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FUNCTIONALIZATION OF PYRIDINES.*
2.† SYNTHESIS OF ACYLPYRIDINES, PYRIDINECARBOXYLIC ACIDS, AND THEIR DERIVATIVES. REVIEW

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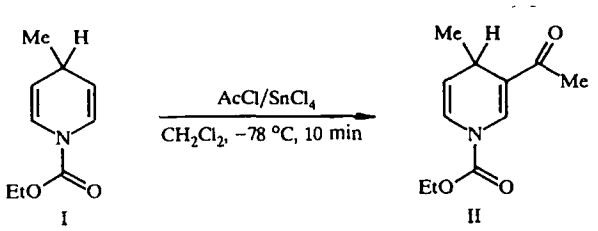
Advances in the synthesis of acylpyridines, pyridinecarboxylic acids, and their derivatives involving direct functionalization of the pyridine ring and substituent modification over the past 15 years are reviewed.

The present review is the second part of a series of reviews on the functionalization of the pyridine ring. In this part, we review the preparation of acylpyridines, pyridinecarboxylic acids, and their derivatives involving both functionalization of the pyridine ring and modification of ring substituents. We should note the general nature of most of the methods examined for the preparation of the various pyridine derivatives containing a wide range of substituents in addition to the indicated functional groups. The limitations of these methods will be noted in each individual case.

1. ACYLPYRIDINES

1.1. Use of Electrophilic Reactions

One of the generally accepted methods for introducing acyl groups into aromatic and heteroaromatic rings is direct Friedel–Crafts acylation. However, the inertness of pyridine relative to electrophilic substitution and its capacity to form complexes with Lewis acids, which further increases the electron deficiency of the ring, makes the use of this method for pyridine derivatives impossible without prior structural modifications. A convenient such modification of the pyridine ring involves prior formation of 1-acyl-, 1-alkoxy-, or 1-aryloxycarbonyldihydropyridines, which are readily available through the Grignard reaction with the corresponding pyridinium salts [1]. Indeed, since the electron density in the β-position of the enamine system of 1-ethoxycarbonyl-1,4-dihydropyridines is enhanced, while its complexation capacity is reduced to zero due to the electron-withdrawing substituent at the nitrogen atom, the acylation of 1-ethoxycarbonyl-4-methyl-1,4-dihydropyridine (I) using acetyl chloride in the presence of $SnCl_4$ proceeds at $C_{(3)}$ in the pyridine ring [2].



I II

*Dedicated to Prof. A. Katritzky on the occasion of his seventieth birthday.
†For Communication 1, see [1].

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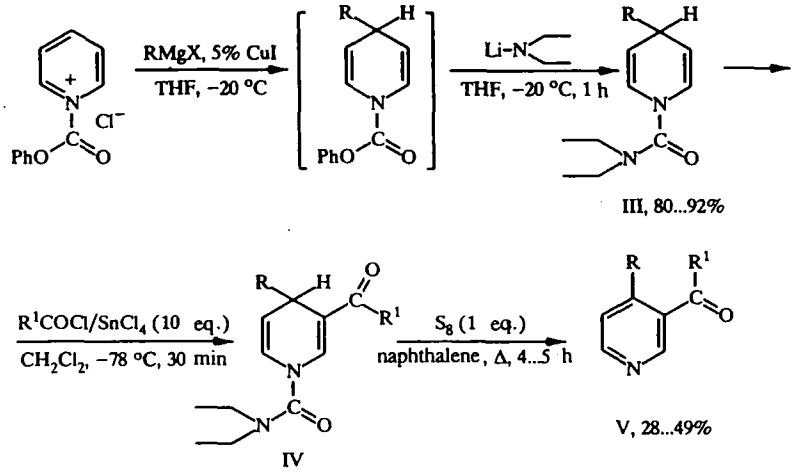
TABLE 1. Friedel–Crafts Acylation of 1-Dialkylcarbamoyl-1,4-dipyridines III

R	R^1	Yield, %
Bu	Me	38
Bu	Et	46
Bu	Pr	42
Bu	*i*-Pr	30
c-C_6H_{11}	Me	49
c-C_6H_{11}	Pr	43
c-C_6H_{11}	*i*-Pr	28
Ph	Me	28
Me	Et	36

TABLE 2. Acylation of 3- and 4-Trimethylstannylpyridines [6]

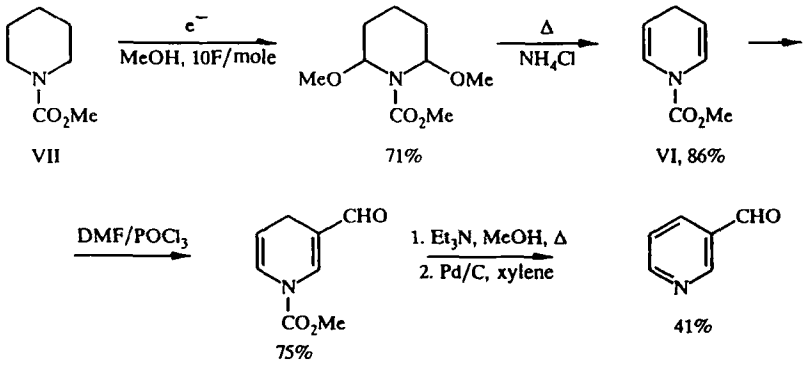
Pyridyl	RCOCl	Catalyst	Reaction time, h	Yield, %
Py-3	*c*-C_6H_{11}	XIa	8	68
Py-3	Ph	XIa	8	67
2-MePy-3	*c*-C_6H_{11}	XIa	8	67
2-MePy-4	Ph	XIa	8	60
2,6-Me_2Py-4	*c*-C_6H_{11}	XIa	8	73
2,6-Me_2Py-4	Ph	XIa	8	70
Py-4	*c*-C_6H_{11}	XI b	3	86

However, the PMR spectral data indicated that the yield of II does not exceed 50% due to the products of the decomposition of dihydropyridine I by Lewis acids [2]. 1-Dialkylcarbamoyl-1,4-dipyridines III are more stable and are better substrates for the Friedel–Crafts reaction. A "one-pot" synthesis has been proposed for the preparation of starting reagents III according to the following scheme:

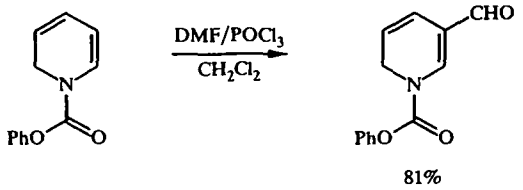


The resultant 3-acyl-1,4-dihydropyridines may be readily aromatized to the corresponding 3-acylpyridines by using various oxidizing agents. Although the overall yields of 4-substituted 3-acylpyridines V do not exceed 49% (Table 1), this three-step process is rather convenient and is an example of the indirect Friedel–Crafts acylation of the pyridine ring [2].

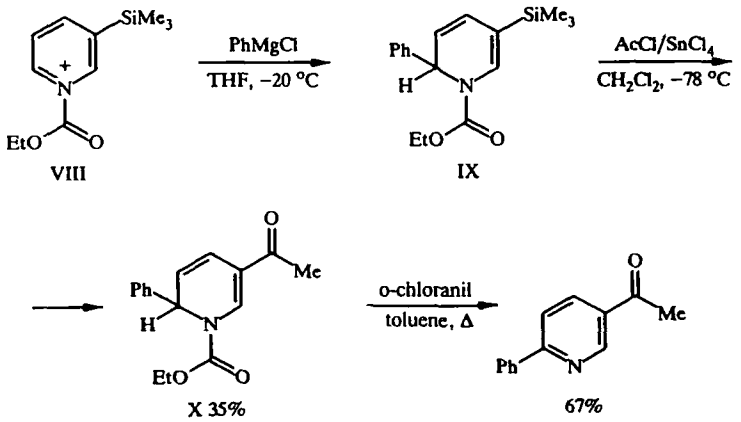
Analogous starting reagents were obtained using the Vilsmeier reaction. An interesting method for obtaining a substrate for the synthesis of 3-formylpyridine, namely, enecarbonate VI, involves the anodic demethoxylation of carbamate VII [3]:



The regioselective formylation of unsubstituted 1-phenoxycarbonyl-1,2-dihydropyridine at $C_{(5)}$ has also been reported [4]:



The use of this method for the synthesis of 2-substituted 5-acylpyridines is hindered by the instability of the 1,2-dihydro species toward Lewis acids, which is more pronounced than for 1,4-dihydropyridines, and the lack of regioselectivity in the synthesis of the starting 2-substituted 1,2-dihydropyridines through the Grignard reaction. These difficulties may be overcome by using 3-trimethylsilyl-1-ethoxycarbonylpyridinium salts VIII as the starting reagents [2, 5]:



The addition of phenylmagnesium bromide proceeds regioselectively at $C_{(6)}$ due to the trimethylsilyl group at $C_{(3)}$ in VIII. Dihydropyridine IX, which is activated toward electrophilic attack by a silicon atom, undergoes acylation–deacylation to give X, which aromatizes by means of chloranil to give 5-acetyl-2-phenylpyridine.

In contrast, use of the bulky triisopropylsilyl group leads not to *ipso*-substitution but rather to acylation at $C_{(3)}$, probably due to steric hindrance. Thus, the corresponding 3-formyl-1,2-dihydropyridine is formed with retention of the trialkylsilyl group in very high yield under Vilsmeier reaction conditions [5].

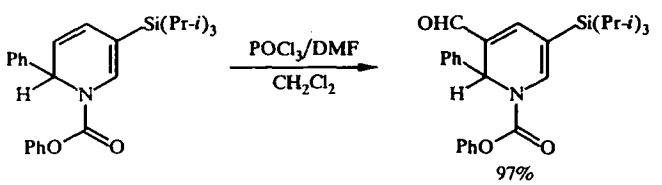
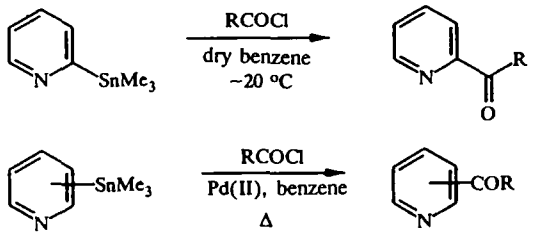


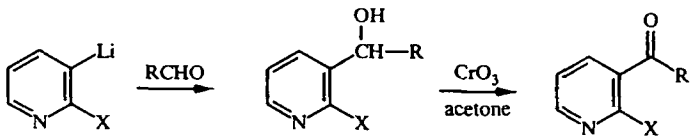
TABLE 3. (α-Carboxybenzoyl)pyridines

XVIII, XIX	R^1	R^2	R^3	Yield, %			
				XVI	XVIII	XVII	XIX
a	OMe	H	H	69	92	85	89
b	H	OMe	H	63	85	77	89
c	H	Cl	H	71	91	90	93
d	H	H	OMe	19	95	6	95

Not only trialkylsilyldihydropyridines may undergo electrophilic *ipso*-acylation but also other heteroorganic pyridine derivatives. For example, 2-trimethylstannylpyridines [6-9] react with acid chlorides to give the corresponding 2-acyl derivatives in good yield, while the use of Pd(II) derivatives — $Pd(PPh_3)_2Cl_2$ (XIa) or $Pd(PPh_3)_2(COC_6H_4)_2$ (XIb) — as catalysts is required for 3- and 4-trimethylstannyl derivatives (Table 2).



