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FUNCTIONALIZATION OF PYRIDINES.* 3.** REACTIONS FORMING A CARBON–HETEROATOM BOND WITH GROUP IV, V, AND VI ELEMENTS

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The literature from the last 15-20 years on the synthesis of heteroatomic pyridine derivatives through the formation of pyridine carbon–heteroatom bonds is reviewed.

This literature review is the third and final part of a series of reviews on methods for direct functionalization of pyridine. It includes the introduction into the pyridine ring of various functional groups through formation of a pyridine carbon–heteroatom bond. In our opinion, the nature of the heteroatom introduced provides the most convenient basis for classification:

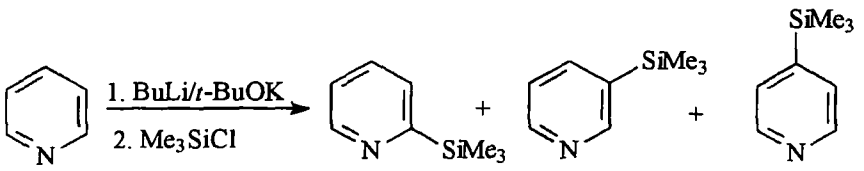
1. Introduction of Group IV elements (Si, Sn); 2. Group V (N, P, As); and 3. Group VI (O, S, Se, Te).

The types of chemical processes used for this are determined mainly by the specifics of the element to which the bond is formed.

1. FORMATION OF C–Si AND C–Sn BONDS

Silyl and stannyl derivatives of pyridine are convenient starting materials for preparing various functionalized pyridines via reactions with various electrophiles (e.g., see [2-9]). Therefore, methods of synthesizing them are of practical interest.

The principal method for preparing silyl pyridines is the reaction of lithiated pyridine derivatives with trialkylchlorosilanes. Thus, a mixture of 2-, 3-, and 4-trimethylsilylpyridines with predominance of the 2-derivative forms after metallation of the unsubstituted pyridine by a mixture of butyllithium and potassium *tert*-butoxide (1:1) in THF–hexane (1:2) at -100°C with subsequent treatment with trimethylchlorosilane [10].



Total yield ~ 90%

* Dedicated to Professor Henk van der Plas on his 70th birthday.

** For No. 2, see [1].

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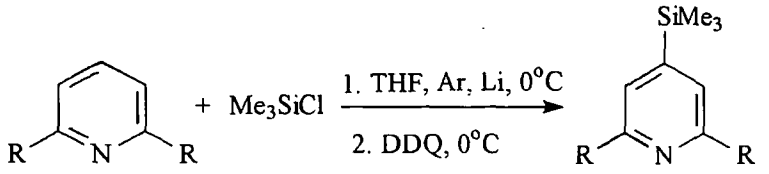
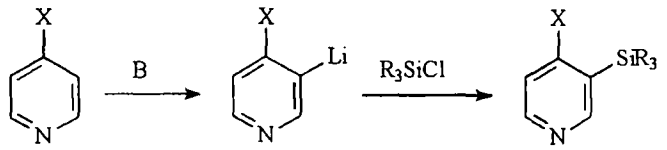
The process becomes more selective (albeit with moderate yields) if the traditional silylation method is used [11]. Thus, the reaction of pyridine and 2,6-lutidine with metallic lithium and Me_3SiCl with subsequent treatment with 1,4-benzoquinone or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives only the 4-trimethylsilyl derivative [11]:



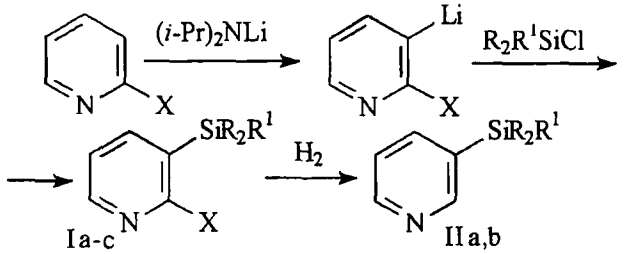
R=H (74%), Me (24%)

The authors suggest that reductive silylation occurs first with formation of the intermediate dihydro compound that contains two trimethylsilyl substituents. Quinone is involved in the aromatization through a mechanism that includes successive transfer of electrons, a proton, and desilylation [11].

However, selective metallation and, consequently, silylation, is most frequently accomplished using starting pyridines containing substituents that strongly control the direction of the lithiation. Halogens are the prime example of such substituents. Thus, 4-halopyridines are selectively *ortho*-lithiated by various lithium amides at low temperature. Subsequent treatment with trialkylchlorosilanes gives high yields of the corresponding 4-halo-3-trialkylsilylpyridines [12, 13].



Analogous results are obtained by using 2-halopyridines [13, 14].



I a X = Cl, R = R^1 = Et, 63% [10]; b X = Cl, R = R^1 = *i*-Pr, 47% [10];
c X = F, R = Me, R^1 = Cl, 56 % [11]

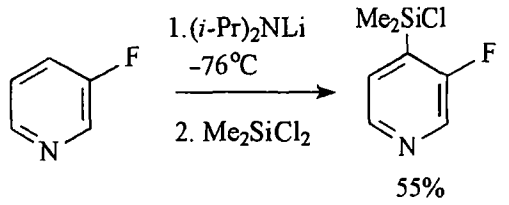
TABLE 1. 4-Halo-3-trialkylsilylpyridines

X	B	R	Yield, %	Ref.
F	BuLi/TMEDA*	Me	75	[12]
Cl	(*i*-Pr)$_2$NLi	Me	70	[12]
Cl	(*i*-Pr)$_2$NLi	Me	61	[13]
Cl	(*i*-Pr)$_2$NLi	Et	56	[13]
Cl	(*i*-Pr)$_2$NLi	Pr	60	[13]
Cl	(*i*-Pr)$_2$NLi	*i*-Pr	93	[13]

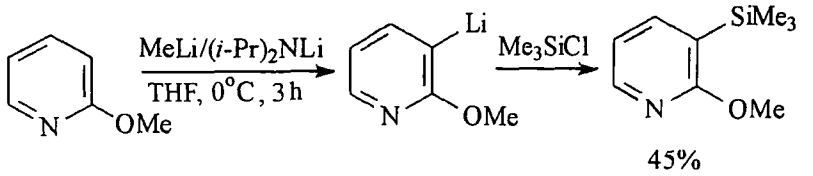
* TMEDA = tetramethylethylenediamine.

An important point is that the chlorine atom in Ia and Ib can be removed by catalytic hydrogenation with practically quantitative formation of 3-(triethylsilyl)- (IIa) and 3-(triisopropylsilyl)pyridine (IIb) [13].

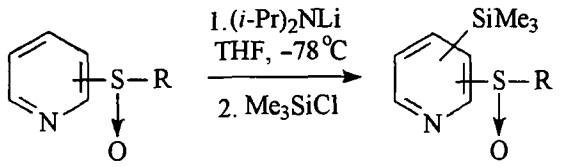
The use of 3-fluoropyridine enabled a silyl substituent to be introduced selectively in the 4-position [14].



Treatment of 2-methoxypyridine with methyllithium in the presence of catalytic amounts of lithium diisopropylamide results in direct lithiation in the 3-position. Subsequent treatment with trimethylchlorosilane gives the corresponding silyl derivative [15].



The sulfoxide group is an excellent *ortho*-directing substituent in pyridine [16, 17]. Thus, 2- and 4-pyridylsulfoxides give the corresponding 3-silyl derivatives upon subsequent treatment with $(i\text{-Pr})_2NLi$ and Me_3SiCl. Under these conditions 3-pyridylsulfoxides are smoothly silylated in the 4-position.



2-(Benzothiazol-2-ylthio)pyridine is also lithiated exclusively in the 3-position. The product of the reaction with trimethylchlorosilane undergoes sulfide cleavage to form 2-alkylthio-3-trimethylsilylpyridines [18]:

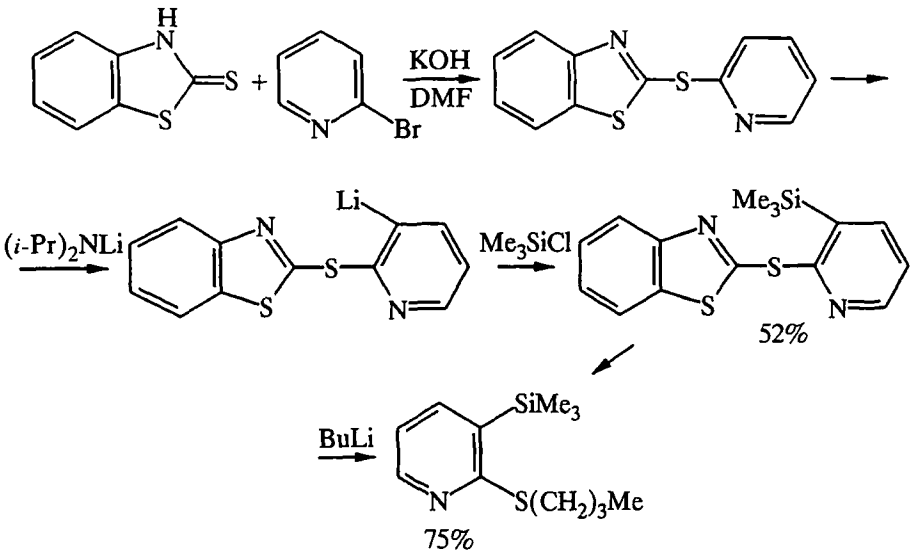
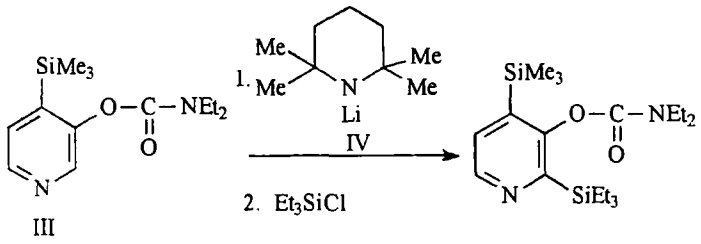


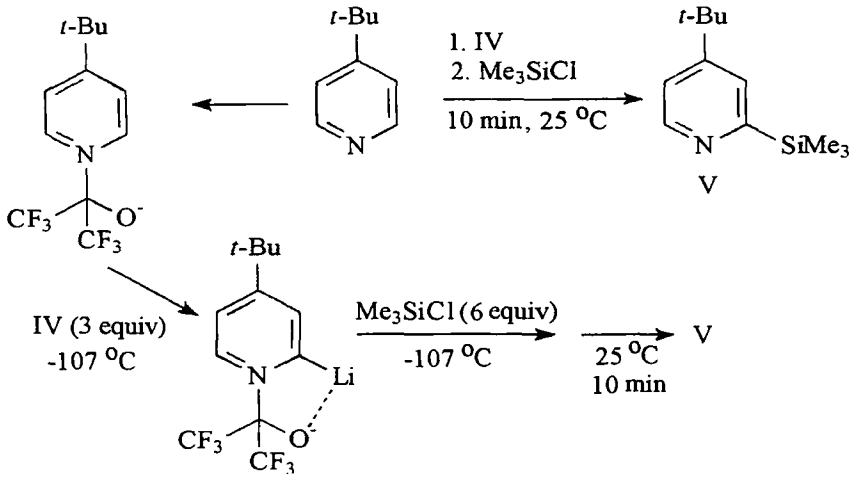
TABLE 2. Trimethylsilylpyridylsulfoxides

SOR	Position of $SiMe_3$ group	Yield, %	Ref.
2-SO-*t*-Bu	3	70	[17]
2-SOPh	3	85	[16]
2-SOPh	3	81	[16]
2-SOPh	4	80	[16]

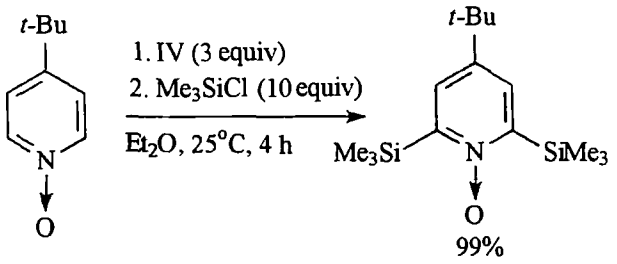
The above methods all enable trialkylsilyl groups to be easily introduced into the 3- and 4-positions of the pyridine core. The preparation of the 2-trialkylsilyl derivatives is a separate problem. One solution is the simultaneous use in pyridine III of protecting 4-trimethylsilyl and directing 3-diethylcarbamoyloxide groups. Such a substituted pyridine can only be lithiated in the 2-position [19].



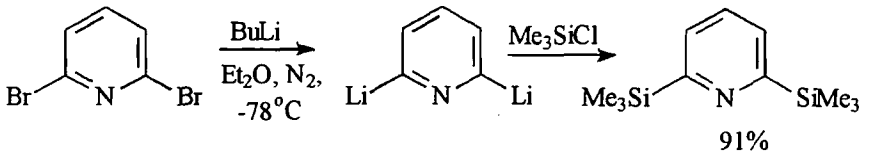
A convenient method for synthesizing 2-substituted pyridines with a bulky substituent in the 4-position is direct lithiation with a sterically hindered lithium amide, lithium 2,2,6,6-tetramethylpiperidide (IV), in the presence of trimethylchlorosilane [2]. However, the yield is low for 4-*tert*-butylpyridine and the process is not preparative. Better results are obtained in the presence of hexafluoroacetone, which forms the corresponding ylide VI with pyridine, in which α-lithiation becomes even more favorable [2].



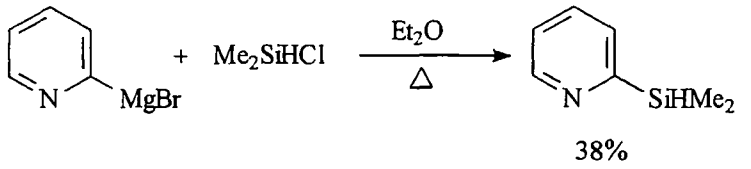
The 2,6-di(trimethylsilyl) derivative forms in very high yield if this method is used with 4-*tert*-butylpyridine-1-oxide [2].



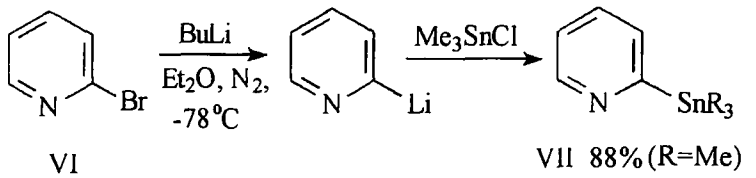
The halogen–lithium exchange reaction of the appropriate bromopyridines with butyllithium and subsequent treatment with trimethylchlorosilane is used in addition to direct lithiation to prepare 2-silyl- and 2,6-disilylpyridines [20].



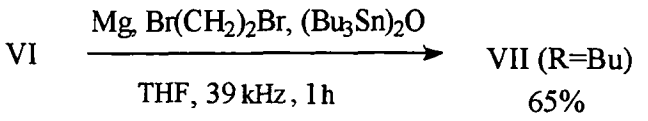
A single example of the use of 2-pyridylmagnesium bromide to prepare the corresponding 2-dimethylsilyl derivative has been reported [21].



Methods for preparing trialkylstannylpyridines are largely similar to those for synthesizing their silyl analogs. Thus, the reaction of 2-lithiopyridine with trimethylchlorostannane gives a rather high yield. Thermally labile 2-lithiopyridines are prepared by direct lithiation or halogen–lithium exchange [22].

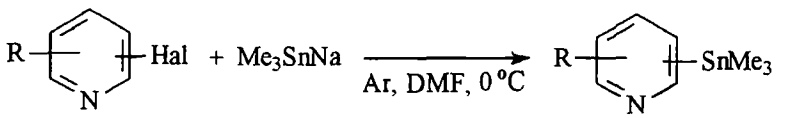


The stannylpyridine VII (R = Bu) was also prepared from VI by the Barbier reaction with ultrasonic activation [23].



It should be noted that the reaction does not occur in the absence of dibromoethane and that 3-chloropyridine does not react.

A specific method for preparing isomeric trimethylstannylpyridines is nucleophilic substitution of the corresponding halopyridines by sodium trimethylstannide generated *in situ* from metallic sodium and Me_3SnCl [24].



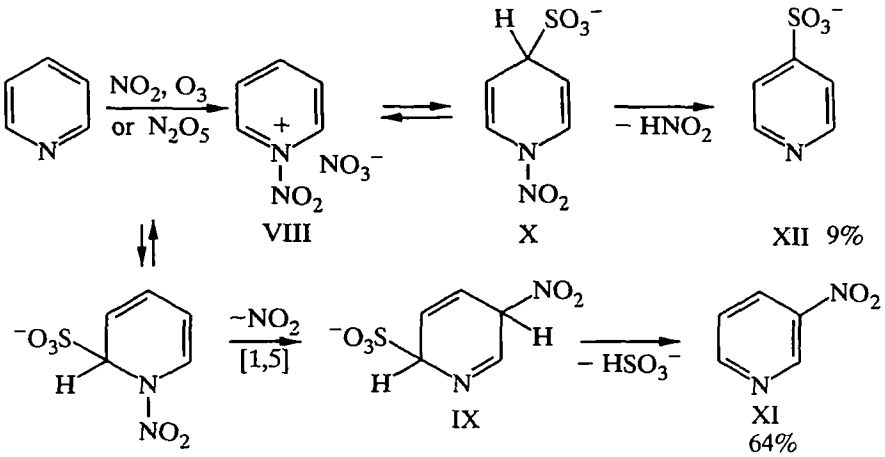
Hal = 2-Cl, R = H (88%), Hal = 3-Br, R = H (87%), Hal = 4-Cl, R = Me (61%)

2. FORMATION OF CARBON–GROUP V ELEMENT BONDS

2.1. Formation of C–N Bonds

2.1.1. Nitration of Pyridines. The most common method for preparing nitroaromatic compounds is direct nitration of aromatic substrates. However, direct nitration of pyridine is exceedingly difficult owing to its well known deficiency of π-electron density and its ability to be protonated in acidic media. Thus, yields of 3-nitropyridine are less than 14% even under very harsh nitrating conditions (HNO_3, H_2SO_4, 300°C) [25].

Therefore, researchers have recently been seeking effective methods of introducing nitro groups into the pyridine core. However, the first attempts to circumvent nitration in acidic media and use NO_2 in the presence of ozone as a nitrating agent in organic solvents were unsuccessful. The yield of 3-nitropyridine was 3.5%; of 3,5-dinitropyridine, 1.2% [26, 27]. Nitration under these conditions changes fundamentally if the reaction mixture is treated after nitration with liquid SO_2, aqueous SO_2, or sodium bisulfite. The yield of 3-nitropyridine reaches 64% [28]. Analogous results for pyridine and several of its derivatives were obtained using N_2O_5 with subsequent treatment with aqueous SO_2 or sodium bisulfite [29-31]. Apparently in both instances the reaction involves N_2O_5, which can be formed from nitrogen dioxide and ozone. The following mechanism is proposed [28, 31]:

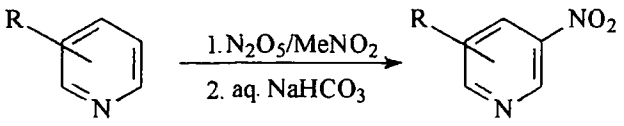


The first step is the formation of N-nitropyridinium nitrate (VIII). Subsequent nucleophilic addition of bisulfite occurs primarily at the α-position to give the 1,2-dihydro adduct IX, which is less stable compared with the 1,4-dihydro intermediate that is formed by attack of the nucleophile at the γ-position of VIII. In adduct IX, [1,5]-migration of the nitro group and elimination of bisulfite occur. This produces 3-nitropyridine (XI). The formation of the sulfonic acid XII in small yield confirms the proposed mechanism. Attempts to use other nucleophiles instead of bisulfite were less successful (Table 3) [28].

