FUROPYRIDINES. SYNTHESIS AND PROPERTIES

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Abstract - This review describes the synthesis of the frameworks of furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine, and reactions of the furopyridines: such as bromination, nitration, H-D exchange and lithiation at the furan ring, chlorination, acetoxylation and cyanation of the *N*-oxides of furopyridines an 2,3-dihydrofuropyridines, and conversion of each substituent into other functional groups.

This review involves the following contents.

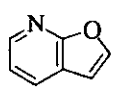
c) Chlorination and acetoxylation of *N*-oxides
d) Nitration, chlorination, acetoxylation and cyanation of *N*-oxides of 2,3-dihydrofuropyridines
e) Photo[2+2]cycloaddition of furo[2,3-*c*]- and -[3,2-*c*]pyridone and their *N*-methyl derivatives
f) Others

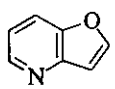
IV. Miscellaneous
a) Basicity
b) NMR spectra

V. Conclusion

I. INTRODUCTION

Furopyridines arise from the fusion of a π-deficient pyridine and a π-excessive furan ring, and the fusion gives rise to six possible isomeric systems which fall into two groups, those that are analogues of quinoline, the [*b*]-fused systems, furo[2,3-*b*]pyridine (**1a**), furo[3,2-*b*]pyridine (**1b**) and furo[3,4-*b*]pyridine (**1e**), and those that are isoquinoline, the [*c*]-fused systems, furo[2,3-*c*]pyridine (**1c**), furo[3,2-*c*]pyridine (**1d**) and furo[3,4-*c*]pyridine (**1f**). Derivatives of all these systems and the five parent frameworks (**1a**, **1b**, **1c**, **1d** and **1f**) are known.


1a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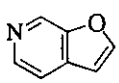
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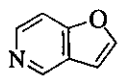
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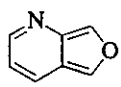
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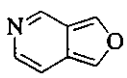

1f

There may be two main reasons for the interest in furopyridines. First, there is obvious experimental and theoretical interest in the behavior of these systems which consist of a π-excessive and a π-deficient ring; particularly, interest of how the annelation will perturb the electronic structure of each individual ring and how this will be manifested in the reactivity of these substrates. Second, the expectation for pharmacologically active substances has led the synthesis of derivatives of these isosteres of quinoline and isoquinoline which are important moieties in many biologically active substances.[1]

Unlike quinoline, isoquinoline and benzofuran, furopyridines do not occur widely in nature. The skeleton of furo[2,3-*b*]quinoline alkaloids isolated from some plants of *Rutaceae* is composed of furo[2,3-*b*]pyridine moiety,[2] but no other natural occurrence of

these systems has been reported.

As is to be expected by simple HMO calculations,[3] the *o*-quinoid isomers (**1e**) and (**1f**) are much less stable. Very little works has so far been reported on furo[3,4-*b*]- and furo[3,4-*c*]pyridine; the parent compound (**1f**) was first synthesized in 1977, but it was found to be very unstable in the air and even at room temperature.[4] The parent compound or derivatives of fully unsaturated furo[3,4-*b*]pyridine have not yet been prepared. Thus, in this review the author does not describe the chemistry of furo[3,4-*b*]- and -[3,4-*c*]pyridine.

II. SYNTESES OF THE FRAMEWORKS

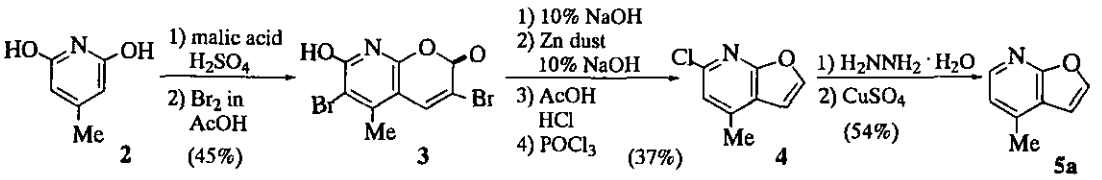
This section is confined to the synthesis of furopyridines and their derivatives through direct construction of the furopyridine systems; the interconversions yielding derivatives from the preformed furopyridines are considered in the subsequent section. Though there have been reported a significant number of papers concerning the synthesis of furopyridines, in this review the author describes the typical and more versatile methods including papers from our laboratory.

Synthetic approaches to furopyridines are conveniently divided into two strategies, according to which heterocyclic ring is constructed, i.e. formation of the furan ring from the preformed pyridine derivatives, and construction of the pyridine nucleus from the preformed furan derivatives. Formation of the pyridine ring by the electrophilic cyclization with strong acid at the carbon in the preformed furan derivatives, which have been adapted for the classical syntheses of quinoline, isoquinoline and thienopyridine skeletons, resulted in unsuccessful with a few exceptions, because of instability of the furan ring under strong acidic conditions.

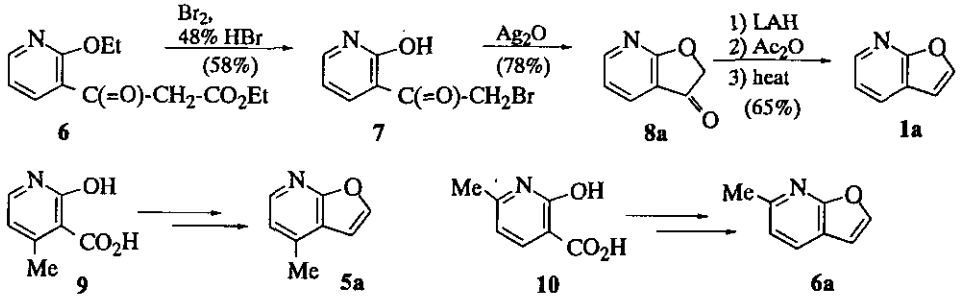
a) Furo[2,3-*b*]pyridine

The first synthesis of the fully aromatic furopyridine (**5a**) was reported by Robinson and Watt,[5] which is based on a coumarilic acid type rearrangement of 3,6-dibromo-7-hydroxy-5-methylpyrano[2,3-*b*]pyridinone (**3**).

