This could be seen from the ^{1}H NMR spectrum of compound **(153)**, in which the two ring protons showed up as two singlets at δ=7.43ppm and δ=8.23ppm, assigned to the C(3) and C(6) protons respectively, and two methyl protons at δ=2.64ppm and δ=2.69ppm. This spectrum indicates that the nitro had substituted at 5-position rather than the more hindered 3-position. [It was very similar to that of compound **(152)**].

A direct conversion of the amine **(162)** to the ketone **(150)** by a Beech reaction, i.e., reaction of the diazonium salts from **(162)** with acetaldoxime and hydrolysis, was also tried. Although this gave a faster synthesis, the yield was poor, and the longer method gave more easily purified product **(150)**.

Nucleophilic displacement of a halogen atom either *ortho* or *para* to an electron withdrawing group has been well established, e.g., <71CC1120, 74JOC(39)3343>. Various nucleophiles can be used, including alkoxides, thiol anions, amines, azide, chloride and hydroxide ions. The mechanism for this displacement is probably an addition-elimination procedure as described in Scheme. 36. Thus, the chlorine atom of 2-chloro-4-methyl-5-nitroacetophenone **(153)**, in which the chlorine atom is activated by the both an *ortho* keto function and a *para* nitro function, on treatment with methanethiolate anion yielded 4-methyl-2-methylthio-5-nitroacetophenone **(154)**. In the ^{1}H NMR spectrum, the S-methyl protons resonated at δ=2.51ppm.

The 4-methyl-2-methylthio-5-nitroacetophenone **(154)** was then treated with hydroxylamine hydrochloride in ethanol to give oxime **(155)** (see Scheme 34), which was further treated with acetic anhydride in pyridine without purification. The resulting material was then recrystallized from ethanol once to give a pale yellow solid. Its ^{1}H NMR spectrum showed the chemical shift of 6-methyl and 3-methyl protons at δ=2.75ppm and δ=2.78ppm as two singlets. The relatively downfield shifts of 6-methyl protons compared to the ring methyl proton shifts (δ=2.30ppm) are probably due to the deshielding effect of the *ortho* nitro group. The loss of the S-methyl group could be also seen from the ^{1}H NMR spectrum, as a signal corresponding to the S-methyl protons was absent. The two aromatic protons at C-7 and C-4 resonated at δ=7.83ppm and δ=8.57ppm as two singlets, respectively. The lower field shift of C-4 proton is due to the higher deshielding effect of the isothiazole ring and the *ortho* nitro group toward that proton. All these observations were in agreement with the fact that loss of the S-methyl group had occurred with cyclization to give the expected 3,6-dimethyl-5-nitro-1,2-benz-isothiazole **(157)**.



Scheme 36

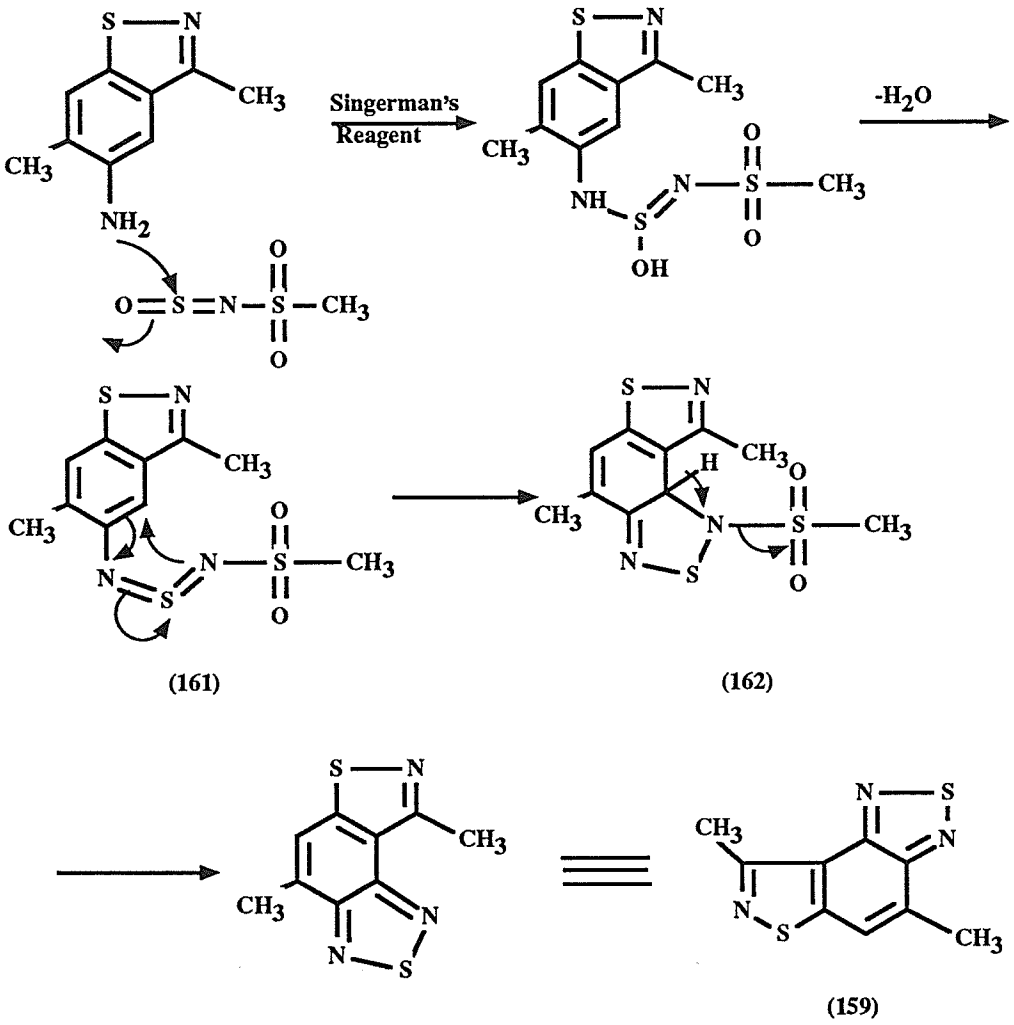
Reduction of the nitrobenzisothiazole derivative **(157)** using stannous chloride and hydrochloric acid gave corresponding 5-amino-3,6-dimethyl-1,2-benzisothiazole **(158)** (see Scheme 34). The ^1H NMR spectrum of compound **(158)** showed two singlets at δ=2.33ppm and δ=2.62ppm, assigned to the 6-methyl and 3-methyl protons respectively. The two aromatic protons were observed at δ=7.13ppm and δ=7.57ppm as two singlets. The protons of the amino group gave a broad singlet at δ=3.77ppm.

Attempts to cyclize the *o*-toluidine moiety by the Singerman's reagent (N-sulfinylmethane-sulfonamide) gave a mixture of two products in approximately 3:1 ratio. They were separated by preparative thick layer chromatography. The two products, giving molecular weights of 221 and 206, were found to have the molecular formula of $C_9H_7N_3S_2$ and $C_9H_5N_2S_2$ respectively,

according to accurate mass spectra, with the latter corresponding to the expected product **(160)**. The ^{13}C spectrum of the major product **(159)** showed that the compound had two primary carbons resonating at δ=18.53ppm and δ=19.66ppm, indicating two methyl groups, consistent with the ^{1}H NMR spectrum displayed which two singlets at δ=2.81ppm and δ=3.13ppm, integrating for three protons each. No secondary carbons were found in this compound as expected and only one tertiary carbon was evident in the ^{13}C NMR spectrum at 120.01ppm. In the ^{1}H NMR spectrum, the proton on this carbon appears as a singlet at δ=7.79ppm, i.e., in the aromatic range. The rest of the six carbons are all quaternary carbons and can be found at δ=124.81ppm, δ=131.61ppm, δ=150.56ppm, δ=155.08ppm, δ=157.74ppm and δ=164.33ppm in the ^{13}C NMR spectrum.

The structure **(159)** is assigned to the major compound which is consistent with all the spectroscopic data. This compound, named 4,8-dimethylbenzisothiazolo[3,4-d:1,2-d]benzo-thiadiazole is probably formed via a pericyclic reaction. A possible mechanism for its formation is illustrated in Scheme 37. Nucleophilic attack at sulfur followed by the loss of water could form intermediate **(161)** which by an electrocyclic reaction would give compound **(162)**. This, on elimination of methanesulfinic acid, would afford 4,8-dimethylbenzisothiazolo-[3,4-d:1,2-d]benzothiadiazole **(159)** as the major product.

The synthesis gave too little material of the minor product for it to be properly identified.



(161) (162)

(159)

Scheme 37

Another attempted approach to this system is shown in the Scheme 38. It has been reported that *ortho* mercapto-benzylamines can be cyclized by oxidation to give 1,2-benzisothiazoles. Thus, our aim was to obtain the precursor **(170),** which on two consecutive ring closure reactions could afford the expected [1,2-c:5,4-d] system.

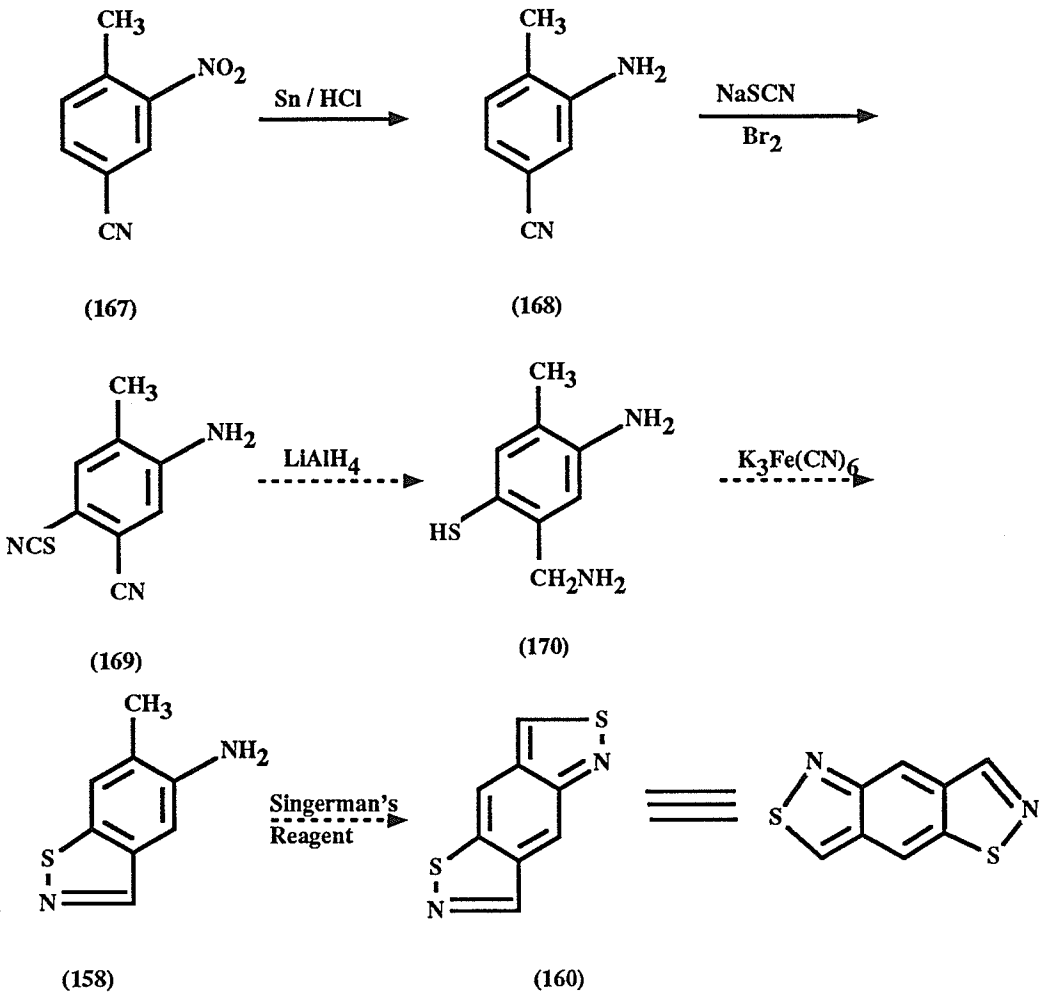
To produce the precursor **(170),** the following synthesis was carried out starting from 3-nitro-4-methylbenzonitrile **(167).** Reduction of this compound by tin and hydrochloric acid gave 3-amino-4-methylbenzonitrile **(168)** <1894B(27)2161>. The amino protons resonated at δ=4.72ppm as a broad singlet, while in the infrared spectrum, the amino stretching was found at 3385cm^{-1} and 3485cm^{-1}, typical for primary amine absorptions.

It was reported <OR(III)257) that thiocyanation of aromatic amines could introduce the thiocyano group *para* to the amino, or if that position were blocked, to an *ortho* position. The method was developed as a useful procedure for introducing a thiocyano function into aromatic primary, secondary, or tertiary amines, and phenols. Also, the reactions are not affected by the presence of other substituents, such as nitro, chloro, bromo, alkoxy, carboxyl or carbethoxy group, except that the presence of a sulfonic acid group may prevent the reaction.

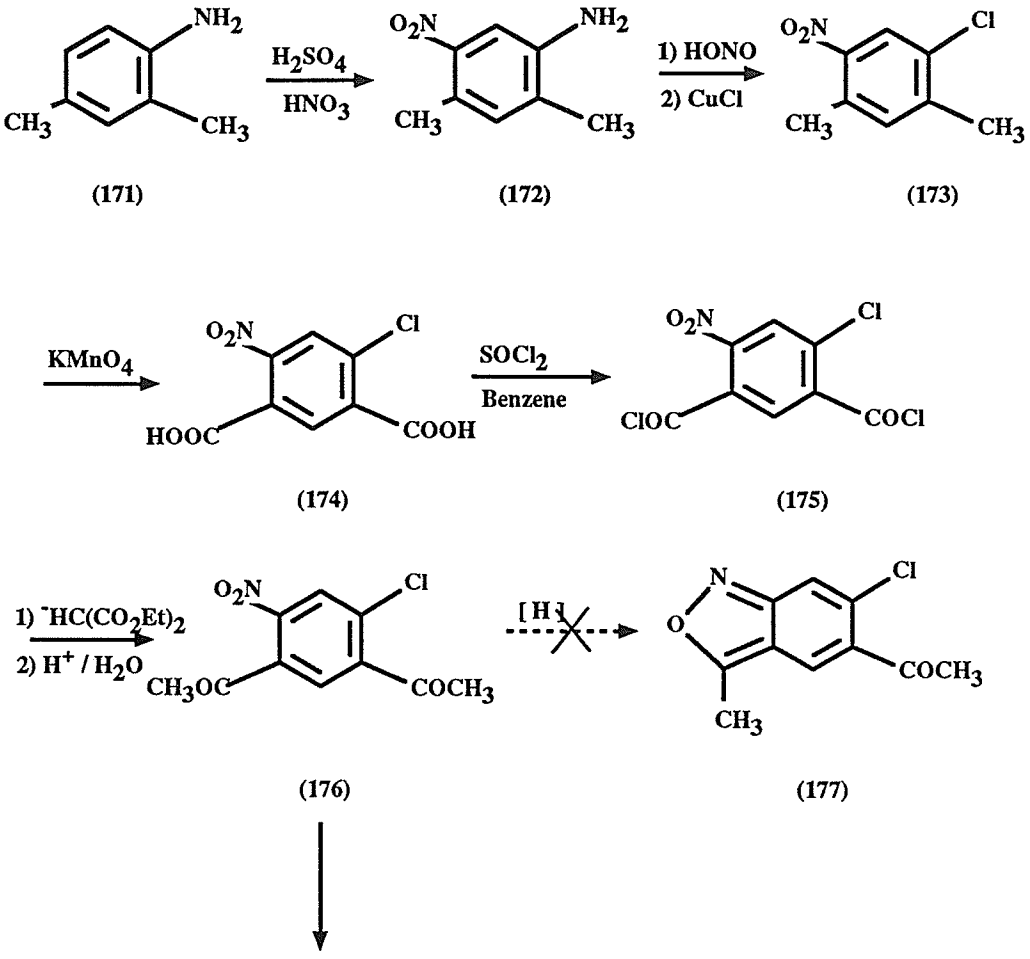
Thus, when 3-amino-4-methylbenzonitrile **(168)** was treated with sodium thiocyanate and bromine, 5-cyano-2-methyl-4-thiocyanoaniline **(169)** was obtained. The infrared spectrum of this compound showed that the two absorptions at 2230cm^{-1} and 2310cm^{-1}, assigned respectively to thiocyano and cyano groups. The -NH_2 stretching absorptions were found at 3480cm^{-1}and 3385cm^{-1}. The ring protons signaled at δ=7.50ppm and δ=7.14ppm as two singlets in ^{1}H NMR spectrum.

However, attempts to reduce compound **(169)** to 5-amino-2-mecapto-4-methylbenzylamine

(170) by lithium aluminum hydride were not successful, giving the unreacted starting material (169). The method was not further investigated.



Scheme 38

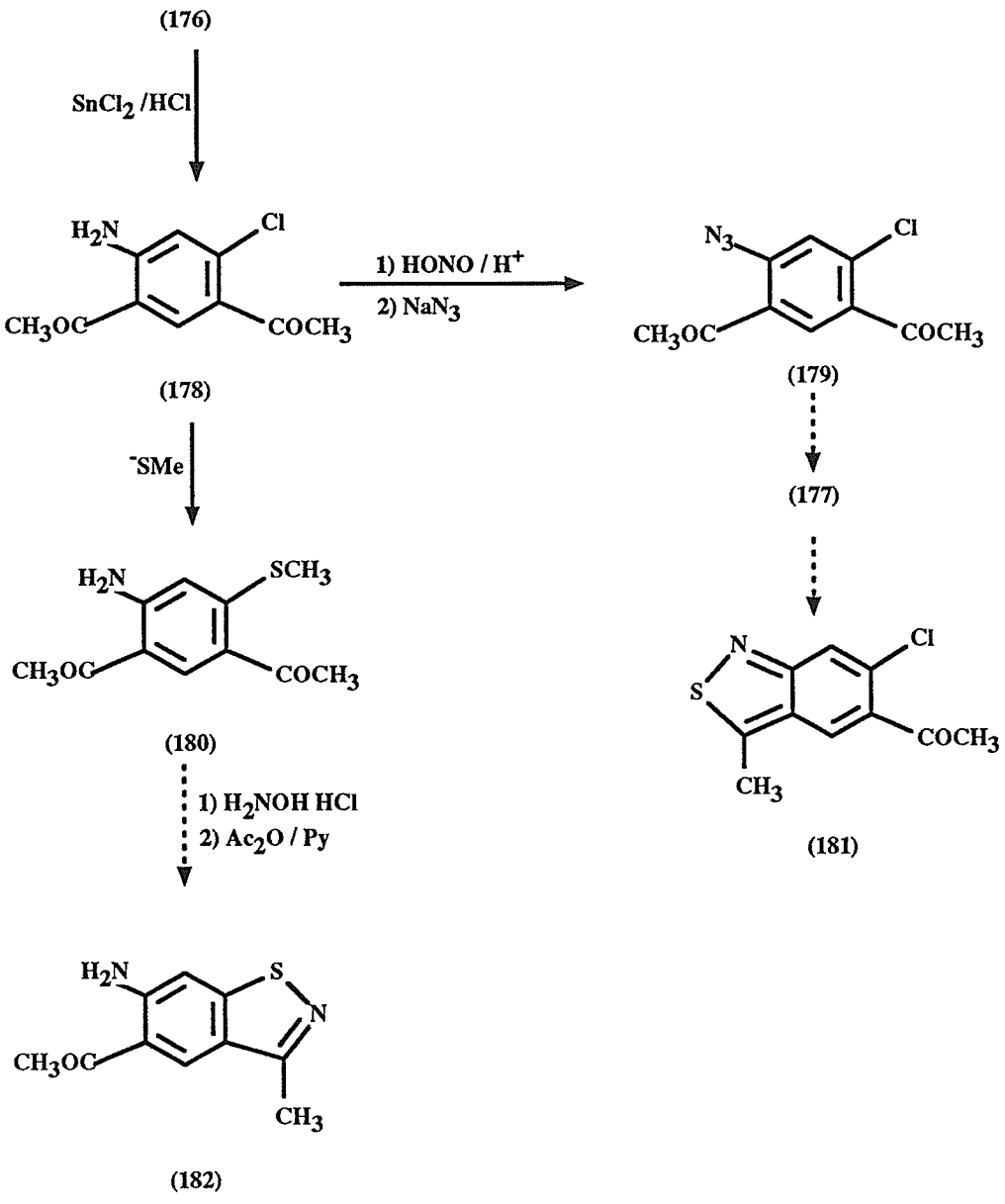


(171) (172) (173)

(174) (175)

(176) (177)

Scheme 39



Scheme 39 (Continued)

3.2. Synthesis of Benzo[1,2-c:4,5-d]diisothiazole

Initially, the synthesis of benzo[1,2-c:4,5-d]diisothiazole was investigated using the method listed in Scheme 39. The most noteworthy point about this approach is the protection of the nitro and adjacent acetyl group in **(176)** by conversion to an anthranil prior to cyclization of the other ring. This might avoid a) having to selectively replace chlorine by SMe (as will be seen below, the nitro group is also replacable by SMe under these conditions), and b) the difficulty of converting only one acetyl group into an oxime. Also, the isoxazole ring could provide an isothiazole ring, as it has been reported <69T(25)389> that isoxazoles can be converted to the isothiazoles with the same substitution pattern when treated with phosphorus pentasulfide.