TABLE 3. Effect of Various Nucleophiles on Yield of 3-Nitropyridine

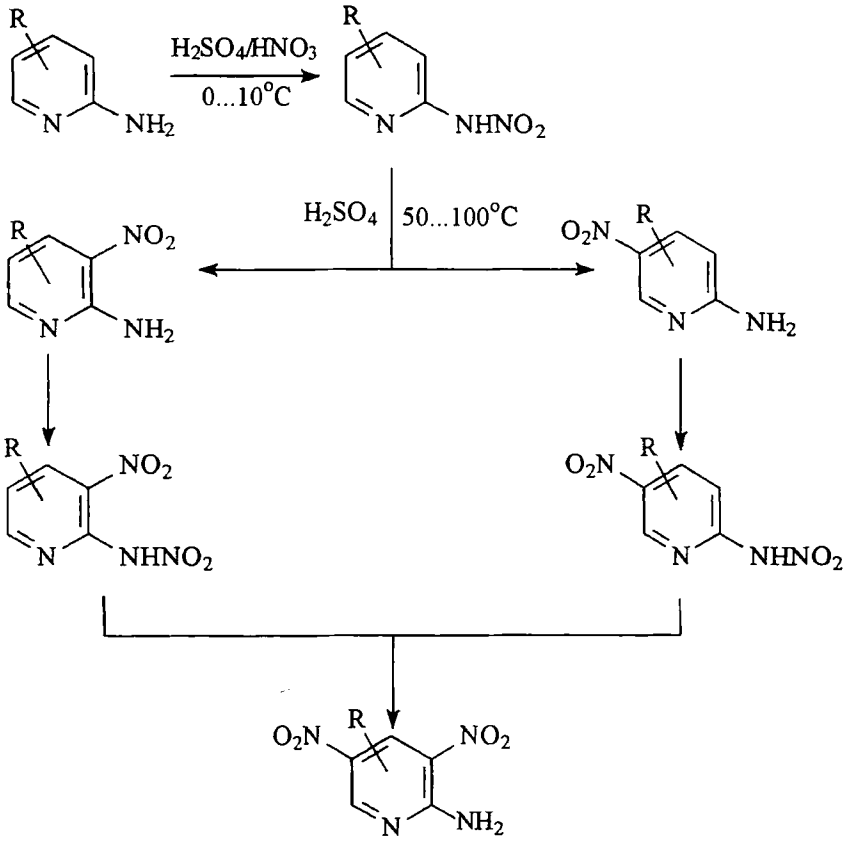
Nucleophile	Equiv.	Yield of 3-nitropyridine, %	Yield of unreacted pyridine
SO_2	15	62	24
$NaHSO_3$	1	44	19
$NaHSO_3$	2	62	9
$NaHSO_3$	4	64	6
$NaHSO_3$	6	56	3
Na_2SO_3	6	16	3
$Na_2S_2O_3$	6	24	70
Na_2SO_4	6	0,5	89
NaI	6	0,2	84
$NaNO_2$	6	0,1	83
None	—	0,1	66

Nitration by N_2O_5 in nitromethane with subsequent treatment with aqueous sodium bisulfite was investigated not only for unsubstituted pyridine but also for several of its derivatives [30].



R = H (68%), 4-Ac (50%), 4-Me (24%), 2-Me (19%), 2-Cl (0%)

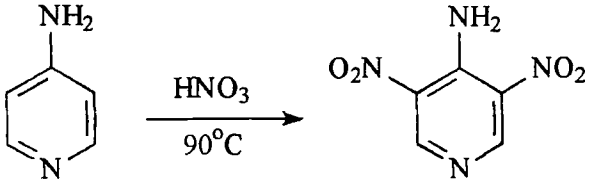
If the pyridine contains electron-donating substituents, nitration is greatly facilitated and the yields are high if the usual nitrating mixture is used. Thus, nitration of 2-chloro-6-methoxypyridine at 0°C gives the corresponding 3-nitropyridine in 80% yield [32]. Using a 1:1 mixture of HNO_3 (1.5) and H_2SO_4 for the nitration gives 2-chloro-6-methoxy-3,5-dinitropyridine in 60% yield [33].



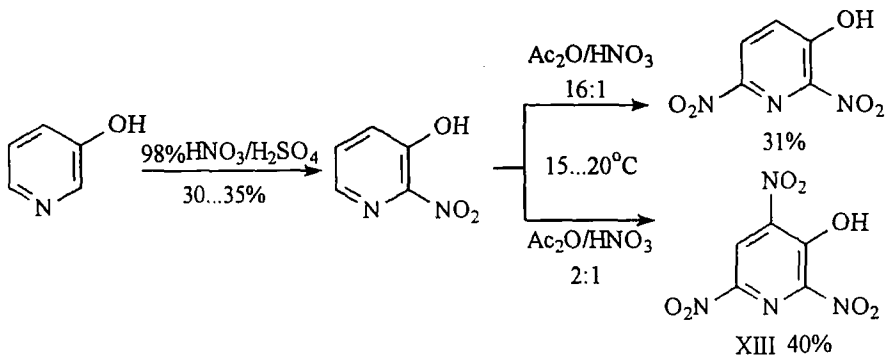
The reaction of 2-aminopyridines with the nitrating mixture gives the amino N-nitro derivatives, which rearrange in acidic medium to the 3- and 5-derivatives. The introduction of a second nitro group into them follows the same scheme [34].

2-Aminoalkylpyridines behave similarly [35-38].

Nitration of 4-aminopyridine by HNO_3 gives the 3,5-dinitro derivative. The intermediate N-nitro compound was not observed [34].

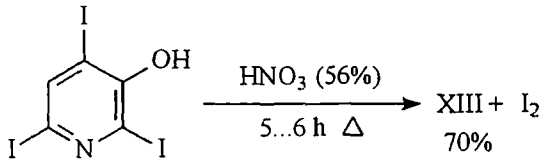


A donor substituent in the 3-position of the pyridine determines the direction of electrophilic substitution, enabling a nitro group to be added to the 2-, 4-, and 6-position. Thus, depending on the temperature and nitrating agent, nitration of 3-hydroxypyridine can form the 2-nitro-, 2,6-dinitro-, and 2,4,6-trinitro derivatives [39].



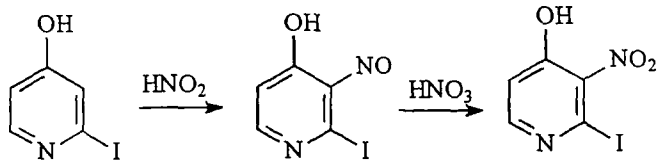
Treating hydroxypyridine with various mixtures of acetic and nitric acids at 40°C leads only to the nitrate of this compound. Increasing the reaction temperature to 85-90°C and using HNO_3–Ac_2O (3:10) produces XIII in ~65% yield.

An interesting version of introducing nitro groups into 3-hydroxypyridine is substitutive nitration in 2,4,6-triiodo-3-hydroxypyridine. This readily gives the trinitro compound XIII [39].



The reaction proceeds analogously for 3,5-diiodo-2-hydroxypyridine, which gives 2-hydroxy-3,5-dinitropyridine in ~75% yield [39].

4-Hydroxy-2-iodo-3-nitropyridine can be prepared by electrophilic nitration of the corresponding pyridine in the 3-position by nitrous acid with subsequent oxidation of the nitroso derivative [40].

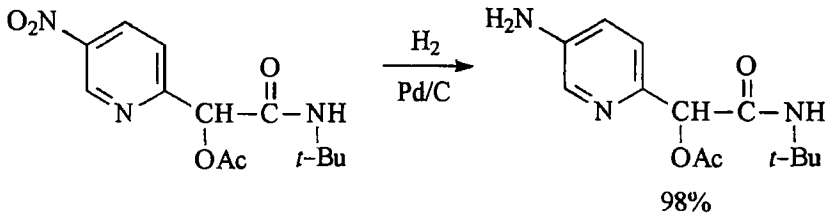


Oxidation of 4-amino derivatives of isomeric halopyridines is yet another method for preparing the corresponding halosubstituted 4-nitropyridines [41].

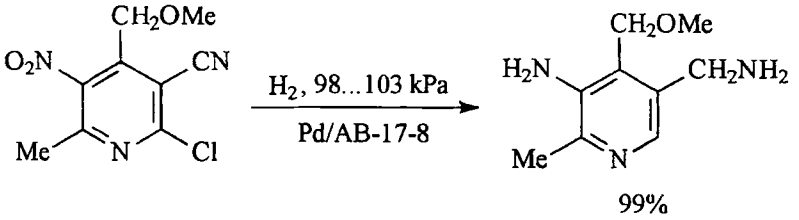
The unusual nitration of pyridine N-oxide by benzoylnitrate in the 3-position has been reported, although electrophilic substitution in N-oxides is commonly known to be directed toward the 2- and 4-positions [42]. The reason is considered to be the formation of an epoxy intermediate.

2.1.2. Synthesis of Aminopyridines. Nitropyridines can be reduced to prepare the amino derivatives. This method is convenient mainly for preparing 3-aminopyridines because the 3-nitro precursors are most widely available. They are prepared by electrophilic addition of the nitro group. Several examples of the reduction of 2- and 4-nitropyridines are known. Owing to the limited availability of nitropyridines, this method has not been widely used. However, the examples described typically give high yields.

For example, catalytic reduction of nitropyridine over palladium on carbon was used to synthesize intermediates for food additives [43].

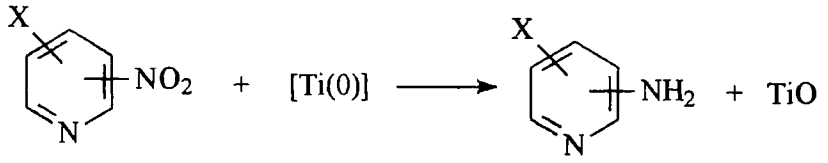


It has been reported that the palladium-containing ion exchanger AV-17-8 is a more stable and active catalyst than Pd/C for reducing nitropyridines [44].



Reduction of the cyano group and reductive dechlorination occur simultaneously with the reduction of the nitro group.

Zero-valent titanium, which is prepared by reduction of $TiCl_4$ in THF by Mg or $LiAlH_4$, is an efficient and selective reductant for the nitro group [45, 46]. In contrast with the catalytic reduction, this method enables halonitropyridines to be reduced with retention of the labile halogen [46].



Like for all nitroaromatic substrates, the degree of reduction of the nitro group in nitropyridines is easily controlled by the reducing agent used. Thus, the use of $Zn/NH_4Cl/EtOH$ as reductant produces 3-(hydroxylamino)-pyridine [47] (Table 5).

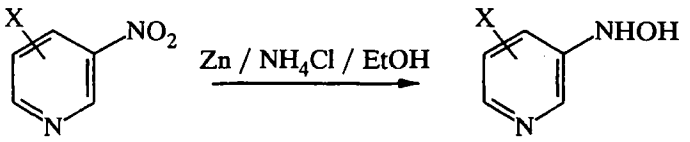


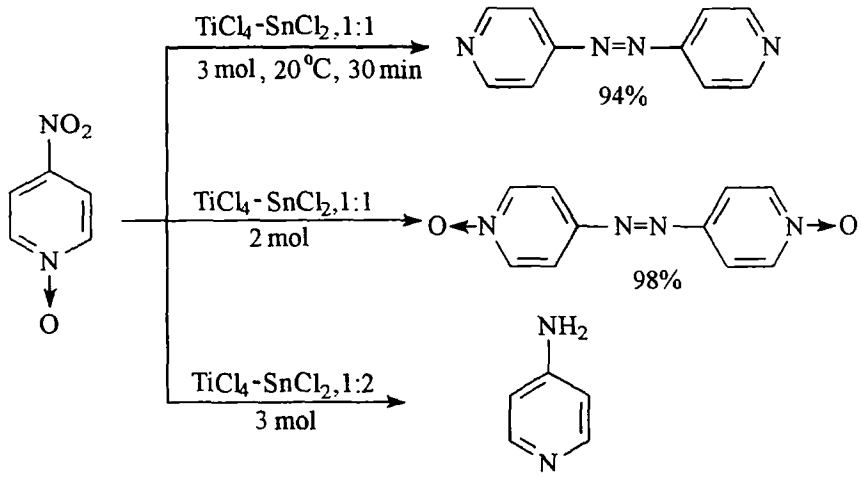
TABLE 4. Reduction of nitropyridines by Ti(0)

Position of NO_2 group	X	Yield, %	Position of NO_2 group	X	Yield, %
3	2-Cl	98	4	H	95
3	2,5-Br_2	96	4	2-Cl	98
3	4-Cl	85	4	2-Br	97
5	2-Cl	99	4	3-Cl	96
5	2-Br	96	2	3-Br	95

TABLE 5. 3-(Hydroxylamino)pyridines

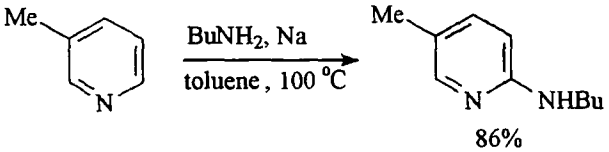
X	Reaction temp., °C	Reaction time, min	Yield, %
2-Cl	10...15	30	95...98
2-OMe	25...30	40	75
2-Cl-5-Me	10...15	30	76
4-OMe	25...30	45	82
4-OEt	40...45	40	92

Different products form depending on the reaction conditions used to reduce 4-nitropyridin-1-oxide with $TiCl_4$–$SnCl_2$ [48]. This system, which generates Ti(II) *in situ*, is very convenient for reducing N-oxides. Depending on the ratio of reagents, the reaction products can be 4,4'-azopyridine, its N-oxide, or 4-aminopyridine:



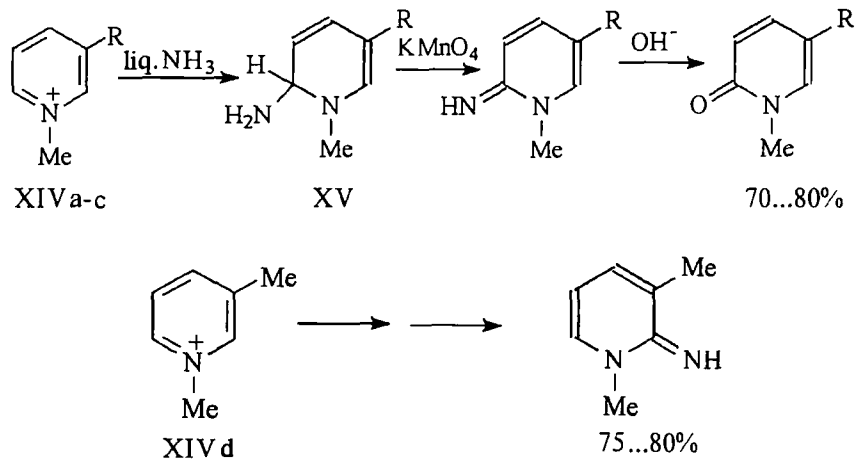
The tendency of pyridine to undergo nucleophilic substitution reactions explains the wide use of these processes to introduce the amine functional group into the molecule. One of these processes is direct amination of pyridines by the Chichibabin reaction. For example, 3-picoline was aminated by sodium amide in the gas phase under a sufficient pressure of ammonia [49, 50]. This gives a mixture of 2-amino-5-methyl- and 2-amino-3-methylpyridines in a 4:1 ratio.

A modification of the Chichibabin reaction consists of treatment of alkylpyridines with alkyl amides that are generated from a primary amine and metallic sodium in toluene [51]. For example, 2-butylamino-5-methylpyridine was prepared by this method in high yield [51].

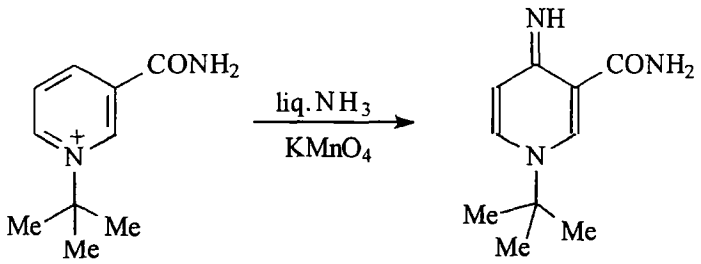


Attempted catalytic gas-phase amination of pyridine and picolines over catalysts containing Co, Ni, Si, Mg, Al, or V oxides gives low yields (~10%) of 2-aminopyridine and its 4- and 6-methyl derivatives [52, 53].

The reaction of 3-substituted pyridinium salts with liquid ammonia in the presence of $KMnO_4$ produces iminopyridines, which are easily hydrolyzed to the corresponding pyridones [54]. The regioselectivity of the imination for 3-substituted N-methylpyridinium salts is determined by the nature of the substituent in the 3-position. Thus, the 6-imino derivatives are formed for salts XIVa-c with R = H, $CONH_2$, and Ph whereas the 2-imino isomer is obtained for salt XIVd (R = Me):

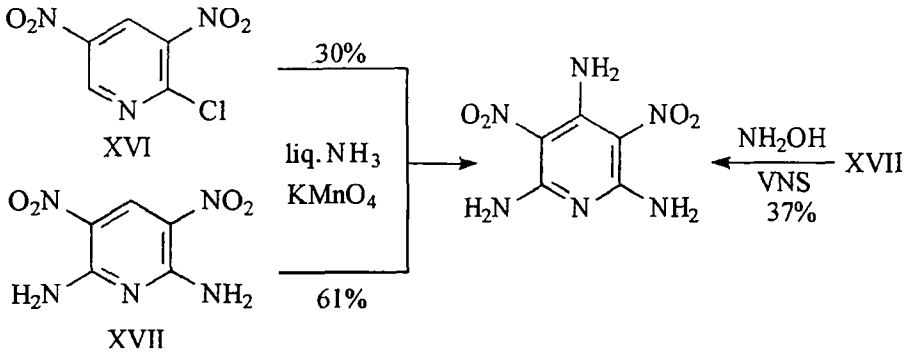


A bulky substituent on the nitrogen atom of the pyridinium salt leads to the production of only the 4-imino compound although PMR spectroscopy indicates that the 4- and 6-σ-adducts form in liquid ammonia [54].



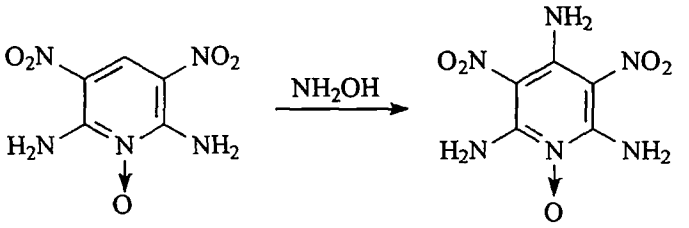
In all these examples, the presence of $KMnO_4$ in the reaction mixture facilitates the effective oxidative elimination of hydride ion from σ-adducts of type XV.

An analogous method was used for direct amination of 2-chloro-3,5-dinitropyridine (XVI) and 2,6-diamino-3,5-dinitropyridine (XVII), which are activated toward nucleophilic substitution by the presence of two acceptor substituents in the 3- and 5-positions [55].



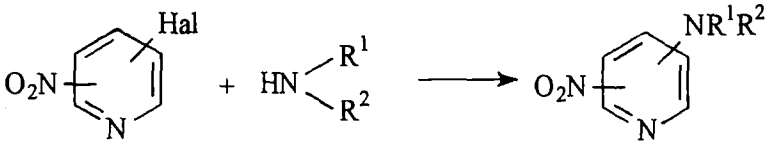
The use of hydroxylamine as the aminating agent is the original version of the amination of dinitropyridine XVII. In this instance the mechanism includes vicarious nucleophilic substitution and does not require an oxidant for aromatization of the Meisenheimer complex. Amination by hydroxylamine occurs analogously for the pyridine N-oxide XVII [55].

It should be noted that the Chichibabin reaction of dinitrochloropyridine XVI, which occurs at the 4- and 6-positions, is accompanied by nucleophilic substitution of the chlorine atom in the 2-position. Namely this substitution of an activated halogen atom in pyridine derivatives containing acceptor substituents is the most convenient and effective method for introducing amine functionality into the pyridine core.



(59% based on reacted N-oxide)

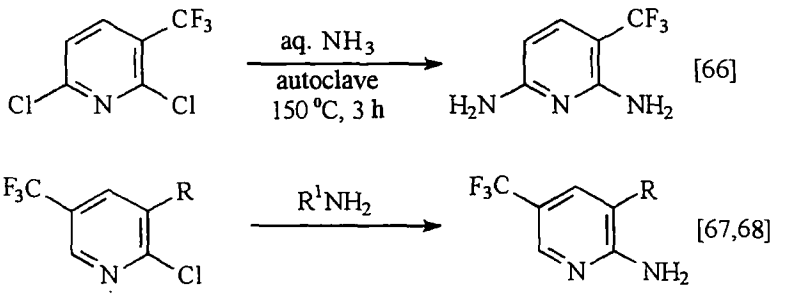
One of the most effective substituents for activating nucleophilic substitution of a halogen is the nitro group. Thus, the reaction of 2-, 4-, or 6-chloro-3-nitropyridine with primary and secondary amines produces the corresponding aminopyridines [56-62]. The reaction occurs in the presence of weak bases (e.g., $NaHCO_3$) in alcohols or DMSO.



The possibility of preparing from a commercially available starting material a diaza-18-crown-6 containing pyridine rings and possessing high specificity for Ag^+ is noteworthy [61].

In addition to the nitro group, a 3-cyano group also activates a chlorine atom in the 2-position of the pyridine ring toward nucleophilic substitution [63-65].

The trifluoromethyl group, which is an inductive acceptor, also activates a halogen atom in the 2-position of the pyridine ring toward substitution by ammonia [66, 67] and primary amines [68]. However, in this instance forcing conditions are necessary (pressure, 100-150°C).

