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STRATEGIES FOR DEVELOPING NEW REACTIONS OF ORGANIC SULFUR COMPOUNDS CONTAINING PYRIDINE AND RELATED HETEROCYCLES

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Characteristic properties of organic sulfur compounds containing heteroaromatics and their reactions are described. Applications of these organic sulfur derivatives in organic synthesis, development of several new reactions and their mechanisms are mentioned as follows: 1) simple sulfoxides such as methyl 2-pyridyl sulfoxide are used as efficient phase transfer catalysts in the S_N2 type displacement reactions and alkylations of active methylene compounds, 2) synthetic application of thione-thiol tautomerism to active esters results in the development of several important reactions, 3) treatment of benzyl 2-pyridyl sulfoxide and several other related compounds with Grignard reagents leads to a new ligand coupling reaction which is initiated by an attack of the Grignard reagent on the sulfinyl sulfur atom to form a sulfurane as an intermediate in which the two ligands can couple with each other, 4) reactions of 2- and 4-sulfinyl or -sulfonyl substituted pyridines with various nucleophiles afford the corresponding *ipso*-substitution products in high yields. The mechanism for this reaction is either an ionic or a radical path, depending on the substrates and reagents used in the reactions. In the case of 2-substituted pyridines the reaction proceeds via an ionic process, namely, nucleophilic aromatic substitution at the carbon atom attached to the sulfur functional group, while in the 4-substituted derivative the reactions with Grignard reagents presumably proceed via an electron transfer process, namely, a radical pathway.

Key words: Ligand coupling, phase transfer catalysis, 2-pyridyl disulfides, 2-pyridyl sulfides, 2-pyridyl sulfones, 2-pyridyl sulfoxides.

I. INTRODUCTION

Recently, the organic chemistry of heteroatom compounds* has attracted the attention of many organic chemists. Typical elements which have been widely studied are sulfur, phosphorus, and silicon.[1] These heteroatoms play important roles, not only in synthetic organic chemistry, but also in studies of their own physical and chemical properties. Among these heteroatoms, however, sulfur has been investigated most intensely, and several outstanding books on the chemistry of organic sulfur compounds have been published.[2]

The characteristic properties of organic sulfur compounds can be summarized as follows. 1) The sulfur atom forms many kinds of compounds having different oxidation

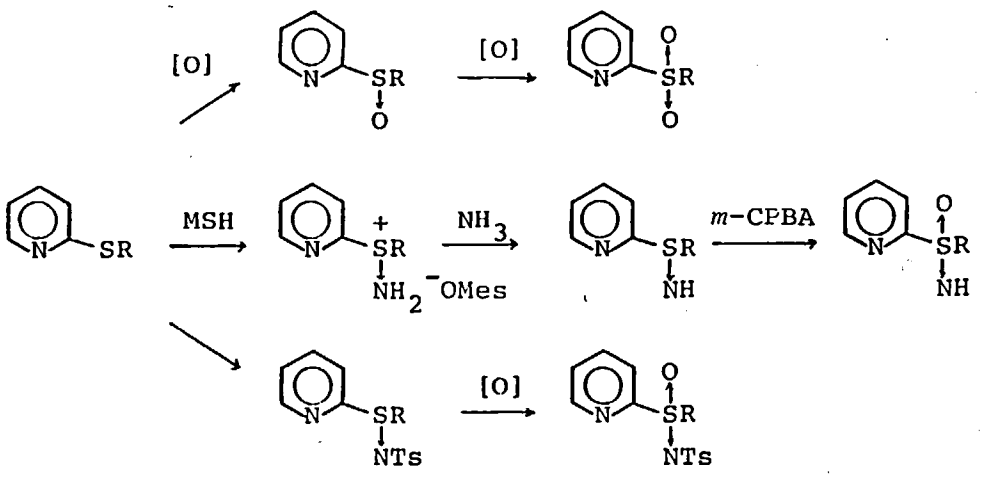
* The term heteroatom as used in this review is defined as the non-metallic typical elements except carbon. These atoms then become reaction centers.

stages from dicoordinated to even hexacoordinated derivatives such as SF_6. 2) Organosulfur compounds become either strong nucleophiles or electrophiles depending upon their attached groups or elements. 3) In general, the bonds involving the sulfur atom can be introduced into or removed from the organic molecules quite readily. In view of the remarkable reactivities as compared with those of the oxygen analogs, the sulfur atom in either di-, tri- or tetracoordinated species can stabilize a carbanionic site adjacent to the sulfur atom, whereas a di-coordinated sulfur atom stabilizes carbonium cation or radical sites generated either in the α- or β-position to the sulfur atom. 4) Stable tri- or tetracoordinated optically active sulfur compounds can be prepared.

Meanwhile, numerous heteroaromatic compounds have been synthesized and investigated with regard to their physical and chemical properties which depend upon the number and nature of the heteroatoms in the heterocycle and ring size. One of the great differences between the nature of heteroaromatics and that of benzene derivatives can be the strong electron-withdrawing property of the heterocycles due to electron localization by the heteroatoms in the ring. Therefore, if one combined these different functionalities, namely the heteroatoms and the heteroaromatics, into one molecule, one could expect to find numerous new types of reactions and to develop new synthetically useful reagents. Earlier, many organic sulfur compounds bearing heterocycles have been utilized as pharmaceuticals, agrochemicals, detergents, dyestuffs and as intermediates. However, the investigation of their reactions still remains an untouched field.[3]

Although many such organosulfur compounds containing heterocycles have become known, here we summarize mainly the chemistry of those sulfur derivatives containing pyridine and related nitrogen-containing heterocyles.

This review describes briefly the following topics: 1) The role of sulfoxides as phase transfer reagents. 2) Synthetic application of the thione-thiol tautomerism of pyridine derivatives to an "active ester" and related derivatives. 3) A new ligand coupling reaction of sulfoxides containing pyridine nuclei with organolithium and Grignard reagents. 4) *ipso*-Substitution reactions of pyridyl derivatives with nucleophiles.



SCHEME 1. Preparation of Organic Sulfur Compounds Containing Pyridine Nuclei

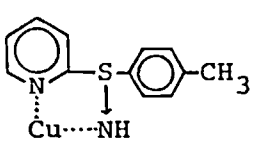
II. PREPARATION OF ORGANIC SULFUR COMPOUNDS CONTAINING PYRIDINE NUCLEI

Normally, thiols and disulfides of pyridyl derivatives are commercially available. The corresponding picolyl derivatives are also prepared from the corresponding halides and thiourea or sodium hydrogen sulfide by the standard procedure. Thus, one can readily prepare many kinds of organic sulfur compounds containing pyridine and other nitrogen-containing heterocycles. Typical preparative methods for 2-pyridyl sulfoxides, sulfones, sulfilimines, and sulfoximines are shown in Scheme 1.[4] Other heterocyclic derivatives can be synthesized similarly.

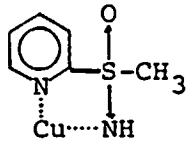
III. REACTIONS OF ORGANIC SULFUR COMPOUNDS BEARING PYRIDINE NUCLEI

III-1. Role of Sulfoxides as Phase Transfer Catalysts

The nitrogen atom in the pyridine ring is recognized to be a good ligand for complex formation with metallic cations[5] and its ability to form a complex would be enhanced by suitable functional groups attached to the 2- or 2,6-positions in the pyridine ring. As such examples, both 2-pyridyl *p*-tolyl sulfilimine and methyl 2-pyridyl sulfoximine form the corresponding 1:1 crystalline complexes (**A**) and (**B**) with $CuCl_2$ as shown below.



(A)

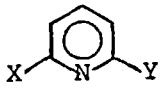


(B)

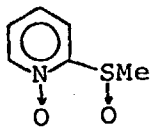
2-Pyridinecarboxylic acid forms an intramolecular hydrogen bond involving both carboxyl oxygen atoms and the pyridyl nitrogen atom, with a consequently diminished acid dissociation constant.[6] A similar phenomenon is observed in the acid dissociation of methyl 2-pyridyl sulfoxide where the proton taken up is chelated both by the oxygen atom of the sulfoxide group and the nitrogen atom of the pyridine ring.[7] Furthermore, an ion transfer experiment has been performed concerning the use of bis[2,6-di(methylsulfinylmethyl)]pyridine as a mediator through an organic liquid membrane and the transport of the Li, Na, and K salts of picric acid.[8]

Phase transfer catalysis reactions (PTC) are an important modern technique in synthetic organic chemistry and various catalysts such as onium salts (ammonium or phosphonium salts), crown ethers, and cryptands have been used for promoting these reactions.[9] Neutral compounds such as tertiary amines[10] and amine *N*-oxides[11] have also been used as catalysts. Sulfoxides are also possible neutral phase transfer catalysts. In fact, methyl 2-pyridyl sulfoxide was found to be a good phase transfer catalyst for S_N2 type reactions of various primary or secondary alkyl halides in a solid-liquid or liquid-liquid two-phase system.[12] Furthermore, many other sulfoxides such as **1a** to **4** have been

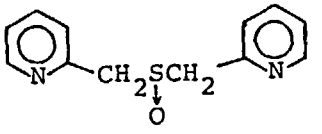
prepared and shown to serve as good phase transfer catalysts which accelerate the S_N2 type reactions of *n*-octyl bromide with various nucleophiles such as thiolate, cyanide, thiocyanate, and phenoxide ions in a solid-liquid two-phase system. The catalysts used and the reactions are illustrated in the following Schemes 2 and 3.



(1a) X = H, Y = SMe
(1b) X = H, Y = S(O)Me
(1c) X = H, Y = $S(O)_2Me$
(1d) X = H, Y = $CH_2S(O)Me$
(2a) X = Y = S(O)Me
(2b) X = Y = $CH_2S(O)Me$
(2c) X = Y = $CH_2S(O)(CH_2)_3S(O)Me$
(2d) X = Y = $CH_2S(O)(CH_2)_3S(O)(CH_2)_3S(O)Me$

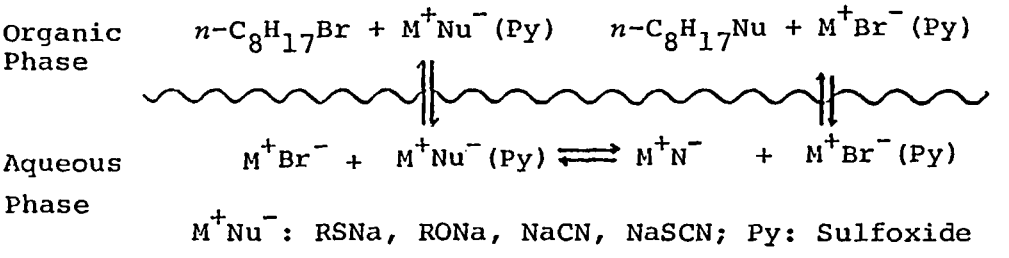


(3)



(4)

SCHEME 2. Phase Transfer Catalysts



SCHEME 3. PTC Reaction

Alkylations of phenylacetonitrile and benzyl methyl ketone with alkyl halides have also been performed in the presence of the above sulfoxides to afford the corresponding monoalkylated products in high yields. Typical examples of S_N2 type reactions and alkylations are shown in Tables 1 and 2.

TABLE I

Substitution Reactions of *n*-Octyl Bromide in the Presence of Sulfoxides

$$n\text{-}C_8H_{17}Br + MNu \xrightarrow[\text{xylene}]{\text{sulfoxide}} n\text{-}C_8H_{17}Nu + MBr$$

MNu	Catalyst*	Temp (°C)	Time (h)	Yield (%)
NaCN	(1b)	100	54	13
NaCN	(1d)	100	46	87
NaCN	(2b)	100	32	84
KSCN	(4)	100	17	75
PhSK	(1d)	r.t.	0.5	91
PhSK	(2a)	r.t.	12	93
PhSK	(2b)	r.t.	12	88
PhSK	(4)	r.t.	0.5	90
PhOK	(1b)	70	36	93
PhOK	(2a)	70	40	33
PhOK	(2b)	70	40	88
PhOK	(4)	70	14	93

*The catalyst used is shown in Scheme 2.
Reference: N. Furukawa, S. Ogawa, T. Kawai, and S. Oae, *J. Chem. Soc., Perkin I,* 1833 (1984).

TABLE II

Alkylation of Benzyl Methyl Ketone in a Two Phase System

$$PhCH_2COMe + RX \xrightarrow[\substack{50\%\text{-NaOH}\\(\text{room temp.})}]{\text{catalyst}} \underset{\displaystyle R}{PhCHCOMe} + NaX$$

RX	Catalyst (mol %)	Time (h)	Yield (%)
MeI	(1b) (10)	2	96
MeI	(2b) (10)	2	93
MeI	(4) (10)	2	100
EtI	(1b) (10)	3	83
EtI	(2b) (10)	3	75
EtI	(2c) (5)	2	92
EtI	(2d) (5)	2	100
EtI	(2d) (1)	4	92

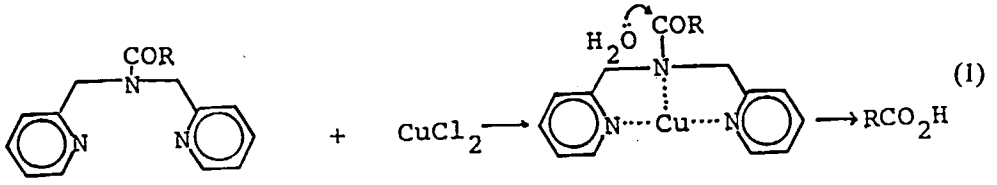
Only the monoalkylation product was obtained.
Reference: N. Furukawa, S. Ogawa, T. Kawai, and S. Oae, *J. Chem. Soc., Perkin I,* 1833 (1984).

Similarly several other sulfoxides such as α-phosphoryl sulfoxides[13] and polysulfoxides of thiacrown ethers[14] have been found to be suitable as phase transfer catalysts.

These sulfoxides containing pyridine rings can be prepared readily and also recovered quantitatively by shaking the reaction mother liquor with any mineral acid; therefore, they are useful and promising phase transfer catalysts.

III.2. Thione-Thiol Tautomers as "Active Esters" and Related Derivatives for Organic Synthesis

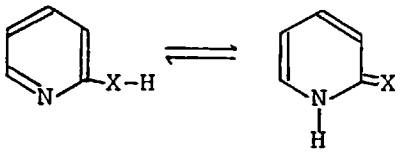
Pyridine itself is a relatively strong base with a pK_a of 5.32. As described in the former chapter, pyridyl derivatives bearing ether, sulfinyl, or amino linkages at the 2- or 2,6-positions of the pyridine nuclei can bind various metallic cations by chelation and these derivatives are utilized as ligands for metallic salts, phase transfer catalysts, or enzyme model compounds. For example, the acid amide (5) has been reported to undergo facile hydrolysis in MeOH in the presence of $CuCl^2$, since the three nitrogen atoms of the pyridine rings and the amide group might form initially a complex (6) which activates the carbonyl carbon atom to undergo facile hydrolysis.[15]



(1)

(5) (6)

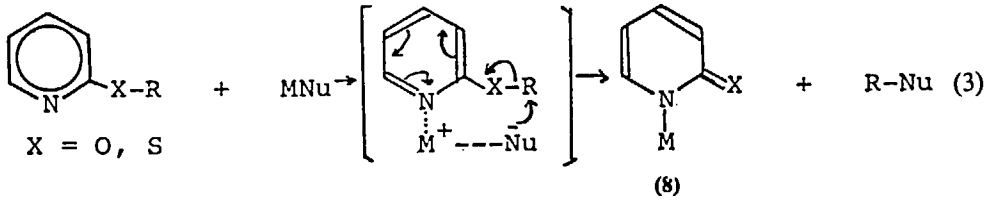
On the other hand, 2- or 4-pyridinol or -thiol are well known to exist as a tautomeric mixture of keto (8) and enol (7) forms and in solution the keto form is thermodynamically preferred over the enol form.[16]



Enol (7) Keto form (8)

	enol	keto form	
X = S	0	100 (in solution)	(2)
O	0	100 (")	
O	72	28 (in the gas phase)	

Furthermore, as shown in the following chapter, pyridine and related heterocycles possess the property of strong electron-withdrawal like the *p*-nitrophenyl group and hence serve as good leaving groups. Therefore, if one treats either the hydroxyl or thiol derivatives of pyridine i.e., ethers, esters, or the corresponding thio derivatives with nucleophiles, the following reactions shown in Eq. 3 should take place easily to afford the corresponding substitution products since the preferential formation of the pyridone or thiopydridone (8) should make the pyridyl group a good leaving group facilitating the substitution reaction.