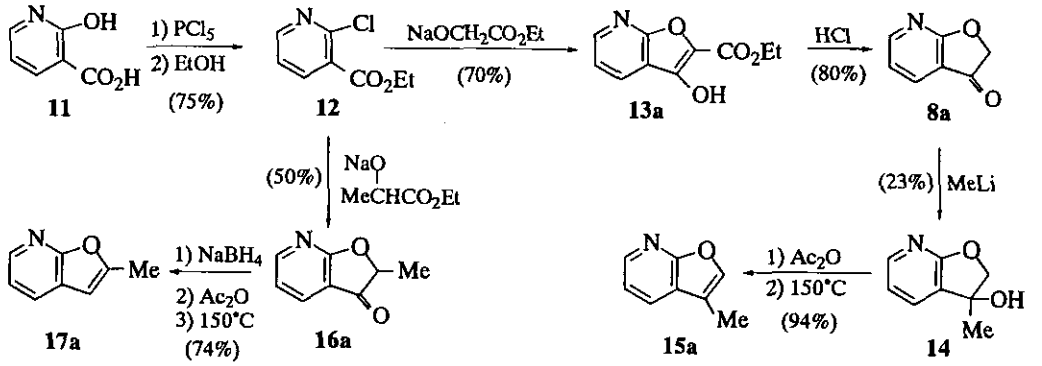
The synthesis of the parent compound (**1a**) was first reported by Sliwa.[6] Chlorination of 2-hydroxynicotinic acid (**11**) with phosphorus pentachloride and the subsequent treatment with sodium ethoxide yielded ethyl 2-chloronicotinate (**12**), which was followed by the



Claisen condensation with ethyl acetate to give compound (**6**). Bromination in hydrobromic acid gave 3-bromoacetylpyridin-2-ol (**7**), which was cyclized with silver oxide to furopyridone (**8a**). Reduction of the ketone (**8a**) with LAH, acetylation of the resulting hydroxy compound and heating of the acetoxy compound yielded (**1a**). 4-Methyl- (**5a**)[7] and 6-methylfuro[2,3-*b*]pyridine (**6a**)[8] were prepared by the essentially same procedure starting from 4-methyl- (**9**) and 6-methyl-2-hydroxynicotinic acid (**10**).

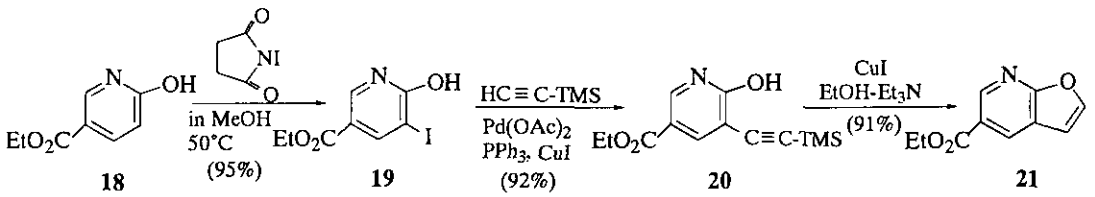


It is well known that Dieckmann cyclization of alkoxycarbonylmethyl ether of ethyl salicylate gives coumaranone or its alkoxycarbonyl derivatives.[9] Shiotani applied this method for the synthesis of the parent furo[2,3-*b*]pyridine (**1a**), its 2-methyl (**17a**) and 3-methyl derivative (**15a**).[10] Ethyl 2-chloronicotinate (**12**) was treated with 2 equivalent moles of sodium ethoxycarbonylmethoxide to give ethyl 3-hydroxyfuro[2,3-*b*]pyridine-2-carboxylate (**13a**). Saponification and the subsequent decarboxylation yielded the keto compound (**8a**), from which the parent molecule (**1a**) was obtained through



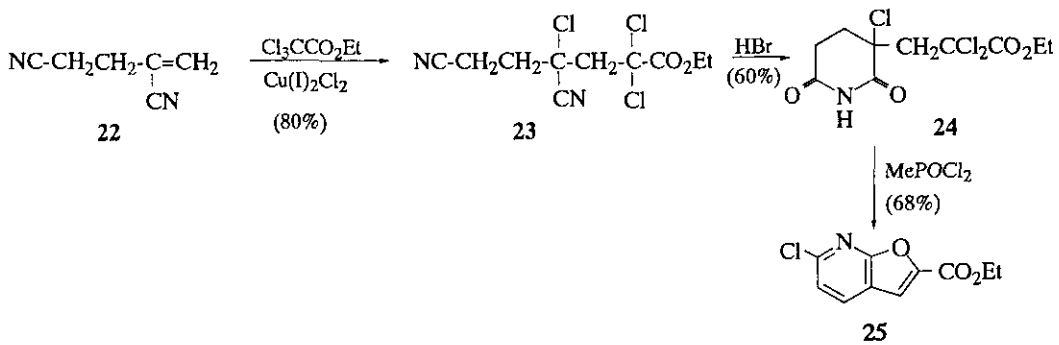
the procedure of Sliwa.[6] Reaction of the ketone (**8a**) with methyllithium gave a tertiary alcohol (**14**) which was acetylated and followed by heating at 160-170°C to afford 3-methyl derivative (**15a**). Analogously, treatment of **12** with sodium 1-ethoxycarbonyl-1-ethoxide afforded 2-methylfuro[2,3-*b*]pyridin-3-one (**16a**), from which 2-methyl derivative (**17a**) was obtained by reduction with sodium borohydride and the subsequent dehydration.