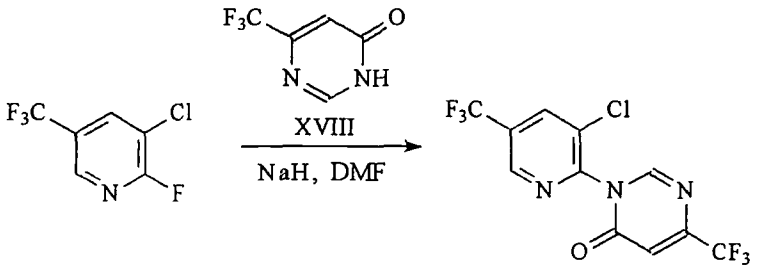


R = H, Cl; R^1 = H, Me, Et

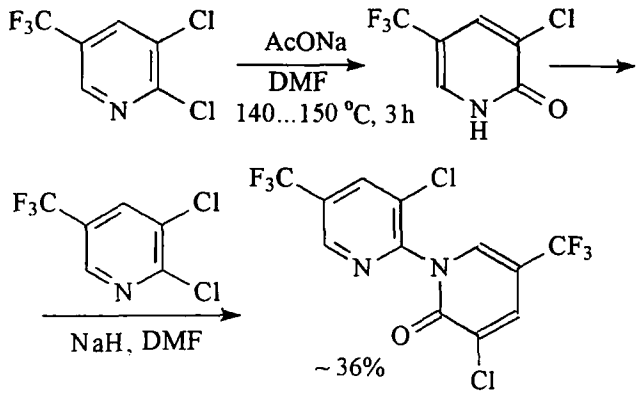
TABLE 6. Nucleophilic Substitution of Chlorine Atom by Amino Group in Nitrochloropyridines

Pyridine	Amine	Yield, %	Ref.
2-Cl-3-NO2	$EtO(CH_2)_2NH_2$	100	[56]
2-NH_2-6-Cl-3-NO_2	*p*-$FC_6H_4CH_2NH_2$		[57]
2-Cl-5-NO_2	Piperidine		[58]
4-Cl-3-NO_2	N-Phenylpiperazine		[59]
2-Cl-3-NO_2	Piperazine	97	[60]
2-Cl-5-NO_2	Diaza-18-crown-6	77	[61]
2-Cl-5-NO_2	$NH_2CH_2COCHN_2$	10	[62]

The pyrimidinone XVIII in DMF in the presence of NaH apparently forms the N-anion, which can substitute nucleophilically the fluorine atom in 3-chloro-2-fluoro-5-trifluoromethylpyridine [69].

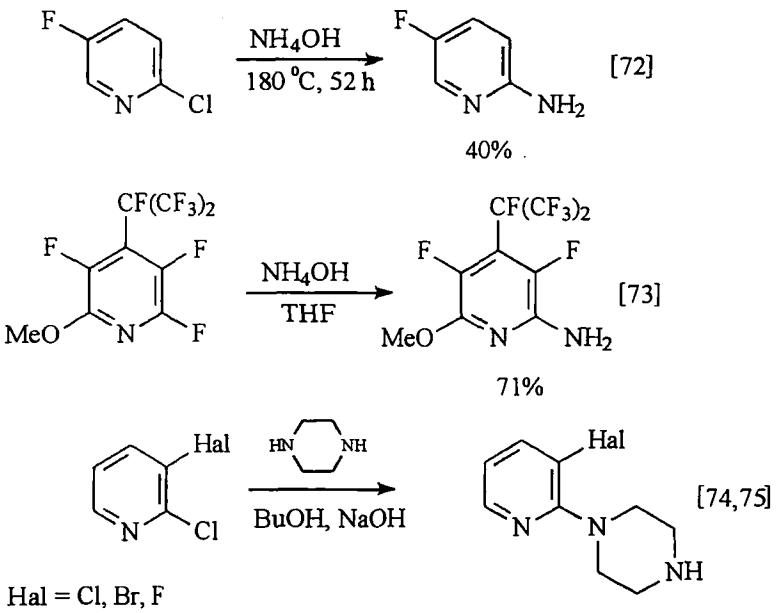


The self-condensation of 2,3-dichloro-5-trifluoromethylpyridine in the presence of sodium acetate apparently follows an analogous path [70].

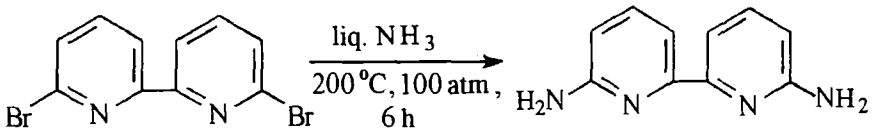


A trifluoromethyl group adjacent to a chlorine atom in the pyridine ring enables nucleophilic replacement of these atoms even in the 3- and 5-positions. For example, in 3,5-dichloro-2,6-di(trifluoromethyl)pyridine chlorine atom is replaced by secondary amine in high yield at 100°C under pressure [71].

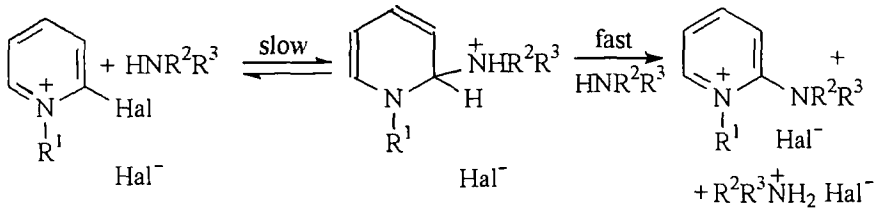
An additional halogen atom in the 3-position of 2-halopyridines facilitates nucleophilic substitution of the halogen atom in the 2-position by ammonia [72, 73] or amines [74, 75].



The pyridine rings in 6,6'-dibromo-2,2'-bipyridyl apparently have a mutual activating effect because the reaction with liquid ammonia proceeds with a yield greater than 80% to give the corresponding diamine, even though under forcing conditions [76].



A very effective method for activating a halogen atom in the 2-position of the pyridine ring toward substitution by primary and secondary aliphatic and aromatic amines is quaternization of the substrate [77-79]. In all instances the reaction in acetonitrile at 25°C goes practically quantitatively and irreversibly. A study of the kinetics demonstrated that the rate-determining step is the formation of the C–N bond.



R^1 = Me, Et; Hal = Br, I; R^2R^3NH = primary and secondary aliphatic amines, anilines

Substitution of the chlorine atom in 4-chloro-1-pyridinopyridinium salts XIXa,b is possible only by primary and secondary aromatic amines because more basic aliphatic amines attack the 2-position of the chlorinated ring, which leads to opening of the ring [80].

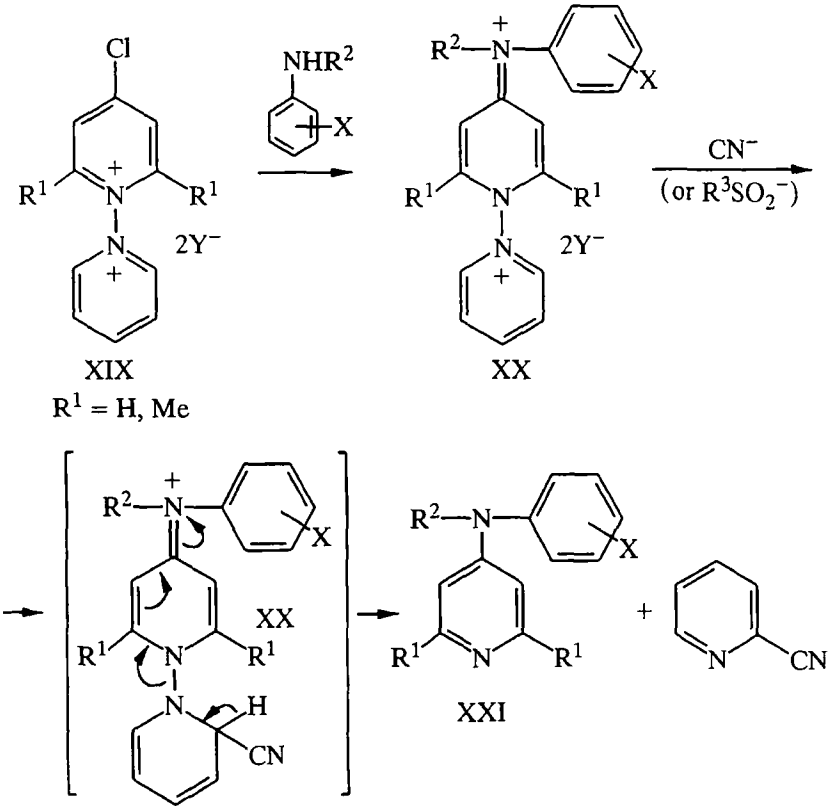


TABLE 7. Yields of 4-pyridylaryliminium Salts XX and 4-Pyridylarylamines XXI (%)

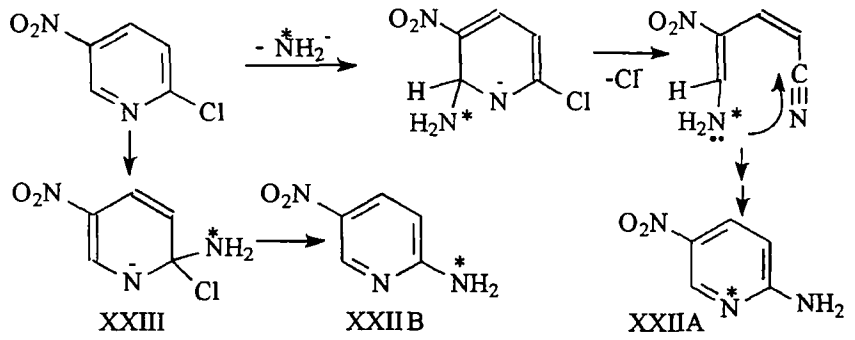
X	R^2	R^1 = H		R^1 = Me	
		XX	XXI	XX	XXI
4-NO_2	H	90	90	89	95
3-NO_2	H	97	87	91	92
2-NO_2	H	26	77	45	89
4-Ac	H	94	75	95	90
4-CO_2Me	H	95	79	97	98
4-COOH	H	85	89	96	95
4-Br	H	90	91	96	87
3-Br	H	92	78	96	85
2-Br	H	89	62	89	81
4-Cl	H	94	91	95	94
3-Cl	H	94	81	94	80
2-Cl	H	91	64	90	75
4-F	H	93	93	87	82
H	H	89	92	96	89
4-Me	H	90	90	93	91
3-Me	H	85	71	94	78
2-Me	H	89	62	88	72
4-OMe	H	85	69	85	70
3-OMe	H	84	65	89	81
4-OH	H	90	92	87	90
3-OH	H	70	87	84	79
H	Me	90	61	91	68
H	Et	91	Spectr.	82	Spectr.
H	Ph	57	Spectr.	34	Spectr.

Reaction of salts XIX with aromatic amines forms in high yields the 4-aryliminium salts XX, which are easily cleaved into the 4-pyridylarylamines XXI by NaCN or the sodium salt of a sulfinic acid.

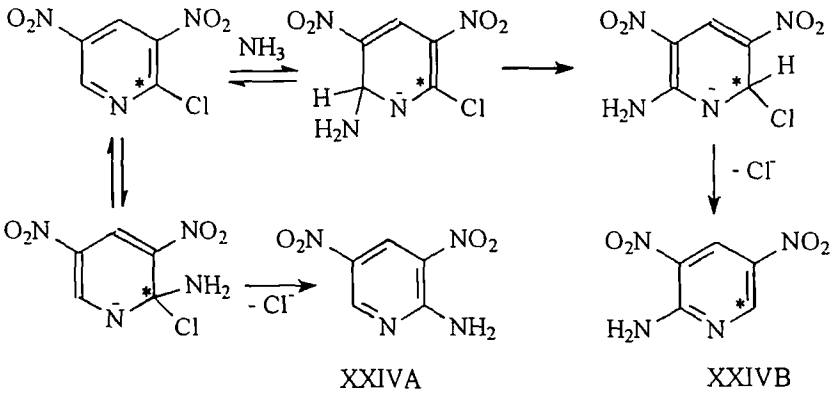
In all examples of nucleophilic substitution of an activated halogen atom in a pyridine ring by an amino group that were given above, standard aromatic nucleophilic substitution apparently occurs. However, more complicated mechanisms can occur during amination by such strong bases as metal amides in liquid ammonia.

Thus, ^{15}N and ^{1}H NMR experiments demonstrated that conversion of 2-chloro-5-nitropyridine into 2-amino-5-nitropyridine by treatment with potassium amide in liquid ammonia proceeds 75% by the S_N[ANRORC] mechanism [81]. The process begins with addition of the nucleophile (usually to the position *meta* to the leaving group), then, the ring opens and subsequently closes.

The inclusion in the ring of XXIIA of 75% ^{15}N confirms that the mechanism is 75% S_N[ANRORC]. The addition–elimination mechanism [$S_N(AE)^{ipso}$] with intermediate formation of the adduct XXIII accounts for 25% (XXIIB).

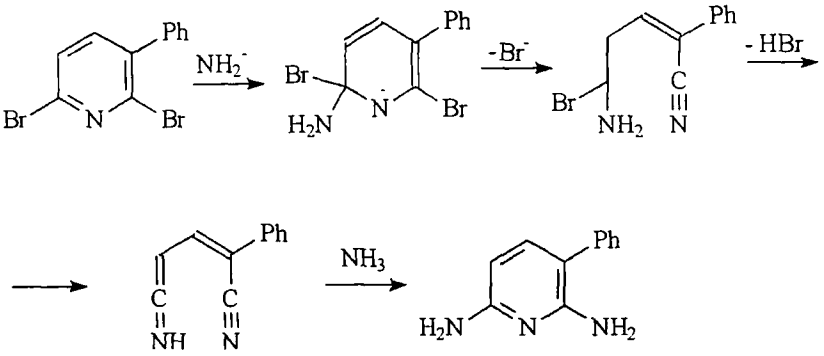


In contrast with this, mass spectrometry (^{15}N) and ^{13}C NMR established that the fraction of the S_N[ANRORC] mechanism is only 7% whereas the $S_N(AE)^{ipso}$ mechanism is 93% for the amination of 2-chloro-3,5-dinitropyridine by liquid ammonia without potassium amide [82]. The ^{13}C NMR experiment enabled an unambiguous choice between the $S_N(AE)^{ipso}$ and $S_N(AE)^{tele}$ mechanisms to be made in favor of the former because XXIVA is formed exclusively. Additional confirmation comes from the use in the reaction of 2-chloro-6-deutero-3,5-dinitropyridine. The retention of the deuterium label during the amination also proves that the process occurs by the $S_N(AE)^{ipso}$ mechanism.



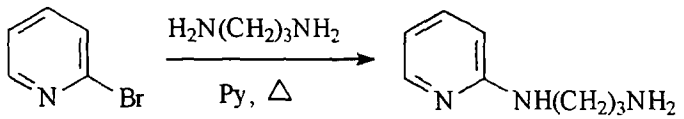
XXIVA XXIVB

The conversion of an unactivated substrate, 2,6-dibromo-3-phenylpyridine, into the corresponding diamino derivative by potassium amide in liquid ammonia also goes by the S_N[ANRORC] mechanism. Neither 2-amino-6-bromo- nor 6-amino-2-bromopyridine is an intermediate [83].



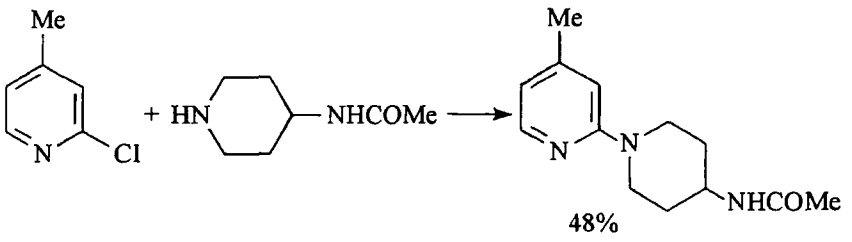
Experience teaches that nucleophilic substitution of a halogen by an amino group can also occur for an otherwise unactivated pyridine substrate. However, as a rule, these processes require more forcing conditions or the use of special methods.

For example, under sufficiently forcing conditions (boiling in pyridine), 2-bromopyridine reacts with 1,3-diaminopropane [84].

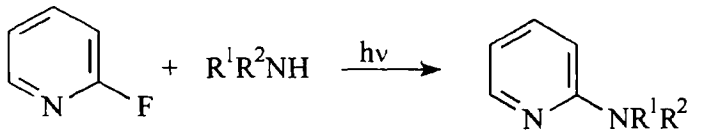


70%

The substitution of the halogen atom in 3- and 4-methyl-2-chloro- and -bromopyridines by reaction with aqueous methylamine in an autoclave at 180°C was described in patents [85, 86]. For 2-chloro-4-methylpyridine under these conditions, the yield of the corresponding 2-methylamino derivative is ~46%. Use of a secondary amine, 4-aminoacetylpiperidine, produces the corresponding 2-aminopyridine in approximately the same yield [87].



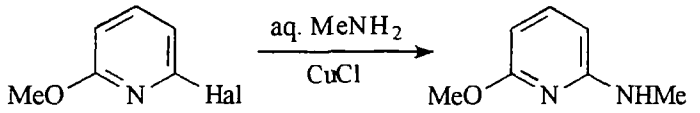
The reaction of 2-fluoropyridine with primary amines under irradiation gives the 2-alkylamino derivatives. The reaction was classified as photoinduced nucleophilic substitution because the pyridine ring was not aminated in the 3-position, which would be evidence of the elimination–addition mechanism [88].



$R^1 = R^2 = Et$, $R^1 = H$, $R^2 = t\text{-Bu}$

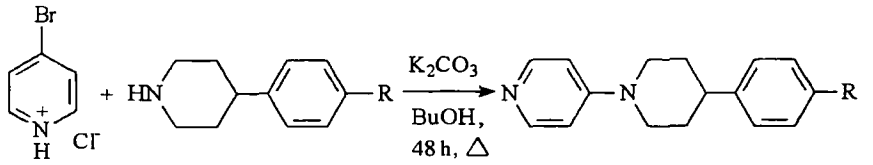
Monoamination of 2,6-dichloropyridine by aqueous methylamine at 130°C in the presence of base [89] and by N-substituted 4-aminopiperidine in DMSO [90] occurs in high yield. This same substrate was used for successive substitution of first chlorine atom by a methylamino moiety and then the second by a methoxy- [91, 92] or dimethylamino group [93].

The halogen atom in 2-halo-6-methoxypyridine can be effectively replaced by a methylamino group by using copper or its salts as a catalyst in an autoclave at 120°C [94].



Hal = Br, Cl Hal = Cl (78%)

Substitution of the bromine atom by a secondary amino group in 4-bromopyridinium hydrochloride occurs under mild conditions [95]. In our opinion, this is explained by the presence in equilibrium concentrations of the activated protonated substrate and the amine as the free base.



Sufficiently high temperatures (boiling in xylene) must be used for the amination of less basic aromatic amines [96].

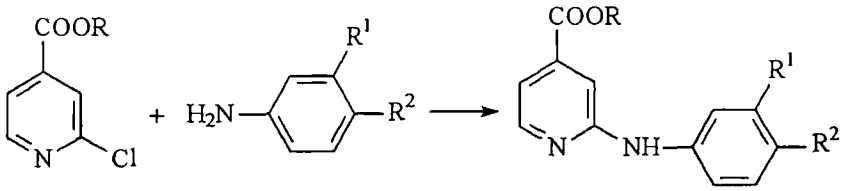
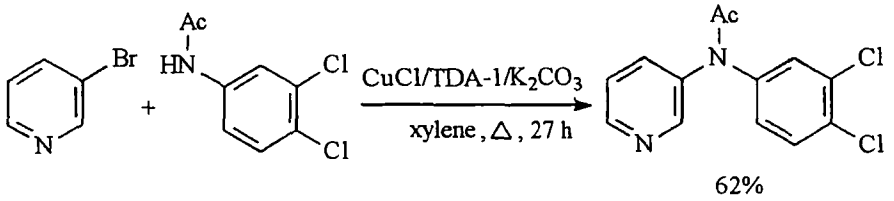


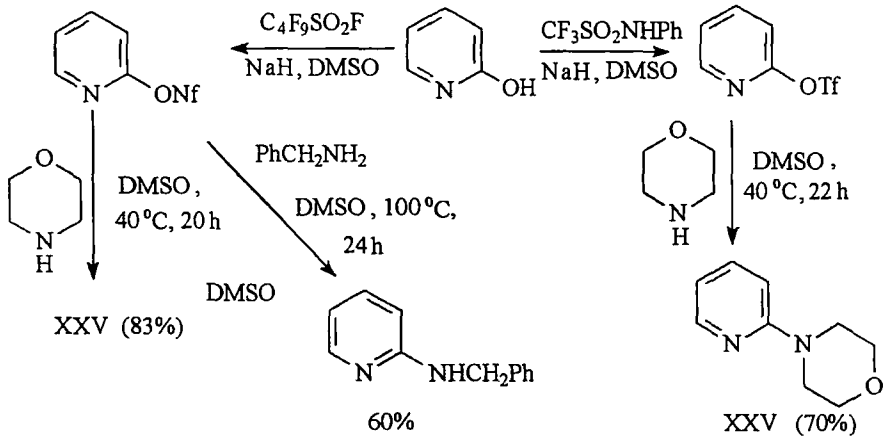
TABLE 8. 2-Arylamino-4-alkoxycarbonylpyridines

R	R^1	R^2	Yield, %
H	Cl	Cl	30
H	H	OMe	64
H	H	Cl	44
Me	Cl	Cl	82
Me	H	Cl	89
Me	CF_3	H	72
Me	H	OMe	90

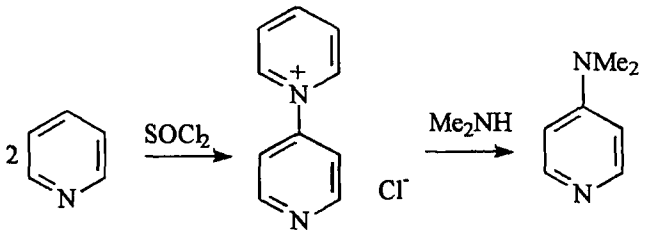
Even a bromine atom in the 3-position of a pyridine ring that is not activated toward nucleophilic reactions can be replaced by acetylaniline if a catalyst consisting of Cu(I) chloride and tris(3,6-dioxaheptyl)amine (TDA-1) is used [97].



