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Recent Developments in the Synthesis and Chemistry of 2(1*H*)-Pyridinethiones and Related Compounds

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RECENT DEVELOPMENTS IN THE SYNTHESIS AND CHEMISTRY OF 2(1*H*)-PYRIDINETHIONES AND RELATED COMPOUNDS

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The synthesis of 2(1*H*)-pyridinethiones from acyclic and cyclic starting materials is reviewed. The chemistry of the 2(1*H*)-pyridinethiones and the use of such compounds in organic synthesis is also covered with special emphasis on the annellation reactions for the preparation of fused heterocyclic systems. The coverage of other sulfur-containing pyridines is less extensive.

Key words: 2(1*H*)-Pyridinethiones, 4(1*H*)-pyridinethiones, alkylation, acylation, desulfuration, *S*-dealkylation, nucleophilic substitution, annellation reactions, redox reactions.

CONTENTS

ABBREVIATIONS (ACRONYMS): DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAE, 2-(*N*,*N*-dimethylamino)ethanol; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; HOSA, hydroxylamine-*O*-sulfonic acid; LDA, lithium diisopropylamide; LR, Lawesson's reagent; MCPBA, *m*-chloroperoxybenzoic acid; TFAA, trifluoroacetic acid anhydride.

* To whom correspondence should be addressed.

1. INTRODUCTION

Pyridines are among the most intensively studied heterocyclic compounds and their chemistry has been reviewed frequently.

Recently the chemistry of sulfur-containing pyridines has received increasing attention. Bauer and Prachayasittikul[1] have reviewed new and interesting aspects of the chemistry and preparation of pyridyl sulfides and this topic will only be mentioned where appropriate. A complementary review by Furukawa[2] also underscores that sulfur-containing pyridines such as 2-pyridyl sulfoxides are becoming increasingly important and versatile catalysts and reagents in organic synthesis. The present review concentrates on the large number of syntheses of pyridinethiones and it should in principle be easy to find a method which can be tailored to prepare a pyridinethione which will meet specific new requirements, for example for use as a catalyst.

The present review is written with this aim in mind and is based on a CAS online search of 2(1*H*)-pyridinethiones (1969-beginning of 1986). The coverage of other sulfur-containing pyridines is less extensive and references to these types of compounds are only included where appropriate in connection with the main topic, the 2(1*H*)-pyridinethiones (or 2-pyridthiones).

Previous and more comprehensive reviews on sulfur and selenium compounds of pyridine have been written by Yale.[3]

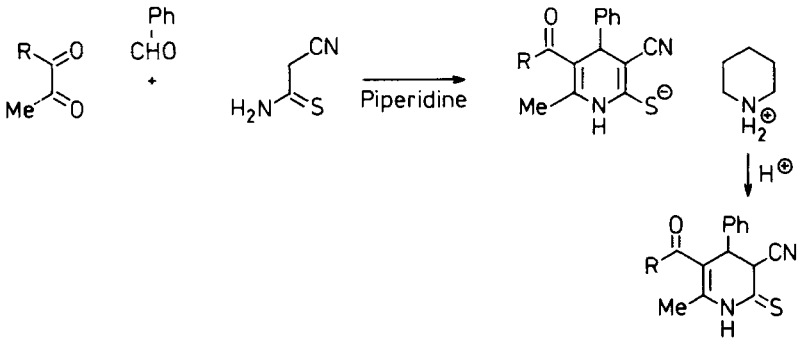
2(1*H*)-Pyridinethiones and other sulfur-containing pyridines are readily available *via* ring synthesis or *via* substitution reactions in the pyridine ring. The versatile chemistry of sulfur is also an important aspect which makes the preparation and functionalization of many pyridines possible starting from sulfur-containing pyridines. Examples are the use of pyridinethiones in the preparation of complex heterocyclic systems such as the syntheses of 5-deazapteridines reported by Taylor *et al.*[4] Other examples of the use of pyridinethiones as reagents in organic synthesis is the use of 1-acyloxy-2(1*H*)-pyridinethiones in controlled radical-chain reactions as reported by Barton *et al.*[5]

2. SYNTHESES FROM ACYCLIC STARTING MATERIALS

2.1. (1+2+3)-Syntheses

There is only a limited number of 2(1*H*)-pyridinethione syntheses from one-, two- and three-atom fragments, a useful example which constitutes a direct one-pot Hantzsch-liké

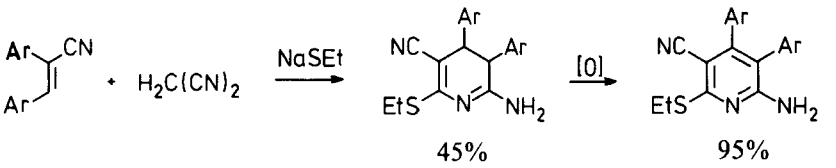
route has been described in a communication by Krause *et al.*[6] The final 3,4-dihydro structure was characterized by ^{1}H NMR, see also refs. 10a, 20 and 21.



A number of the pyridinethiones described in the following section (2.2.) could in principle also be prepared *via* similar one-pot reactions, provided the correct reaction conditions could be found. Depending upon the solvent and the reaction conditions used, monothiomalonoamides may in some cases react with methyl formate to give pyrimidinethiones or pyridinethiones.[7]

2-Cyanocinnamates and malononitrile yield 2(1*H*)-pyridones.[8]

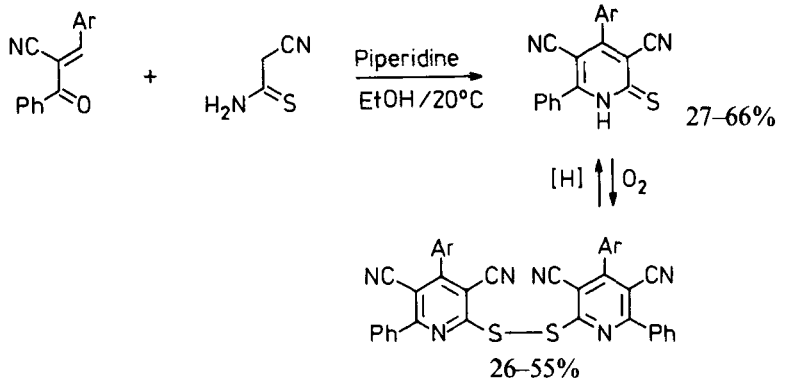
In the presence of sodium ethanethiolate 3,4-dihydropyridines are obtained. These are readily oxidized to 6-alkylthiopyridines with DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).



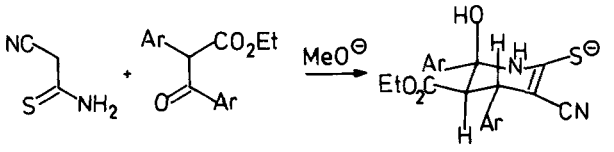
2.2 (3+3)-Syntheses

A large variety of 2(1*H*)-pyridones have been prepared by cyclization reactions of cyanoacetamides, cyanoacetates, and related compounds involving Michael-type additions and condensations under basic reaction conditions. The corresponding useful routes to pyridinethiones start from α-alkoxycarbonylthioacetamide or cyanothioacetamide. Thus Enchinas *et al.*[10] have shown that the reaction depicted below takes place at room temperature in dry ethanol, yielding the thiones in fair yields. Subsequent oxidation with various oxidation reagents such as iodine, dimethyl sulfoxide or sodium nitrite gives the disulfides. These are reduced with 2-mercaptoethanol or 1,2-ethanedithiol to 2(1*H*)-pyridinethiones.

If this reaction[10b] is carried out in MeOH/NaOMe solution the intermediate 1,4-

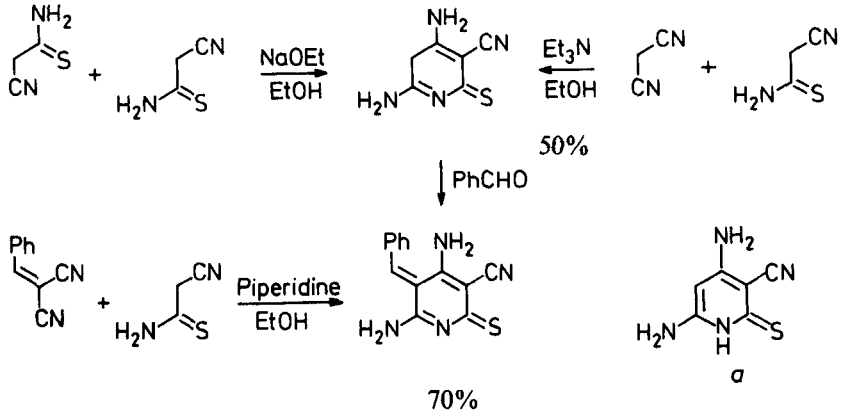


dihydropyridine-2-thiolate can be isolated. In this compound $J_{4,5} = 12$ Hz indicates an *E*-diaxial configuration, a result of strong intramolecular hydrogen bonding of the ester and the hydroxy groups.

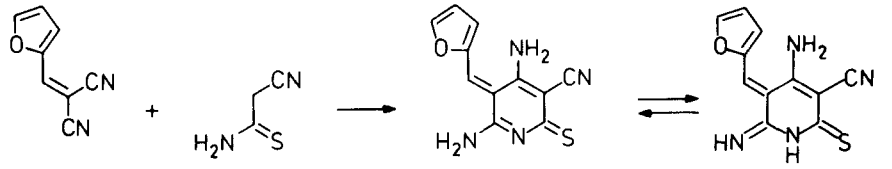


Daboun and Riad[11] have isolated the same 2(1*H*)-pyridinethione by reaction at reflux temperature without isolating the disulfide. The reaction conditions used in the reactions above seem important for the outcome. For example the presence of oxygen may result in formation of the fully aromatic system, high temperature and long reaction time will also favour the thermodynamically most stable product. In some cases disproportionation eventually results in aromatization with concomitant formation of the disulfide. Fahmy and Mohareb[12] describe the self-condensation of cyanothioacetamide as well as its reaction with malononitrile to give the thione shown below. The CH-form was proposed by Fahmy and Mohareb on the basis of IR and ^{1}H NMR spectra.

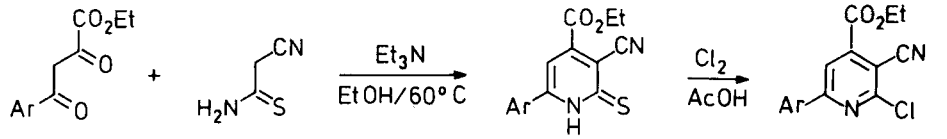
However, the NH-form *a* could not be completely excluded.



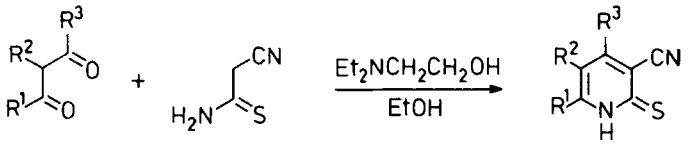
Subsequent reaction of the thione with benzaldehyde yielded the 5-benzylidene derivative, also accessible from cinnamonitrile and cyanothioacetamide. The corresponding furan or thiophene analogues also gave rise[13] to 5-methylenepyridine-2(1*H*)-thiones.



High yields of 2(1*H*)-pyridinethiones can be obtained from ethyl benzoylpyruvate and cyanothioacetamide.[14]

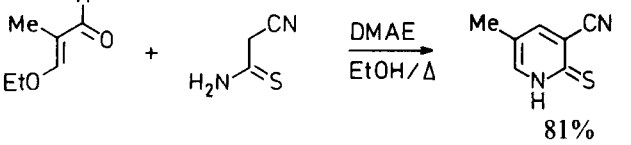


This reaction is actually an application of the original Schmidt-Kubitzek[15] synthesis of 2(1*H*)-pyridinethiones from cyanothioacetamide and β-diketones.

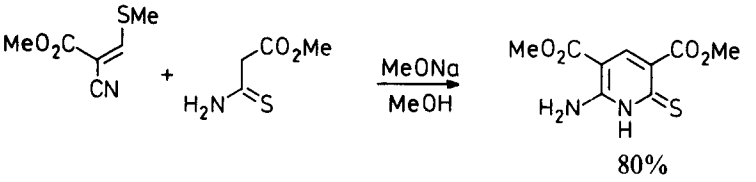


R^1	R^2	R^3	yield %
Me	H	Me	100
Ph	H	Me	95
Me	H	CO_2Et	93
Me	CO_2Me	Me	88
Me	CONHMe	Me	60
OH	H	Me	42
Me	H	H	90

Taylor *et al.*[4] obtained the related 3-cyano-5-methyl-2(1*H*)-pyridinethione from cyanothioacetamide in high yield; here the 1,3-dialdehyde equivalent results in formation of the fully aromatic 2(1*H*)-pyridinethione (DMAE = 2-(*N*,*N*-dimethylamino)ethanol).

