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Review of Some Recent Syntheses, Reactions and Bio Activities of Pyridyl Sulfides

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REVIEW OF SOME RECENT SYNTHESES, REACTIONS AND BIOACTIVITIES OF PYRIDYL SULFIDES

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Some of the recent chemistry of pyridyl sulfides is presented. Syntheses of pyridyl sulfides by aromatic nucleophilic displacements of halopyridines by thiolate ions or S-alkylations of pyridthiones (pyridinethiols) are reviewed. Other viable, but perhaps more limited syntheses, are also reviewed. The scope of deoxydative substitutions of pyridine 1-oxides by thiols to form 2- and 3-pyridyl sulfides is discussed. The preparation of 2-pyridyl sulfides by free-radical decarboxylative rearrangements of 1-acyloxy-2-pyridthiones is evaluated. Classical syntheses of 3-pyridyl sulfides by diazotizing 3-aminopyridines, followed by displacement of the diazonium group by thiols, are illustrated. Preparations of 4-pyridyl sulfides from 4-nitropyridine 1-oxides and 1-(4′-pyridyl)pyridinium salts are discussed. Cyclizations of some pyridyl sulfides to thienopyridines and related systems are included. A brief review of some of the bioactivities of pyridyl sulfides, sulfoxides and sulfones is presented.

Key words: Pyridyl sulfides, synthesis, halopyridines, pyridthiones, thienopyridines, bioactivities.

CONTENTS

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INTRODUCTION

This Review summarizes some of the more general methods of synthesis of pyridyl sulfides. In addition, some of the reactions and bioactivities of pyridyl sulfides are discussed. The synthetic sections are organized according to reaction type. The examples were chosen by surveying the literature through 1985 Chemical Abstracts.

Although the majority of the reactions in this review are drawn from the literature of pyridines, the reader should be aware that similar reactions take place in such heterocycles as the quinolines, diazines (pyridazines, pyrimidines, pyrazines, and their benzo derivatives) and in important polyaza systems, such as purines and pteridines.

1. THE SYNTHESIS OF PYRIDYL SULFIDES BY AROMATIC NUCLEOPHILIC SUBSTITUTIONS (DISPLACEMENTS)

1.1. General Considerations

Aliphatic sulfides are usually synthesized by nucleophilic displacements of halides, sulfonates or epoxides by thiolate ions. Such reactions on sp^3-hybridized carbons are considered generally to be of the S_N2 type.[1] Substitution of a halo group (X) by a thiolate ion (RS^-) on an sp^2-hybridized alkene carbon takes places only in special cases, for example at the β-carbon of an α,β-unsaturated system (e.g., X–CH = CH–Y = Z). Such a displacement involves, first, nucleophilic attack by RS^- at the β-carbon of the electrophilic alkene to generate an intermediate [RS–CH(X)–$\ddot{C}$H–Y = Z] (Michael reaction) which is followed by the elimination of X^- (retro-Michael) to form RS–CH = CH–Y = Z.[2] Substitutions of groups on aromatic rings by thiolate ions are well-established routes to aromatic sulfides. Mechanistically, aromatic nucleophilic

substitutions are placed into four general categories, S_N1, S_NAr, benzyne, and $S_{RN}1$,[3] but only two of these are discussed in any detail as they pertain to this Review.

1.2. Substitutions by an S_NAr Mechanism

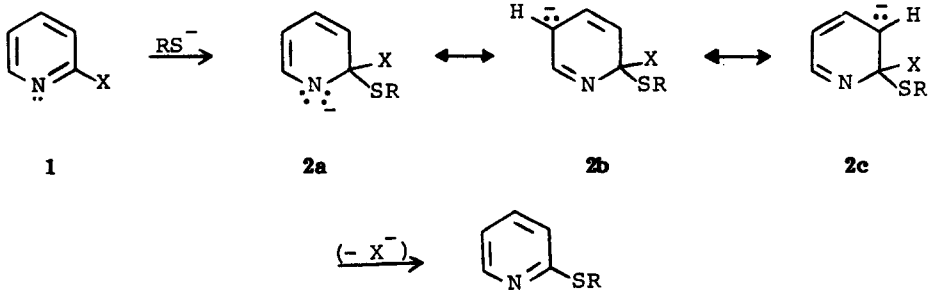
Aromatic nucleophilic substitutions *via* an S_NAr mechanism are initiated by attack of the nucleophile at the carbon bearing the leaving group to form a transient resonance-stabilized tetrahedral intermediate, followed by the departure of the nucleofuge to restore aromaticity. Electron-attracting groups ortho and/or para to the departing group greatly enhance the rates of such substitutions. When passing from benzenoid to heteroaromatic systems of the azine and diazine type, inherent structural considerations due to the presence of the ring nitrogen(s) determine the relative rates of similar displacements at various ring positions.

1.2.1. Substitutions of halobenzenes by thiolate ions Displacements of unactivated halobenzenes by thiolate ions tend to be relatively slow but recent reports indicate that these reactions are speeded up considerably when aprotic polar solvents are employed. In such solvents, the attacking nucleophile is less solvated and assumes greater nucleophilic character. Unactivated aryl halides are substituted by either $C_2H_5S^-$ or $(CH_3)_2CHS^-$ in hexamethylphosphoramide (HMPA) between 0 and 100 °C in excellent yields.[4] For example, the sodium salt of 2-propanethiol converts 1,2,3-trichlorobenzene at 100 °C to 1,2,3-*tris*(isopropylthio)benzene in 3 hours in 88% yield.[4] In a related development, tetraethyleneglycol dimethyl ether (tetraglyme) is reported as the best solvent for the substitution of all of the halo groups in polyhalobenzenes.[5] Thus, 1,2,4-trifluoro- or 1,2,4-tribromobenzenes react with the sodium salt of 1-dodecanethiol in tetraglyme at 150 °C (20 hours) to produce the corresponding tris-sulfides in 75 and 68% yield, respectively. The authors tried these displacements initially in *N*,*N*-dimethylformamide (DMF), to avoid the use of the carcinogenic HMPA, but discovered that tetraglyme is the solvent of choice.

1.2.2. Substitutions of halopyridines by thiolate ions No attempt is made to critically analyze the relative rates of reactions in terms of the structure of the attacking nucleophiles, the nature of the leaving groups, effects of solvents, steric encumbrance towards the formation of tetrahedral intermediates and other factors affecting such substitutions. Rather, the relative rates of similar displacements by thiolate anions are examined in terms of the structure of the halopyridine and the position of the halo group relative to the ring nitrogen.

Selective substitution of halo groups attached at different ring positions in pyridine is frequently possible since the ring nitrogen excerts a directing effect. Displacements would be expected to take place most readily at "activated" α (C–2, C–6) and γ (C–4) positions, and less readily at β (C–3, C–5) ring carbons.

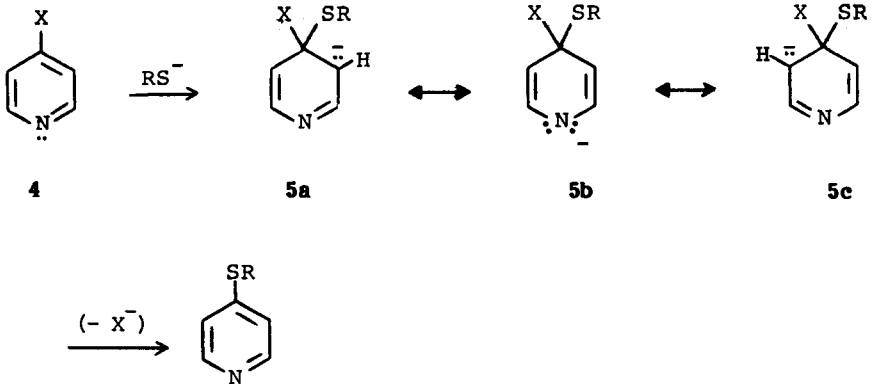
General theories governing aromatic nucleophilic substitutions[3] can be applied to this system. Nucleophilic attack on a ring carbon bearing a halo group by thiolate ion generates a negatively charged resonance-stabilized tetrahedral intermediate. Successful delocalization of the negative charge onto the most electronegative atom(s) in and attached to the system determines in part the relative rate of the displacement.



1 2a 2b 2c

3

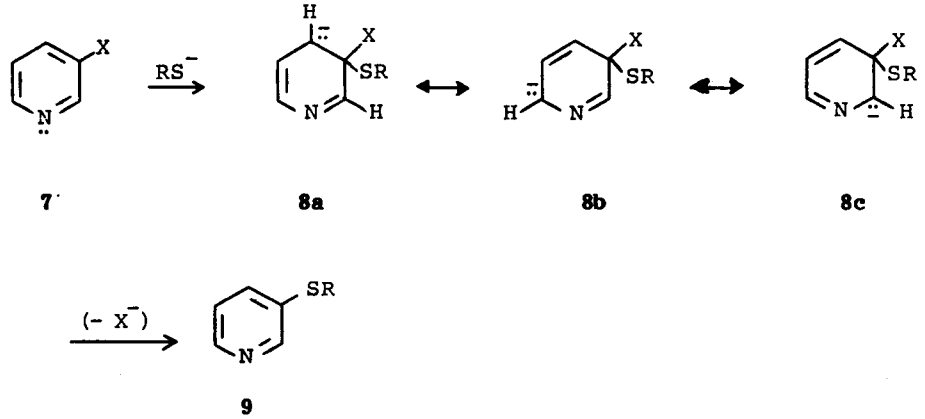
Attack of thiolate ion at C–2 of a 2-halopyridine (**1**) generates the resonance-stabilized intermediate, **2**, in which the negative charge is delocalized onto the ring nitrogen. The reaction is completed when **2** loses a halide ion to form a 2-pyridyl sulfide (**3**).



4 5a 5b 5c

6

A similar sequence of events is pictured for the displacement of the 4-halo group in **4**, *via* the fleeting intermediate **5** which aromatizes to give **6**.



7 8a 8b 8c

9

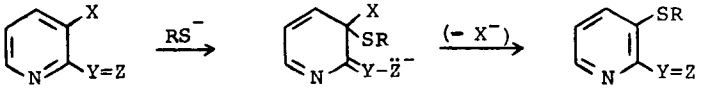
However, displacement of the 3-halo group in **7** involves an intermediate (**8**) in which the negative charge cannot be delocalized to involve the ring nitrogen and it is expected that more energetic conditions are required to form the final product (**9**).