(3)

(8)

Based on this concept, various so-called active esters or thioesters and related compounds have been synthesized and utilized as elegant reagents for organic synthesis. Several examples have been presented by Staab *et al.* for the synthesis of ketones[17] and by Sakan *et al.* for the preparation of esters or amides.[18] Subsequently, various new reagents or reaction systems have been invented by Mukaiyama and co-workers involving *i.e.*, a convenient one-step synthesis of ketones using 2-pyridyl thioesters (9) and Grignard reagents[19] as shown in Eq. 4 and direct coupling reactions of alkyl or allyl halides with the esters (9) in the presence of a nickel catalyst.[20]

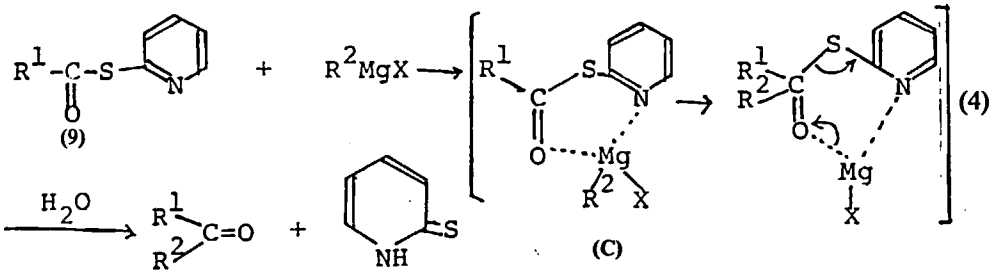
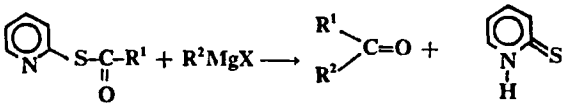


TABLE III

Preparation of Ketones

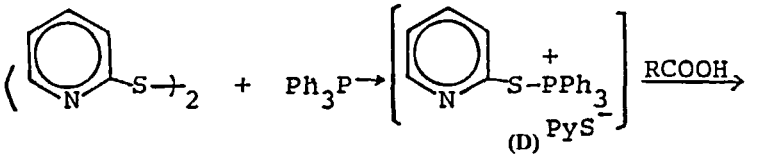


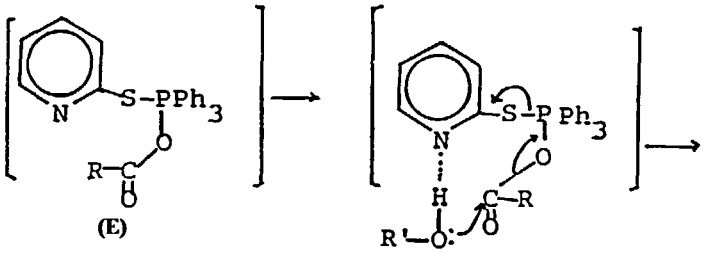
R^1	R^2	Ketone (%)
$PhCH_2CH_2$	n-C_4H_9	94
$PhCH_2CH_2$	cyclo-C_6H_{11}	97
CH_3	Ph	95
$-(CH_2)_4-$	Ph	92
Ph	Ph	94
	n-C_5H_{11}	98

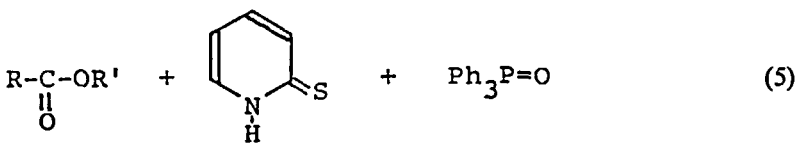
Reference: M. Araki, S. Sakata, H. Takei, and T. Mukaiyama, *Bull. Chem. Soc., Jpn.*, 47, 1777 (1974).

Generally, carboxylic acid esters react with Grignard reagents to give ketones in moderate yields since the reactions always form tertiary alcohols as by-products. However, as shown in Table 3, in the present reactions, the yields of ketones are high without concomitant formation of a tertiary alcohol. This might be due to the formation of the "ate complex" (C) which activates the thioesters, resulting in the chemoselective forma-

tion of ketones. Another interesting and versatile system as a condensing agent for the formation of esters or acid amides has been explored by Mukaiyama *et al.* in their use of pyridyl disulfide and triphenylphosphine. The original concept for this Ph_3P-$(PyS)_2$ system is based on the initial formation of an active phosphonium salt (D) with which the carboxylic acid reacts to form the hypothetical phosphorane (E). Thus, carboxylic acids can be activated towards facile attack by alcohols or amines to the final esters or amides. The mechanism for these condensations is of a concerted nature as shown in Eq. 5.



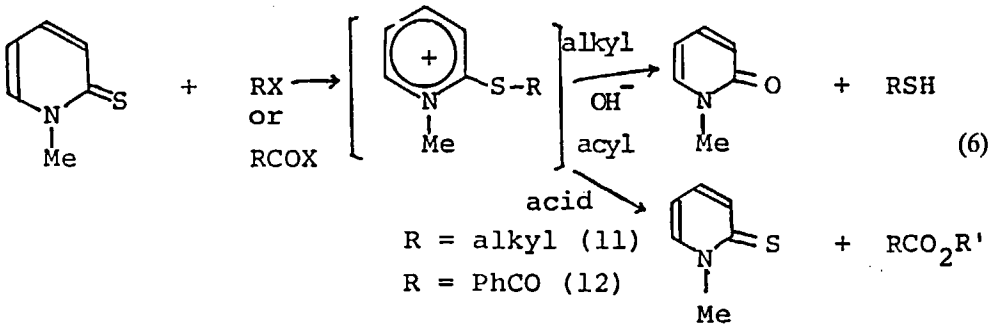




(5)

This system has been successfully applied to the synthesis of various peptides.[21] Similar condensation systems and their utilization for organic synthesis have been developed by many others.[22]

The thiocarbonyl group in *N*-alkyl-2-(1H)-thiopyridones is highly nucleophilic and hence reacts with alkyl halides or acyl chlorides to afford the quite reactive pyridinium salts (11) or (12). These salts are more reactive than the original pyridine derivatives and the salts (11) or (12) undergo hydrolysis upon treatment with aqueous alkali or acid to give the corresponding thiols[23] or acid anhydrides in high yields.[24]



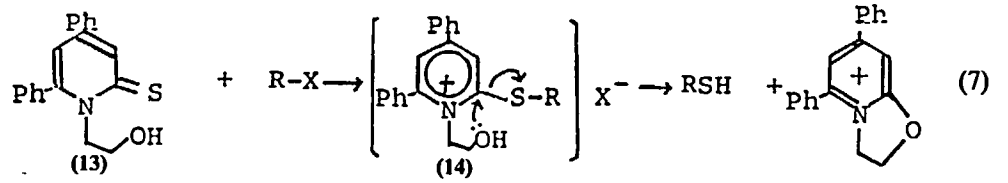
(6)

(11) RX: R=$PhCH_2$, $PhCH_2CH_2$, c-Hexyl, $ClCH_2COPh$

(12) $R'CO_2H$: R'=$Ph(CH_2)_2$, $PhCOCH_2$, Me_2CH_2, p-Tol.

Yields: 75–83%.

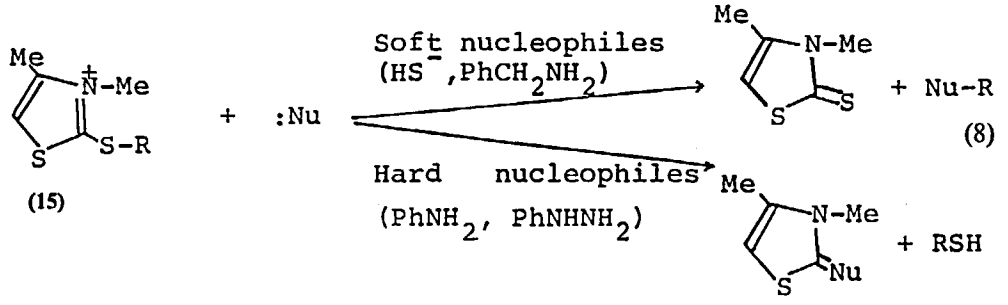
Recently, Katritzky *et al.*[25] reported that alkyl halides dare converted to thiols in one pot by treatment with the thiopyridone (**13**) which is converted to the pyridinium salt (**14**). Intramolecular substitution in **14** takes place to afford the corresponding thiols (Eq. 7).



(7)

R: $C_6H_5CH_2$, *n*-C_6H_{13}, *n*-C_4H_9. Yields: 61–89%.

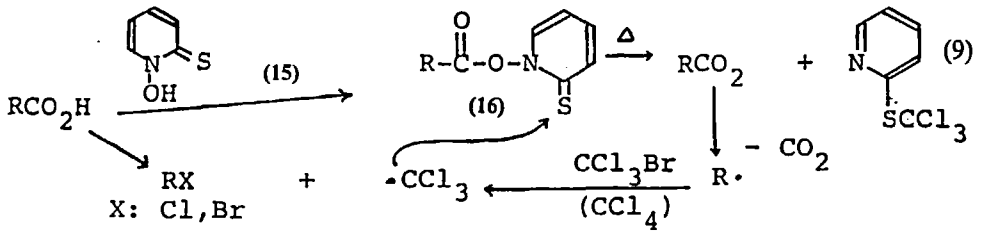
These reactions of the pyridinium salts (**11**) and (**14**) shown in Eqns. 6 and 7 should proceed via nucleophilic substitution on the carbon atom of the pyridine ring (S_NAR). However, the site of attack should change with changing nucleophiles since it is well known that in the reactions of thiazolinium salts (**15**) with nucleophiles different products have been obtained by changing the reagents. Namely, the harder nucleophiles attack the harder site, *i.e.*., the carbon atom of the thiazole ring, while the softer nucleophiles attack preferentially the softer site, *i.e.*, the carbon atom adjacent to the sulfur atom as shown in the following Eq. 8.[26]



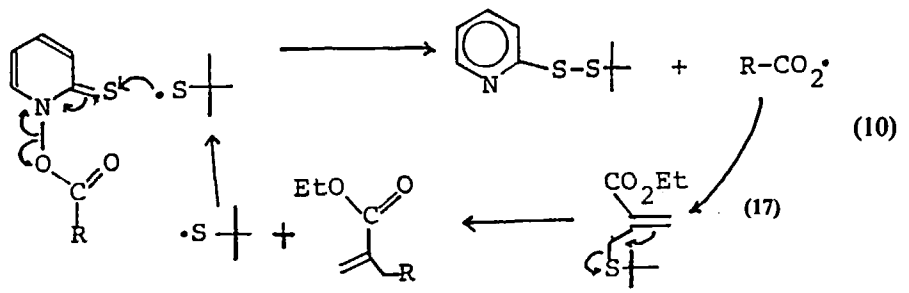
(8)

The detailed mechanism for this nucleophilic substitution on the heteroaromatic ring is described in the following chapter.

Recently, Barton *et al.* reported that upon pyrolysis of thiohydroxamic acids (**16**) which can be prepared from 1-hydroxy-2-thiopyridone (**15**) and acyl chlorides, alkyl radicals can be generated via an initial C–O bond fission in **16**. The alkyl radicals thus formed are converted to the corresponding hydrocarbons, alkyl halides, or adducts to olefins. The reactions are schematically illustrated in Eq. 9. This reaction is considered as a modified Hunsdiecker rection without the use of heavy-metal salts, but mediated by thiopyridone.[27]



When one treats the allylic olefin (**17**) with **16**, the radical R·, obtained from pyrolysis of **16**, adds to the terminal carbon of **17** with concomitant isomerization of the double bond and ejection of *t*-BuS· which may become a chain carrier in the reaction as shown below.[28] (Eq. 10).



R: $CH_3(CH_2)_{14}$, 1-Adamantyl, c-Hexyl, etc.

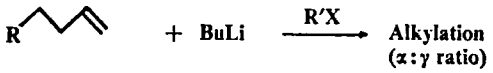
Furthermore, Barton *et al.* have also reported a convenient procedure for the generation of alkyl radicals directly from the corresponding tertiary alcohols by the following method, namely, the tertiary alcohol is converted initially to the half oxalate of **16** from which the *t*-alkyl radicals are generated upon pyrolysis similar to that of **16**. Then the *t*-alkyl radicals are found to add to olefins; thus quarternary carbon compounds are obtained in moderate yields.[29]

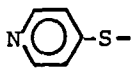
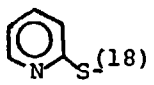
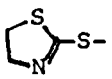
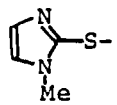
III-3. Reactions of Sulfoxides and Sulfones Containing Pyridine Nuclei with Base and Nucleophiles

a. A new ligand coupling reaction of sulfoxides containing pyridine nuclei with organolithium and Grignard reagents When allyl 2-pyridyl (**18**) and related sulfides bearing heterocycles are treated with strong base such as BuLi, the corresponding α-sulfenylated carbanions are obtained and alkylation of these carbanions takes place in the α-position relative to the sulfur atom with high regioselectivity as shown in Table 4.[30]

TABLE IV

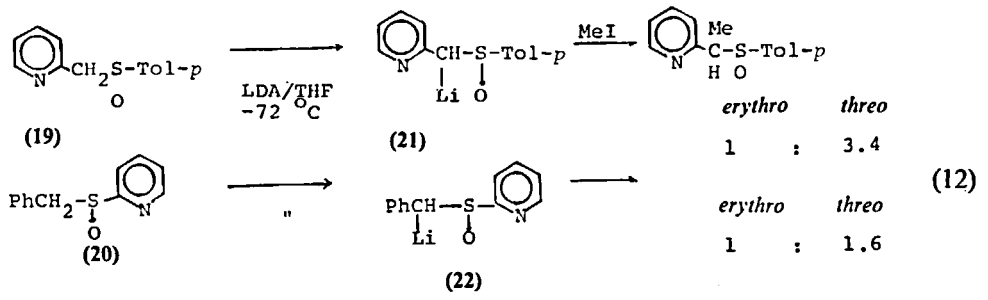
Alkylation of Heterocyclic Sulfides



R	Yield (%)	α:γ ratio
	93	75:25
 (18)	90	99:1
	95	>99:1
	92	99:1

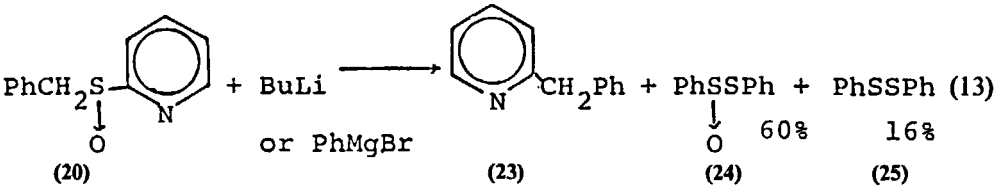
Reference: D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, 7, 147 (1974).