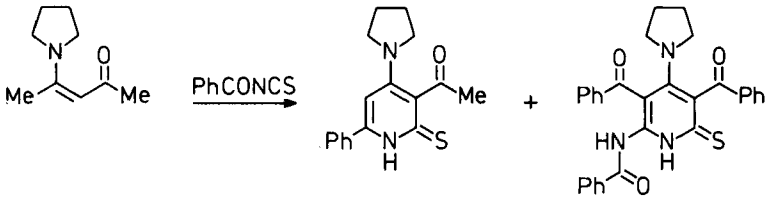


Gewald[16] has reported another effective synthesis of this type of thione using a vinyl sulfide as the carbonyl equivalent. A related synthesis is described in ref. 25.



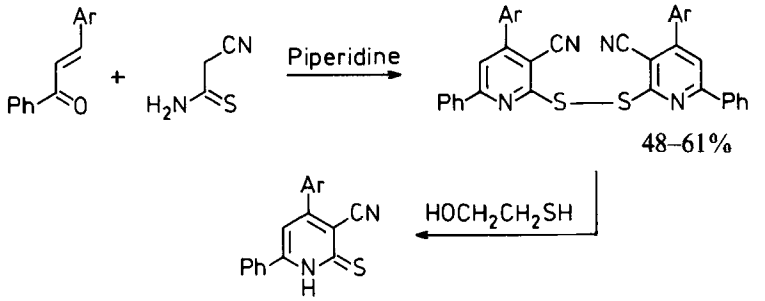
80%

Depending upon the reaction conditions used, diketone equivalents such as enamino ketones and benzoyl isothiocyanate in a complex manner give 2(1*H*)-pyridinethiones in modest yields.[17]



13% 27%

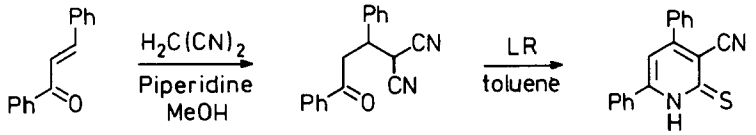
Soto *et al.*[18] have reported a comprehensive investigation of the reaction of chalcone and 2-cyanothioacetamide with piperidine as catalyst.



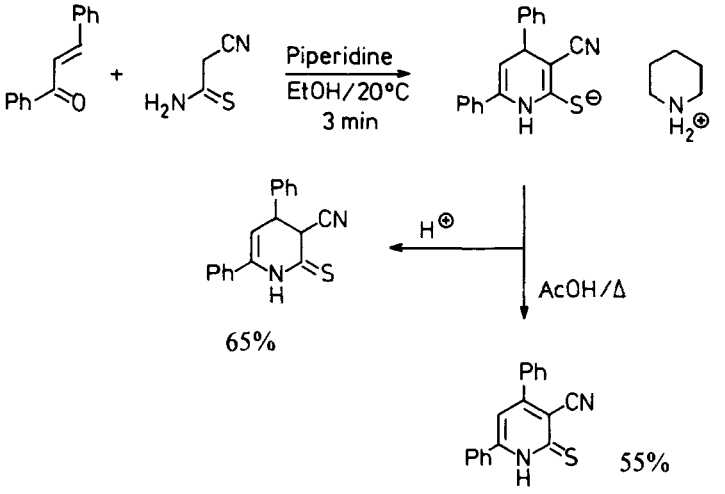
48–61%

30–68%

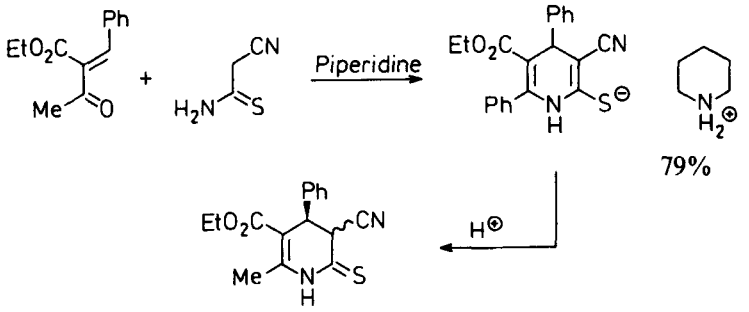
The oxidative dimerisation can be prevented by addition of 2-mercaptoethanol to the reaction mixture. An alternative method[18] yielding the same thione is to start from malonitrile using Lawesson's reagent[19] (LR) or P_2S_5.



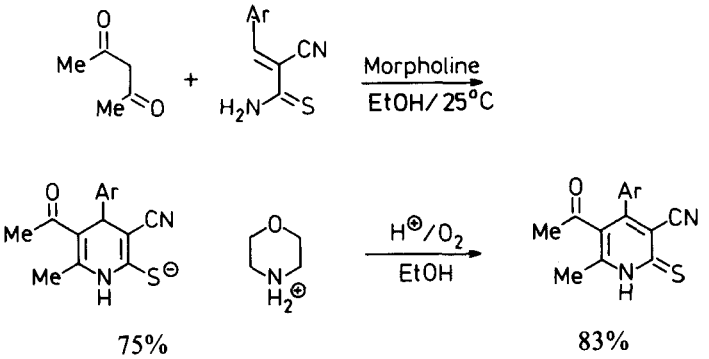
Essentially the same method has been reported by Krause *et al.*[20] If the reaction is run a few minutes at room temperature the relatively unstable 1,4-dihydropyridinium salt separates. Its isolation avoids the formation of disulfides. Its protonation leads to the 3,4-dihydro-2(1*H*)-pyridinethiones while prolonged heating in the presence of air gives the aromatic thiones in modest yields.



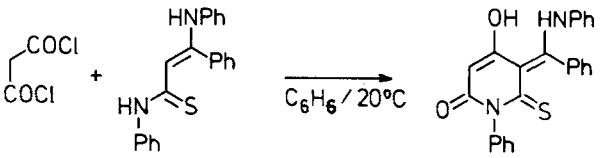
In the following example Krause *et al.*[21] report the isolation of a crystalline piperidinium salt from which a 55:45 mixture of *Z*- and *E*-isomers can be obtained; the structures of the *E*- and *Z*-forms were assigned from the ^{1}H NMR spectra on the basis of the Karplus equation.



The next scheme shows a variation[22] of this method in which acetylacetone is used as the active methylene component. The structures of the intermediate 1,4- and 3,4-dihydropyridines were again assigned on the basis of spectral data.

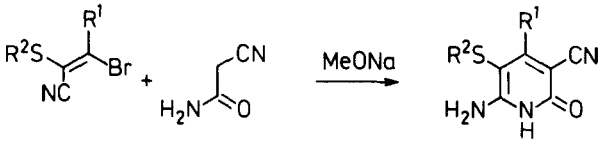


The following reaction[23] of malonyl chloride and a thioamide gives a 3-methylene-2(1*H*)-pyridinethione, the structure of which was tentatively assigned.



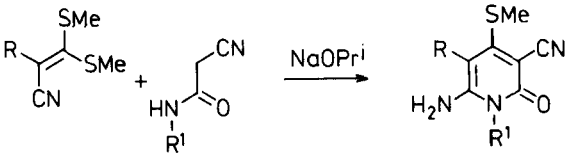
45%

Pochat[24] has reported a useful preparation of 3-alkylthio-2(1*H*)-pyridones from cyanoacetamides by the following method.



R^1 = H, alkyl aryl R^2 = alkyl, aryl 20–91%

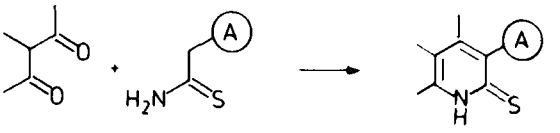
Ketenedithio acetals are versatile starting materials in the synthesis of heterocycles which here can be used for the preparation of a variety of alkylthio substituted heterocyclic systems since the methylthio group is easily displaced by a nucleophile. For example, α-cyanoketene dithioacetals and cyanoacetamides give 4-methyl-2(1*H*)-pyridones in the following reaction reported by Junjappa *et al.*[25]



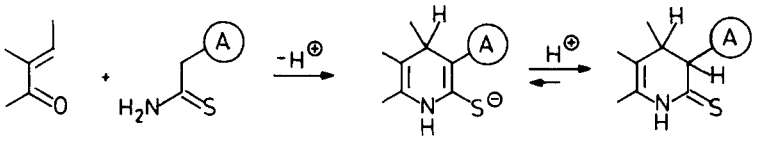
R = aryl, CN R^1 = alkyl 46–68%

The above reactions starting from various cyanothioacetamides can be summarized in the following way:

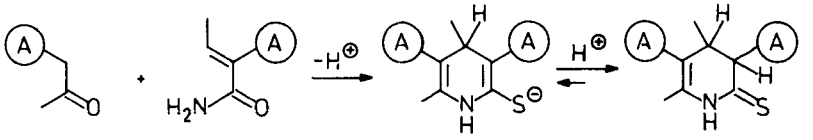
Depending on the oxidation state of the starting material the pyridine system formed in a given synthesis can either be fully aromatic or a reduced system. Thus a 1,3-diketone or its equivalent gives an aromatic system in which group A is an electron-withdrawing group.



On the other hand α,β-unsaturated ketones give rise to dihydropyridines.



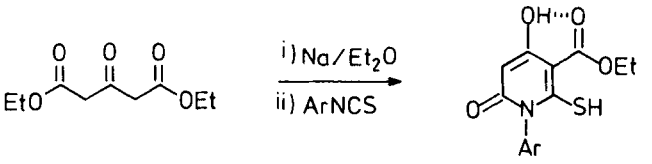
The primary product is a 1,4-dihydro system which upon heating rearranges to the corresponding 3,4-dihydropyridine. In a variation of this reaction the subsequent Michael reaction also results in the formation of a primary 1,4-dihydro system.



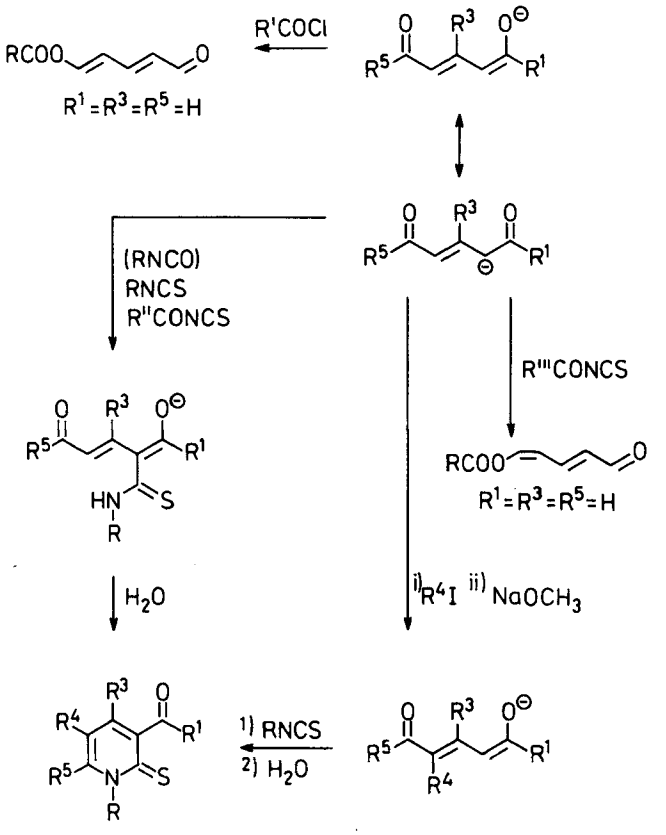
The 1,4-dihydropyridine systems in the examples above are only stable as the thiolate anions as demonstrated in a number of examples described in the previous section.

2.3 (4+2)-Syntheses

In 1939 Worral[26] prepared a 2-mercapto-4,6-dioxopyridine from the sodium enolate of diethylacetonedicarboxylate and an aryl isothiocyanate. The product was assigned the structure shown below on the basis of spectral data.[49]



In a series of papers Becher *et al.*[27] have demonstrated that the glutaconaldehyde enol anion and related C_5 enol anions in a general synthesis react with isothiocyanates (as well as with isoselenocyanates and with some arylisocyanates) to yield 3-formyl-2-(1*H*)-pyridinethiones:



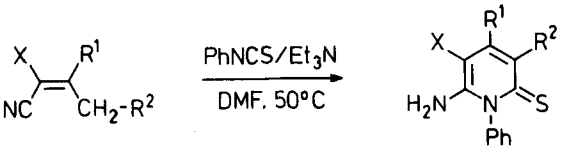
R^1 and R^5 = H, alkyl, aryl; R^3 = H, OR, SR, alkyl, aryl;

R^4 = H, alkyl.