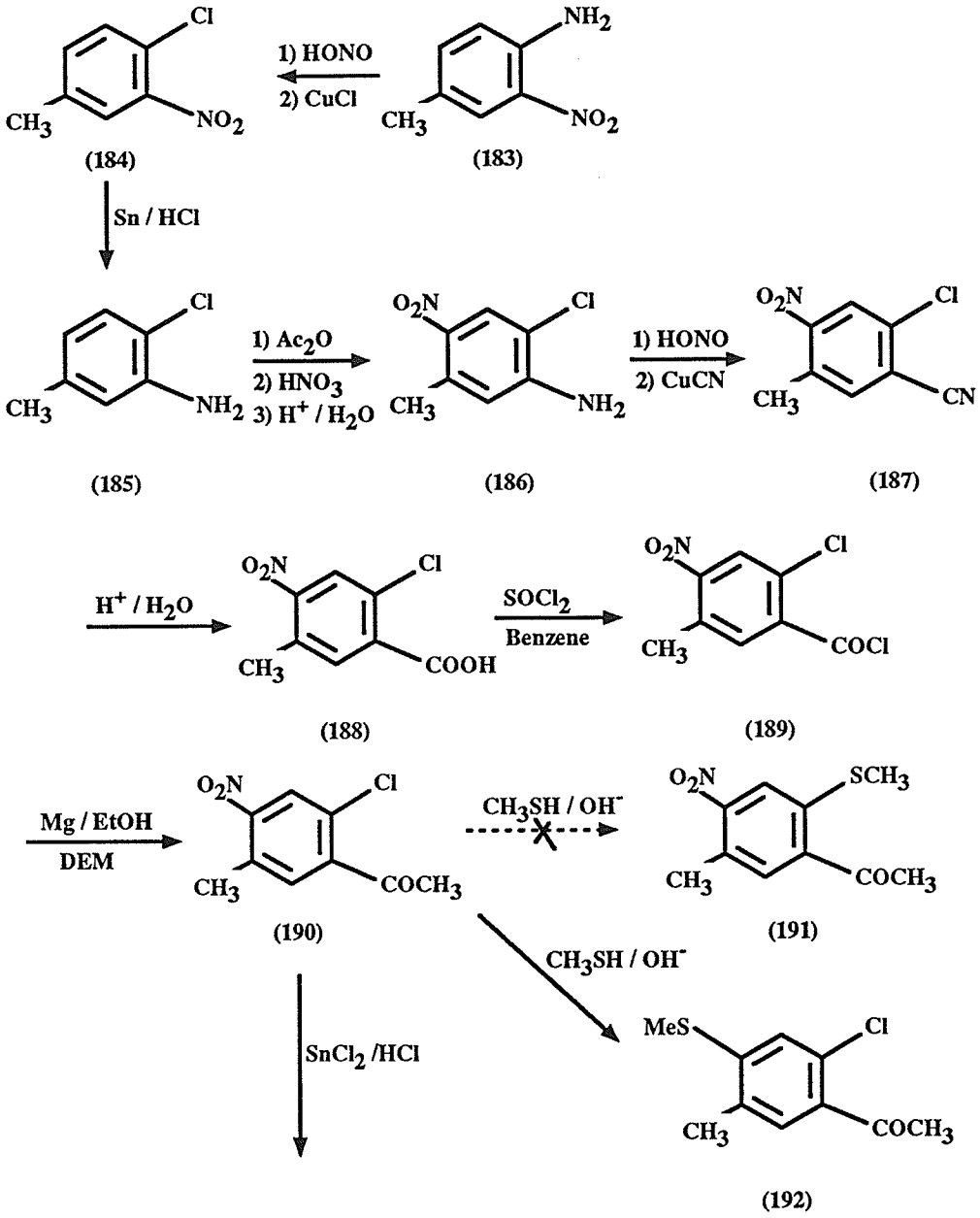
Although the amino group is usually considered as an *o*, *p* directing substituent, it can also act as a *meta* directing substituent, if protonated to an ammonium ion. Thus, nitration of 2,4-dimethylaniline **(171)** in concentrated sulfuric acid with nitric acid introduced a nitro group *meta* to the amino group, giving 2,4-dimethyl-5-nitroaniline **(172)**. Its ^{1}H NMR spectrum showed two singlets in the upfield area at δ=2.17ppm and δ=2.46ppm for the two methyl protons, and the ring protons as two singlets at δ=6.70ppm and δ=7.32ppm, confirming that the nitro group had substituted at the 5-position. Diazotization under Sandmeyer conditions using copper(I) chloride gave the expected chloro substituted product **(173)**, which on oxidation with potassium permanganate gave the corresponding diacid **(174)**. Further conversion to the acid chloride **(175)** was accomplished by using thionyl chloride in benzene and treatment of compound **(175)** with ethoxymagnesium malonic ester followed by hydrolysis gave 4-chloro-6-nitro-1,3-diacetophenone **(176)**. Its ^{1}H NMR spectrum showed two singlets at δ=2.55ppm and δ=2.70ppm, assigned respectively to the 3-, and 1-acetyl methyl protons, and two singlets at δ=7.58ppm and δ=8.11ppm for the two aromatic protons. The infrared spectrum showed the carbonyl stretching at 1710cm^{-1}.

It was reported that the *ortho* nitro-acetyl function could be converted to the isoxazole ring by using appropriate reducing agents <70T1085>. However, attempts at cyclization to the anthranil derivative **(177)** by using various mild reducing agents, including sodium thiosulfate, zinc and acetic acid, triethyl phosphite, stannous chloride and hydrochloric acid, all failed. The use of stannous chloride and hydrochloric acid gave 4-amino-6-chloro-1,3-diacetophenone **(178)**, rather than the expected 5-acetyl-6-chloro-3-methylanthranil **(177)**. Its infrared spectrum displayed double absorptions at 3396cm^{-1} and 3290cm^{-1}, which is typical for -NH_2 stretching. The carbonyl stretching could be found at 1654cm^{-1}.

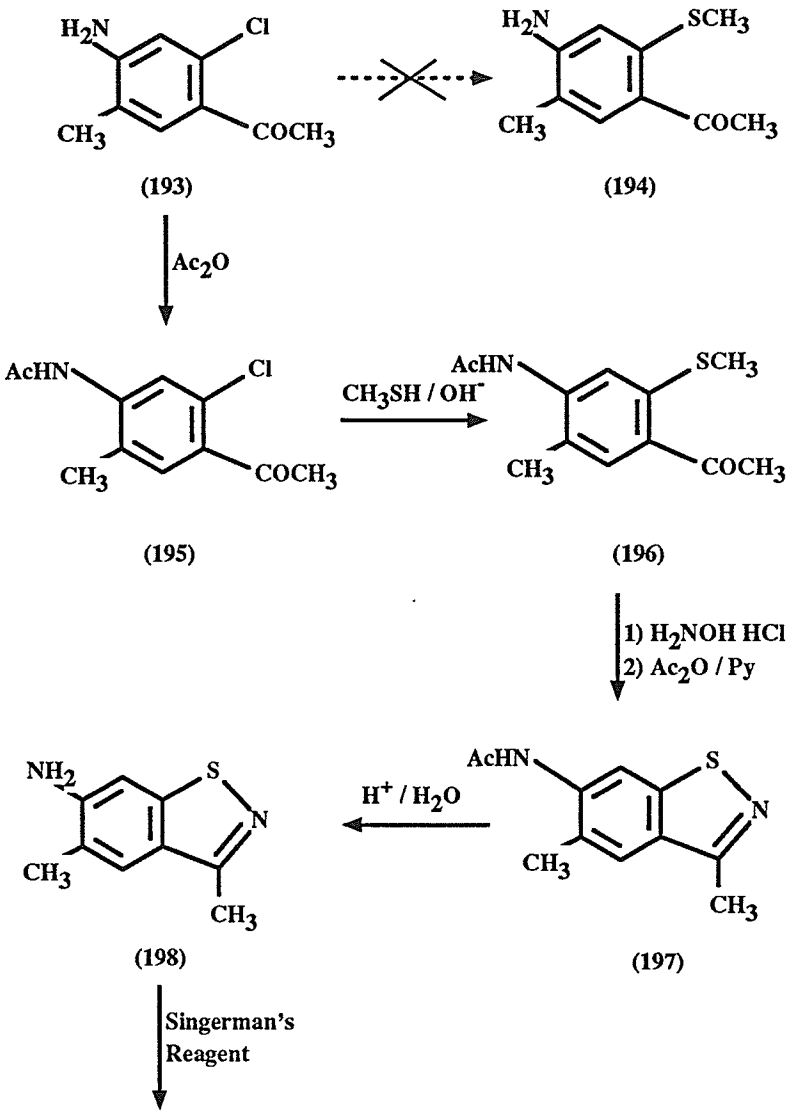
The amino derivative **(178)** was diazotized and the diazonium salt was further converted to the azide derivative **(179)** by treatment of sodium azide. It was reported that thermolysis of the azide derivative with an adjacent acetyl function could produce the anthranil system <66T(S)49>. Thus, the obtained azide derivative was treated with acetic acid under reflux for 20 min. The ^{1}H NMR spectrum of the product showed a singlet at δ=2.60ppm, integrating for three protons and two singlets at δ=7.69ppm and δ=8.08ppm, integrating for one proton each. Its mass spectrum displayed a peak at 211 rather than the expected 209. The ^{1}H NMR spectrum displayed only one methyl group. We could see no explanation for the loss of the other methyl group. This compound was not further characterized.

Since it is activated by both *ortho* and *para* acetyl groups, the 6-chloro group of compound **(178)** should be replacable by methanethiolate anion. After treating compound **(178)** with methanethiol and lithium hydroxide in DMF at room temperature for two hours, 4-amino-6-methylthio-1,3-diacetophenone **(180)** was obtained in 93% yield. Its ^{1}H NMR spectrum in acetone-d_6, displayed three singlets at δ=2.38ppm, δ=2.58ppm and δ=2.61ppm, corresponding to the two acetyl methyl protons and S-methyl protons. The aromatic protons were found at

δ=6.38ppm and δ=8.34ppm as two singlets, assigned to C-5 and C-2 protons respectively. The lower field shift of the C-2 proton is due to the deshielding effect of the two *ortho* acetyl groups. Attempts at selective conversion of the acetyl group *ortho* to the methylthio group to the corresponding oxime, failed. When one equivalent of hydroxylamine hydrochloride was used, the reaction did not occur, while the use of two equivalents of hydroxylamine hydrochloride afforded the corresponding dioxime which was of no use for the further synthesis. Because of these difficulties, the method was not further investigated.


Cl
CH3
NO2
(184)
1) HONO
2) CuCl
NH2
CH3
NO2
(183)
Sn / HCl
Cl
CH3
NH2
(185)
1) Ac2O
2) HNO3
3) H+ / H2O
O2N
Cl
CH3
NH2
(186)
1) HONO
2) CuCN
O2N
Cl
CH3
CN
(187)
H+ / H2O
O2N
Cl
CH3
COOH
(188)
SOCl2
Benzene
O2N
Cl
CH3
COCl
(189)
Mg / EtOH
DEM
O2N
Cl
CH3
COCH3
(190)
CH3SH / OH-
O2N
SCH3
CH3
COCH3
(191)
CH3SH / OH-
SnCl2 /HCl
MeS
Cl
CH3
COCH3
(192)

Scheme 40



Scheme 40 (Continued)

An alternative approach to the synthesis of benzo[1,2-c:4,5-d]diisothiazole started from 2-chloro-5-methylaniline **(185)** (which was made by diazotization and reduction from 2-nitro-4-methylaniline **(183)**) (Scheme 40). Since it is possible to introduce a nitro group at the 4-position and the corresponding amino group could be eventually converted to an acetyl group, this would provide a suitable precursor for the [1,2-c:4,5-d] system. Nitration of 2-chloro-5-methylacetanilide in concentrated sulfuric acid using one equivalent of nitric acid followed by acidic hydrolysis introduced a nitro group at the 4-position, giving 2-chloro-5-methyl-4-nitroaniline **(186)**. Its C-5 methyl protons were found at δ=2.58ppm in the ^{1}H NMR spectrum at a slightly lower field in comparison to a normal ring methyl shift (δ=2.30ppm). The deshielding effect of the *ortho* nitro group contributed greatly to this downfield shift. The amino protons resonated at δ=4.68ppm as a broad singlet integrating to two protons. The two ring protons were evident at δ=6.59ppm and δ=8.15ppm, assigned to the C-6 and C-3 protons, respectively. The lower field shift of the C-3 proton is due to the deshielding effect caused by the nitro group *ortho* to it.

Compound **(186)** was then diazotized at 0°C in sodium nitrite and sulfuric acid, and the diazonium salt converted to the cyano derivative by using copper(I) cyanide. Thus, 2-chloro-5-methyl-4-nitrobenzonitrile **(187)** was obtained in 53% yield. Its infrared spectrum showed the CN stretched at 2250cm^{-1}. The C-5 methyl protons resonated in the ^{1}H NMR spectrum at δ=2.65ppm. Thus, there is a small downfield shift due to the *ortho* and *meta* electron-withdrawing nitro and cyano groups. The two aromatic protons were found at δ=7.66ppm and δ=8.10ppm, assigned to C-6 and C-3 protons, respectively. The benzonitrile derivative **(187)** was further hydrolyzed in acid to the corresponding benzoic acid derivative **(188)**. Its ^{1}H NMR spectrum displayed two aromatic protons at δ=8.05ppm and δ=8.18ppm. The acidic proton signal was found at δ=9.10ppm as a broad singlet, which was typical for the acid proton.

The acid **(188)** was then converted by thionyl chloride to the acid chloride **(189)**, which was reacted with ethoxymagnesium malonic ester and followed by acid hydrolysis to yield 2-chloro-5-methyl-4-nitroacetophenone **(190)**. Its ^{1}H NMR spectrum displayed two singlets at δ=2.62ppm and δ=2.65ppm with an equal integration of three protons each, assigned to the 5-methyl and acetyl methyl protons. The two ring protons appeared as two singlets at δ=7.47ppm and δ=8.03ppm. Its mass spectrum gave the parent peak at 213, confirming the identity of the compound.

When 2-chloro-5-methyl-4-nitroacetophenone **(190)** was treated with methanethiolate anion, the mass spectrum data of the compound obtained showed surprisingly that the methylthio had displaced the 4-nitro group in preference to the chlorine. It showed a parent ion peak at 214 with a chlorine isotopic peak at 216, indicating the presence of chlorine in the molecule. The molecular weight of 214, which is in agreement with the molecular formula $C_{10}H_{11}ClOS$, suggested that a displacement of the nitro group had taken place yielding a product which was useless for further synthesis. It appeared that the desired 5-methyl-2-methylthio-4-nitroaceto-phenone was not obtained.

The ^{1}H NMR spectrum of the compound having mass 214/216 showed three methyl protons in upfield positions at δ=2.23ppm, δ=2.48ppm and δ=2.61ppm, indicating the displacement with methanethiolate anion. The two aromatic protons could be found at δ=7.05ppm and δ=7.38ppm as two singlets.

It has been reported previously that nitro displacement involves activation by either *ortho* or *para* methylthio <78JOC2048>, *ortho* cyano, carboxylic acid, ester or aldehyde groups or a *para* ketone group <71CC1121>. Although, in the case of compound **(190)**, the chloro group

was activated by an *ortho* acetyl group and the nitro group was activated by the same group at the *para* position, the displacement of the nitro group was in preference to that of the chlorine for some reason. This observation is consistent with previous observations which found that sometimes the relative rate of nitro displacement is much faster than that of chlorine <78JOC2048>.

Since the facile displacement of the nitro group gives the useless 2-chloro-5-methyl-4-methylthioacetophenone **(192)**, an alternative method would involve reduction of the nitro to the amino function before treating it with methylthiolate anion. Thus, 4-amino-2-chloro-5-methylacetophenone **(193)** was obtained by reduction of **(190)** with stannous chloride in hydrochloric acid. The ^{1}H NMR spectrum of this compound showed two methyl groups as two singlets in the upfield region with two ring protons at a more downfield position. The amino protons could be found at δ=4.02ppm as a broad singlet due to the hydrogen bonding. Attempts to convert the 4-amino-2-chloro-5-methylacetophenone into the corresponding 4-amino-5-methyl-2-methylthioacetophenone **(194)** were not successful, even under fairly strong conditions, i.e., treatment with methylthiolate anion in a sealed pressure bottle overnight at 150°C. Monitoring by ^{1}H NMR spectroscopy showed that no substitution reaction had taken place. Evidently the conjugating effect of the amino function on the acetyl function so reduces the electron withdrawing properties of the latter that nucleophilic substitution is inhibited.

It seemed reasonable to conclude that, if the deactivating effect caused by the amino group could be reduced to some extent, then the activating force exerted by the *ortho* acetyl function would become dominant, and the nucleophilic substitution reaction could still take place. Thus, 4-amino-2-chloro-5-methylacetophenone was first converted by acetic anhydride to the 4-acetamido-2-chloro-5-methylacetophenone **(195)**, which was treated with methylthiolate anion in a pressure bottle, overnight at 100°C. This time the substitution of chlorine did occur giving

the desired product, 4-acetyl-2-methyl-5-methylthioacetanilide **(196)**. The ^{1}H NMR spectrum showed three methyl groups resonating at δ=2.28ppm, δ=2.33ppm and δ=2.45ppm and two aromatic protons at δ=7.66ppm and δ=8.15ppm. The N-proton appearing at δ=7.35 was evident as a broad singlet integrating for one proton. Its infrared spectrum showed single N-H stretching absorption at 3270cm^{-1}, indicating an secondary amine, and an absorption at 1664cm^{-1} assigned to a carbonyl stretch.

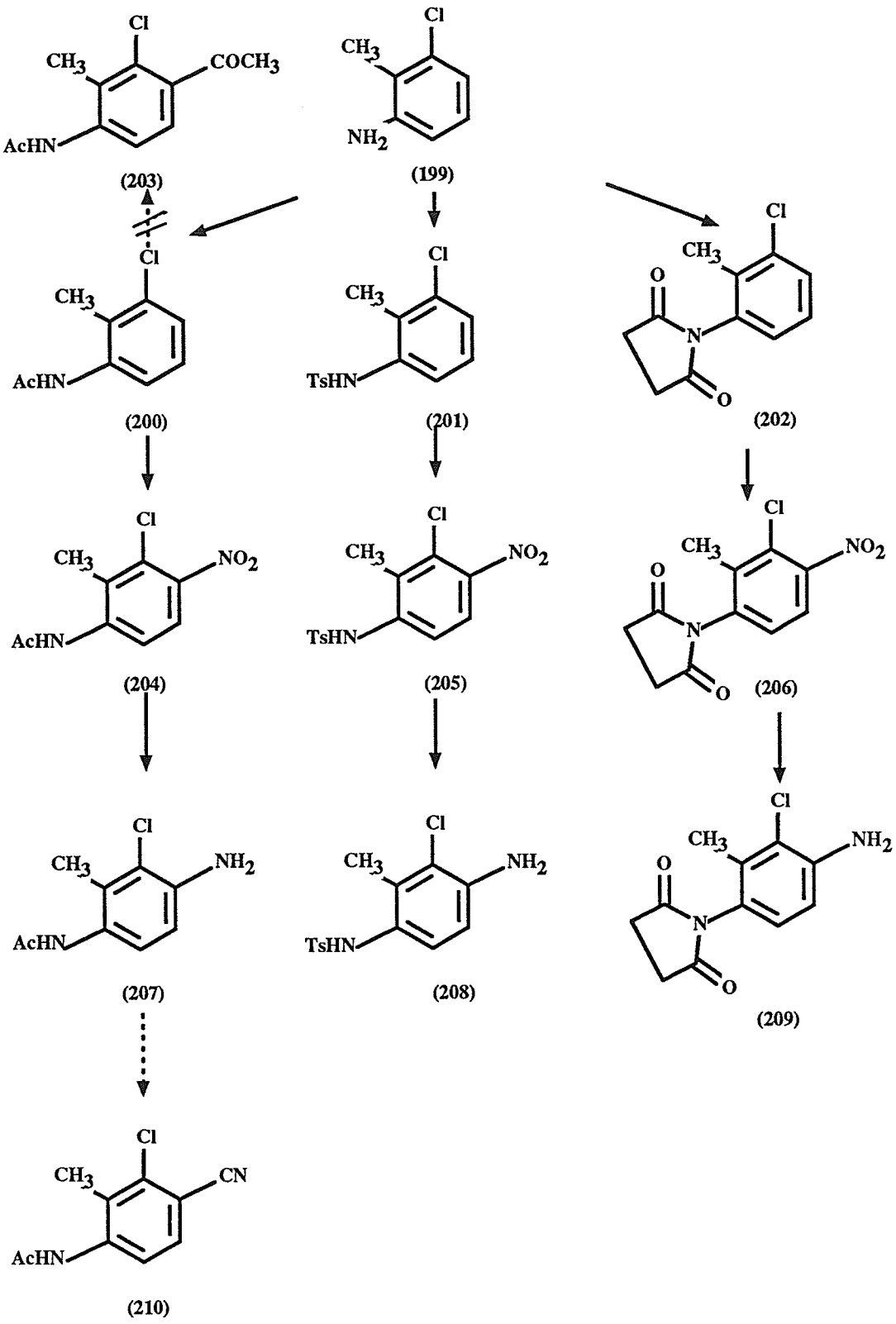
Using the *ortho*-methylthio-ketoxime method for the 1,2-benzisothiazole, the compound **(196)** was converted to 6-acetamido-3,5-dimethyl-1,2-benzisothiazole **(197)** via its intermediate oxime. Hydrolysis of **(197)** in acid gave 6-amino-3,5-dimethyl-1,2-benzisothiazole in high yield. Its ^{1}H NMR spectrum showed that the two methyl protons resonating at δ=2.31ppm and δ=2.62ppm and the two ring protons at δ=7.06ppm and δ=7.57ppm. The amino protons could be found at δ=3.73ppm as a broad singlet. Due to the long synthesis, the material **(198)** was obtained insufficient quantities for further synthetic investigations.

3.3. An Approach to Benzo[1,2-c:4,3-d]diisothiazole

In the initial approach to the title compound (Scheme 41), it was hoped that the commercially available 3-chloro-2-methylaniline **(199)** could be used as a starting point. Acetylation of the acetanilide derivative **(200)** at the 4-position may give a suitable precursor **(203)** which could be further converted to the desired system. However, acetylation of 3-chloro-2-methyl-acetanilide **(200)** under Friedel-Crafts conditions failed. Treatment with acetic anhydride with iodine as the catalyst or acetyl chloride with aluminum chloride both yielded the starting acetanilide. Even the Vilsmeier reaction failed in this case. This maybe because, although protected by an acetyl group, the acetamide nitrogen can still coordinate with the catalysts such as aluminum chloride or iodine, which are electron-deficient.