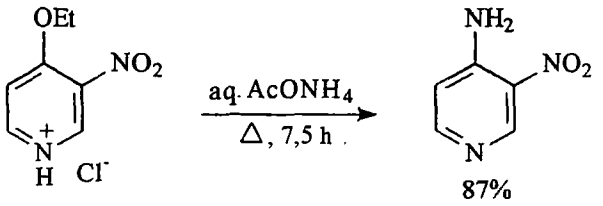
Not only halopyridines but also any other pyridines containing good leaving groups can be successfully used as substrates to prepare aminopyridines by nucleophilic substitution. Thus, high yields of aminopyridines were obtained by using 2-pyridyl triflates or nonaflates, which are formed by reacting 2-hydroxypyridine with sodium hydride and the N-phenylamide of trifluoromethansulfonic acid or perfluoro-1-butanesulfonyl fluoride, respectively [98]. These compounds may be further aminated without isolation ("one-pot" synthesis) [98].



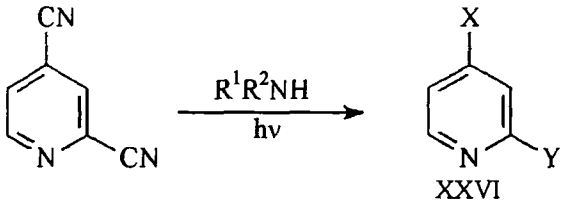
The pyridine molecule is a good leaving group in 1,4'-bipyridinium chloride. This enables a dimethylamino group to be introduced in the 4-position of the pyridine ring [99].



The ethoxy substituent in 4-ethoxy-3-nitropyridine that is activated by the *ortho*-nitro group is replaced in high yield by an amino group on boiling with aqueous ammonium acetate [100].



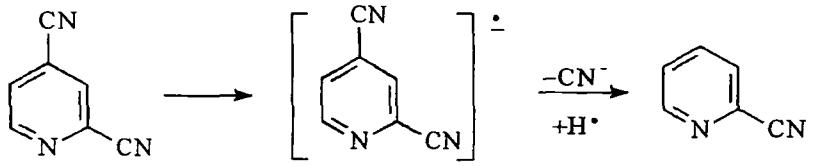
Only one of the nitrile groups is replaced during photoinduced reaction of 2,4-dicyanopyridines with primary or secondary amines [101].



a X = NR^1R^2, Y = CN; b X = CN, Y = NR^1R^2; c X = H, Y = CN

Attention is drawn to the fact that this is a photoinduced reaction (the reaction does not occur without irradiation), the direction of which depends largely on the structure of the amine.

The formation of a product without cyanide (XXVIc) can be explained by the formation of an intermediate anion-radical followed by the elimination of a nitrile group and capture of a hydrogen radical from the amine.



Several unique methods for preparing aminopyridines are known that do not fall under the classifications used above. For example, the reaction of various pyridines with fluorine–carbonitrile–water produces 2-acylaminopyridines XXVII and small amounts of the 2-fluoro derivatives XXVIII [102].

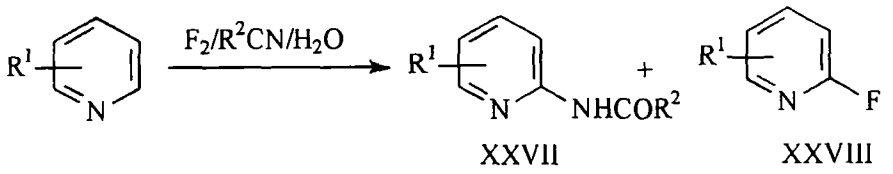
TABLE 9. Amination of Dicyanopyridine

Amine		XXVI	XXVI	Yield, %	
R^1	R^2	a/b	(a + b)/c	a + b	a + b + c
Pr	H	0,58	0,27	10	46
i-Pr	H	0,76	0,24	12	60
t-Bu	H	0,63	0,62	14	37
C_6H_{11}	H	0,67	0,27	11	52
Et	Et	1,36	0,53	26	76
Pr	Pr	1,83	0,83	37	82
$-(CH_2)_4-$		1,07	0,27	13	62
$-(CH_2)_5-$		0,52	0,36	17	63
$-(CH_2)_2O(CH_2)_2-$		0,82	1,38	20	34

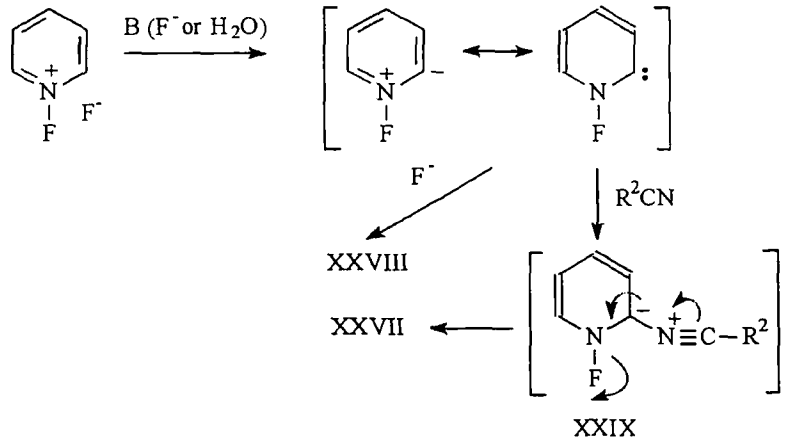
TABLE 10. Yields of 2-Acylamino- and 2-Fluoropyridines

R^1	R^2	Yield, %	
		XXVII	XXVIII
H	Me	67	15
H	Pr	58	18
3-Me	Me	21 (3-Me) 6 (5-Me)	23 (3-Me) 5 (5-Me)
3-Br	Me	54	17
3-CN	Me	44	9

The reaction with 3-picoline gives a mixture of isomeric acylamino derivatives whereas only the 2-acylamino derivatives are formed from 3-bromo and 3-cyanopyridines.

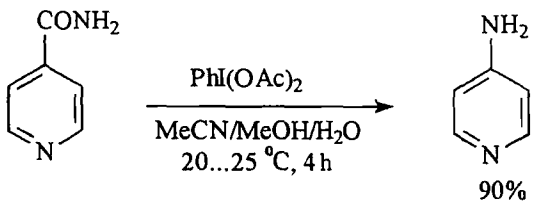


It is proposed that the carbene that is formed by loss of a proton from the strongly activated 2-position of the previously formed N-fluoropyridinium fluoride reacts with a nitrile to produce the ylide XXIX (a precursor of the acylamines XXVII) or with a fluoride ion to give the 2-fluoropyridines XXVIII as minor products.

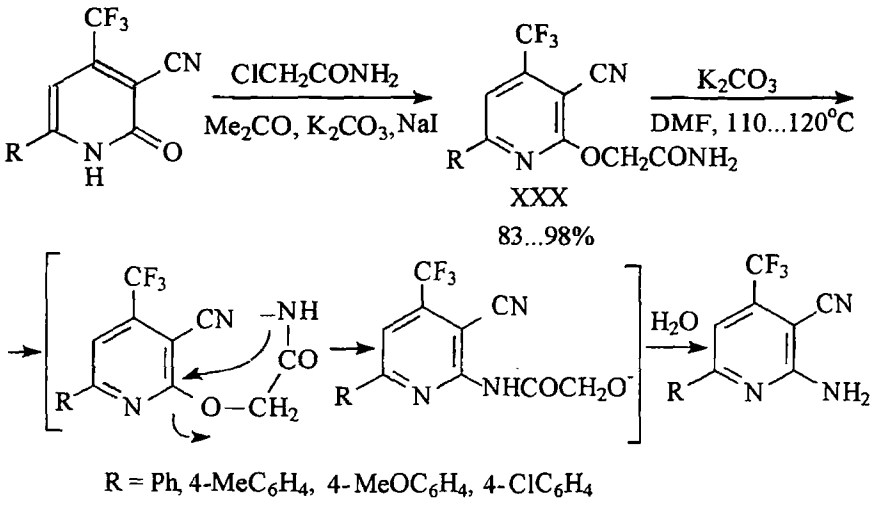


The formation of only 3-bromo- or 3-cyano-2-acylpyridines is explained by the greater acidity of the proton in the 2-position compared with the 6-position.

Another unique method for preparing aminopyridines is the use of phenylacetoxyiodonium acetate as the oxidant in the Hofmann rearrangement of nicotinamide to 4-aminopyridine [103].

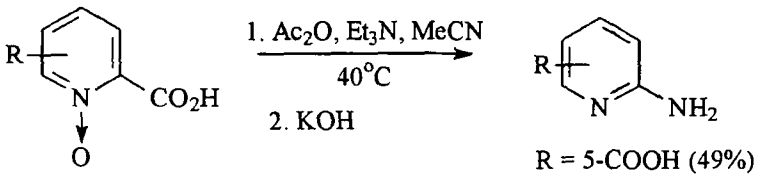


2-Amino-6-cyano-4-trifluoromethyl-6-substituted pyridines were prepared from the corresponding pyrid-2-ones by an interesting intramolecular rearrangement of 2-O-acetamido intermediates XXX [104].



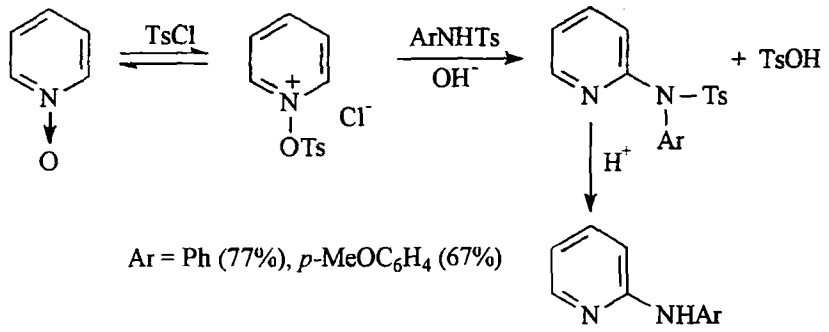
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

The conversion of N-oxides of picolinic acids into the corresponding 2-aminopyridines by reaction with carboxylic acid anhydrides, carbonitrile, and triethylamine has been described. The reaction proceeds under mild conditions with evolution of CO_2. The mechanism is unknown [105].



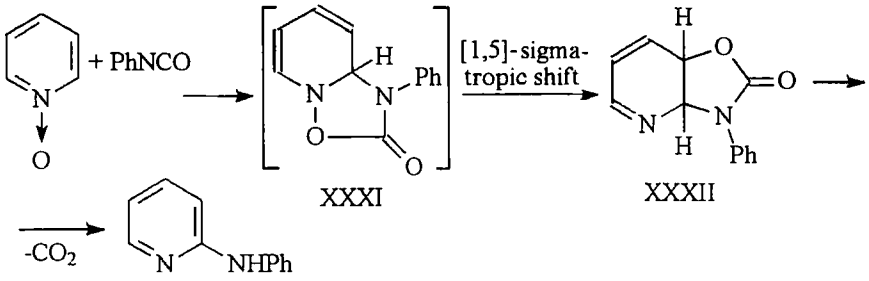
R = H, COOH, Ar, Alk

In fact, besides this exotic example, N-oxides are widely used as starting materials for preparing amino derivatives of pyridine. For example, acylamination of the pyridine ring at the 2-position was found to occur easily by reacting pyridine N-oxide with sulfonylanilides and tosyl chloride in basic medium [106-108]. The reaction proceeds with preliminary formation of the O-tosylpyridinium salt, which is activated to nucleophilic attack at the 2-position by the amide anion formed in basic medium.



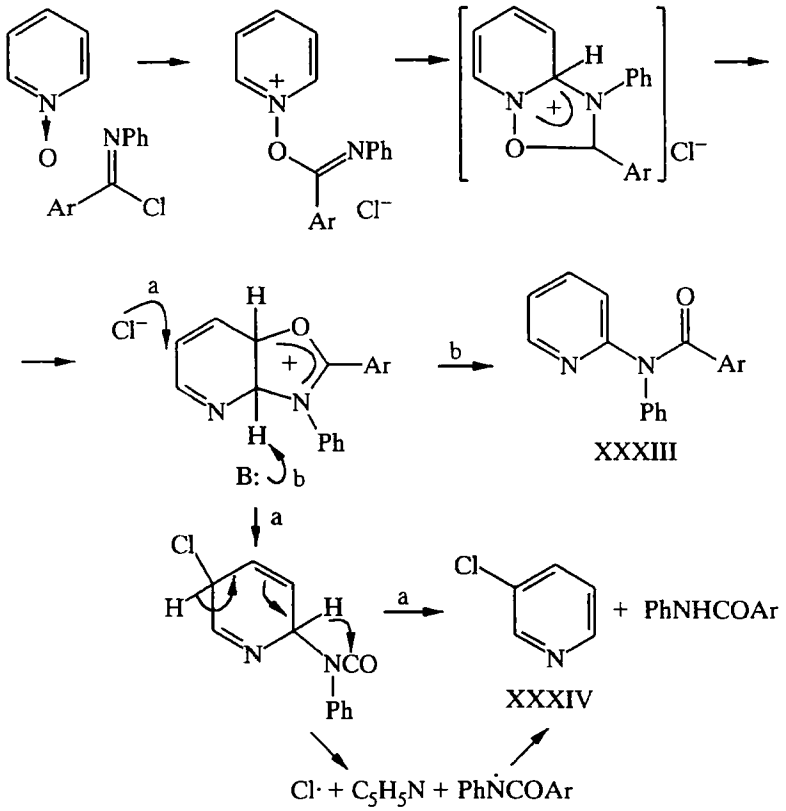
Ar = Ph (77%), *p*-$MeOC_6H_4$ (67%)

Aromatic N-oxides are known to react readily by 1,3-dipolar cycloaddition to phenylisocyanate to give α-amino derivatives. A study of the kinetics and the isolation of the intermediate XXXII established the exact mechanism for the reaction of pyridine N-oxide with phenylisocyanate [109].



As it turned out, the 1,2-dihydropyridine intermediate XXXI that is formed by 1,3-dipolar cycloaddition instantly rearranges to the 2,3-dihydro compound XXXII, which leads to the formation of 2-phenylaminopyridine.

Pyridine N-oxide reacts with N-phenylbenzimidoyl chlorides by an analogous mechanism to give 2-(N-aroylamino)pyridines XXXIII and 3-chloropyridine (XXXIV) [110]. The N-fluoropyridine does not form if imidoyl fluorides are used.



The reaction goes through multiple steps. The nature of the substituents on the imidoyl chloride can affect each of them. In the general instance, electron-donating substituents in the *para*-position enhance the amination whereas acceptor substituents hinder both reactions (Table 11).

Aromatic nucleophilic substitution with catalysis by polyphosphoric acid can be used to aminate pyridine and 3-picoline N-oxides with hexamethylphosphoramide (HMPA). This method is a new approach to dimethylamino derivatives of pyridine [108].

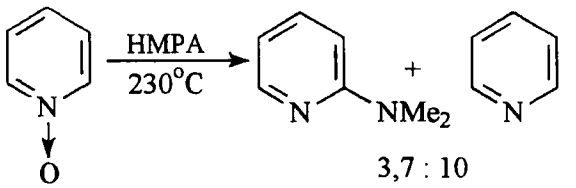
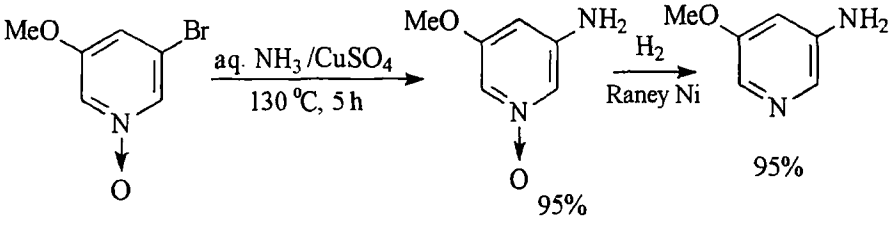


TABLE 11. Substituent Effect in Ar Substituent of N-Phenylarylimidoyl-chloride on Formation of Amino Derivatives of Pyridine XXXIII and 3-Chloropyridine XXXIV

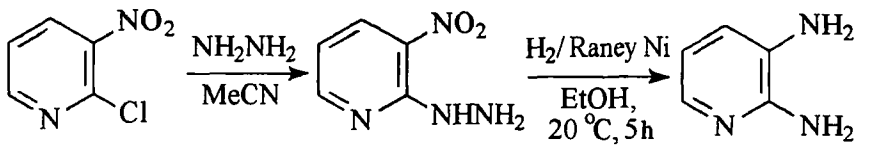
Substituent in Ar	Yield, %		Substituent in Ar	Yield, %	
	XXXIV	XXXIII		XXXIV	XXXIII
H	28	57	3,5-$(OMe)_2$	29	44
2-Me	22	51	2-Cl	29	46
4-Me	1,7	59	3-Cl	32	45
2,4-Me_2	9,8	52	2,4-Cl_2	30	40
3,5-Me_2	24	54	3,4-Cl_2	23	49
2-OMe	12	26	2-NO_2	30	31
3-OMe	31	47	3-NO_2	41	30
4-OMe	15	53	2,4-$(NO_2)_2$	19	0
2,4-$(OMe)_2$	10	46	3,5-$(NO_2)_2$	3,7	0

Using 3-picoline N-oxide gives a mixture of 3-picoline and the 6- and 2-dimethylamino derivatives with a two-fold predominance of the 6-isomer. The amination of 2- and 4-picoline goes into the side chain forming the 2- and 4-dimethylaminomethyl derivatives.

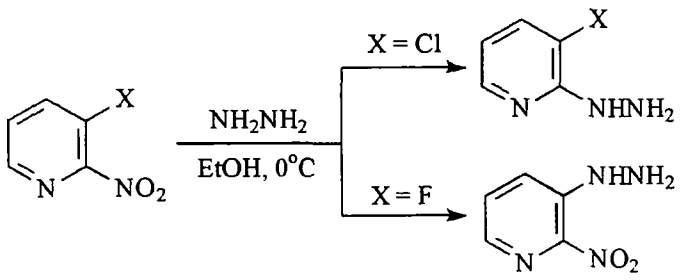
In the presence of Cu(II) sulfate at 130°C in a sealed tube nucleophilic substitution by ammonia of the 3-bromo atom in 3-bromo-5-methoxypyridine N-oxide followed by deoxygenation produces 3-amino-5-methoxypyridine [112].



2.1.3. Pyridine Hydrazines and Azides. A halogen atom activated by an additional acceptor substituent in the pyridine molecule is easily replaced by hydrazines. Thus, hydrazine hydrate reacts with 2-chloro-3-nitropyridine to form 2-hydrazino-3-nitropyridine. Subsequent reduction of the product over Raney nickel gives 2,3-diaminopyridine [113].

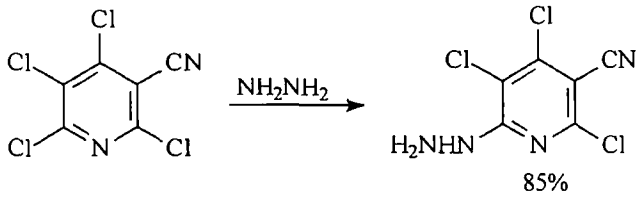


It is interesting that only a fluorine atom in 3-halo-2-nitropyridines undergoes *ipso*-substitution. For the 3-chloro derivative, the nitro group is *ipso*-substituted. This agrees with MNDO and CNDO quantum-chemical calculations [114].

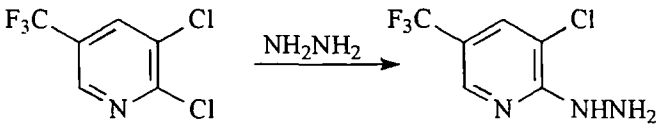


The fluorine atoms in the 2- and 4-positions are substituted in perfluoropyridine by lithium hydrazonides [115].

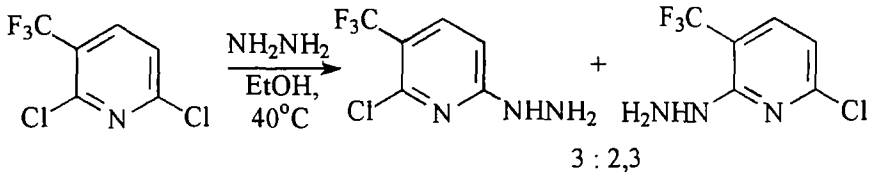
X-ray crystallographic studies found that the reaction of 2,4,5,6-tetrachloronicotinonitrile even with an excess of hydrazine hydrate at 20°C in dioxane, THF, or DMF or at -35°C in dichloromethane produces exclusively 6-hydrazino-2,4,5-trichloronicotinonitrile [116].