R′ = alkyl, aryl, benzoyl; R″ = Me_2NCO; R‴ = EtO

R = alkyl, aryl

In a related base-catalysed reaction[28] phenyl isothiocyanate reacts with alkylidenemalononitriles to yield 6-amino-2(1*H*)-pyridinethiones.

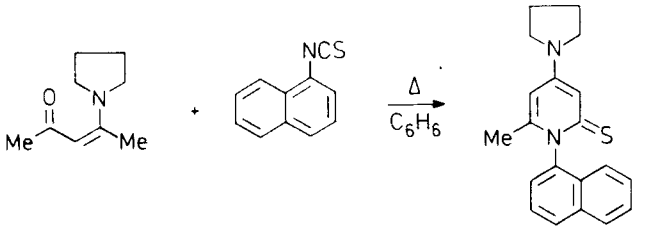


X = CN, CO_2Et 30–80%

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

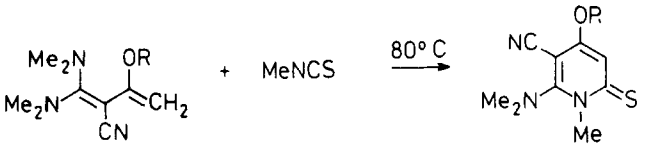
Enaminoketones have also been used in the (4 + 2)-synthesis of pyridinethiones, thus

1-naphthyl isothiocyanate and an enaminoketone gave[29] a modest yield of the pyridinethione shown below.



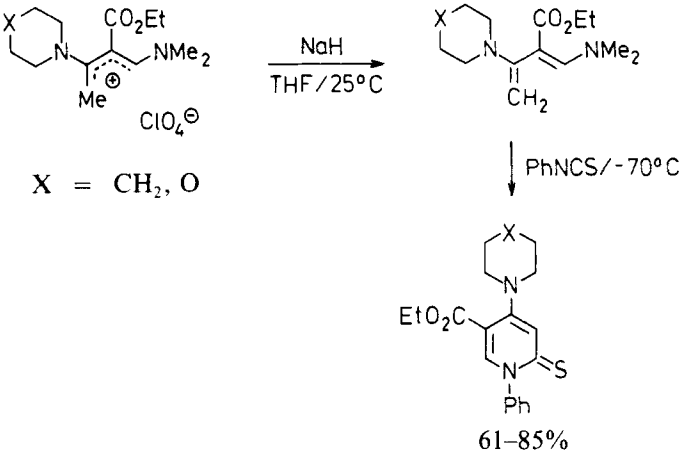
17%

Better yields are obtained[30] with vinylidenediamines and methyl isothiocyanate which cyclize with concomitant elimination of dimethylamine.



R = Me, Et 45–68%

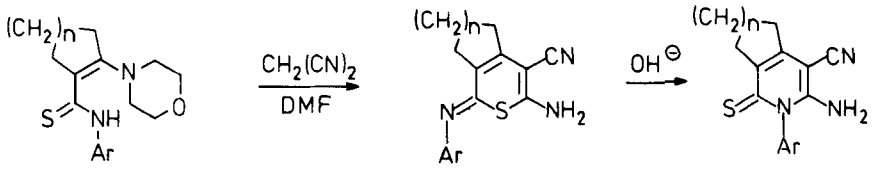
Vinylogous amidinium salts give reactive 1,3-butadienes with sodium hydride, whereupon reaction[31] with phenyl isothiocyanate gives pyridinethiones in fair yields.



X = CH_2, O 61–85%

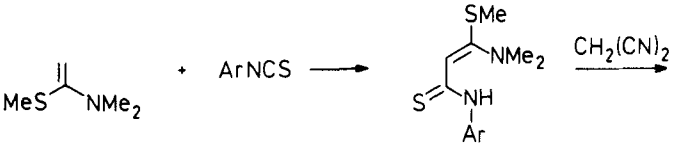
Gewald *et al.*[32] as well as Bogdanowicz-Szwed[33] have shown that β-aminothioacryloamides can readily be prepared from alkylidenemalononitriles and aryl isothiocyanates; these compounds react easily with malononitrile in a general synthesis yielding 6-amino-2(1*H*)-pyridinethiones.

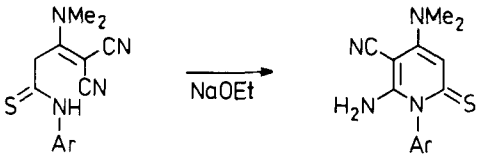
This reaction takes place *via* a base-catalyzed Dimroth-type rearrangement of an intermediate 5-amino-2-iminopyrane. Similar reactions are described in section 3.3.1.



n = 1, 2, 3 67–94%

In a related reaction polyfunctionalized 2(1*H*)-pyridinethiones can be obtained[34] from ketene *N*,*S*-acetals and malononitriles as shown below.

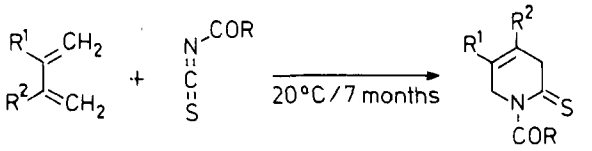




80–86%

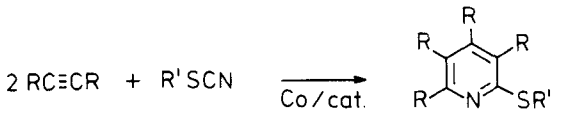
2.4. *Cycloaddition reactions*

Although a number of cycloaddition reactions leading to pyridines are known, relatively few reactions of this type yielding sulfur-substituted pyridines have been reported. However, 3,6-dihydro-2-pyridinethiones may be prepared from acyl isothiocyanates and dienes, albeit in a very slow reaction, as shown below in the example reported by Arbuzov and Zobova.[35]



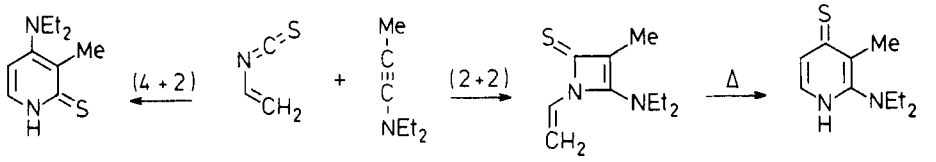
R^1, R^2 = alkyl; R = alkyl, aryl 39–50%

2-Alkylthiopyridines can be prepared[36] by cycloadditions of alkynes and alkyl thiocyanates in the presence of cobalt catalysts.



47–94% total yield

Dondoni, Kniezo, and Medici[37] have reported that (4+2)- and (2+2)-cycloadditions of heterocumulenes with vinyl isothiocyanates give rise to 2(1*H*)- and 4(1*H*)-pyridinethiones, resp., in low yields.

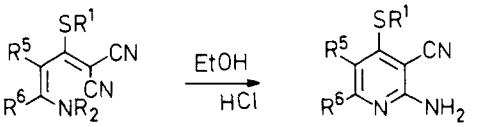


3.5% 20%

2.5. Syntheses by C_5 chain cyclisations

A number of pyridine syntheses are based upon cyclisations of C_5 units; also 4-alkylthiopyridines can be obtained by such methods using various ketene dithioacetals.

A convenient method described in a patent by Poetsch[38] starts from 1,1-dicyano-2-alkylthio-4-amino-1,3-alkadienes.



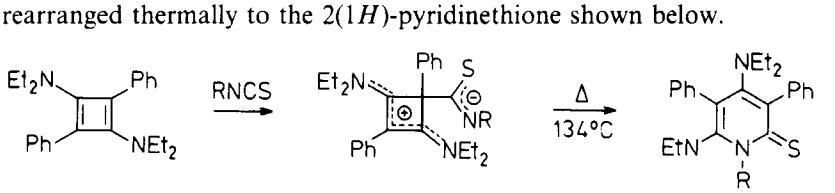
R^5, R^6 = alkyl

The starting materials used in the synthesis described above can easily be prepared from simple enamines and dicyanoketene dithioacetals. A related one-pot method has been reported by Yokoyama.[39]

3. SYNTHESES FROM CYCLIC STARTING MATERIALS

3.1. From 4-membered rings

The 4-membered antiaromatic ring system 1,3-bis-(*N*,*N*-diethylamino)-2,4-diphenyl-1,3-cyclobutadiene reacts with isothiocyanates to form[40] a zwitterionic product which can be rearranged thermally to the 2(1*H*)-pyridinethione shown below.

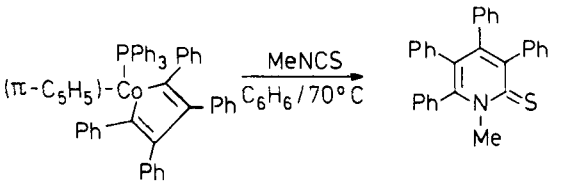


R = Ph, SO_2Ph

3.2. From 5-membered rings

Whereas pyridines can be prepared from a number of 5-membered rings only one example of a pyridinethione synthesis of this type seems to have been reported. Thus,

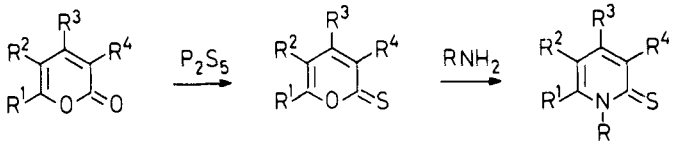
a cobaltacyclopentadiene[41] complex reacts with methyl isothiocyanate to give a low yield of 1-methyl-3,4,5,6-tetraphenyl-2(1*H*)-pyridinethione.



10%

3.3. *From 6-membered rings*

3.3.1. From pyranethiones This route is a useful synthesis for pyridinethiones provided the required pyrane can be obtained. Pyrones can easily be converted to thiopyrones which then react with amines to give 2(1*H*)-pyridinethiones.[42]

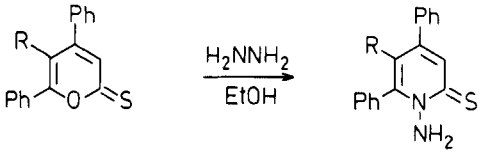


R^1, R^2, R^3 = aryl; R^2 = ArO 69–94%

R^4 = H; R = Me[42] and R = CH_2Ar[43]

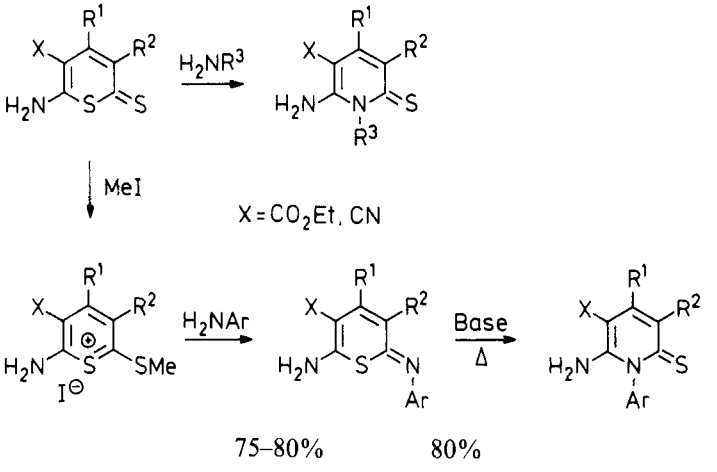
With benzylamines (R = CH_2Ar) 2-pyridinethiones are obtained[43] in 65–85% yield.

When hydrazine is used *N*-amino-2(1*H*)-pyridinethiones are obtained[44]. These compounds are excellent starting materials for (1–2)-annellations, see section 4.4.1.