Houpis *et al.* reported synthesis of ethyl furo[2,3-*b*]pyridine-5-carboxylate (**21**) from ethyl 6-hydroxynicotinate (**18**), *via* a Pd-catalyzed coupling of 5-iodo-6-hydroxynicotinate (**19**) with trimethylsilylacetylene followed by cyclization of the resulting alkynylpyridone intermediate (**20**).[11]



18 **19** **20** **21**

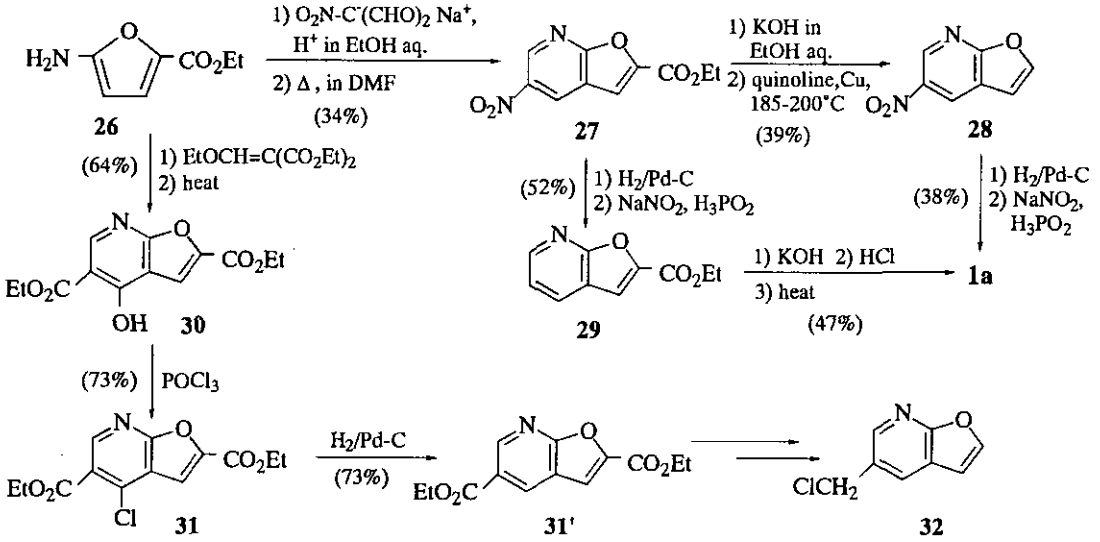
A unique method to prepare ethyl 6-chlorofuro[2,3-*b*]pyridine-2-carboxylate (**25**) has been reported by Weis.[12] The addition of ethyl trichloroacetate to the double bond of α-methyleneglutaronitrile (**22**) in the presence of copper(I) chloride yielded ethyl 4,6-dicyano-2,2,4-trichlorohexanecarboxylate (**23**). This ester was cyclized with hydrogen bromide followed by hydrolysis to give 3,3-disubstituted 2,6-piperidinedione (**24**). Treatment of **24** with methylphosphonyl chloride at 160°C yielded ethyl ester (**25**). Compound (**25**) can be converted to the parent compound (**1a**) through replacement of the chlorine by hydrogen and decarboxylation.



22 **23** **24** **25**

Another strategy towards furo[2,3-*b*]pyridine is to construct a pyridine ring from suitably substituted furans. Snyder and Ebentino carried out condensation of ethyl 5-amino-2-furoate (**26**).[13] When compound (**26**) was treated with sodium salt of nitro-

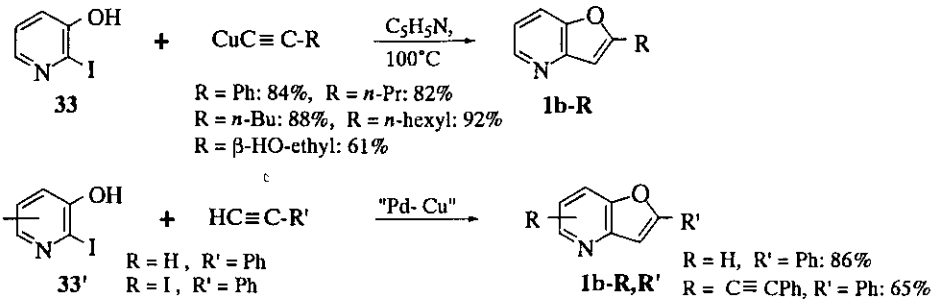
malonedialdehyde in acidic aqueous solution, a condensation product was formed which was immediately cyclized in DMF to give ethyl 5-nitrofuro[2,3-*b*]pyridine-2-carboxylate (**27**). Compound (**27**) was converted to furo[2,3-*b*]pyridine (**1a**) by reduction of the nitro group, deamination, saponification and decarboxylation. Condensation of **26** with diethyl ethoxymethlenemalonate and the subsequent intramolecular cyclization afforded diethyl 4-hydroxyfuro[2,3-*b*]pyridine-2,5-dicarboxylate (**30**), from which dicarboxylate (**31'**) was obtained. Recently, conversion of the diester (**31'**) to 5-chloromethyl compound (**32**) was reported, which was used as a side chain of L-754,394, a key pharmacophore of the HIV protease inhibitor.[14]



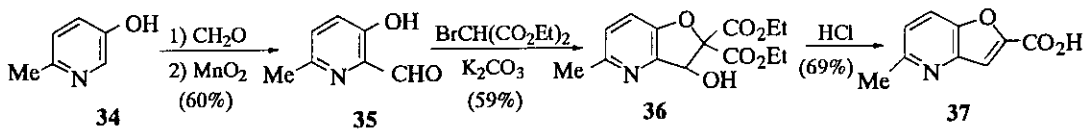
b) Furo[3,2-b]pyridine

This system has been prepared also from both the preformed pyridines and furan derivatives.