Although the discussion above centers around pyridines, one can extend these concepts to quinolines, diazines and their benzo derivatives. The rates of substitutions of similar groups at different ring positions of diazines are influenced by the positions of the sp^2-hybridized azine ring nitrogens relative to the group to be displaced. Sometimes, substitutions are greatly enhanced when two such ring nitrogens are placed 1,3 to each other, such as in pyrimidines. It is therefore not surprising that 2-, 4- or 6-halopyrimidines (the halo group being α and γ to a ring nitrogen) react much faster with thiolate ions than the corresponding 2- and 4-halopyridines.

Azine nitrogens in azoles (oxazoles, imidazoles, thiazoles, etc.) play similar roles in the sense that halo groups on carbons α to an azine nitrogen atom are displaced relatively fast, provided that such a nitrogen can stabilize the negative change generated when a thiolate attacks the carbon bearing the nucleofuge.

1.2.3. Effect of ring substituents No critical evaluation is made of the effect of one (or more) substitutents on the rates of displacement of halo groups attached to a pyridine ring. A considerable effort has been expended to establish criteria which could be used predictively on how certain substitutents affect the rates of these S_NAr reactions. One question addressed by a number of investigators concerns the effect of a substituent on C–3 on the rate of displacement of a group at C–2. It was found that a neighboring methyl group accelerates the rate of reaction of 2-bromo-3-methylpyridine over that of either 2-bromopyridine and 2-bromo-5-methylpyridine with potassium benzenethiolate in methanol. This "*o*-effect" is attributed to a probable combined effect of London forces and ion–ion dipole interactions.[6,7]

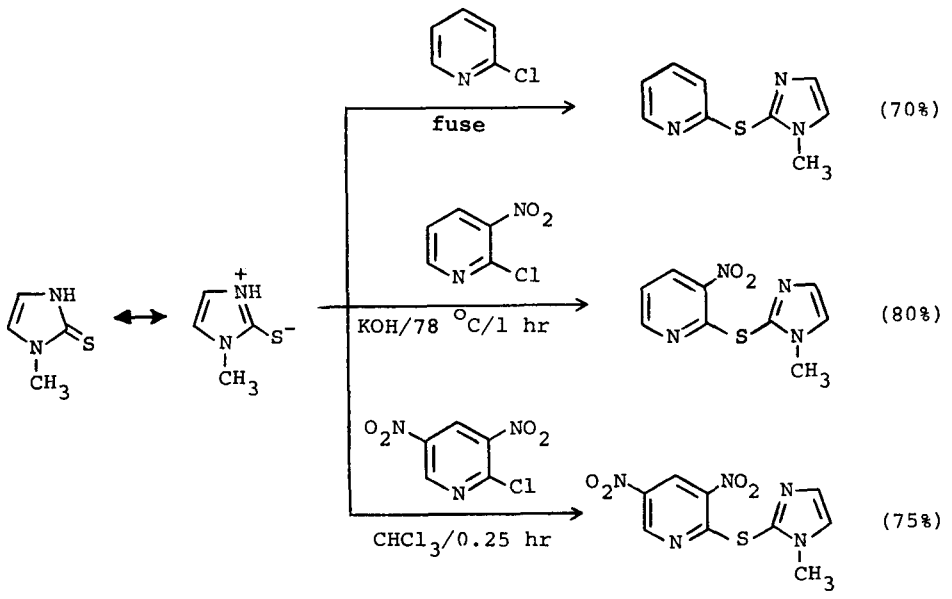
In general, the rates of these reactions are increased when electron-attracting groups, (e.g. nitro, acid or acid derivatives, nitrile, etc., represented by Y=Z) are attached ortho



10 **11** **12**

or para to a halo group. Such groups can help delocalize the negative charge generated upon attack of RS^-. For example, such an attack on **10** generates intermediate **11** which collapses to furnish **12**.

Such inductive and resonance effects due to the presence of certain electron-attracting groups are neatly illustrated by the following examples. 1-Methyl-2-mercaptoimidazole (MMI, which is really a thione) reacts with 2-chloropyridine to form a sulfide when the reaction mixture is heated at the fusion point. The introduction of an *o*-nitro group activates the chloro group in 2-chloro-3-nitropyridine to such an extent that the reaction takes place readily at a lower temperature, e.g. in boiling ethanol. With two suitably



placed nitro groups, as in 3,5-dinitro-2-chloropyridine, this effect is further amplified and MMI reacts instantly in cooled chloroform.[8]

1.3. Substitutions by an $S_{RN}1$ Mechanism

Although the S_NAr mechanism is the oldest one which is accepted for the displacement of halopyridines by thiolate ions, evidence is emerging that some of these substitutions involve a radical chain mechanism, namely $S_{RN}1$. Examples of aromatic nucleophilic displacements involving thiolate anions which take place *via* an $S_{RN}1$ mechanism are well documented.[3b,9a] To initiate these reactions, an injection of electrons is required, provided usually either photochemically, electro-chemically, by the ammoniated electron (alkali metals dissolved in liquid ammonia) or by redox reagents. However, in the absence of these electron-providers, it is postulated that thiolate ion reacts with the halopyridine to generate a thiyl radical and an anion-radical in an initiation step. The whole sequence then is presented by Scheme I.

There is considerable support for such processes and some of the arguments and

Initiation

$$RS^- + PyX \longrightarrow RS^{\cdot} + [PyX]^{\cdot -}$$

Propagation

$$[PyX]^{\cdot -} \longrightarrow Py^{\cdot} + X^-$$

$$Py^{\cdot} + RS^- \longrightarrow [PySR]^{\cdot -}$$

$$[PySR]^{\cdot -} + PyX \longrightarrow PySR + [PyX]^{\cdot -}$$

where Py represents a pyridyl residue.

Scheme I

evidence are cited. For example, strongly electron-attracting groups would not be necessary to activate an aromatic halide. Also, the step in which a new pyridine–sulfur bond is formed, ($Py^{\cdot} + RS^{-} \rightarrow [PySR]^{\cdot}$) would be insensitive to steric hindrance unlike the formation of a σ-complex in the S_NAr mechanism.[3b] Recent experiments[9b,10] support an $S_{RN}1$ mechanism for the displacement of 2-halopyridines with certain thiolate ions, provided the reaction proceeds best (or better) if irradiated by UV light. Some of these substitutions were inhibited considerably when free-radical scavengers were added to the reaction mixture. For example, 2-bromopyridine reacts with sodium benzenethiolate in DMF at 80 °C with or without UV light to yield 2-pyridyl phenyl sulfide (52%) after 4 hours. When *p*-dinitrobenzene, benzoquinone, or azobenzene, all known free-radical scavengers, were added to such reactions, the yield of the sulfide dropped to 5–10%.[9] These and other observations support $S_{RN}1$ mechanisms, particularly if photostimulation enhances the yield of the product.

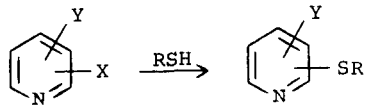
1.4. Scope of Substitutions (Displacements) of Halopyridines by Thiolate Ions

Irrespective of the mechanisms, the scope of pyridyl sulfide syntheses from halopyridines is perhaps best appreciated by examining some typical and recent examples compiled in Tables 1 and 2.

1.5. Substitutions of Polyhalopyridines by Thiolate Ions

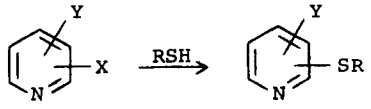
Relatively few studies have been reported which examined the selective substitution of one of the halo groups in 2,4-dihalopyridines by a thiolate ion. However, preferential displacement of one of the halo groups in 2,3-, 2,5- and 2,6-dihalopyridines has been investigated extensively. Several recent papers have reported on the selective substitution of one of the halo groups in 2,6-dihalopyridines (**13**) to provide 2-alkylthio-6-halopyridines in excellent yields (Table 1). Using phase transfer conditions (aqueous base, benzene,

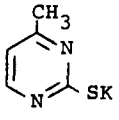
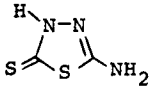
Table 1. Pyridyl sulfides from the reactions of halopyridines with thiols



Substituents		Nucleophile	Solvent	Temp. (°C)	Time in hours	Yield, %	Reference
X	Y						
2-Cl	H	n-C_3H_7SNa	DMF	reflux	4	20	13
2-Cl	H	n-$C_8H_{17}SNa$	DMF	reflux	4	27	13
2-F	H	C_6H_5SNa	DMF	80	4	7	9
2-Cl	H	C_6H_5SNa	DMF	80	4	5	9
2-Br	H	C_6H_5SNa	HMPA	80	4	65	9
2-Br	H	C_6H_5SNa	DMF	80	4	52	6
2-I	H	C_6H_5SNa	DMF	80	4	58	9
2-Cl	H	C_6H_5SH	NEt_3	100	48	93	14

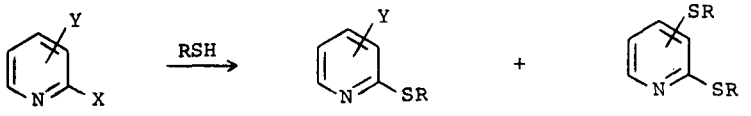
Table 1. (*Continued*)



Substituents		Nucleophile	Solvent	Temp. (°C)	Time in hours	Yield, %	Reference
X	Y						
2-Br	3-CH_3	CH_3SK	CH_3OH	58	–	61	6
2-Br	3-CH_3	C_6H_5SK	HMPA	110	–	73	6
2-Cl	4-CH_3	C_6H_5SH	NEt_3	reflux	5	100	15
2-Cl	4-CH_3	n-$C_8H_{17}SK$	DMF	100	3	79	15
2-Br	5-CH_3	CH_3SK	CH_3OH	58	–	53	6
2-Br	5-CH_3	C_6H_5SK	HMPA	120	–	79	6
2-Cl	6-CH_3	n-C_3H_7SNa	DMF	reflux	2	25	16
2-Cl	3-NO_2	n-C_3H_7Na	C_2H_5OH	reflux	0.25	65	17a
2-Cl	3-NO_2	t-C_4H_9SNa	THF	reflux	0.3	28	17b
2-Cl	3-NO_2	t-C_4H_9SNa	THF	reflux	0.5	58	17c
2-Cl	3-CN-4,6-$(CH_3)_2$	t-C_4H_9SNa	THF	reflux	2	90	17d
2-Cl	5-NO_2	t-C_4H_9SK	C_2H_5OH	reflux	1	80	8
2-Cl	5-NO_2		C_2H_5OH	reflux	1.5	83	18
2-Cl	5-NO_2	 (K_2CO_3)	C_2H_5OH	reflux	1.5	89	18
3-Br	H	C_6H_5SNa	DMF	80	4	24	9
4-Cl	H	n-C_3H_7SNa	DMF	reflux	4	80	13
4-Cl	H	n-C_4H_9SNa	DMF	100	4	25	19
4-Cl	H	n-$C_8H_{17}SNa$	DMF	reflux	4	58	13
4-Cl	H	t-C_4H_9SNa	DMF	95	3.5	48	20
4-Cl	H	1-AdmSNa[a]	DMF	95	1	45	21
4-Cl	2-CH_3	C_2H_5SNa	n-$C_5H_{11}OH$	130	6	63	22
4-Cl	2-CH_3	n-C_4H_9SK	DMF	100	3	74	22
4-Cl	2-CH_3- (1-oxide)	n-C_3H_7SNa	$(C_2H_5)_2O$	reflux	5	78	22
4-Cl	2,6-$(CO_2CH_3)_2$	C_6H_5SH	C_2H_5OH	reflux	6	74	23

[a] 1-Adm stands for 1-Adamantyl.