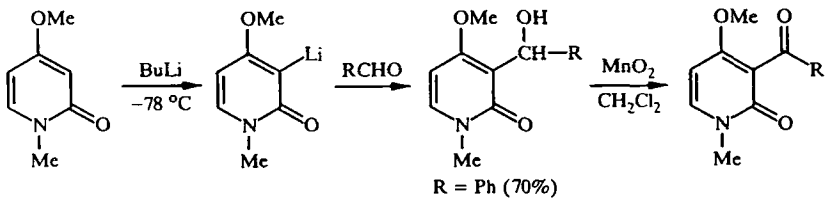
The use of lithiated pyridines to obtain acyl derivatives involves the question of the regioselectivity of the lithiation of the pyridine ring, which was examined in detail in Part I of our previous review [1, section 4]. In contrast to other heteroorganic derivatives of pyridine, the acylpyridines examined in most studies devoted to the use of lithiated pyridines were obtained in a two-step process featuring the initial reaction of the lithiated pyridines with carbonyl compounds and subsequent oxidation of the carbinols obtained [10-12] rather than a direct reaction using acyl halides as the reagents. Thus, 2-halopyridines are lithiated by lithium dialkylamides at $C_{(3)}$ without halogen−lithium exchange [10, 12], which yields 2-halo-3-acylpyridines through the route indicated above:



XII a X = Cl, b X = F, c X = Br, R = H

2-Fluoro-3-acylpyridines XIIb were obtained using this scheme in yields: R = Me (84%), Ph (82%), 2-thienyl (81%), 2-methoxyphenyl (88%), 4-methoxyphenyl (88%), and 2-nitrophenyl (79%) [11].

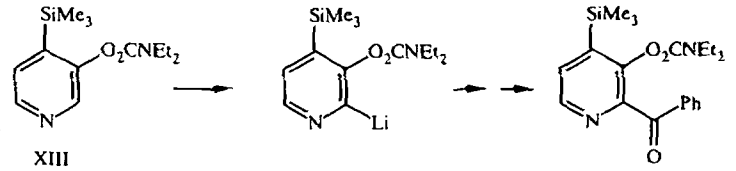
3-Acyl derivatives of 1,4-disubstituted 2-pyridones were analogously obtained [13]:



R = Ph (70%)

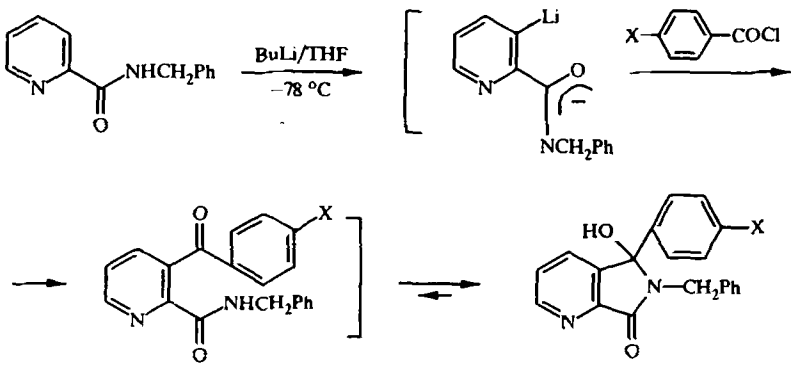
R = Ph (99%), R = 2-butenyl (26% overall yield without separation of the alcohol)

The metallation of N,N-diethyl-O-[(4-trimethylsilyl)-3-pyridyl]carbamate (XIII) proceeds selectively at $C_{(2)}$, which permits the preparation of polysubstituted pyridine derivatives containing an acyl group [14].



XIII

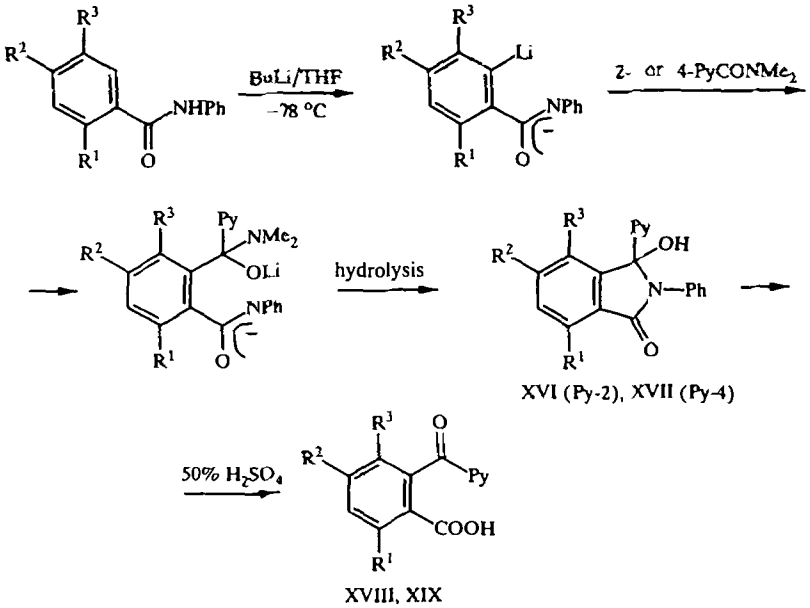
Only one example of the direct preparation of substituted 3-benzoylpyridines by the action of benzoyl chlorides on lithium has been reported, namely, the lithiation of 2-(N-benzylcarbamoyl)pyridine by butyllithium followed by treatment with the corresponding acid chlorides to give 3-benzoylpyridines XIV, although these 2,3-disubstituted pyridines undergo spontaneous cyclization to give stable bicyclic systems XV [15], i.e., ketones XV, which are subject to ring–chain tautomerism, exist predominantly as the tautomeric cyclic form, 7-aza-3-hydroxy-3-aryl-1-isoindolinone.



XIV a-c XV a-c

XV a X = H (80%), b X = Cl (82%), c X = Me (89%)

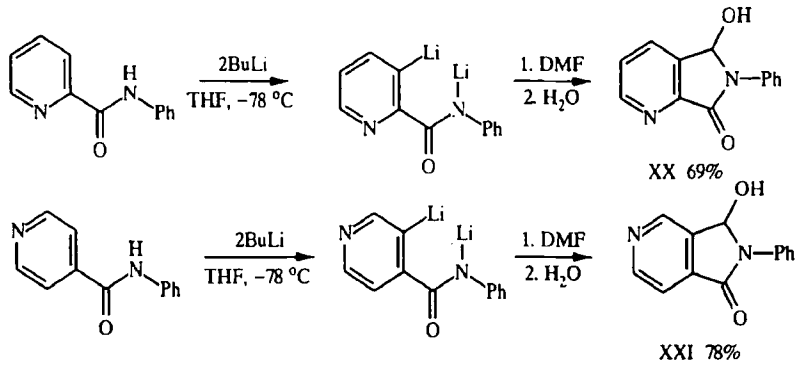
The isomeric bicyclic structures, namely, 3-hydroxy-3-pyridylisoindolines, were obtained using lithiated benzanilide derivatives and N,N-dimethylamides (or ethyl ethers) of pyridine-2- and pyridine-4-carboxylic acids [16]. 3-Pyridylisoindolines XVI and XVII are converted in high yield upon heating at reflux with sulfuric acid to the corresponding (α-carboxybenzoyl)pyridines XVIII and XIX (Table 3).



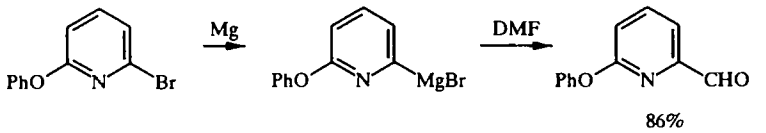
XVI (Py-2), XVII (Py-4)

XVIII, XIX

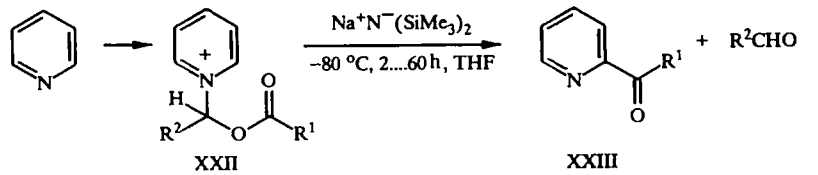
4- and 6-Azaphthalides XX and XXI are obtained analogously in the formylation of lithium derivatives of 2- and 4-(N-phenylcarbamoyl)pyridines using DMF [17].



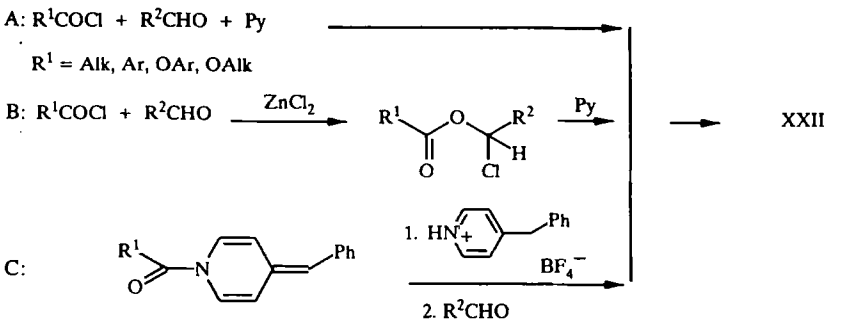
Pyridylmagnesium halides may be used for the electrophilic introduction of acyl substituents into the pyridine ring. Thus, 6-phenoxypyridine is formylated at $C_{(2)}$ by formation of the Grignard reagent and the subsequent action of DMF on this reagent [18].



Special interest is found in a simple method for introducing acyl groups at the α-position of the unsubstituted pyridine ring through an intramolecular, regiospecific electrophilic reaction proceeding upon the action of sodium bis(trimethylsilyl)amide on N-[1-(acyloxy)alkyl]pyridinium salts XXII [19]:



Three methods have been described for the preparation of salts XXII. Method A involves use of acyl chlorides (including ethyl chloroformate), aldehydes, and pyridine. In Method B, 1-chloroalkyl esters of carboxylic acids, obtained *in situ* from acid chlorides and aldehydes in the presence of zinc chloride, react with pyridine. As a rule, the yield of salts XXII depends on the nature of the substituent although method A is usually more efficient. Method C was developed specially to obtain unstable 4-benzylpyridinium salts XXIIm-q (Table 4).



We should note the electronic effect of substituent R^2 on the yield of salts XXII. The yield of salt XXIIc in the case of an electron-withdrawing substituent (R^2 = *p*-$NO_2C_6H_4$) is 67%, while the yield of salt XXIIa (R^2 = Ph) is 89%. The yields of salts XXII increase with increasing reaction time up to 60 h (Table 5).

This reaction is regiospecific. The isomeric 3- and 4-acylpyridines or polyacylation products were not formed in any case.