Since the direct acetylation was not successful, nitro substitution at the 4-position was considered. This group could be eventually converted to the acetyl group by reduction to amine, diazotization, conversion to the nitrile, hydrolysis, and conversion to the ketone. The nitro derivatives **(204)**, **(205)**, **(206)** could be obtained in moderate yield upon nitration of the corresponding protected amino derivatives. However difficulty was experienced in reducing the nitro derivatives to the amino compounds. Various reducing agents including sodium hydrosulfite, iron/acetic acid, tin/hydrochloric acid and Raney Ni/NH_2NH_2, were tried on compounds **(204)**, **(205)**, **(206)**, but none of them gave satisfactory results, due to either poor yields or poorly defined products.

Because of the difficulty during the reduction, this approach was not further investigated and an alternative approach was tried starting from *m*-toluidine **(211)** (Scheme 42).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CH3
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AcHN
(203)
Cl
CH3
NH2
(199)
Cl
CH3
AcHN
(200)
Cl
CH3
TsHN
(201)
Cl
CH3
O
N
O
(202)
Cl
CH3
NO2
AcHN
(204)
Cl
CH3
NO2
TsHN
(205)
Cl
CH3
NO2
O
N
O
(206)
Cl
CH3
NH2
AcHN
(207)
Cl
CH3
NH2
TsHN
(208)
Cl
CH3
NH2
O
N
O
(209)
Cl
CH3
CN
AcHN
(210)

Scheme 41

This was originally explored as a potential route to the [1,2-c:4,5-d] system. Thus, acetylation of *m*-toluidine **(211)** by acetic anhydride under the usual conditions gave 3-methylacetanilide **(212)**, which upon nitration afforded 3-methyl-4-nitroacetanilide **(213)** as expected. This compound was chlorinated with expectation of chlorine substitution *ortho* to the acetamido group due to less steric hindrance. The chlorinated compound **(215)** might have been a potential precursor for the synthesis of the [1,2-c:4,5-d] system. However, the result showed that the chlorine atom was introduced to the sterically more hindered position giving 2-chloro-4-nitro-3-methylacetanilide **(214)**. This could be observed from its ^{1}H NMR spectrum, in which the two aromatic protons could be found at δ=7.35ppm and δ=7.74ppm as two doublets with coupling constant J=8.4Hz, which is typical for *ortho* coupling. That this is the correct isomer assignment is shown by the melting point, 110°C, different than authentic 2-chloro-5-methyl-4-nitroacetanilide (m.p. 134-135°C) prepared by another method <26JCS2343>.

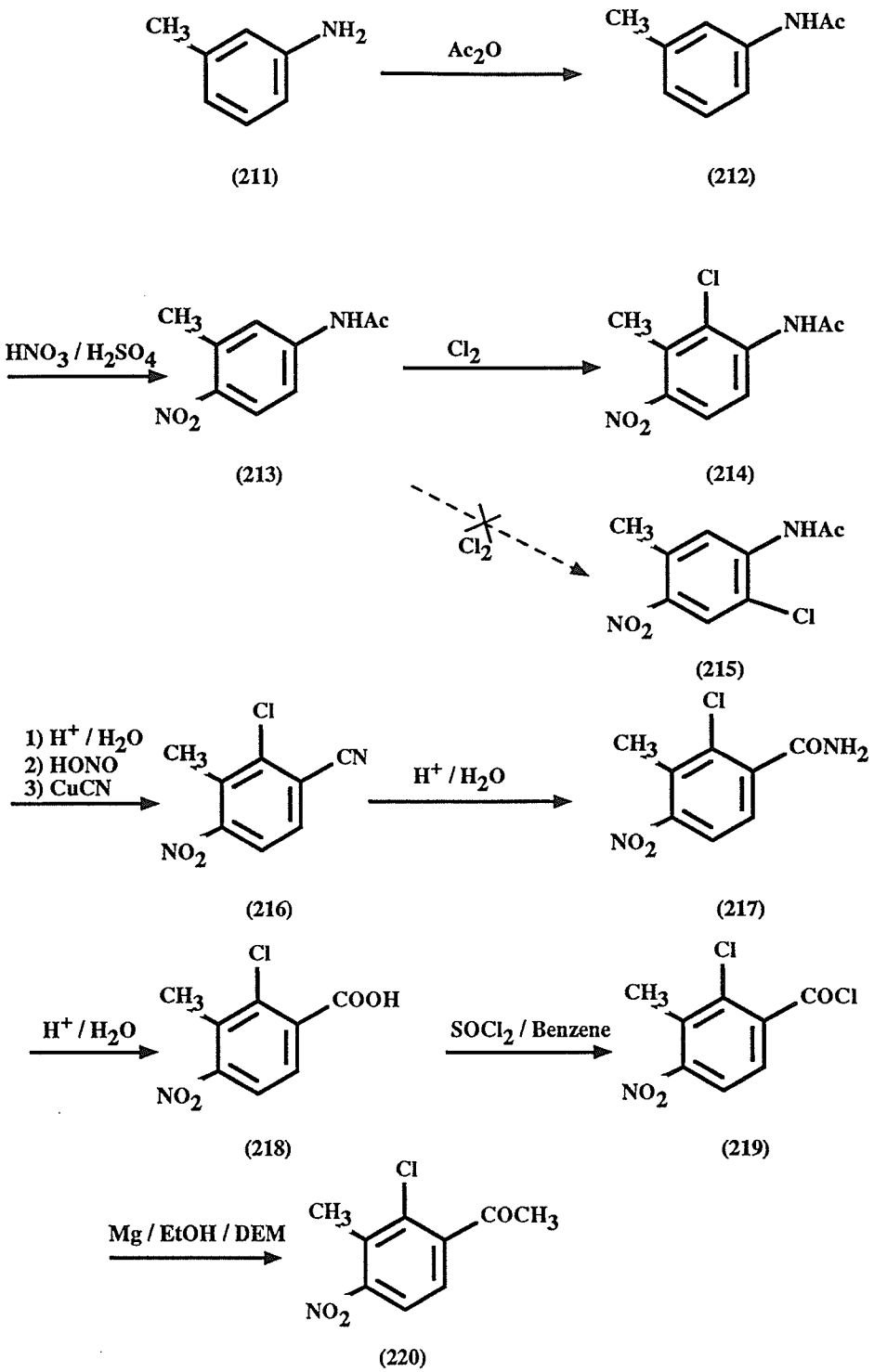
Further hydrolysis of 2-chloro-3-methyl-4-nitroacetanilide **(214)** gave the corresponding amine which could be converted to the benzonitrile derivative under Sandmeyer conditions. Thus, 2-chloro-3-methyl-4-nitrobenzenenitrile **(216)** was obtained in 59% yield. Its C≡N stretch could be found at 2244cm^{-1} in the IR spectrum.

2-Chloro-3-methyl-4-nitrobenzenenitrile **(216)** was hydrolyzed to the amide **(217)** and then further to the acid **(218)** under acidic conditions. The 2-chloro-3-methyl-4-nitrobenzoic acid **(218)** exhibited in its ^{1}H NMR spectrum a broad signal at a very low field (~δ10.62ppm), and its IR spectrum also gave a broad absorption at ~3000cm^{-1}. Both were characteristic absorptions for the acid. The acid was converted to the acid chloride **(219)** by refluxing with thionyl chloride in benzene. 2-Chloro-3-methyl-4-nitroacetophenone **(220)** could be obtained

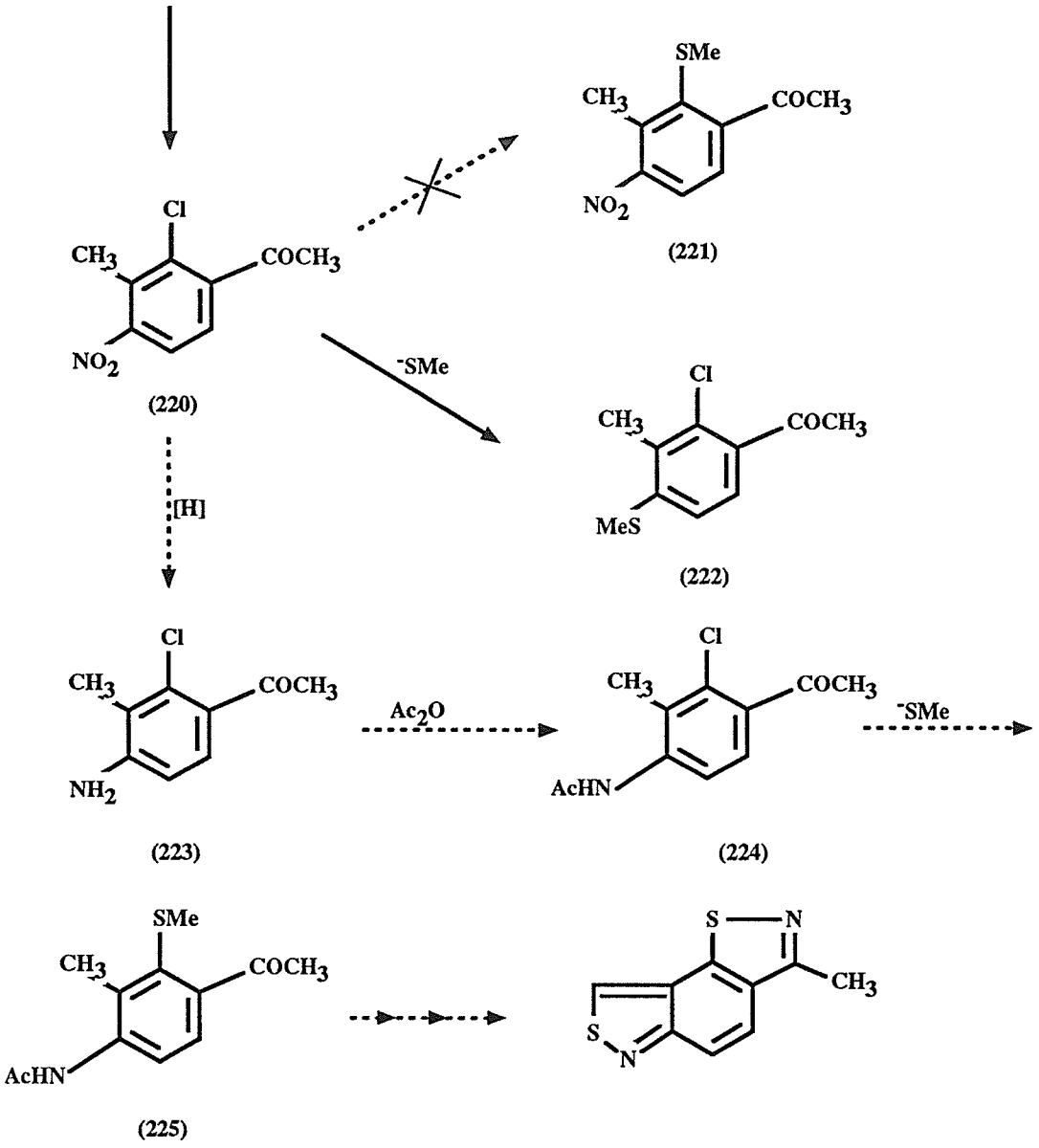
under usual condition by treatment of the acid chloride by ethoxymagnesium malonic ester followed by acid hydrolysis.

Attempts to substitute the chlorine also failed at this point, similar to analogue **(190)**. 2-Chloro-3-methyl-4-nitroacetophenone gave the compound **(222)** in which the 4-nitro group was displaced instead of the chlorine. Thus, 2-chloro-3-methyl-4-methylthioacetophenone **(222)** was obtained with a parent peak of 214, with chlorine isotopic peak of 216, in the mass spectrum, which was consistent with the formula $C_{10}H_{11}ClOS$. Its ^1H NMR spectrum showed that three methyl protons at δ=2.47ppm, δ=2.52ppm and δ=2.62ppm as three singlets with integration for three protons each. Its aromatic protons could be found at lower field at δ=7.12ppm and δ=7.45ppm as two doublets with coupling constant J=8.4Hz. The C-Cl stretching absorption was observed at 725cm^{-1} in its infrared spectrum. Like its isomer 2-chloro-5-methyl-4-nitroacetophenone **(190)**, the facile nitro displacement may be also due to the activating effect caused by *para* acetyl function.

It may be possible to reduce the nitro group prior to the methylthio substitution, and then consecutively cyclize the two rings to reach the expected system. This approach needs to be further investigated, but the long synthesis provided too little material for this to be investigated properly.


CH3
NH2
Ac2O
NHAc
(211)
(212)
HNO3 / H2SO4
NO2
Cl2
Cl
(213)
(214)
Cl2
(215)
1) H+ / H2O
2) HONO
3) CuCN
CN
H+ / H2O
CONH2
(216)
(217)
COOH
SOCl2 / Benzene
COCl
(218)
(219)
Mg / EtOH / DEM
COCH3
(220)

Scheme 42



Scheme 42 (Continued)

3.4. An Approach to Benzo[1,2-c:3,4-d]diisothiazole

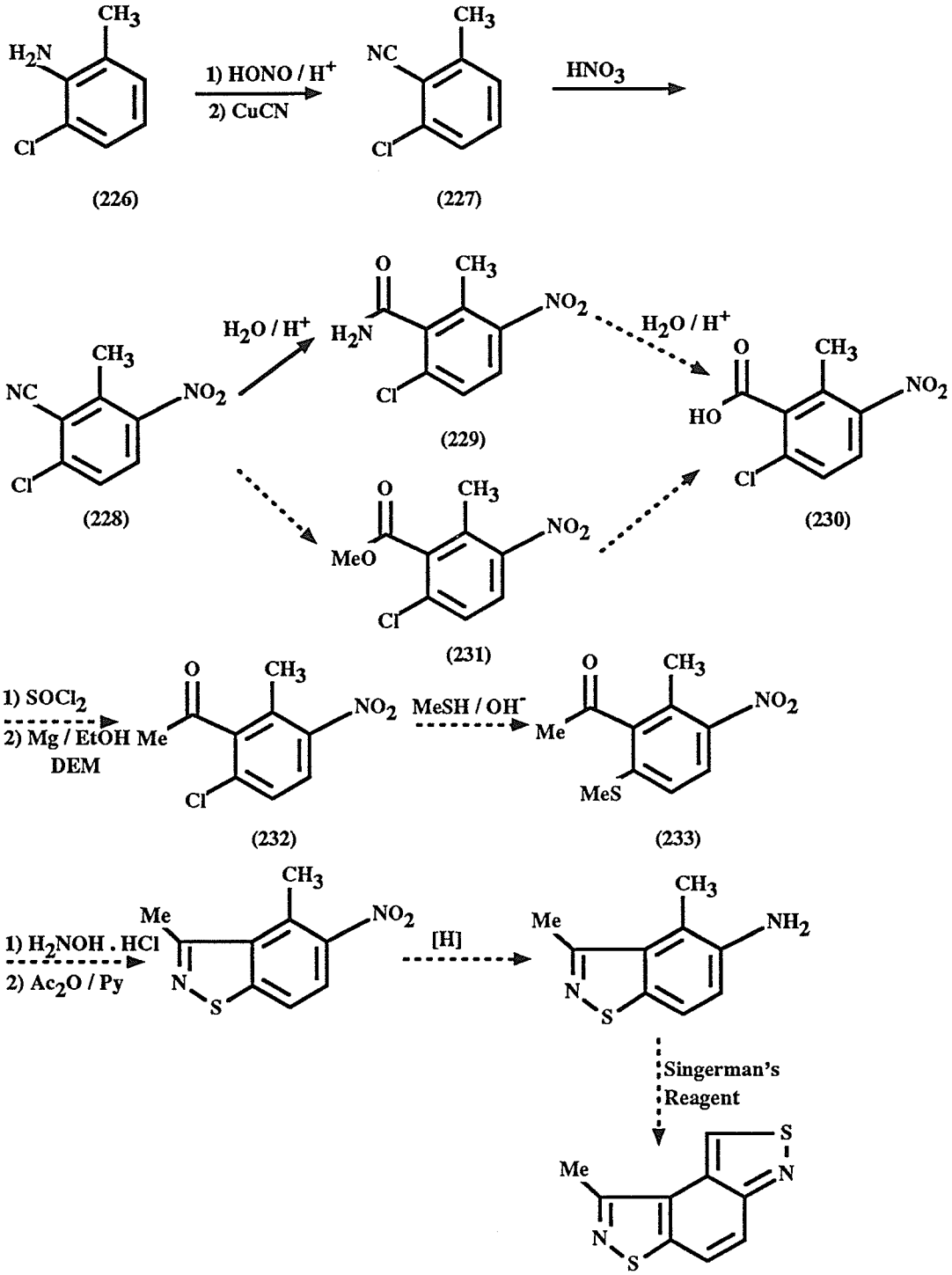
Little work has been performed to investigate the methods for the synthesis of this system. Only one approach has so far been tried, but without success (Scheme 43).

The commercially available 2-chloro-6-methylaniline **(226)** was diazotized under Sandmeyer conditions, and further treatment of the diazonium salt with copper(I) cyanide gave 2-chloro-6-methylbenzonitrile **(227)**.

Nitration of the benzonitrile derivative **(227)** in concentrated sulfuric acid at 5°C afforded two isomeric nitro-substituted derivatives in which the nitro group was at 3- or 5-position. These two isomers were separated by fractional recrystallization in ethanol, which gave the desired isomer 2-chloro-5-nitro-6-methylbenzenenitrile **(228)** as a major product <70JCS(C)997>. Its characterization was supported by its ^{1}H NMR spectrum, in which the two ring protons appeared at δ=7.54ppm and δ=8.08ppm as two doublets with coupling constant J=8.8Hz, consistent with *ortho* coupling.

Attempts to hydrolyze the nitrile to the corresponding acid have not been successful. The only product so far obtained by various acidic hydrolyses was the corresponding amide **(229)**, and this could not be further hydrolyzed to the acid **(230)** under acidic conditions. Basic hydrolysis seemed unlikely to be satisfactory owing to the possible nucleophilic displacement of the chlorine. An attempted conversion of **(229)** to **(230)**, using nitrous acid (compare <32JAS(54)3438>) also failed. Conversion of the nitrile **(228)** to the methyl ester **(231)** (possibly more easily hydrolyzable) also failed.

If the acid **(230)** could have been obtained, it could have been converted to the acetyl function via the acid chloride. Activated by an *ortho* acetyl group and *para* nitro function, the chlorine should have been easily displaced by methylthio and further conversion could reach the desired system.


CH3
H2N
Cl
1) HONO / H+
2) CuCN
NC
HNO3
(226)
(227)
H2O / H+
O
CH3
NO2
H2N
Cl
(229)
(228)
(230)
HO
MeO
(231)
1) SOCl2
2) Mg / EtOH Me
DEM
MeSH / OH-
Me
MeS
(232)
(233)
1) H2NOH . HCl
2) Ac2O / Py
[H]
NH2
N
S
Singerman's
Reagent

Scheme 43

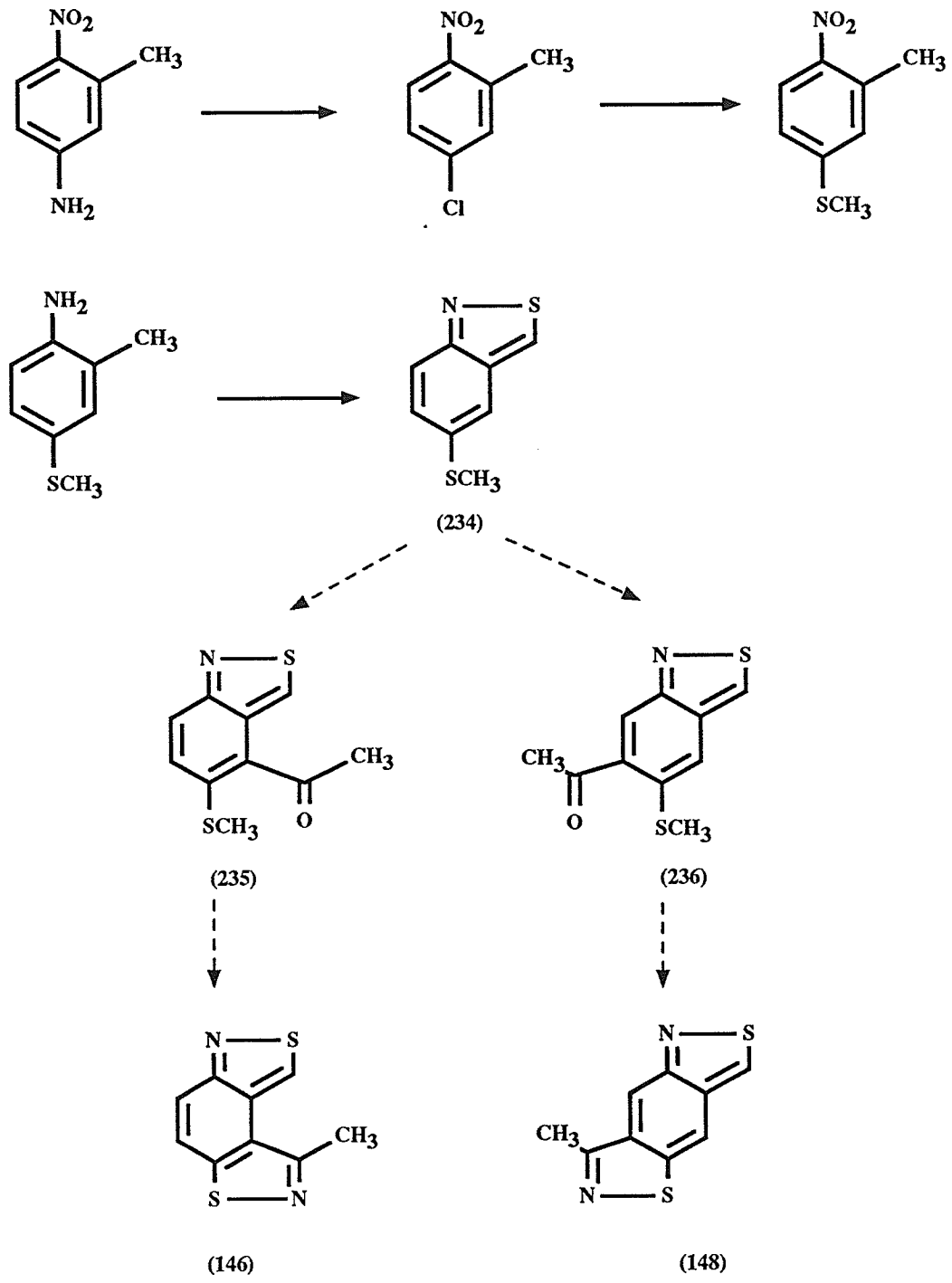
3.5 SUGGESTIONS FOR FURTHER RESEARCH

For the synthesis of the benzo[1,2-c:4,3-d]diisothiazole system, as with the benzo[1,2-c:4,5-d]diisothiazole system, the major problem is to effect the selective methanethiolate substitution of the chlorine atom on compound **(220)** rather then the nitro group. As shown, the nitro group was replaced in preference to chlorine when compound **(220)** was treated with methanethiolate. It might be possible to reduce the nitro compound to the amino compound **(223)** and then acylate to the acetamido compound **(224)** before treatment with the methanethiolate ion, as with the attempts to the [1,2-c:4,5-d] system. Thus, 4-acetamido-3-methyl-2-methylthioacetophenone **(225)** might be obtained, which would be a precursor with groups suitable for further elaboration to the two isothiazole rings, and would finally make the desired system accessible.