Similarly, the sulfoxides (**19**) and (**20**) were found to afford the corresponding carbanions upon treatment with lithium diisopropyl amide (LDA) in THF at −72 °C. Methylation of the carbanions (**21**) and (**22**) gave a mixture of the two diastereomers, the *erythro* and the *threo* form. However, the diastereoselectivity of the methylated product obtained from **21** is higher than **22**, *i.e.*, at −72 °C, the ratio of *erythro:threo* is 1:1.6 from **22** and 1:3.3 from **21**, respectively.



(12)

This higher stereoselectivity of the methylation of **21** as compared to that of **22** can be ascribed to the rather strong chelation of the Li atom by the sulfinyl oxygen atom and the nitrogen atom of the pyridine ring in **21**.[31] Unexpectedly, however, when the sulfoxide (**20**) was treated with BuLi in THF, carbanion formation was not observed at all, but 2-benzylpyridine (**23**) was obtained in more than 95% yield. Furthermore, Grignard reagents such as ethyl and benzyl also reacted with **20** to afford the same product as shown in Eq. 13.

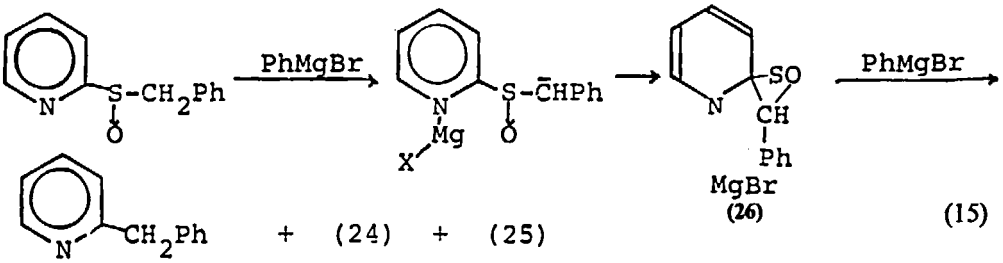


(13)

In this reaction, both the thiolsulfinate (**24**) and the disulfide (**25**) were isolated in 60 and 16% yield, respectively.[32] This result seems to rule out a Pummerer type reaction such as that observed in the reaction of dimethyl sulfoxide or methyl phenyl sulfoxide with Grignard reagents.[33] (Eq. 14).

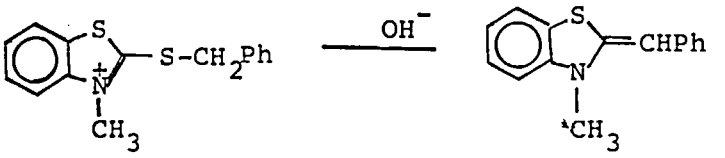
(14)

According to the detailed product analysis apparently the reaction proceeds via initial attack by the Grignard reagent on the sulfinyl sulfur atom followed by a coupling reaction between the pyridyl and benzyl groups since isolation of **24** and **25** seems to support this process. However, as it is well known that BuLi or Grignard reagents possess dual properties as strong base and nucleophile, the following Ramberg-Bäcklund type desulfinylation, namely, the initial proton abstraction followed by formation of the epi-sulfoxide (**26**) which the Grignard reagent subsequently attacks to eliminate the sulfinyl group as shown in Eq. 15.



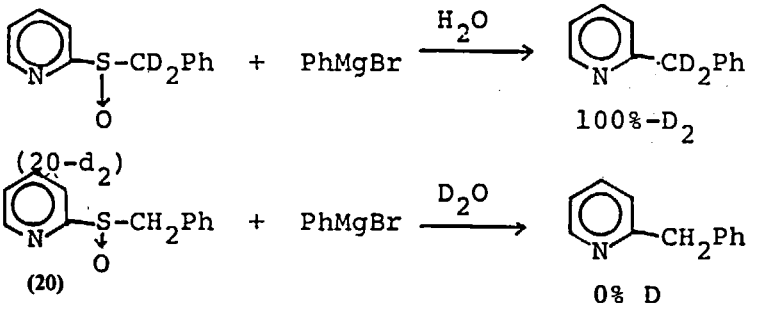
(15)

Similar desulfurization and ligand coupling reactions of several heterocyclic compounds have been reported.[34] One example is shown in Eq. 16.



(16)

However, this hypothesis could be ruled out completely by the following deuterium tracer experiments shown in Eq. 17 since if the initial proton abstraction takes place, the product obtained from 20-d_2 by work-up with H_2O should exhibit a 50% deuterium content.

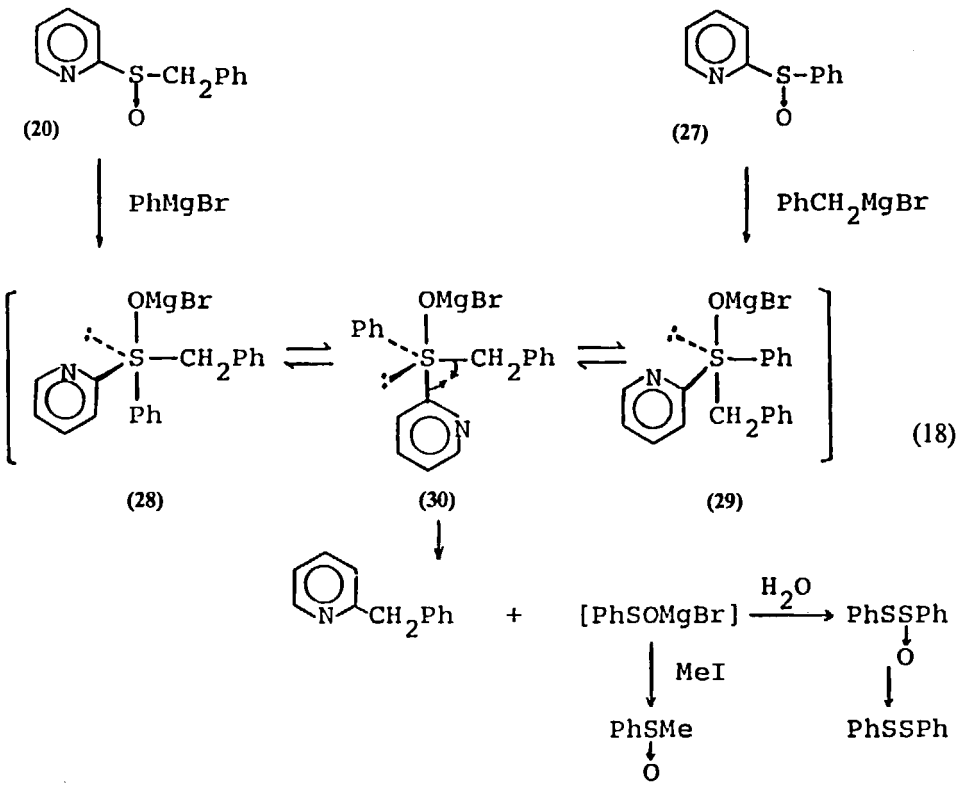


(17)

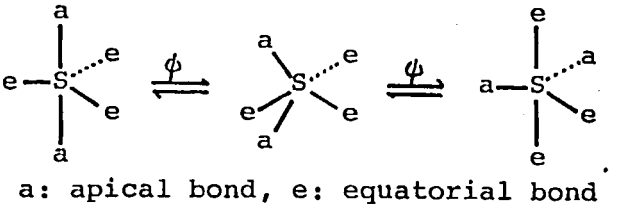
Similarly, in the reaction of **20** with PhMgBr, then work-up of the solution with D_2O, no deuterium incorporation in the product was observed, also ruling out a Ramberg-Bäcklund-type mechanism.

Apparently, these results demonstrate that the Grignard reagent attacks initially the sulfinyl sulfur atom to form a sulfurane as an intermediate in which the coupling reaction between the pyridyl and benzyl groups takes place to yield the final product. In order to further confirm this mechanism, pyridyl phenyl sulfoxide (**27**) and benzylmagnesium bromide were treated similarly as described above. Consequently, the products thus isolated were an almost identical mixture in the same yields as those shown in Eqn. **18**. Therefore, the reaction should proceed via an initial attack of the Grignard reagent on the sulfinyl sulfur atom of either the sulfoxide (**20**) or (**27**) to form the corresponding sulfurane (**28**) or (**29**), respectively, as a discrete intermediate from which mutual ligand conversion takes place to furnish the common sulfurane (**30**) by pseudorotation.[35]

The structure of sulfuranes is known to be that of a trigonal bipyramid (TB structure) in which, according to the Muetterties rule, the two electronegative ligands occupy the apical positions, while the remaining ligands are in the equatorial positions.[36] These



ligands can exchange their position by pseudorotation. The arrangement of the ligands in the TB structure of the sulfurane is illustrated in the following Scheme 4.



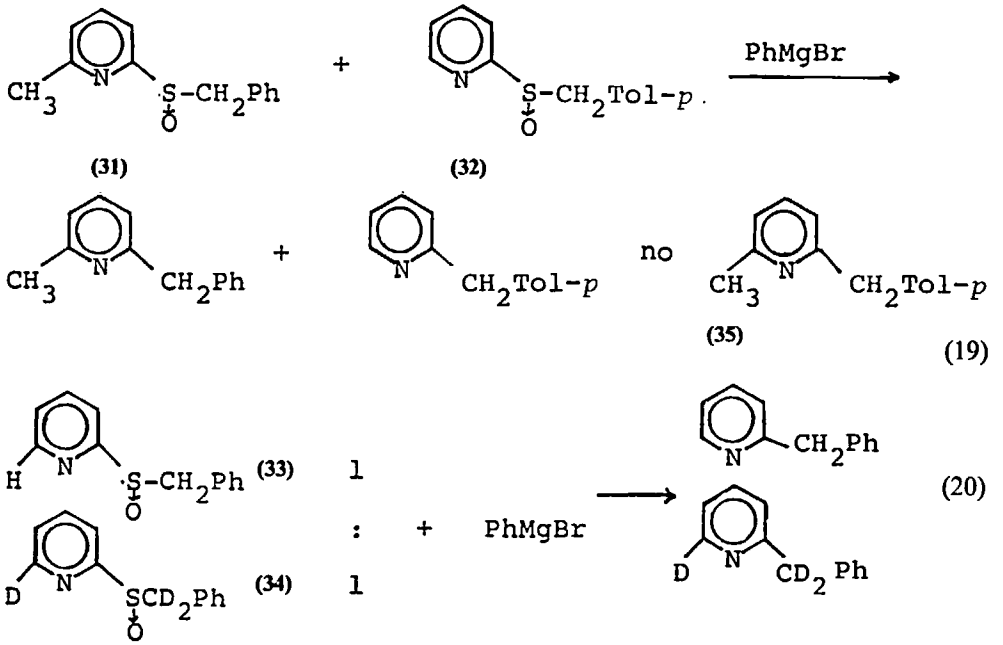
SCHEME 4. Trigonal Bipyramidal Structure (TB) and Pseudorotation

In general it has been proposed that in substitution reactions at the sulfur atom an attacking group should approach from the apical side and also a leaving group should leave from the apical positon.[36]

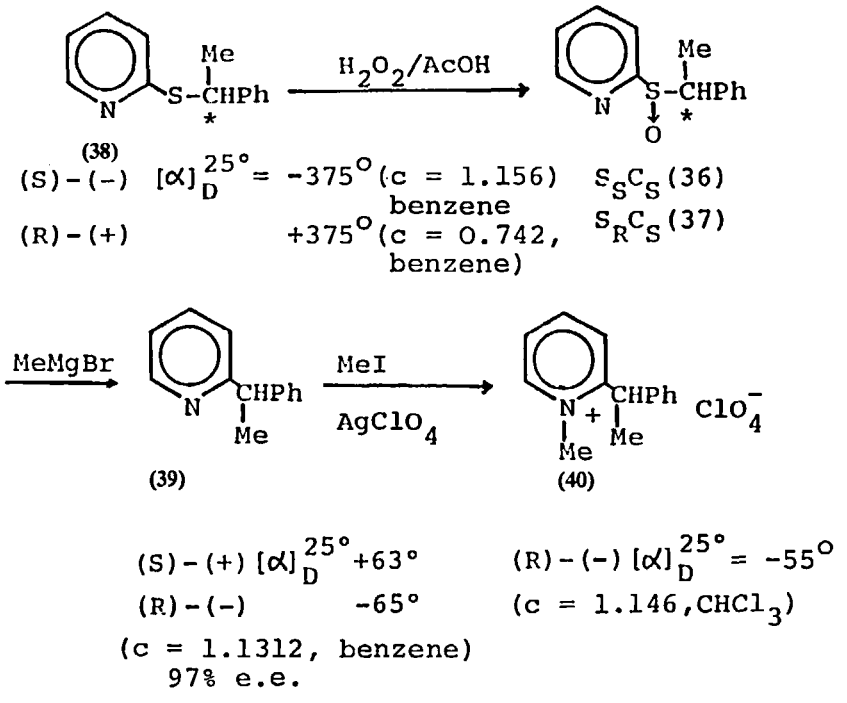
Therefore, in the present reactions of sulfoxide (20) or (27) with Grignard reagent, the most negative ligand on the sulfur atom, namely the oxygen atom of the sulfoxide group and the attacking group, here the carbon atom of the Grignard reagent, should be oriented concurrently to the two apical positions and the remainder of the ligands including lone electron pairs should occupy the equatorial positions in the TB structure

of the sulfurane as shown in **28** or **29**, respectively. In the sulfurane (**29**) the angle between the pyridyl and the benzyl group is 90° and hence this might be suitable positions for intramolecular ligand coupling, while in the sulfurane (**28**), the angle between the pyridyl and the benzyl group is 120° which is unfavorable for ligand coupling. Then pseudorotation would take place in **28** to give **30** from which the coupling product, 2-benzylpyridine, could be obtained.