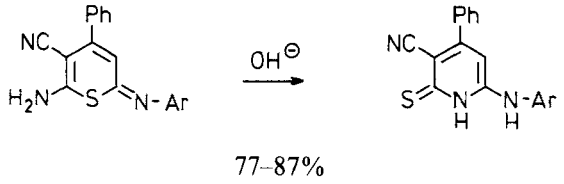


R = H, ArO 45%

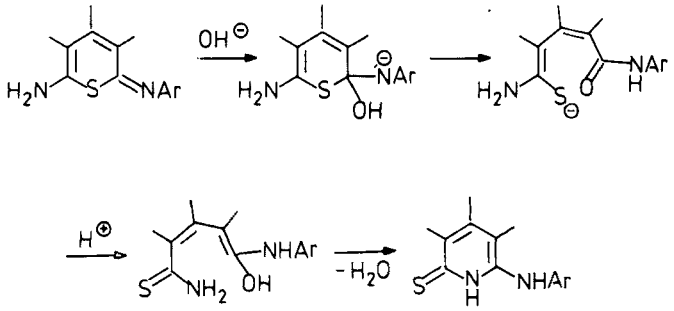
3.3.2. From thiopyranethiones Gewald *et al.*[45] have demonstrated that 6-amino-2(1*H*)-thiopyranethiones are readily accessible. By reaction with amines the corresponding 2-methylthiopyrylium salts yield 2-iminothiopyranes which, in a base-promoted Dimroth rearrangement, give 6-amino-2(1*H*)-pyridinethiones in fair yields.



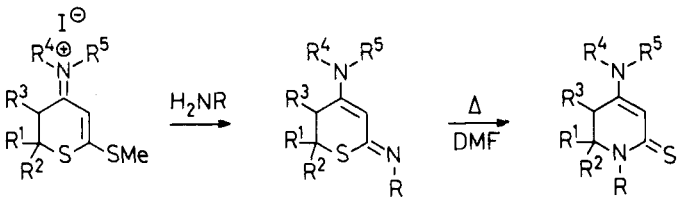
Later work by Augustyn and Bogdanowicz-Szwed[46] showed that a corresponding 2-iminothiopyrane under similar conditions also rearranges to the more stable 6-arylamino-2(1*H*)-pyridinethione system.



The reaction described above probably takes place *via* the mechanism described in the following scheme.

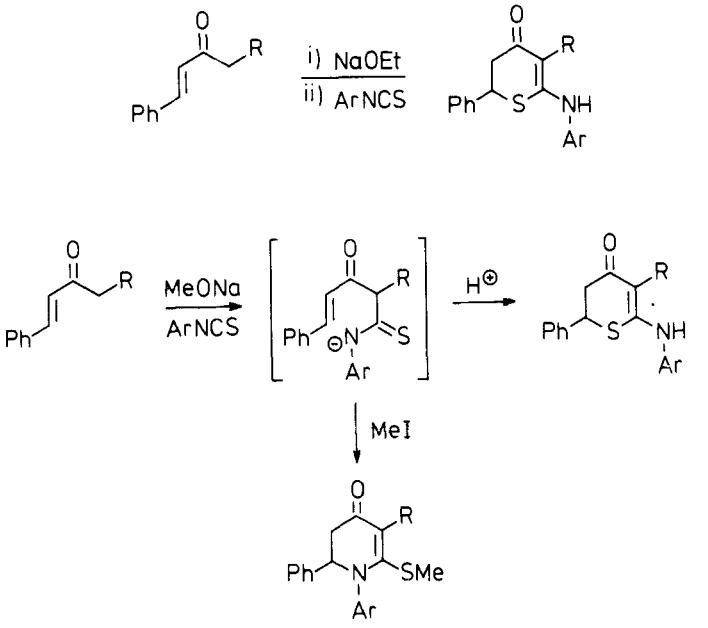


Apparently, nucleophilic attack takes place at the 2-imino carbon. Thus subtle changes in the type of substituents on the ring determine whether reaction takes place at C-2 or C-6. Schweiger[47] has reported a related thermal Dimroth rearrangement.



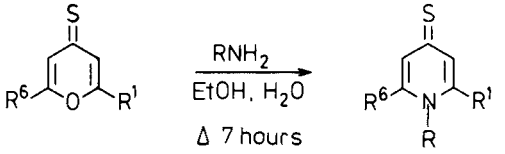
R = alkyl, aryl, R^1, R^2, R^3 = H, alkyl, aryl; R^4, R^5 = alkyl

Augustin *et al.*[48] demonstrated that the styryl ketone shown below (R = CN) yields a thiopyrane with phenyl isothiocyanate; however, if the intramolecular Michael addition of the mercapto group is prevented by *S*-methylation of the intermediate then the corresponding 2-methylthiopyridine is obtained. Treatment with base did not give any rearrangement to a pyridine system. Change of the substituent R from a cyano group to another electron-withdrawing group such as an acyl or an ethoxycarbonyl group likewise resulted[49] in formation of thiopyranes in fair yields.



R = CN, COMe, CO_2Et

4(1*H*)-Pyridinethiones can be prepared from amines and 4-pyranethiones as in the corresponding 2(1*H*)-pyridinethione series.[50]



R^1, R^6 = alkyl, aryl, benzyl

3.3.3. From other pyridines and pyridinium salts The most widely used method for the preparation of 2(1*H*)-pyridinethiones as well as of 4(1*H*)-pyridinethiones is nucleophilic substitution of halopyridines and halopyridinium salts. This method was originally used by Markwald *et al.*[51] in the synthesis of the parent 2(1*H*)-pyridinethione.

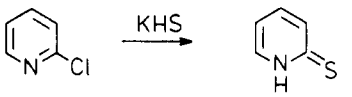
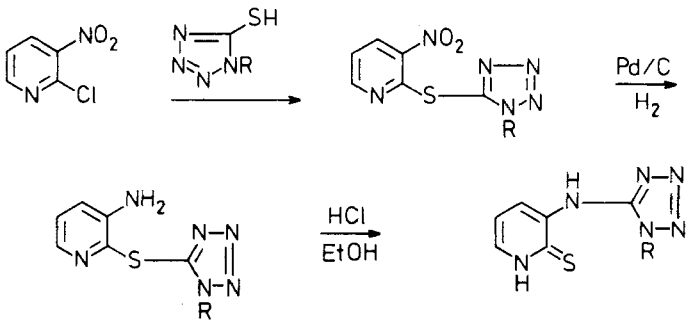


Table 1 compiles the most common sulfur nucleophiles which have been used in this type of synthesis.

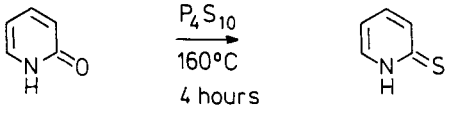
Table 1.

Nucleophile	Reference
KHS	51, 52, 53, 54, 55
NaHS	56, 57, 58, 59, 60, 61, 62
H_2NCSNH_2	55, 63, 64, 65, 66
$HSCH_2CH_2SH$	67, 68

An alternative method is based on the Smiles rearrangement[69] of an intermediate mercaptotetrazole.

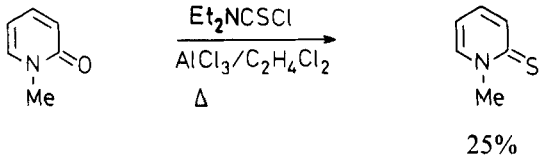


Another useful method is the preparation from a pyridone by reaction with the standard sulfuration reagent, phosphorus pentasulfide, as in the original Renault[70] synthesis shown below.

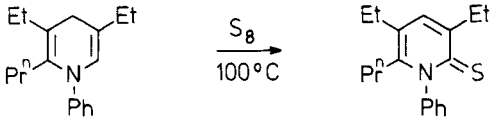


Toluene is often the solvent of choice for these types of reactions.[70,71,72,73]

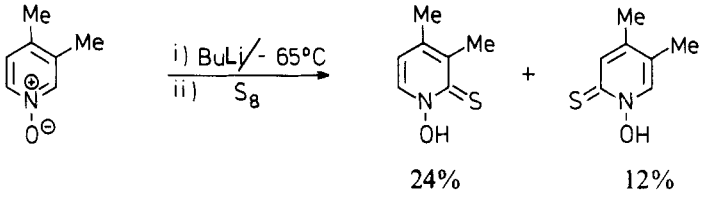
As an alternative to phosphorus pentasulfide, *N,N*-diethylthiocarbamoyl chloride has been used,[74] although this method seems to be less attractive due to the relatively low yield.



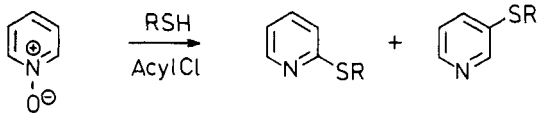
Likewise, elemental sulfur only gives a modest yield of the pyridinethione[75] starting from a 1,4-dihydropyridine.



Elemental sulfur reacts with the anions formed from pyridine *N*-oxides and butyllithium.[60,76] However, substantial amounts of disulfides are also produced.

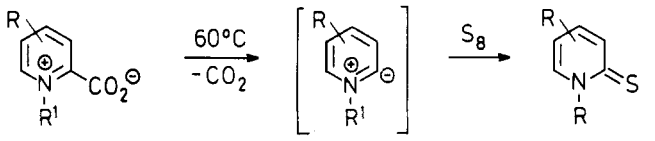


By deoxidative substitution of pyridine *N*-oxides with alkyl sulfides in the presence of alkylating agents it is possible to prepare 2- and 3-pyridyl sulfides.[77] In this reaction the 2-pyridyl sulfides are the main products.



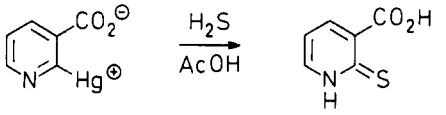
R = alkyl

The following reaction[78] is another example of the use of elemenal sulfur as an effective sulfuration agent in the decarboxylation of pyridinium-2-carboxylates.

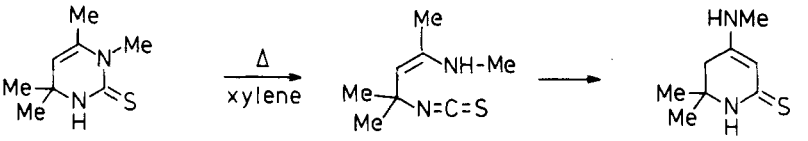


35–72%

Mercuration of pyridine in the 2-position is possible when pyridine-2,3-dicarboxylic acid anhydride is decarboxylated in the presence of mercury(II) oxide, the 2-mercuropyridine derivative formed then reacts with hydrogen sulfide to give the 2(1*H*)-pyridinethione[79] shown below.

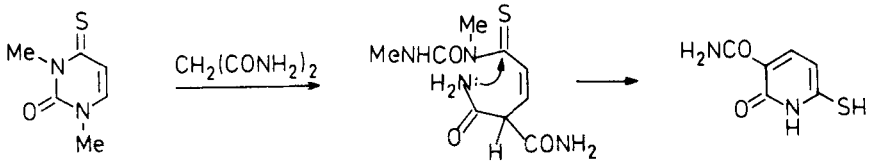


3.3.4. From diazines Heating of dihydro-2(1*H*)-pyrimidinethione derivatives[80] results in ring opening and formation of the corresponding 2-pyridinethione derivatives.



60%

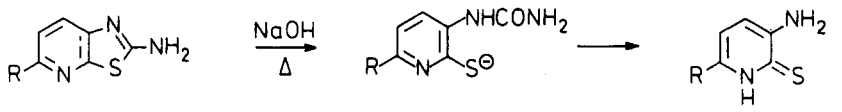
1,3-Dimethyl-4-thiouracil and malonoamide react in a related ring-opening ring-closure reaction[81] resulting in the formation of a 2(1*H*)-pyridinethione in high yield.



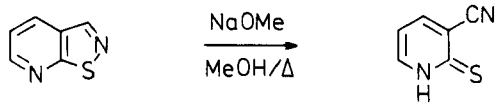
83%

3.4. From bicyclic systems

In some cases annellated pyridine systems can be used for the preparation of pyridinethiones. Thiazolo(5,4-*b*)pyridines[82] ring open with aqueous sodium hydroxide in the following reaction.



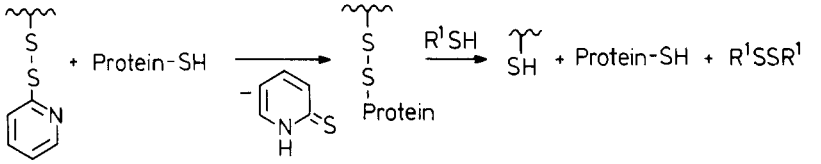
In a related reaction 1,2-thiazolo(5,4-*b*)pyridine can be ring opened with sodium methoxide.[83]



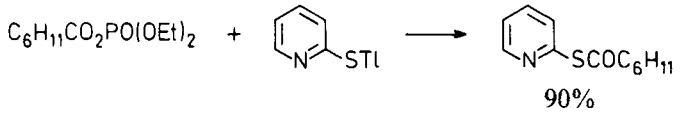
4. REACTIONS AND CHEMISTRY OF PYRIDINETHIONES AND RELATED COMPOUNDS

4.1. Alkylation and acylation reactions, pyridinethiones as reagents in organic synthesis

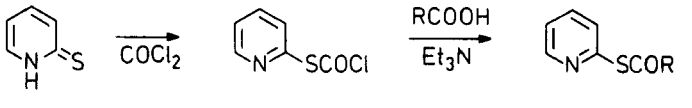
Pyridinethiones have been shown to be useful as reagents for various acylation and alkylation reactions; such reactions are based on the stability of the heteroaromatic 2(1*H*)-pyridinethione system which renders it an excellent leaving group. This property is also the reason for the use of 2-pyridyl sulfides (sepharose-glutathione 2-pyridyl sulfide) in affinity chromatography[84] of thiol-containing peptides. The scheme below outlines the principle.