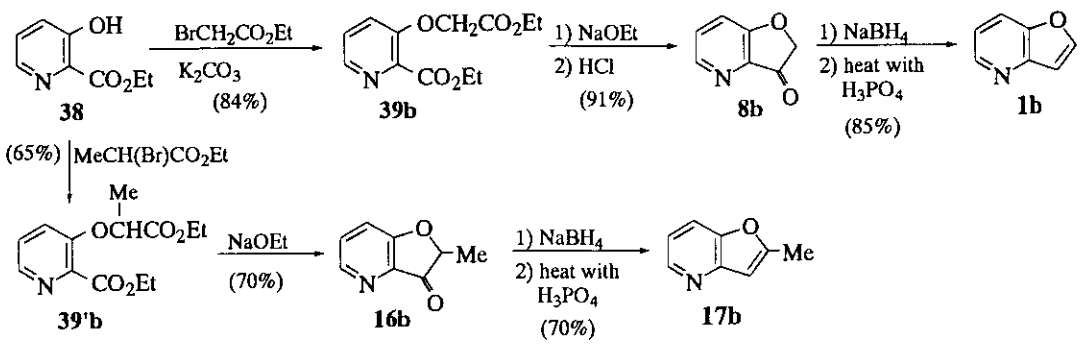
Substitution of a carbon-halogen bond with a copper(I) acetylide and subsequent or synchronous copper catalyzed addition of the neighboring nucleophilic substituent to the triple bond constructs a heterocyclic ring. Mlandenovic and Castro utilized this reaction for the syntheses of 2-substituted furo[3,2-*b*]pyridines (**1b-R**).[15] Some derivatives (**1b-R, R'**) of furo[3,2-*b*]pyridine were synthesized from 2-iodo-3-pyridinols (**33'**) and terminal acetylenes by use of a combined catalyst, $Cl_2Pd(Ph_3)_2$-CuI.[16-19]

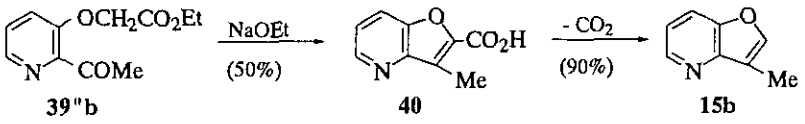


Weis reported the synthesis of 5-methylfuro[3,2-*b*]pyridine-2-carboxylic acid (**37**) from 6-methyl-3-pyridinol (**34**) through a series of reactions including hydroxymethylation at the 2-position, oxidation of the hydroxymethyl group to aldehyde, condensation with diethyl bromomalonate and the subsequent hydrolysis and decarboxylation with hydrochloric acid.[20]



A convenient route to prepare the parent molecule and/or simple substituted derivative in moderate quantities by a simple procedure was developed by Shiotani.[21] *O*-Alkylation of ethyl 3-hydroxypyridine-2-carboxylate (**38**) with ethyl bromoacetate afforded a diester (**39b**), from which furo[3,2-*b*]pyridin-3(2*H*)-one (**8b**) was obtained by the Dieckmann condensation and the subsequent hydrolysis and decarboxylation. Reduction of the carbonyl group with sodium borohydride and dehydration of the resulting hydroxy compound with phosphoric acid yielded the parent furopyridine (**1b**). Analogously, 2-methyl derivative (**17b**) was prepared from ethyl 2-(2-ethoxycarbonyl-3-pyridyloxy)-propionate (**39'**). Analogous cyclization of ethyl 2-(2-acetyl-3-pyridyloxy)acetate (**39"**)

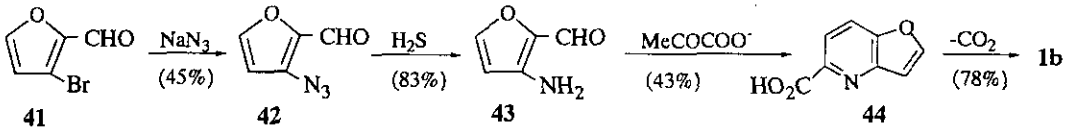




39"b 40 15b

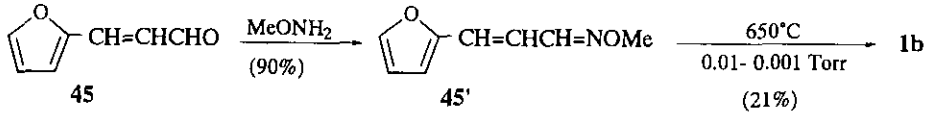
gave 3-methyl derivative (**15b**).

Gronowitz *et al.* first synthesized the parent furo[3,2-*b*]pyridine (**1b**) by using Friedländer reaction of 3-amino-2-formylfuran (**43**) with pyruvic acid and the subsequent decarboxylation. The same reaction of **43** with acetone gave 5-methyl derivative in 71% yield.[22]



41 42 43 44

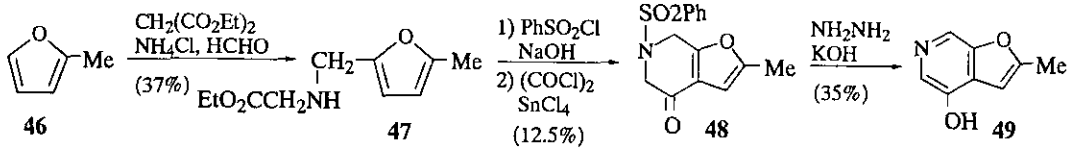
A simple procedure to give furo[3,2-*b*]pyridine (**1b**) was based upon the one-step formation of pyridine ring by high-vacuum pyrolysis of *O*-methyloxime (**45'**) of conjugated furylaldehyde (**45**).[23]



45 45'

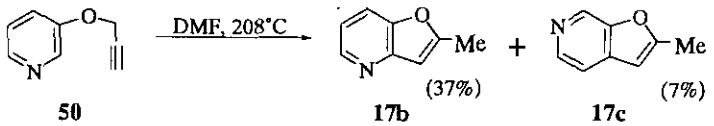
c) Furo[2,3-*c*]pyridine

The first synthesis of furo[2,3-*c*]pyridine derivative was reported by Mertes *et al.*[24] The Mannich condensation of 2-methylfuran (**46**) with diethyl malonate, ammonium chloride and formaldehyde gave compound (**47**). The *N*-benzenesulfonated derivative was cyclized with oxalyl chloride and $SnCl_4$ to yield a furo[2,3-c]pyridine compound (**48**), which was transformed to 2-methyl-4-hydroxyfuro[2,3-*c*]pyridine (**49**).