This coupling reaction was ascertained to proceed via an intramolecular pathway by the following two additional experiments. One are the cross-over experiments shown in Eqns. 19 and 20. In these reactions, no cross-over product, such as **35** was detected at all, thus indicating that the coupling reaction takes place via an intramolecular process as shown in Eq. 18.[32]



Furthermore, the intramolecular nature of the coupling reaction was verified by investigating the stereochemistry of the reaction by using either the diastereomeric sulfoxides (**36**) or (**37**) or a mixture of **36** and **37** with methylmagnesium bromide. The diastereoisomers **36** or **37** were prepared from the optically pure sulfide (**38**) (S or R configuration) with hydrogen peroxide. The results thus obtained are shown in the following Scheme 5. Whether the reaction started with the optically active sulfoxide (**36**) or (**37**) [S_sC_s or S_rC_s], the configuration of the carbon atom in the coupling product 2-(1-phenylethyl)pyridine (**39**) obtained is S in more than 97% enantiomeric excess. The configuration of the product (**39**) was determined by X-ray crystallographic analysis[37] after conversion of **39** to the crystalline pyridinium salt (**40**). This result shows clearly that the stereochemical course of the reaction is retention and agrees well with the proposed mechanism. Namely, if the coupling reaction proceeds as shown in Eq. 13, the pyridyl anion should attack the benzylic carbon atom from the front side and hence this must give retention analogous to the Wagner-Meerwein rearrangement.[38]

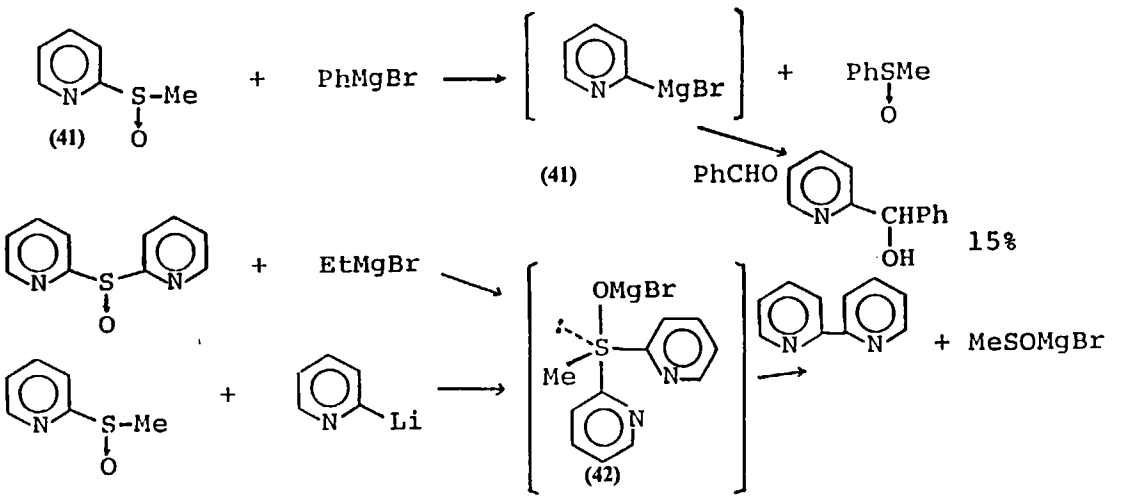


SCHEME 5. Stereochemistry of the Coupling Reaction

Besides these rections of benzyl or 1-phenylethyl 2-pyridyl sulfoxide with various Grignard reagents, other 2-pyridyl alkyl or aryl sulfoxides also react with Grignard reagent affording the ligand coupling products except in the case of the reaction of methyl pyridyl sulfoxide with various Grignard reagents. The results are shown in Table 5.

Inspection of Table 5 reveals that any combination of alkyl 2-pyridyl sulfoxides and Grignard reagents produces a mixture of 2-alkyl- (or aryl) pyridine the alkyl or aryl group of which comes from either the sulfoxide or the Grignard reagent.

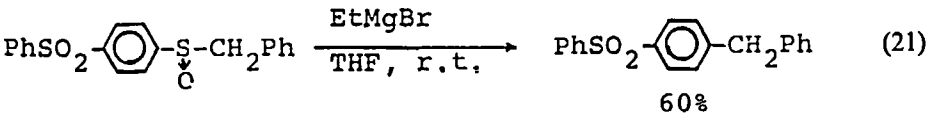
However, methyl 2-pyridyl sulfoxide (41) upon treatment with any Grignard reagent except the benzylic derivative, gives solely 2,2′-bipyridine in moderate yield. Since it is well known that the 2-pyridyl anion is unstable and hence highly reactive, thus once Grignard reagents attack the sulfinyl sulfur atom of methyl 2-pyridyl sulfoxide, a Grignard exchange reaction would take place initially to give the highly nucleophilic 2-pyridyl anion. This 2-pyridyl anion once formed would immediately attack the starting sulfoxide to give the sulfurane (42) in which pyridyl-pyridyl ligand coupling could take place to afford 2,2′-bipyridine. Actually, 2-pyridylmagnesium bromide has been trapped by adding benzaldehyde in 15% yield. The complete reaction scheme is shown in the following.



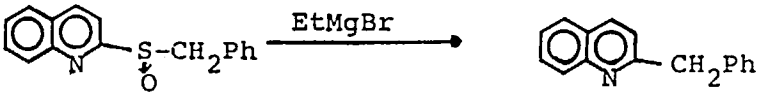
SCHEME 6. Formation of Bipyridine

Similarly, other substituted 2,2′-bipyridines have been prepared[39] in moderate yields as shown in Table 6. Although several preparative methods for bipyridines have been reported,[40] the present procedure is one of the more convenient ones for the synthesis of 2,2′-bipyridines.

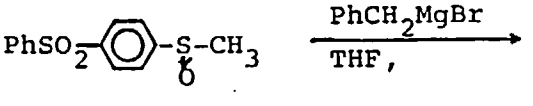
The ligand coupling reaction has been tested with other heterocyclic sulfoxides. It was found that not only benzyl 2-pyridyl sulfoxide, but also some other benzyl heterocyclic sulfoxides, such as 2-quinolyl, 2-pyrimidyl, and 2-benzothiazolyl undergo similar coupling reactions upon treatment with Grignard reagents. Furthermore, even phenyl group substituted sulfoxides with a strongly electron-withdrawing *p*-phenylsulfonyl group react with Grignard reagents to afford coupling products.[41] The results are summarized in the Eqns. 21–25.



(21)



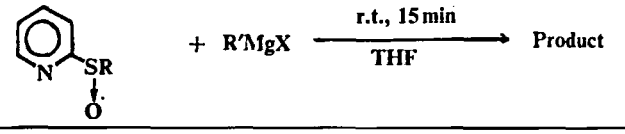
(22)



(23)

TABLE V

Coupling Reactions of Pyridyl Sulfoxides with Grignard Reagents



R	R′	Product (%)
CH_2Ph	CH_3	2-benzylpyridine (83)
CH_2Ph	C_2H_5	2-benzylpyridine (90)
CH_2Ph	Ph	2-benzylpyridine (98)
CH_2Ph	n-BuLi	2-benzylpyridine (46)
CH_2Ph	α-Pyridyl	2-benzylpyridine (26)
CH_3	CH_3	2,2-bipyridine (73)
CH_3	Ph	2,2-bipyridine (79) $PhSCH_3$ (36)
C_2H_5	C_2H_5	2-ethylpyridine (55)
$CH(CH_3)_2$	C_2H_5	2-ethylpyridine (identified) 2-isopropylpyridine (identified)
$C(CH_3)_3$	C_2H_5	2-ethylpyridine (39) 2-*t*-butylpyridine (24)
$CH_2CH{=}CH_2$	Ph	2-allylpyridine (61)
Ph	C_2H_5	2,2′-bipyridine (42)
Ph	$PhCH_2$	2-benzylpyridine (71)
	C_2H_5	2,2′-bipyridine (63)
	$PhCH_2$	2-benzylpyridine (40)

An equimolar or half-molar equivalent of Grignard reagent was used.

Reference: S. Oae, T. Kawai, and N. Furukawa, *Tetrahedron Lett.*, **25**, 69 (1984). *Idem, Bull. Chem. Soc., Jpn., submitted.*

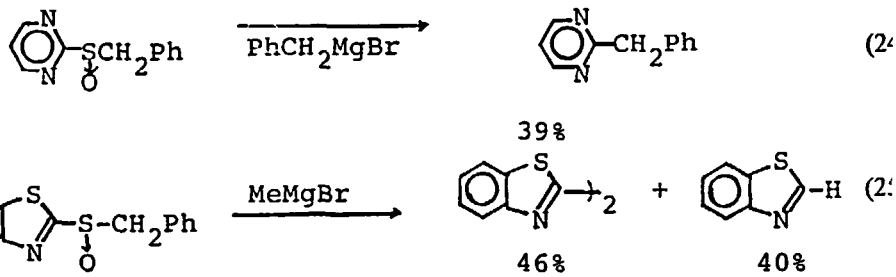
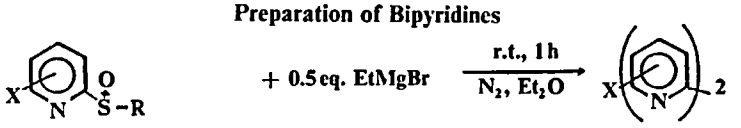


TABLE VI

Preparation of Bipyridines



X	R	Yield (%)
H	CH_3	30
6-SCH_3	CH_3	61
4-CH_3	C_2H_5	12
5-CH_3	C_2H_5	10
6-CH_3	C_2H_5	57
5-Cl	CH_3	40
6-Cl	CH_3	55
5-Br	CH_3	40
6-Br	CH_3	50
3,5-Cl_2	CH_3	52
6-C_2H_5	CH_3	30
6-piperidyl	CH_3	22

Reference: T. Kawai, N. Furukawa, and S. Oae, *Tetrahedron Lett.*, **25**, 2549 (1984).

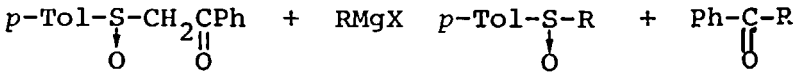
Furthermore, upon treatment with PhMgBr in THF, benzyl 4-pyridyl sulfoxide also affords the coupling product, 4-benzyl-pyridine in 60% yield, while the 3-derivative did not give rise to the corresponding 3-benzylpyridine, but gave the substitution product of the attack at the sulfinyl sulfur atom, namely, benzyl phenyl sulfoxide, besides diphenyl sulfoxide in 15 and 48% yield, respectively.[42]

b. General reactions of sulfoxides and sulfonium salts with Grignard reagents or alkyllithiums Reactions of alkyl aryl or diaryl sulfoxides with Grignard reagents or alkyllithium have been investigated by several authors. They have obtained mostly the sulfoxides which are produced by Grignard reagent ligand exchange reactions, namely substitution reaction at the sulfinyl sulfur atom is the generally observed course of these reactions.[43] (Eqns. 26–28)

$$\mathrm{Ar{-}\overset{\overset{\downarrow}{O}}{S}{-}CH_3} + \begin{matrix}\mathrm{RMgX}\\ \mathrm{RLi}\end{matrix} \longrightarrow \mathrm{R{-}\overset{\overset{\downarrow}{O}}{S}{-}CH_3} \qquad (26)$$

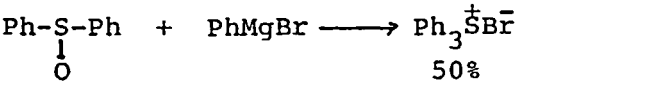
Ar: Ph, *p*-Tol, *n*-Bu, Et, etc.

$$\mathrm{Ar{-}\overset{\overset{\downarrow}{O}}{S}{-}CH_2X} + \mathrm{RMgX} \longrightarrow \mathrm{R{-}\overset{\overset{\downarrow}{O}}{S}{-}Ar} \qquad (27)$$

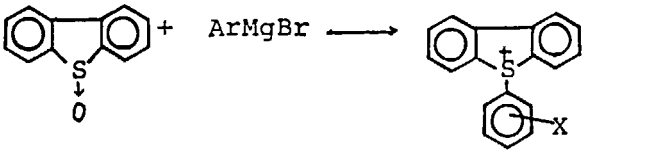


(28)

The stereochemistry of these substitution reactions has been investigated by means of optically active sulfoxides and their reactions with Grignard reagents or alkyllithium reagents. The results demonstrate that the sulfoxides obtained possess a configuration completely opposite to that of the starting sulfoxides. Meanwhile, diaryl sulfoxides have been observed to react with aryl Grignard reagents to give triarylsulfonium salts as shown in the following equations.[44]

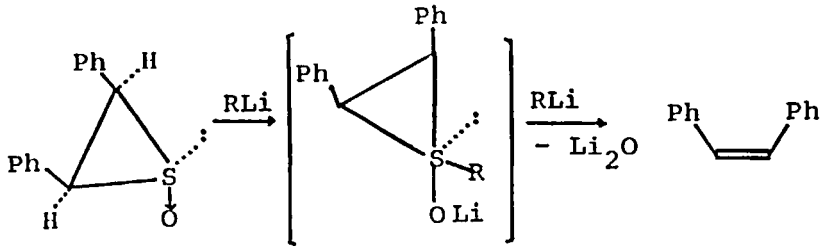


(29)



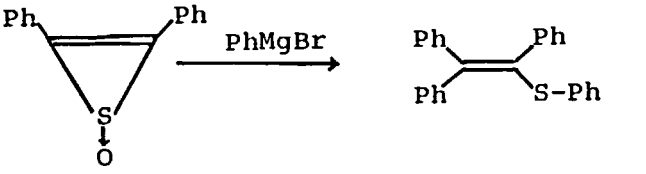
(30)

Besides these reactions, the episulfoxides (43), (44) and even episulfide (45) react with alkyllithium or Grignard reagents to give olefins stereospecifically. These reactions appear also to be initiated by the attack of the metalorganic reagents on the sulfinyl or the sulfenyl sulfur atom as shown in Eqns. 31–33.[45]



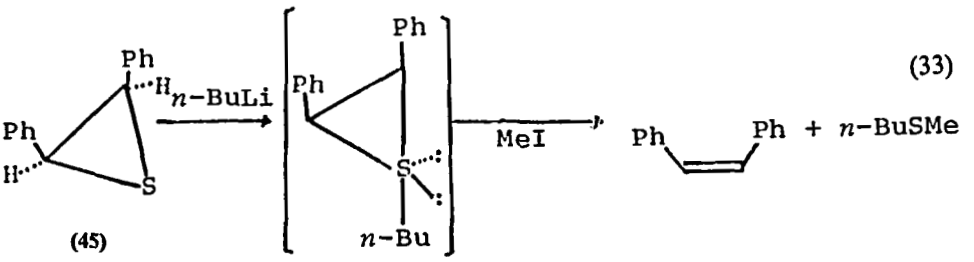
(43)

(31)



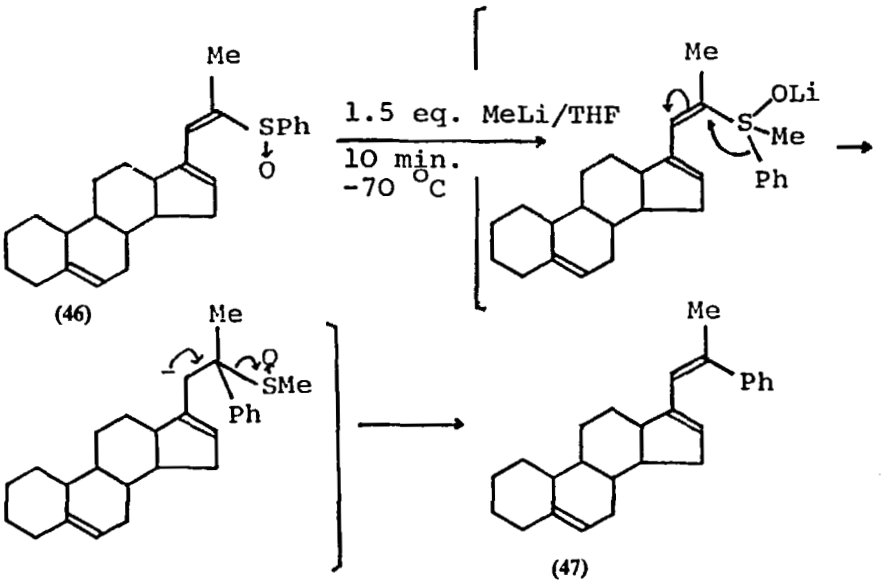
(44)

(32)



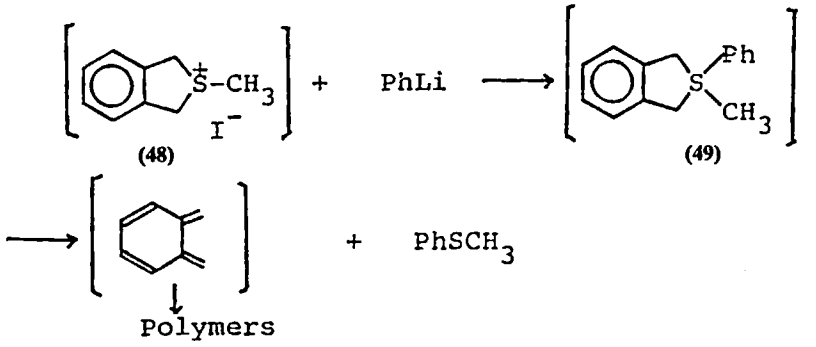
(33)

Among the few known examples of ligand coupling of sulfoxides with alkyllithiums, Nef *et al.* have reported the following reaction of **46** with MeLi to give the ligand coupling product (**47**) which is obtained via the initial formation of a sulfurane as an intermediate. They have reported that the reaction proceeds stereospecifically.[46] (Scheme 7).