TABLE 4. N-[1-(Alkoxy)alkyl]pyridinium Salts

Salt XXII	R^1	R^2	Pyridine	X^-	Yield, %		
					A	B	C
a	Ph	Ph	Py	Cl	89	69	
b	Ph	*p*-MeC_6H_4	Py	Cl	79	73	
c	Ph	*p*-$NO_2C_6H_4$	Py	Cl	67		
d	Ph	1-нафтил	Py	Cl	75		
e	Ph	Et	Py	Cl	75		
f	Ph	Pr	Py	Cl	78		
g	*t*-Bu	*p*-MeC_6H_4	Py	Cl	46		
h	*p*-MeC_6H_4	Ph	Py	Cl	79		
i	*p*-$MeOC_6H_4$	Ph	Py	Cl	89		
j	*p*-ClC_6H_4	Ph	Py	Cl	91		
k	1-naphthyl	Ph	Py	Cl	83		
l	*p*-MeC_6H_4	*p*-MeC_6H_4	Py	Cl	81		
m	Ph	*p*-MeC_6H_4	4-BnPy	BF_4			52
n	Ph	*i*-Pr	4-BnPy	BF_4			53
o	Ph	CH_2Ph	4-BnPy	BF_4			52
p	Ph	CH_2Ph	4-BnPy	BF_4			72
q	Me	CH_2Ph	4-BnPy	BF_4			42
r	Ph	*p*-MeC_6H_4	4-NMe_2-Py	Cl	63		
s	Ph	*p*-MeC_6H_4	4-*t*-BuPy	Cl	62		
t	*p*-MeC_6H_4	*p*-MeC_6H_4	4-*t*-BuPy	Cl	77		

TABLE 5. 2-Acylpyridines

Starting salt XXII	R^1	Pyridine	Yield, %	
			2 h	60 h
a	Ph	Py	35	71
c	Ph	Py		36
k	1-naphthyl	Py		50
g	*t*-Bu	Py	51	
l	*p*-MeC_6H_4	Py		60
j	*p*-ClC_6H_4	Py		31
s	Ph	4-*t*-BuPy		46
t	*p*-MeC_6H_4	4-*t*-BuPy		32

TABLE 6. Synthesis of Acylpyridines by the Oxidative Decyanation of Nitriles XXXI

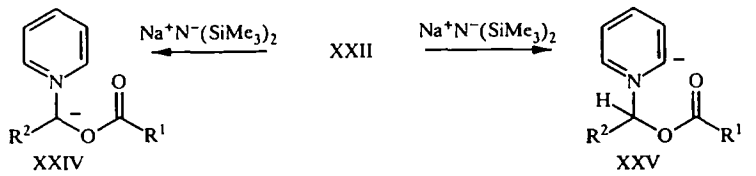
Pyridyl	R	Yield, %	Pyridyl	R	Yield, %
2-(6-BrPy)	Ph	95	4-Py	Ph	93
2-(6-ClPy)	Ph	96	3-Py	Ph	99
2-[6-(α-cyanobenzyl)pyridyl]	Ph	99	2-Py	Me*	45
2-Py	Ph	99	2-Py	*i*-Pr*	55

*Extension of the reaction time from 3 to 48 and 24 h, respectively.

TABLE 7. Trifluoromethylpyridinecarboxylic Acids

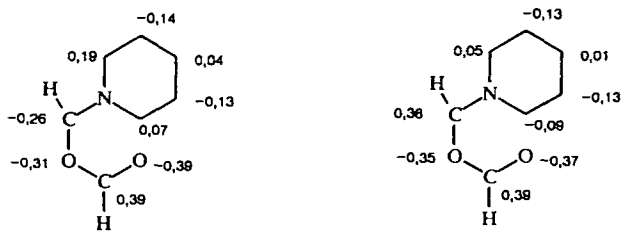
R^1	R2	R^3	Reaction time, min	Yield, %
H	H	H	40...60	72...76
CF_3	H	H	40	57
H	CF_3	H	3...15	81...89
H	H	CF_3	40	51...58

Information on the pathway of the intramolecular acylation may be obtained by examining the structure of intermediates XXIV and XXV, which are the products of the deprotonation of salts XXII by sodium bis(trimethylsilyl)amide.



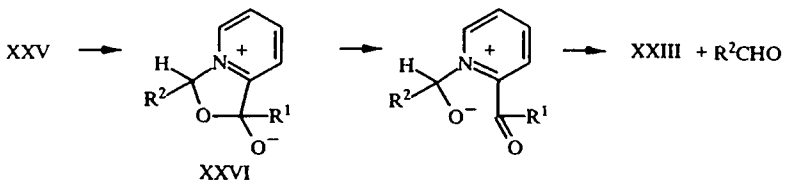
XXIV XXV

The experimental and theoretical data indicate that structure XXV is preferred over XXIV under kinetic control conditions ($\Delta\delta H_f$ = 26.4 kJ/mole). The charges obtained for intermediates XXIV and XXV from a MNDO calculation indicate that 2-acylpyridines XXIII may form only from structure XXV due to intramolecular electrophilic attack.



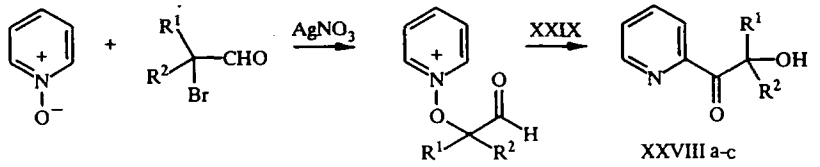
XXIV (δHf = 63.6 kJ/mole) XXV (δHf = 37.2 kJ/mole)

This reaction probably proceeds through intermediate XXVI:



XXVI

Alkoxypyridinium salts XXVII obtained upon the reaction of pyridine N-oxide with α-substituted 2-bromoaldehydes undergo analogous intramolecular electrophilic rearrangement upon the action of base [20].



XXVII a-c

XXVIII a $R^1 = R^2$ = Me (85%), b R^1 = Me, R^2 = Ph (94%), c $R^1 = R^2$ = Ph (92%)

2-(α-Hydroxyacyl)pyridines are formed in high yield in this reaction. A sterically hindered base, 2,2,6,6-tetramethylpiperidine (XXIX), is used in this reaction to avoid side-reactions, namely, nucleophilic attack at the carbonyl group and opening of the pyridine ring. The following reaction mechanism is proposed:

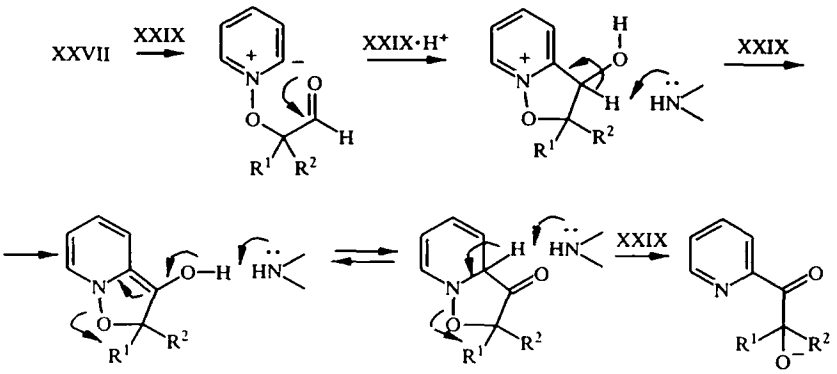


TABLE 8. N-Methylcarbamoylpyridines

N-Methylcarbamoylpyridines		Reaction time	Yield, %
R	position of CONHMe group		
H	2	5 days	17
	4		2
2-Me	6	57 h	11
3-Me	6	7 days	21
4-Me	2	32 h	38
2,6-Me_2	4	29 h	8

TABLE 9. Liquid-Phase Oxidation of Picolines

Picoline	Temperature, °C	Time, h	Base	Yield, %
4-	25	96	KOH	80
4-	25	12	*t*-BuOK	57
2-	25	96	KOH	85
2-	60	12	KOH	58
3-	60	12	*t*-BuOK	25

TABLE 10. Transformation of Halopyridines into Pyridine Carboxylic Acid Esters

Halopyridine	Reaction product	Yield, %
3,5-Br_2Py	Diethyl dinicotinate	100
3,5-Cl_2Py	5-Chloroethyl nicotinate	35
5-Br-3-CNPy	5-Cyanoethyl nicotinate	100

As in the previous case, the key step is α-deprotonation of the pyridine ring by the action of base XXIX followed by closure of the isoxazoline ring and its subsequent opening. Base XXIX is the proton carrier in all the steps.

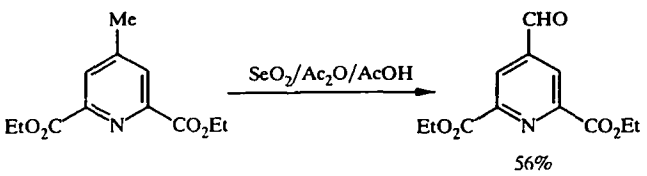
1.2. Modification

In addition to electrophilic introduction of an acyl group into the pyridine ring, modification of substituents already present in the pyridine molecule holds an important place in the methods for acylpyridine synthesis. Oxidation of alkyl substituents is the most prominent of such modifications.

1.2.1. Oxidation Reactions. Oxidative methods for the preparation of formyl- and acylpyridines involve both catalytic and chemical processes. Thus, for example, the oxidation of 2-picoline in the gas phase to give 2-pyridinecarbaldehyde is carried out in the presence of 4% V_2O_5/TiO_5 catalyst [21]. The formation of mono- and dipyridinecarbaldehydes in the gas-phase catalytic oxidation of 2,6-lutidine on vanadium–molybdenum catalysts is a function of the addition of promoters [22]. The major oxidation product is usually 2,6-diformylpyridine. On the other hand, the addition of Ag_2O or Bi_2O_3 as promoters leads to the preparation of mono- and dipyridinecarbaldehydes in different amounts, while the use of V_2O_5 promoted by 8% CsF or RbF leads to the predominant formation of 6-methyl-2-formylpyridine.

Various alkyl- and benzylpyridines form the corresponding ketones in high yield upon oxidation by *tert*-butyl peroxide in the presence of $ZrCrO_3$–HTlc as catalyst (Htlc = hydrotalcite-like compounds, namely, laminar binary hydroxides with the general formula $[Mg_{1-x}Al_x(OH)_2]\cdot[A]_{n-x/n}\cdot(zH_2O)]$) [23].

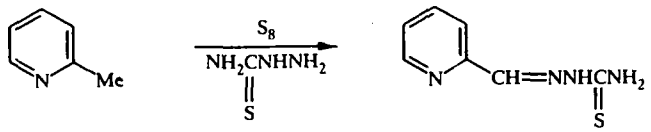
Both standard and unusual oxidizing agents are employed in the chemical oxidation methods. Thus, previously unreported 2,6-diethoxycarbonyl-4-formylpyridine was obtained using the well-known oxidizing agent, selenium dioxide [24]:



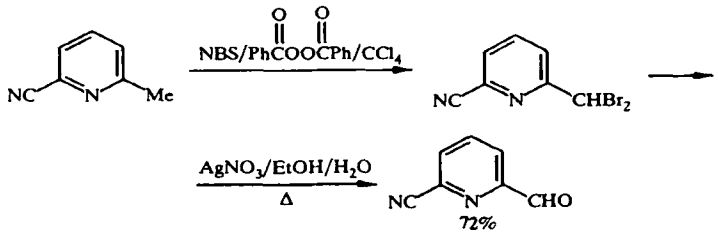
56%

Iodine in DMSO was used for the synthesis of 3-fluoro-4-formylpyridine from the corresponding 3-fluoro-γ-picoline [25].

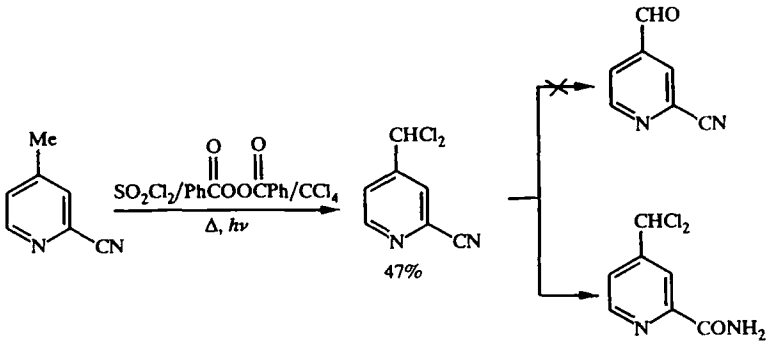
The oxidation of 2-picoline by sulfur in the presence of thiosemicarbazide leads to the thiosemicarbazone of 2-formylpyridine [26].



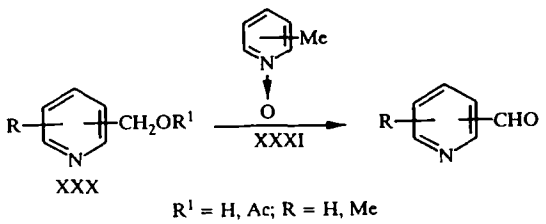
The photochemical dibromination of the methyl group in 2-methyl-6-cyanopyridine may also be considered an oxidative modification of alkyl substituents. Subsequent hydrolysis of the dibromo derivative in the presence of $AgNO_3$ yields the corresponding formylpyridine in good yield [27].