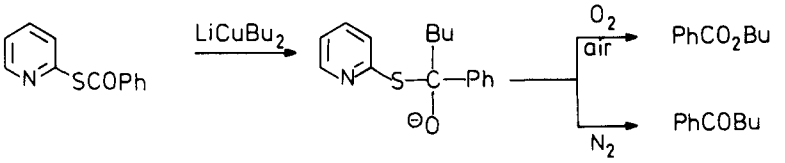
The biochemically important acetylcoenzyme A is a thiolacetic acid ester and functions as an acylation enzyme. A general and selective synthesis of thioesters via Tl(I) salts has been reported by Masamune *et al.*[85]



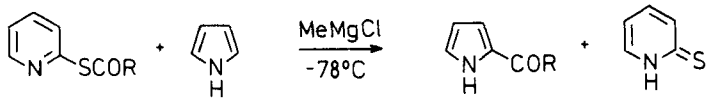
Usually 2-pyridinethiol carboxylic acid esters are prepared from 2,2′-dipyridyl disulfide. Another new method is the use of 2-pyridyl thiochloroformate reported by Corey *et al.*[86]



Such 2-pyridyl thiolesters are excellent acylation reagents and are becoming increasingly important in the synthesis of peptides, ketones, macrocyclic lactones and β-lactams,[86,87] for example.



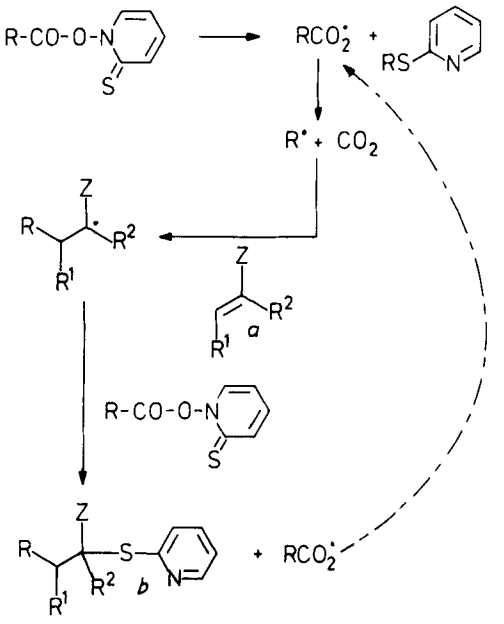
In the presence of oxygen, carboxylic acid esters are formed while reaction under nitrogen yields ketones. Another example is the selective *C*-acylation of pyrrols which can be used for natural product synthesis.[88]



R = alkyl, aryl 80–95%

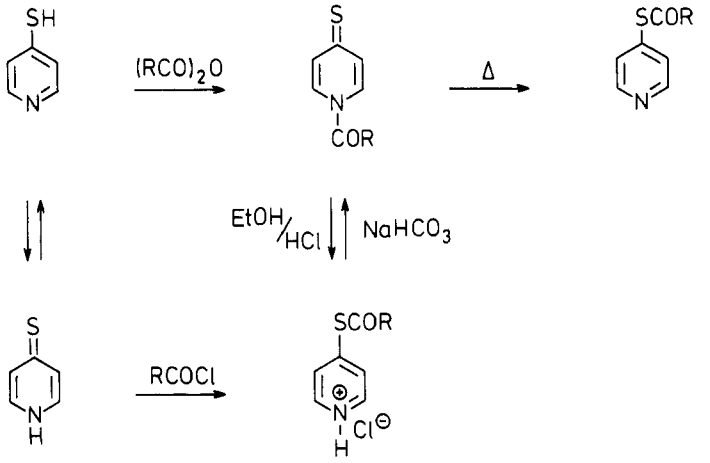
Related *C*-glycosidations of pyridyl thioglycosides have been described by Williams and Steward[89] while phosphorylations *via* *S*-(2-pyridyl) phosphorothioates have been described by Mukaiyama and Hashimoto.[90] The usefulness of 2-pyridyl sulfides in the total synthesis of complex natural products is exemplified by the elegant synthesis of bicyclomycin.[91]

An important new method for inducing radical chain reactions by irradiation of 1-acyloxy-2(1*H*)-pyridinethiones has been developed by Barton *et al.*[5,92]. This method avoids the usual complication due to polymerization in radical reactions; to some extent the pyridinethione system stabilizes the radicals, the overall reaction follows the mechanism shown below.

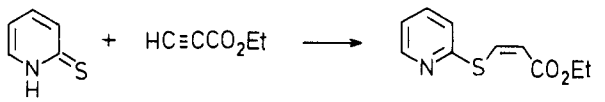


The radical thus formed can be intercepted with a variety of reagents, for example α,β-unsaturated compounds *e.g.* nitroolefins *a*. The nitro sulfides *b* (Z = NO_2) thus produced subsequently yield ketones after reductive cleavage with $TiCl_2$. Dialkylaminyl radicals can also be generated *via* 1-hydroxy-2(1*H*)-pyridinethione carbamates.[93]

2-Pyridinethiols and 2(1*H*)-pyridinethiones normally give *S*-substituted products by reaction with various halides.[1] However, *N*- or *S*-acylation of 4(1*H*)-pyridinethiones is strongly dependent upon the reaction conditions;[94] heating in acetonitrile rearranges the *N*-acylated thione to the thiol ester according to the scheme shown below.

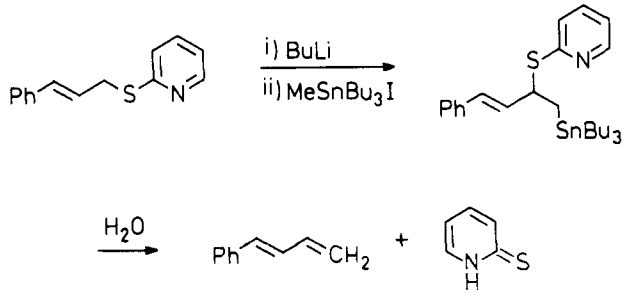


Dou *et al.*[95] have described the selective *S*-alkylation of 2(1*H*)-pyridinethione under phase transfer conditions. Reaction of acetylenes with 2(1*H*)-pyridinethiones gives vinylthiopyridines in a Michael type reaction[96]; an example is shown below.



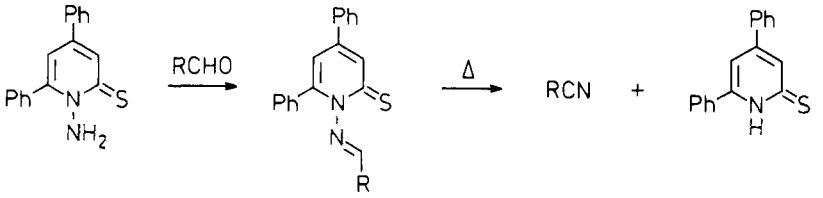
60%

Mukaiyama *et al.*[97] have prepared various olefins *via* 2-pyridyl sulfides, again using reactions in which the formation of the parent 2(1*H*)-pyridinethione is the major driving force. A related synthesis has been reported by Ochiai *et al.*[98]



73%

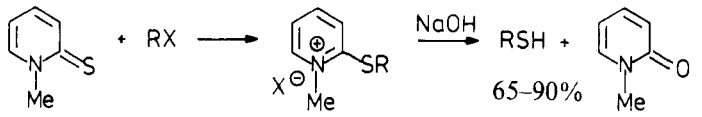
The following example demonstrates how a 2(1*H*)-pyridinethione can be used for the preparation of nitriles from aldehydes.[99]



R = aryl, styryl 90–98%

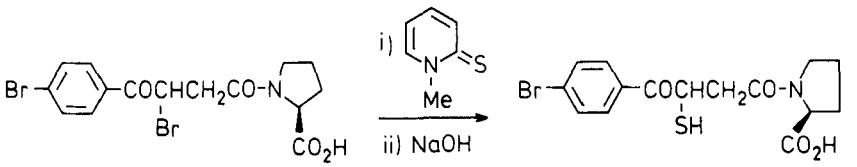
4.2. Desulfuration, S-dealkylation and rearrangement reactions

4-Alkylthiopyridines are usually prepared[1] from 4-halopyridines with methanethiolate salts. Recent examples of this type of reaction can be found in ref. 100. Yamada *et al.*[101] have used 1-methyl-2(1*H*)-pyridinethiones for the preparation of alkanethiols.

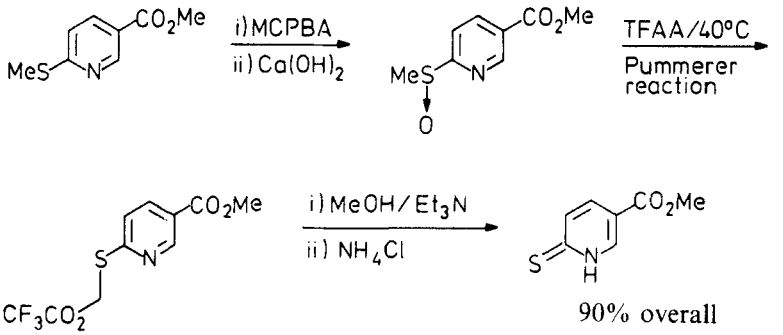


81–84%

In the following example[102] such a thiolation reaction was used for the preparation of a complicated thiol without affecting the carbonyl groups present in the molecule.

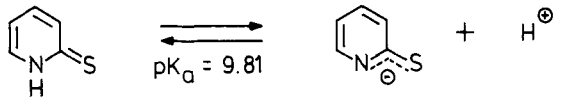


It is possible to carry out *S*-demethylation of 2-methylthiopyridines via the following reaction sequence.[103] It involves a regiospecific Pummerer rearrangement to a hemithioacetal acetate which is readily hydrolyzed. (MCPBA = 3-chloroperbenzoic acid, TFAA = trifluoroacetic acid anhydride.)



90% overall

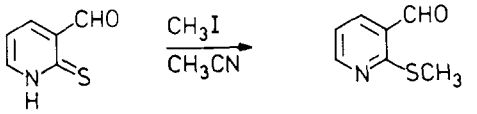
Substituents on a pyridinethione ring will have an influence on the reactivity of the thioamide sulfur. The parent 2(1*H*)-pyridinethione system is a weak acid and can formally give an ambident anion (pK_a = 9.81).



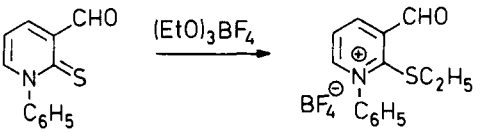
Alkylation and acylation take place on sulfur, but due to the stability of the pyridinethione system the S-CO and the S-CH_3 bonds in the compounds below are relatively weak.

The effect of a 3-formyl group can be used here as an example for the demonstration of the influence which this electron-withdrawing substituent has upon the reactivity of the 2(1*H*)-pyridinethione ring.

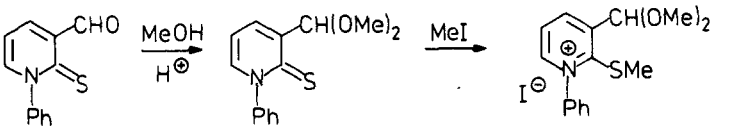
Alkylation of 3-formyl-2(1*H*)-pyridinethione with methyl iodide in acetonitrile gives the 2-methylthio derivative in high yield.[14]



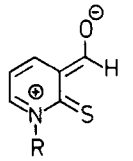
However, 1-phenyl-3-formyl-2(1*H*)-pyridinethione cannot be *S*-alkylated with methyl iodide, but only with the harder Meerwein reagent[152] since the thioamide in this case is tertiary.



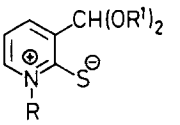
If the 3-formyl group is deactivated by acetalization the *S*-alkylation proceeds easily with methyl iodide. When the alkylation was carried out in an alkohol a two-step reaction took place, acetal formation followed by *S*-alkylation.



As a conclusion the following two systems can be used to explain the reactivity.