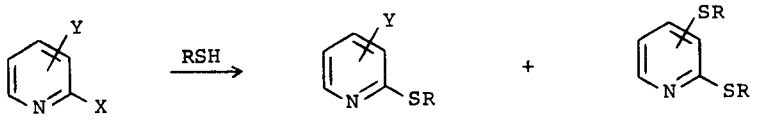
Table 2. Reactions of dihalopyridines with thiols



A B

Substituents			Nucleophile	Solvent (catalyst)	Temp. (°C)	Time in hours	Yield, %		Reference
X	Y	Others					A	B	
2-Cl	3-Cl	–	CH_3SNa	DMF	80	0.25	88	–	12
2-Cl	3-Cl	–	i-C_3H_7SNa	DMF	80	0.25	85	–	12
2-Cl	3-Cl	–	CH_3SNa	DMF	80	5	–	80	12
2-Cl	3-Cl	–	i-C_3H_7SNa	DMF	80	5	–	88	12
2-Cl	3-Cl	6-CO_2H	CH_3SNa	DMSO	135	2	–	89	24
2-Cl	3-Cl	6-CO_2H	C_2H_5SNa	DMSO	135	2	–	95	24
2-Br	3-Br	–	CH_3SK	HMPA	100	24	56	–	6
2-Br	3-Br	–	C_6H_5SK	CH_3OH	80	24	only[e]	–	7
2-Cl	4-Cl	–	CH_3SNa	DMF	140	6	–	88	24
2-Br	5-Br	–	CH_3SK	HMPA	110	24	83	–	6
2-Br	5-Br	–	CH_3SNa	DMF	25	0.25	93	–	12
2-Br	5-Br	–	i-C_3H_7SNa	DMF	25	0.25	90	–	12
2-Br	5-Br	–	CH_3SNa	DMF	80	5	–	90	12
2-Br	5-Br	–	i-C_3H_7SNa	DMF	80	5	–	79	12
2-Cl	5-Cl	6-CO_2CH_3	CH_3SK	DMF	100	2	–	82[c]	24
2-Cl	5-Cl	6-CO_2CH_3	C_2H_5SNa	DMSO	135	2	–	95	24
2-Cl	5-Cl	6-CO_2CH_3	C_6H_5SK	DMF	100	2	–	72[c]	24
2-Cl	5-Cl	6-CO_2CH_3	$C_6H_5CH_2SK$	DMF	100	2	–	44[c]	24
2-F	6-F	–	CH_3SK	DMSO	130[a]	2	–	56[b]	24
2-Cl	6-Cl	–	CH_3SNa	C_6H_6/H_2O $[(n\text{-}C_4H_9)_4N^+Br^-]$	reflux	6	98	–	11
2-Cl	6-Cl	–	C_2H_5SNa	C_6H_6/H_2O $[(n\text{-}C_4H_9)_4N^+Br^-]$	reflux	6	89	–	11
2-Cl	6-Cl	–	n-C_4H_9SNa	C_6H_6/H_2O $[(n\text{-}C_4H_9)_4N^+Br^-]$	reflux	6	82	–	11
2-Cl	6-Cl	–	$C_6H_5CH_2SNa$	C_6H_6/H_2O $[(n\text{-}C_4H_9)_4N^+Br^-]$	reflux	6	82	–	11
2-Br	6-Br	–	CH_3SNa	C_6H_6/H_2O $[(n\text{-}C_4H_9)_4N^+Br^-]$	reflux	6	97	–	11
2-Br	6-Br	–	CH_3SNa	DMF	25	0.25	90	–	12
2-Br	6-Br	–	i-C_3H_7SNa	DMF	25	2	94	–	12

Table 2. (*Continued*)

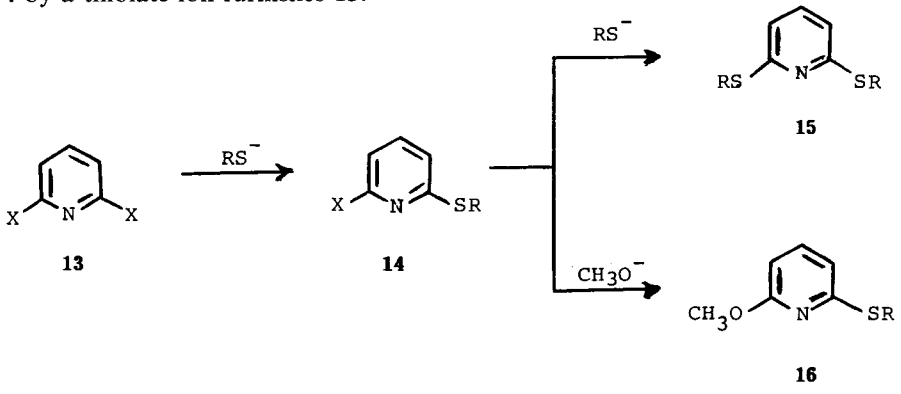


A B

Substituents			Nucleophile	Solvent (catalyst)	Temp. (°C)	Time in hours	Yield, %		Reference
X	Y						A	B	
2-Br	6-Br	–	CH_3SNa	DMF	80	5	–	90	12
2-Br	6-Br	–	i-C_3H_7SNa	DMF	80	5	–	90	12
2-Cl	6-SCH_3	–	CH_3SNa	C_2H_5OH	reflux	13	–	83	11
3-Cl	5-Cl	–	CH_3SNa	DMF	80	0.25	95	–	12
3-Cl	5-Cl	–	CH_3SNa	DMF	80	15	–	88	12
3-Cl	5-Cl	–	i-C_3H_7SNa	DMF	80	0.25	85	–	12
3-Cl	5-Cl	–	i-C_3H_7SNa	DMFF	80	15	–	88	12
3-Cl	5-Cl	2-CN	CH_3SK	THF	12	–[d]	–	95	24
3-Br	5-Br	2,6-$(CO_2CH_3)_2$	MBSNa[f]	THF	reflux	2	–	55	25

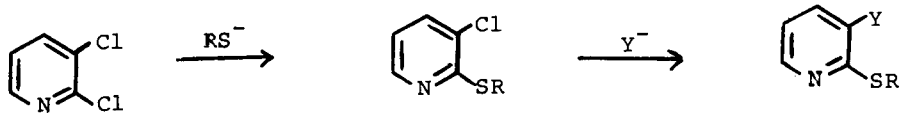
[a] Reaction was exothermic (−30 to 105 °C).
[b] Not isolated as bis-sulfide but product was oxidized immediately with 30% H_2O_2 in CF_3CO_2H at 65–75 °C (2 hr), and was isolated as the bis-sulfone.
[c] Isolated as the corresponding carboxylic acid.
[d] Indefinite time.
[e] Yield was not stated.
[f] MB stands for 4-methoxybenzyl.

tetrabutylammonium bromide),[11] one of the halo groups in **13** is displaced by thiolate ions to form **14** in excellent yield. Under these conditions, one of the halo groups in 2,6-dichloro- or 2,6-dibromopyridine was displaced by methane-, ethane, 1-butane-, phenylmethanethiol in 82–98% yield.[11] Subsequent substitution of the other halo group in **14** by a thiolate ion furnishes **15**.[11]

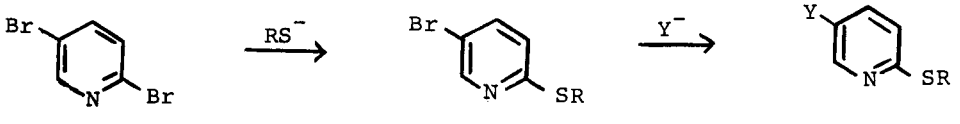


13 **14** **15** **16**

In a contemporary study, monosubstitutions of one of the halo groups in 2,3-dichloropyridine (**17**), 2,5-dibromopyridine (**20**), and 2,6-dibromopyridine (**13**, X = Br), as well as 3,5-dichloropyridine (**23**), were explored extensively.[12] Very mild conditions were used and the reactions were monitored by thin layer chromatography (tlc). Once the monosulfide was formed predominantly, the reaction was quenched and **14**, **18**, **21**, and **24** were isolated in 85–96% yield. For example, reactions of **13** (X = Br) with sodium methanethiolate or sodium 2-propanethiolate in DMF at room temperature for short periods of time produced the requisite halo sulfides **14** in excellent yields.[12] Selective substitution of the α- over the β-halo group took place preferentially in **17** and **20** to generate **18** and **21**, respectively, in outstanding yields.[12]

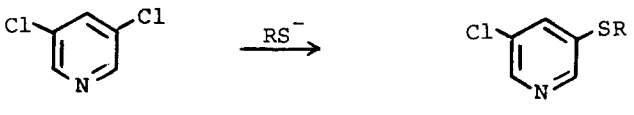


17 **18** **19**



20 **21** **22**

Monosubstitution of one of the β-halo groups in **23** by a thiolate ion was effected at 80 °C using longer reaction periods and led to **24** (85–95%).[12]



23 **24**

Eventually, β-halo groups in **18**, **21** and **24** can also be displaced by RS^-, but the reaction had to be carried out in DMF at 80 °C for longer periods (5–15 hours).