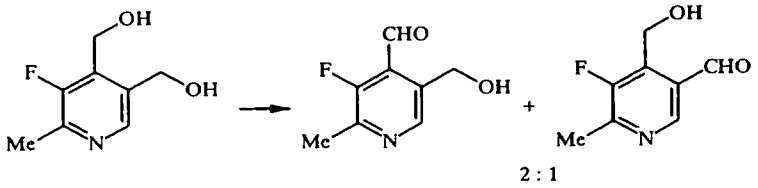
We should note that the analogous dichloro derivative of 4-methyl-6-cyanopyridine is not formed in the hydrolysis of 4-formyl-6-cyanopyridine, but rather is converted into the corresponding carbamide with retention of the dichloromethyl substituent:



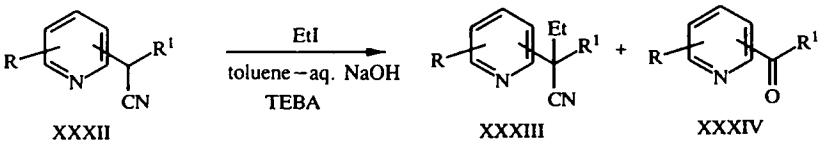
The oxidation of pyridylcarbinols XXX or their acetates by pyridine N-oxide XXXI at 200-220°C also leads to the corresponding pyridinecarboxaldehydes [28].



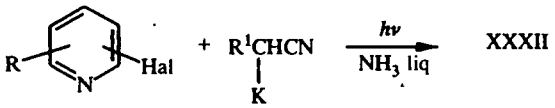
The oxidation of 2-methyl-3-fluoro-4,5-di(hydroxymethyl)pyridine by pyridinium chlorochromate at room temperature is a step in the synthesis of an analog of coenzyme B_6. This reaction proceeds in 85% yield but nonselectively to give a 2:1 mixture of the corresponding 4- and 5-formyl derivatives [29].



An unusual oxidative decyanation reaction was discovered in an attempt to alkylate nitrile XXXII under phase transfer catalysis conditions [30].

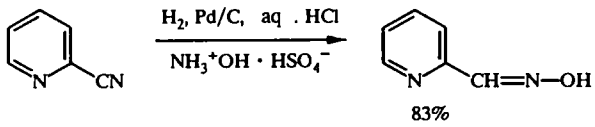


Under these conditions without protection from atmospheric oxygen, a mixture of the expected nitrile XXXIII with ketone XXXIV was obtained. Ketones XXXIV are formed in very high yield under the same conditions in the absence of an alkylating agent. Thus, this oxidative decyanation may serve as a convenient preparative method for a very wide variety of acylpyridines (Table 6), especially since starting nitriles XXXII are readily available using a photochemical S_NR reaction of the corresponding pyridyl halides with the carbanions of various nitriles.

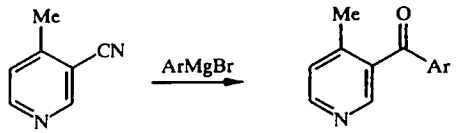


1.2.2. Reduction. Several examples of the use of the reduction of substituents in a higher oxidation state for the preparation of formylpyridines have been reported. Thus, the electrochemical reduction of picolinic acid on a mercury electrode in strongly acidic buffer media leads to the formation of 2-pyridinecarbaldehyde as the major product [31].

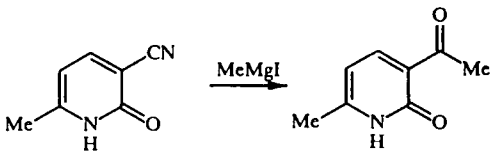
The reduction of 4- and 5-substituted picolinic acids in the presence of hydroxylamine gives oximes of the corresponding 2-formylpyridines [32]. Oximes of 2-pyridinecarbaldehyde and their alkyl derivatives were obtained by the hydrogenation of 2-cyanopyridines in the presence of hydroxylamine salts [33].



1.2.3. Modification of Pyridinecarboxylic Acids. The presence of a nitrile group on the pyridine ring opens broad possibilities for its modification into an acyl group. The most common variant involves reaction with various Grignard reagents. Thus, the reaction of 4-methyl-3-cyanopyridine with substituted phenylmagnesium bromides was used for the preparation of various herbicides [34], for example:

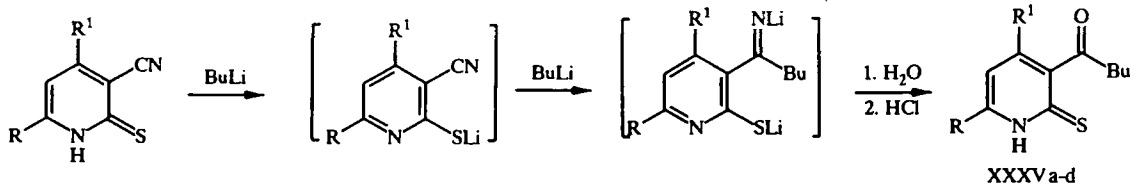


The analogous reaction of 6-methyl-3-cyano-2-pyridone with methylmagnesium iodide yields the corresponding 3-acetyl derivatives [35].



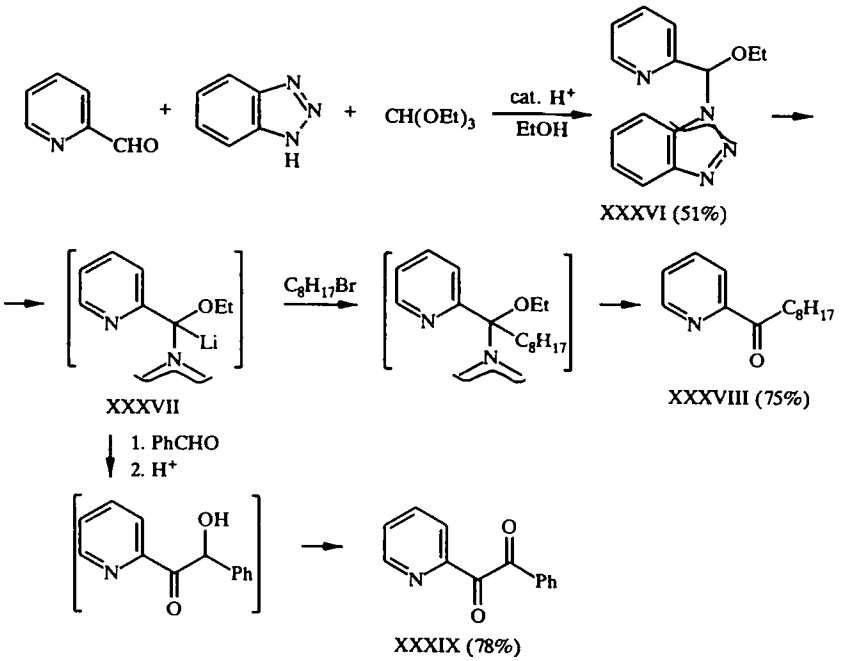
The feasibility of using organolithium compounds instead of Grignard reagents has recently been demonstrated in the case of 3-cyano-2(1H)-pyridinethiones [36].

The Grignard reaction with the acid chloride derivatives of pyridinecarboxylic acids also serves as a convenient method for the preparation of acyl derivatives, for example, the reaction of the acid chloride of 3-chloronicotinic acid with methylmagnesium iodide yields 2-chloro-3-acetylpyridine [37].



XXXV a R = Me, R^1 = H (60%), b R = Pr, R^1 = H (90%),
c R = iso-Bu, R^1 = H (70%), d R = R^1 = Me (80%)

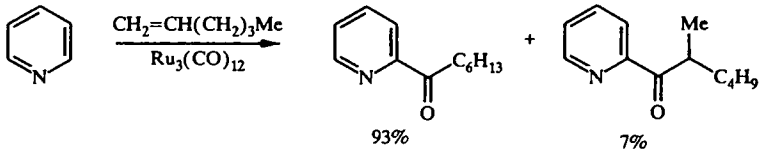
The transformation of the aldehyde group into a ketone group, proposed by Katritzky et al. [38] and common for aryl and hetaryl derivatives, holds promise for the synthesis of pyridine ketones with various substituents in the side-chain. This reaction proceeds in several steps and appears as follows for 2-pyridinecarbaldehyde.



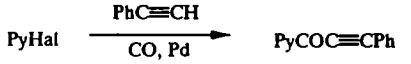
2-Pyridinecarbaldehyde reacts with benzotriazole and triethyl orthoformate to give [α-(1-benzotriazolyl)-α-(2-pyridyl)methyl] ethyl ether (XXXVI). This new acyl anion precursor is smoothly lithiated at the methyl group. Subsequent treatment of lithium derivative XXXVII with octyl bromide or benzaldehyde leads to 2-pyridyl ketones XXXVIII or XXXIX in good yields. Unfortunately, Katritzky et al. [38] did not discuss the formation of diketone XXXIX instead of the expected α-hydroxyketone when lithium intermediate XXVII was treated with benzaldehyde. The formation of diketone XXXIX probably occurs as the result of some oxidative process. No data are given concerning this conclusion by Katritzky [38] although the structure of XXXIX was established beyond doubt on the basis of NMR and mass spectral data.

1.3. Use of Metal Complex Catalysis for the Synthesis of Acylpyridines

Progress in the synthesis of acylpyridines using the direct catalytic carbonylation of pyridine or its halogen derivatives is attributed to the broad introduction of metal complex catalysis into modern synthetic organic chemistry. Thus, 2-pyridyl hexyl ketone was obtained regioselectively in 93% yield along with 7% 2-pyridyl 1-methylpentyl ketone upon the treatment of unsubstituted pyridine with 1-hexene and CO in the presence of ruthenium dodecacarbonyl at 150°C in an autoclave [39].

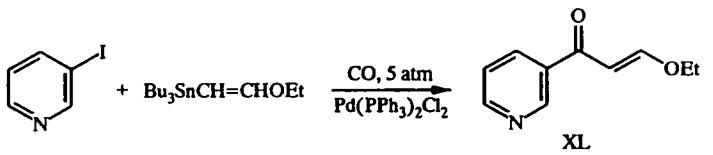


The palladium-catalyzed carbonylation of halopyridines in the presence of terminal acetylenes and triethylamine at 120°C and 20 atm CO is used to obtain acetylenic pyridyl ketones [40]:

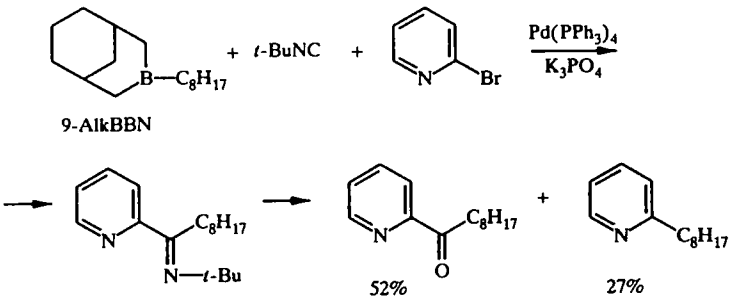


The best ligands for the palladium complex catalyst are phosphines, $R^2P(CH_2)_4PR_2$ (R = Ph, Bu, *cyclo*-C_6H_{11}), 1,1′-bis(diphenylphosphino)ferrocene, and 1,1′-bis(diphenylarsino)ferrocene.

The carbonylation of 3-iodopyridine catalyzed by $Pd(PPh_3)_2Cl_2$ in the presence of (*Z*)-1-ethoxy-2- (tributylstannyl)ethylene in chloroform leads to pyridyl ketone XL in 44% yield, while 2-bromo- and 2-iodopyridines react under these conditions to give only 8 and 32% product, respectively [41].