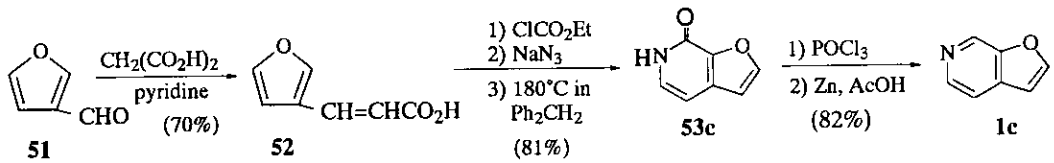
46 47 48 49

The Claisen rearrangement of 3-(2-propynyloxy)pyridine (**50**) by heating in DMF afforded 2-methylfuro[3,2-*b*]pyridine (**17b**) and 2-methylfuro[2,3-*c*]pyridine (**17c**).[25]



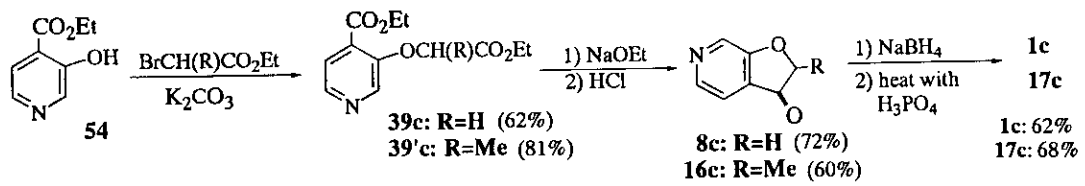
50 17b 17c

The parent compound (**1c**) was first synthesized by Shiotani applying the method of Eloy and Deryckere[26] for the synthesis of furo[3,2-*c*]pyridine. β-(3-Furyl)acrylic acid (**52**) obtained by condensation of 3-furaldehyde (**51**) with malonic acid was converted to the azide. The azide was cyclized to give furo[2,3-*c*]pyridine-7(6*H*)-one (**53c**) by heating at 180°C in diphenylmethane. Conversion of the pyridone (**53c**) to 7-chloro derivative and the successive replacement of the chlorine with hydrogen by treating with zinc in acetic acid yielded the parent compound (**1c**).[27]



51 **52** **53c** **1c**

A convenient route to furo[2,3-*c*]pyridine from pyridine derivatives was also developed by Shiotani. Ethyl ester of 3-hydroxyisonicotinic acid was *O*-alkylated with ethyl bromoacetate (or ethyl bromopropionate) in the presence of potassium carbonate to give diester (**36c**) (or **37c**). The Dieckmann cyclization of the diester (**36c**) (or **37c**) and the subsequent decarboxylation gave 3-furopyridinone (**8c**) or (**16c**). Reduction of the carbonyl group with sodium borohydride and the successive dehydration with phosphoric acid afforded the parent molecule (**1c**) (or 2-methyl derivative **17c**).[28]



54

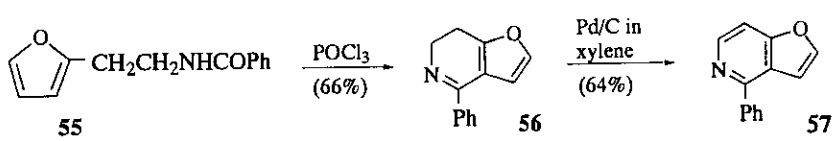
39c: R=H (62%)
39'c: R=Me (81%)

8c: R=H (72%)
16c: R=Me (60%)

1c: 62%
17c: 68%

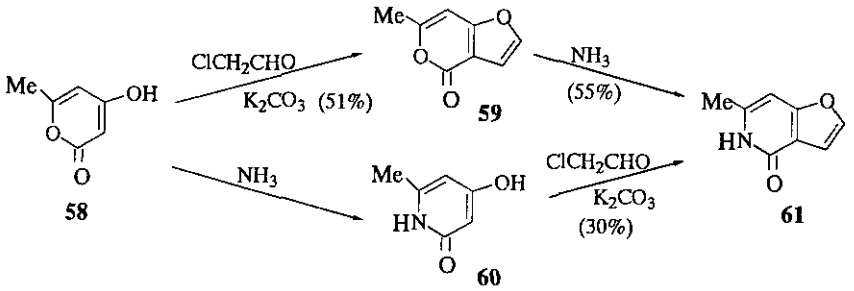
d) Furo[3,2-*c*]pyridine

This system also has been synthesized starting either from preformed pyridines and furans. The preparation of derivatives of furo[3,2-*c*]pyridine (**57**) was first described by Herz who applied Bischler-Napieralski reaction to *N*-acyl derivatives of β-(2-furyl)-ethylamine (**55**).[29]