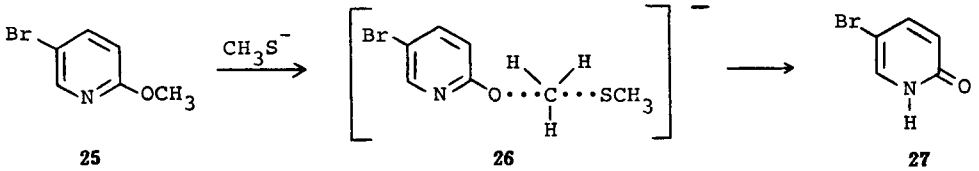
1.6. Comparisons of Substitutions by Thiolate and Alkoxide Ions

For these aromatic nucleophilic substitutions, thiolate ion proved to be a far better nucleophile than alkoxide ion. When reaction times were extended, even in cold DMF, β-halo groups in **18** and **21** were displaced by RS^- to furnish and **19** and **22** (Y = SR). But, methoxide ion in DMF substituted only α- and *not* β-halo groups in **17** and **20**, even after 90 hours at 80 °C, to afford 3- and 5-halo-2-methoxypyridines only.[12] Displacement of a β-halo group by methoxide ion requires considerably more stringent conditions. By way of comparison, bis-2,6-dimethoxypyridine was obtained from **13** (X = Br) and sodium methoxide at 80 °C for 2.5 hours (DMF, 65%). However, the reaction of

2,3-dichloropyridine, **17** (X = Cl) with sodium methoxide for 90 hours in DMF (80 °C) produced 2,3-dimethoxypyridine in only 6% yield. Attempts to substitute both bromo groups in **20** (X = Br) failed completely after 90 hours at 80 °C, the only product being 2-methoxy-5-bromopyridine, (**25**, 86%). But both halo groups in **23** could be displaced to yield 3,5-dimethoxypyridine (DMF, 80 °C, 38 hr, 59%). It is somewhat of a mystery why both β-halo groups in **23** are substituted by methoxide ion while the β-halo group in 2-methoxy-3-bromopyridine (**25**) resists displacement, even after 90 hours. Noticeably, the ether group in **25** remains intact while under attack by methoxide ion, which differs from the reactions of some pyridyl ethers with thiolate ions, as is discussed in the next Section.

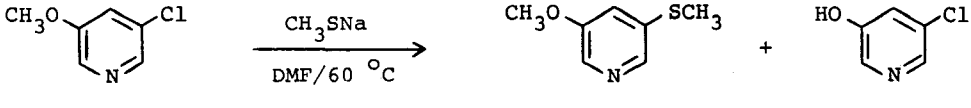
1.7. Reactions of Halopyridyl Ethers with Thiolate Ions

It was expected that the halo group in halopyridyl ethers would be substituted relatively easily by methanethiolate ion.[12] Reactions of 2-bromo-3-methoxy- and 2-bromo-6-methoxypyridine with CH_3S^- in DMF at 60 °C (2–4 hours) furnished 2-methylthio-3-methoxy- and 2-methylthio-6-methoxypyridines in 95 and 66% yields, respectively. While β-halo groups frequently resist substitution by methoxide ion, even under forcing conditions, methanethiolate ion generally substitutes β-halo groups at somewhat higher temperatures. Under these relatively more stringent conditions, thiolate ion attacked methoxy groups at α-pyridine carbons. It is perhaps unexpected that the reaction of 2-methoxy-5-bromopyridine (**25**) with sodium methanethiolate in DMF (60 °C, 4 hours) yielded 5-bromo-2-pyridone as the only isolable product (**27**, 50%). While the β-halo group in **25** is not displaced under these conditions, an S_N2 reaction took place on the methyl ether, conceivably *via* **26**.



25 **26** **27**

The cleavage of aromatic methyl ethers by thiolate ions to form phenols is well established.[26] The transformation of **25** to **27** is greatly facilitated since the 2-pyridone anion is an excellent leaving group. It is perhaps unexpected that 3-chloro-5-methoxypyridine **28** underwent substitution on the aromatic ring as well as methyl ether cleavage to give **29** and **30**.[12]

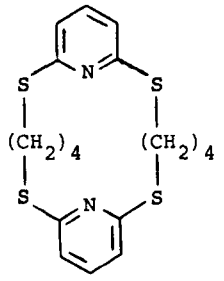


28 **29** (35%) **30** (30%)

1.8. Macrocycles Based on the 2,6-Bis(alkylthio)pyridine System

Attempts to synthesize crown ethers incorporating the 2,6-pyridyl bis(sulfide) system proved to be quite difficult. For example, the reaction of 2,6-dichloropyridine (**13**,

X = Cl), with 1,4-butanedithiol gave (amongst other products), the macrocycle **31** in less than 0.5% yield and even then **31** was not fully characterized.[27] Among the more interesting macrocycles related to the 2,6-disubstituted pyridine system are those represent by **32–34** which were recently reported by Furukawa and his group.[11]



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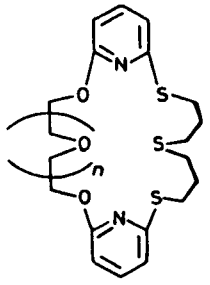
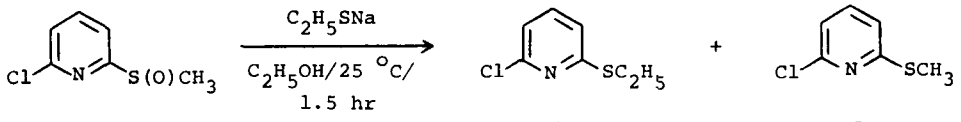


32, n = 1 (31%)

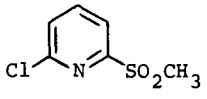
33, n = 2 (36%)

34, n = 3 (26%)

Syntheses of **32–34** were achieved by using, in part, a different (than halo) leaving group (e.g., sulfoxide or sulfone) displacements on the ring. It was shown that 2-pyridyl sulfoxides and sulfones were substituted by thiolate ions. It is quite reasonable that an electron-attracting sulfoxide or sulfone groups placed at an activated position (e.g., an α-carbon of **1**) would be very susceptible to displacement by thiolate ion. Such a reaction is illustrated by the conversion of **35** in part to **36** (68%) together with the reduced product (**37**, 20%).[11] Under similar conditions, 6-chloro-2-pyridyl methyl sulfone (**38**) reacts with ethanethiolate ion to form **36** in 90% yield.



35 **36** **37**

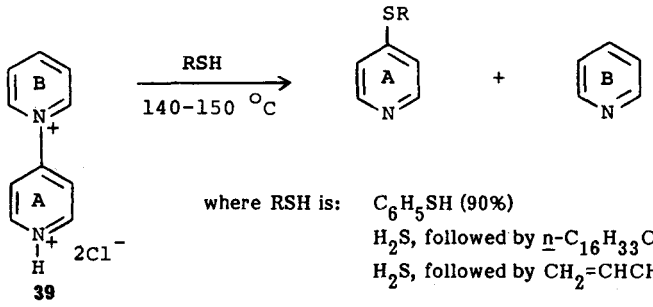


38

2. AROMATIC NUCLEOPHILIC SUBSTITUTIONS OF NITROGEN-CONTAINING GROUPS BY THIOLS

2.1. Displacement of the Pyridinium Cation

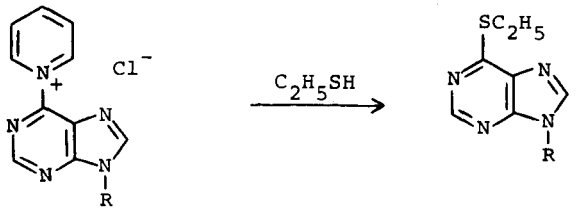
Other pyridyl sulfide syntheses consist of displacement of some nitrogen-containing groups. Good examples are provided for convenient syntheses of 4-pyridyl sulfides. The starting material is 1-(4′-pyridyl)pyridinium chloride hydrochloride (**39**) which is made from pyridine and thionyl chloride. Displacements on **39** by thiols take place in good yield but require relatively high temperatures. Protonation of ring A aids the displacement at the γ-position of that ring which bears a good leaving group.[28,29] With thiophenols, this methods leads to aryl 4-pyridyl sulfides. However, alkyl 4-pyridyl sulfides can be prepared in one of 3 methods, each starting from **39**. There is, of course, the direct displacement. Better yields are sometimes obtained by treating **39** first with hydrogen sulfide which forms 4-pyridthione which, in turn, reacted with an alkyl halide to form the 4-alkylthiopyridine.



39

Another way is to heat **39** first with thiourea to form 4-pyridthione, which is then alkylated, as described above.

An interesting application of such a displacement of a pyridinium moiety by ethanethiol has been reported recently when the purine derivative **40** was converted to **41** in 85% yield.[30]

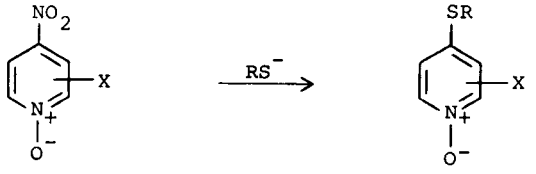


40 **41**

R = 2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl

2.2. Displacement of the Nitro Group

Nitro substituted heteroarenes are not as frequently encountered as nitrobenzenes. However, some of the easiest 4-substituted pyridines to synthesize are 4-nitropyridine 1-oxides (**42**), which are made by nitration of pyridine 1-oxides. The 4-nitro group is substituted by thiolate ions to form 4-alkylthiopyridine 1-oxides (**43**) in respectable yields. The *N*-oxide function can be reduced readily leading to 4-alkylthiopyridines.