Cross-coupling reactions may also be used for the synthesis of acylpyridines. For example, the cross-coupling of 2-bromopyridine with 9-octyl-9-borabicyclo[3.3.1]nonane (9-alkylBBN) and *tert*-butyl isocyanate catalyzed by Pd^0 in dioxane at 50°C in the presence of potassium phosphate leads to 2-pyridyl octyl ketone through the intermediate formation of an imine derivative [42]. 9-AlkylBBN is generated *in situ* by the hydroborylation of terminal alkenes. The reaction mixture also contained 27% 2-octylpyridine.

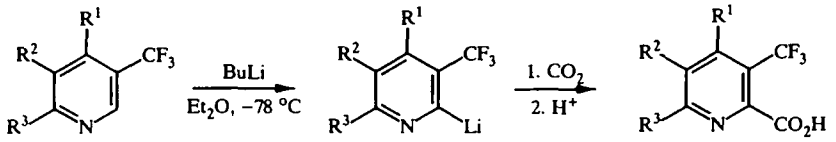


Epsztajn et al. [42] consider that the cross-coupling involves the following steps: 1) oxidative addition of bromopyridine to the Pd(0) complex, 2) formation of iminoacylpalladium(II) halide, 3) transfer of the alkyl group from boron to palladium, and 4) reductive elimination of the iminoketone.

2. METHODS FOR THE PREPARATION OF PYRIDINECARBOXYLIC ACIDS AND THEIR DERIVATIVES

2.1. Use of Electrophilic Reactions

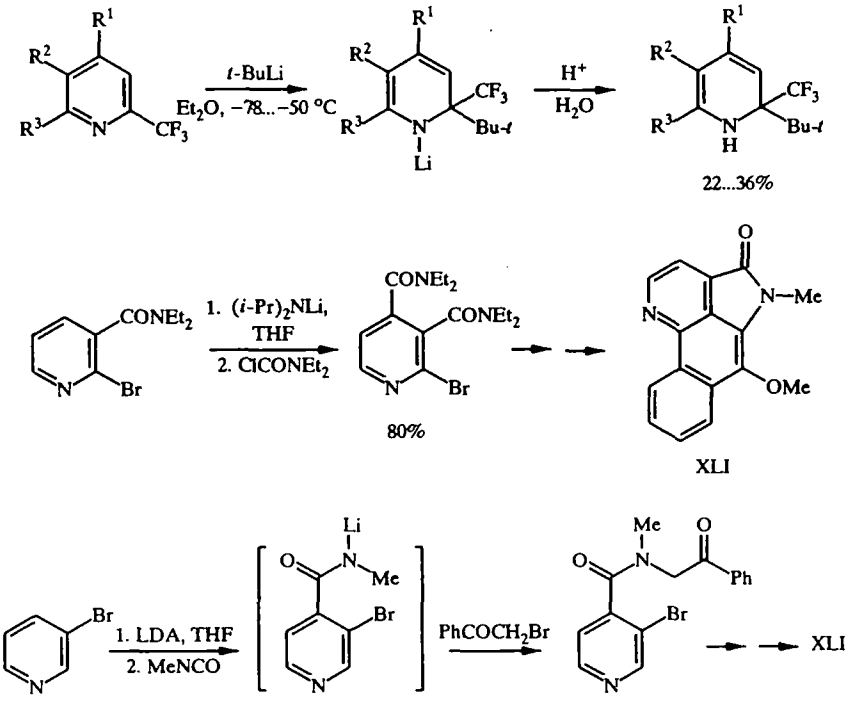
Lithiation is a common method of making the pyridine ring susceptible toward attack by electrophiles. Pyridines are not lithiated in the absence of an electron-withdrawing substituent. As expected, 3-fluoromethylpyridines are selectively lithiated at $C_{(2)}$, which provides a facile pathway for the preparation of trifluoromethylpyridinecarboxylic acids [43] (Table 7):



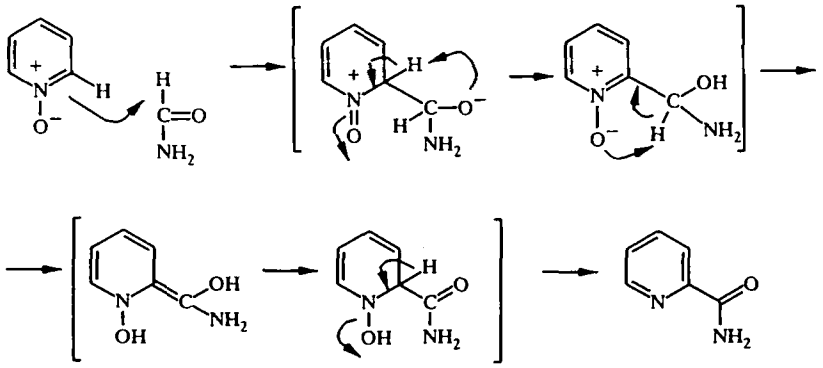
Under the same conditions, 2-trifluoro-, 2,4-, and 2,6-bistrifluoromethylpyridines react with butyllithium to give polymers. However, products of the addition of *tert*-butyllithium an the C=N bond were isolated in the reaction with *tert*-butyllithium.

It is interesting that 2,5-bistrifluoromethylpyridine, which reacts at −78°C with both butyllithium and *tert*-butyllithium to give metallated derivatives, reacts with *tert*-butyllithium at −50°C to give only the addition product in 18% yield.

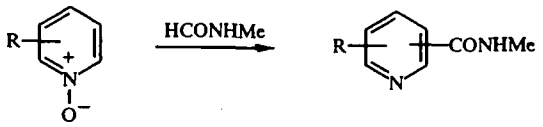
The metallation of pyridines with subsequent formation of pyridinecarboxylic acid derivatives has also been used in various syntheses of the natural alkaloid, eupolauramine (XLI) [44, 45].



Preparation of the N-oxide is another method of modifying the pyridine ring for electrophilic attack. Thus, pyridine N-oxides react in excess formamide at reflux to give 2-carbamoylpyridines. The following mechanism was proposed [46]:

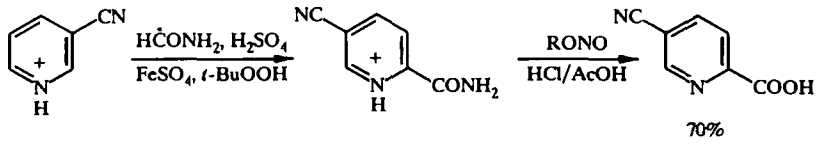


The yield of the carbamoylpyridine products was 2% in the case of unsubstituted pyridine and 10% for 3-methylpyridine. Somewhat higher yields were achieved in the reaction with N-methylformamide [47] (Table 8):

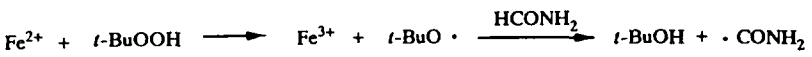


2.2. Attack by Nucleophilic Species

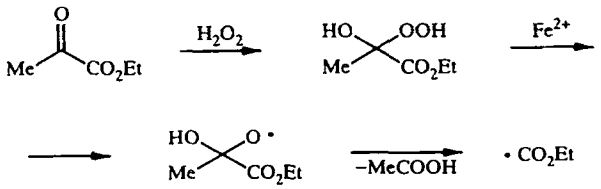
Protonation of the pyridine ring is nucleofugic. However, the nucleophile in reaction with this ring should not have basic properties in order to avoid deprotonation. Alkoxycarbonyl and aminocarbonyl ($ROC{\cdot}=O$) and aminocarbonyl radicals ($H_2NC{\cdot}=O$) meet this criterion. Thus, the amide of 5-cyanopicolinic acid is formed in the reaction of nicotinonitrile with the aminocarbonyl radical, which may be selectively hydrolyzed to 5-cyanopicolinic acid [48]:



The aminocarbonyl radical is obtained upon the oxidation of formamide by means of the *tert*-butoxy radical as follows:



The ethoxycarbonyl radical is generated by the reductive dissociation of the product of the addition of hydrogen peroxide to ethyl pyruvate:

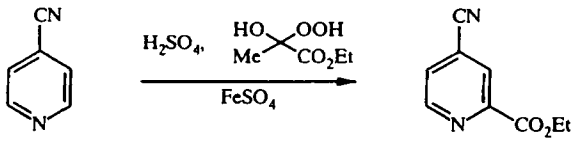


A mixture of di- and trisubstitution products is formed in the reaction of isonicotinonitrile with the ethoxycarbonyl radical since the electron deficiency of the ring increases upon formation of the monosubstitution product. However, multiple substitution may be avoided by carrying out the reaction in a two-phase H_2O/CH_2Cl_2 system. The monosubstitution product

TABLE 11. Dependence of the Regioorientation in the Cyanation Using Me_3SiCN on the Polarity of the Medium

CH_2Cl_2, %	Toluene, %	Isomer ratio, %		Total yield, %
		XLVI	XLVII	
100	0	69	31	62
75	25	79	21	90
50	50	86	14	27
25	75	100	0	66
0	100	100	0	65
100% CH_2Cl_2 (CuI)		100	0	53
THF (CuI)		100	0	65
MeCN (CuI)		100	0	21

enters the organic phase due to increases in lyophilicity and diminished basicity. Indeed, using this method, the product of the monosubstitution of isonicotinonitrile, namely, 2-ethoxycarbonyl-4-cyanopyridine, is formed in 80% yield [49].



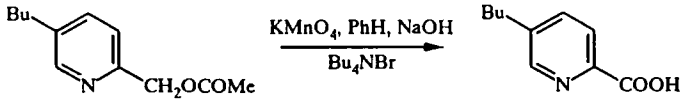
A mixture of the three possible monosubstitution products is formed by carrying out this reaction with nicotinonitrile, which may be separated chromatographically [49].

2.3. Oxidation of Substituents

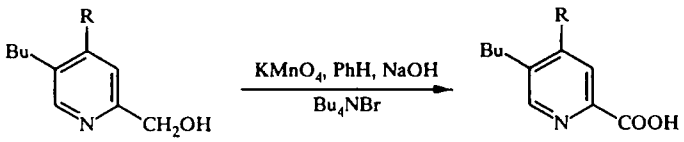
The oxidation of alkylpyridines by atmospheric oxygen in the presence of various catalysts is an industrial method for the preparation of pyridinecarboxylic acids. Thus, 3-picoline is oxidized in the gas phase by oxygen in the presence of steam and vanadium and titanium catalysts at 250-290°C to give nicotinic acid in 82-86% yield [50]. Picolines are oxidized by atmospheric oxygen in the liquid phase at about 200°C and 21 atm in the presence of cobalt and manganese acetates to the corresponding picolinic acids. The conversion for 3-, 4-, and 2-picoline is 57, 66, and 27%, respectively [51] (Table 9).

The liquid-phase oxidation of picolines may also be carried out under milder conditions in dimethoxyethane in the presence of base and a crown ether [52, 53]. This system efficiently generates and oxidizes carbanions formed from picolines. The oxidation of β-picoline is the most difficult due to its low CH-acidity (the nicotinic acid yield does not exceed 25% even at 80°C), while the oxidation of γ- and α-picolines at 25°C leads to isonicotinic and picolinic acids in 80-85% yield [53].