In the synthesis of the benzo[1,2-c:3,4-d]diisothiazole system, the main difficulty in the method investigated was the hydrolysis of the amide **(229)** to the corresponding acid **(230)**. If the acid could be obtained, synthesis of compound **(232)** should be achieved without problem. Since acid catalyzed methods appeared to be unsuccessful, perhaps basic conditions could be tried, but care would be needed to avoid nucleophilic displacement of the chlorine, as it is activated by the potential carboxylic acid (and nitro) groups. Further synthesis from **(232)** also requires the selective replacement of the chlorine by methanethiol. In this compound, the chlorine atom is activated by two electron-withdrawing groups, nitro and acetyl, at the *para* and *ortho* positions respectively, while there is no activating groups for the nitro group. Thus, the substitution by methanethiol will most likely successfully occur at chlorine rather than at the nitro group, giving the precursor **(233)**, which after two consecutive ring closures could give the benzo[1,2-c:3,4-d]diisothiazole.

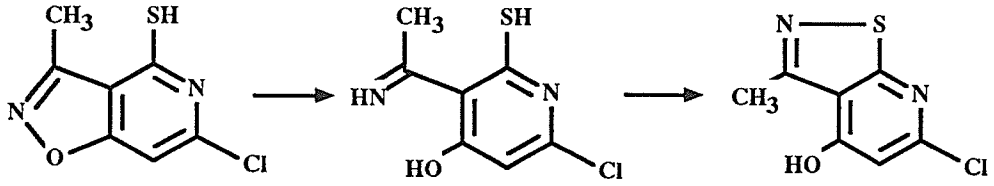
Another possible approach for this system is described in Scheme 44. The question about this approach concerns the Friedel-Crafts reaction on 5-methylthio-2,1-benzisothiazole **(234)** and the required synthesis of 5-methylthio-2,1-benzisothiazole. Although it was reported that acylation reactions on the parent compound were unsuccessful, it would be interesting to know whether they would occur on compound **(234)**, as it should be somewhat activated to electrophilic substitution by the alkylthio group. If the acetyl function could be introduced to the 4-position, then compound **(235)** would be a suitable precursor for the benzo[1,2-c:3,4-d]diisothiazole via its intermediate oxime. If the acetyl group could be introduced to the 6-position **(236)**, it would be another possible approach to the [1,2-c-5,4-d] system. Also, this would involve less steps than the synthesis reported above.

The isolation of a thiadiazole **(159)** from the amine **(158)** by reaction with N-sulfinyl methanesulfonamide deserves further investigation. Since apparently only an amine function is necessary, these conditions should be tried on simpler amines to determine the scope of the synthesis.

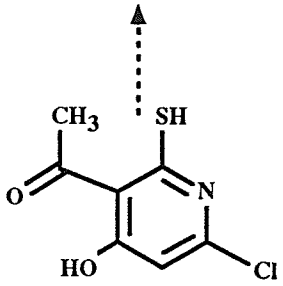

NO2
CH3
NH2
NO2
CH3
Cl
NO2
CH3
SCH3
NH2
CH3
SCH3
N
S
SCH3
(234)
N
S
CH3
O
SCH3
(235)
N
S
CH3
O
SCH3
(236)
N
S
CH3
S
N
(146)
N
S
CH3
N
S
(148)

Scheme 44

It was reported that some of the isothiazolopyridine derivatives **(239)** could be obtained from the corresponding isoxazolopyridine derivatives **(237)** by cleavage of the N-O bond and formation of the N-S bond via intermediates like **(238)** <90JCS(P1)1477>. This leads us to think that if the principle were also applied to an analogous benzenoid system, possible precursor of benzodiisothiazoles might be available from benzisoxazoles. Also, 1,2-benzisothiazoles are formed by treatment of *o*-mercaptoacetophenones with hydroxylamine O-sulfonic acid. This might give some improvements over the oxime / acetic acid / pyridine method we have used.



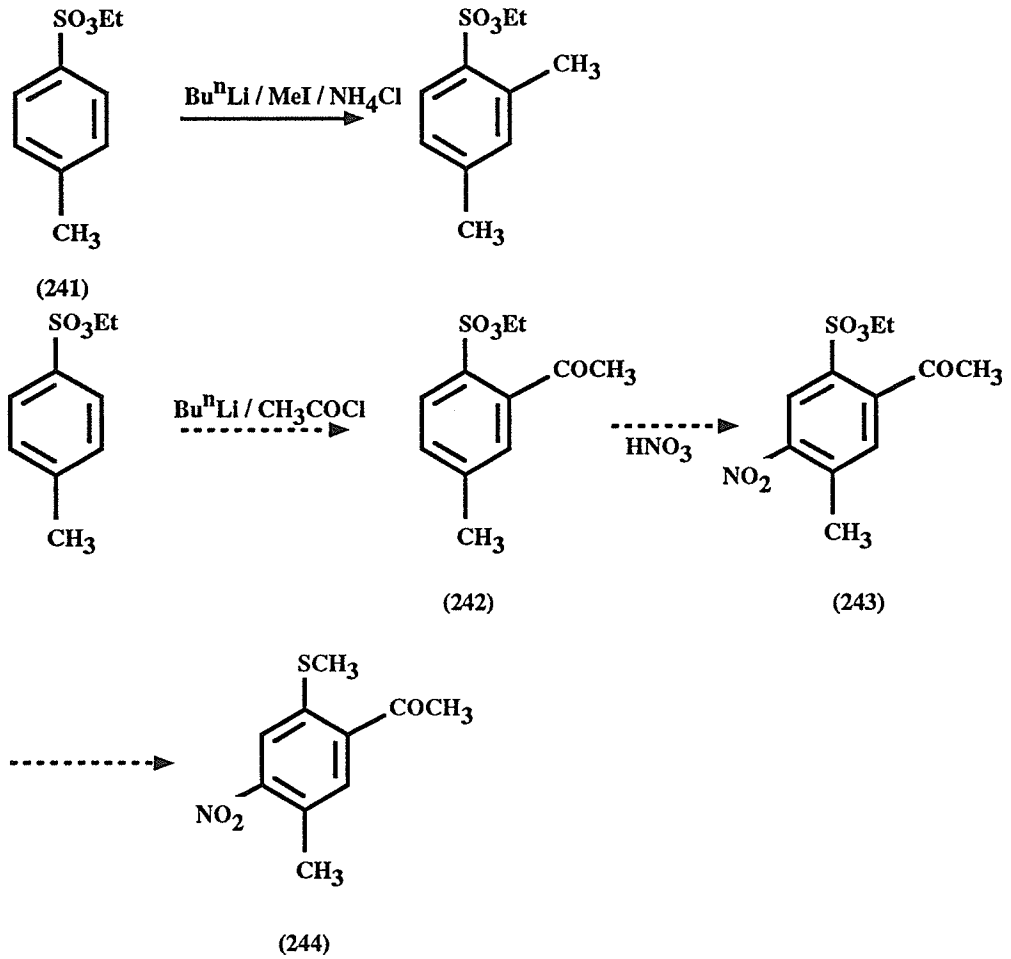
(237) **(238)** **(239)**



(240)

Another method which seems useful for our research is described in <90JCS(P1)1611>. It was reported that ethyl 4-methylbenzenesulfonate **(241)** could be lithiated at the 2-position. Subsequent treatment with methyl iodide introduced a methyl group to that position. It might be helpful to investigate this reaction following the same procedure as it was reported except

using acetyl chloride as a potential electrophile. If the acetyl function could be introduced into the 2-position, then nitration of ethyl 2-acetyl-4-methylbenzenesulfonate **(242)** probably would give compound **(243)**. The ethylsulfonate function in compound **(243)** could be eventually converted to the methylthio function by reduction and alkylation. Thus, 5-methyl-2-methylthio-4-nitroacetophenone **(244)** might be obtained which is a precursor for benzo[1,2-c:4,5-d]diisothiazole system.



3.6 CONCLUSIONS

Different approaches have been explored towards the syntheses of four isomeric benzo[c,d]diisothiazole systems **(145), (146), (147)** and **(148)**. The major approach was to synthesis various 2-methylthioacetophenones, containing also amino and methyl groups *ortho* situated to each other. The methylthio and keto groups could hopefully provide a 1,2-benzisothiazole ring, and the latter, i.e., amino and methyl groups a 2,1-benzisothiazole ring by established methods. 5-Amino-3,6-dimethyl-1,2-benzisothiazole was synthesized by a eleven-stage process from 4-methylaniline, as an approach to the benzo[1,2-c:5,4-d]-diisothiazole system, but gave 4,8-dimethylbenzisothiazolo[3,4-d:1,2-d]benzothiadiazole **(159)** as the major product by an unexpected reaction, possibly involving a pericyclic reaction. The desired benzodiisothiazole was probably produced in only trace amounts. Although the reactions of Singerman's reagent with suitable *o*-toluidines to form 2,1-benzisothiazole have been well established, we found here that the reaction could also give a benzothiadiazole derivative under these conditions.

For the synthesis of benzo[1,2-c:4,5-d]diisothiazole, the method described in Scheme 39 involves too many stages that it gave too little material of 6-amino-3,5-dimethyl-1,2-benzisothiazole. Thus, the reaction with N-sulfinylmethanesulfonamide could not be properly investigated.

Other approaches leading to benzo[1,2-c:4,3-d] and [1,2-c:3,4-d]diisothiazole systems were finally abandoned because of various problems, such as hydrolysis of the amide, displacement of the unexpected group, etc. Obviously, more work needs to be done on these systems.

It was also found that in two approaches that the nitro group is more easily displaced than chlorine under nucleophilic attack by methanethiolate. Although it has been reported that the activating effect on an *ortho* position was more powerful than that on a *para* position, it was found in this work that for the compounds **(190)** and **(220)**, the nitro group even in a *para* position to an activating group was displaced rather than chlorine situated in an *ortho* position. The reason for this facile nitro displacement is not clear, but adds to the general body of knowledge of this phenomenon.

In general, these approaches have all suffered from the length of the desired syntheses, even problems such as diazotization and conversion of the nitrile, hydrolysis of the nitrile and the amide, or displacability of groups, etc. can be solved.

4. EXPERIMENTAL

All melting points given were determined on a Reichert hot stage melting point apparatus, and are uncorrected.

All organic solutions were dried over anhydrous magnesium sulfate.

All ^1H NMR spectra were obtained in chloroform-d_3 solution (unless otherwise specified) using tetramethylsilane as an internal standard. ^1H NMR spectra were obtained on either a Varian model EM-360 spectrometer or a Bruker model AM-300 spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer model 881 spectrophotometer in Nujol mulls. Mass spectra were obtained on a V. G. model 7070E mass spectrometer.

Thick layer chromatography was performed on Merck "Kieselgel 60 PF_{254}" silica gel supplied by Terochem laboratories. Silica gel used in column chromatography was supplied by Terochem laboratories, 20-45 microns. Thin layer chromatography was performed on silica gel F_{254} supplied by Whatman Ltd.. Lithium hydroxide used was the lithium hydroxide monohydrate supplied by Fisher Scientific Company.

N-Sulfinylmethanesulfonamide was made by the method of Singerman <75JHC(12)877>.

Monoximes can exist in two geometrical forms, and dioximes in three forms. The products obtained from the oxime forming reactions in most cases appeared to be mixtures, as indicated by melting point and ^1H NMR spectra. No attempts were made to separate, or further purify them and materials were simply used in the form isolated for the next stage in the reaction.

4.1. SYNTHESIS OF BENZO[1,2-c:5,4-d]DIISOTHIAZOLE

2-Chloro-4-methylaniline (162)

2-Chloro-4-methylaniline was prepared according to the procedure described in the literature <40JAS2103>. Thus, *p*-methylacetanilide (150 g, 1.01 mol) in acetic acid (300 mL) and concentrated hydrochloric acid (450 mL) was cooled to 5°C with stirring. To it was added slowly a solution of sodium chlorate (45 g, 0.42 mol) in water (60 mL), maintaining the temperature at 5°C. After introducing all of the sodium chlorate, the mixture was allowed to stand for 0.5 h with stirring and then refluxed for two hours after which it was steam distilled to remove oily material and acetic acid. The residue was made basic to liberate the amine. The mixture was steam distilled, extracted with ether, the distillate saturated with salt and then extracted with ether. The ether was dried and evaporated, and the residue distilled. The colorless amine was collected at b.p. 220-225°C. yield = ~63%

2-Chloro-4-methyl-acetophenone (150) (By a Beech Reaction)

2-Chloro-4-methylaniline (36 g, 0.25 mol) was dissolved in concentrated hydrochloric acid (57 mL) and water (50 mL), then sodium nitrite (17.5 g, 0.25 mol) in water (25 mL) was added slowly at 0°C with stirring. Sodium acetate (22 g) was added to neutralize the acid and the mixture was then run below the surface of a stirred solution of acetaldoxime (22.5 g, 0.38 mol) [made from acetaldehyde (22 g, 0.5 mol) and hydroxylamine hydrochloride (35 g, 0.5 mol) in water (75 mL) with sodium hydroxide (20 g)], cupric sulfate (12.5 g), sodium sulfite (1.0 g) and sodium acetate (165 g) at 15°C. The mixture was left at room temperature for 16 h, then the aqueous solution was decanted off, and concentrated hydrochloric acid (200 mL) was added. The mixture was refluxed for 2 h, and steam distilled to give ~18 g of oily material which was then fractionally distilled collecting a fraction that boiled at 148-152°C/1mmHg to

give 8 g of the ketone.

2-Chloro-4-methylbenzenenitrile (163)

2-Chloro-4-methylaniline (30 g, 0.213 mol) was dissolved in water (65 mL) with concentrated sulfuric acid (25 mL) and diazotized with sodium nitrite (14.2 g, 0.206 mol) in water (20 mL) at 0°C. After the diazotization, the mixture was added with stirring below the surface of a warm solution of copper(I) cyanide dissolved in potassium cyanide (32 g) and water (100 mL) prepared as below. It was allowed to stand on a steam bath for 0.5 h. After cooling to room temperature, it was extracted with ethyl acetate. Evaporation of the solvent gave a reddish sticky solid which was then dissolved in ethanol and treated with charcoal and boiled for another 0.5 h. The charcoal was filtered off and the filtrate was concentrated. An orange crystalline solid was deposited from the solution and was collected. m.p. 56-58°C (lit. m.p. 61-2°C) yield = 25 g = 78%

^{1}H NMR spectrum: δ:2.43(3H, s, 4-methyl protons), 7.15(1H, d, J=8Hz, C-5 aromatic proton), 7.33(1H, d, J=8Hz, C-6 aromatic proton), 7.33(1H, s, C-3 aromatic proton)

IR spectrum: 2232cm^{-1}(-C≡N str.)

Preparation of copper(I) cyanide

Hydrated copper sulfate ($CuSO_4.5H_2O$) (64 g, 0.256 mol) was dissolved in water (200 mL), acidified with concentrated sulfuric acid (2.5 mL) and to it was added a solution of sodium bisulfite (17.6 g, 0.165 mol) in water (48 mL). A solution of potassium cyanide (17.6 g) in water(48 mL) was added slowly with stirring. The white precipitate was filtered off and dissolved in a solution of potassium cyanide (32 g) and water (100 mL). It was then sealed and kept for later use. Usually, it was used within 24 h.

2-Chloro-4-methyl-benzamide (164)

2-Chloro-4-methylbenzenenitrile (11.7 g, 0.077 mol) was dissolved in concentrated sulfuric acid (25 mL) and heated on a steam bath for 15 min. The mixture was cooled and poured over ice. The white precipitate was filtered off, dried, and recrystallized from ethanol as off-white needles. m.p. 180°C (lit. m.p. 182°C) (yield = 11.8 g = 90%) It was used in the next stage without further purification.

^{1}H NMR spectrum: δ:2.38(3H, s, 4-methyl protons), 7.15(1H, d, J=8Hz, C-5 aromatic proton), 7.75(1H, d, J=8Hz, C-6 aromatic proton), 7.25(1H, s, C-3 aromatic proton)

IR spectrum: 3366cm^{-1}, 3177cm^{-1} (-NH_2 str.), 1651cm^{-1}(C=O str.)

2-Chloro-4-methylbenzoic acid (165)

Crude 2-chloro-4-methylbenzamide (11.8 g, 0.069 mol) was dissolved in 30% sulfuric acid (50 mL) and heated under reflux for 3 h. After cooling to room temperature, the white precipitate was filtered off and dried. Recrystallization from ethanol gave colorless needles. m.p. 154-156°C (lit. m.p. 155-7°C) yield = 10.4 g = 88%

^{1}H NMR spectrum: δ:2.38(3H, s, 4-methyl protons), 7.13(1H, d, J=8Hz, C-5 aromatic proton), 7.93(1H, s, J=8Hz, C-6 aromatic proton), 7.29(1H, s, C-3 aromatic proton), 10.9(1H, s, acidic proton)

2-Chloro-4-methylbenzoyl chloride (166)

Crude 2-chloro-4-methylbenzoic acid (10.7 g, 0.0629 mol) was dissolved in dry benzene (50 mL) and thionyl chloride (25 mL) was added. The mixture was heated under reflux overnight.

Benzene and excess thionyl chloride were removed by evaporating under reduced pressure and the acid chloride was obtained as an oil. (yield = 11.8 g = 99%) The compound was used in the next stage without further purification.

2-Chloro-4-methylacetophenone (150)

In a three-neck flask, magnesium turnings (3.1 g, 0.129 mol) were mixed with anhydrous ethanol (9 mL), dry benzene (100 mL) and a catalytic amount of iodine. The mixture was warmed to initiate the reaction, then a mixture of diethyl malonate (20.4 g, 0.128 mol), anhydrous ethanol (10 mL) in dry benzene (50 mL) was added dropwise. Reflux was continued until all of the magnesium turnings had dissolved. The condenser was removed and the excess ethanol was evaporated. Then a solution of the acid chloride (11.5 g, 0.061 mol) in benzene (20 mL) was added dropwise with stirring. The mixture was heated under reflux for 16 h. After cooling, 10% sulfuric acid (100 mL) was added and the mixture was stirred under reflux for another 15 min. The oily layer was separated and the aqueous layer extracted with dichloromethane. The organic layers were combined and evaporated giving a reddish oil. A mixture of glacial acetic acid (30 mL), concentrated sulfuric acid (3 mL) and water (10 mL) was added after which it was refluxed for 6 h. It was then cooled and poured into ice/water, and extracted with dichloromethane. Evaporation of the organic solvent gave a yellow oil which was not further purified. (lit. b.p.260-2°C) <16B(49)2222> yield = 8.64 g = 84%

^{1}H NMR spectrum: δ:2.30(3H, s, 4-methyl protons), 2.58(3H, s, acetyl methyl protons), 7.06(1H, d, J=8Hz, C-5 aromatic proton), 7.46(1H, d, J=8Hz, C-6 aromatic proton), 7.17(1H, s, C-3 aromatic proton)

IR spectrum: 1710cm^{-1}(C=O str.)

2-Chloro-4-methyl-5-nitroacetophenone (153)

2-Chloro-4-methylacetophenone (8.64 g, 0.051 mol) was dissolved in concentrated sulfuric acid (20 mL) and cooled in an ice bath to <5°C. Nitric acid (70%) (4.6 g, 0.051 mol) in concentrated sulfuric acid (20 mL) was added dropwise to the stirred mixture and the temperature was kept below 5°C. After introducing all of the nitric acid, the reaction mixture was stirred at room temperature for another 2 h. The solution was poured into ice/water to give a semi-solid yellow precipitate. Extraction with dichloromethane and evaporation of the solvent gave a thick oil.(yield = 7.8 g = 71%)

^{1}H NMR spectrum: δ:2.64(3H, s, 4-methyl protons), 2.69(3H, s, acetyl methyl protons), 7.43(1H, s, C-3 aromatic proton), 8.23(1H, s, C-6 aromatic proton)

MS: $C_9H_8ClNO_3$ requires 214, found: m/z 214(20), 199 (100, -CH_3), 184 (15, -CH_3)

4-Methyl-2-methylthio-5-nitroacetophenone (154)

2-Chloro-4-methyl-5-nitroacetophenone (5.8 g, 0.027 mol) was dissolved in DMF (20 mL). To it was added lithium hydroxide (1.14 g, 0.027 mol) and methanethiol (~2 mL). The mixture was left at room temperature for 16 h. It was then poured over ice/water and left at room temperature for 1 h. The precipitate was filtered off and recrystallized from ethanol to give the product as yellow needles. (yield = 4.5 g = 73%)

^{1}H NMR spectrum: δ:2.51(3H, s, S-methyl protons), 2.68(3H, s, 4-methyl protons), 2.74(3H, s, acetyl methyl protons), 7.23(1H, s, C-3 aromatic proton), 8.66(1H, s, C-6 aromatic proton)

IR spectrum: 1673cm^{-1}(C=O str.)