SCHEME 7

Although the ligand coupling reaction is rather unique among the reactions of sulfoxides and organometallic reagents, a variety of sulfonium salts are known to undergo ligand coupling reactions upon treatment of the salts with organolithium reagents. Bornstein *et al.* have found that the sulfonium salt (**48**) reacts with PhLi to give thioanisole besides polymeric products which are formed via the sulfurane (**49**)[47] (equation 34).

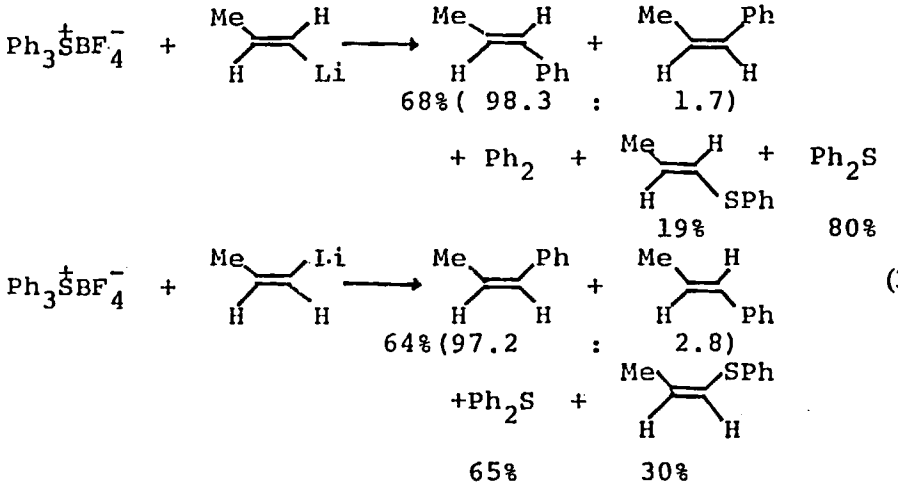


(34)

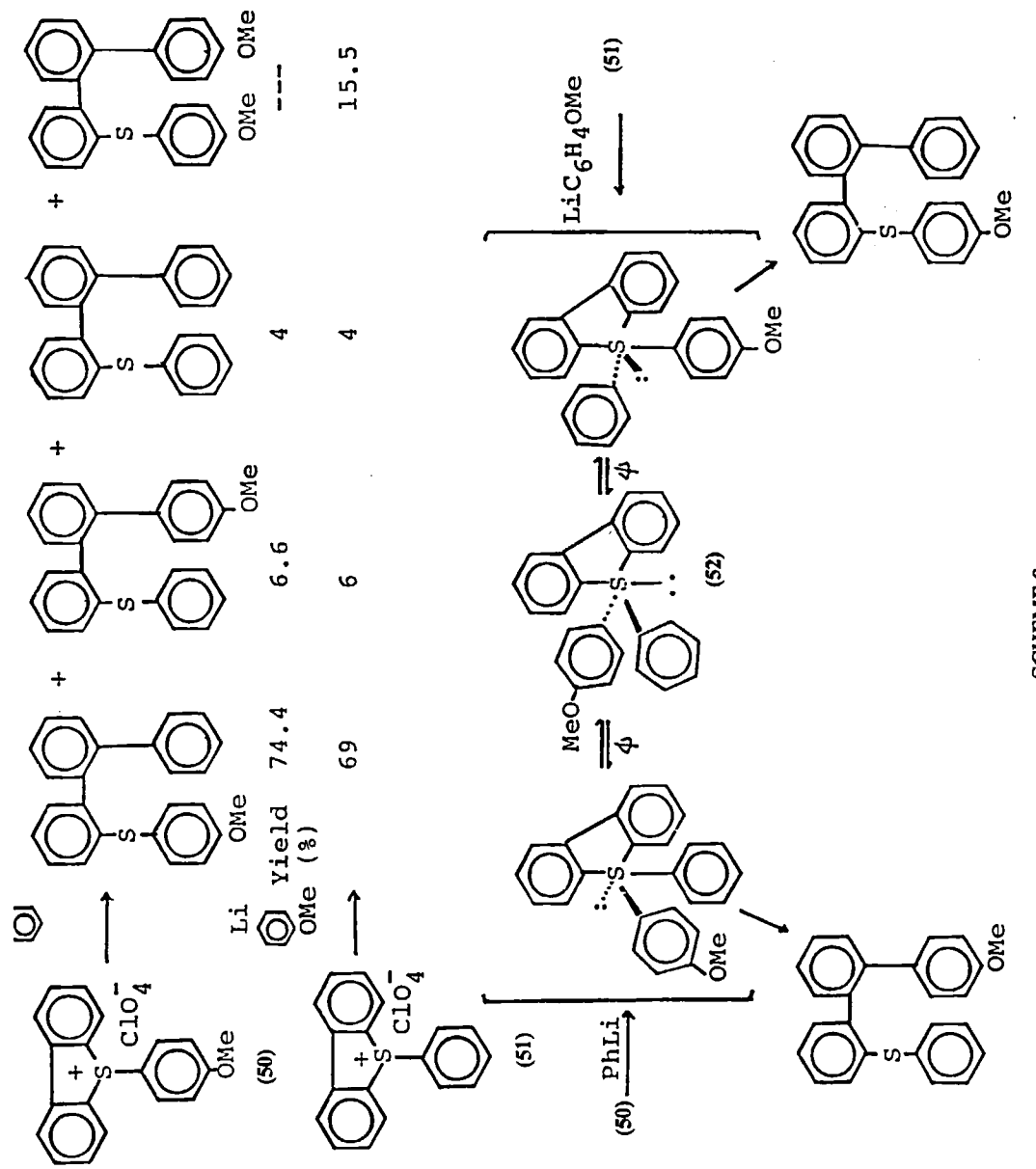
The reactions of triarylsulfonium salts with organolithium reagent have been investigated by many authors. All these reactions are considered to involve the formation of the corresponding sulfuranes from which the ligand coupling reactions[48] or benzyne formation[49] are postulated to take place. With respect to these reactions Hori *et al.*[50] have found that either the sulfonium salt (**50**) or (**51**) reacts with phenyllithium or *p*-methoxyphenyllithium to afford similar products in similar distributions as shown in the following Scheme 8.

Thus, they propose that the reactions proceed via a common intermediate, the sulfurane (**42**), which interconverts readily by pseudorotation.

Trost *et al.*[51] have worked with many reactions of sulfonium salts with alkyllithium reagents and found that the ligand coupling reactions take place via a sulfurane. They have demonstrated that the reactions are not only valuable in organic synthesis such as carbon-carbon bond formation mediated by the sulfur atom, but have also taken interest in the mechanism of the reactions. In the course of their stereochemical investigations they have revealed that the coupling reactions take place via a highly stereoselective process which has been proved by using a triphenylsulfonium salt and propenyl- or styryllithium[52] as shown in Eq. 35.



(35)



SCHEME 8

All these coupling reactions as described above are postulated to involve the initial formation of the tetracoordinated or pentacoordinated species "sulfurane" from which the ligand coupling takes place to give the final product. As a proof of this assumption Sheppard *et al.* actually found the σ-sulfurane (53) as a discrete intermediate by the following reaction of SF_4 (54) or $C_6F_5SF_3$ (55) with phenyllithium, observed directly by ^{19}F nmr at low temperature[53] (Eq. 36).

When the solution of 53 is warmed to 0 °C, only the ^{19}F spectra of the coupling product (56) and the sulfide (57) were detected with disappearance of the corresponding ^{19}F nmr signals of 53.

$$\begin{array}{l} 3C_6F_5Li + C_6F_5SF_3 \\ \qquad\qquad (55) \\ 4C_6F_5Li + SF_4 \\ \qquad\qquad (54) \end{array} \xrightarrow{-80\ ^\circ C} (C_6F_5)_4S \xrightarrow{0\ ^\circ C} (C_6F_5)_2 + (C_6F_5)_2S \qquad (36)$$

(53) (56) (57)

On the basis of these results concerning the reactions of tricoordinate sulfur compounds with organometallic reagents the following conclusive remarks are made. Namely, tricoordinate organic sulfur compounds such as sulfoxides or sulfonium salts react readily with Grignard or organolithium reagents to give either the corresponding ligand exchange or coupling products with high stereoselectivity. In the case of the coupling reactions, the corresponding sulfurane should become a discrete intermediate since in these reactions the ligands attached to the central sulfur atom are rather strong electron-withdrawing groups such as the pyridyl group or the two ligands are fixed in a five-membered ring and for these reasons the bonds attached to the central sulfur atom would be stabilized. On the other hand, if the ligands of the tricoordinate sulfur atom would be too weak to stabilize the bonds of the sulfur atom of the sulfurane the sulfurane could not become an intermediate, but would remain a transition state. Therefore, the reactions could proceed via S_N2 type substitution at the tricoordinate sulfur atom.

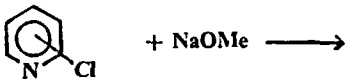
III-4. ipso-*Substitution of a Sulfinyl or Sulfonyl Group on the Pyridine Ring*

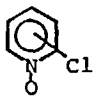
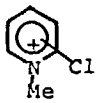
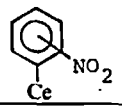
a. Nucleophilic aromatic substitution with sulfonyl compounds As shown in the previous chapter, 2-sulfinyl substituted pyridines and other heterocycles undergo ligand coupling reactions when they are treated with Grignard reagents or alkyllithiums. However, 2- or 4-sulfinyl or -sulfonyl substituted pyridines or other heterocycles containing nitrogen atoms give unexpectedly the corresponding *ipso*-substitution products upon treatment with other common nucleophiles such as RO^-, RS^-, CN^-, RNH^- etc. The corresponding sulfones also have been found to undergo similar *ipso*-substitution reactions when they react with not only ordinary nucleophiles but also with Grignard reagents. These *ipso*-substitution reactions have been investigated by Barlin and Brown earlier in the late 1960s.[54] Pyridine and other nitrogen-containing heterocycles are known to possess stronger electron-withdrawing properties than the phenyl group, almost as strong as the *p*-nitrophenyl group. This strong electron-withdrawing property of the pyridine ring corresponds to a facile nucleophilic substitution at the carbon atom of the pyridine ring.

The rates of substitution increase enormously by changing from pyridine derivatives as substrates to the corresponding *N*-oxides or pyridinium salts. The relative rates of typical examples for nucleophilic substitution of 2- or 4-halopyridines and their derivatives with MeO^- are shown in the following Table 7.[55]

TABLE VII

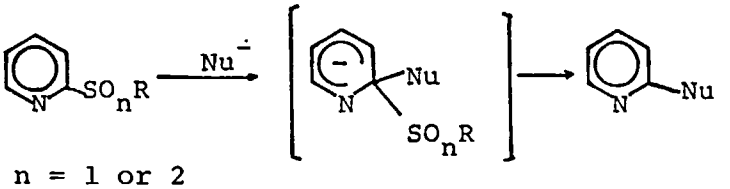
Relative Reactivity of Pyridyl Derivatives in Nucleophilic Substitution



Position of Cl		Relative Rate
Chlorobenzene		1.0
	2-	2.76×10^8
	3-	9.12×10^4
	4-	7.43×10^9
	2-	5.30×10^{12}
	3-	9.67×10^9
	4-	8.33×10^{12}
	2-	1.28×10^{21}
	3-	2.62×10^{13}
	4-	4.23×10^{19}
	2-	2.10×10^{10}
	4-	7.1×10^{10}

Reference: G. Illuminati, *Adv. Heterocycl. Chem.*, 4, 285 (1964).

In aromatic nucleophilic substitution using *p*-nitrophenyl derivatives, the approximate order of leaving group ability has been reported as follows; $F > NO_2 > OTs > SOPh > Cl \cong Br \cong I > N_3 > \overset{+}{N}R_3 \cong OAr \cong OR > SR > SO_2R > NH_2$.[56] Interestingly, the nitro group is one of the better leaving groups. Among the halogens fluorine is the best leaving group due to its strong electronegativity. However, the sulfonyl group is not substituted at all in these reactions.[57] As a remarkable contrast to these results, in nucleophilic substitution reactions of heteroaromatic compounds, the sulfonyl, sulfinyl, and even the ammonium groups are better leaving groups than halogen. The leaving group ability of the sulfonyl or sulfinyl group depends upon the nature of the attached heterocycles and these sulfur groups are substituted by nucleophiles ca. 10–100 times faster than chlorine or bromine atoms as shown below. Based on kinetic investigations, Barlin *et al.*[54] concluded that the reactions should proceed via the formation of a Meisenheimer-type complex in the rate-determining step as shown below (Eq. 37).



(37)

n = 1 or 2

Nu: OH, RO^-, RS^-, CN^-, $MeNH_2$, $n\text{-}PrNH_2$.

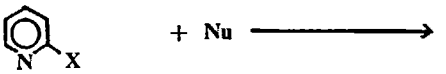
Solvent: alcohol or DMF

In the case of pyridine, substitution in the 4-position proceeds faster than in the 2-position.