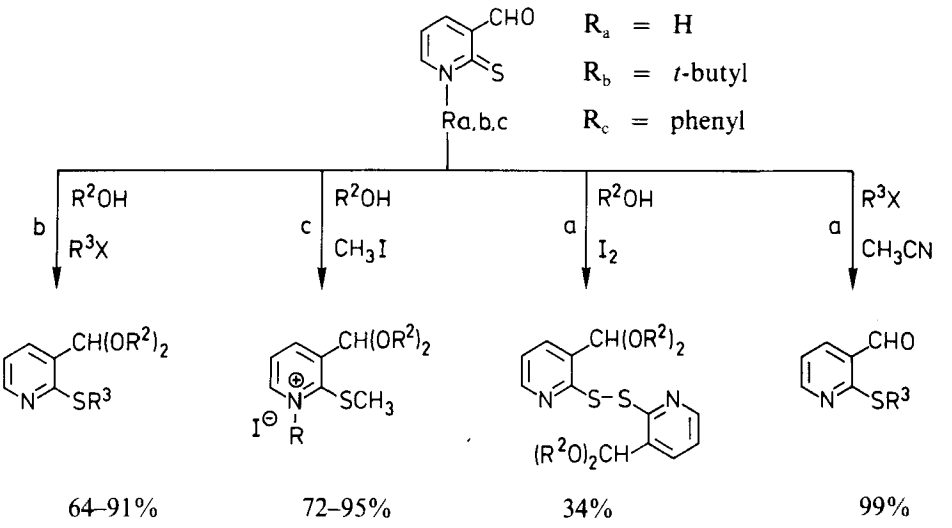


difficult to
alkylate on sulfur

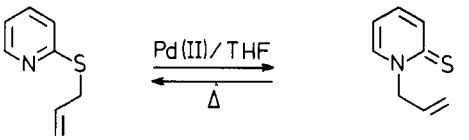


alkylates
easily on sulfur

The alkylation of this type of pyridinethiones can be summarized[104] as follows.

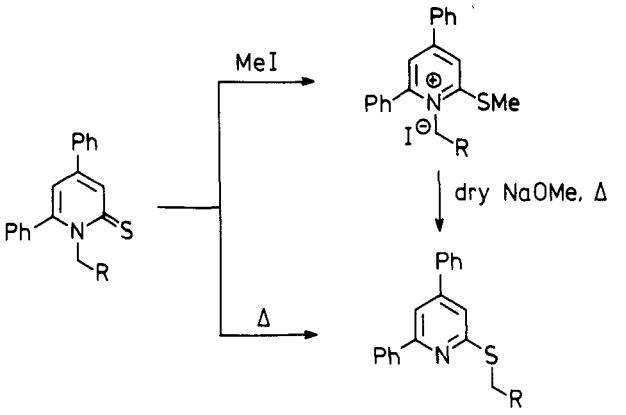


In the pyridine series Tamura *et al.*[105] have demonstrated that a hetero-Claisen reaction is catalyzed by palladium, in the example shown below the *N*-allyl-2(1*H*)-pyridinethione was actually isolated as a palladium(II) complex.



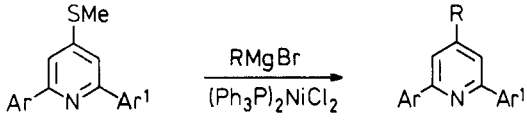
100%

In a related rearrangement Molina *et al.*[106] have found that a 1-benzyl-2-methylthiopyridinium salt gives a 2-benzylthiopyridine when heated with dry sodium methoxide.



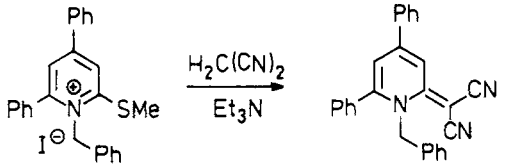
4.3. Nucleophilic substitution of alkylthio groups

2- And 4-alkylthio groups on pyridine rings do not react with nucleophiles unless additionally activated by, *i*) electron-withdrawing substituents in the *o*- or *p*-positions to sulfur, *ii*) quarternization of the ring, or *iii*) by complex formation. For example, Wenkert *et al.*[107] have demonstrated that it is possible to replace a pyridine 4-methylthio group with hydrogen, an alkyl or an aryl group *via* a nickel-catalyzed Grignard reaction.



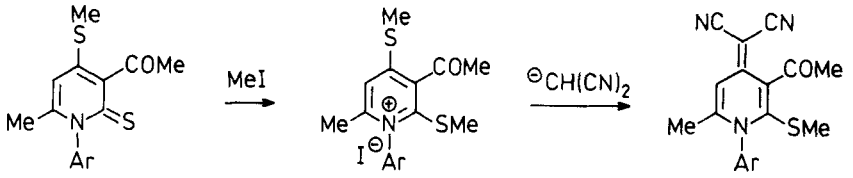
R = H, alkyl, aryl 23–89%

As described above, quarternization renders the resulting pyridinium ring more suceptible to nucleophilic attack and the following reaction demonstrates the reactivity of a 2-methylthiopyridinium salt towards the malononitrile anion,[108] which gives 2-methylene-1,2-dihydropyridine derivatives in high yields.



In a pyridinium salt containing two methylthio groups at the 2- and 4-positions nucleophilic displacement reactions with carbanions are regioselective taking place at the latter position as demonstrated in the following synthesis of a 4-methylene-1,4-dihydropyridine.[109] The regioselectivity may be due to steric hindrance of the 2-position.

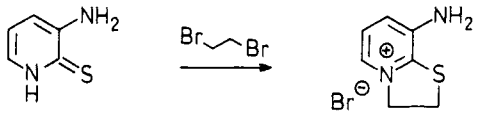
Therefore, nucleophilic displacement reactions in alkylthio substituted pyridines and pyridinium salts are useful reactions when the required alkylthiopyridines are readily available, for example from ring closure reactions.



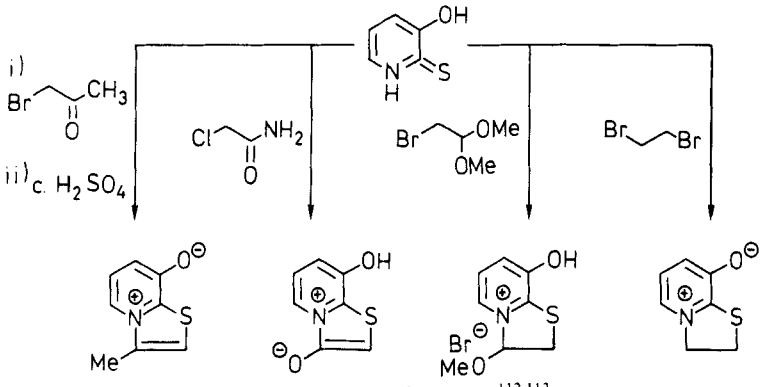
4.4. Annellation reactions based on pyridinethiones

4.4.1 (1–2)-Annellations The reactions of methylthio groups described above have in many cases been used in annellation reactions with simultaneous elimination of methanethiolate, leading to various types of fused pyridines. However, preparation of annellated pyridines from 2(1*H*)-pyridinethiones with retention of sulfur will be discussed first.

Starting from simple 2(1*H*)-pyridinethiones or from the corresponding 3-hydroxy-2(1*H*)-pyridinethiones Undheim and his group have carried out a number of annellation reactions leading either to a fused pyridinium system or, in the case of 3-hydroxy-2(1*H*)-pyridinethione as the starting material, to a betaine system. The ambient 3-hydroxy- as well as the corresponding 1-amino- or 3-amino-2(1*H*)-pyridinethione systems are interesting since alkylation may take place at three positions. However, in all cases alkylation first takes place at sulfur. In the reaction shown below alkylation is carried out with 1,3-dibromoethane.[110]



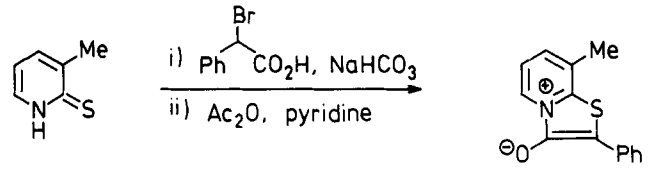
With 3-hydroxy-2(1*H*)-pyridinethione as substrate[111] a 9-oxidobetaine is obtained.



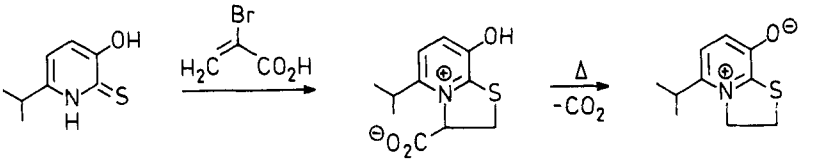
Similar betaines are obtained from α-halo ketones.[112,113]

When the reaction with the α-halo ketone is followed by reaction with concentrated sulfuric acid the fully aromatic thiazolo[3,2-*a*]pyridinium betaine is obtained.[114]

With α-bromophenylacetic acid the oxido-2-phenyl-2,3-dihydrothiazolo[3,2-*b*]pyridinium betaine is obtained.[115]

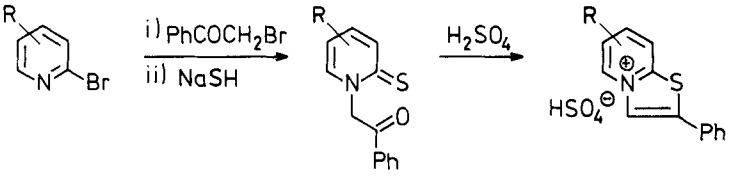


When 2-bromopropenoic acid is used the primarily formed betaine easily decarboxylates which results in the formation of the 9-oxidobetaine system.[116,117,118]



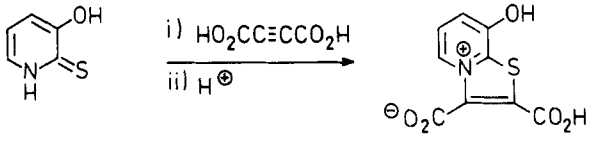
92%

Synthesis of fused thiazolopyridines is also possible starting from a 2-bromopyridine using *N*-alkylation followed by thiolation as shown in the reaction scheme[119,120] below.

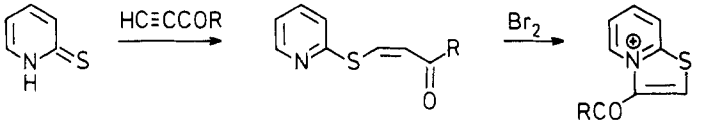


88%

Mercapto groups are often reactive in Michael-type additions, a variety of thiazolopyridines can be obtained *via* this type of reaction;[121] the synthesis shown below is an example.

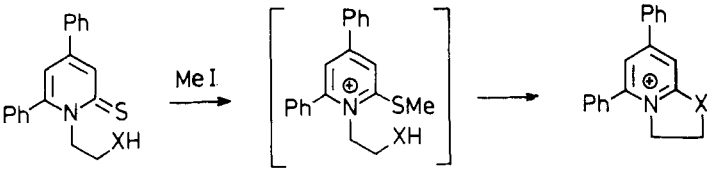


2-Propynyl derivatives give vinylthiopyridines which can be cyclized by reaction with bromine in an intramolecular reaction, again taking advantage of the easy alkylation of sulfur.[122]



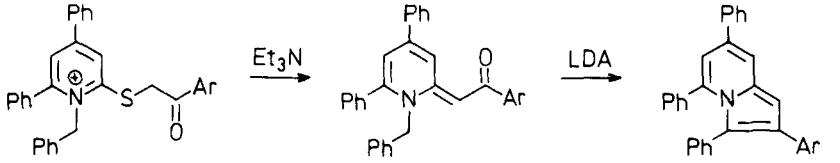
R = Me, OEt, NHMe, $CHMe_2$ 70–80%

The second type of annellation reactions discussed in the beginning of this section involves nucleophilic displacement of a 2-methylthio group, these reactions have been used extensively by Molina *et al.* The reaction below is an example of such an intramolecular displacement reaction[123] in which a thiolate reacts as the nucleophile.

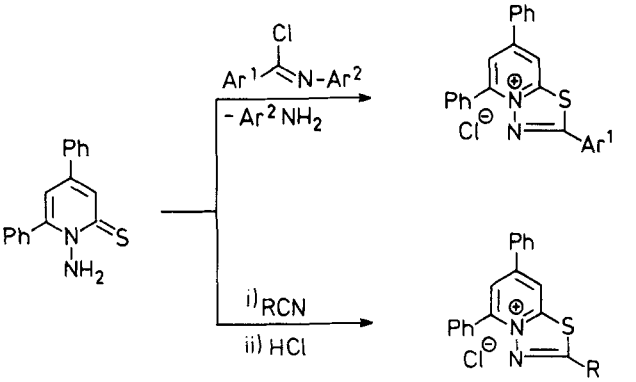


X = S, 54%; X = O, 79%

A useful indolizine synthesis is based on a 2-phenacylthiopyridinium salt[124] which upon treatment with triethylamine, probably *via* a thiirane intermediate, eliminates sulfur. Subsequent cyclization to indolizine is promoted by LDA (LDA = lithium diisopropylamide).