MS: $C_{10}H_{11}NO_3S$ requires 225, found: m/z 225(32), 210(100, -CH_3)

4-Methyl-2-methylthio-5-nitroacetophenone oxime (155)

To the ketone (0.38 g, 1.7 mmol) in ethanol (10 mL) and pyridine (1 mL) was added hydroxylamine hydrochloride (0.38 g, 0.0055 mol) and the solution refluxed for 2 h. The mixture was then poured into ice/water and the precipitate was collected and recrystallized from ethanol. (yield = 0.33 g = 81%) The material was used in the next stage without further purification.

3,6-Dimethyl-5-nitro-1,2-benzisothiazole (157)

The crude oxime (0.33 g, 1.4 mmol) in acetic anhydride (1 mL) and pyridine (5 mL) was heated under reflux for 18 h. The mixture became dark. After pouring into ice/water, the precipitate was collected and treated with charcoal. Recrystallization from ethanol gave light brown needles. m.p. 166-167°C (yield = 0.24 g = 80%)

^{1}H NMR spectrum: δ:2.75(3H, s, 6-methyl protons), 2.78(3H, s, 3-methyl protons), 7.83(1H, s, C-7 aromatic proton), 8.57(1H, s, C-4 aromatic proton)

IR spectrum: 1607cm^{-1}(C=N str.), 1515cm^{-1}

MS: $C_9H_8N_2O_2S$ requires 208, found: m/z 208(15), 191(100)

5-Amino-3,6-dimethyl-1,2-benzisothiazole (158)

3,6-Dimethyl-5-nitro-1,2-benzisothiazole (0.1 g, 0.48 mmol) was added slowly to a solution of stannous chloride (0.5 g, 2.22 mmol) in concentrated hydrochloric acid (2 mL) and the mixture warmed on a steam bath for 1 h. The mixture was diluted with water and neutralized with a solution of sodium hydroxide and then extracted with chloroform. Evaporation of the organic layer gave the desired amine as pale yellow needles. m.p. 193-195°C. This was used in the next stage without further purification.

^{1}H NMR spectrum: δ:2.33(3H, s, 6-methyl protons), 2.62(3H, s, 3-methyl protons), 3.77(2H, s, amino protons), 7.13(1H, s, C-7 aromatic proton), 7.57(1H, s, C-4 aromatic proton)

IR spectrum: 3422cm^{-1}, 3340cm^{-1}(-NH_2 str.)

MS: 178(100), 163(11, -CH_3)

Accurate mass calcd. for $C_9H_{10}N_2S$: 178.0565, found: 178.0568

4,8-Dimethylbenzisothiazole[3,4-d:1,2-d]benzothiadiazole (159)

To a ice-cooled solution of 5-amino-3,6-dimethyl-1,2-benzisothiazole (0.1 g, 5.6×10^{-4} mol) in dry benzene (10 mL) was added a solution of N-sulfinylmethanesulfonamide (0.3 g, 0.002 mol) in dry benzene (2 mL) with stirring. Then pyridine (0.2 g, 0.002 mol) in dry benzene (2 mL) was added to the chilled mixture. A white precipitate was formed at this stage. The mixture was stirred and heated under reflux for 18 h. The benzene and pyridine were removed from the reaction mixture by evaporation under reduced pressure. The residue was cooled in an ice-bath and diluted with water (1 mL), The mixture was allowed to stand at room temperature for 30 min and then extracted with chloroform. Evaporation of the organic solvent gave a yellow crystalline material. It was purified by preparative thick layer chromatography using 1:1 hexane:ethyl acetate as eluent. The major component was found to have m.p. 128-130°C. (yield = 0.06 g = 48%)

^{1}H NMR spectrum: δ:2.81(3H, s, 4-methyl protons), 3.13(3H, s, 8-methyl protons), 7.79(1H, s, C-3 aromatic proton)

MS: m/z 221(17), 206 (4, -CH_3), 178(39)

accurate mass found for $C_9H_7N_3S_2$: 221.0089, calcd.: 221.0081

^{13}C NMR spectrum: 1°C: 18.527(C-4 or C-8 methyl carbon), 19.664(C-8 or C-4 methyl

carbon) 3°C: 120.011(C-7) 4°C: 124.811(C-4a), 131.606(C-8), 150.560(C-6a), 155.078(C-1a or C-3a or C-4), 157.738(C-1a or C-3a C-4), 164.332(C-1a or C-3a or C-4)

Acetylation of 3-chlorotoluene (150), (151)

Acetylation was carried out according to the literature procedure described by Ishikawa <85CPB(33)2809>. 3-Chlorotoluene (64.32 g, 0.5 mol) was mixed with acetyl chloride (51 g, 0.65 mol) in dichloromethane (200 mL). To it, aluminum chloride (67 g, 0.5 mol) was added slowly with stirring. The mixture was allowed to stand at room temperature for 72 h. The color gradually darkened. After pouring over ice, it was extracted with dichloromethane. The organic layer was dried and the solvent was evaporated. The residue was then distilled at 100-110°C/8mmHg. (yield = 70 g = 82%) This was a mixture of 2-chloro-4-methyl-acetophenone and 4-chloro-2-methylacetophenone. This was taken to the next stage without further isolation and identification.

Nitration of the mixture of 2-chloro-4-methylacetophenone

The mixture of of acetophenones (see above) (34 g, 0.2 mol) was dissolved in concentrated sulfuric acid (100 mL), and cooled in an ice-salt bath to <5°C. Concentrated nitric acid (70%) (18 g, 0.2 mol) in concentrated sulfuric acid (20 mL) was added slowly with stirring while the temperature was kept below 10°C. The mixture was allowed to stand overnight at room temperature. After pouring into ice/water, the precipitate was collected. Fractional crystallization from ethanol gave pale yellow needles. (m.p. 50-55°C)

^{1}H NMR spectrum: δ:2.59(3H, s, 2-methyl protons), 2.62(3H, s, acetyl methyl protons), 7.47(1H, s, C-3 aromatic proton), 8.28(1H,s, C-6 aromatic proton)

IR spectrum: 1710cm^{-1}(C=O str.)

2-Chloro-4-methyl-5-nitroacetophenone was eventually obtained as a crude yellowish oil (from the mother liquors of the above crystallizing solution). It appeared to have virtually identical spectroscopic properties.

3-Amino-4-methylbenzonitrile (168)

This was made according to the procedure described in literature <1894B(27)2161>. Thus, 3-nitro-4-methylbenzonitrile (0.4 g, 0.002 mol) was treated with tin (0.5 g, 0.004 mol) in concentrated hydrochloric acid (2 mL) and the mixture was warmed on a steam bath for 1.5 h. It was diluted with a large amount of water and basified by addition of a solution of sodium hydroxide. The tin oxide formed during neutralization was filtered off and washed with ether. The filtrate was extracted with ether and after drying and evaporation of the solvent, colorless prisms were obtained. m.p. 80-81°C (lit. m.p. 81-82°C) (yield = 0.2 g = 61%)

^{1}H NMR spectrum: δ:2.20(3H, s, methyl protons), 4.72(2H, s, amino protons), 6.88(1H, d, J=9.2Hz, C-3 aromatic proton), 7.15(1H, d, J=9.2Hz, C-4 aromatic proton), 6.97(1H, s, C-6 aromatic proton)

IR spectrum: 3385cm^{-1}, 3485cm^{-1}(-NH_2 str.), 2230cm^{-1}(-CN str.)

MS: $C_8H_8N_2$ requires 132, found: m/z 132(87), 131(100)

3-Amino-4-methyl-6-thiocyanatobenzonitrile (169)

The thiocyanation of 3-amino-4-methylbenzonitrile **(168)** was performed by the method described by Kaufmann <29B(62)390>. 3-amino-4-methylbenzonitrile (0.2 g, 0.0015 mol) was treated with sodium thiocyanate (0.4 g, 0.005 mol) in methanol (5 mL) and cooled in an ice bath to 5°C. Bromine (0.26 g, 0.0016 mol) in methanol (2 mL), saturated with sodium

bromide, was added slowly with stirring. The reaction mixture was poured into water (60 mL) and neutralized with potassium carbonate. The product separated as pale yellow crystals which were collected and recrystallized from ethanol. m.p. 126-128°C (yield = 0.2 g = 70%)

^{1}H NMR spectrum: δ:2.27(3H,s, methyl protons), 5.19(2H, s, amino protons), 7.15(1H, s, C-3 or C-6 aromatic proton), 7.50(1H, s, C-6 or C-3 aromatic proton)

IR spectrum: 3480cm^{-1}, 3385cm^{-1}(-NH_2 str.), 2230cm^{-1}(SC≡N str.), 2310cm^{-1}(C≡N str.)

MS: $C_9H_7N_3S$ requires 189, found: m/z 189(14), 166(60), 131(100)

Reduction of 3-amino-4-methyl-6-thiocyanatobenzonitrile to 5-amino-2-mercapto-4-methylbenzylamine (170)

5-Cyano-2-methyl-4-thiocyanoaniline (0.2 g, 0.0011 mol) was dissolved in dry ether and lithium aluminum hydride (0.06 g, 0.0015 mol) was added. The reaction mixture was heated under reflux for 18 h. Ethyl acetate was added to decompose the excess lithium aluminum hydride. The mixture was diluted with water and the aluminum oxides were filtered off. The filtrate was extracted with ether and after evaporation of the organic solvent, bright yellow crystals were obtained. Examination of the thin layer chromatography showed that it was the unreacted starting material. Due to the difficulty of reduction, this approach was not further investigated.

4.2. SYNTHESIS OF BENZO[1,2-c:4,5-d]DI-ISOTHIAZOLE

2,4-Dimethyl-5-nitroaniline (172)

2,4-Dimethylaniline **(171)** (4.4 g, 0.036 mol) was dissolved in concentrated sulfuric acid (65 mL) and cooled to -10°C with dry ice in acetone. Nitric acid (70%) (3.2 g, 0.072 mol) in sulfuric acid (10 mL) was added with stirring. The temperature was kept <-5°C. After the addition of all of the nitric acid, the reaction mixture was allowed to stand until it warmed to room temperature. It was then diluted with ice/water and neutralized with sodium hydroxide to pH=8. An orange crystalline precipitate separated and was collected. Recrystallization from ethanol gave orange prisms. m.p.123°C (lit. m.p. 123°C) yield = 4.2 g = 70%

^{1}H NMR spectrum: δ:2.17(3H, s, C-2 methyl protons), 2.46(3H, s, C-4 methyl protons), 3.75(2H, s, amino protons), 6.70(1H, s, C-3 aromatic proton), 7.32(1H, s, C-6 aromatic proton)
IR spectrum: 3470cm^{-1}, 3387cm^{-1}(-NH_2 str.)
MS: $C_8H_{10}N_2O_2$ requires 166, found: 166(100), 149(64), 121(73)

1-Chloro-2,4-dimethyl-5-nitrobenzene (173)

2,4-Dimethyl-5-nitroaniline **(172)** (3.92 g, 0.024 mol) was dissolved in concentrated hydrochloric acid (6 mL) and water (6 mL) and the mixture was cooled to 0°C in an ice-salt bath with vigorous stirring. A solution of sodium nitrite (1.7 g, 0.024 mol) in water (3.6 mL) was added slowly. After introducing all of the nitrite solution, the reaction mixture was allowed to stand in ice-salt bath for another 0.5 h. The cold solution of diazonium salt was poured slowly with stirring into the cold solution of cuprous chloride in concentrated hydrochloric acid (8 mL) (For the method of preparing fresh cuprous chloride, see below.) The reaction mixture was allowed to warm to room temperature. Nitrogen was liberated during this

warming. It was then extracted with dichloromethane and the organic layer was boiled with charcoal. After filtering off the charcoal, the organic solvent was evaporated to give a dark brown oil. This was used without further purification. yield = 3.4 g = 78%

^{1}H NMR spectrum: δ:2.40(3H, s, 3-methyl protons), 2.53(3H, s, 1-methyl protons), 7.15(1H, s, C-2 aromatic proton), 7.91(1H, s, C-5 aromatic proton)

IR spectrum: 3111cm^{-1}(Ph-H str.), 1610cm^{-1}, 1474cm^{-1} (C=C aromatic str.), 1552cm^{-1}, 1357cm^{-1} (N=O str.)

Preparation of Cuprous Chloride (CuCl)

Hydrated copper sulfate ($CuSO_4.5H_2O$) (7.5 g, 0.03 mol) and sodium chloride (2.0 g, 0.034 mol) were dissolved in water (24 mL) and the solution was warmed on a steam bath. A solution of sodium bisulfite (1.6 g, 0.015 mol) and sodium hydroxide (1.05 g, 0.026 mol) in water (12 mL) was added to the warm solution with stirring. The reaction mixture was cooled to room temperature and the liquid was decanted from the white precipitate of cuprous chloride. The precipitate was washed twice with water containing a small amount of sulfurous acid to prevent further oxidation. The moist cuprous chloride was dissolved in 12 mL of concentrated hydrochloric acid. It was stoppered and kept in a freezer for later use. Usually it was used within 24 h.

4-Chloro-2-nitro-1,5-benzenedicarboxylic acid (174)

4-chloro-1,5-dimethyl-2-nitrobenzene **(173)** (3 g, 0.016 mol) was treated with potassium permanganate (24 g, 0.152 mol) and sodium hydroxide (3 g, 0.075 mol) in water (450 mL). The reaction mixture was stirred under reflux for 18 h after which ~10 mL of ethanol was added to destroy the excess potassium permanganate, and the manganese dioxide was removed

by filtering. The filtrate was acidified with hydrochloric acid and concentrated by evaporation of the water. It was then cooled in an ice/water bath and a colorless crystalline product precipitated. This was filtered off and used in the next stage without further purification or identification. (yield = 2.1 g = 53%)

4-Chloro-2-nitro-1,5-benzene-dicarbonylchloride (175)

The diacid **(174)** (10 g, 0.04 mol) in benzene (40 mL) and thionyl chloride (20 mL) was heated under reflux for 24 h. The benzene and excess thionyl chloride were evaporated under reduced pressure and a pale yellow oil was obtained. This was used in the next stage without further purification or identification.

^{1}H NMR spectrum: δ:8.19(1H, s C-3 aromatic proton), 8.50(1H, s, C-6 aromatic proton)

1.5-Diacetyl-4-chloro-2-nitrobenzene (176)

The crude diacid chloride **(175)** (2.7 g, 0.01 mol) in benzene (10 mL) was added with stirring to the solution of ethoxymagnesium malonate which was prepared from magnesium turnings (1 g, 0.042 mol), anhydrous ethanol (6 mL) and diethyl malonate (6.7 g, 0.042 mol) according to the procedure described for the preparation of 2-chloro-4-methylacetophenone. Following the same procedure as described there, a pale yellow crystalline product was obtained. It was purified by recrystallization from benzene. m.p. 87-89°C (yield = 0.8 g = 94%)

^{1}H NMR spectrum: δ:2.55(3H, s, 5-acetyl methyl protons), 2.70(3H, s, 1-acetyl methyl protons), 7.58(1H, s, C-3 aromatic proton), 8.11(1H, s, C-6 aromatic proton)

IR spectrum: 1710cm^{-1}(C=O str.)

MS: m/z 241(2), 226(100)

Accurate mass found for $C_{10}H_8{}^{35}ClNO_4$: 241.0120, cald.: 241.0098

Attempted reduction of 1,5-diacetyl-4-chloro-2-nitrobenzene (176) with sodium hydrosulfite

Using the method described <70T(26)1085>, a solution of 1,5-diacetyl-4-chloro-2-nitrobenzene **(176)** (0.4 g, 0.0017 mol) in ethanol (15 mL) was warmed to 60°C. A solution of sodium hydrosulfite (0.18 g, 0.001 mol) in water (12.5 mL) was added to it. The reaction mixture was kept at 60-70°C for 30 min, after which, it was diluted with water. Extraction with dichloromethane and evaporation of the organic solvent gave a yellow solid. ^{1}H NMR spectrum and thin layer chromatography indicated that the starting material was recovered.

Attempted reduction of 1,5-diacetyl-4-chloro-2-nitrobenzene with zinc and acetic acid

1,5-Diacetyl-4-chloro-2-nitrobenzene (0.3 g, 0.0012 mol) was treated with zinc (0.16 g, 0.0025 mol) and acetic acid (10 mL) and the reaction mixture was heated under reflux for 18 h after which it was poured into ice/water. The precipitate obtained was collected and recrystallized from benzene to give a yellow crystalline product whose ^{1}H NMR spectrum and thin layer chromatography indicated that the starting material had been recovered.

Attempted reduction of 1,5-diacetyl-4-chloro-2-nitrobenzene with tin/hydrochloric acid/acetic acid

Using the type of procedure described <66T(S)49>, 1,5-diacetyl-4-chloro-2-nitrobenzene (0.14 g, 0.58 mmol) in 10 M hydrochloric acid (1 mL) and acetic acid (1 mL) was treated with tin (0.12 g, 0.001 mol) and the reaction mixture was heated under reflux for 2 h after which water was added and the mixture neutralized with sodium carbonate. The solution was then extracted with ether and evaporation of the organic solvent under reduced pressure gave a pale yellow

crystalline solid. m.p. 165-170°C Examination of the mass spectrum and ^{1}H NMR spectrum confirmed that it was 2-amino-4-chloro-1,5-diacetylbenzene.

^{1}H NMR spectrum: δ:2.59(3H, s, 1-acetyl methyl protons), 2.64(3H, s, 5-acetyl methyl protons), 6.69(1H, s, C-3 aromatic proton), 7.28(1H, s, C-6 aromatic proton), 6.70(2H, s, amino protons)

IR spectrum: 3396cm^{-1}, 3290cm^{-1}(-NH_2 str.), 1654cm^{-1}(C=O str.)

MS: m/z 211(33), 196(100)

Accurate mass found for $C_{10}H_{10}{}^{35}ClNO_2$: 211.0403, calcd. 211.0395

Attempted reduction of 4-chloro-1,5-diacetyl-2-nitrobenzene by triethylphosphite

4-Chloro-1,5-diacetyl-2-nitrobenzene (0.5 g, 0.021 mol) in ethanol (5 ml) was heated to reflux with triethylphosphite (5 ml) for 6 h after which it was poured into ice/water and allowed to stand for 1 h to hydrolyze the excess ester. Steam distillation was applied on the reaction mixture. Examination of the ^{1}H NMR spectrum of the product indicated that the starting material had been recovered.

Attempted reduction of 4-chloro-1,5-diacetyl-2-nitrobenzene by stannous chloride and hydrochloric acid (178)

The method described was used <47JAS(69)1910>. The diketone (0.5 g, 0.0021 mol) was added in small portions to a warm solution of stannous chloride (2.3 g, 0.012 mol) in concentrated hydrochloric acid (5.7 ml) with stirring. After all of the diketone had been introduced into the solution, it was left at room temperature for 2 h. During this time, a pale yellow precipitate separated from the reaction mixture. It was collected and recrystallized from ethanol to give pale yellow needles. m.p. 165-170°C (yield = 0.43 g = 99%)

^{1}H NMR spectrum: δ:2.59(3H, s, 1-acetyl methyl protons), 2.64(3H, s, 5-acetyl methyl protons), 6.69(1H, s, C-3 aromatic proton), 8.29(1H, s, C-6 aromatic proton)

IR spectrum: 3396cm^{-1}, 3290cm^{-1}(-NH_2 str.), 1654cm^{-1}(C=O str.)

MS: $C_{10}H_{10}{}^{35}ClNO_2$ requires 211, found: m/z 211(33.7), 196(100, -CH_3)

Attempted cyclization of 2-amino-4-chloro-1,5-diacetylbenzene to 5-acetyl-6-chloro-3-methylanthranil

The crude amine (0.12 g, 0.57 mmol) was diazotized at 0°C in a mixture of sulfuric acid (0.5 mL) and acetic acid (1 mL) by addition of sodium nitrite (0.1 g, 1.4 mmol) in water (0.5 mL). The reaction mixture was stirred until the solution became clear (~15 min). Sodium azide (0.2 g, 0.003 mol) in water (0.8 mL) was added with stirring. Nitrogen gas was liberated and after dilution with water, a pale yellow precipitate was collected. It was converted directly without purification into the anthranil by refluxing in acetic acid for 20 min. This solution was cooled, diluted with water and the precipitate filtered off and recrystallized from ethanol.

^{1}H NMR spectrum: δ:2.60(3H, s), 7.69(1H, s), 8.08(1H, s)

MS: $C_{10}H_8{}^{35}ClNO_2$ requires 209, found: m/z 211(32), 196(100, -CH_3)

2-Amino-1,5-diacetyl-4-methylthiobenzene (180)

2-Amino-4-chloro-1,5-diacetophenone (0.5 g, 0.0024 mol) was dissolved in N,N-dimethyl formamide (10 mL) with lithium hydroxide (0.1 g, 0.0024 mol) and ~1 mL methyl mercaptan, and the reaction mixture left at room temperature for 2 h. It was poured into ice/water and left at room temperature for another 1 h. The pale yellow precipitate was filtered off and recrystallized from ethanol. m.p. 168-173°C (yield = 0.48 g = 91%)

^{1}H NMR spectrum (in aceton-d_6): δ:2.38(3H, s, S-methyl protons), 2.58(3H, s, 1-acetyl methyl protons), 2.61(3H, s, 5-acetyl methyl protons), 6.38(1H, s, C-3 aromatic proton), 8.34(1H, s, 6-aromatic proton), 6.84(2H, s, broad, amino protons)

IR spectrum: 3436cm^{-1}, 3315cm^{-1}(-NH_2 str.)