Potassium permanganate is often used as the oxidizing agent. Thus, corresponding acetate in the synthesis of fusaric acid is oxidized in a two-phase system in 77% yield [54]:

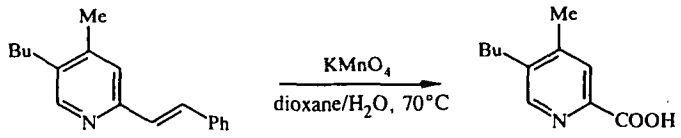


The same method was used to prepare fusaric acid analogs [55]:



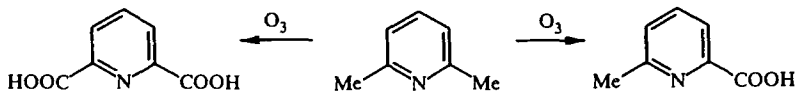
R = NO_2 (85%), OMe (69%), OEt (27%), Cl (17%)

Benzylidene derivatives such as XLII are oxidized by potassium permanganate in much lower yields, for example [55]:



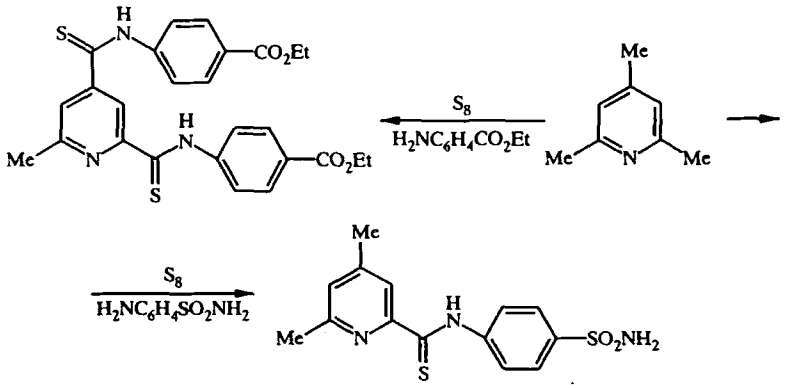
XLII 16%

Picolines may be oxidized in good yield by ozone. Thus, 1,6-lutidine may be oxidized by ozone in an aqueous medium at room temperature in the presence of acetic acid and manganese hydrophosphate to give both the mono- and diacid [56]:

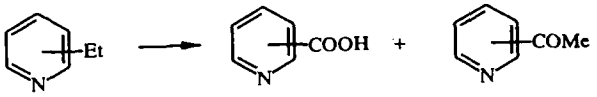


74% 73%

symm-Collidine is oxidized by sulfur under conditions of the Willgerodt–Kindler reaction. Either the mono- or bisthioamide is formed depending on the amine employed [57]:



The electrochemical oxidation of alkylpyridines to give acids in a membrane cell with a PbO_2 anode has been reported [58]. A solution of sodium sulfate and sulfuric acid was used as the cation exchanger, while aq. NaOH was used as the cation exchanger. In the reaction 2-, 3-, and 4-picolines are oxidized to picolinic, nicotinic, and isonicotinic acids in 90, 65, and 75% yield, respectively. 2,6-Lutidine gives the diacid upon electrochemical oxidation in 40% yield. The oxidation of 3,5-lutidine gives a mixture of 3,5-pyridinedicarboxylic (35%) and 5-methylnicotinic acids (5%). Under these conditions, ethylpyridines give a mixture of acids and acetylpyridines:



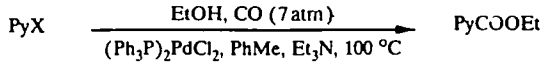
2-Et	30%	40%
3-Et	55%	45%
4-Et	15%	39%

Of the other reported methods, we note the oxidation of the methyl group in substrates such as 3-alkoxy-6-methylpyridines by selenium dioxide at 140-150°C and the preparation of nicotinic acid by the fermentation of 3-alkylpyridines [60].

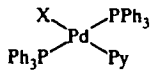
2.4. Use of Metal Complex Catalysis

The most efficient methods for the transformation of halopyridines into pyridinecarboxylic acid derivatives involve use of metal complex catalysis.

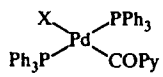
Halopyridines, especially bromopyridines, usually undergo facile reaction with CO and alcohols in the presence of palladium catalysts [61, 62] (Table 10).



Complexes XLIII are formed in the reaction of halopyridines with palladium triphenylphosphine complexes. Subsequent insertion of CO into the Py–Pd bond in this complex leads to intermediates XLIV. Esters of pyridinecarboxylic acids are formed upon decomposition of these intermediates by alcohols [63].



XLIII

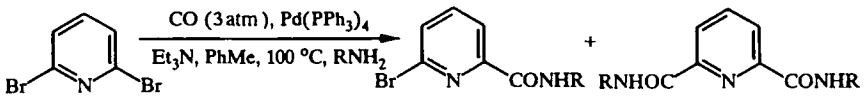


XLIV

If triethylphosphine is used instead of triphenylphosphine, CO does not react with the complex formed since triethylphosphine is a stronger σ-donor.

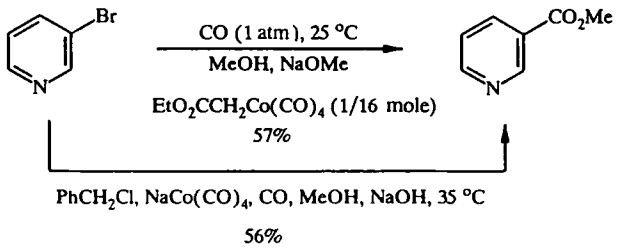
In contrast to 3- and 5-halopyridines, 2-bromo- or 2-chloropyridines lacking other ring substituents form a complex, $[PdX(Py)PPh_3]_2$, which does not react subsequently with CO.

2,6-Dibromopyridine reacts with $Pd(PPh_3)_4$ to give a complex active relative to CO, which, after removal of CO, may be decomposed by amines, leading to the formation of a mixture of mono- and diamines [64]:



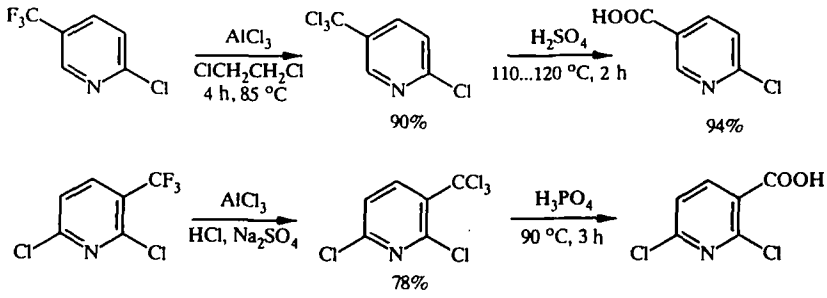
R = Ph	55%	37%
R = 2-Py	47%	36%
R = $PhCH_2$	49%	12%
R = n-C_6H_{13}	57%	30%

Cobalt complexes, including complexes generated *in situ*, may also serve as catalysts in carbonylation reactions [65]:

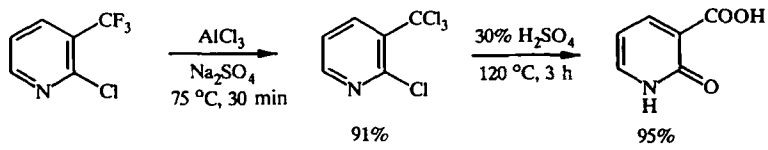


2.5. Preparation of Pyridinecarboxylic Acids by Hydrolysis of Various Derivatives

Trifluoromethylpyridines may be converted into acids through their initial transformation into trichloromethylpyridines upon heating with $AlCl_3$ and subsequent hydrolysis. This method is convenient, for example, for the preparation of chloronicotinic acids [66, 67]:



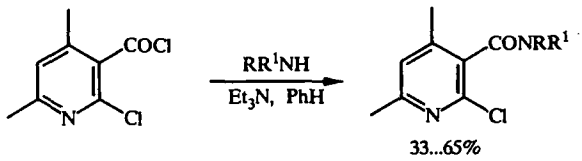
Pyridonecarboxylic acid is obtained upon hydrolysis by more dilute acid [68]:



The nitrile of picolinic acid is hydrolyzed by water to give picolinamide in 70-72% yield in an autoclave at 200-220°C upon dilution 1:8300 [69]. Nicotinonitrile and isonicotinonitrile are hydrolyzed by aqueous ammonia (0.08-0.1 mole ammonia per mole nitrile) at 280°C to the corresponding amides in yields of about 75% [70]. Acids are formed in 90-95% yield when 2.0-2.5 moles ammonia is taken per mole nitrile.

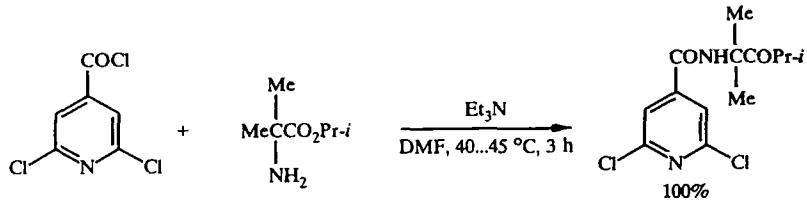
2.6. Modification of Functional Groups

Standard methods are used, as a rule, to prepare pyridinecarboxylic acid derivatives. Thus, for example, amides of pyridinecarboxylic acids are obtained by the usual method from the acid chlorides of the corresponding acids [71, 72]:

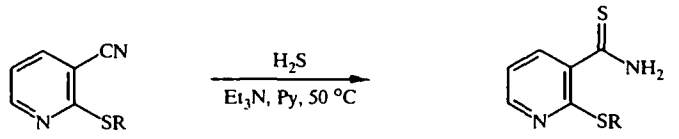


R = H, R^1 = Pr, Bu, *t*-Bu, *i*-Am, *c*-C_6H_{11}, *c*-C_3H_5, R, R^1 = $(CH_2)_5$, $(CH_2CH_2)_2O$

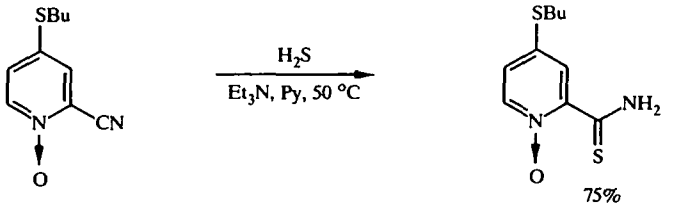
The patent literature indicates the quantitative yield of amides containing a bulky amine fragment (the residue of the isopropyl ether of 2-methylalanine) in DMF by this method [72]:



The nitrile group of cyanopyridines serves as a very convenient substituent for modification to a wide variety of pyridinecarboxylic acid derivatives. Thus, the transformation of nitriles by the action of hydrogen sulfide was used to obtain thioamides of pyridinecarboxylic acids [73]:

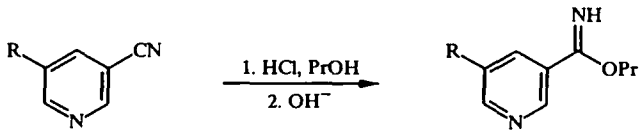


R = Pr (74%), Bu (84%)

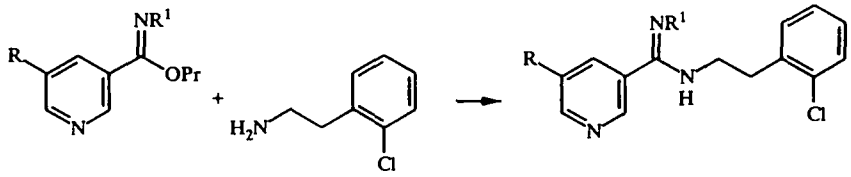


75%

The reaction of pyridinecarbonitriles with alcohols in the presence of HCl is a convenient method for obtaining iminoesters [74], which, in turn, may be converted into the corresponding amidines by the action of primary amines [74, 75].