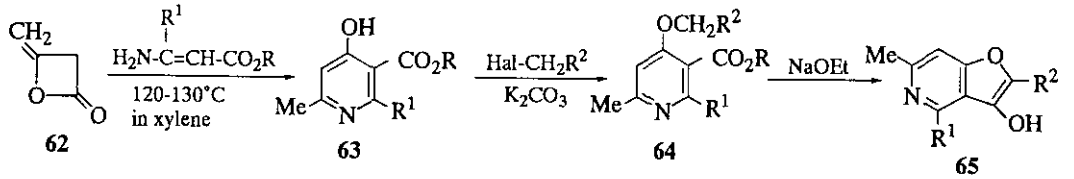


55 **56** **57**

It has also been proved that 4-hydroxy-6-methylpyran-2-one (**58**) is a useful precursor for the synthesis of furo[3,2-*c*]pyridines. Compound (**58**) was converted to 6-methylfuro[3,2-*c*]pyridin-4(5*H*)-one (**61**) *via* two routes: 1) Condensation of **58** with chloroacetaldehyde in the presence of potassium carbonate and the successive dehydration yielded compound (**59**), which was converted to **61** by treatment with ammonia. 2) Treatment of **58** with ammonia gave 4-hydroxy-6-methylpyridin-2(3*H*)-one (**60**). Condensation of **60** with chloroacetaldehyde yielded **61**.[30]

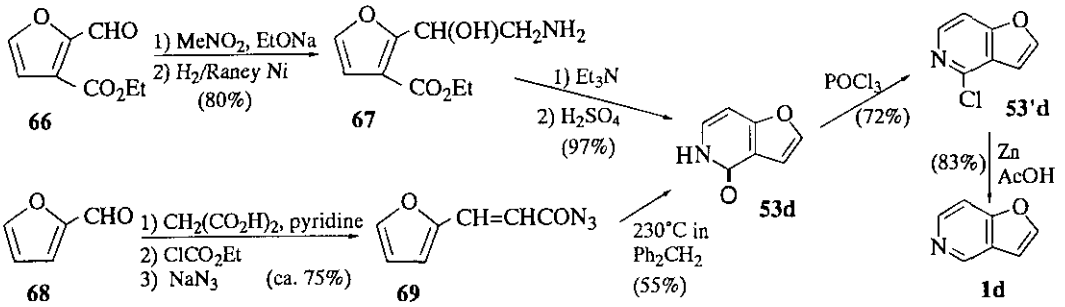


Hörlein *et al.* have reported the synthesis of derivatives of furo[3,2-*c*]pyridin-3-ol (**65**) by cyclization of 2,6-disubstituted 4-alkoxypyridine-3-carboxylates (**64**). 4-Hydroxypyridine-3-carboxylates (**63**), which were prepared from diketene (**62**) and β-aminoacrylic esters, were reacted with α-halo ketones in the presence of potassium carbonate to give compounds of type (**64**).[31]

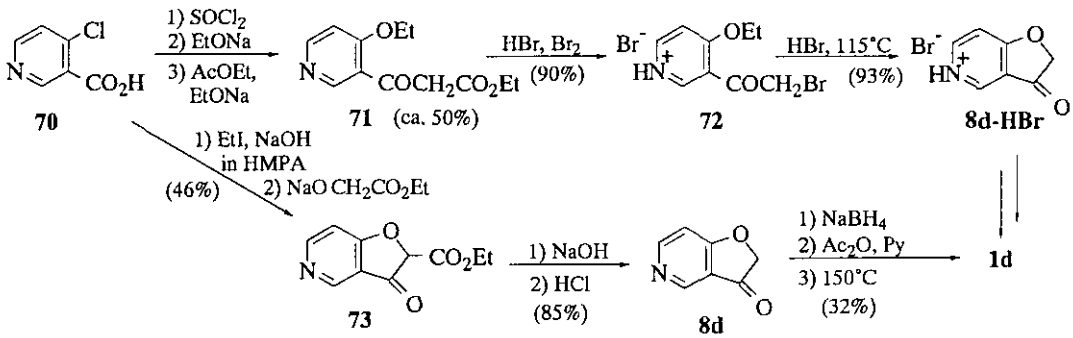


R: Et, Me R¹: Me, Ph, OEt R²: CN, CO_2Et, COMe, COPh etc

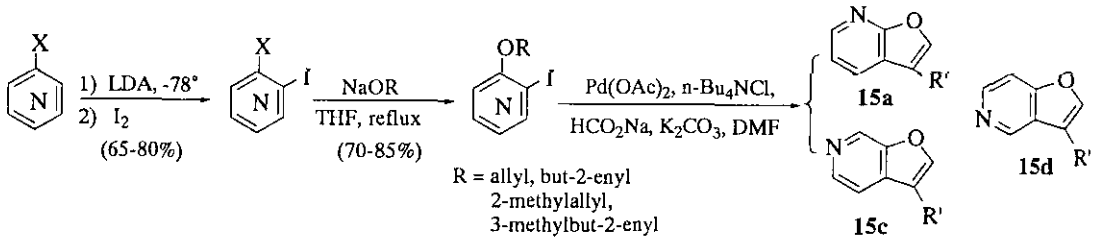
The parent structure of furo[3,2-*c*]pyridine (**1d**) has been synthesized by several methods starting both from furan and from pyridine derivatives. Condensation of ethyl 2-formylfuran-3-carboxylate (**66**) with nitromethane yielded a nitro alcohol, which was successively reduced, cyclized and dehydrated to give furo[3,2-*c*]pyridin-4(5*H*)-one (**53d**).[32] The furopyridinone (**53d**) was also prepared from β-(2-furyl)acrylic acid by conversion of the acid to an azide (**69**) and heating the azide at 230°C.[26] Chlorination of **53d** and replacement of the chlorine with hydrogen afforded the parent molecule (**1d**). 2-Methyl derivative (**17d**) was also prepared by this method from 5-methylfurfural.[26] The construction of the furan ring starting from 4-chloronicotinic acid (**70**) has also proved



useful for the synthesis of furo[3,2-*c*]pyridines. Sliwa transformed **70** to 3-bromoacetyl-4-ethoxypyridine hydrobromide (**72**). Chlorination of **70** with thionyl chloride was followed by treatment with sodium ethoxide to give ethyl 4-ethoxynicotinate, which was converted to the ketoester (**71**) by the Claisen condensation with ethyl acetate The bromination of **71** with bromine in concentrated hydrobromic acid and acetic acid gave **72**. Heating the compound (**72**) with hydrogen bromide in acetic acid afforded furo[3,2-*c*]-pyridin-3(2*H*)-one (**8d**). The parent compound (**1d**) was obtained by reduction of **8d-HBr** with sodium borohydride, acetylation of the resulting hydroxy compound and heating the acetoxy derivative at 150°C.[33,34] Shiotani also prepared the ketone (**8d**) from 4-chloronicotinic acid (**70**) by esterification, condensation of the ester with sodium ethoxycarbonylmethoxide, cyclization and the subsequent decarboxylation.[35]