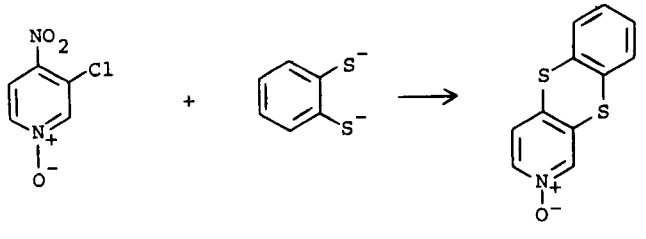
42 **43**

X = 2-CH_3; R = C_2H_5 (72%)[22]

X = 2-CH_3; R = n-C_3H_7 (78%)[22]

X = 3-CH_3; R = n-C_3H_7 (60%)[16]

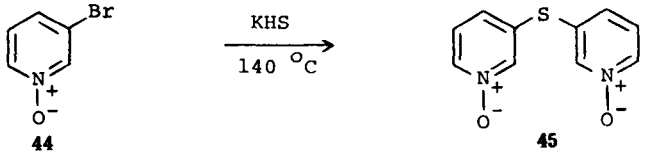
In an extensive study, it was shown that the reaction of 4-nitroquinoline 1-oxides with thioglycolic acid produced a number of 4-[(carboxymethyl)thio]quinoline 1-oxides in good yield.[31a] A neat synthesis of 2-azathianthrene 2-oxide was reported when 1,2-benzenedithiol was treated with 3-chloro-4-nitropyridine 1-oxide in the presence of sodium hydride in boiling DMF (89%).[31b] During this reaction both the nitro and chloro groups were replaced, as one would have predicted.



3. ALKYLATION OF PYRIDTHIONES (PYRIDINETHIOLS)

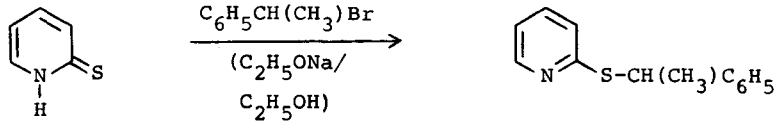
It is generally accepted that 2- and 4-pyridthiones are represented best by the thione form.[32] In widely recognized aliphatic substitutions, these thiones are alkylated invariably on sulfur to produce sulfides in good yield. Limitations imposed on such syntheses are those associated with S_N2 substitutions, namely lack of displacements with tertiary, vinyl and aryl halides. Then alternate syntheses must be sought.

2- And 4-pyridthiones are conveniently prepared from the corresponding pyridone with either P_2S_5 or Lawesson reagent,[33] or, from the halo compound with thiourea.[23,34] Sodium hydrogen sulfide nonahydrate has been used on halopyridines.[35] In the reactions with hydrosulfide ion, HS^-, the thione (or thiol) may be formed, but there exists the risk of further reaction to form a symmetrical sulfide. An example of such a reaction is that of 3-bromopyridine 1-oxide (**44**) with KSH at 140 °C for 5 hours to furnish the sulfide **45** in 36% yield.[36]



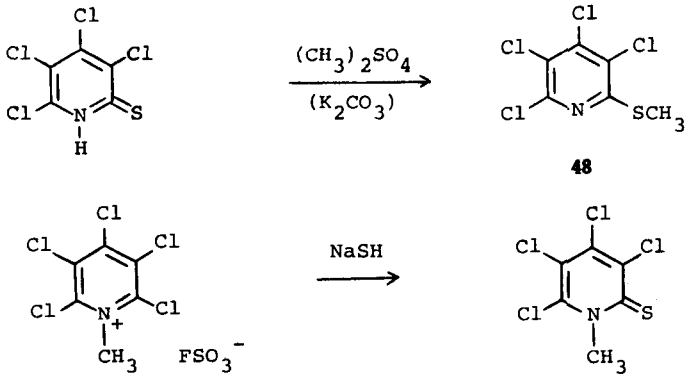
44 **45**

A typical example of an alkylation of 2-pyridthione (**46**) is the one by 1-bromo-1-phenylethane to give **47** which was resolved into its enantiomers by fractional crystallization.[37]



46 **47**

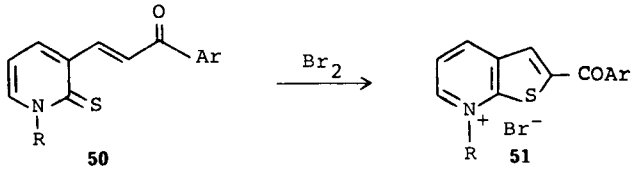
Methylation of tetrachloro-2-pyridthione with methyl sulfate gave the expected sulfide, **48**. The isomeric *N*-methyl isomer **49** had to be prepared by an alternate route, as shown.[38]



48

49

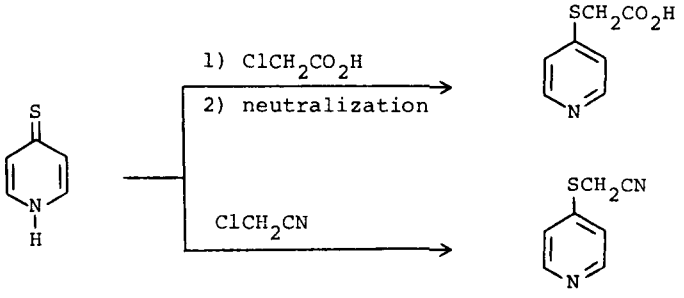
Use of these alkylations is made in the synthesis of some thienopyridines. For example, the addition of bromine to the unsaturated ketone, **50**, resulted in the formation of the bicyclic system, **51**.[39]



2-Pyridthione also adds to acetylene to produce 2-vinylthiopyridine, **52**.[40a]

52

The Michael addition of a number of 2-pyridthiones to ethyl propiolate led to *cis* ethyl 3-(2-pyridylthio)acrylates.[40b] 4-Pyridthione (**53**) is also alkylated exclusively on sulfur, as illustrated by these examples:[41]

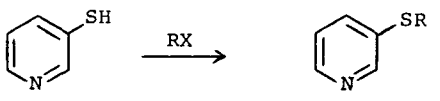


53

One of the best methods of synthesizing 4-pyridthione is by the reaction of **39** with hydrogen sulfide at 100 °C (70% yield).[28] The best method of preparing 4-pyridyl sulfides is to immediately alkylate the 4-pyridthione without isolating it.[26]

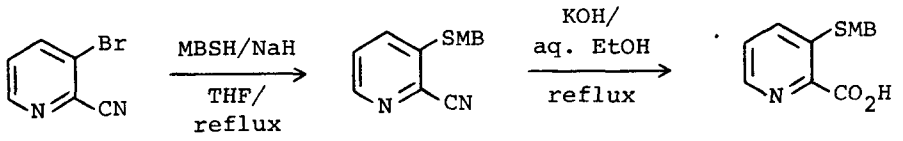
3-Pyridinethiol alkylates on sulfur also as shown by its reaction with 1-bromobutane[19] or 1-bromooctane[13] to produce the 3-sulfides [**54**, (R = *n*–C_4H_9), 30 and (R = *n*–C_8H_{17}) 50%, respectively]. Alkylation of 3-pyridinethiol, with several β-aminoalkyl halides is reported to give 3-pyridyl β-aminoalkyl sulfides in high yields.[42]

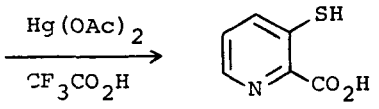
Examples of alkylations of 3-pyridinethiols are relatively sparse, which is due in part to the relative inaccessibility of that thiol. One of the best recent methods of preparing

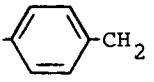


54

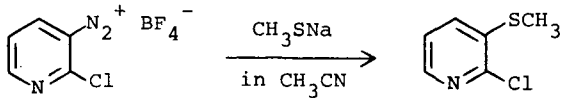
3-pyridinethiols is *via* the reduction of the corresponding 3-(*p*-methoxybenzyl) sulfide, which is made from the corresponding bromopyridine[25] as illustrated by this sequence:





where MB stands for  and OAc for CH_3CO_2.

It is easier perhaps to make 3-sulfides by diazotizing a 3-aminopyridine followed by reaction with suitable thiolate ions.[43]



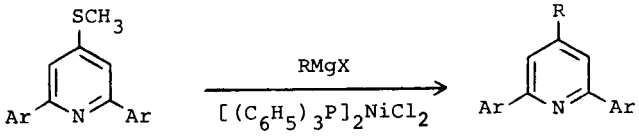
Diazotization of heterocyclic amines[44] and subsequent displacements of the diazonium salts by thiolate ions[45] have been reviewed.

4. HYDROLYSIS AND OTHER SUBSTITUTIONS OF PYRIDYL SULFIDES

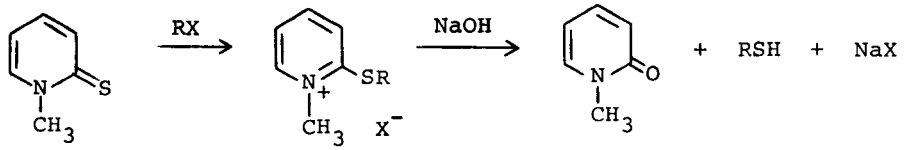
In general, a sulfide group attached to even activated carbons of pyridines is not readily displaced by other nucleophiles. Of course, there are some exceptions. For example, 2,6-bis(methylthio)pyridine reacts with 4 equivalents of sodium methoxide at 80 °C in DMF to yield 2-methoxy-6-methylthiopyridine **16** (R = CH_3) in 68% yield.[12]

As might be expected, when the electrophilicity at α- and γ-positions of pyridine is increased considerably through complexation, protonation, *N*-oxidation or quarternization of the ring nitrogen, appropriate ring substituents can also exert an activating effect. An interesting example of an unexpected displacement of a sulfide by a Grignard reagent

reagent is reported. The reaction took place only in the presence of bis(triphenylphosphino)nickel dichloride.[46]