MS: $C_{11}H_{13}NO_2S$ requires 223, found: m/z 223(28), 208(100, -CH_3)

2-Amino-1,5-diacetyl-4-methylthiobenzene dioxime

To 2-amino-1,5-diacetyl-4-methylthio (0.1 g, 0.45 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (0.063 g, 0.009 mol) and pyridine (1 mL). The mixture was heated under reflux for 2 h after which the ethanol was evaporated and the pale yellow precipitate which formed upon the addition of water were collected and dried. The dioxime obtained was used in the next stage without further purification.

MS: $C_{11}H_{15}N_3O_2S$ requires 253, found: m/z 253(8), 236(10, -OH), 221(83, -CH_3), 204(95, -OH)

Attempted cyclization of 2-amino-1,5-diacetyl-4-methylthiobenzene dioxime

Crude dioxime (0.1 g, 0.4 mmol) was treated with pyridine (5 mL) and acetic anhydride (0.5 mL) and heated under reflux for 24 h after which water was added. Dilute hydrochloric acid was added until the odor of pyridine was not detectable. The solution was then extracted with dichloromethane. Evaporation of the solvent gave a thick brown oil. Examination by thin layer chromatography showed that it was a complex mixture. This was not further separated or characterized.

4-Chloro-3-nitrotoluene (184)

The title compound was prepared following a literature procedure by diazotization of the corresponding 2-nitro-4-methylaniline (17.8 g, 0.12 mol) which is commercially available. <POC(III)190, 600> yield = 15.5 g = 91%

^{1}H NMR spectrum: δ:2.43(3H, s, methyl protons), 7.45(2H, s, C-5, C-6 aromatic protons), 7.72(1H, s, C-2 aromatic proton)

IR spectrum: 3074cm^{-1} (=C-H str.), 1559cm^{-1}, 1356cm^{-1} (N=O str.)

2-Chloro-5-methylaniline (185)

4-Chloro-3-nitrotoluene (17.2 g, 0.1 mol) and tin (20 g, 0.17 mol) in concentrated hydrochloric acid (50 mL) were heated under reflux for 2 h. A solution of sodium hydroxide was added until pH=9 to liberate the amine, after which the tin oxide, formed during the neutralization, was filtered off and washed with dichloromethane. The filtrate was extracted with dichloromethane and evaporated to give a brown oil which gradually crystallized. m.p. 28-29°C (lit. m.p. 29-30°C) yield = 13.8 g= 97%

^{1}H NMR spectrum: δ:2.15(3H, s, 5-methyl protons), 3.86(2H, s, amino protons), 6.41(1H, d, J=8Hz, C-4 aromatic proton), 7.05(1H, d, J=8Hz, C-3 aromatic proton), 6.45(1H, s, C-6 aromatic proton)

IR spectrum: 3476cm^{-1}, 3377cm^{-1} (-NH_2 str.)

2-Chloro-5-methylacetanilide

2-chloro-5-methylaniline (13.8 g, 0.098 mol) was dissolved in acetic anhydride (20 mL) and

warmed on a steam bath for 10 min. Water (~5 mL) was added to decompose the excess acetic anhydride. After heating for 5 min, the mixture was poured into ice/water and the light brown precipitate which separated was collected, washed with water and recrystallized from ethanol to give colorless needles. m.p. 92-93°C (lit. m.p. 93-94°C) <1886B(19)2438> yield = 15.2 g = 85%.

2-Chloro-5-methyl-4-nitroacetanilide

2-Chloro-5-methylacetanilide (9 g, 0.049 mol), dissolved in acetic acid (10 mL) and concentrated sulfuric acid (50 mL), was cooled in ice-salt bath to <5°C. Nitric acid (70%) (4.4 g, 0.049 mol) was added slowly with stirring and the temperature was kept <5°C. After all of the nitric acid had been introduced, the reaction mixture was allowed to stand at room temperature with stirring for 18 h after which it was poured into ice/water and precipitate collected. Recrystallization from ethanol gave pale yellow prisms. m.p. 128-130°C (lit. m.p. 134-5°C) yield = 7.4 g = 66%

^{1}H NMR spectrum: δ:2.38(3H, s, 5-methyl protons), 2.68(3H, s, acetyl methyl protons), 7.80(1H, s, N-proton), 8.16(1H, s, C-6 aromatic proton), 8.47(1H, s, C-3 aromatic proton)

IR spectrum: 3382cm^{-1} (-NH str.), 1708cm^{-1} (C=O str.)

MS: $C_9H_9{}^{35}ClN_2O_3$ requires 228, found: m/z 228(21), 193(66, -CH_3), 186(77), 169(100)

2-Chloro-5-methyl-4-nitroaniline (186)

2-Chloro-5-methyl-4-nitroacetanilide (22.3 g, 0.12 mol), dissolved in ethanol (40 mL) and concentrated hydrochloric acid (40 mL), was heated under reflux for 4 h. After cooling, water, and then a solution of sodium hydroxide was added to liberate the amine. The yellow precipitate was collected and recrystallized from ethanol. m.p. 120-122°C (lit. m.p. 120-1°C)

<25JCS(127)2347> yield = 7.3 g = 40%

^{1}H NMR spectrum: δ:2.58(3H, s, 5-methyl protons), 4.68(2H, s, amino protons), 6.59(1H, s, C-6 aromatic proton), 8.15(1H, s, C-3 aromatic proton)

IR spectrum: 3480cm^{-1}, 3374cm^{-1}(-NH_2 str.)

MS: $C_7H_7{}^{35}ClN_2O_2$ requires 186, found: m/z 186(97), 169(98)

2-Chloro-5-methyl-4-nitrobenzonitrile (187)

2-Chloro-5-methyl-4-nitroaniline (5 g, 0.0269 mol) in water (8 mL) and concentrated sulfuric acid (3 mL) was diazotized at 0°C with sodium nitrite (1.9 g, 0.0275 mol) at 0°C. After the diazotization, the mixture was added with stirring below the surface of a warm solution (~60°C) of copper(I) cyanide and potassium cyanide (2.2 g, 0.034 mol) in water (6 mL), following the procedure described above for the preparation of 2-chloro-4-methylbenzonitrile. The product was isolated using the same procedure, to give pale orange prisms. m.p. 127-129°C yield = 3.1 g = 58%

^{1}H NMR spectrum: δ:2.60(3H, s, 5-methyl protons), 7.69(1H, s, C-6 aromatic proton), 8.08(1H, s, C-3 aromatic proton)

IR spectrum: 2250cm^{-1}(-C≡N str.), 1524cm^{-1}(-N=O str.)

MS: m/z 196(22), 181(33), 179(100)

Accurate mass found for $C_8H_5{}^{35}ClN_2O_2$: 196.0057, calcd. 196.0040

2-Chloro-5-methyl-4-nitrobenzamide

2-Chloro-5-methyl-4-nitrobenzonitrile (0.9 g, 4.59 mmol) dissolved in concentrated sulfuric acid (20 mL) was heated on a steam bath for 20 min. Water was then added and the brown

precipitate collected and dried. It was used in the next stage without further purification. m.p. 170-173°C yield = 0.9 g = 92%

2-Chloro-5-methyl-4-nitrobenzoic acid (188)

Crude 2-Chloro-5-methyl-4-nitrobenzamide (0.9 g, 0.0042 mol), dissolved in 30% sulfuric acid (30 mL), was heated under reflux for 3 h after which it was cooled. The white precipitate was collected and dried. Colorless needles were obtained. m.p. 180-182°C yield = 0.7 g = 77%

^{1}H NMR spectrum: δ:2.62(3H, s, 5-methyl protons), 8.05(1H, s, C-6 aromatic proton), 8.18(1H, s, C-3 aromatic proton), 9.10(1H, s, acidic proton)

IR spectrum: 1708cm^{-1}(C=O str.), ~3000cm^{-1}(-COOH str.), 1528cm^{-1}(N=O str.), 714cm^{-1}(C-Cl str.)

MS: m/z 215(27), 198(100, -OH), 170(22, -C=O)

Accurate mass found for $C_8H_6{}^{35}ClNO_4$: 214.9996, calcd. 214.9985

2-Chloro-5-methyl-4-nitrobenzoyl chloride (189)

The benzoic acid **(188)** (0.7 g, 0.0033 mol) in dry benzene (20 mL) and thionyl chloride (20 mL) was boiled under reflux for 24 h after which benzene and excess thionyl chloride were evaporated giving a pale yellow thick oil. This was used in the next step without further purification or characterization. yield = 0.7 g = 92%

2-Chloro-5-methyl-4-nitroacetophenone (190)

The crude acid chloride (0.7 g, 0.003 mol) in benzene (3 mL) was added with stirring to the solution of ethoxymagnesium malonic ester which was made from magnesium turnings (0.15 g, 0.00625 mol), anhydrous ethanol (0.5 mL), diethyl malonate (1 g, 0.0062 mol), benzene (9

mL) and a catalytic amount of iodine according to the procedure used for the preparation of 2-chloro-4-methylacetophenone. Following the same procedure, a yellow crystalline was obtained and recrystallization from ethanol gave pale yellow needles. m.p. 50-52°C yield = 0.4 g = 63%

^{1}H NMR spectrum: δ:2.62(3H, s, 5-methyl protons) 2.65(3H, s, acetyl methyl protons), 7.47(1H, s, C-6 aromatic proton), 8.03(1H, s, C-3 aromatic proton)

IR spectrum: 1700cm^{-1}

MS: m/z 213(18), 198(100, -CH_3)

Accurate mass found for $C_9H_8{}^{35}ClNO_3$: 213.0178, calcd. 213.0163

Attempted preparation of 5-methyl-2-methylthio-4-nitroactophenone (191)

2-Chloro-5-methyl-4-nitroacetophenone (0.8 g, 0.0037 mol) was dissolved in N,N-dimethyl formamide (15 mL) with lithium hydroxide (0.16 g, 0.0037 mol). Methanethiol (1 mL) was added and the reaction mixture was left at room temperature for 4 h. It was then poured into ice/water. A pale yellow precipitate separated from the aqueous solution and was filtered off and dried. It was purified by preparative thick layer chromatography by using 7:5 / hexane:ethyl acetate as eluent. Yellow crystals m.p. 58-60°C were obtained. yield = 0.64 g = 80%

^{1}H NMR spectrum: δ:2.23(3H, s, 5-methyl protons), 2.48(3H, s, S-methyl protons), 2.61(3H, s, acetyl methyl protons), 7.05(1H, s, C-3 aromatic proton), 7.38(1H, s, C-6 aromatic proton)

IR spectrum: 1711cm^{-1}(C=O str.), 723cm^{-1}(C-Cl str.)

MS: m/z 214(40), 199(100, -CH_3), 164(4)

Accurate mass for $C_{10}H_{11}{}^{35}ClOS$ found: 214.0219, calcd. 214.0219

These data are consistent with the formation of 2-chloro-5-methyl-4-methylthioacetophenone **(192)** by displacement of a nitro group.

4-Amino-2-chloro-5-methylacetophenone (193)

2-Chloro-5-methyl-4-nitroacetophenone (0.5 g, 0.0023 mol) was added in small portions to a solution of stannous chloride (2.3 g, 0.012 mol) in concentrated hydrochloric acid (5.7 mL) with stirring. After introducing all of the ketone into the solution, the reaction mixture was allowed to stand at room temperature with stirring for another 2 h. The solution was then diluted with water and dilute aqueous sodium hydroxide added to neutralize the solution. The precipitate formed during neutralization was filtered off and the filtrate was extracted with dichloromethane. A pale yellow crystalline solid was obtained after evaporation of the solvent. m.p. 128-131°C yield = 0.36 g = 84%

^{1}H NMR spectrum: δ:2.13(3H, s, 5-methyl protons), 2.61(3H, s, acetyl methyl protons), 4.02(2H, s, amino protons), 6.64(1H, s, C-3 aromatic proton), 7.52(1H, s, C-6 aromatic proton)

IR spectrum: 3457cm^{-1}, 3364cm^{-1}(-NH_2 str.), 1712cm^{-1}(C=O str.)

MS: 183(36), 168(100, -CH_3), 140(20, -C=O)

Accurate mass found for $C_9H_{10}{}^{35}ClNO$: 183.0445, calcd. 183.0439

Attempted Reaction of 4-Amino-2-chloro-5-methylacetophenone with methanethiol (194)

To 4-amino-2-chloro-5-methylacetophenone **(193)** (0.3 g, 0.0016 mol) dissolved in N,N-dimethyl formamide (10 mL) was added lithium hydroxide (0.069 g, 0.0016 mol) and methanethiol (~0.5 mL). The reaction mixture was allowed to stand at room temperature for 0.5 h after which it was poured into water and the yellow precipitate collected. Examination of the ^{1}H NMR showed that the starting material was recovered.

More vigorous reaction conditions were then tried. 4-Amino-2-chloro-5-methylacetophenone (0.3 g, 0.0016 mol) in N,N-dimethyl formamide (10 mL) was added to lithium hydroxide (0.069 g, 0.0016 mol) and methanethiol (~5 mL). The reaction mixture was sealed in a pressure bottle and heated in wax-bath at 150°C for 18 h. Following the work up procedure above, it was also found that the starting material was recovered.

Acetylation of 4-amino-2-chloro-5-methylacetophenone (195)

4-Amino-2-chloro-5-methylacetophenone **(193)** (0.5 g, 0.0027 mol), dissolved in acetic anhydride, was heated on a steam bath for 0.5 h then cooled and poured into water. The aqueous solution was then made basic by sodium hydroxide and extracted with dichloromethane. Evaporation of the organic solvent gave a dark brown thick oil. yield = 0.6 g = 99%

^{1}H NMR spectrum: δ:2.24(6H, s, 5-methyl and N-acetyl methyl protons), 2.63(3H, s, acetyl methyl protons), 7.42(1H, s, C-3 aromatic proton), 8.11(1H, s, C-6 aromatic proton)

4-Acetamido-5-methyl-2-methylthioacetophenone (196)

To 4-acetamido-2-chloro-5-methylacetophenone (0.6 g, 0.0027 mol) dissolved in N,N-dimethyl formamide (10 mL) was added lithium hydroxide (0.13 g, 0.0031 mol) and methanethiol (~0.5 mL). The mixture was sealed in a pressure bottle and heated at 100°C for 18 h. Then, water was added and the precipitate separated was collected and recrystallized from ethanol to give yellow needles. m.p. 126-128°C yield = 0.6 g = 95%

^{1}H NMR spectrum: δ:2.275(3H, s, 5-methyl protons), 2.325(3H, s, N-acetyl methyl protons),

2.45(3H, s, S-methyl protons), 2.60(3H, s, acetyl methyl protons), 7.66(1H, s, C-3 aromatic proton), 8.15(1H, s, C-6 aromatic proton), 7.35(1H, s, N-H proton)

IR spectrum: 3270cm^{-1}(N-H str.), 1664cm^{-1}(C=O str.), 1563cm^{-1}(C-N str.)

MS: m/z 237(17), 223(42), 194(2.5)

Accurate mass for $C_{12}H_{15}NO_2S$ found: 237.0850, calcd. 237.0823

4-Acetamido-5-methyl-2-methylthioacetophenone oxime

To 4-acetamido-5-methyl-2-methylthioacetophenone (0.6 g, 0.0025 mol) in ethanol (20 mL) was added hydroxylamine hydrochloride (0.6 g, 0.012 mol) and sodium hydroxide (0.3 g). The mixture was heated under reflux for 3 h after which the ethanol was evaporated and water was added. It was then extracted with dichloromethane and after evaporation of the dried organic solvent, a pale yellow solid was obtained. It was used in the next stage without further purification and identification. m.p. 160-163°C yield = 0.6 g = 94%

MS: $C_{12}H_{16}N_2O_2S$ requires 252, found: m/z 252(15), 235(65, -OH), 220(48, -CH_3)

6-Acetamido-3,5-dimethylbenzisothiazole (197)

The crude oxime (0.6 g, 0.00238 mol) dissolved in acetic anhydride (4 mL) and pyridine (20 mL) was heated under reflux for 24 h after which water and dilute hydrochloric acid added until the smell of pyridine was no longer evident. It was then extracted with dichloromethane. Evaporation of the organic solvent gave a dark brown oil. (yield = 0.4 g = 76%) This was not further characterized but converted to the amine below.

MS: $C_{11}H_{12}N_2OS$ requires 220, found: m/z 220(45), 178(100)

6-Amino-3,5-dimethyl-1,2-benzisothiazole (198)

6-Acetamido-3,5-dimethylbenzisothiazole (0.4 g, 0.0018 mol) dissolved in ethanol (10 mL) and concentrated hydrochloric acid (5 mL) was heated under reflux for 2 h after which water and a solution of dilute aqueous sodium hydroxide added to liberate the amine. Extraction with dichloromethane and removal of the solvent gave a yellow crystalline product. It was purified by preparative thick layer chromatography using 1:1 hexane:ethyl acetate as eluent. m.p. 172°C yield = 0.3 g = 93%

^{1}H NMR spectrum: δ:2.31(3H, s, 5-methyl protons), 2.62(3H, s, C-3 methyl protons), 3.73(2H, s, amino protons), 7.06(1H, s, c-7 aromatic proton), 7.57(1H, s, C-4 aromatic proton)

MS: m/z 178(100), 163(7, -CH_3)

Accurate mass calcd. for $C_9H_{10}N_2S$: 178.0565, found: 178.0567

4.3. An APPROACH TO THE BENZO[1,2-c:4,3-d]DI-ISOTHIAZOLE SYSTEM

Acylation of 3-chloro-2-methyl aniline (200)

To 3-chloro-2-methylaniline **(199)** (50 g, 0.355 mol) was added acetic anhydride (40 mL) and the reaction mixture was heated on steam bath for 1 h. After cooling, it was poured into water and the white needles were collected and recrystallized from ethanol. m.p. 134°C (lit. m.p. 136°C) It was used in the next step without further characterization or purification.

Attempted Acylation of 3-chloro-2-methylacetanilide (203) Using Iodine Catalyst

3-Chloro-2-methylacetanilide (4 g, 0.022 mol) in acetic anhydride (4 mL) was refluxed with iodine (0.3 g, 0.0012 mol), while collecting the distillate through a 38 cm Vigreux column (~2 mL). An additional 2 mL of acetic anhydride was added to the reaction mixture and ~0.4 mL of distillate was collected. The reaction mixture was then poured into water (26 mL), the organic layer separated. The aqueous layer was extracted with dichloromethane, and the excess iodine removed by washing with sodium bisulfite solution. The organic layer was combined and solvent was removed under reduced pressure. The residue was hydrolyzed by refluxing for 1 h with concentrated hydrochloric acid (4 mL) after which it was made strongly alkaline by adding solution of sodium hydroxide, followed by two extractions with dichloromethane. The organic layer was washed with water until it was neutral. The organic solvent was removed under reduced pressure and the residue was distilled. Approximately 3 g of the material was obtained. The ^{1}H NMR spectrum was identical to the starting material.

Attempted Friedel-Crafts Reaction of 3-chloro-2-methylanilide Using Aluminum Chloride Catalyst

To 3-chloro-2-methylacetanilide (1.83 g, 0.01 mol) in dichloromethane was added acetyl chloride (1 g, 0.0123 mol) and aluminum chloride (3 g, 0.023 mol) and the reaction mixture was left at room temperature for 16 h after which water was added. The solution was extracted with dichloromethane followed by evaporation of the organic solvent to give a material which was examined by thin layer chromatography. The major spot on TLC had the same R_f as the starting material.

Acylation of 3-chloro-2-methylaniline by toluene-*p*-sulfonyl chloride (201)

This was made by the procedure described in the literature <24JCS(125)1597>. 3-Chloro-2-methylaniline **(199)** (45 g, 0.32 mol) was treated with toluene-*p*-sulfonyl chloride (60 g, 0.32 mol), the solidified mixture being heated on steam bath for 1 h. It was then cooled and recrystallized from ethanol to give the product. The product was treated in the next step without further purification or characterization. yield = 58 g = 62%

N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide (205)

This was made by the procedure described in the literature <24JCS(125)1597>. N(3-chloro-2-methylphenyl)toluene-*p*-sulfonamide (20 g, 0.068 mol) was added to a solution of nitric acid (70%) (20 g, 0.32 mol) in water (100 mL). The reaction mixture was heated with stirring for 14 h and after cooling, the product was collected and twice recrystallized from ethanol. m.p. 150-157°C yield = 16.5 g = 72%

^{1}H NMR spectrum: δ:2.30(3H, s, 2-methyl protons), 2.43(3H, s, methyl protons),

7.26-7.79(6H, m, aromatic protons), 8.42(1H, s, broad, N-proton)

IR spectrum: 3247cm^{-1}(N-H str.), 1590cm^{-1}(-N=O str.)

Nitration of 3-chloro-2-methylacetanilide (204)

3-Chloro-2-methylacetanilide (60 g, 0.328 mol) dissolved in acetic acid (60 mL) and concentrated sulfuric acid (120 mL) was cooled to 0°C. Nitric acid (70%) (40 g, 0.442 mol) in concentrated sulfuric acid (25 mL) was added with stirring. The reaction mixture was then poured into ice/water and the product was collected. It was then recrystallized from ethanol.

^{1}H NMR spectrum: δ:2.30(3H, s, 2-methyl protons), 2.39(3H, s, acetyl methyl protons), 7.52(1H, d, J=10Hz, C-6 aromatic proton), 7.96(1H, d, J=10Hz, C-5 aromatic proton), 8.63(1H, s, broad, N-proton)

N(2-methyl-3-chlorophenyl)succinimide (202)

3-Chloro-2-methylaniline (14.1 g, 0.1 mol) in succinic acid (11.8 g, 0.1 mol) was heated at 140°C until all water was evolved (~1 h). It was then cooled and recrystallized from ethanol as pink prisms. The product was used without further purification.