Most recently, a Korean group reported the synthesis of 3-alkyl derivatives of furo[2,3-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine by the Pd-catalyzed cyclization of iodopyridinyl allyl ethers derived from dihalopyridines and sodium allyl alkoxides.[36]



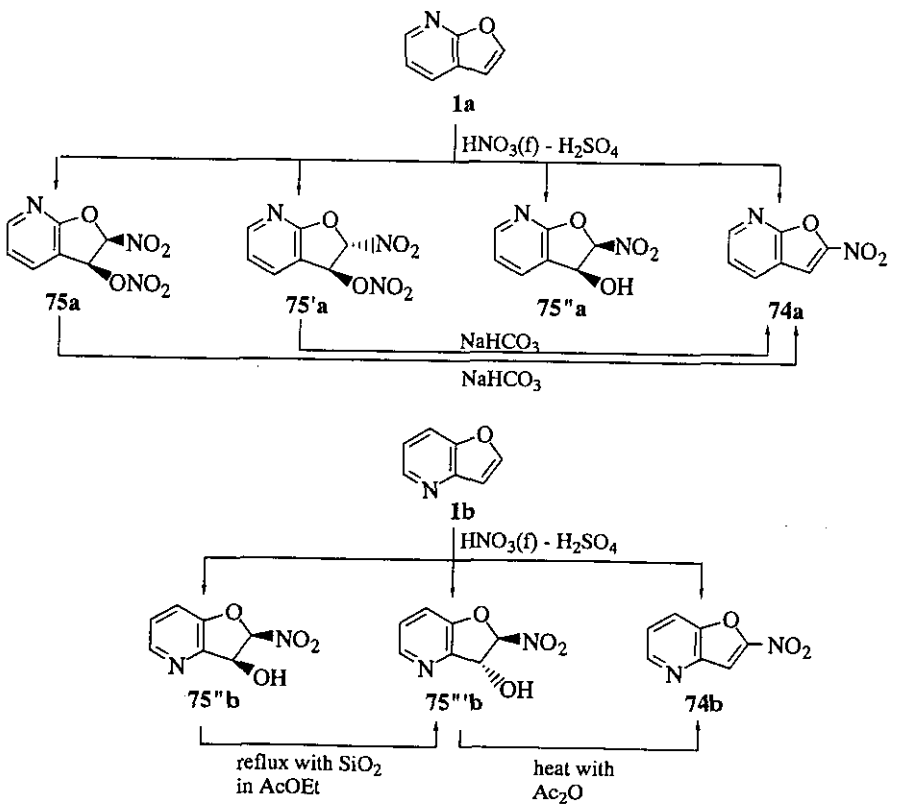
III. REACTION OF FUROPYRIDINES

There had been only a few reports concerning the chemical properties of furopyridines, until Shiotani and coworkers reported the systematic research on the electrophilic reactions of furopyridines (**1a**, **1b**, **1c** and **1d**) in 1984.[37]

III-1. Reaction of the furan ring of furopyridines

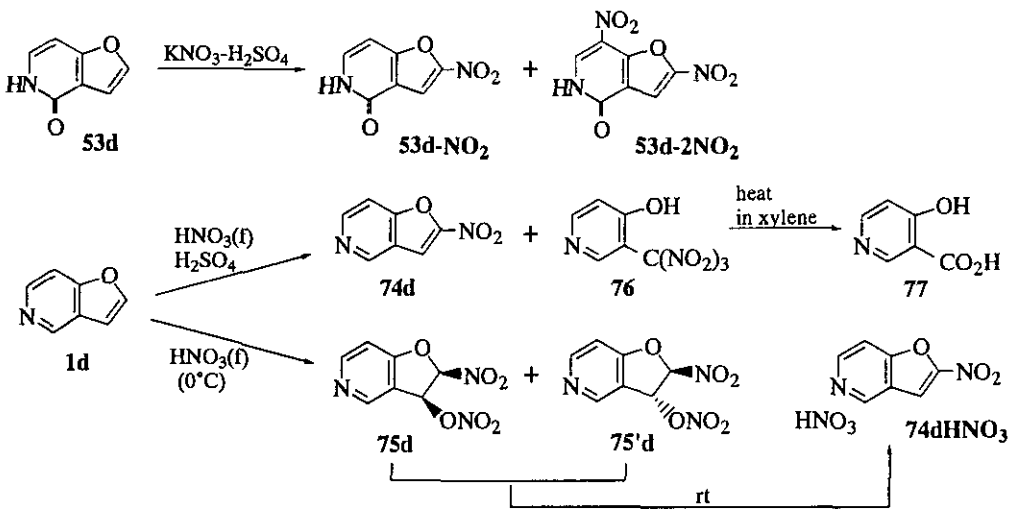
a) Nitration[37]

Treatment of the quinoline isostere (**1a**) with a mixture of fuming nitric acid and sulfuric acid afforded a mixture of 2-nitro compound (**74a**) and addition products, 2-nitro-3-hydroxy-2,3-dihydro derivative (**75"a**) and the nitrates (**75**) and (**75'a**) (approximate ratio: 2:20:5:1) in good yield, from which compound (**74a**) was obtained by treatment with sodium hydrogen carbonate.