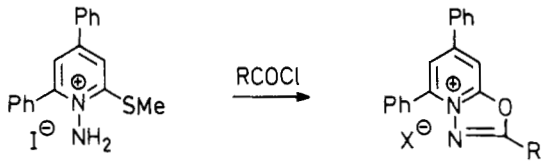


In an extensive investigation Molina and his group have used 1-amino-2(1*H*)-pyridinethiones as versatile starting materials for annellated pyridine systems, for example reactions with both imidoyl chlorides and with nitriles give 1,3,4-thiazolo[3,2-*a*]pyridines.[125]



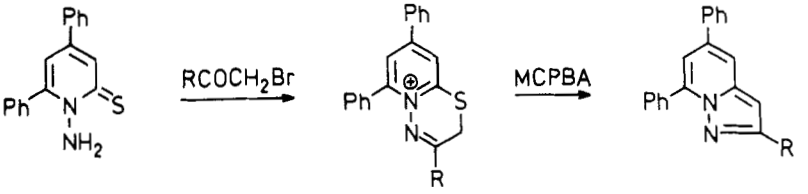
R = alkyl, aryl 70–98%

S-Alkylation of 1-amino-2(1*H*)-pyridinethione gives a pyridinium salt in which intramolecular displacement reactions easily can take place; thus, reaction with acid chlorides directly yields oxadiazolo[3,2-*a*]pyridinium salts.[126]



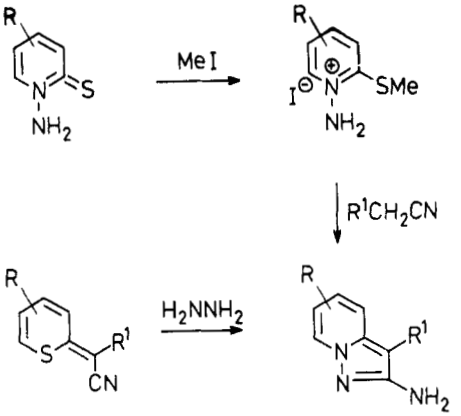
72–90% ($X^- = ClO_4^-, BF_4^-$)

The synthesis described in the scheme below is also an example of an intramolecular reaction in which the α-ylid formed by treatment with base, after oxidation with *m*-chloroperbenzoic acid (MCPBA) to the *S,S*-dioxide leads to elimination of sulfur resulting in the formation of pyrazolo[1,5-*a*]pyridines.[127]



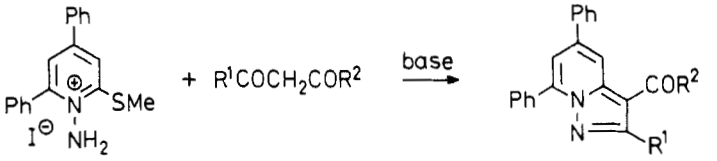
82–97% 49–88%

The examples in the scheme below reported by Gewald *et al.*[128] and by Molina *et al.*[129] are of the same type, as the synthesis described above; here the aminothiazolo[2,3-*a*]pyridines were also prepared from the methylene-1,2-dihydrothiopyrane.[129]



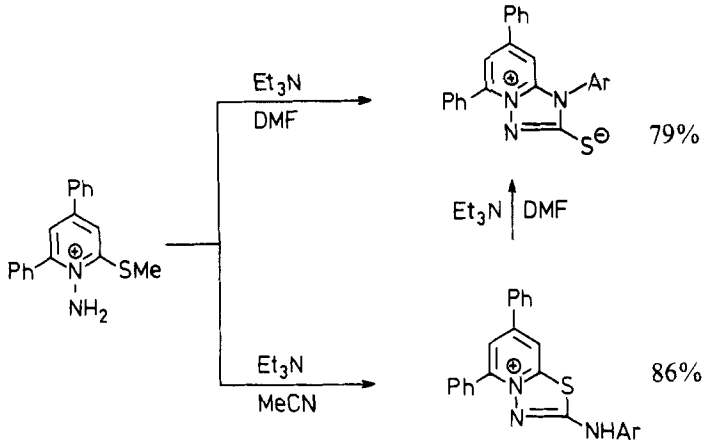
R^1 = CN, CO_2R, $CONH_2$, $CONHNH_2$ 17–82%

Various 1,3-dicarbonyl compounds react similarly.[13]

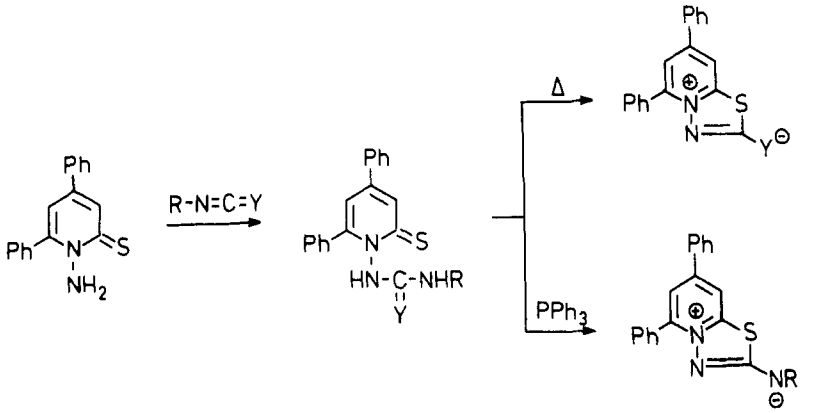


R^1 = alkyl, aryl, OH; R^2 = Me, OMe, OEt 50–75%

Displacement and rearrangement take place with aryl isothiocyanates, resulting in the formation of mesoionic pyridine systems.[131]

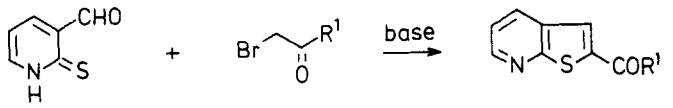


With an *N,N'*-disubstituted urea or a thiourea group at the pyridine nitrogen another type of mesoionic pyridine was prepared by Molina *et al.*[131]



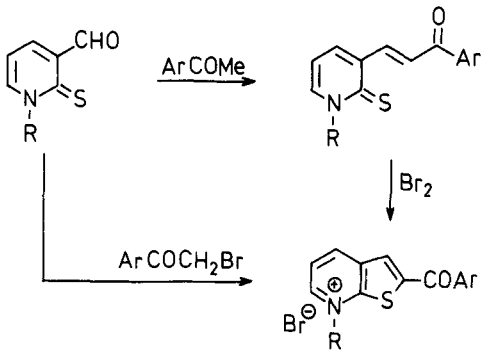
Y = O, S; R = aryl, CO_2Et

4.4.2. (2–3)-Annellations A large number of (2–3)-annellations using suitable 3-substituted 2(1*H*)-pyridinethiones as starting materials are known and some of the more representative examples will be discussed here. The most important system are the thieno[2,3-*b*]pyridines which have been extensively studied and reviewed by Barker.[132] A simple synthesis of this ring system is the reaction of 3-formyl-2(1*H*)-pyridinethione with a 2-halocarbonyl compound.[133]



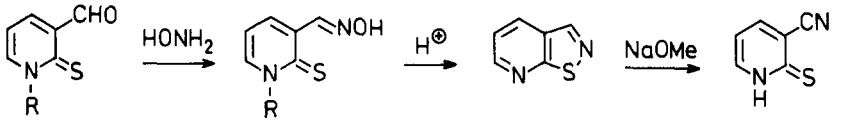
R^1 = OEt, alkyl, aryl 64–92%

By a related reaction the *N*-quarternary system can be obtained *via* the condensation reaction shown below or directly as described above.[134]



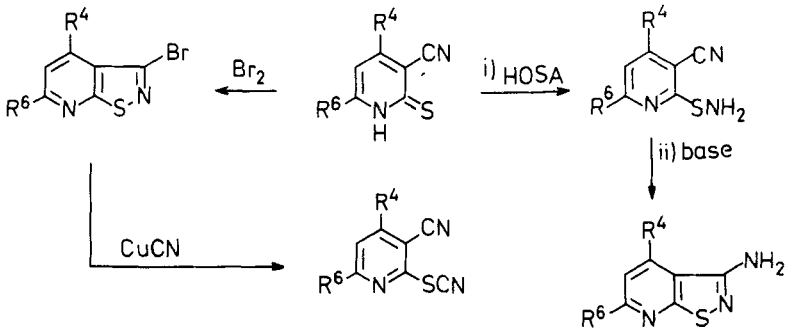
R = alkyl, aryl 37–76%

From the 3-formyl-2(1*H*)-pyridinethione it is also possible to obtain the parent isothiazolo[5,4-*b*]pyridine in high yield, directly or *via* the oxime.[133] Treatment of the oxime with mineral acid promotes cyclization and elimination of the *N*-substituent, if this is a *t*-butyl group, which under the acidic reaction conditions is eliminated as isobutene.



R = H, Me, *t*-Bu, $CH_2C_6H_5$

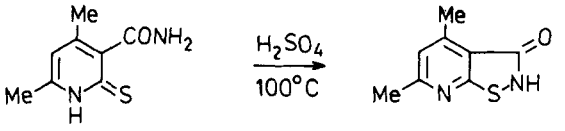
Due to the easy ring opening of the isothiazole ring isothiazolo[5,4-*b*]pyridine is a convenient starting material for 3-cyano-2(1*H*)-pyridinethione.[135] Gewald *et al.*[136] have used this compound as starting material for the preparation of 3-aminoisothiazolo-[5,4-*b*]pyridines by treatment with hydroxylamine-*O*-sulfonic acid (HOSA).



37% (R^4 = R^6 = Me) 46–88% R^4 = H, alkyl, CO_2Et; R^6 = alkyl, aryl

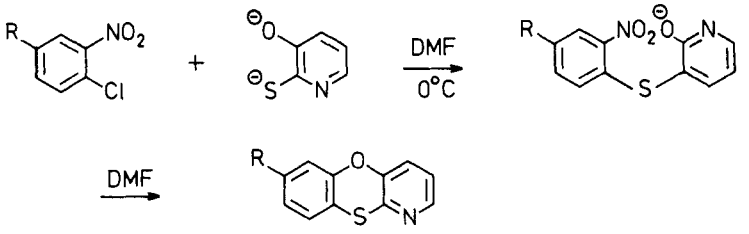
Bromination results in the formation of the corresponding 3-bromoisothiazolo[5,4-*b*]-pyridine; interestingly, ring opening of this isothiazole with copper(I) cyanide gives

3-cyano-2-thiocyanatopyridine.[135] Treatment of a 3-carbamoyl-2(1*H*)-pyridinethione with concentrated sulfuric acid results in oxidative cyclization to a 3-hydroxyisothiazolo[5,4-*b*]pyridine.[137]



80%

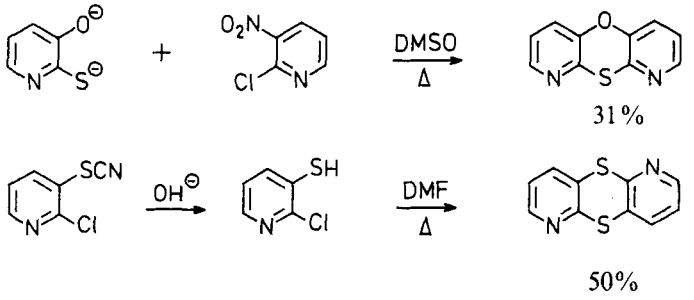
The pharmacologically active phenothiazine ring system is well known,[138] and simple related azaphenoxathiins can be prepared from 2(1*H*)-pyridinethiones.[139]



R = NO_2, Cl 19–20%

By the method described above Davies *et al.*[140] obtained acceptable yields of the corresponding 1,9-diazaphenoxathiins.

The corresponding 1,6-diazathianthrene was obtained from 2-chloro-3-mercaptopyridine as shown below; here the first sequence involves a displacement of the nitro group by the oxygen anion.