We have investigated the preparation of heterocycles containing sulfur functional groups. In the course of this study we have found that the sulfinyl or sulfonyl group can

TABLE VIII

ipso-Substitution of Sulfur Compounds Bearing Pyridine Nuclei



Substrate X	Nucleophile	Solvent	Temp. (°C)	Time (h)	Products Yield (%)
2-SCH_3	C_2H_5ONa	EtOH	reflux	5	no reaction
2-SCH_3	C_2H_5SNa	EtOH	reflux	5	no reaction
2-$S(O)CH_3$	C_2H_5ONa	EtOH	50	2	73 (sulfide 8)
2-$S(O)CH_3$	C_2H_5SNa	EtOH	50	5	74 (sulfide 18)
2-$S(O)CH_3$	PhSK	*t*-BuOH	reflux	5	47 (sulfide 7)
2-$S(O)CH_3$	PhOK	*t*-BuOH	reflux	18	no reaction
2-$(O)CH_2Ph$	C_2H_5ONa	EtOH	reflux	1.5	80
4-$S(O)CH_3$	C_2H_5ONa	EtOH	reflux	3	63 (sulfide 21)
2-Cl-6-$S(O)CH_3$	C_2H_5ONa	EtOH	50	1	74[a] (sulfide 13)
2-Cl-6-$S(O)CH_3$	C_2H_5SNa	EtOH	r.t.	1.5	68[a] (sulfide 20)
2-$S(O)_2CH_3$	C_2H_5SNa	EtOH	reflux	1.5	79
2-$S(O)_2Ph$	C_2H_5SNa	EtOH	reflux	0.2	87
2-Cl-6-$S(O)_2CH_3$	C_2H_5SNa	EtOH	50	1	84[a]
2-Cl-6-$S(O)_2CH_3$	C_2H_5SNa	EtOH	r.t.	1.5	90
2-Cl-6-$S(O)_2CH_3$	C_2H_5SNa[b]	benzene	reflux	0.25	100
2-Cl-6-$S(O)_2CH_3$	NaCN	DMF	r.t.	162	94
2-Cl-6-$S(O)_2CH_3$	NaCN	DMF	60	12	76

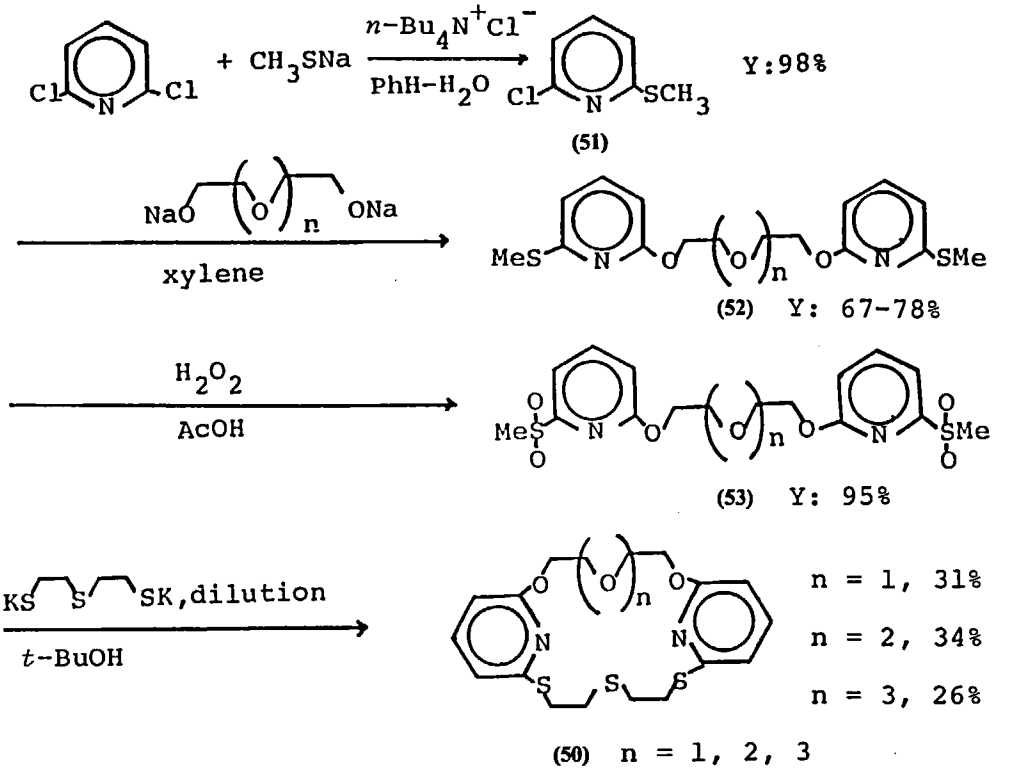
[a] Only 2-chloro-6-substituted product was obtained.

[b] In the presence of 18-crown-6.

Reference: N. Furukawa, S. Ogawa, T. Kawai, and S. Oae, *J. Chem. Soc., Perkin I*, 1839 (1984).

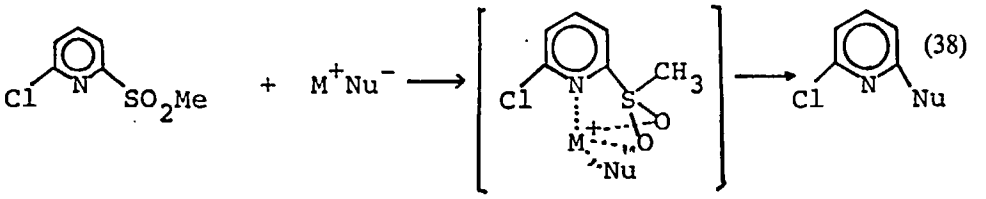
be substituted quite readily with various nucleophiles to afford the corresponding pyridine derivatives as shown in Eq. 37. Furthermore when 2-chloro-6-sulfinyl- or sulfonylpyridine was treated with nucleophiles, the sulfinyl or sulfonyl group was preferentially substituted by nucleophiles to give 6-substituted 2-chloropyridine derivatives which further react with other nucleophiles to afford the pyridyl derivatives bearing different substituents at the 2- and 6-positions regiospecifically in good yields. This result shows an intramolecular competitive reaction between the sulfonyl or sulfinyl group and the halogen atom in the pyridine ring toward nucleophiles, thus demonstrating clearly that the sulfur functional groups possess better leaving group ability than halogens. The results of these reactions are summarized in Table 8.[58]

These reactions were applied to the preparation of macrocycles containing pyridine and different heterocyclic ring systems such as **50**. The starting material for this synthesis of **50** was 2,6-dichloropyridine which was converted to 2-chloro-6-methylthiopyridine (**51**) without any contamination by the disulfenylated pyridine when the reaction was carried out with methanethiolate under phase transfer reaction conditions. Oxidation of **51** with peracid or H_2O_2 yielded the sulfone (**52**) which was treated with either the disodium salts of polyethylene glycols or polyethylenepolythiolates to give **53**. Then the compounds (**53**) were finially cyclized to the macrocycles (**50**) with different side arms. The synthetic procedure for **50** is shown in Scheme 9.[59]



SCHEME 9. Preparation of Macrocycles

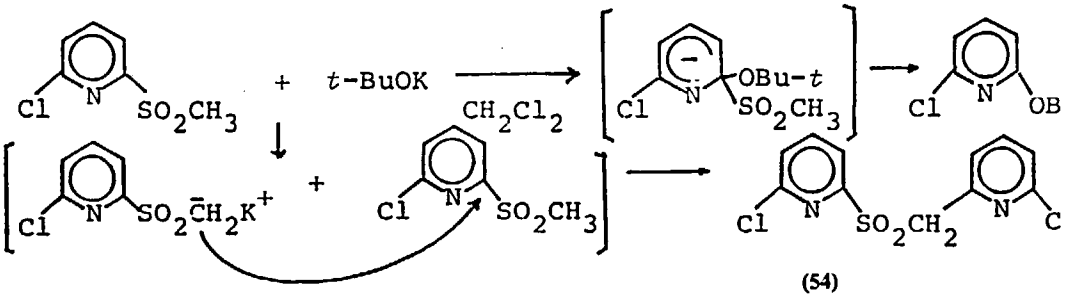
As shown in Table 8, further interesting results have been obtained by using amines or amide anion as nucleophiles. Both primary and secondary aliphatic amines react *in situ* with 2-chloro-6-methylsulfonylpyridine in high yield while tertiary or aromatic amines do not react at all with **52**. Even the primary amine *t*-$BuNH_2$ did not react at all with **52** whereas lithium piperidide reacts with **52** to give 2-chloro-6-piperidylpyridine in moderate yield.[60] The reason for this remarkable difference in the relative leaving group ability of a halogen atom and the sulfinyl or sulfonyl group and also the regioselectivity in the attack of amine or amide anion on the pyridine ring are not fully understood as yet. One possible explanation for the relative leaving abilities of halogen atoms and the sulfinyl or sulfonyl group is chelation of the metal cations by both the oxygen atoms on the sulfonyl group and the nitrogen atom of the pyridine ring; thus the carbon atom attached to these groups might be more electropositive than that carrying the halogen atom as shown below (Eq. 38).



(38)

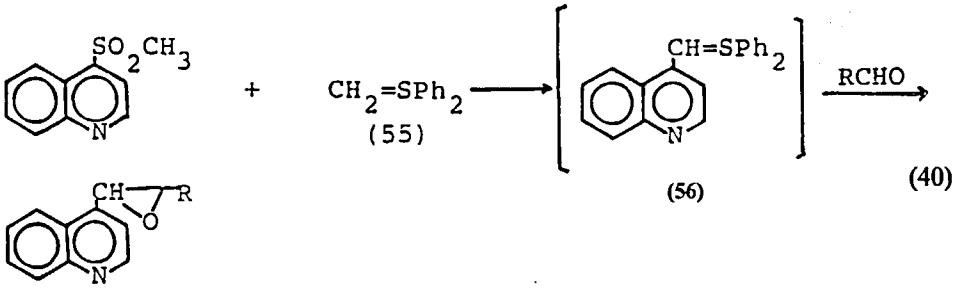
Thus, the nucleophile should preferably attack the 2-carbon atom attached to the sulfonyl group. Meanwhile, in the case of amines, the amino proton might take part in hydrogen bonding between the chlorine and the pyridine nitrogen atom; thus the carbon atom attached to the halogen atom becomes too electropositive to be substituted by amines. However, another question, namely, whether the reactions actually proceed via an ionic mechanism or if a radical process such as a single-electron transfer process (SET) might be involved in the reactions, is so far unanswered and further experiments are awaited.

Another interesting reaction of sulfonylpyridines or 2-chloro-6-sulfonylpyridines as shown in Table 8 is that with *t*-BuOK in CH_2Cl_2. In these reactions even bulky alkoxides such as *t*-BuOK substitute the sulfonyl group to give 2-*t*-butoxypyridine in substantial yield together with **54**. The formation of **54** can be accounted for by the initial formation of an α-sulfonyl carbanion which reacts further with the starting sulfone to afford the product **54** as shown below.[61]



(54)

These reactions also demonstrate that even a carbanion can substitute the sulfonyl group more readily than the chlorine atom, thus these reactions might constitute a synthetically useful process for introducing a carbon skeleton in heterocycles. One such example has been presented in the reaction of 4-methylsulfonylquinoline with the ylide (55) to give 56 as an intermediate which then reacts with an aldehyde to yield an ethylene oxide derivative of quinoline as shown in Eq. 40.[62]



(40)

Before describing the detailed reactions of the sulfonylpyridines and other derivatives with Grignard reagents, the fate of the sulfur moiety which is to function as the leaving group, namely, the sulfinyl or sulfonyl group in these substitution reactions, has to be described.

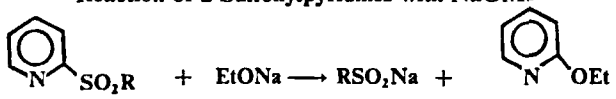
b. A convenient preparation of sulfinic acids After nucleophilic substitution of the sulfinyl- or sulfonylpyridines, these substitutents could be detected as the corresponding metal salts of sulfenic or sulfinic acids. Thus, if one carried out these *ipso*-substitutions with simple nucleophiles such as hydroxide or alkoxide anion, various sulfenic or sulfinic acids can be prepared in one step, since a variety of alkyl or aryl pyridyl sulfides can be prepared easily. However, sulfenic acids are known to be unstable except for a few derivatives.[63] Therefore, we attempted only the preparation of sulfinic acids by the present *ipso*-substitution reaction.[64] The results are shown in Table 9.

As shown in Table 9, 2-(primary alkyl-, benzyl-, or phenylsulfonyl)pyridines react with an equimolar amount of $NaOCH_3$ to afford the corresponding sodium salt of the sulfinic acid in high yield. However, the reaction with secondary alkylsulfonyl derivatives gives a low yield or the reaction requires more drastic conditions, i.e., the reaction needs longer time or higher concentration of the base. Since it is known that nucleophilic reactions of pyridine *N*-oxides proceed much faster than those of pyridyl derivatives, various sulfonyl pyridine *N*-oxides were prepared and subjected to the reaction with NaOMe in MeOH analogous to the one described above and the results are shown in Table 10.[64]

Although several methods for the preparation of sulfinic acids have been reported,[65] the present results indicate that our reaction is a very convenient method for the preparation of any kind of sulfinic acids, i.e., even 1,1-dimethylethanesulfinic acid, under mild reaction condition. One characteristic point for this preparation of sulfinic acids is as follows: since 2-methylsulfonylpyridine *N*-oxides (57) can be prepared by ordinary S_N2 reactions of 2-mercaptopyridine *N*-oxide with MeI or $(MeO)_2SO_2$, followed by

TABLE IX

Reaction of 2-Sulfonylpyridines with NaOMe



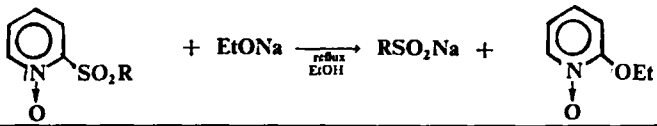
R	Ratio[a]	Time (h)	Yield (RSO_2Na)
CH_3	1:3	0.25	58[b]
$PhCH_2$	1:3	0.25	52
Ph	1:3	0.25	65
Ph	1:1	19	92[c]
i-Pr	1:1	1	no reaction
i-Pr	1:2.5	48	38

[a] Ratio sulfone:EtONa,
[b] 2-ethoxypyridine 52%
[c] $PhSO_2Na$ + MeI → $PhSO_2Me$ (73%)
Reference: N. Furukawa, M. Tsuruoka, and H. Fujihara, *submitted to Heterocycles.*

treatment with hydrogen peroxide, the *N*-oxides (**57**) become a starting material for any kind of sulfones which can be obtained by treatment of **57** with thiols under alkaline conditions. In general, 2-(*t*-butylsulfonyl)pyridine (**58**) cannot be prepared by the ordinary method. However, using *ipso*-substitution of **57** with *t*-BuSNA, followed by oxida-

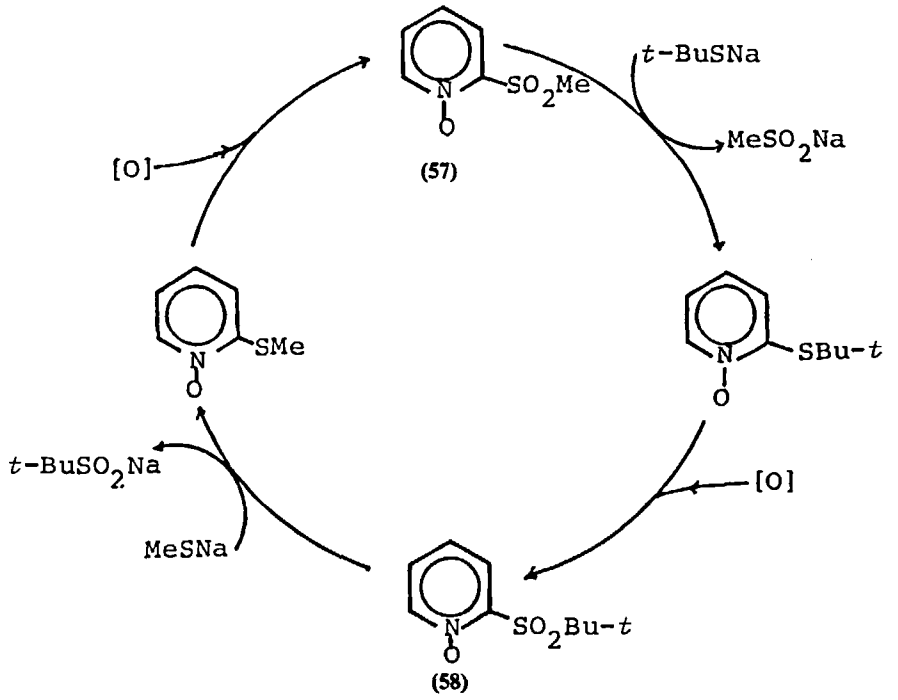
TABLE X

Reaction of 2-Sulfonylpyridine *N*-oxides with EtONa



R	Time (h)	Yield (RSO_2Na %)	(RSO_2Me)(%)[a]
n-Oct	30	89	68
i-Pr	15	quant. (95)[b]	–
t-Bu	15	quant. (95)[b]	–
$PhCH_2$	15	quant. (95)[b]	79
PhCH(Me)	15	quant. (95)[b]	–
Ph	15	89	68