Nitration of N(2-methyl-3-chlorophenyl)succinimide (206)

N(2-methyl-3-chlorophenyl)succinimide (2.5 g, 0.0143 mol) dissolved in concentrated sulfuric acid (20 mL) was cooled to 0°C with stirring. Nitric acid (70%) (1.4 g, 0.016 mol) was added and the reaction mixture was allowed to stand at 0°C for another 1 h after which it was poured into ice/water. The yellow precipitate was collected and recrystallized from ethanol. m.p. 130-131°C yield = 80%

^{1}H NMR spectrum: δ:2.30(3H, s, 2-methyl protons), 3.02(4H, s,two methylene protons), 7.68(1H, d, J=8.8Hz, C-6 aromatic proton), 8.08(1H, d, J=8.8Hz, C-5 aromatic proton)

IR spectrum: 1724cm^{-1}(C=O str.)

Attempted Reduction of N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide by sodium hydrosulfite (208)

To N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide (1 g, 0.003 mol), dissolved in ethanol (20 mL) and water (5 mL), was added sodium hydrosulfite (1 g, 0.0057 mol) and the reaction mixture was heated under reflux for 14 h. The unreacted sodium hydrosulfite was filtered off and the aqueous layer was extracted with dichloromethane. Evaporation of the solvent gave yellow crystals in low yield. yield = 0.5 g = 55% m.p. 173-175°C

^{1}H NMR spectrum: δ:2.10(3H, s, 2-methyl protons), 2.47(3H, s, toluene methyl protons), 4.03(2H, s, broad, amino protons), 6.18(1H, s, broad, N-proton), 6.58(1H, d, J=9 Hz, C-5 aromatic proton), 6.86(1H, d, J=9 Hz, C-6 aromatic proton), 7.25(2H, d, J=8.0Hz, aromatic protons *ortho* to methyl), 7.61(2H, d, J=8.0Hz, aromatic protons *ortho* to sulfonyl function)

IR spectrum: 3474cm^{-1}, 3383cm^{-1}(-NH_2 str.)

Attempted Reduction of N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide by tin and hydrochloric acid (208)

To N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide (1 g, 0.003 mol) in concentrated hydrochloric acid (5 mL), water (5 mL) and ethanol (5 mL), was added tin (2 g, 0.017 mol), and the mixture was refluxed for 3 h. After cooling, it was made alkaline by adding a solution of aqueous sodium hydroxide. The tin oxides formed were filtered off and washed with dichloromethane. The filtrate was extracted with dichloromethane and evaporation of the

organic solvent gave the product in low yield. m.p. 174-175°C

^{1}H NMR spectrum: δ:2.10(3H, s, 2-methyl protons), 2.47(3H, s, toluene methyl protons), 4.03(2H, s, broad, amino protons), 6.18(1H, s, broad, N-proton), 6.58(1H, d, J=9 Hz,C-5 aromatic proton), 6.86(1H, d, J=9 Hz, C-6 aromatic proton), 7.25(2H, d, J=8.0 Hz, aromatic protons *ortho* to methyl), 7.61(2H, d, J=8.0 Hz, aromatic protons *ortho* to sulfonyl function)
IR spectrum: 3472cm^{-1}, 3382cm^{-1}(-NH_2 str.)

Attempted Reduction of N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide by iron/acetic acid (208)

N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide (1 g, 0.0063 mol) in acetic acid (10 mL), water (2 mL) and iron powder (2 g, 0.0357 mol) was boiled at 100°C for 14 h. After cooling, water and sodium hydroxide were added and the precipitate was filtered off. The aqueous solution was then extracted with dichloromethane. Evaporation of the solvent gave a pale yellow solid in low yield. Due to the low yield, it was not further purified or characterized.

Attempted Reduction of N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide by Raney Ni/hydrazine (208)

N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide (1 g, 0.003 mol) was reacted with Raney Ni (Prepared in the usual manner from nickel aluminum alloy and kept under ethanol until use.). Hydrazine (~5 mL) was then added. The reaction mixture was heated on a steam bath for 2 h after which water was added and precipitate was filtered off. The filtrate was extracted with dichloromethane. Evaporation of the solvent gave a thick oil. Examination of the thin layer chromatogram showed that it was a mixture of several components. Due to the

difficulty of separation, this was not further characterized.

Attempted Reduction of N(3-chloro-2-methyl-4-nitro)succinimide by tin/hydrochloric acid (209)

To N(3-chloro-2-methyl-4-nitro)succinimide (1 g, 0.0045 mol) in ethanol (5 mL), water (5 mL) and concentrated hydrochloric acid (5 mL), was added tin (2 g, 0.0169 mol). The reaction mixture was refluxed for 12 h after which it was made basic and tin oxides formed were removed by filtering. The aqueous layer was extracted by dichloromethane and evaporation of the solvent gave a thick dark brown oil. yield = 0.3 g = 34%

IR spectrum: 3440cm^{-1}, 3373cm^{-1}(-NH_2 str.), 1715cm^{-1}(C=O str.)

Attempted Reduction of N(3-chloro-2-methyl-4-nitro)succinimide by iron/acetic acid (209)

To N(3-chloro-2-methyl-4-nitro)succinimide (1 g, 0.0045 mol) in 50% acetic acid/water (10 mL) and tetrahydrofuran (~5 mL) was added iron powder (2 g, 0.036 mol). The mixture was heated at 80°C for 3 h. Following the same procedure as the attempted reduction of N(3-chloro-2-methyl-4-nitrophenyl)toluene-*p*-sulfonamide by iron and acetic acid, thick brown oil was obtained. Because thin layer chromatography showed that it was a mixture of several components, it was not further purified or characterized.

Acylation of *m*-toluidine (212)

This was prepared by following a literature procedure for acylation of *m*-toluidine (25 g, 0.23 mol) <78BCJ(51)3083>. The crude product was recrystallized from ethanol to give needles. m.p. 64-65°C (Lit. m.p. 65.5°C) yield = 30 g = 86%

3-Methyl-4-nitroacetanilide (213)

3-Methylacetanilide (30 g, 0.2 mol) in acetic acid (25 mL) and concentrated sulfuric acid (50 mL) were cooled to 0°C in an ice-salt bath. Concentrated nitric acid (70%) (18.5 g, 0.21 mol) in concentrated sulfuric acid (7 mL) was added slowly below 10°C. The solution was allowed to stand at room temperature for 1 h after which it was poured onto ice. The precipitate was collected and recrystallized from ethanol as yellow needles. m.p. 102°C (lit. m.p. 102°C) <68JOC(33)3498> yield = 29 g = 74%

Chlorination of 4-nitro-3-methylacetanilide (214)

Into a solution of 4-nitro-3-methylacetanilide (3.5 g, 0.018 mol) in acetic acid (20 mL) was passed chlorine gas until the weight had increased by 1.5 g. The mixture warmed to ~40°C during the addition. After cooling, the solution was poured into water. The initial oily precipitate gradually crystallized. It was collected and recrystallized from toluene as pale yellow prisms. m.p. 110°C yield = 3.7 g = 91%

^{1}H NMR spectrum (in acetone-d_6): δ:2.29(3H, s, 3-methyl protons), 2.58(3H, s, acetyl methyl protons), 7.76(1H, d, J=10.8Hz, C-6 aromatic proton), 8.42(1H, d, J=10.8Hz, C-5 aromatic proton)

MS: m/z 149(20), 97(26) (No parent ion)

The product of the chlorination had a ^{1}H NMR spectrum and melting point identical to 2-chloro-3-methyl-4-nitroacetanilide (**214**). (The other isomer, 2-chloro-5-methyl-4-nitroacetanilide (**215**) has a melting point of 134-5°C <25JCS2347>.

2-Chloro-3-methyl-4-nitroaniline

The amide (3.7 g, 0.016 mol) was boiled in concentrated hydrochloric acid for 3 h. After cooling, ammonium hydroxide was added to liberate the amine. The precipitate was collected and recrystallized from ethanol as yellow prisms. m.p. 124-125°C yield = 2.6 g = 86%

^{1}H NMR spectrum: δ:2.65(3H, s, 3-methyl protons), 4.80(2H, s, broad, amino protons), 6.65(1H, d, J=10.2Hz, C-6 aromatic proton), 7.82(1H, d, J=10.2Hz, C-5 aromatic proton)

MS: $C_7H_7{}^{35}ClN_2O_2$ requires 186, found: m/z 186(21), 188(75), 169(60)

2-Chloro-3-methyl-4-nitrobenzonitrile (216)

2-Chloro-3-methyl-4-nitroaniline (16 g, 0.086 mol) in water (25 mL) and hydrochloric acid (25 mL) was diazotized with sodium nitrite (5.75 g, 0.0086 mol) at 0°C. The diazonium salt solution was added below the surface of a warm solution (60°C) of copper(I) cyanide which was made from copper(II) sulfate (25 g, 0.1 mol), sodium bisulfite (7 g, 0.067 mol), concentrated sulfuric acid (1 mL), potassium cyanide (20 g) and water (80 mL) according to the method of preparation of 2-chloro-4-methylbenzonitrile. Following that procedure, pale pink prisms were obtained. m.p. 98°C yield = 10 g = 59%

^{1}H NMR spectrum: δ:2.55(3H, s, 3-methyl protons), 7.90(2H, s, aromatic protons)

IR spectrum: 2244cm^{-1}(-C≡N str.)

MS: m/z 196(18), 179(100), 151(70)

Accurate mass for $C_8H_5{}^{35}ClN_2O_2$: found: 196.0061, calcd.: 196.0039

Hydrolysis of 2-chloro-3-methyl-4-nitrobenzonitrile to amide (217)

2-Chloro-3-methyl-4-nitrobenzonitrile (10 g, 0.051 mol) dissolved in concentrated sulfuric acid (50 mL) was heated on steam bath for 20 min. It was then poured into ice/water and the precipitate was collected. The crude material was usually used for the next stage, i.e., conversion to the acid, but a small sample was recrystallized from ethanol/water as pale yellow needles. m.p. 132-135°C yield = 9 g = 82%

2-Chloro-3-methyl-4-nitrobenzoic acid (218)

Crude 2-chloro-3-methyl-4-nitrobenzamide (9 g, 0.042 mol) from above was boiled with 30% sulfuric acid (30 mL) for 3 h. The insoluble oil was decanted off. Cooling of the aqueous solution gave colorless needles which were collected. m.p. 148-150°C yield = 7 g = 77%

^{1}H NMR spectrum: δ:2.57(3H, s, 3-methyl protons), 7.70(1H, d, J=8.5Hz, C-5 or C-6 aromatic proton), 7.87(1H, d, J=8.5Hz, C-6 or C-5 aromatic proton), ~10.62(1H, s, broad, O-H proton)

IR spectrum: ~3000cm^{-1}(broad, -OH str.), 1716cm^{-1}(C=O str.)

MS: 215(14), 198(100, -OH)

Accurate mass for $C_8H_6{}^{35}ClNO_4$: found: 215.0015, calcd.:214.9985

2-Chloro-3-methyl-4-nitroacetophenone (220)

2-Chloro-3-methyl-4-nitrobenzoic acid **(218)** (9 g, 0.042 mol) was refluxed with thionyl chloride (~10 mL) in benzene (50 mL). The acid chloride obtained by evaporation was converted to 2-chloro-3-methyl-4-nitro-acetophenone **(220)** following the same procedure as for the preparation of 2-chloro-4-methylacetophenone. The product was obtained as a yellow oil. yield = 6 g = 67%

^{1}H NMR spectrum: δ:2.52(3H, s, 3-methyl protons), 2.60(3H, s, acetyl methyl protons), 7.32(1H, d, J=8Hz, C-6 aromatic proton), 7.68(1H, d, J=8Hz, C-5 aromatic proton)

IR spectrum: 1712cm^{-1}(C=O str.)

MS: 213(14), 198(100, -CH_3), 152(38)

Accurate mass for $C_9H_8{}^{35}ClNO_3$: found: 213.0207, calcd.:213.0194

Attempted Reaction of 2-chloro-3-methyl-4-nitroacetophenone with methanethiol

To 2-chloro-3-methyl-4-nitroacetophenone (6 g, 0.028 mol) in N.N-dimethyl formamide (50 mL) was added lithium hydroxide (1.2 g, 0.143 mol) and methanethiol (~5 mL). The mixture was allowed to stand at room temperature with stirring for 1.5 h. It was then poured into water. Dilute hydrochloric acid was added and the mixture extracted with dichloromethane. Evaporation of the organic solvent gave an oil which on dilution with water gave a crystalline precipitate. The precipitate was filtered off and recrystallized from ethanol as colorless needles. m.p. 44-46°C (yield = 5.5 g = 91%)

^{1}H NMR spectrum: δ:2.41(3H, s, S-methyl protons), 2.48(3H, s, 3-methyl protons), 2.63(3H, s, acetyl methyl protons), 7.08(1H, d, J=9.6Hz, C-5 aromatic proton), 7.35(1H, d, J=9.6Hz, C-6 aromatic proton)

IR spectrum: 1710cm^{-1}(C=O str.)

MS: m/z 216(15), 214(39), 201(36, -CH_3), 199(100)

The data show that the product is actually 2-chloro-4-methylthio-3-methylacetophenone (**222**).

4.4 APPROACH TO THE BENZO[1,2-c:3,4-d]DI-ISOTHIAZOLE

2-Chloro-6-methylbenzonitrile (227)

This was prepared following a literature procedure by diazotization of 2-chloro-6-methylaniline and then treatment of the diazonium salt with copper (I) cyanide which was also made according to the literature procedure <21JCS1452>. Recrystallization from hexane gave light red prisms. m.p. 80.2-82.5°C (lit. m.p. 83-85°C) (yield = 9 g = 58%)

6-Chloro-2-methyl-3-nitrobenzonitrile (228)

To 2-chloro-6-methylbenzonitrile (2.82 g, 0.02 mol) in concentrated sulfuric acid (20 mL) was added concentrated nitric acid (70%) (1.8 g, 0.02 mol) at 5°C. After all of the nitric acid was introduced, the reaction mixture was allowed to stand for 0.5 h with stirring, then it was poured into ice/water. The precipitate was collected and twice recrystallized from ethanol. m.p. 75-80°C yield = 3.1 g = 85%

^{1}H NMR spectrum: δ:2.80(3H, s, 2-methyl protons), 7.54(1H, d, J=8.8Hz, C-5 aromatic proton), 8.08(1H, d, J=8.8Hz, C-4 aromatic proton)

IR spectrum: 2270cm^{-1}(-C≡N str.)

Hydrolysis of 6-chloro-2-methyl-3-nitrobenzonitrile to 6-chloro-2-methyl-3-nitro-benzamide (229)

6-Chloro-2-methyl-3-nitrobenzonitrile (1 g, 0.005 mol) was dissolved in concentrated sulfuric acid (10 mL). The mixture was heated on a steam bath for 15 min after which it was poured into ice/water. A fine white precipitate was collected.

^{1}H NMR spectrum: δ:2.55(3H, s, 2-methyl protons), 6.17(2H, s, broad, amino protons), 7.38(1H, d, J=8.8Hz, C-5 aromatic proton), 7.83(1H, d, J=8.8Hz, C-4 aromatic proton)

IR spectrum: 3365cm^{-1}, 3185cm^{-1}(-NH_2 str.), 1655cm^{-1} (C=O str.)

MS spectrum: m/z 214(21), 198(35, -NH_2), 179(33)

Further hydrolysis to the acid using various concentrations of sulfuric acid failed.

Attempted conversion of 6-chloro-2-methyl-3-nitrobenzamide to the acid by sodium nitrite (230)

6-Chloro-2-methyl-3-nitrobenzamide (1.1 g, 0.0051 mol) was dissolved in concentrated sulfuric acid (0.25 mL) and water (5 mL). The mixture was warmed to 60°C to effect solution, then was cooled to 35°C with stirring. A solution of sodium nitrite (0.35 g, 0.0051 mol) in water (2.5 mL) was added followed by another 0.13 mL concentrated sulfuric acid, and then another 0.18 g sodium nitrite in 1.5 mL water. Stirring was continued for another 2 h until all gas evolution had ceased. The solution was then extracted with dichloromethane. Evaporation of the organic solvent gave a pale yellow solid. The ^{1}H NMR and IR spectra were identical to the starting material.

Attempted conversion of 6-chloro-2-methyl-3-nitrobenzonitrile to methyl ester by methanol/hydrochloric acid (231)

6-Chloro-2-methyl-3-nitrobenzonitrile (1 g, 0.0051 mol) dissolved in methanol (10 mL) was saturated with hydrogen chloride. The reaction mixture was left at room temperature over night after which it was poured into water and the precipitate collected. The ^{1}H NMR and IR spectra were identical to the starting nitrile.

Attempted conversion of 6-chloro-2-methyl-3-nitrobenzonitrile to the methyl ester by sulfuric acid and methanol/water (231)

6-Chloro-2-methyl-3-nitrobenzonitrile (1 g, 0.0051 mol), dissolved in concentrated sulfuric acid (10 mL), was heated on a steam bath for 0.5 h. Methanol (~10 mL) was added dropwise with stirring and the mixture was let stand at room temperature for 15 min. It was then poured into ice/water and extracted with dichloromethane. Evaporation of the solvent gave a pale yellow solid. An examination of ^{1}H NMR and IR spectra showed this was the starting nitrile.

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SPECTRA

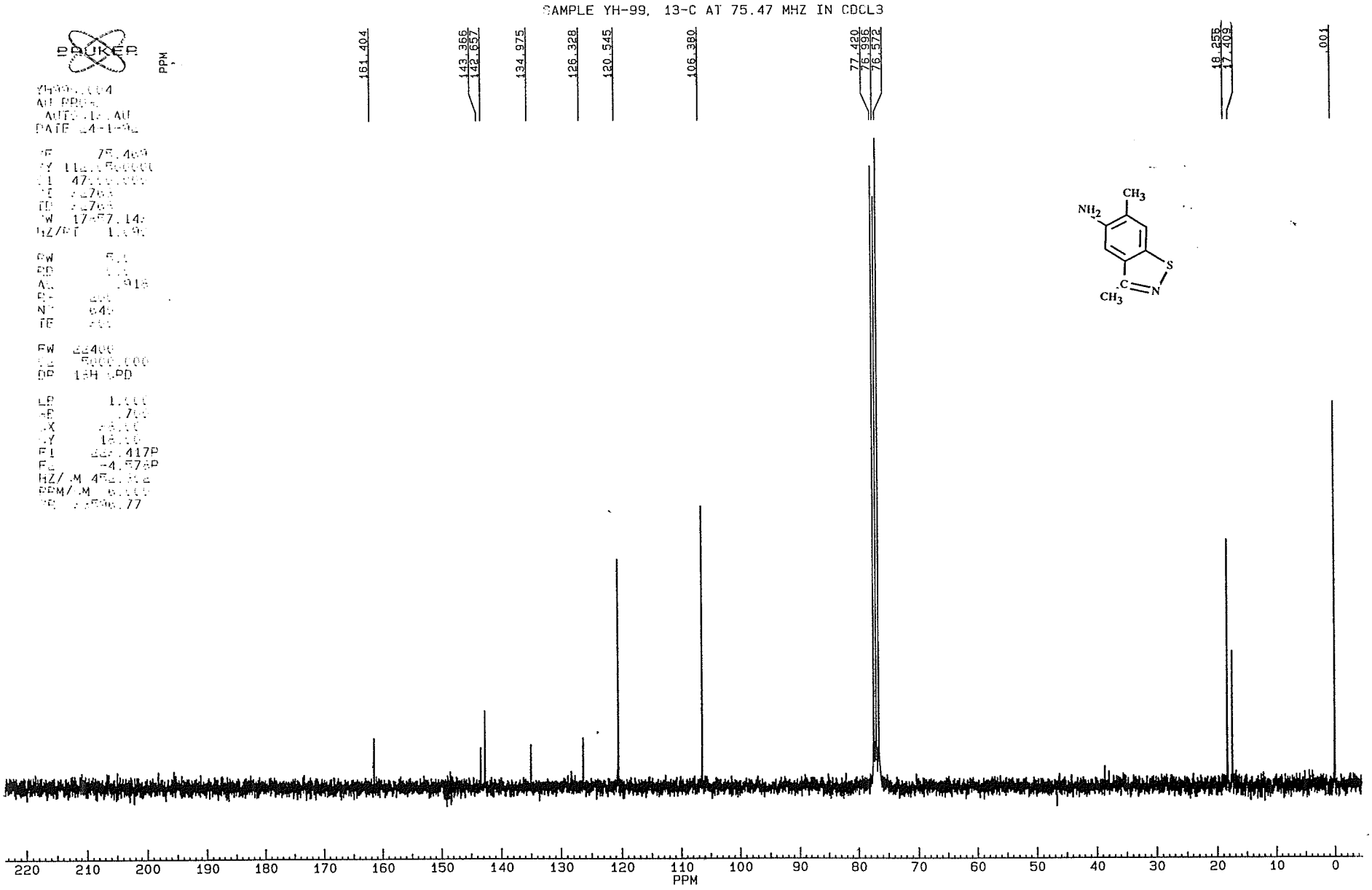
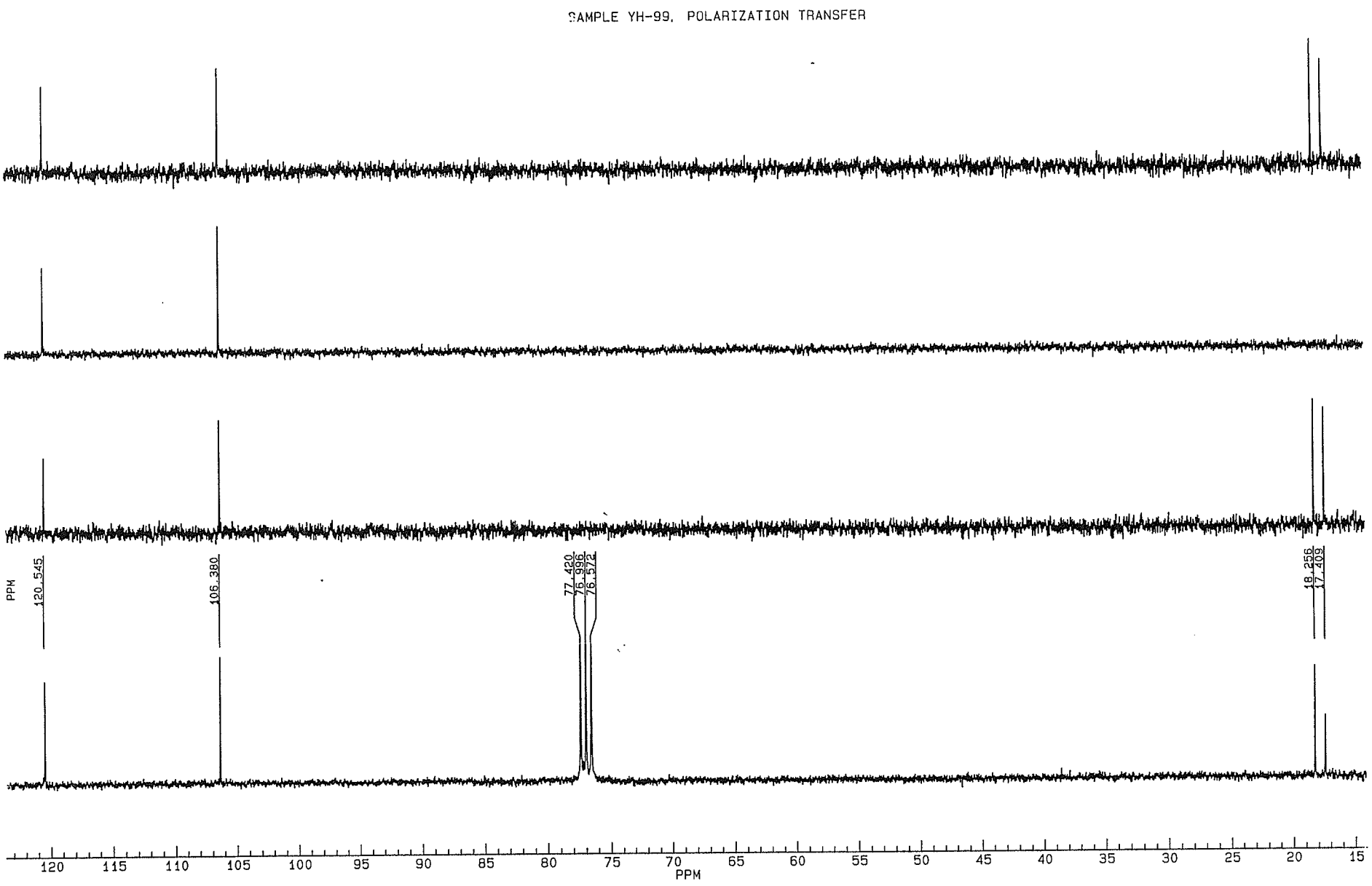