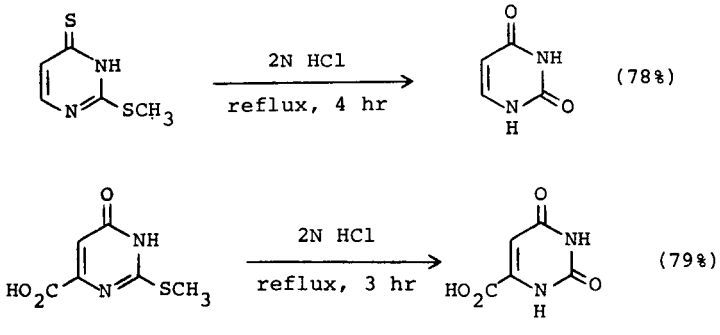


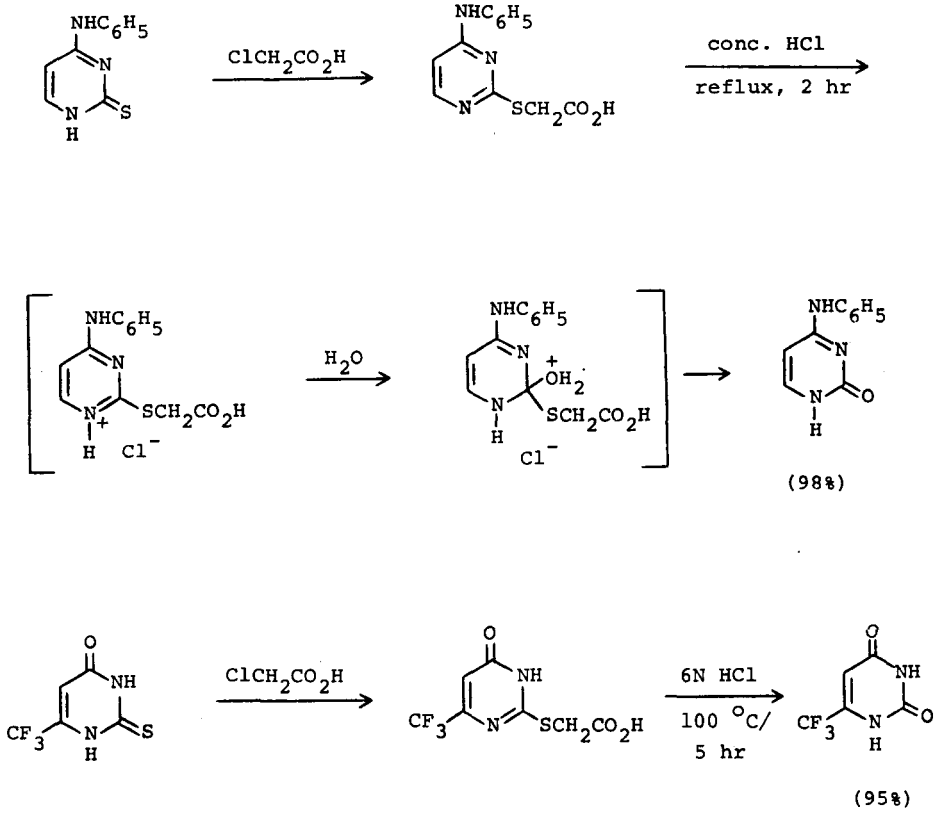
Of course, quaternization of the ring nitrogen really enhances displacements at α- or γ-carbons. The following reaction sequence, in part, illustrates this principle very well. Alkylations of 1-methyl-2-pyridthione generate 1-methyl-2-alkylthiopyridinium salts (**55**), which are hydrolyzed readily by sodium hydroxide to 1-methyl-2-pyridone (**56**) with the release of a mercaptan (**57**).[47] As a matter of fact, this reaction sequence has been suggested as a good synthetic route to mercaptans.



55 **56** **57**

Usually, the "thione" group in 2- and 4-pyridthiones is not hydrolyzed. Although the additional azine nitrogen in the pyrimidine ring imparts further electrophilic character to the α- and γ-positions, 2- and 4-pyrimidthiones are not hydrolyzed directly, either. However, a series of experiments have been reported which purport such hydrolyses. However, on close examination, these hydrolyses do not take place without an auxiliary reagent, namely chloroacetic acid. Thus, in fact, these "hydrolyses" takes place *via* corresponding sulfides, namely an *S*-carboxymethyl derivative. It had been demonstrated that independent acid-catalyzed hydrolysis of some pyrimidyl sulfides leads to the corresponding pyrimidones. Examples of such acid-catalyzed hydrolyses are the conversions of 2-methylthio-4-pyrimidthione to 4-thiouracil[50] and of 2-methylthio-6-carboxy-4-pyrimidone to 6-carboxyorotic acid.[51]





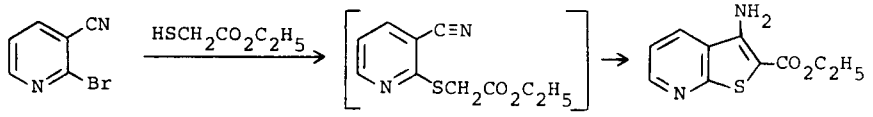
Scheme II

It is reasonable to assume that the "hydrolyses" of 4-anilino-2-pyrimidthione to the corresponding 2-pyrimidone[48] and 6-trifluoro-2-thiouracil to the corresponding uracil[49] takes place according to the processes outlined in Scheme II.

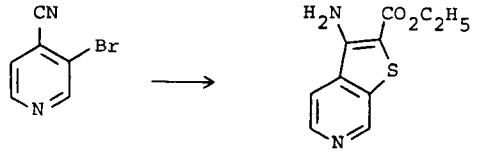
5. SYNTHESES OF THIENOPYRIDINES AND RELATED COMPOUNDS BY CYCLIZATIONS OF PYRIDYL SULFIDES WITH NEIGHBORING GROUPS

Occasionally, after a pyridyl sulfide has been formed further reactions can take place with a neighboring group on the ring giving rise to a cyclic system. Such a sequence frequently leads to thienopyridines and other condensed systems. A few examples of these popular syntheses are provided.

A photo-stimulated (UV) reaction of 2-bromonicotinonitrile (**58**) with ethyl thioglycolate in liquid ammonia generates a thienopyridine (**59**) in 90% yield.[10] Similarly, **60** was converted to **61** (98%[10], with UV, 75%[52] without irradiation).

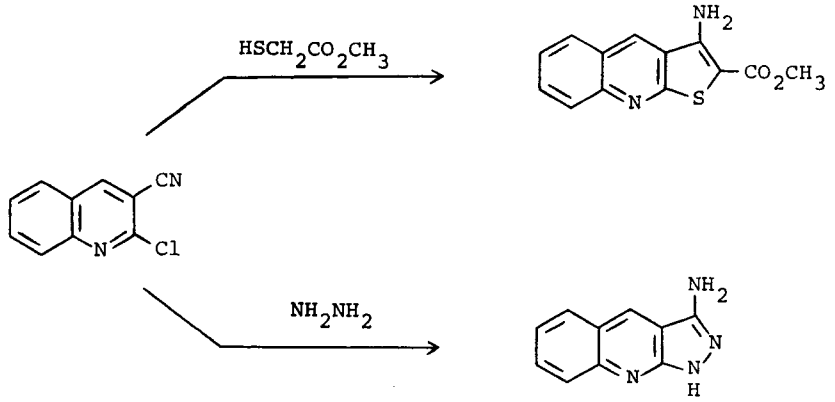


58 59

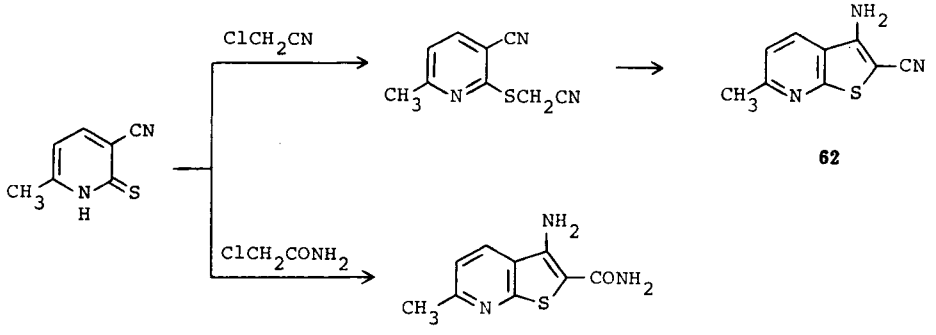


60 61

This approach was utilized recently in the synthesis of members belonging to the thieno[2,3-*b*]quinoline and the pyrazolo[3,4-*b*]quinoline systems.[53]



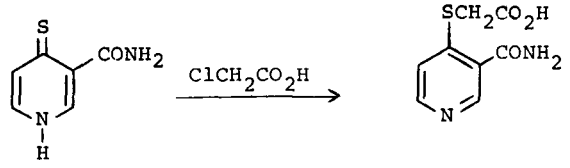
In related syntheses, but using the thione alkylation method, functionalized sulfides have cyclized spontaneously to the corresponding thienopyridines, **62** and **63**.[54a] Apparently, under the basic conditions of these reactions, the active methylene group added to the ring nitrile. After work-up and upon tautomerization, the thiophene ring is established.



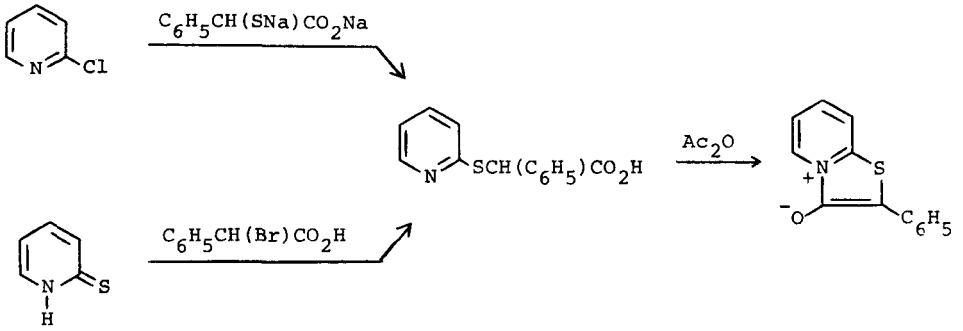
62

63 (66%)

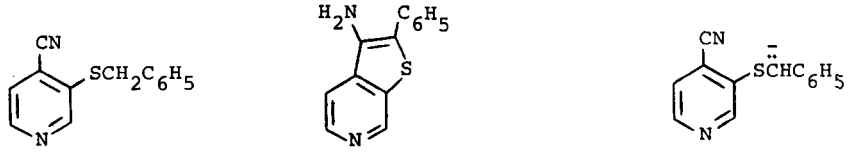
Normal products can be anticipated if interactions between neighboring groups do not encourage cyclization. For example, the product in the reaction of 4-mercaptonicotinamide with chloroacetic acid led to the expected sulfide.[54b]



Some interesting zwitterionic systems were prepared by one of two principal approaches as shown by these reactions.[55]

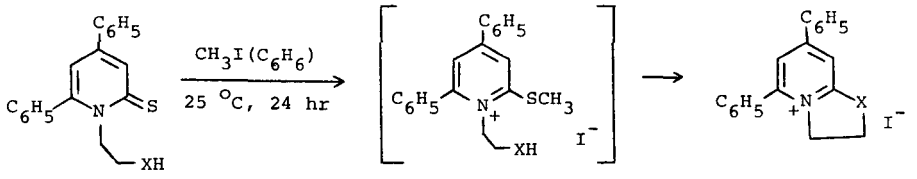


When **60** was treated with $C_6H_5CH_2SNa$, there were obtained the expected sulfide **64** (69%) and the thienopyridine **65** (12%).[52] The latter would be formed by the cyclization of the carbanion **66**.