[a] RSO_2Na + MeI → RSO_2Me
[b] Yield of 2-ethoxypyridine
Reference: N. Furukawa, M. Tsuruoka, and H. Fujihara, *submitted to Heterocycles.*



SCHEME 10. Preparation of Sulfinic Acids

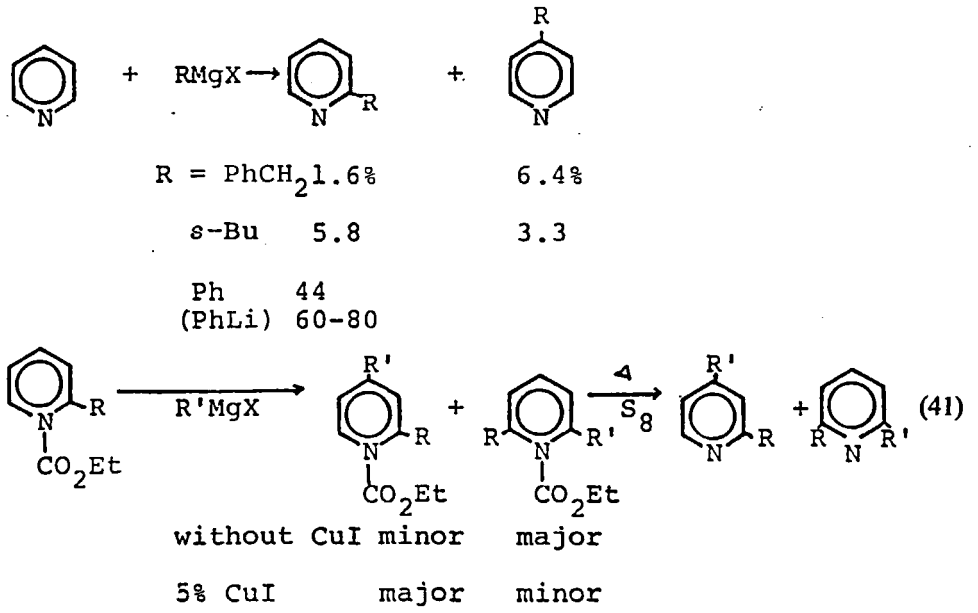
tion to *t*-butylsulfonylpyridine **58** in high yield. Consequently, as shown in Scheme 10, one can prepare any kind of sulfinic acids via the sulfone (**57**).

A similar preparation of sulfinic acids involving benzothiazole derivatives has been reported recently.[66]

c. Reactions of 2- and 4-sulfonylpyridines with Grignard reagents Pyridine itself is known to react with strong bases such as $NaNH_2$ in liquid ammonia to afford 2-aminopyridine; this is known as the Tshitshibabin reaction.[67] Furthermore, various organolithium reagents,[68] Grignard reagents,[69] and 2-lithio-1,3-dithiolane[70] also react with pyridine itself to give both 2- and 4-substituted pyridine derivatives. The yields or regioselectivity of the products depend markedly on the reagents and conditions used in the reactions. In general, these reactions afford more the 2-substituted derivatives than the 4-isomers. The distribution of the products reflects on the lower electron density of the 2-position as compared to the 4-position in the pyridine ring as shown in the following examples.[70]

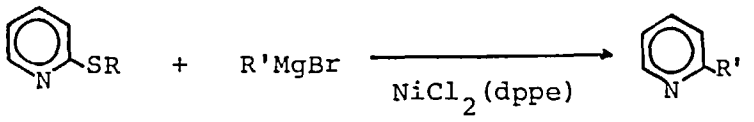
The mechanisms for these reactions do not seem to have been established, namely, whether the reactions proceed via an ionic or a radical process. According to recent investigations the substitution at the 2-position may proceed via an ionic process like the Tshitshibabin reaction, while the substitution at the 4-position is supposedly a radical coupling process initiated by a one-electron transfer process.[71] These reactions are quite interesting, not only mechanistically, but also because of their synthetic value for the

introduction of an alkyl or aryl moiety into the 2- or 4-position of the pyridine ring. However, direct treatment of pyridine with organometallic reagents results in ambiguous regioselectivity and product distribution, depending upon the reaction conditions and reagents used and hence from a synthetic point of view these reactions seem to require appropriate modifications. Recently, in an attempt to introduce organometallic reagents into the 2- or 4-position of the pyridine ring with higher regioselectivity, *N*-acylpyridinium salts were treated with Grignard reagents. In this procedure the pyridine derivative is converted to the *N*-ethoxycarbonyl derivative (**59**) from which then upon treatment with Grignard reagents, either in the presence or absence of CuI as catalyst, either the 4- or 2-substituted pyridines are obtained regioselectively. Thus, removal of the ethoxycarbonyl group affords either 2- or 4-substituted pyridines, respectively, as shown in Eqn. 41.[72]



(41)

Several similar reactions have been reported by other authors.[73-76] Recently, a useful synthetic application of pyridine derivatives containing sulfur functional groups for the introduction of a carbon skeleton into pyridine and other heterocyclic compounds has been investigated by Takei *et al.*[77] Their method for the introduction of the carbon group into the appropriate position of the pyridine ring is for example treatment of the corresponding sulfides or even thiols with Grignard reagents in the presence of $NiCl_2$(dppe) (dppe = $Ph_2P(CH_2)_3PPh_2$) as catalyst. This reaction is assumed to proceed via initial complex formation between sulfide-Ni-Grignard reagent from which ligand coupling or *ipso*-substitution would be a possible process. The yields of the coupling products are high and the regioselectivity is 100%. Some results are shown in the following Eqn. 42.

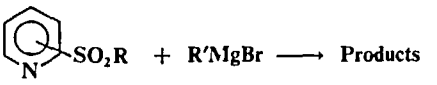


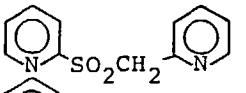
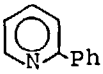
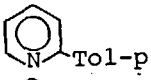
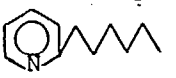
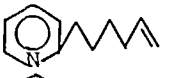
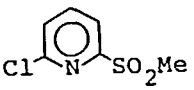
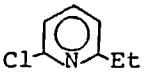
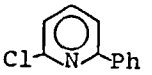
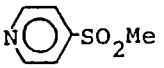
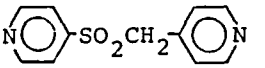
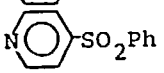
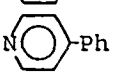
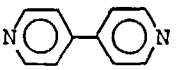
(42)

R: Me, H; R':Ph Yield: 80-94%

TABLE XI

Reaction of Sulfonylpyridines with Grignard Reagents

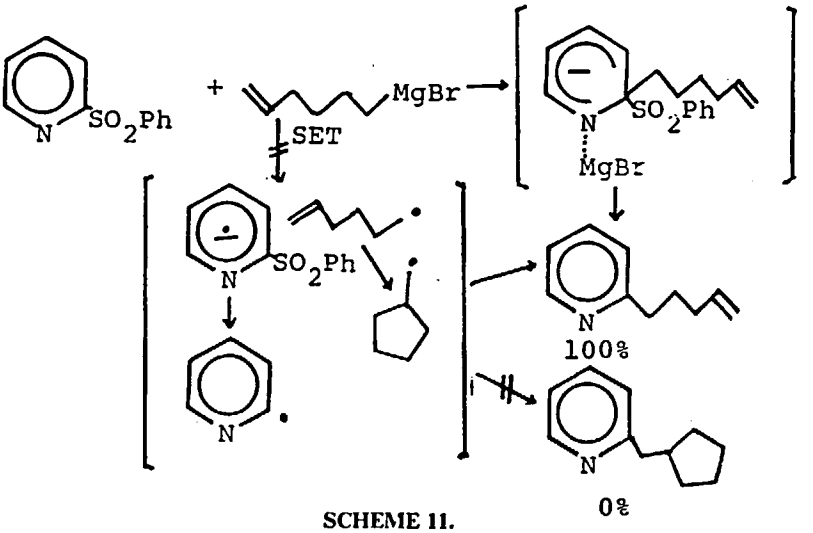


R	R'	Time (min)	Product (Yield %)		Recovered
SO_2Me	Ph	60		65	25
SO_2Ph	Ph	60		53	39
SO_2Ph	*p*-Tol	60		72	21
SO_2Ph		30		95	–
SO_2Ph		30		99	–
	Et	15		79	–
"		30		44	27
"		30		51	–
"	Ph	120		25	–
	Ph	60		13	32
	Ph	240		51	10
"	Dodecyl	240		54	17
"	Et	240	"	28	–

Reference: N. Furukawa, M. Tsuruoka, and H. Fujihara, *submitted to Chem. Lett.*

Wenkert *et al.* have used this process for introducing an alkyl or aryl group into the 4-position of the pyridine ring.[78] The sulfonyl group attached to the heterocycles could be substituted readily with various nucleophiles as described before. As such an example, methyl 2-pyridyl sulfone gave 2-picolylsulfonylpyridine upon treatment with *t*-BuOK, together with 2-*t*-butyloxypyridine. This seems to demonstrate that carbanions also function as good nucleophiles in aromatic *ipso*-substitution reactions with heterocycles. Thus, both 2- and 4-sulfonylpyridines have been prepared and allowed to react with Grignard reagents in an effort to ascertain whether *ipso*-substitution actually takes place or not and also to elucidate the mechanism of the reaction.[79] The results are shown in Table 11.

From these results shown in the Table, the following conclusions were obtained. In the case of 2-sulfonyl substituted pyridines, Grignard reagents substitute directly the sulfonyl group and the carbon-carbon bond formation takes place regioselectively at the 2-position. Furthermore, treatment of 2-chloro-6-sulfonylpyridines with Grignard reagents affords solely 6-substituted 2-chloropyridines in high yields and no 2-substituted 6-sulfonylpyridines at all. This indicates that these reactions are highly useful to prepare 2,6-disubstituted pyridine derivatives with different substituents. Another characteristic point in this reaction is the fact that when one treats 2-phenylsulfonyl- or 2,6-chlorophenylsulfonylpyridine with 5-hexenylmagnesium bromide, one obtains only (5-hexenyl)pyridine in high yield without contaminating 2-(cyclopentylmethyl)pyridine derivatives which might be the product of a radical reaction. This result indicates clearly that at least in the *ipso*-substitution of 2-sulfonylpyridines with Grignard reagents, the ionic mechanism is the actual process and the SET mechanism can be ruled out at this moment.[80] In many reactions of heterocycles with organometallic reagents the SET process has been recognized as described before.[81,82] Furthermore, recently the phenylsulfonyl group on styrene has been reported to be substituted by Grignard reagents via the SET mechanism.[83] Therefore, the present result should give an answer to this ambiguous question of the mechanism of the *ipso*-substitution reaction of the 2-sulfonyl derivations of pyridine with Grignard reagents. The proposed mechanism is shown in the following Scheme 11.



SCHEME 11.

For the time being the reactions of 4-sulfonylpyridines with Grignard reagents are rather uncertain. In the reactions with aryl Grignard reagents, *ipso*-substitution takes place, whereas alkyl Grignard reagents in their reactions with 4-sulfonylpyridines afford both 4,4′-bipyridine and 4-alkyl substituted pyridines in rather low yields, together with unidentified products.

The formation of 4,4′-bipyridine suggests the intervention of the 4-pyridyl radical the coupling of which leads to 4,4′-bipyridine. However, when one uses the 5-hexenyl Grignard reagent, 4-(5-hexenyl)pyridine is obtained as the sole *ipso*-substitution product. This appears to rule out the SET mechanism under these reaction conditions. In order to clarify the mechanism in detail, further experiments are required.

However, at least the reactions of 2-sulfonylpyridine derivatives with Grignard reagents are synthetically useful procedures to introduce carbon groups in the 2- or 2,6-positions of the pyridine ring.

REFERENCES

1. H. Kwart and K. G. King, *d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur* (Springer-Verlag, Berlin, 1977).
2a. E. Block, *Reactions of Organosulfur Compounds* (Academic Press, New York 1978).
2b. S. Oae, E., *Organic Chemistry of Sulfur* (Plenum Press, New York, 1977).
2c. S. Oae, Ed., *Chemistry of Organosulfur Compounds* (Yuki-Iô-Kagaku, in Japanese, Kagaku-Dojin, Kyoto, 1982).
2d. D. R. Hogg, Ed., *Organic Compounds of Sulfur, Selenium, and Tellurium* (The Royal Society of Chemistry, London, 1981), Vol. 1–6.
2e. D. N. Jones, Ed., *Comprehensive Organic Chemistry* (Pergamon Press, Oxford, 1979), Vol. 3, pp. 1–488.
2f. F. Bernardi, Ed., *Organic Sulfur Chemistry* (Elsevier, Amsterdam, 1985).
3. A. R. Katritzky *et al.*, Ed., *Advances in Heterocyclic Chemistry* (Academic Press, New York, 1960–1985), *Vols.* **1–37.**
4. N. Furukawa, F. Takahashi, T. Kawai, K. Kishimoto, S. Ogawa, and S. Oae, *Phosphorus Sulfur,* **16,** 167 (1983).
5a. A. E. Martell, Ed., *Coordination Chemistry* (ACS Monograph 174, American Chemical Society, 1978), *Vols.* **1–2.**
5b. R. P. Houghton, *Metal Complexes in Organic Chemistry* (Cambridge University Press, London, 1979).
6. P. O. Lumme, *Suomen Kemistilehti,* **30b,** 168 (1957). D. P. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution* (Butterworth, London, 1965), p. 150.
7. N. Furukawa, K. Iida, T. Kawai, S. Ogawa, and S. Oae, *Phosphorus Sulfur,* **19,** 239 (1984).
8. N. Furukawa, S. Ogawa, T. Kawai, K. Kishimoto, H. Fujihara, and S. Oae, *Heterocycles,* **19,** 204 (1982).
9a. C. M. Starks and C. Liotta, *Phase Transfer Catalysis* (Academic Press, New York, 1978).
9b. F. Montanari, D. Landini, and F. Rolla, *Host Guest Complex Chemistry II,* F. Vögtle, Ed., (Springer-Verlag, Berlin, 1982), pp. 147–200.
10. G. W. Gokel and B. J. Garcia, *Tetrahedron Lett.,* 1743 (1978).
11. B. J. Garcia, A. Leopold, and G. W. Gokel, *Tetrahedron Lett.,* 2115 (1980).
12a. N. Furukawa, K. Kishimoto, S. Ogawa, T. Kawai, H. Fujihara, and S. Oae, *Tetrahedron Lett.,* **22,** 4409 (1981).
12b. N. Furukawa, S. Ogawa, T. Kawai, and S. Oae, *J. Chem. Soc. Perkin I,* 1833 (1984).
13a. M. Mikołajczyk, S. Grezejszczak, A. Zatorski, F. Montanari, and M. Cinquini, *Tetrahedron Lett.,* 3757 (1975).
13b. S. Banfi, M. Cinquini, and S. Colonna, *Bull. Chem. Soc., Jpn.,* **54,** 1841 (1981).
14. H. Fujihara, K. Imaoka, N. Furukawa, and S. Oae, *Chem. Lett.,* 1293 (1981).
15. R. P. Houghton and R. R. Puttner, *J. Chem. Soc., D,* 1270 (1970).
16a. A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.,* **1,** 311 (1963).