Figure 1. ^{13}C NMR spectrum of 5-amino-3,6-dimethyl-1,2-benzisothiazole **(99)**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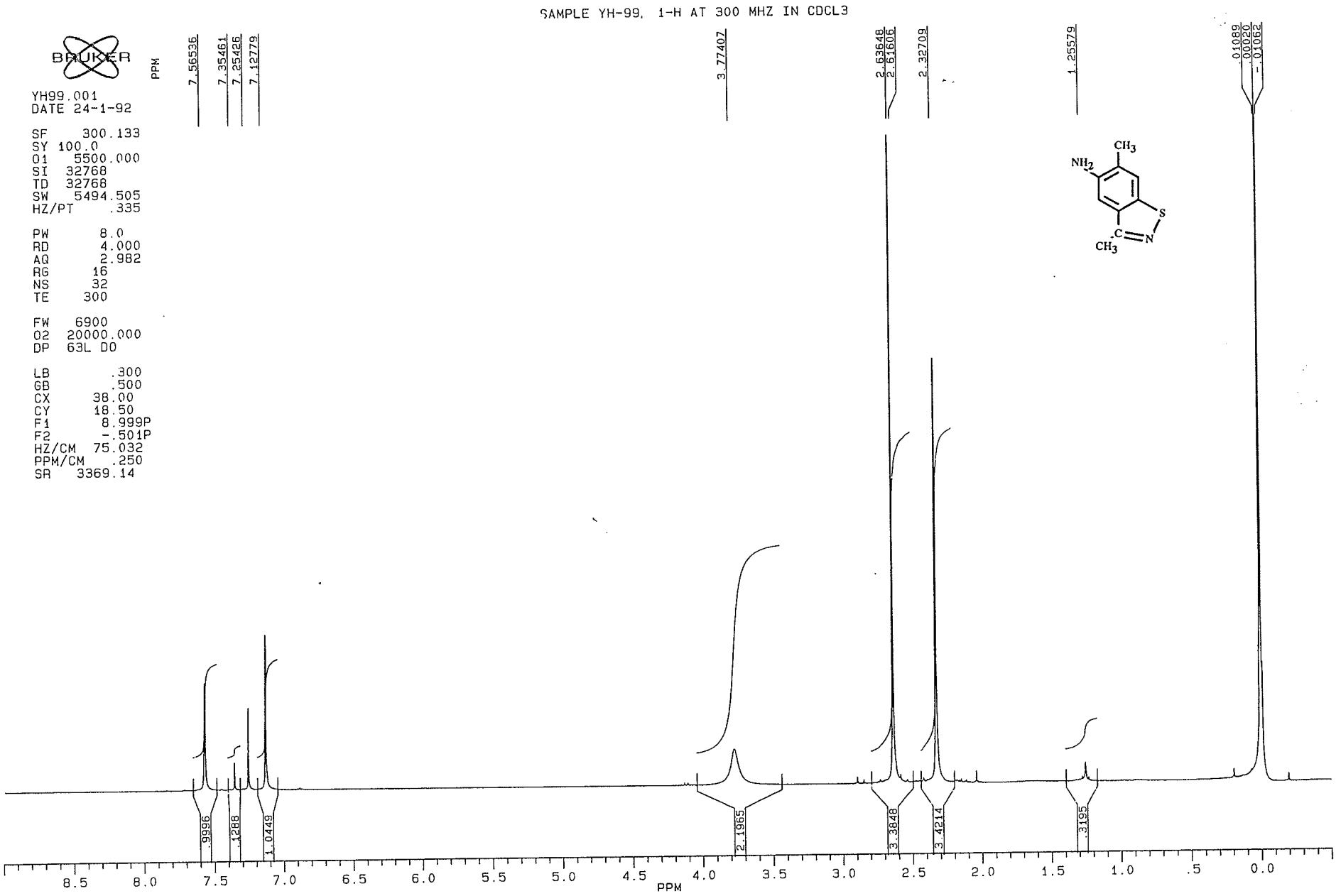

Figure 2. ^{1}H NMR spectrum of 5-amino-3,6-dimethyl-1,2-benzisothiazole (**99**)

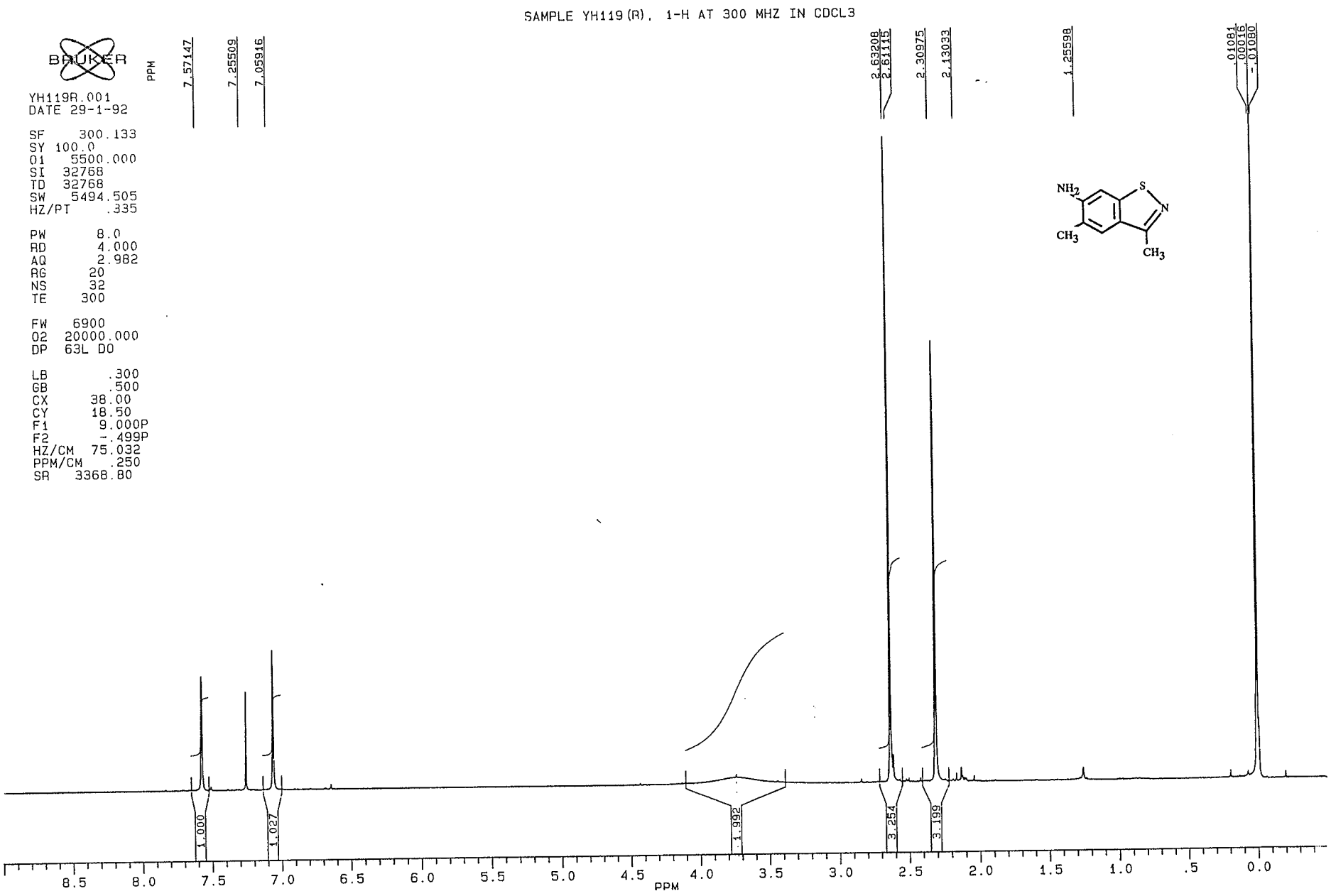

Figure 3. ^{1}H NMR spectrum of 6-amino-3,5-dimethyl-1,2-benzisothiazole ((**119**)

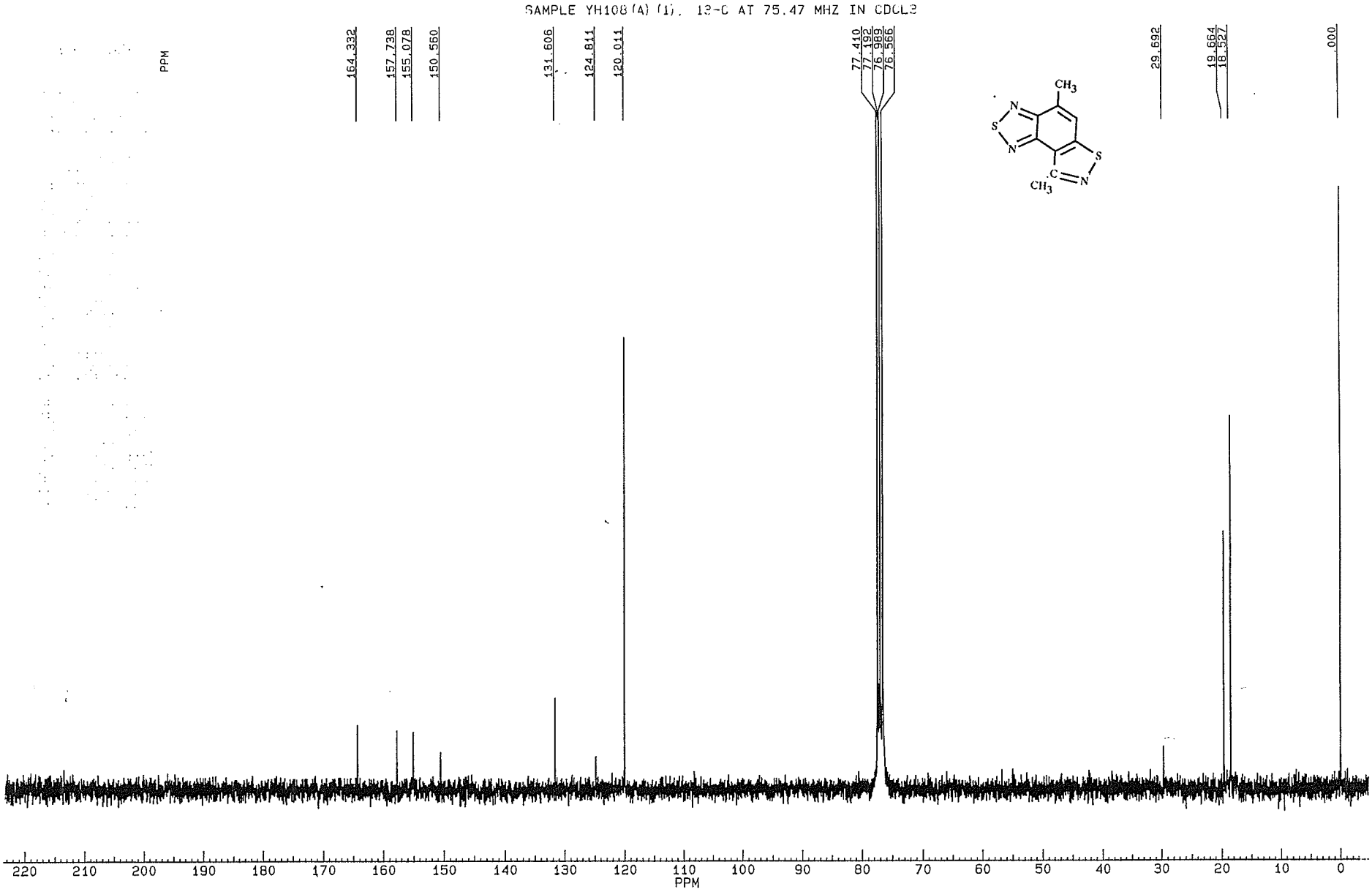

Figure 4. ^{13}C NMR spectrum of 4,8-dimethylbenzisothiazolo-[3,4-d:1,2-d]benzothiadiazole (**159**)

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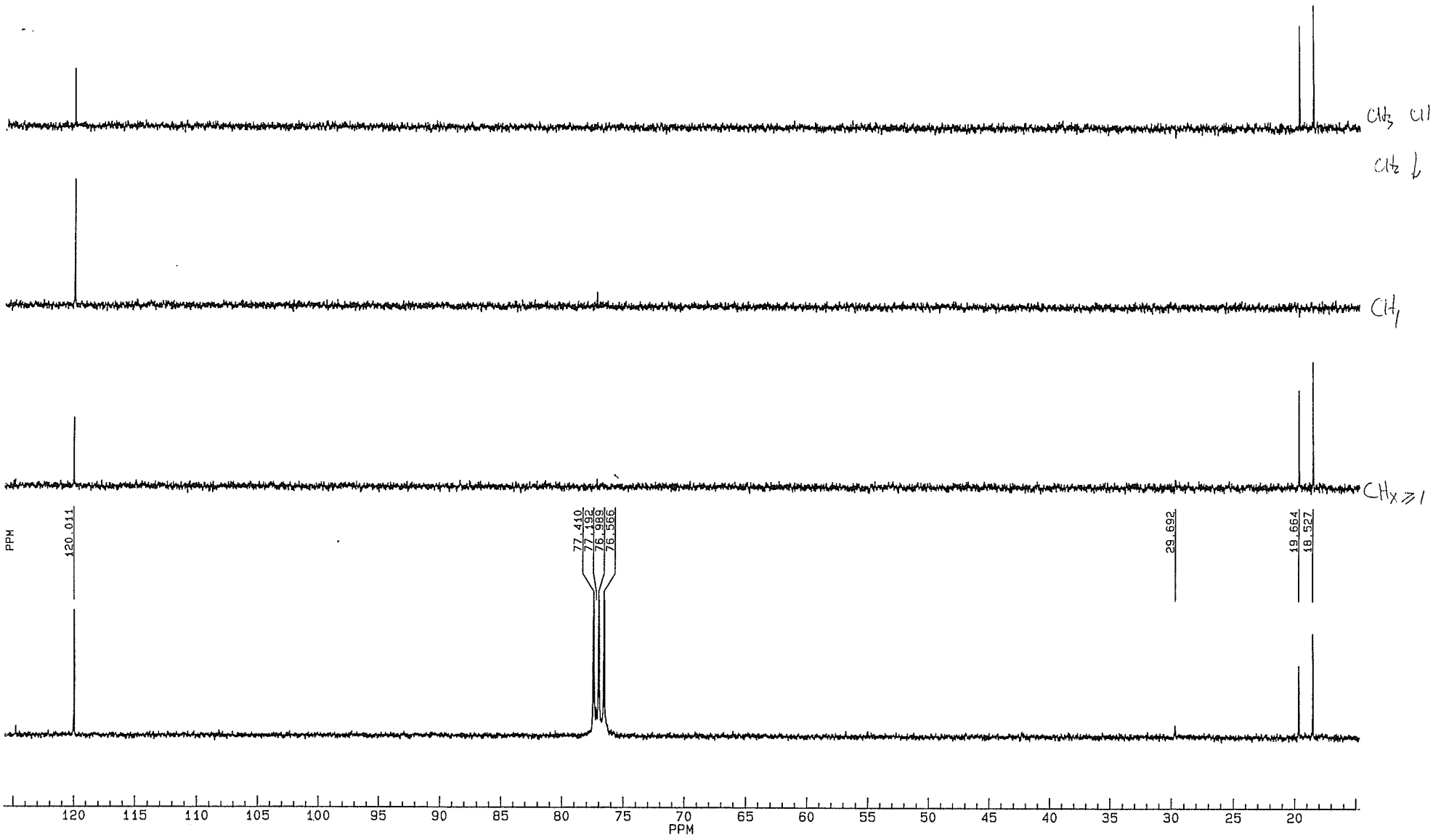

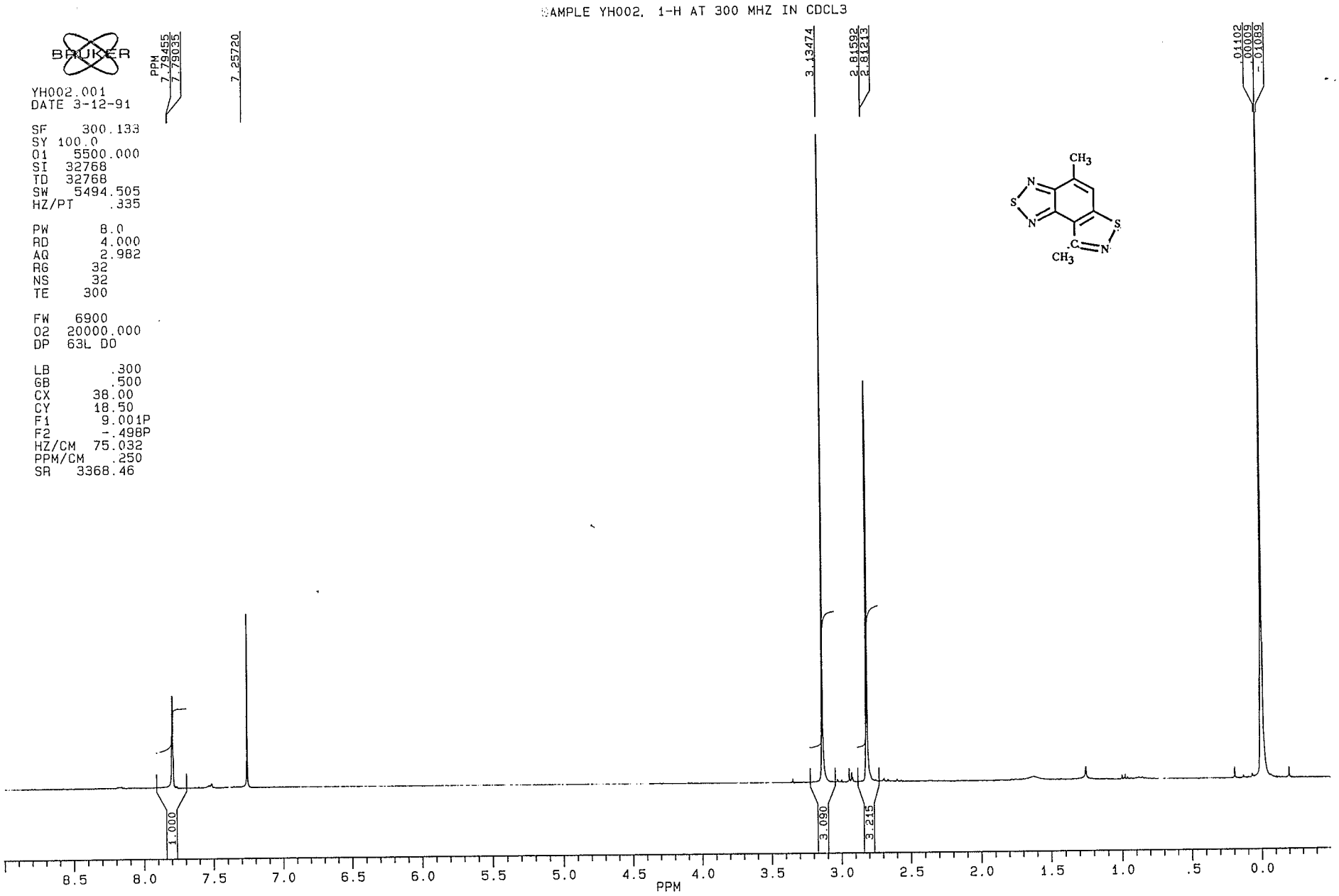

Figure 5. ^{1}H NMR spectrum of 4,8-dimethylbenzisothiazolo-[3,4-d:1,2-d]benzothiadiazole (**159**)