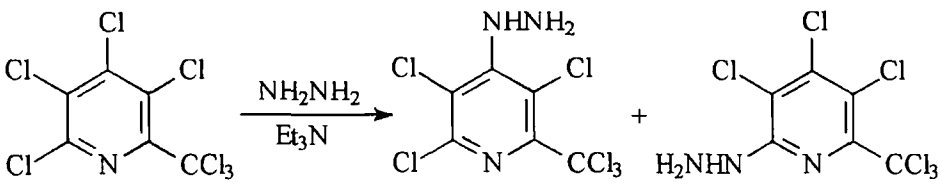
The chlorine atom in the 2-position is substituted in 2,3-dichloro-5-trifluoromethylpyridine [117, 118].



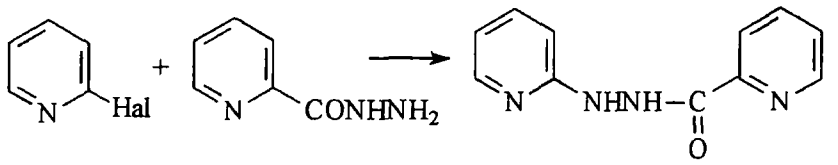
If two substitutable chlorine atoms are present in the 2- and 6-positions, a mixture of hydrazines forms in a total yield of about 40% [119].



The trichloromethyl group in 3,4,5,6-tetrachloro-2-trichloromethylpyridine does not activate the neighbouring chlorine atom. As a result, two isomeric hydrazines with predominance of the 4-derivative form [120].

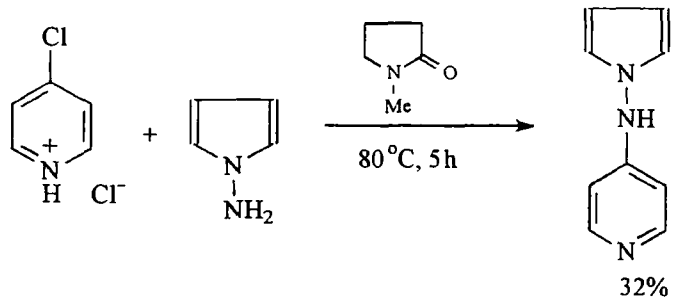


An example of the substitution by hydrazine of a halogen atom in the 2-position that is not activated by any additional substituents has been reported [121].

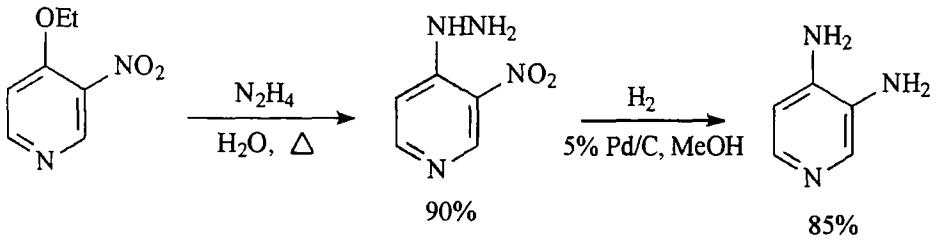


Hal= Cl, I, Br

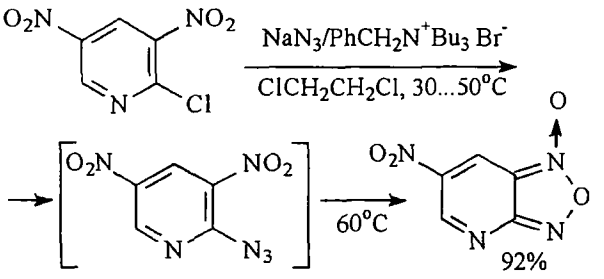
The reaction of 4-chloropyridine hydrochloride with N-aminopyrrole in N-methylpyrrolidone gives a low yield of 4-(pyrrolylamino)pyridine, one member of a class of potential drugs for curing Alzheimer's disease [122].



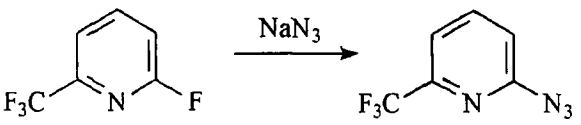
Other groups besides halogens can be substituted analogously to the preparation of aminopyridines in order to synthesize pyridylhydrazines. For example, the reaction of 2-ethoxy-3-nitropyridine with hydrazine gives the corresponding nitropyridylhydrazine. Subsequent hydrogenation causes simultaneous reduction of the nitro group and cleavage of the hydrazine to the amine [123]. This succession of reactions is a convenient path to pyridyldiamines.



Much less has been reported in the literature about the introduction of an azide group into the pyridine ring. It is known that sodium azide reacts with 2-chloro-3,5-dinitropyridine under phase-transfer catalysis conditions to form the intermediate azide that undergoes intramolecular cyclization to the pyridofuroxane [124, 125].



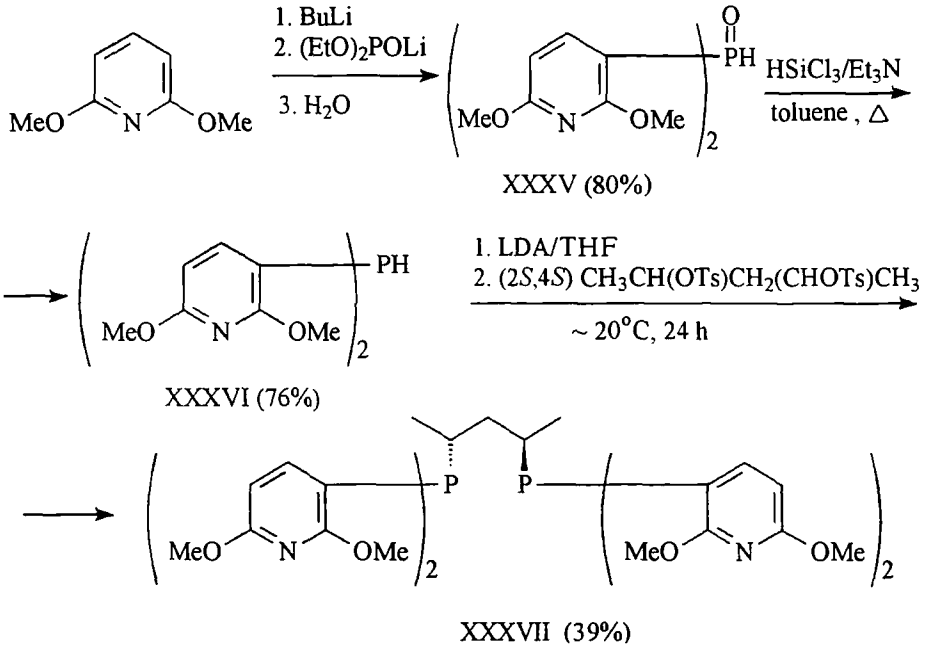
According to a patent, 2-azidopyridine forms by substitution of an unactivated fluorine atom [126].



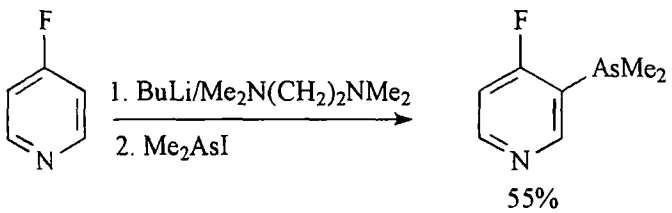
2.2. Formation of C–P and C–As Bonds

Methods for phosphorylating pyridines that were published before 1985 have been reviewed [127]. Both traditional methods using metallated pyridines and several new methods have been developed in the intervening years.

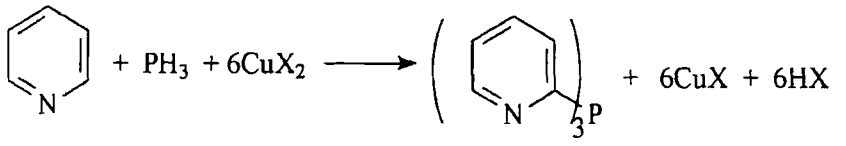
For example, lithiation of 2,6-dimethoxypyridine by butyllithium at -40°C in THF with subsequent treatment by lithium diethylphosphide gives bis[3-(2,6-dimethoxypyridyl)]phosphine oxide (XXXV). Reduction of XXXV by trichlorosilane in the presence of triethylamine produces bis[3-(2,6-dimethoxypyridyl)]phosphine (XXXVI) in good yield. This phosphine was then used to synthesize the derivative of a chiral ligand (2*R*,4*R*)-Skewphos (XXXVII), which is stable in air [128].



Selective *ortho*-lithiation of 4-fluoropyridine by the BuLi–tetramethylethylenediamine chelate with subsequent treatment with dimethylarsine iodide produces a $C_{(3)}$–As bond [12].



As it turns out, the formation of a C–P bond in pyridines does not always require preliminary metallation. Nucleophilic substitution of hydrogen in both unactivated and activated pyridine substrates can be used. Thus, oxidative phosphorylation of pyridine in the presence of Cu(II) salts with close to a quantitative yield was recently observed for the first time [129].



The reaction includes the following key steps:

$$Cu_2X_3(PH_3)(C_5H_5N) \rightleftharpoons Cu_2X_2(PH_2)(C_5H_5N) \quad (1)$$

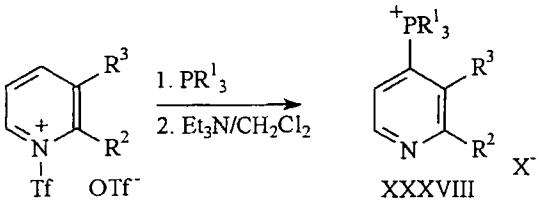
$$Cu_2X_2(PH_2)(C_5H_5N) \longrightarrow Cu_2X_2(H)(C_5H_4NPH_2) \quad (2)$$

$$Cu_2X_2(H)(C_5H_4NPH_2) \longrightarrow Cu + HX + C_5H_4NPH_2 + CuX \quad (3)$$

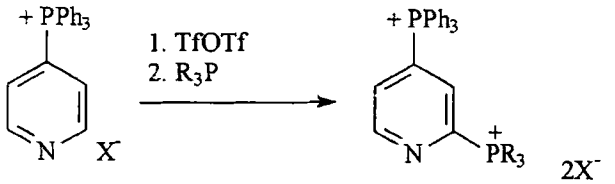
$$Cu + CuX_2 \rightleftharpoons 2CuX \quad (4)$$

The pyridylphosphine is formed by nucleophilic addition of phosphide to the pyridine $C_{(2)}$ atom with subsequent elimination of hydride by Cu(II), which decomposes into Cu and HX (3). Pyridylphosphine and dipyridylphosphine were not observed among the products because they react faster than PH_3. Mixed-valent dimeric Cu(II)–Cu(I) complexes promote the reaction of phosphine with pyridine because they create the optimal conditions for coordination of the reactants (Py and PH_3) and their reaction in the coordination sphere. Only Cu(I), in contrast with Cu(II), forms complexes with phosphine.

Activated substrates, N-trifluoromethanesulfonylpyridinium salts, are regioselectively converted by phosphines to 4-pyridylphosphonium salts XXXVIII [130-131].



The salts XXXVIII can be converted to the 2,4-diphosphonium salts by an analogous method. For example:



R=Ph (88%), Bu (26%)

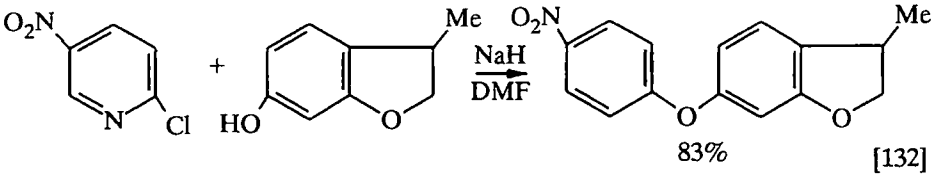
TABLE 12. (4-Pyridyl)phosphonium Salts

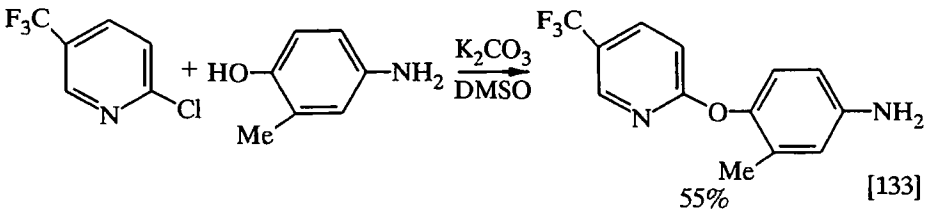
R^1	R^2	R^3	Yield, %
Ph	H	H	91
Ph	Et	H	62
Ph	CH_2Ph	H	70
Ph	Br	H	64
Ph	H	Me	21
Bu	H	H	39

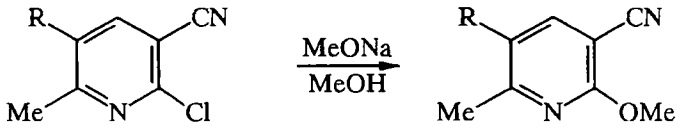
3. FORMATION OF C–O, C–S, AND C–Te BONDS

3.1. Formation of C–O Bonds

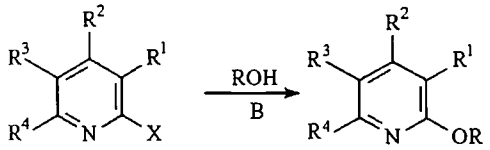
A general method for synthesizing oxy-substituted pyridine derivatives is nucleophilic substitution of a halogen by various O-nucleophiles such as alkoxides, phenoxides, and alkali-metal hydroxides. Activated halopyridine substrates are usually used for this. For example:



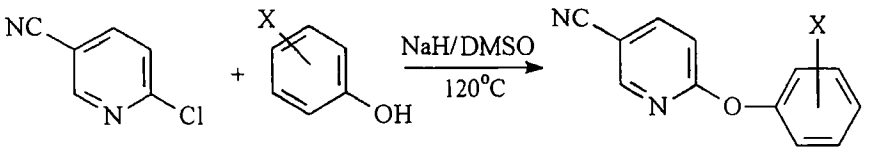




In this manner mostly derivatives of 2-hydroxypyridine are prepared. Data for these compounds are given in Table 13.



A chlorine atom in the pyridine 2-position that is activated by a 5-cyano group is easily replaced by various phenoxides [155]:

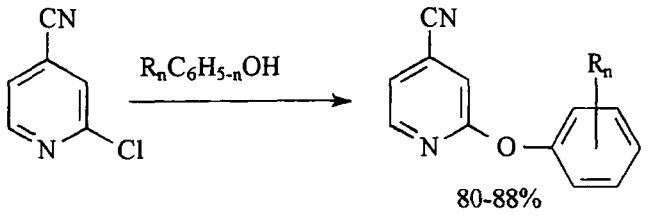


X = 4-Cl, 4-COMe, H, 3,4-Cl_2, 4-F, 4-Me

Despite the fact that the cyano group in 2-chloro-4-cyanopyridine is situated *meta* to the halogen, the substitution by phenoxides goes in rather high yields [156].

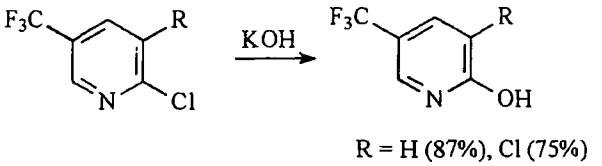
TABLE 13. Preparation of 2-Hydroxypyridine Derivatives

R^1	R^2	R^3	R^4	X	R	B	Ref.
Cl	H	CF_3	H	Cl	Ph	K_2CO_3	[135]
Cl	H	CF_3	H	Cl	*m*-$H_2NC_6H_4$		[136]
Cl	H	CF_3	H	Cl	*p*-$RO_2CCH(Me)C_6H_4$	NaH DMSO	[137]
Cl	H		H	Cl	2-Cl-4-NH_2-6-CO_2Et-C_6H_2		[138]
H	H	H	H	Cl	*o*-MeC_6H_4		[139]
H	H	NO_2	H	Cl	2-Naphtyl	K_2CO_3 DMSO	[140]
Cl	H	CF_3	H	Cl	*p*-$RO_2CCH(Me)OC_6H_4$	K_2CO_3 2-butanone	[141]
H	H	CF_3	H	Cl	$NH_2C_6H_4(CH_2)_2$	NaH DMF	[142]
Cl	H	CF_3	H	Cl	*o*-$EtO_2CC_6H_4$		[143]
Cl	H	CF_3	H	Cl	*p*-HOC_6H_4	KOH NaOH	[144, 145]
H	H	NO_2	CO_2Et	Cl	2-CF_3-4,6-$Cl_2C_6H_2$	$BuO^-/CHCl_3$	[146]
H	H	CF_3	H	Cl	*p*-HOC_6H_4		[147]
H	H	NO_2	H	Cl	1-Naphtyl	K_2CO_3	[148]
Cl	H	CF_3	H	Cl	5-Nitroquinolyl-8		[149]
2-Thionyl	H	H	H	Cl	4-$(Me_2N(CH_2)_2)C_6H_4$	NaH DMF	[150]
H	H	NO_2	H	Cl	*p*-*t*-$BuOC_6H_4$	$Ca(OH)_2$ DMSO	[151]
F	H	Cl	H	F	*p*-$MeO_2CCH(Me)C_6H_4$	K_2CO_3 MeCN 18-Crown-6	[152]
Cl	H	I	H	Cl	*p*-$MeO_2CCH(Me)C_6H_4$		[153]
H	CCl_3	H	Cl	Cl	$(CH_2)_2OCH_2$-2-Fur	NaOH H_2O 45°C	[154]

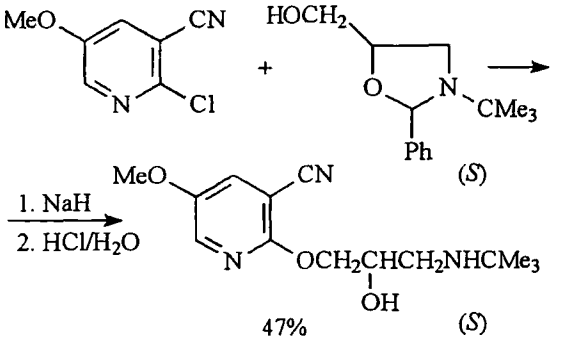


R_n = H, 4-Cl, 2,4-Cl_2, 2-Me, 4-Me, 4-CO_2Et

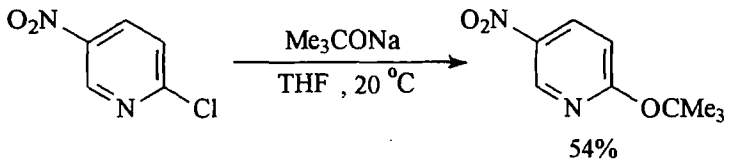
Hydroxides [68] and alkoxides [157] can be used as nucleophiles in addition to phenoxides.



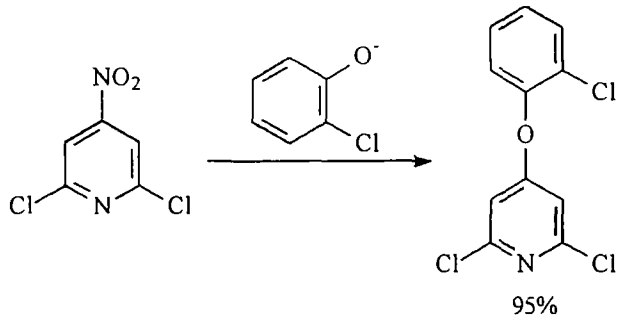
R = H (87%), Cl (75%)



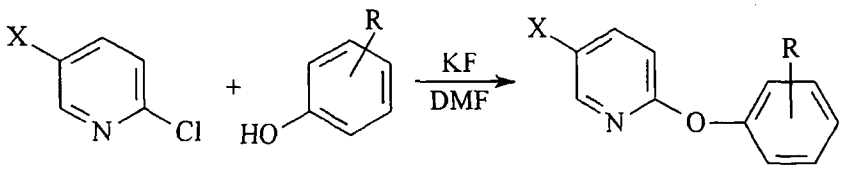
Even *tert*-butoxy pyridine derivatives were prepared by this method [158].



Unespectedly, the nitro group and not the chlorine atoms in the α-positions of the pyridine ring undergoes nucleophilic substitution by phenoxide in 2,6-dichloro-4-nitropyridine [159].