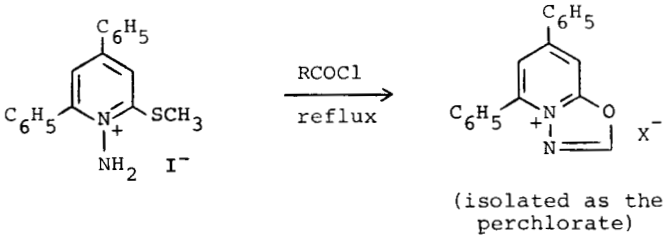
64 **65** **66**

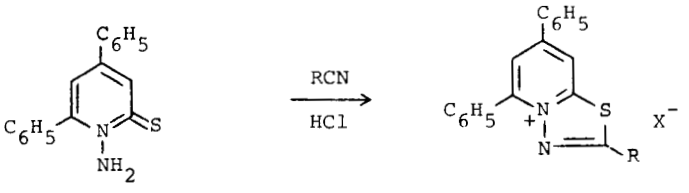
The alkylation of **67** with methyl iodide resulted in the spontaneous cyclization of the intermediate salt by a displacement of the methylthio group by either the alcohol or mercaptan in the side chain, to form the 5-membered ring of **68**.[56]



67 **68** X = O (79%)
= S (45%)

Some unique condensed systems were obtained when 1-aminopyridine derivatives were treated with either an acid chloride or a nitrile.[57]

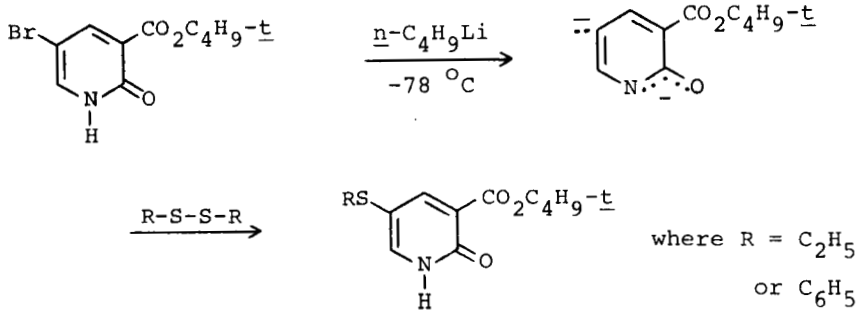




6. OTHER SYNTHESES OF PYRIDYL SULFIDES

6.1. By Displacement of a Carbanion on Disulfides

A novel approach to the synthesis of several 3-pyridyl sulfides was undertaken by Domagala.[58] He prepared the lithio dianion of the bromopyridone ester and treated it with various aliphatic and aromatic disulfides to produce a new sulfide.



This kind of sulfide synthesis was successfully applied recently to convert 3-bromosydnones to 3-sydnonyl sulfides.[59]

6.2. Deoxydative Substitutions of Pyridine 1-Oxides by Thiols

The deoxydative substitution of pyridine 1-oxide (**69**) by thiols in the presence of an acid

chloride or anhydride produces a mixture of 2- and 3-pyridyl sulfides (**70** and **71**) with the 4-isomer being conspicuously absent.[60] Some of the effective acylating agents for this reaction are acetic anhydride, phosgene, acetyl, benzoyl, dimethylcarbamoyl, dimethylsulfamoyl, and benzenesulfonyl chloride. Representative examples of these substitutions of pyridine 1-oxide are listed in Table 3.

It appears that a greater percentage of the 2- relative to the 3-isomer is formed when carbonyl or carbamoyl chlorides are used. The proportion of the 3-isomers tends to increase considerably when either sulfonyl or sulfamoyl chlorides are employed. Any of the acylating agents listed in Table 3 will promote the substitution by thiols. However,

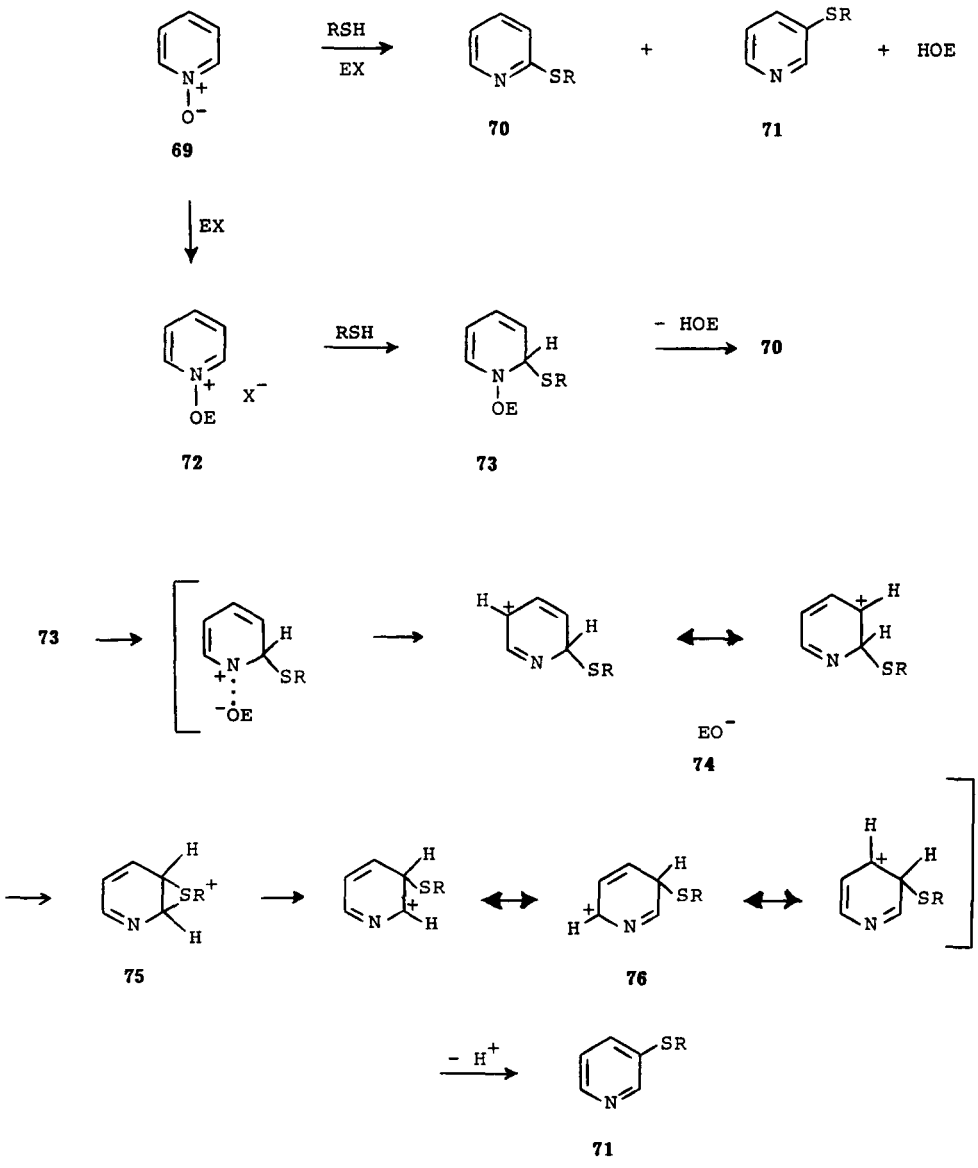
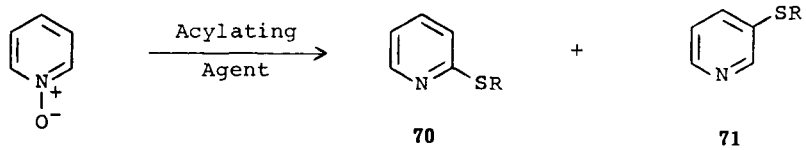


Table 3. Deoxydative substitution of pyridine 1-oxide



70 **71**

R in RSH	Acylating Agents	Solvents	Temp., °C	Time, hours	Yield, %	Ratio of 70:71	Reference
CH_3	$(CH_3CO)_2O$	$(CH_3CO)_2O$	95	3	38	52:48	20
n-C_3H_7	$(CH_3CO)_2O$	$(CH_3CO)_2O$	95	3	46	76:24	20
n-C_4H_9	$(CH_3CO)_2O$	$(CH_3CO)_2O$	95	3	67	61:39	20
n-C_4H_9	C_6H_5COCl	n-C_4H_9SH	95	0.5	19	82:18	19
n-C_4H_9	$C_6H_5SO_2Cl$	n-C_4H_9SH	95	0.5	32	50:50	19
n-C_4H_9	$COCl_2$	C_6H_6	reflux	2	10	81:19	61
n-C_4H_9	$COCl_2$	C_6H_6/NEt_3	reflux	2	67	89:11	61
n-C_4H_9	$(C_2H_5)_2NCOCl$	C_6H_6	reflux	2	68	98:2	61
n-C_4H_9	$(C_2H_5)_2NCOCl$	C_6H_6	reflux	2	67	100:1	61
n-C_4H_9	$C_6H_5SO_2Cl$	C_6H_6	reflux	2	34	68:32	61
n-C_4H_9	$(CH_3)_2NSO_2Cl$	C_6H_6	reflux	2	57	62:38	61
t-C_4H_9	$(CH_3CO)_2O$	$(CH_3CO)_2O$	95	3	62	70:30	20
t-C_4H_9	$(CH_3CO)_2O$	$(CH_3CO)_2O/NEt_3$	95	2	41	90:10	62
t-C_4H_9	$(CH_3)_2NCOCl$	C_6H_6	reflux	2	21	93:7	61
t-C_4H_9	$(CH_3)_2NSO_2Cl$	C_6H_6	reflux	2	31	48:52	61
t-C_4H_9	$(CH_3)_2NSO_2Cl$	C_6H_6/NEt_3	reflux	2	37	38:62	61
t-C_4H_9	$C_6H_5SO_2Cl$	C_6H_6	reflux	2	18	35:65	61
1-Adm[a]	$(CH_3CO)_2O$	$(CH_3CO)_2O$	95	3	44	68:32	21
1-Adm[a]	$(CH_3CO)_2O$	$(CH_3CO)_2O/NEt_3$	95	3	35	80:20	21
C_6H_5	CH_3SO_2Cl	C_6H_6	5	0.5	27	40:60	63
C_6H_5	$C_6H_5SO_2Cl$	C_6H_6	5	0.5	30	41:59	63
C_6H_5	$C_6H_5SO_2Cl$	$CHCl_3$	5	0.5	46	39:61	63
4-ClC_6H_4	$C_6H_5SO_2Cl$	$CHCl_3$	5	0.5	50	37:63	63
4-t-$C_4H_9C_6H_4$	$C_6H_5SO_2Cl$	C_6H_6	5	0.5	33	32:68	63