16b. P. Beak, F. S. Fry, Jr., J. Lee, and F. Steele, *J. Am. Chem. Soc.*, **98**, 171 (1976).
17. H. A. Staab and E. Jost, *Liebigs Ann. Chem.*, **655**, 90 (1962).
18. T. Sakan and Y. Mori, *Chem. Lett.*, 793 (1972).
19a. T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.*, **95**, 4763 (1973).
19b. M. Araki, S. Sakata, H. Takei, and T. Mukaiyama, *Bull. Chem. Soc., Jpn.*, **47**, 1777 (1974).
20a. T. Mukaiyama, *Angew. Chem. Int. Ed., Engl.*, **15**, 707 (1979).
20b. M. Onaka, T. Goto, and T. Mukaiyama, *Chem. Lett.*, 1483 (1979).
20c. T. Goto, M. Onaka, and T. Mukaiyama, *ibid.*, **51** (1980).
20d. M. Onaka, Y. Matsuoka, and T. Mukaiyama, *ibid.*, 905 (1980).
20e. T. Mukaiyama, F.-C. Pai, M. Onaka, and K. Narasaka, *ibid.*, 563 (1980).
20f. M. Onaka, Y. Matsuoka, and T. Mukaiyama, *ibid.*, 531 (1981).
21a. T. Mukaiyama, R. Matsuda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970).
21b. T. Mukaiyama, R. Matsuda, and M. Hashimoto, *J. Synth. Org. Chem.*, **32**, 56 (1974).
22a. E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).
22b. E. J. Corey and D. J. Brunelle, *Tetrahedron Lett.*, 3409 (1976).
22c. S. Masamune, S. Sakata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975).
22d. U. Schmidt and D. Heermann, *Angew. Chem. Int. Ed., Engl.*, **18**, 2308 (1979).
22e. H. Gerlach and A. Thalmann, *Helv. Chim. Acta*, **57**, 2662 (1974).
23. M. Yamada, K. Sotoya, T. Sakakibara, T. Takamoto, and R. Sudoh, *J. Org. Chem.*, **42**, 2180 (1977).
24. M. Yamada, Y. Watabe, T. Sakakibara, and R. Sudoh, *J. Chem. Soc., Chem. Commun.*, 179 (1979).
25. P. Molina, A. Alajarin, M. J. Vilaplana, and A. R. Katritzky, *Tetrahedron Lett.*, **26**, 469 (1985).
26. Y. Gelernt and P. Sykes, *J. Chem. Soc., Perkin I* 2610 (1974).
27a. D. H. R. Barton and G. Kretzschmar, *Tetrahedron Lett.*, **24**, 5889 (1983).
27b. D. H. R. Barton, D. Crich, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 939 (1983).
27c. D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron Lett.*, **24**, 4979 (1983).
27d. D. H. R. Barton, D. Crich, and G. Kretzschmar, *ibid.*, **25**, 1055 (1984).
28a. D. H., R. Barton and D. Crich, *Tetrahedron Lett.*, **25**, 5777 (1984).
29. D. H. R. Barton and D. Crich, *Tetrahedron Lett.*, **26**, 757 (1985).
30. D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
31. N. Furukawa and T. Kawai, *unpublished results.*
32. S. Oae, T. Kawai, and N. Furukawa, *Tetrahedron Lett.*, **25**, 69 (1984).
33a. R. Oda and K. Yamamoto, *J. Org. Chem.*, **26**, 4679 (1961).
33b. P. Manya, A. Sekera, and P. Rumpf, *Tetrahedron*, **26**, 467 (1970).
34a. M. Roth, P. Dubs, E. Gōtschi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971).
34b. M. Takaku, S. Mitamura, and H. Nozaki, *Tetrahedron Lett.*, 3561 (1969).
34c. Y. Ueno and M. Okawara, *Bull. Chem. Soc., Jpn.*, **45**, 1797 (1972).
35a. F. Westheimer, *Acc. Chem. Res.*, **1**, 65 (1968).
35b. K. Mislow, *ibid.*, **3**, 321 (1970).
36. E. L. Muetterties and R. A. Schunn, *Quart. Revs.*, **20**, 245 (1966).
37. F. Iwasaki, *private communication.*
38. T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry* (2nd Ed.) (Harper and Row Publishers, New York, 1981). p. 280.
39. T. Kawai, N. Furukawa, and S. Oae, *Tetrahedron Lett.*, **25**, 2549 (1984).
40a. G. R. Newkome and D. C. Hager, *J. Am. Chem. Soc.*, **100**, 5567 (1978).
40b. P. E. Fanta, *Chem. Rev.*, 613 (1964).
40c. J. E. Parks, B. E. Wagner, and R. H. Holm, *J. Organomet. Chem.*, **56**, 53 (1973).
40d. T. Taguchi, M. Nishi, K. Watanabe, and T. Mukaiyama, *Chem. Lett.*, 130-7 (1973).
41. T. Kawai, Y,. Kotera, N. Furukawa, and S. Oae, *submitted.*
42. T. Kawai, N. Furukawa, and S. Oae, *unpublished results.*
43a, J. Jacobus and K. Mislow, *J. Am. Chem. Soc.*, **89**, 5228 (1967).
43b. T. Durst, M. J. LeBelle, R. van Den Elzen, and K.-C. Tin, *Can. J. Chem.*, **52**, 761 (1974).
43c. J. P. Lockard, C. W. Schroeck, and C. R. Johnson, *Synthesis*, 485 (1973).
43d. M. Hojo, R. Masuda, T. Saeki, K. Fujimori, and S. Tsutsumi, *Synthesis*, 789 (1977).
43e. J. Nokami, N. Kunieda, and M. Kinoshita, *Chem. Lett.*, 249 (1977).
44a. B. S. Wildi, S. W. Taylor, and H. A. Potratz, *J. Am. Chem. Soc.*, **73**, 1965 (1951).
44b. M. Hori, T. Kataoka, H. Shimizu, and M. Miyagaki, *Yakugaku Zashi*, **93**, 476 (1973).
45a. B. F. Bonini, G. Maccagnari, G. Mazzanti, and P. Piccinelli, *Tetrahedron Lett.*, 3987 (1979).
45b. L. A. Carpino and H.-W. Chen, *J. Am. Chem. Soc.*, **93**, 785 (1971).
46. G. Nef, U. Eder, and A. Seeger, *Tetrahedron Lett.*, **21**, 903 (1980).
47. J. Bornstein, J. E. Shields, and J. H. Supple, *J. Org. Chem.*, **32**, 1499 (1967).

48a. V. Franzen and C. Mertz, *Ann.*, **643**, 24 (1961).
48b. B. M. Trost, R. LaRochelle, and R. C. Atkins, *J. Am. Chem. Soc.*, **91**, 2175 (1969).
48c. D. Harrington, J. Weston, J. Jacobus, and K. Mislow, *J. Chem. Soc., Chem. Commun.*, 1079 (1972).
48d. G. H. Wiegand and W. E. McEwen, *J. Org. Chem.*, **33**, 2671 (1968).
49a. Y. H. Khim and S. Oae, *Bull. Chem. Soc., Jpn.*, **42**, 1968 (1969).
49b. K. K. Andersen, S. A. Yeager, and N. B. Peynircioglu, *Tetrahedron Lett.*, 2485 (1970).
50. M. Hori, T. Kataoka, H. Shimizu, and M. Miyagaki, *Chem. Pharm. Bull.*, **22**, 1711, 2004, 2020 1974).
51a. B. M. Trost, W. L. Schinski, and I. B. Mantz, *J. Am. Chem. Soc.*, **91**, 4320 (1969).
51b. B. M. Trost, R. C. Atkins, and L. Hoffman, *ibid.*, **95**,1285 (1973).
51c. B. M. Trost, W. L. Schinski, F. Chen, and I.B. Mantz, *ibid.*, **93**, 676 (1971).
51d. B. M. Trost and S. D. Ziman, *ibid.*, **93**, 3825 (1971).
51e. M. J. Bogdanowicz and B. M. Trost, *Tetrahedron Lett.*, 887 (1972).
52. R. W. LaRochelle and B. M. Trost, *J. Am. Chem. Soc.*, **93**, 6077 (1971).
53. W. A. Sheppard, *J. Am. Chem. Soc.*, **93**, 5597 (1971).
54a. G. B. Barlin and W. V. Brown, *J. Chem. Soc., (B)*, 568, 648, 954 (1967).
54b. *idem, J. Chem. Soc., (C)*, 954, 2473 (1967).
54c. *idem, J. Chem. Soc., (B)*, 333 (1969).
54d. G. B. Barlin and A. C. Young, *J. Chem. Soc., (C)*, 921 (1969),
54e. *idem, J. Chem. Soc., Perkin I*, 1269 (1972).
54f. D. J. Brown and R. V. Foster, *Aust. J. Chem.*, **19**, 1487, 2322 (1966).
54g. D. J. Brown and P. W. Ford, *J. Chem. Soc., (C)*, 568 (1969).
55a. M. Liveris and J. Miller, *Aust. J. Chem.*, **11**, 297 (1958).
55b. G. Illuminati, *Adv. Heterocycl. Chem.*, **4**, 285 (1964).
56. J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (2nd Ed.)* (McGraw-Hill, London, 1977) p. 498.
57a. S. Oae and Y. H. Khim, *Bull. Chem. Soc., Jpn.*, **40**, 1716 (1967).
57b. *idem, ibid.*, **42**, 1622 (1969).
58. N. Furukawa, S. Ogawa, T. Kawai, and S. Oae, *J. Chem. Soc., Perkin I*, 1839 (1984).
59. Ref. *12b*).
60. N. Furukawa and T. Kawai, *unpublished result.*
61. N. Furukawa, M. Tsuruoka, T. Kawai, and H. Fujihara, *Heterocycles, submitted.*
62. E. C. Taylor and S. F. Martin, *J. Am. Chem. Soc.*, **94**, 6218 (1972).
63a. T. C. Bruice and A. B. Sayigh, *J. Am. Chem. Soc.*, **81**, 3416 (1959).
63b. T. S. Chou, J. R. Burgtorf, A. L. Ellis, R. S. Lammert, and S. P. Kukolja, *J. Am. Chem. Soc.*, **96**, 1609 (1974).
63c. F. A. Davis, S. G. Yocklovich, and G. S. Baker, *Tetrahedron Lett.*, 97, (1978).
63d. N. Nakamura, *J. Am. Chem. Soc.*, **105**, 7172 (1983).
64. N. Furukawa, T. Tsuruoka, and H. Fujihara, *unpublished results.*
65a. K. K. Andersen, *Ref. 2e*, pp. 317–330.
65b. *Houben-Weyl E11*, 614 (1985).
66. Y. Ueno, A. Kojima, and M. Okawara, *Chem. Lett.*, 46. 1216 (1984).
67a. A. E. Tschitschibabin and O. A. Seide, *J. Russ. Phys. Chem., Soc.*, **46**, 1216 (1914).
67b. R. A. Abramovitch and J. G. Saha, *Adv. Heterocycl. Chem.*, **6**, 229 (1966).
68. F. W. Bergstrom and S. H. McAllister, *J. Am. Chem. Soc.*, **52**, 2845 (1930).
69a. R. F. Francis, W. Davis, and J. T. Wisener, *J. Org. Chem.*, **39**, 59 (1974).
69b. R. F. Francis, H. M. Howell, and D. T. Fetzer, *J. Org. Chem.*, **46**, 2213 (1981).
69c. C. S. Giam and S. D. Abbott, *J. Am. Chem. Soc.*, **93**, 1294 (1971).
70. T. Taguchi, N. Nishi, K. Watanabe, and T. Mukaiyama, *Chem. Lett.*, 1307 (1973).
71a. D. B. Smith, P. J. Morris, and B. J. Wakefield, *J. Chem. Soc., Perkin I*, 1977 (1976).
71b. H. G. Richey, Jr. and J. Farkas, Jr., *Tetrahedron Lett.*, **26**, 275 (1983).
71c. G. R. Newkome and D. C. Hager, *J. Org. Chem.*, **47**, 599 (1982).
73a. D. L. Comins, A. H. Abdullah, and N. B. Mantlo, *Tetrahedron Lett.*, **25**, 4867 (1984).
73b. D. L. Comins and A. H. Abdullah, *ibid.*, **26**, 43 (1983).
72. D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, **47**, 4315 (1982).
74. T. R. Webb, *Tetrahedron Lett.*, **26**, 3191 (1985).
75. G. Courtois, A. Al-Arnaout, and L. Miginiac, *Tetrahedron Lett.*, **26**, 1027 (1985).
76. R. Yamaguchi, M. Moriyasu, M. Yoshioka, and M. Kawanishi, *J. Org. Chem.*, **50**, 287 (1985).
77. H. Takei, M. Miura, H. Sugimura, and H. Okamura, *Chem. Lett.*, 1447 (1979).
78. E. Wenkert, J. M. Hanna, Jr., M. H. Leftin, E. L. Mihelotti, K. T. Potts, and D. Usifer, *J. Org. Chem.*, **50**, 1125 (1985).

79. N. Furukawa, M. Tsuruoka, and H. Fujihara, *unpublished results.*
80a. N. Kornblum, *Angew. Chem., Int. Ed. Eng.*, **14**, 734 (1975).
80b. G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, **88**, 5663 (1966).
80c. E. C. Ashby and A. B. Goel, *J. Am. Chem. Soc.*, **103**, 4983 (1981).
80d. E. C. Ashby and J. R. Bowers Jr., *ibid.*, **103**, 2242 (1981).
80e. E. C. Ashby, A. B. Goel, R. N. DePriest, and H. S. Prasad, *ibid.*, **103**, 973 (1981).
80f. A. Pross, *Acc. Chem. Res.*, **18**, 212 (1985).
81. A. R. Katritzky, M. A. Kashmiri, G. Z. de Ville, and R. C. Patel, *J. Am. Chem. Soc.*, **105**, 90 (1983).
82a. J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978).
82b. D. R. Carver, A. P. Komin, J. S. Hubbard, and J. F. Wolfe, *J. Org. Chem.*, **46**, 294 (1981).
82c. M. Tiecco, *Acc. Chem. Res.*, **13**, 51 (1980).
82d. G. Bartoli, *Acc. Chem. Res.*, **17**, 109 (1984).
83. J. J. Eisch, M. Benrooz, and J. E. Galle, *Tetrahedron Lett.*, **25**, 4851 (1984).