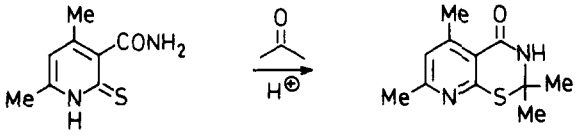


31%

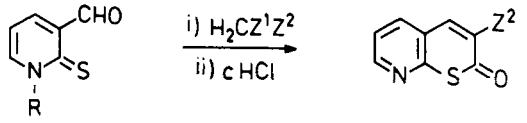
50%

Related 1-azaphenoxathiins have also been prepared.[141]

From 3-carbamoyl-2(1*H*)-pyridinethione Zawisza and Malinka[142] have obtained a fair yield of the pyrido[3,2-*e*]thiazine shown below.

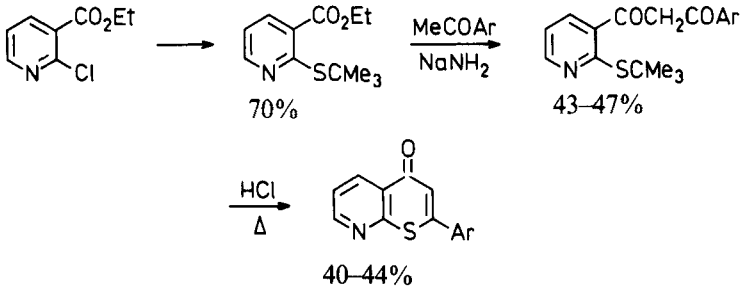


The thiopyrano[2,3-*b*]pyridine system can be prepared either from the 3-formyl-2(1*H*)-pyridinethiones or their *N*-protected equivalents *via* Knoevenagel or Wittig reactions with active methylene compounds.[143]



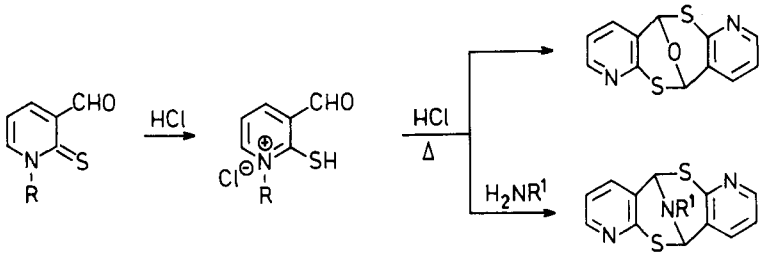
R = H, *t*-Bu; Z^1 = Z^2 = CN, CO_2Et, $CONH_2$ 31–92%

Thiopyrano[2,3-*b*]pyridines can be prepared *via* the reaction sequence shown below. Here isobutene is easily eliminated from the 2-*t*-butylthiopyridine yielding the 2(1*H*)-pyridinethione which cyclises under the reaction conditions.[144]



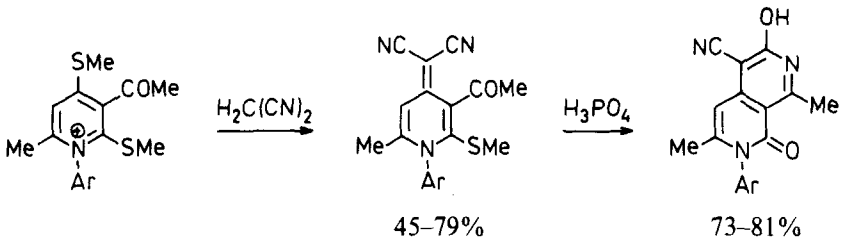
When 3-formyl-2(1*H*)-pyridinethione or a precursor is refluxed with hydrochloric acid a high yield of a bis-monothioacetal, a 1,5-dithiocine,[145] is obtained.

Heating of the pyridinethione with an amine hydrochloride results in the formation of a 5,11-imino-1,5-dithiocine in high yield[146] when the group R is *t*-butyl or methylbenzyl which can be eliminated under the reaction conditions.



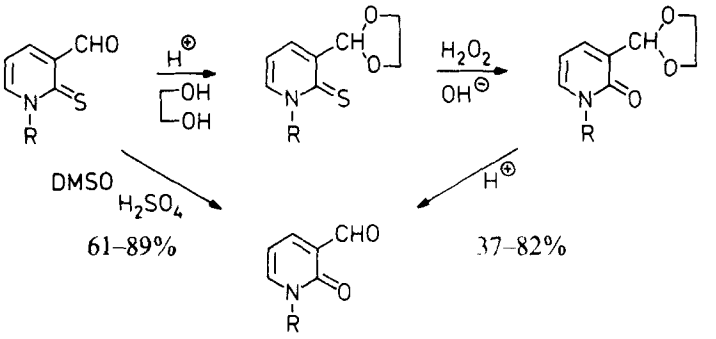
R H, *t*-Bu, $CH(CH_3)C_6H_5$; R^1 = alkyl, aryl 31–93%

1-Aryl-2,4-bisalkylthiopyridinium salts are used for the preparation of naphthyridones. As part of this synthesis, the resulting methide is cyclized in acid.[109] Again, displacement of the 4-alkylthio group is due to the activation of the quarternary pyridinium ring.

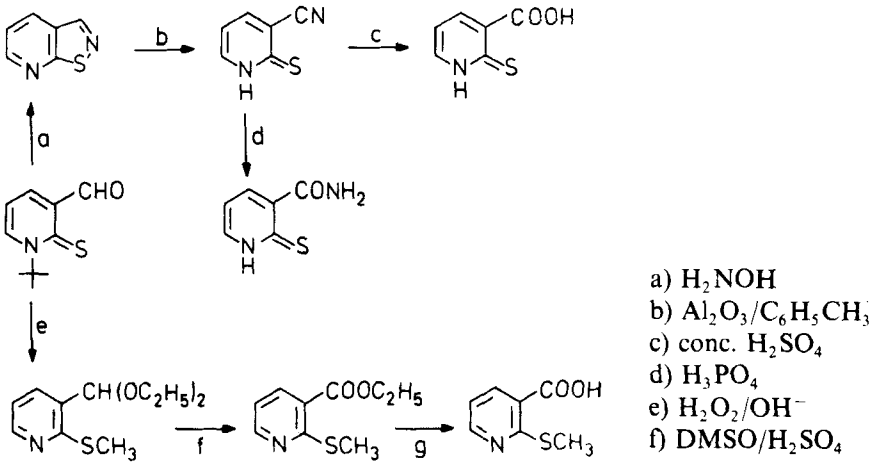


4.5. Redox reactions

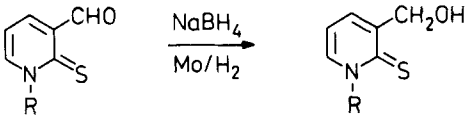
The thioamide sulfur of the 2(1*H*)-pyridinethiones is easily oxidized resulting in the formation of the corresponding 2(1*H*)-pyridones. The oxidation of the 3-formyl-2(1*H*)-pyridinethiones constitutes an example.[147]



The scheme below outlines[149] a number of functionalizations which have been carried out in this series. It is seen that oxidation of the formyl group to the carboxylic acid can be carried out *via* the nitrile without affecting the thioamide sulfur.



Borohydride reduction of the formyl group results in a high yield of the 3-hydroxymethyl-2(1*H*)-pyridinethione. This product can also be obtained by high-pressure hydrogenation with a molybdenum catalyst (Harshaw W-0602 T 1/8, 100 °C, 100 atm.), without affecting the pyridine ring.[83]

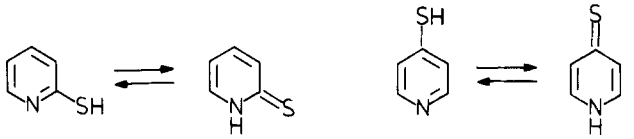


R = H, *t*-butyl, methyl, α-methylbenzyl, cyclohexyl, phenyl

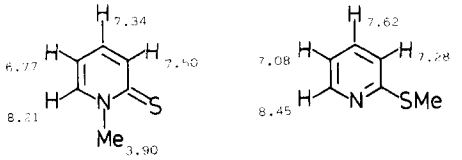
Electrochemical determination of trace amounts of pyridinethiones can be carried out *via* cathodic stripping voltammetry.[148] A related careful electrochemical investigation of 2(1*H*)-pyridinethione-5-carboxylic acid has been reported by Lejeune *et al.*[149]

4.6. Tautomerism, spectra, and structures

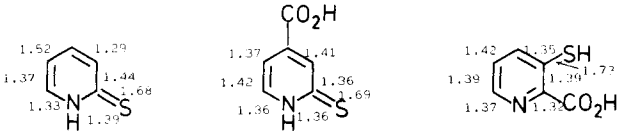
In the equilibria of 2- and 4-mercaptopyridine with their pyridthiones the thione forms are strongly favoured over the mercapto forms in solution, while the mercapto forms predominate in the gas phase.[150]



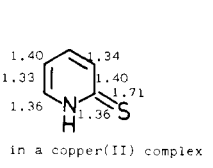
The mercapto form was also found to predominate in the gas phase in the 3-formyl-2(1*H*)-pyridinethione series.[151] Ref. 151 also reports the ^{1}H and ^{13}C NMR spectra of these compounds while access to the NMR data for other 2(1*H*)- and 4(1*H*)-pyridinethiones can be found in ref. 152.

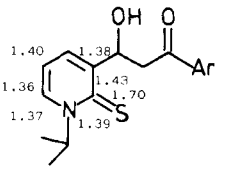


The X-ray structural determination of the parent 2(1*H*)-pyridinethione system was first reported by Penfold[153] and German *et al.*[154] who report the following data for three sulfur derivatives of pyridine, bond lengths in Å.



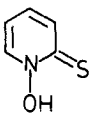
Other structure determinations can be found in ref. [155] which gives the following bond lengths for the 2(1*H*)-pyridinethione ring in a copper(II) complex.





4.7. Biological activity of some pyridinethiones

A number of 2(1*H*)-pyridinethiones are biologically active. 1-Hydroxy-2(1*H*)-pyridinethione and its salts are used commercially as bactericides.

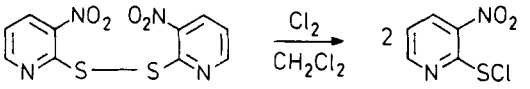


The toxicity of this pyridine derivative has been reviewed by Black and Howes.[156] A useful compilation of biologically active sulfur derivatives of pyridines has been reported by Göbel *et al.*,[157] other aspects of the biological activity of 2(1*H*)-pyridinethiones can be found in ref. 158.

5. OTHER SULFUR DERIVATIVES OF PYRIDINES RELATED TO 2(1*H*)-PYRIDINETHIONES

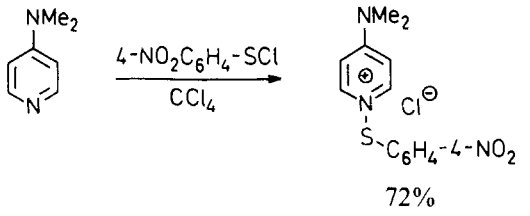
Deoxidative substitution of pyridine *N*-oxides by thiols in the presence of an acid chloride or an acid anhydride leads to 2- and 3-pyridyl sulfides.[159]

Pyridinesulfenyl halides can be prepared from dipyridyl disulfides.[160]



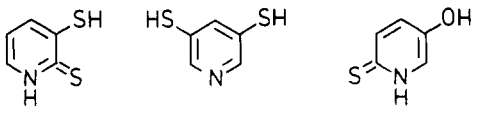
100%

Pyridine *N*-sulfides have been isolated and unambigously characterised by Abramovitch *et al.*[161] for the first time. The preparation is outlined in the following scheme.



72%

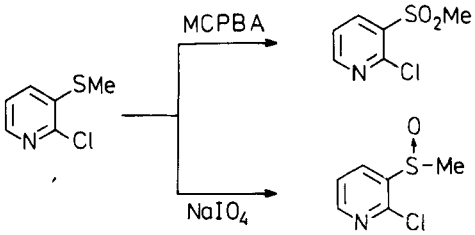
New pyridinethiols and thiones have been prepared by Krowicki *via* various replacement reactions.[162]



a *b* *c*

Compound *a* was found to be unstable, it begins to evolve H_2S at 130 °C and melts at 216–220 °C; *b* has m.p. 122–124 °C and *c* has m.p. 210–202 °C.

3,3′-Thiobispyridine can be obtained in 60% yield from 3-pyridinethiol and 3-bromopyridine.[100c] A large number of macrocyclic compounds possessing 2,5-pyridylene subunits connected by carbon-sulfur linkages have been prepared from 2,6-dihalopyridines by Newkome *et al.*[163] A number of 3-(alkylthio)-2-halopyridines have been prepared by functionalization of various pyridine derivatives.[164] Oxidation of such 3-alkylthiopyridines can give sulfoxides or sulfones depending on the reaction conditions; for example:



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