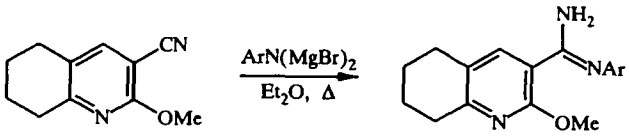


R = Me, Br, NO_2, NR_2, CO_2Me



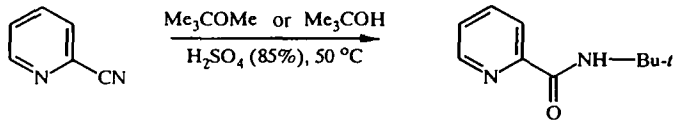
R = CN, Ac, CO_2Me

Pyridinecarbonitriles may be converted into the corresponding amidines, avoiding the step involving iminoester formation, by the action of N-dimagnesium derivatives of aromatic amines [76]:



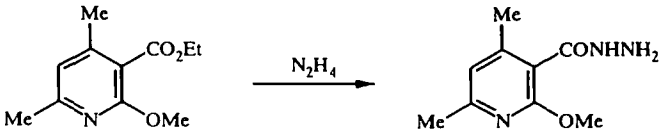
Ar = Ph (61%), p-MeC_6H_4 (50%), p-$MeOC_6H_4$ (55%), p-ClC_6H_4 (60%), p-BrC_6H_4 (54%)

The transformation of nitriles into amides in high yield occurs upon the action of tertiary carbocations (Ritter reaction) [77]:

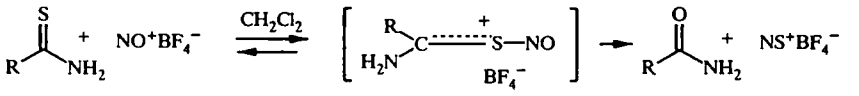


87...93%

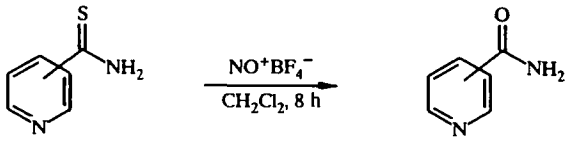
The conversion of pyridinecarboxylic acid esters into hydrazides is accomplished by the standard procedure, for example [78]:



Thioamides may be converted into amides by the action of nitrosonium tetrafluoroborate [79]. This conversion proceeds as follows:



This pathway was utilized for the conversion of 3- and 4-thiocarbamoylpyridines into nicotinamides and isonicotinamides, respectively:



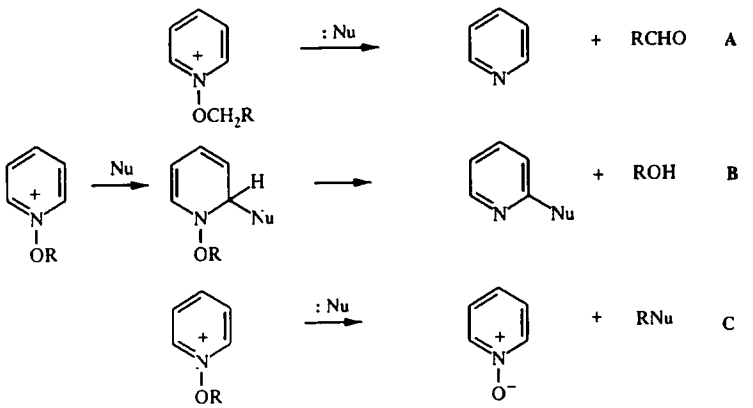
3-$CONH_2$ (74%), 4-$CONH_2$ (68%)

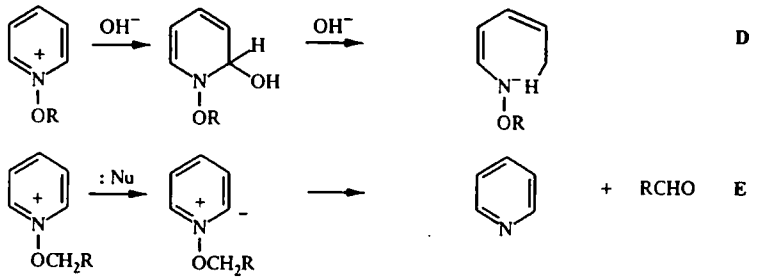
3. METHODS FOR THE PREPARATION OF PYRIDINECARBONITRILES

3.1. Direct Cyanation of the Pyridine Ring

The direct introduction of the cyano group requires prior activation of the pyridine ring, which is most often accomplished by forming various pyridinium salts. A convenient method for activation involves the prior formation of alkoxy-, acyloxy-, or ethoxycarbonylpyridinium salts by means of the Reissert–Hantsch reaction. Fife and Seriven [80] reviewed the literature on this highly efficient and regiospecific method for the preparation of 2- and 4-cyanopyridines up to 1984. Hence, only later literature sources will be cited in our present review.

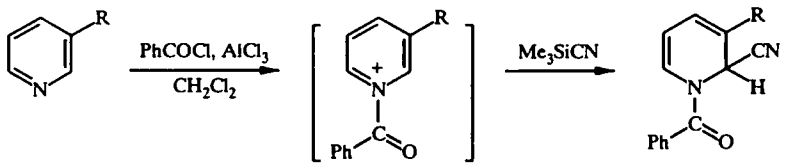
The Reissert–Hantsch reaction should be considered in the general context of the reactions of N-alkoxy- and N-acyloxypyridinium salts with nucleophiles, which were classified by Katritzky into types A-D [81] and by Abramovich, who proposed type E [82]:





According to this classification, the direct cyanation of the pyridine ring is a type-B reaction and proceeds through an addition–elimination mechanism [83].

Trimethylsilyl cyanide is a source of the cyanide ion for the selective introduction of the nitrile group at $C_{(2)}$. Thus, pyridinic Reissert compounds XLV containing a benzoyl substituent at the nitrogen atom rather than an alkoxy or acyloxy group were initially obtained by the action of Me_3SiCN on N-benzoylpyridinium salts [84]:

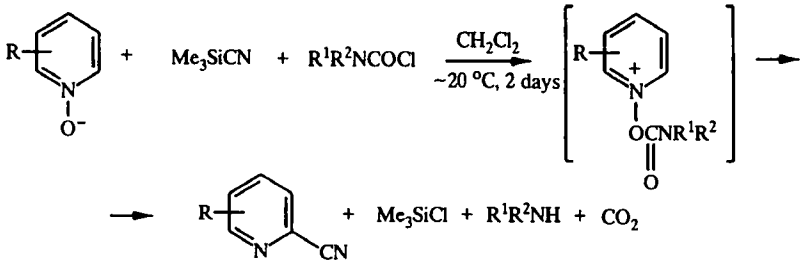


XLV a-d

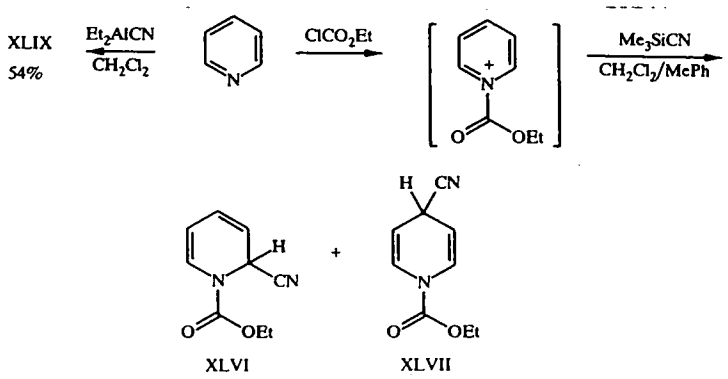
a R = H (80%), b R = COMe (30...45%), c R = CO_2Me (16%), d R = CN (13%)

The low yields of XLVb-d are attributed to the predominant attack of the cyanide ion at the carbonyl group of the benzoyl moiety rather than at $C_{(2)}$. Evidence for this hypothesis is the extensive formation of benzoyl cyanide, which accompanies the formation of XLVb-d (i.e., a type-C reaction according to the Katritzky classification).

Prior treatment of pyridine N-oxides by dialkylcarbamoyl chlorides followed by reaction with Me_3SiCN leads selectively to 2-cyanopyridines in high yield [85, 86].



It was later shown that the reaction with trimethylsilyl cyanide is not always regioselective. Thus, 1,2- and 1,4-isomers are formed using 1-ethoxycarbonylpyridinium salts. The ratio of these isomers depends both on the solvent polarity and the addition of CuI (Table 11) [87].

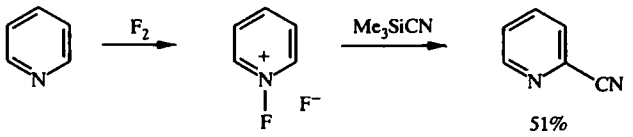


XLVI XLVII

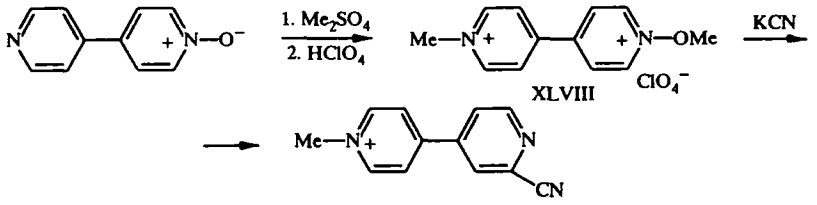
The yield of 1,2-regioisomer XLVI increases with decreasing polarity of the medium and the reaction becomes regiospecific even when the toluene content in the reaction solvent is 75%. The same effect is produced by using anhydrous cuprous iodide at the catalyst.

Diethylaluminum cyanide serves as a specific reagent for obtaining 1,4-dihydropyridinecarbonitriles XLVII from N-ethoxycarbonylpyridinium salts [87, 88].

A new strategy for obtaining the nitrile of picolinic acid involves use of N-fluoropyridinium fluoride as a substrate in reaction with trimethylsilyl cyanide [89]:



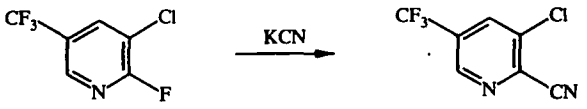
The cyanation of pyridinium salt XLVIII obtained by treating the mono-N-oxide of 4,4'-dipyridyl by potassium cyanide proceeds selectively at the α-position of the N-methoxypyridinium fragment [90]:



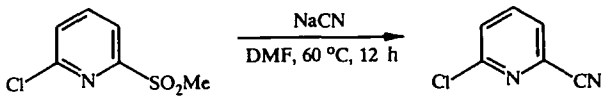
3.2. Nucleophilic Substitution of a Halogen Atom

A halogen atom at $C_{(2)}$ in pyridines activated by an additional electron-withdrawing substituent is capable of nucleophilic substitution by a cyano group. Thus, the chlorine atom at $C_{(2)}$ selectively undergoes nucleophilic substitution in the reaction of 2,6-dichloro-3-nitropyridine with cuprous cyanide [91].

One step in the synthesis of some pyridine herbicides is substitution of the fluorine atom at $C_{(2)}$ activated by a CF_3 group at $C_{(5)}$ using potassium cyanide [92]:



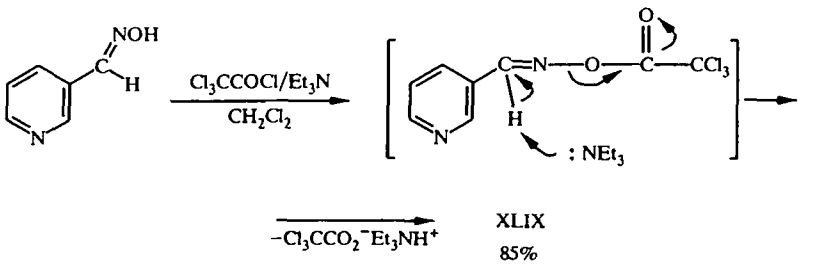
When two different groups at $C_{(2)}$ and $C_{(6)}$ capable of nucleophilic substitution are present in a pyridine molecule, the better leaving group is exchanged by the cyano group [93]:



While halogen atoms at $C_{(2)}$ and $C_{(6)}$ of a pyridine molecule readily undergo nucleophilic substitution, the conversion of 3-halopyridines into nicotinonitriles requires use of metal complex catalysis. Thus, the cyanation of 3-bromopyridines may be accomplished in the presence of $Ni(PPh_3)_3$ generated *in situ* using dipolar solvents and potassium or sodium cyanide. Nicotinonitrile (XLIX) is obtained in this case from 3-bromopyridine in good yield [94].