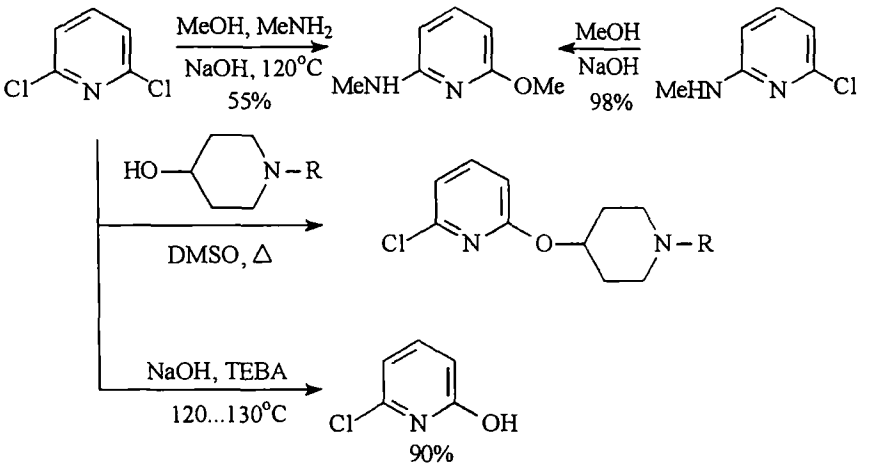


Potassium fluoride can be used as the base in the reactions of chloropyridines with phenols. This makes it possible to carry out the reaction in neutral medium [160].



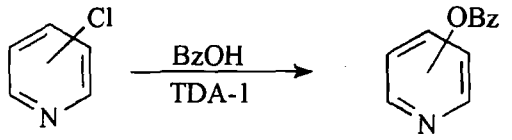
X=NO_2, CF_3 R = 2,4-Cl_2, 4-NO_2, 4-OMe, 4-$OCH(CH_3)CO_2Bu$

Nucleophilic substitution can be achieved in unactivated substrates under forcing conditions with effective catalysts [90, 92, 161].



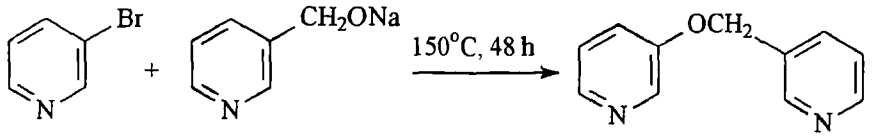
Phase-transfer catalysts give good results [162].

Tris(3,6-dioxaheptyl)amine (TDA-1) was also used to catalyze the alcoholysis of unactivated halopyridines. The yields can be very high [163]. However, the chlorine atom in 2-chloro-3-methoxypyridine could not be replaced under these conditions.



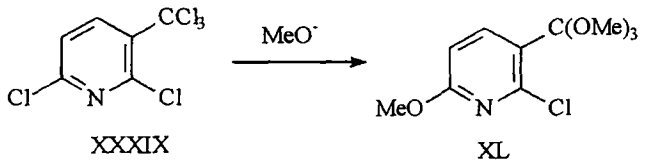
2-OBz (84%), 4-OBz (86%)

Under forcing conditions a halogen in the 3-position of an unactivated pyridine can be replaced, although in low yield [164].

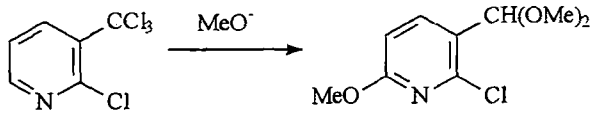


14%

The CCl_3 group, which is usually stable toward nucleophiles, undergoes interesting nucleophilic-substitution reactions if it is located in the 3-position of the pyridine ring [165]. Thus, methoxide reacts with the 2,6-dichloro derivative XXXIX to give the orthoester XL. The monochloro derivative XLI gives the acetal XLII.

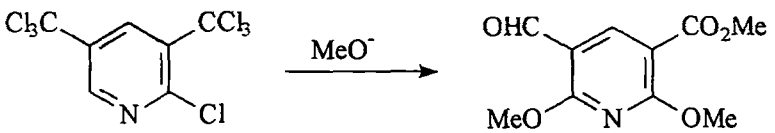


XXXIX XL



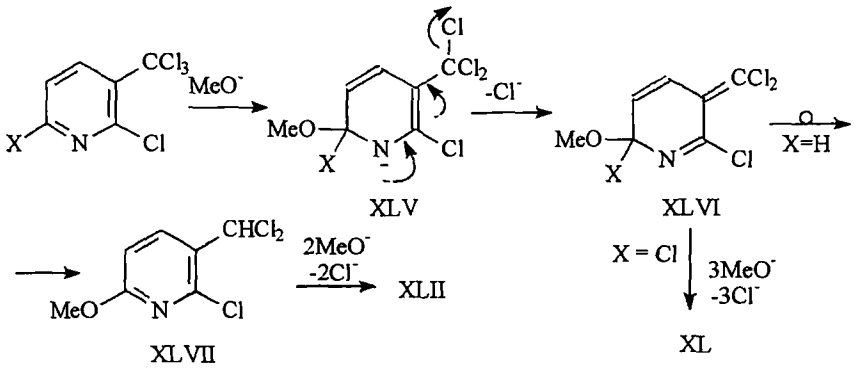
XLI XLII

Treatment of the reaction mixture with water hydrolyzes XLI and XLII to the ester and aldehyde, respectively. An analogous succession of reactions for 2-chloro-3,5-bis(trichloromethyl)pyridine (XLIII) produces the polyfunctional compound XLIV, which contains both aldehyde and ester groups:

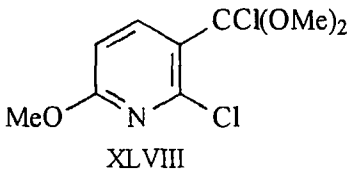


XLIII XLIV

The data suggest the following reaction scheme:

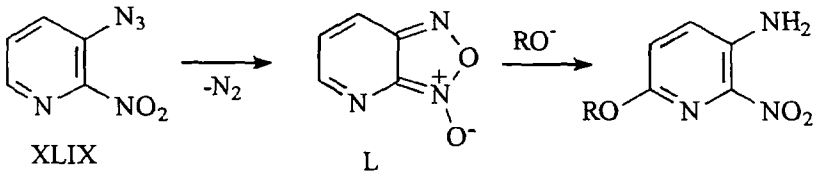


Eliminating Cl^- from the σ-complex XLV produces the intermediate XLVI. For X = Cl, XLVI becomes aromatic after attack of methoxide on the CCl_2 group. After repetition of the analogous steps, it gives the orthoester XL. Isolation of the intermediate XLVIII by quick processing of the reaction mixture provides evidence for this.



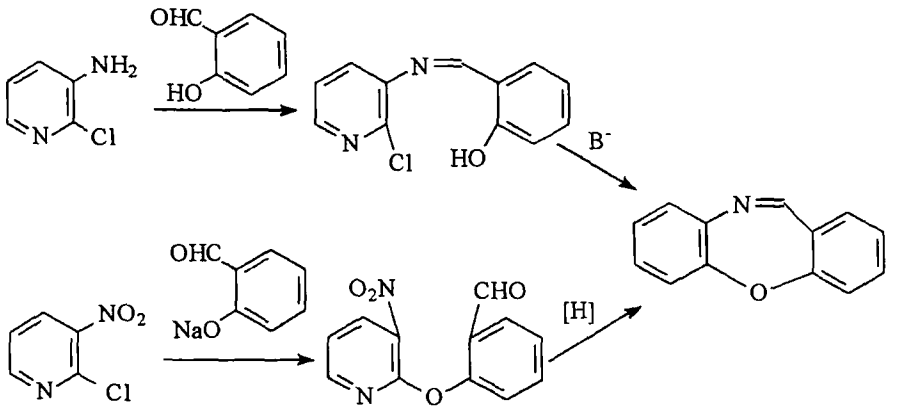
For X = H in XLVI, a [1,5]-shift of the hydrogen occurs to form XLVII, from which the acetal XLII then forms.

It is interesting that the reaction of sodium hydroxide and alkoxides with 3-azido-2-nitropyridine (XLIX) does not replace the azido group but results in nucleophilic substitution of the $H_{(6)}$ and simultaneous conversion of the azide to an amine [166]. Apparently in this instance the Meisenheimer complex aromatizes by an intramolecular hydrogen migration.

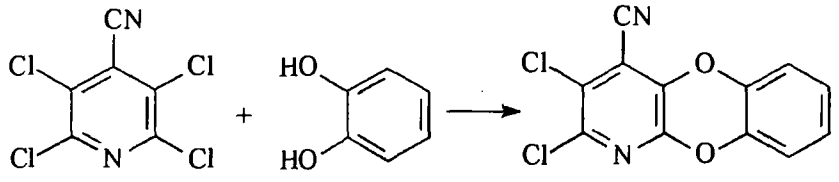


It was hypothesized that the reaction involves formation of the furoxane L, which is formed from the starting azide XLIX by heating in the absence of nucleophiles. Then reaction with nucleophiles gives 6-hydroxy(alkoxy)-2-nitro-3-aminopyridines in 80-85% yields.

Nucleophilic substitution of a halogen by phenoxides may be the first step in constructing condensed systems. For example [167]:

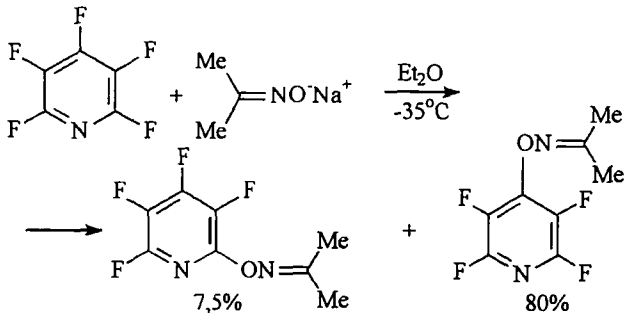


Despite the fact that tetrachloro-4-cyanopyridine reacts with nucleophiles only at the 2- or 2- and 6-positions, the reaction with pyrocatechol gives a single product in which two chlorine atoms in the 2- and 3-positions are simultaneously substituted to form the dioxinopyridine LI in >92% yield [168].

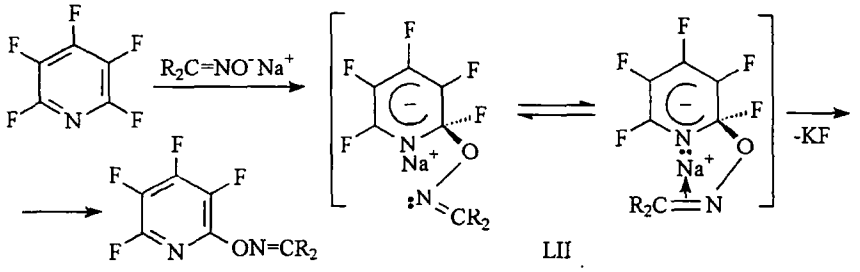


LI

Sodium oximates were also used as the O-containing nucleophiles [169]. Thus, pentafluoropyridine reacts to form products in which only one fluorine atom is substituted in the 2- or 4-position, with the latter predominating.

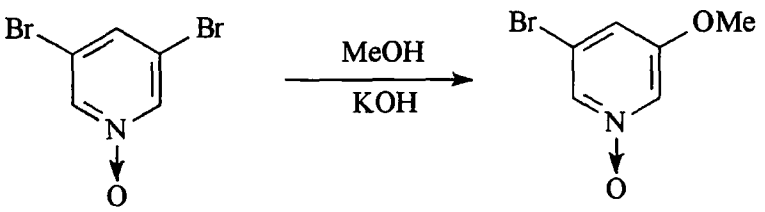


Only 4-substitution occurs in homogeneous solution in methanol or acetone, which can solvate Na^+ ions. It was suggested that the increased yield of the 2-substituted product in nonpolar aprotic solvents is due to stabilization of the σ-complex LII by Na^+.

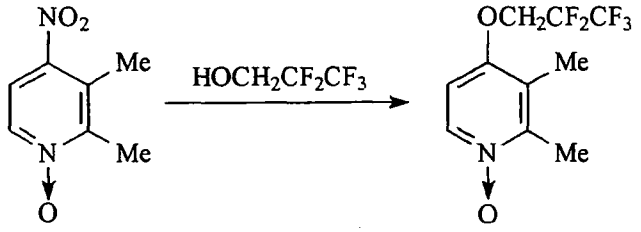


LII

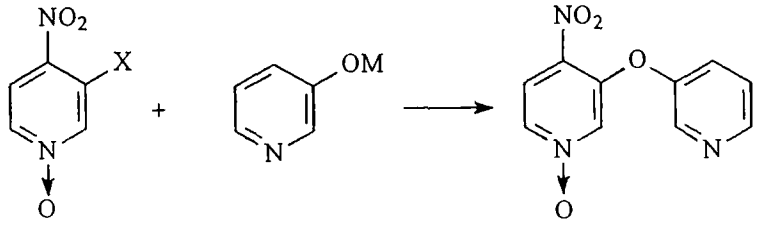
Pyridine N-oxides are known to undergo facile nucleophilic substitution. Various suitable leaving groups in the 3- and 4-positions are susceptible to substitution. For example, one of the bromine atoms in 3,5-dibromopyridine N-oxide is replaced in good yield even by reacting with KOH in methanol [170, 112].



An example of nucleophilic substitution of the nitro group in 2,3-dimethyl-4-nitropyridine N-oxide by an aliphatic alcohol is known.

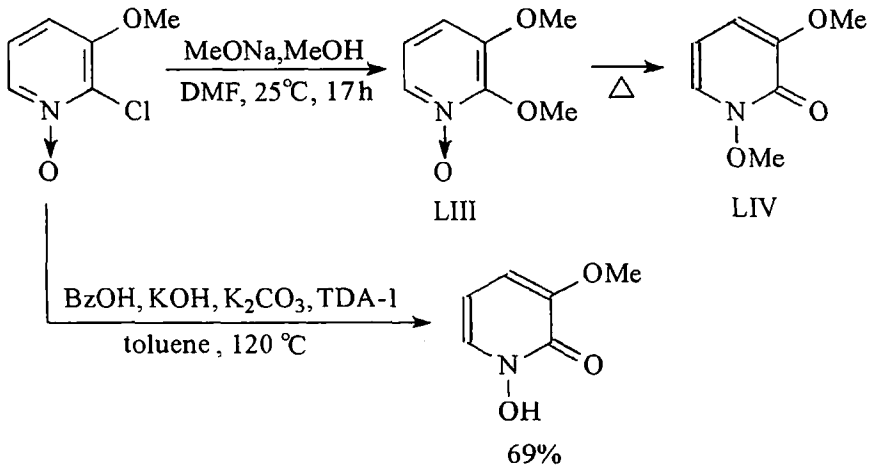


If the molecule contains both a halogen in the 3-position and a nitro group in the 4-position, then the halogen is first substituted by an O-nucleophile [171, 172].



X = F, Br; M = K, Na

Nucleophilic substitution can be used to replace a halogen in N-oxides if it cannot be accomplished in the corresponding pyridines. For example [163]:



An N-oxide of the type LIII readily rearranges into the pyridone LIV in the presence of basic reagents under forcing conditions. Therefore, the pyridone forms immediately under different reaction conditions.

Oxidation is another method besides nucleophilic substitution for forming a C–O bond in pyridines. Basic oxidation of pyridinium salts is a good preparative method for preparing pyridones. However, a mixture of two isomeric pyridones forms if a substituent is present in the 3-position. The ratio of isomers depends both on the size of group at nitrogen atom and 3-position in pyridine. For example, replacing a 3-isopropyl group by *tert*-butyl practically reverses the ratio of isomers. Increasing the size of a substituent in the 1-position increases even more the fraction of the 6-pyridone [173].

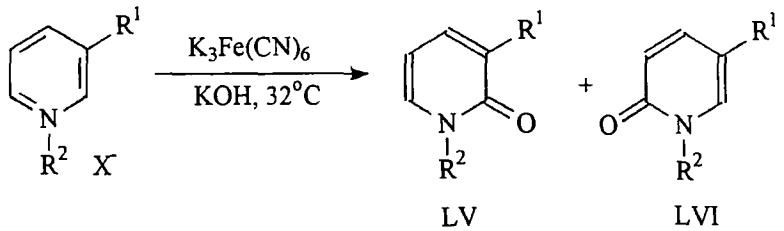
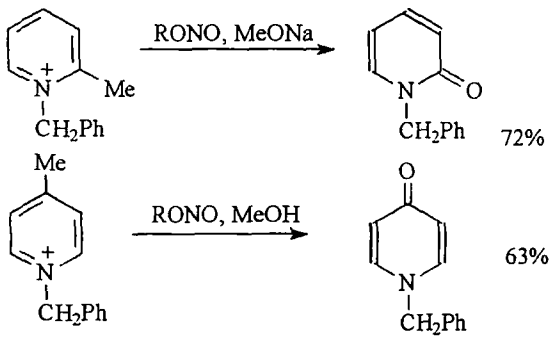


TABLE 14. Substituent Effect on Formation of Isomeric Pyridones by Oxidation of Pyridinium Salts

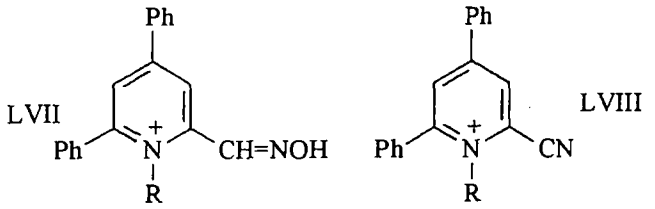
R^1	R^2	X	Total yield, %	LV	LVI
Me	Me	I	82	93	7
Me	$ArCH_2$*	Cl	68	92	8
Me	$Ar(CH_2)_2$	Br	76	94	6
Et	Me	I	86	87	13
Et	$Ph(CH_2)_2$	Br	86	85	15
Et	$Ar(CH_2)_2$	Br	71	88	12
i-Pr	Me	I	88	71	29
i-Pr	$Ar(CH_2)_2$	Br	79	71	29
i-Bu	Me	I	89	14	86
t-Bu	$PhCH_2$	Br	74	9	91
t-Bu	$Ph(CH_2)_2$	Br	65	2	98
t-Bu	$Ar(CH_2)_2$	Br	57	0	100

* Here and further in the table, Ar = 3,4-$(MeO)_2C_6H_3$

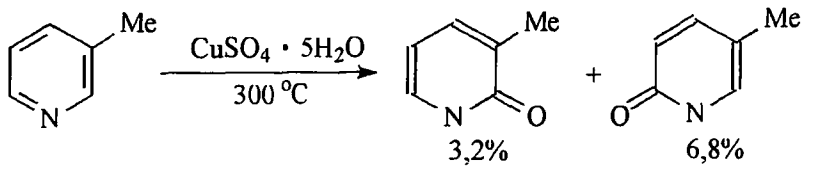
1-Substituted 2- and 4-methylpyridinium salts are oxidized by alkylnitrites and sodium methoxide to the corresponding 2- and 4-pyridones [174]:



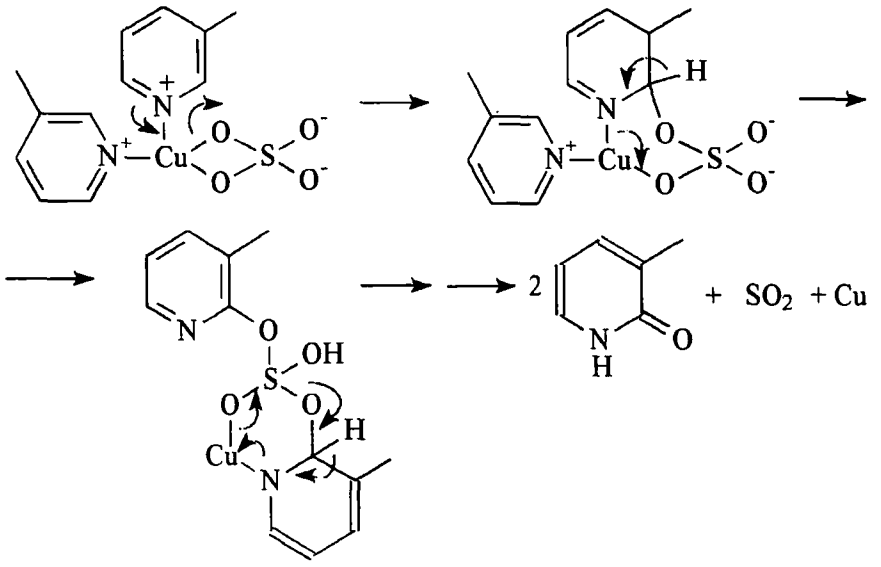
It is hypothesized that the reaction includes oximes LVII or nitriles LVIII as intermediates. This was confirmed in one instance (R = *p*-tolyl) by isolating the oxime LVII, the conversion of which into a pyridone is known.



Pyridines can also be oxidized to pyridones by copper sulfate at high temperatures [175]. Such an oxidation can only be carried out for 3- and 3,5-substituted pyridines. The alkyl substituents are destroyed for the 2- and 4-alkylsubstituted compounds.