[a] 1-Adm stands for 1-adamantyl.

sulfonyl or sulfamoyl halides are required before thiophenols react to form pyridyl aryl sulfides. The inclusion of an amine, (e.g. triethylamine) causes a considerable increase in the percentage of the 2-isomer. This observation is in keeping with the proposed mechanism.[60]

It is postulated that the *N*-oxide, **69**, quaternizes to form an intermediate salt (**72**), *in situ*, which is attacked by the thiol at one of the highly electrophilic α-carbons to generate

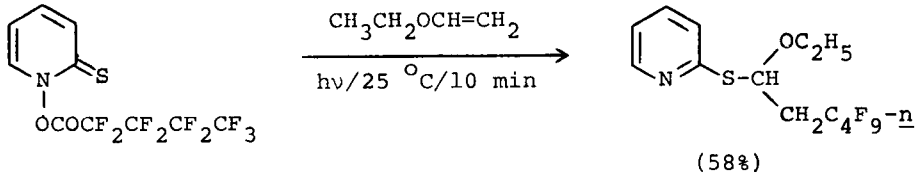
the dihydropyridine, **73**. The overall loss of HOE from such an intermediate would be expected to generate **70**. However, simple elimination of HOE from **73** does not account for significant amounts of β-substitution.

To explain the β-substitution, it is suggested that **73** separates first to an ion pair in a solvent cage (**74**). As C–3 becomes more electrophilic, migration of the neighboring sulfide group from C–2 allows it to participate in forming an episulfonium ion (**75**). Such an ion can open to form a favorable resonance stabilized cation, **76**. Subsequent loss of a proton from **76** leads to **71**. With better leaving groups, such as sulfonate and sulfamate ions from **73**, one could postulate that the electrophilicity on C–3 increases thereby allowing a more facile rearrangement of the sulfide in **74** to **76**, via the episulfonium ion, **75**, and in effect allow more β-substitution.

Furthermore, the overall mechanism explains why the presence of an amine affects the ratio of **70:71**. Although H–2 in **73** is perhaps not too acidic, an amine like triethylamine could aid in the abstraction of H–2 prior to migration of the sulfide group and thereby facilitate the elimination of HOE to give **70**.

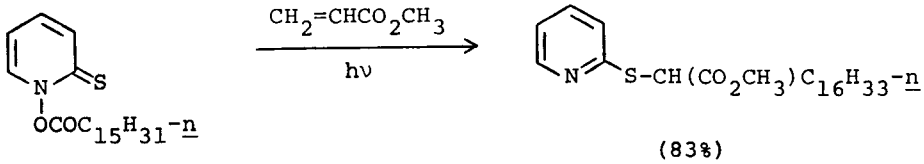
6.3. *Pyridyl Sulfides from 1-Acyloxy-2-pyridthiones by Free-radical Induced Decarboxylative S-Alkylation*

Irradiation of 1-acyloxy-2-pyridthiones, **77**, results in the formation of 2-pyridyl sulfides.[64] A free-radical mechanism has been proposed[64,65] and this method has definite preparative value. The overall equation converts **77** to **70** with the loss of carbon dioxide. After initial attack on **77** by a free radical, arbitrarily designated as Fr$^{\cdot}$, there is formed a free radical which loses a carboxyl radical, $RCO_2^{\cdot}$. The latter readily loses CO_2 and generates an alkyl (or aryl) free radical, R$^{\cdot}$. The process then propagates according to the following equations. The mechanism is summarized in Scheme III.

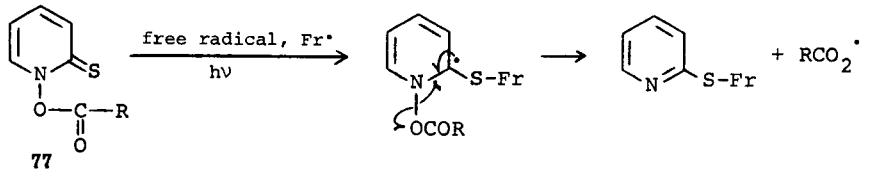


For example, photolysis of a number of perfluoroacyloxy-2-pyridthiones furnishes 2-perfluoroalkylthiopyridines in excellent yields [**70**, R = CF_3 (98%), R = C_2F_5 (94%); R = n–C_4F_9].

When these reactions are carried out in the presence of an alkene, $ZCH{=}CH_2$, The initial radical (R$^{\cdot}$) is trapped by the alkene to generate a new alkyl radical, **78**, which in turn can react with **77** to form the new sulfide **79**. An example is as follows.[64b]
Another example is one in which the alkene was methyl acrylate and palmitoyl the acyl residue:



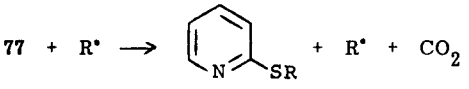
Initiation



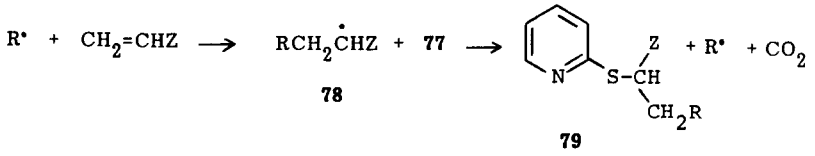
77

$$RCO_2^{\bullet} \longrightarrow R^{\bullet} + CO_2$$

Propagation



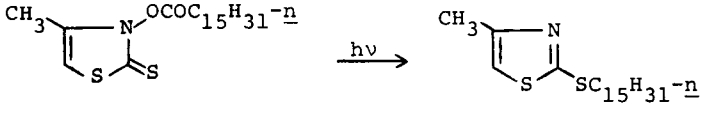
Propagation in the presence of an alkene, CH_2=CHZ



Scheme III

These methods are expected to produce many fruitful syntheses of interesting and functionalized 2-pyridyl sulfides in the future.

Related cyclic 5-membered *N*-hydroxythione hydroxamic acids can be photolyzed to form an aromatic sulfide. In the following example illumination of **80** with a 100 W medium pressure mercury lamp gave **81** in 24% yield.[64a]

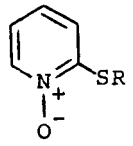


80 **81**

7. BIOACTIVITY OF PYRIDYL SULFIDES AND RELATED COMPOUNDS

This section briefly reviews some of the bioactivities of pyridyl sulfides and related compounds.

A number of 2-alkyl- and 2-arylthiopyridines and some *N*-oxides (**82–85**) have been reported to possess a variety of biological activities. Cyclic thionhydroxamic acids (shown in the tautomeric form, **82**, R = H) are antibacterials.[66] The best known example is the zinc salt of 1-hydroxy-2-pyridthione which is the active ingredient in some popular anti-dandruff shampoos.



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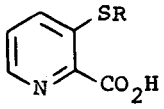

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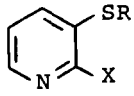

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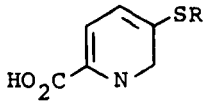
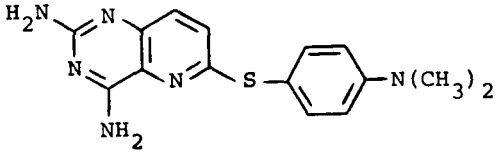


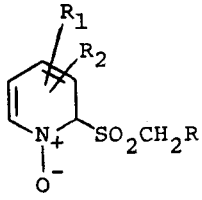
85

3-Mercapto-2-pyridinecarboxylic acid and its derivatives, **83** (R = H, $CH_2C_6H_5$, $COCH_3$, COC_6H_5) exhibit hypoglycemic activity,[25,67,68] while related amides and nitriles **84** [R = H, $CON(CH_3)_2$, X = $CONH_2$, CN] possess hyperglycemic activity.[67,69] It has been reported that 5-alkylthio-2-pyridinecarboxylic acids **85** (R = n–C_4H_9, $CH_2C_6H_4$, $CH_2C_6H_4CF_3$–m, $(CH_2)_3C_6H_5$) are active antihypertensive agents.[69] The condensed pyridine sulfide **86** showed considerable antimalarial activity.[70]



86

A number of compounds at higher oxidation states than pyridyl sulfides (e.g., *N*-oxides, sulfoxides and sulfones) have proved to be herbicides.[70–73] Representative structures are **87** (where R is alkyl or aryl, and R_1, R_2 are C_1 to C_4 alkyl groups), **88** (X is alkyl, aryl or nitro) and **89** (R is alkyl).



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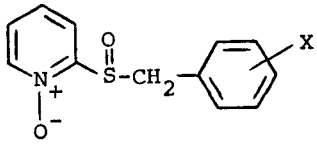

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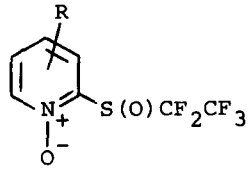
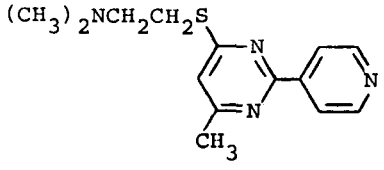


89

It is of interest to note that a number of 2-pyridinesulfonamides are active herbicides.[75–77]

Although some simpler (β- or γ-dialkylamino)alkylthio- or (carboxamidomethyl)thiopyridines, pyrazines, quinolines showed little or no activity as amplifiers of phleomycin,[78a] some related polyaza derivatives exhibited good activities.[78b] Some of the simpler, but representative examples showing relatively good activity as amplifiers are **90** and **91**.,



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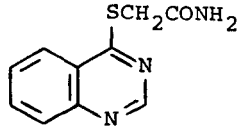

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