3.3. Conversion of Pyridinecarbaldehyde Derivatives into Nitriles

Both *E*- and *Z*-isomers of pyridinecarbaldehyde oximes may be converted into nitriles of pyridinecarboxylic acids by the action of a system consisting of trichloroacetyl chloride and triethylamine. This reaction proceeds as follows [95]:



The use of this method for 3-pyridinaldoxime gives nicotinonitrile XLIX in good yield [95].

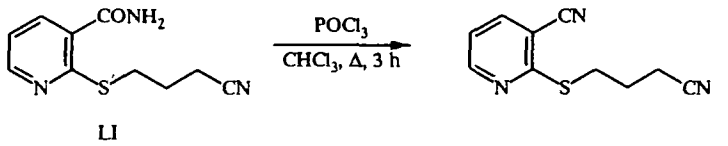
The oxidative conversion of N,N-dimethylhydrazones of pyridinecarbaldehydes into the corresponding nitriles by the action of hydrogen peroxide or 3-chloroperbenzoic acid has also been reported [96].

3.4. Conversion of Amides of Pyridinecarboxylic Acids into Nitriles

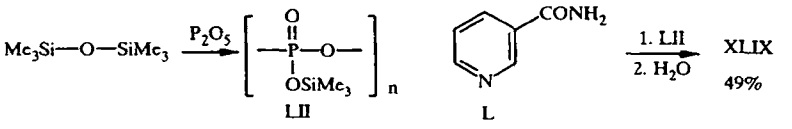
One of the most convenient methods for the preparation of pyridinecarbonitriles not involving use of toxic cyanides is dehydration of the corresponding amides. Both standard and original dehydrating agents have been used for these reactions.

Among the standard methods, we should initially note P_2O_5 used for the conversion of 3-carbamoylpyridine (L) into nicotinonitrile (XLIX) [97].

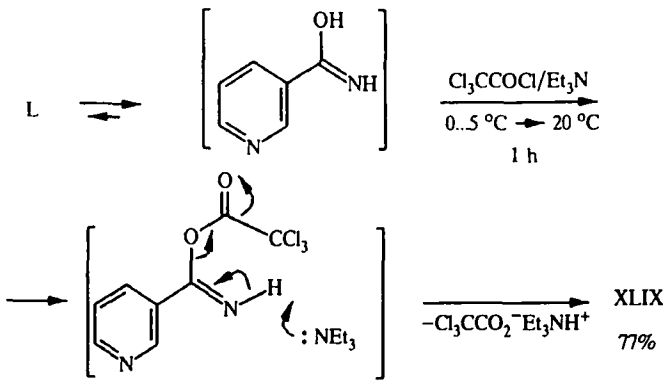
A key step in the synthesis of a new heterocyclic system, thieno[1,2-*f*]naphthyridine, is the conversion of amide LI into a nitrile by the action of $POCl_3$ in chloroform at reflux [98]:



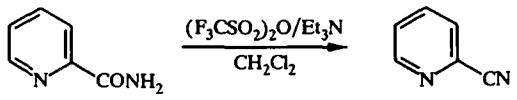
Yokoyama et al. [99] have proposed use of trimethylsilyl polyphosphate (LII), readily obtained by heating P_2O_5 with HMDS in organic solvents such as CH_2Cl_2, $CHCl_3$, or benzene at reflux for 20-30 min instead of the ethyl polyphosphorate, which is a standard dehydration agent whose preparation requires 2-3 days.



The treatment of nicotinoamide L by reagent LII involves initial formation of a trimethylsilyl derivative of nicotinonitrile, which gives the free nitrile upon reaction with water. This reaction requires 5 min. Anhydrides of strong organic acids and sulfonic acids in the presence of trimethylamine may be used as the dehydration agents. Thus, trichloroacetyl chloride in the presence of triethylamine has been used to convert amide L into nitrile XLIX under very mild conditions [100]:

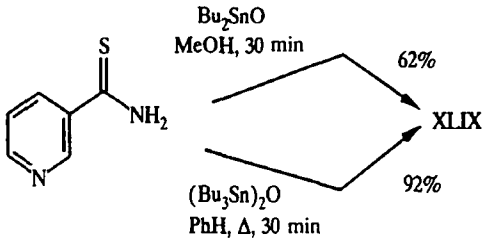


Trifluoromethanesulfonic acid anhydride has been used for the conversion of picolinamide into the corresponding nitrile [101]:

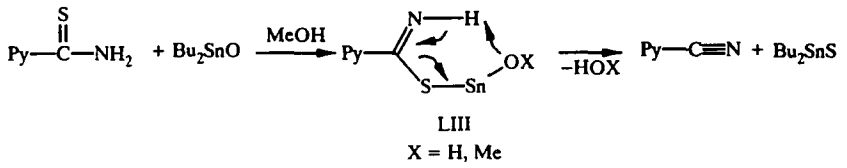


The dehydration of carbamoylpyridines to give nitriles by zeolites has been reported [102].

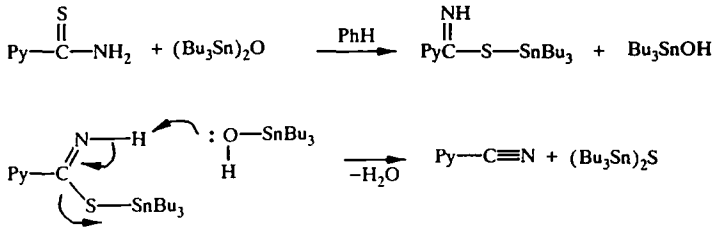
Dibutylstannic oxide and bis(tributyl)stannic oxide are specific reagents for the transformation of thioamides to nitriles (amides do not react under these conditions) [103]:



The use of dibutylstannic oxide for the dehydrosulfurization involves initial attack by sulfur at the Sn=O group to give intermediate LIII, which undergoes β-elimination to give nitrile XLIX and dibutylstannic sulfide:



The reaction with bis(tributyl)stannic oxide proceeds through a similar mechanism:



3.5. Oxidative Ammonolysis of Alkylpyridines

The modification of alkyl groups of alkylpyridines by oxidative ammonolysis is a common and often most convenient method for the preparation of cyanopyridines. This reaction is carried out in the gas phase above 320°C in the presence of various catalysts. Atmospheric oxygen and ammonia are coreagents. Vanadium oxide is most often used as the catalyst.

For example, 3-cyanopyridine (XLIX) and 3-picoline are obtained by this method in yields over 60% [104-107]. A study of various vanadium oxides as catalysts showed that V_2O_5 and V_6O_{13} or their complex have greatest activity and selectivity [104, 106]. The addition of water vapor to the reaction mixture enhances the catalyst activity and provides for a ≥85% yield of nitrile XLIX. However, in the case, the formation of nicotinic acid and its amide (up to 1-1.5%) occurs in parallel to the major reaction [108, 109]. Various modifications of the catalyst by adding titanium oxide [110] or antimony and uranium oxides [111] or using SiO_2 [112] or Al_2O_3 [113] as the support also lead to an increase in the yield of nitrile XLIX up to 93%. Nicotinonitrile XLIX is formed in 90% yield in the oxidative ammonolysis of 3-picoline in the presence of fused $V_2O_5 \cdot 0.5SnO_2$ as the catalyst [114]. An increase in the amount of ammonia from 0.5 to 1.5 mole per mole of 3-picoline enhances the catalyst activity: the conversion at 320-340°C is increased and becomes virtually quantitative at 360°C. The selectivity for the formation of nicotinonitrile XLIX is improved in this case and the amount of extensive oxidation products is reduced. The addition of water vapor has the same effect. A further increase in the ammonia/3-picoline ratio led to a decrease in conversion, probably due to blockage of the catalyst by ammonia. The selectivity for the formation of 3-cyanopyridine XLIX also drops and the amount of extensive oxidation products increases.

The oxidative ammonolysis of various 4-substituted pyridines (4-ethyl-, 4-vinyl-, and 4-acetylpyridines) [115] and 4-picoline [116] is also one of the most efficient methods for the synthesis of 4-cyanopyridine. Fused vanadium–titanium oxides, vanadium–tin oxides, and other more complex oxides are recommended as the catalyst for this reaction. A yield of 85% is achieved using V·4Ti·4Sn·xO as the catalyst at 330-390°C. The addition of water vapor also enhances the catalyst activity and reaction selectivity (the yield of 4-cyanopyridine is increased to 97-99%).

2-Cyanopyridine is obtained analogously from 2-picoline on a vanadium–phosphorus oxide catalyst (P:V ratio equal to 1.15) and an increase in the ammonia/2-picoline mole ratio from 5 to 15 leads to an increase in the total conversion and in the yield of 2-cyanopyridine from 40 to 80-90% [117].

Studies of the oxidative ammonolysis of 2,6-, 2,5-, and 3,5-lutidines in the presence of vanadium oxide and water vapor at 360-400°C showed that the selectivity for formation of the corresponding dicyano derivatives is 60-80% [117-119]. The greatest reactivity was found for 2,6-lutidine due, on one hand, to the electronic structure of this molecule and, on the other, to its orientation on the catalyst surface. A vanadium–titanium catalyst with V_2O_5:TiO_2 = 1:16 displays the lowest activity in this reaction such that 2-methyl-6-cyanopyridine becomes the major product [120].

2-Methyl-6-cyanopyridine and 2,6-dicyanopyridine are also reaction products in the oxidative ammonolysis of 2,6-lutidine on the vanadium–phosphorus catalyst [117]. The conversion of starting 2,6-lutidine increases from 65 to 100% in going from 340 to 420°C and the yield of 2-methyl-6-cyanopyridine decreases from 40 to 4% with a simultaneous increase in the 2,6-dicyanopyridine yield from 10 to 55%. Under these conditions, the yield of the oxidative decomposition products (2-cyanopyridine and pyridine) does not exceed 15%. The most favorable conditions for 2,6-dicyanopyridine formation include a lutidine–oxygen–ammonia mole ratio equal to 1:(96-120):28 at 420°C. The dinitrile is formed under these conditions in 64-66% yield with 2-cyanopyridine in 10% yield. The addition of water vapor facilitates oxidative decomposition, which reduces the dinitrile yield to 44% and increases the yield of 2-cyanopyridine.

The oxidative ammonolysis of 2-methyl-5-ethylpyridine on vanadium catalysts is more complicated and gives lower yields of about 25% [107]. A vanadium–titanium catalyst is one of the most efficient for this reaction [121]. Depending on the reaction conditions, 5-cyano-5-ethylpyridine, 2,5-dicyanopyridine, or 3-cyanopyridine may be obtained as the major product. 3-Cyanopyridine holds the greatest interest for further use. In this regard, the major interest in the study of the oxidative ammonolysis of industrially-available 2-methyl-3-ethylpyridine is given to the preparation of 3-cyanopyridine. When a vanadium–titanium catalyst is used, 3-cyanopyridine may be obtained as the major product in 69% yield [121]. On the other hand, the addition of small amounts of tungsten, titanium, and aluminum oxides has no significant effect on the yield of 3-cyanopyridine, which remains at 65-72% [109].

Thus, there is a vast variety of approaches to the preparation of acylpyridines and derivatives of pyridinecarboxylic acids, which, in turn, may be used as building blocks in synthesis and in the search for new pyridine derivatives possessing useful properties.

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