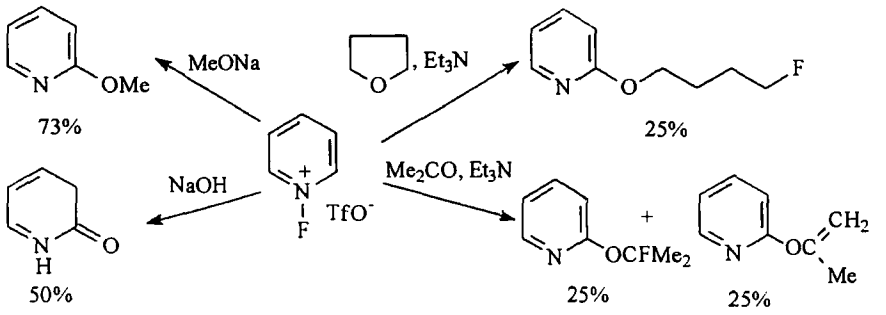


The following reaction mechanism was proposed:

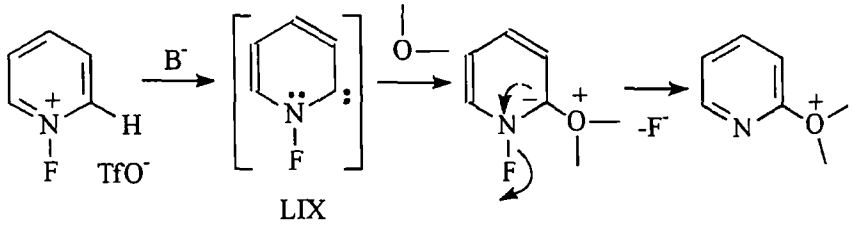


The lack of an effect from air or peroxides indicates that the process most likely does not involve free radicals.

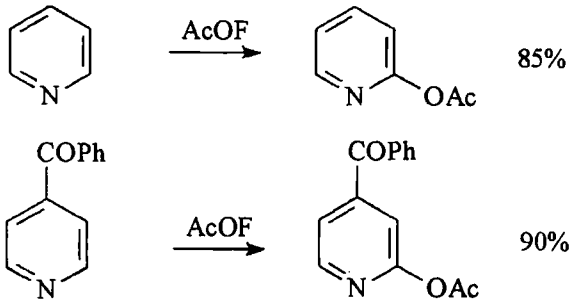
Various derivatives of 2-hydroxypyridine can be prepared by reacting triethylamine with N-fluoropyridinium triflate in various O-containing solvents [176].



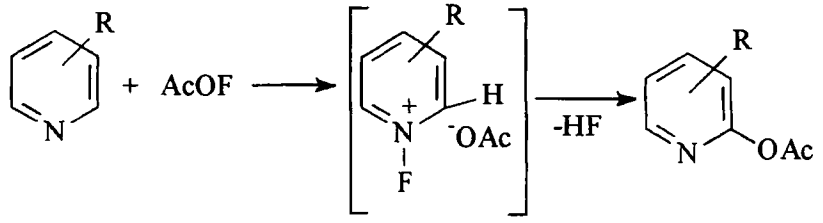
Apparently the carbene LIX is first formed and then reacts with nucleophiles.



Treatment of pyridines with acetylhypofluorite in an inert solvent produces 2-acetoxypyridines, which are easily hydrolyzed to pyridones [177].



3-Picoline gives a mixture of equal amounts of the 2- and 6-acetoxy derivatives. However, the 2-isomers are exclusively formed from the 3-acetyl- and 3-fluoropyridines [178]. It was proposed that the ion pair LX is first formed. Then, HF is eliminated to give the aromatic system:

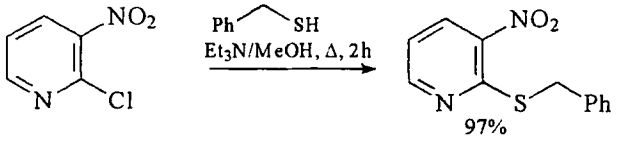


LX

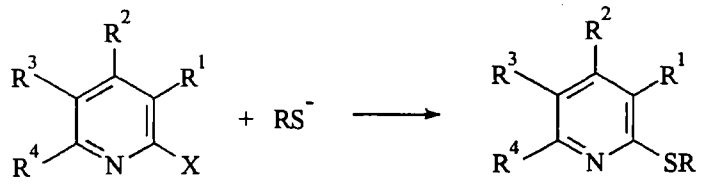
Under these conditions 2-benzoyl-, 2-chloro-, and 2-cyanopyridines do not react because an N–F bond is not formed owing to the reduced basicity of the pyridine ring. 2-Phenylpyridine gives the 6-acetoxy derivative in 75% yield [178]. The corresponding 2-alkoxy derivatives are formed in about 70% yield if the reaction is performed in methanol or ethanol [179].

3.2. Formation of Pyridine–S, –Se, and –Te Bonds

An activated halogen atom is usually easily replaced by thiolates [180]:



Other examples of similar substitution reactions of 2-halogens are given in Table 15.



The reaction of sodium disulfide with 2-chloro-3-nitropyridine gives the disulfide in good yield. The product can then be converted to the sulfenyl chloride [191]:

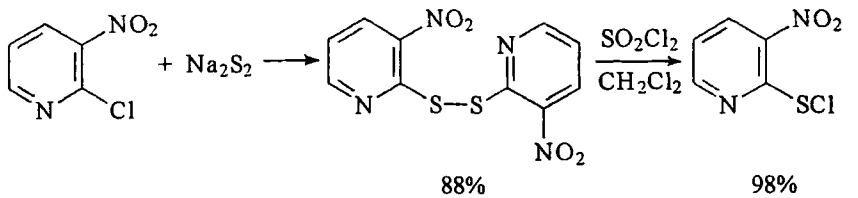
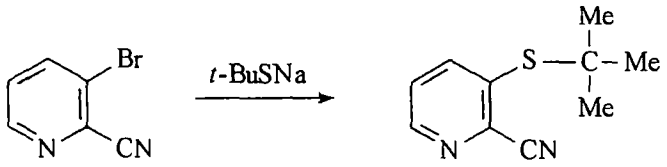


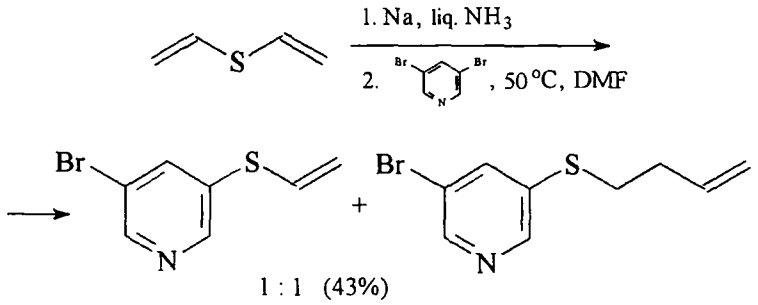
TABLE 15. Substitution of Activated Halogen by Various Thiolates

R^1	R^2	R^3	R^4	X	R	Yield, %	Ref.
NO_2	H	H	H	Cl	H	72	[181]
COOH	H	Me	H	Cl	H	82...85	[182]
NO_2	H	H	H	Cl	*t*-Bu	32, 58	[183, 184]
NO_2	H	H	H	Cl	CH_2COOEt	64	[185]
NO_2	H	NO_2	H	Cl	CH_2COOEt		[186]
H	H	NO_2	H	Cl	4-Cl-C_6H_4		[187]
Cl	H	H	H	Cl	$PhCH_2$		[188]
NO_2	H	H	H	Cl	$PhCH_2$		[189]
H	Me	H	H	Br	2,5-Me_2-$C_6H_3CH_2$		[190]

An activated halogen in the 3-position can also be easily replaced in almost quantitative yield [192]:

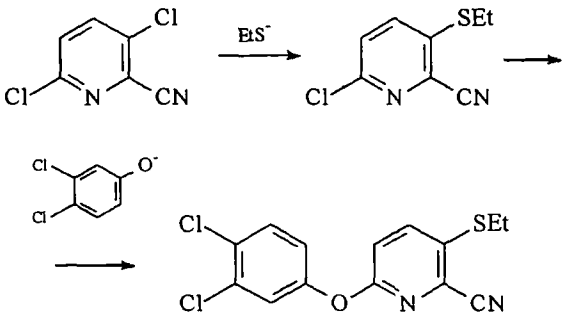


A vinylthiolate was also used in a similar reaction [193]:



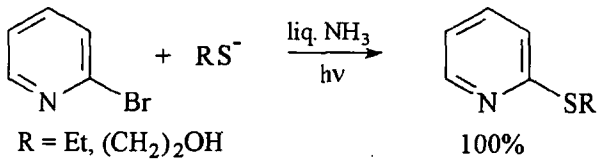
The formation of butenylthiopyridine was explained by rearrangements occuring in parallel with the cleavage of the divinyl sulfide by sodium.

A chlorine atom in the 3-position of 3,6-dichloro-2-cyanopyridine is even more labile than one in the 6-position and is substituted first [194]:

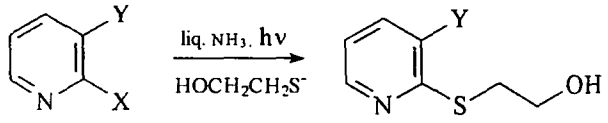


The reactivity of the halogen decreases in the order I ~ Br >> Cl ~ F for the reaction of 2-halopyridine with thiophenoxide in DMF at 80°C [195]. The reaction is inhibited by azobenzene and benzoquinone. This suggests that the mechanism involves a radical chain with one-electron transfer ($S_{RN}1$). The results of the reaction with 3-bromopyridine suggest an aryne mechanism.

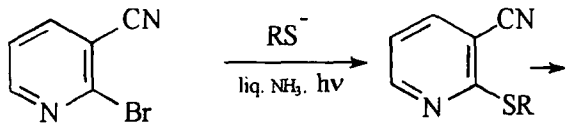
Irradiation with UV light successfully promotes $S_{RN}1$ reactions in liquid ammonia [196]. Thus, 2-ethylthiopyridine forms in quantitative yield.



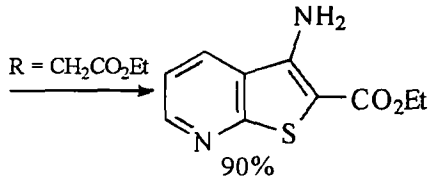
Both activated and unactivated substrates react in this manner:

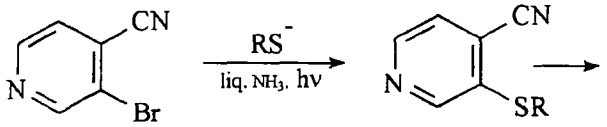


X = Cl, Y = NH_2 45%
X = Br, Y = OMe 60%

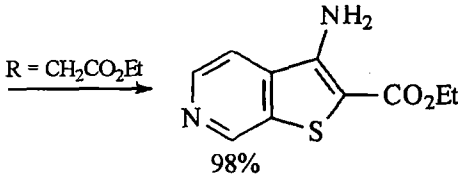


R = Et, CH_2CH_2OH, $CH_2CH_2CO_2Et$, CH_2Ph

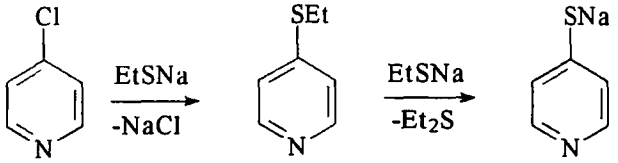




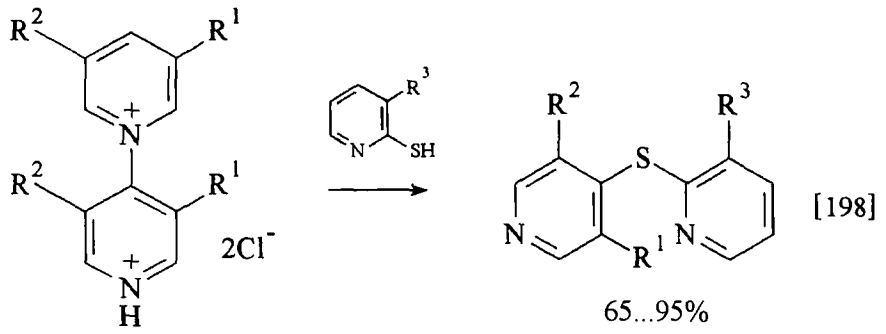
R = Et, CH_2CH_2OH, $CH_2CH_2CO_2Et$



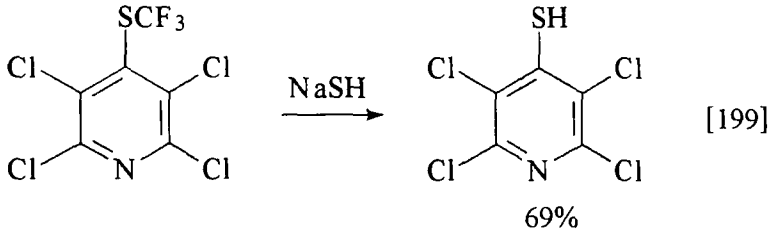
Boiling 4-chloropyridine with sodium ethyl sulfide in DMF gives 4-pyridinethiol in 70% yield owing to cleavage of the initially formed 4-ethylthiopyridine [197]:



Other leaving groups besides a halogen can also be used:

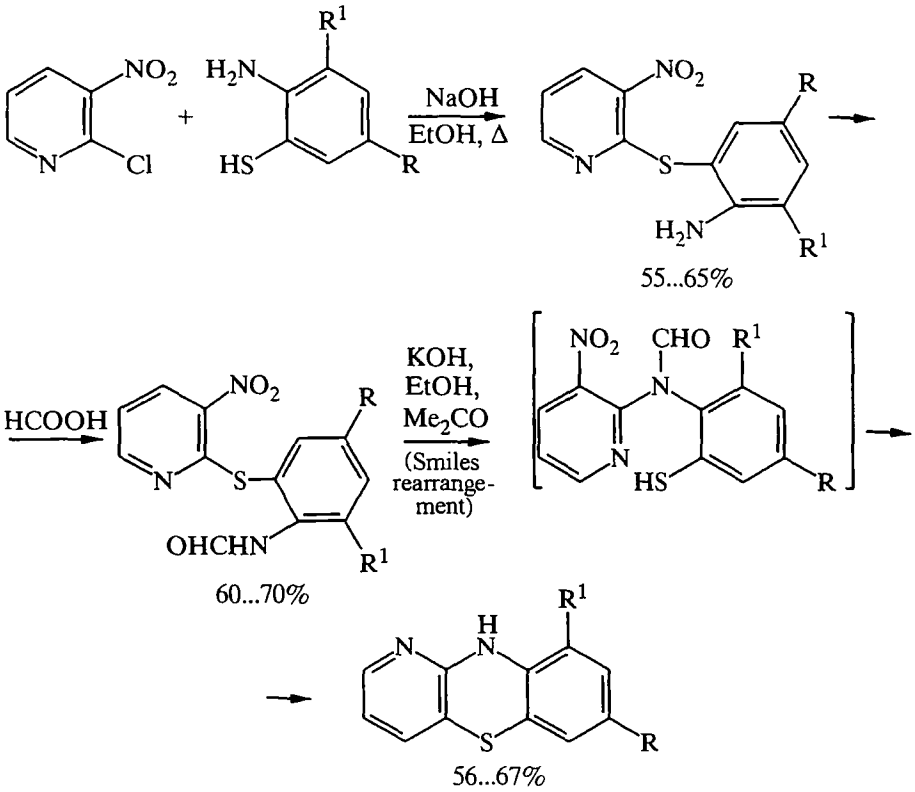


[198]



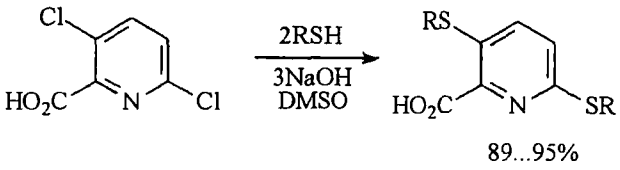
[199]

The chlorine atom and nitro group in 2-chloro-3-nitropyridine can be successively replaced by reacting it with *ortho*-aminothiophenols [200]:



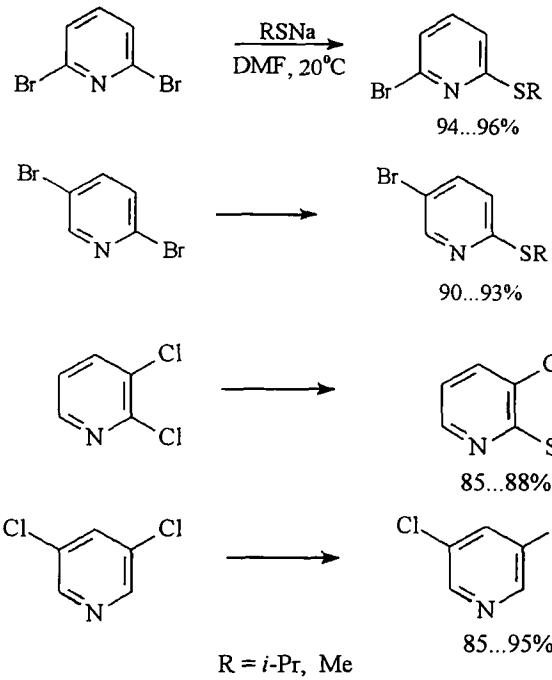
R = Br, MeO, EtO; R^1 = H, Me

Dihalopyridines are easily disubstituted by reacting them with thiolates generated from the corresponding thiols in superbasic solutions [201]:



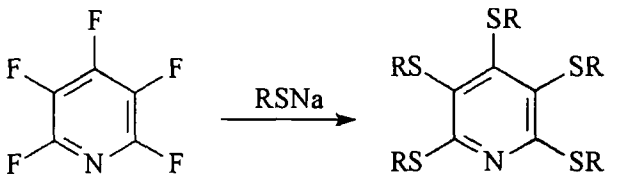
89...95%

The reaction can often be stopped at the monosubstituted stage by using equimolar amounts of thiolate [202]:



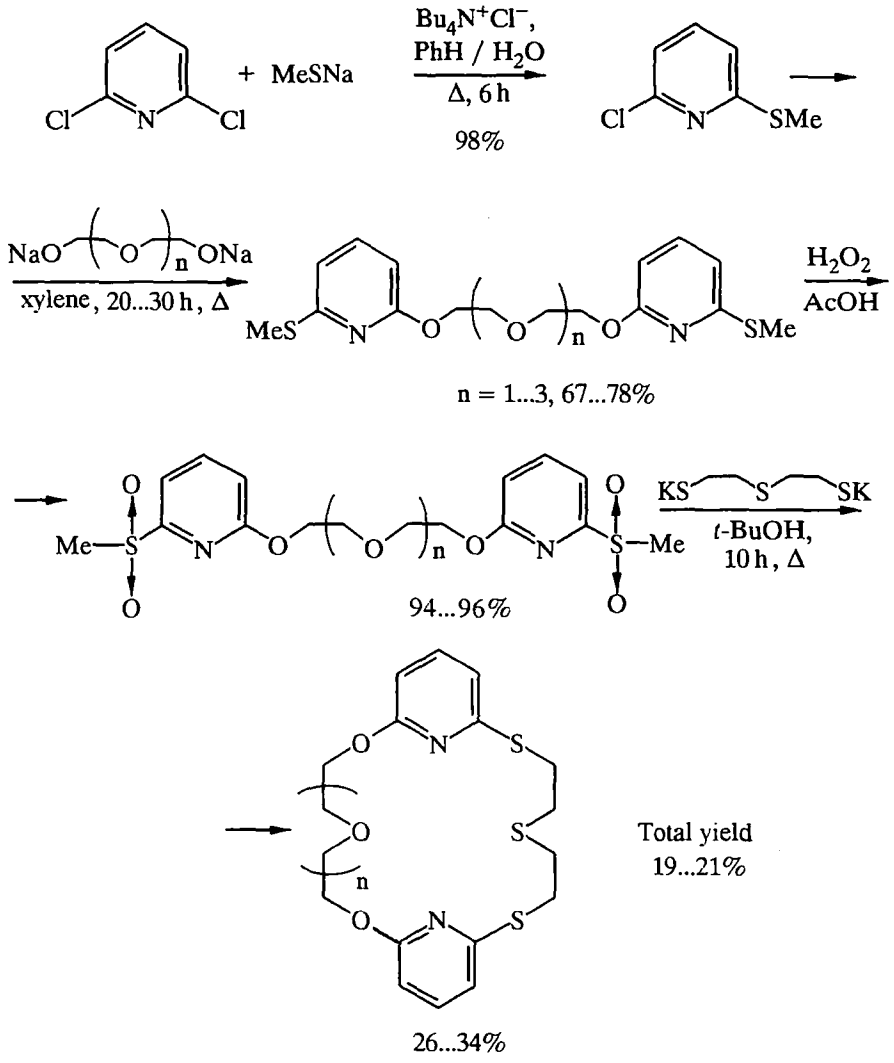
These dihalo compounds give the disubstituted products in 73-90% yields if a four-fold excess of the thiolate is used and the reaction temperature is raised to 80°C.

All five fluorine atoms can be replaced in pentafluoropyridine [202].

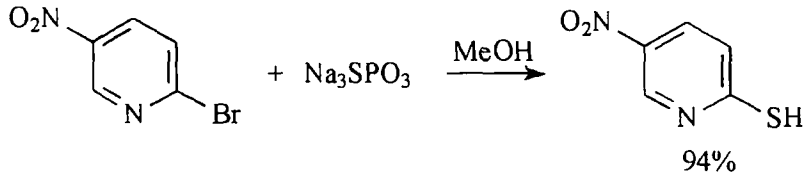


R = Me (96%), *i*-Pr (95%)

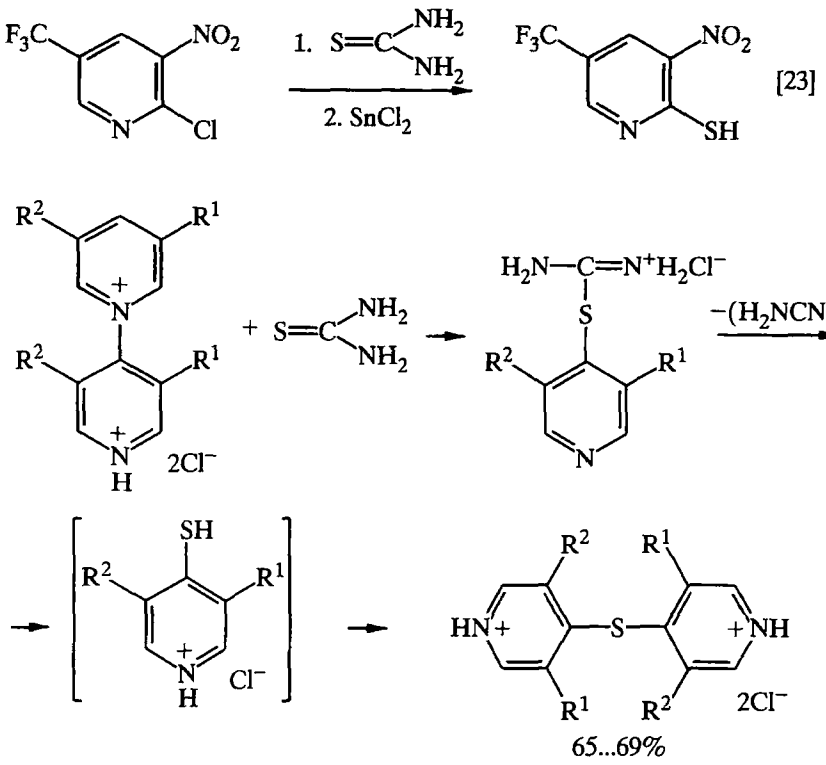
The reaction should be carried out under phase-transfer catalysis conditions in order to substitute only one halogen in 2,6-dihalopyridines [203, 204]. The second halogen atom is then easily replaced by other O- or S-nucleophiles, which was used to synthesize macrocycles:



Other S-containing nucleophiles in addition to thiolates have been used to form C–S bonds through nucleophilic substitution reactions. The products formed by substitution by sodium thiophosphate are easily hydrolyzed to the pyridinethiols [205].



Thiourea has been successfully used in nucleophilic substitution reactions, including the synthesis of pyridinethiols [206, 198].



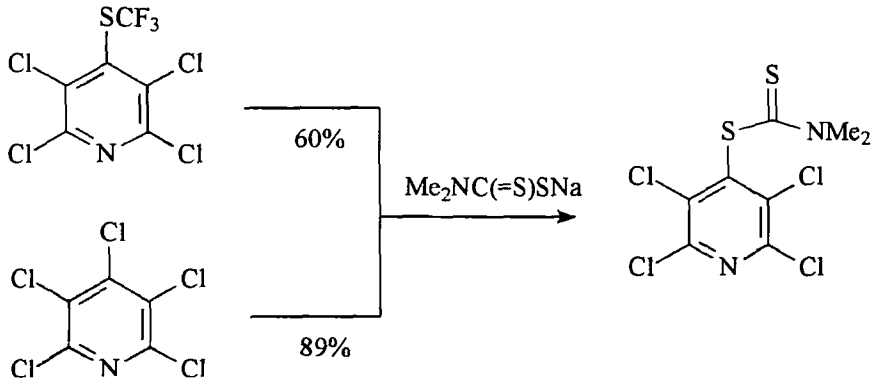
[23]

[15]

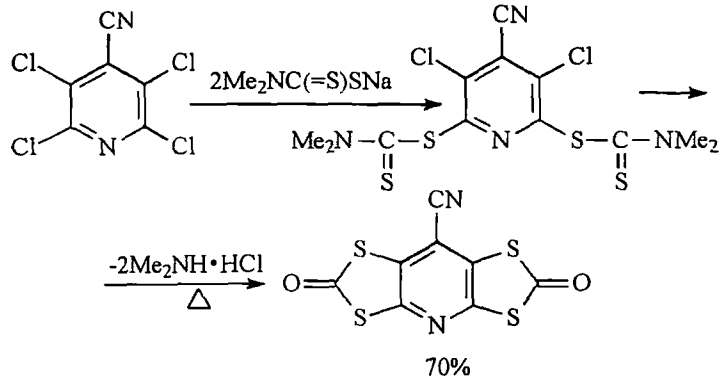
65...69%

R^1 = H, Me, Et; R^2 = H, Me

A good nucleophile is N,N-diethyldithiocarbamate [199, 207].

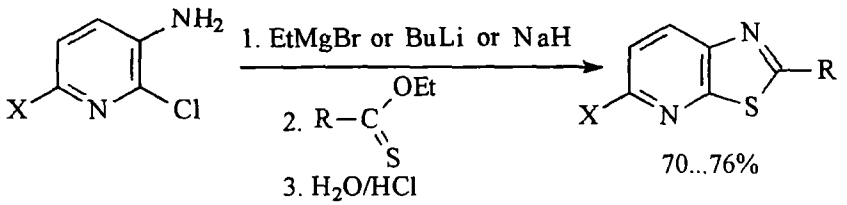


If the 3-position in the pyridine is also activated, then the reaction with N,N-dimethyldithiocarbamate can lead to further cyclization [207]:

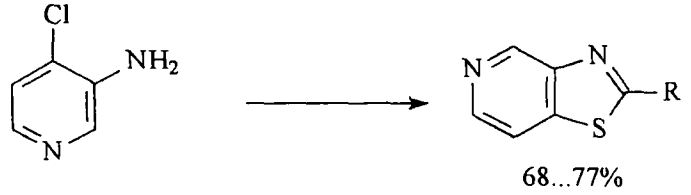


70%

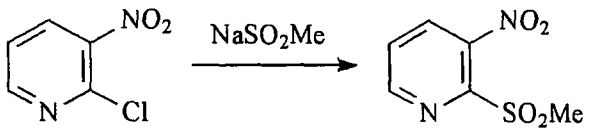
Thiazolopyridines are formed in strongly basic media by reacting *o*-chloroaminopyridines and thioesters [208].



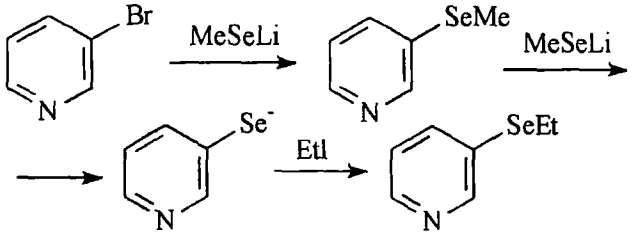
X = H, Cl; R = Ph, *p*-$CH_3C_6H_4$, Me, PhCH=CH



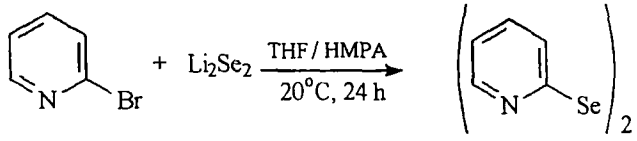
The use of sodium methanesulfonate to synthesize pyridinesulfones has also been reported [209].



Selenides react under nucleophilic-substitution conditions similarly to thiolates. Thus, PhSeNa in DMF reacts with 2- and 3-bromo-, 4-chloro-, 2,6-dibromo-, 2,5-dibromo-, 2,3-dichloro-, and 3,5-dichloropyridines to give the monosubstitution products in good yields (58-92%) [210]. The disubstituted products can be obtained from the dihalopyridines by using an excess of PhSeNa and more forcing reaction conditions. 2-Bromo- and 4-chloropyridine react smoothly with lithium methylselenide to give the corresponding selenides in good yields. For 3-bromopyridine, the 3-pyridylselenide ion forms, as demonstrated by treatment of the reaction mixture with ethyl iodide.

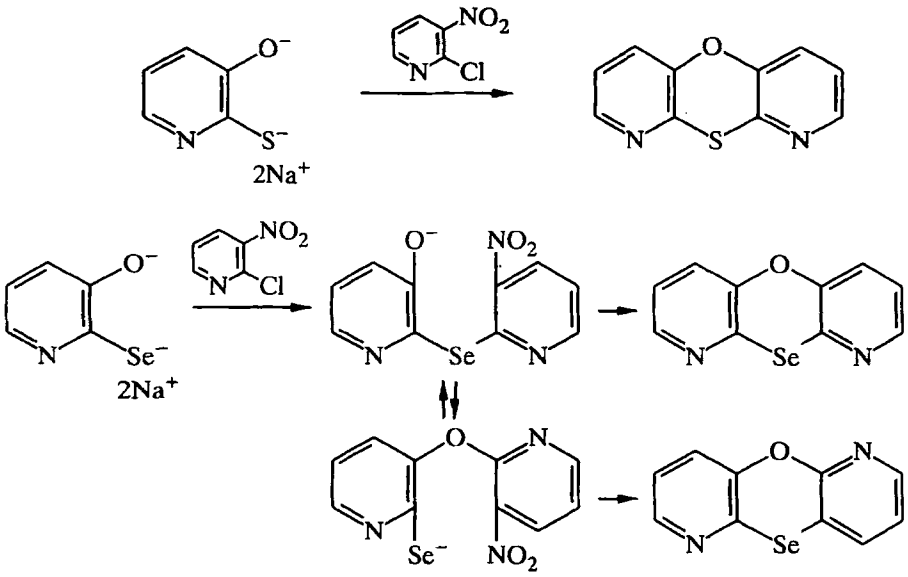


The reaction of selenium with lithium in THF in the presence of phenylacetylene as a catalyst gives lithium diselenide, which reacts with 2-bromopyridine to form the corresponding diselenide [211].

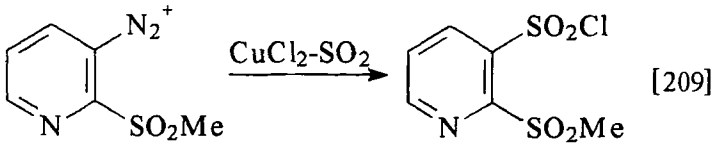


54%

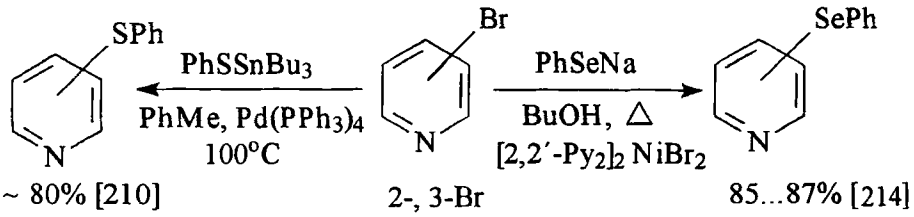
In contrast with the sulfur analog, the dianion obtained from 3-hydroxypyridineselen-2-one reacts with 2-chloro-3-nitropyridine to give a mixture of isomeric condensed heterocycles [212].



In several instances catalysis by transition metals was used to form C–S and C–Se bonds using nucleophilic substitution:

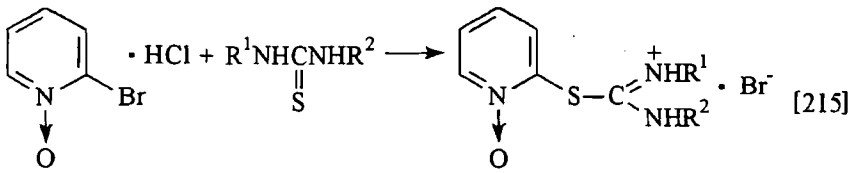


[209]



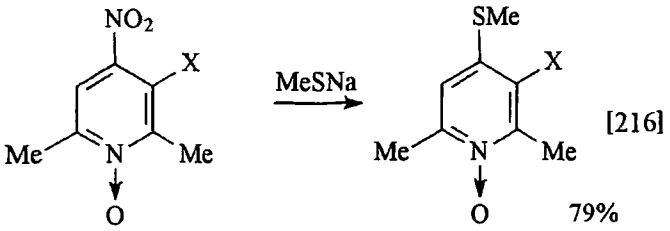
~ 80% [210] 2-, 3-Br 85...87% [214]

N-Oxides of halosubstituted pyridines react with S-nucleophiles owing to the additional activation [215, 216].



[215]

R^1 = H, Me, Et, Ph; R^2 = H, Alk, Ph, 2-Py; R^1,R^2 = $(CH_2)_2$, $(CH_2)_3$

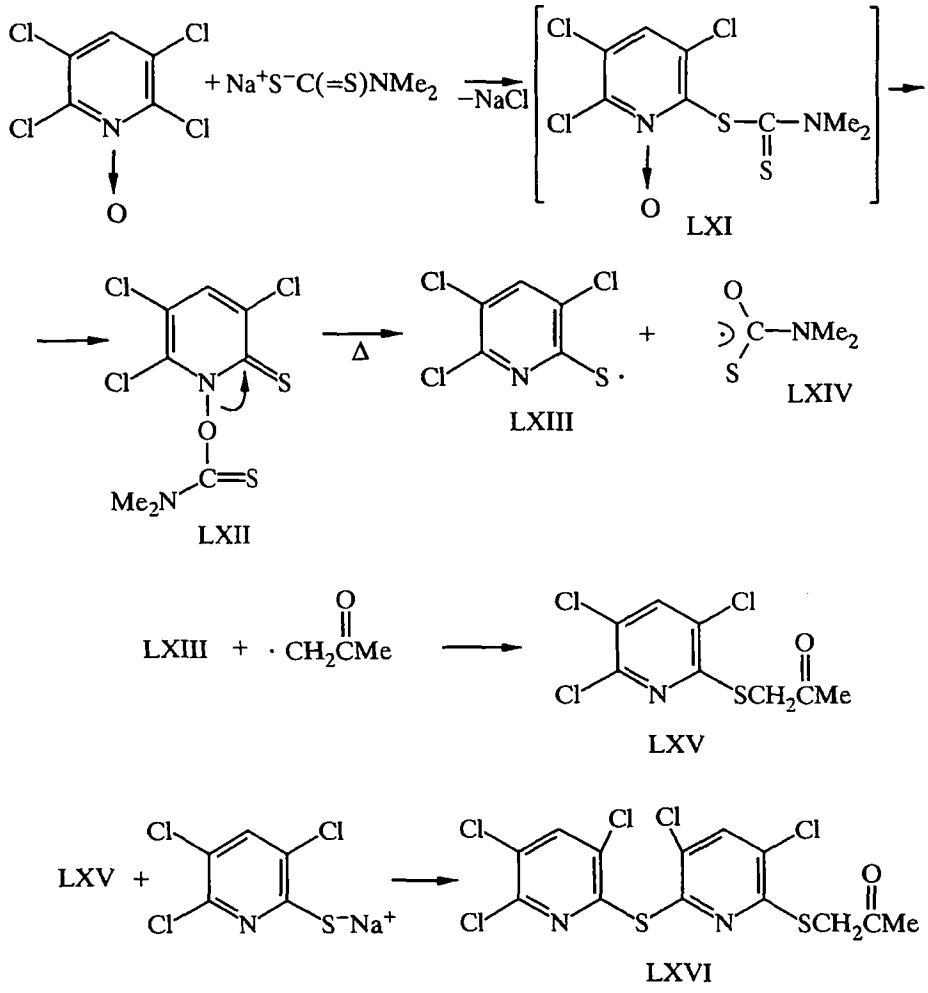


[216]

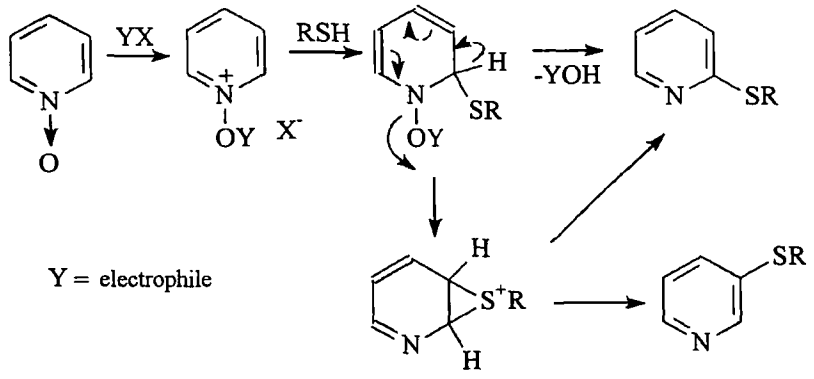
79%

X = Cl, Br

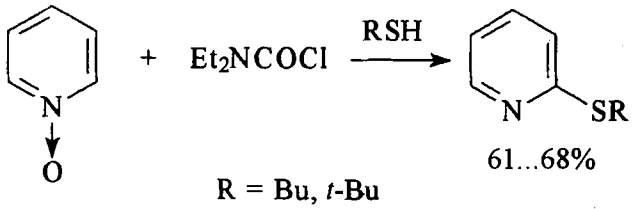
Interesting conversions occur during the reaction of sodium N,N-dimethyldithiocarbamate with 2,3,5,6-tetrachloropyridine N-oxide in acetone [217, 218]. The product of nucleophilic substitution LXI rearranges into the thermodynamically more stable LXII, which decomposes homolytically upon heating into the radicals LXIII and LXIV. The reaction of LXIII with the acetonyl radical, which is formed from acetone, produces LXV, which can react further with the trichloropyridinethiolate anion to give LXVI. The last product was isolated as the main product in 25% yield.



Pyridine sulfides are formed by a deoxygenative nucleophilic substitution during the reaction with thiols of pyridine N-oxides acylated on the oxygen atom. The substitution occurs mainly at the 2-position although a certain amount of the 3-substituted isomer is almost always obtained. The reaction mechanism is as follows [219, 220]:

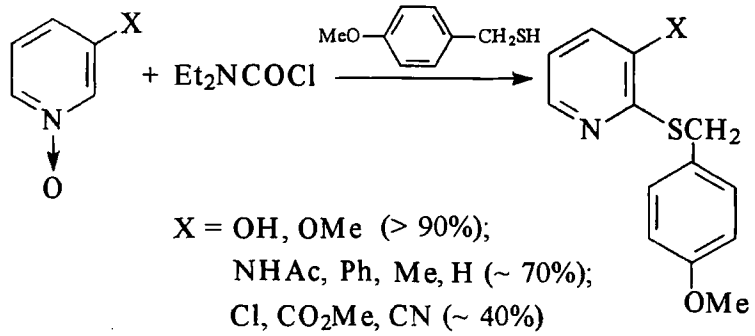


The following reactions provide examples of similar transformations:



[219]

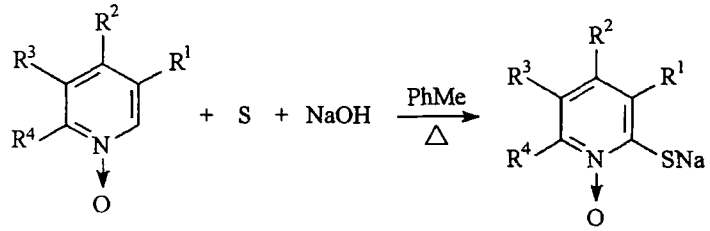
R = Bu, *t*-Bu



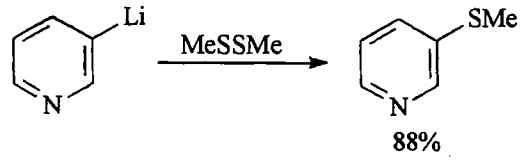
[220]

X = OH, OMe (> 90%);
NHAc, Ph, Me, H (~ 70%);
Cl, CO_2Me, CN (~ 40%)

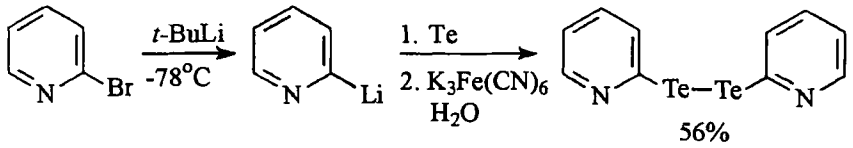
Yet another method for forming C–S bonds using pyridine N-oxides as substrates is the oxidation with elemental sulfur under basic conditions to form 2-pyridinethiol N-oxides [221-223].



If metallated pyridine derivatives are used as substrates, electrophilic substitution can be used to form C–heteroatom bonds. The metallated pyridine derivatives readily react with disulfides and diselenides to form sulfides and selenides, respectively [19, 224-226]. For example:



Even pyridine ditelluride was prepared in this manner [227]:



The literature data presented in the review are evidence of the great synthetic capabilities of direct functionalization of the pyridine ring to prepare a wide variety of pyridine derivatives that contain C(pyridine ring)–heteroatom bonds.

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