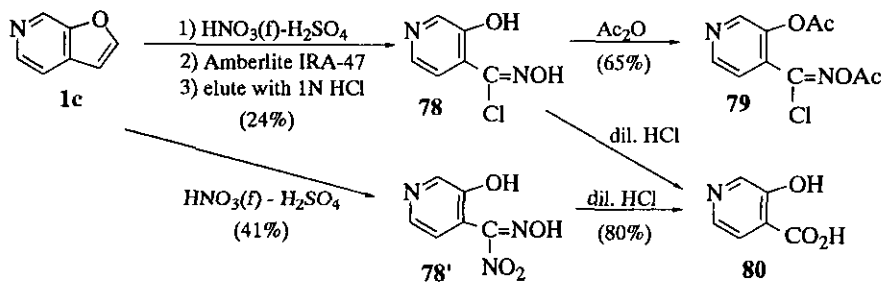


Compound (**1b**) was also treated with a mixture of fuming nitric acid and sulfuric acid to give a mixture of 2-nitro derivative (**74b**) and addition products (**75"b**) and (**75"'b**) (approximate ratio: 1:3:2). The addition products were converted to 2-nitro derivative (**74b**).

Treatment of furo[3,2-*c*]pyridin-4(5*H*)-one (**53d**) with potassium nitrate in sulfuric acid gave a mixture of 2-nitro (**53d-NO$_2$**) and 2,7-dinitro derivative (**53d-2NO$_2$**) (ratio: 85:15).[32] McFarland reported that furo[3,2-*c*]pyridine (**1d**) was nitrated with a mixture of fuming nitric acid and sulfuric acid below 0°C to give 2-nitro compound (**74d**).[38] Shiotani, however, reexamined the nitration of **1d**, and isolated the 2-nitro derivative (**74d**) (33%) as an ether-soluble product and another chloroform-soluble compound (**76**) (20%). Compound (**76**) was converted to 4-hydroxynicotinic acid (**77**) by heating in xylene. Treatment of **1d** with fuming nitric acid at 0°C yielded a mixture of addition products (**75d** and **75'd**), which rapidly changed to **74d-HNO$_3$** at room temperature.[37]

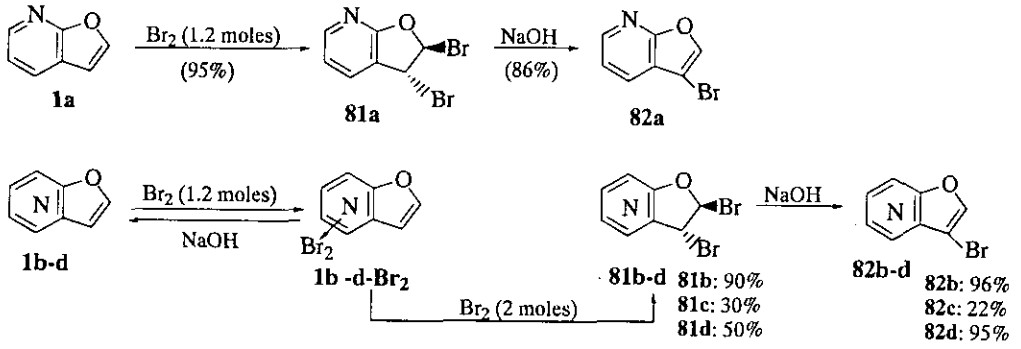


Treatment of -[2,3-*c*]- (**1c**) with a mixture of fuming nitric acid and sulfuric acid yielded water-soluble 3-hydroxypyridine-4-nitrolic acid (**78'**) in 41% yield.[37]



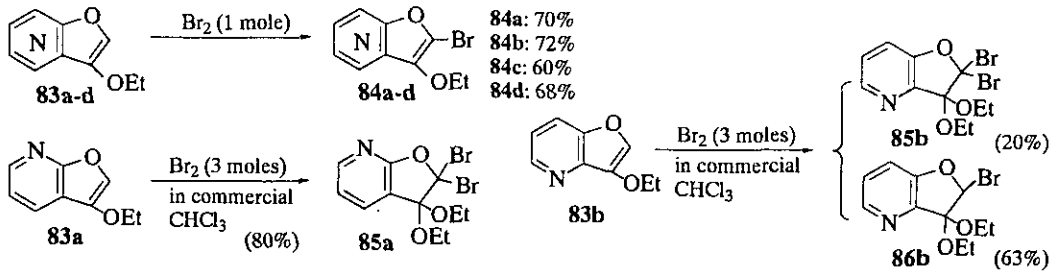
b) Bromination[35,37]

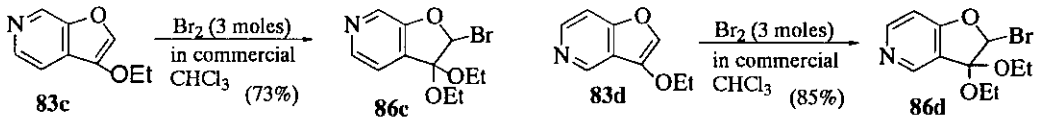
McFarland reported also that halogenation of furo[3,2-*c*]pyridine (**1d**) in carbon tetrachloride afforded the corresponding 2,3-dihalo-2,3-dihydro compound.[38] The more detailed works by Shiotani revealed that the bromination of -[2,3-*b*]- (**1a**), a very weak base (pKa 0.87), with 1.2 equivalent moles of bromine in carbon tetrachloride gave 2,3-dibromo-2,3-dihydro derivative (**81a**), while the other furopyridines, stronger bases, yielded perbromides (**1-Br$_2$**). The bromination of the three isomeric furopyridines with 3.0 equivalent moles of bromine afforded 2,3-dibromo-2,3-dihydro derivatives (**81b**), (**81c**), and (**81d**) or their perbromides. Dehydrobromination of the dibromo adducts with sodium hydroxide in methanol yielded 3-bromofuropyridines (**82a**, **82b**, **82c** and **82d**) in excellent yield.[37]



These results resemble the bromination of benzo[*b*]furan rather than those of furan itself and thienopyridines.

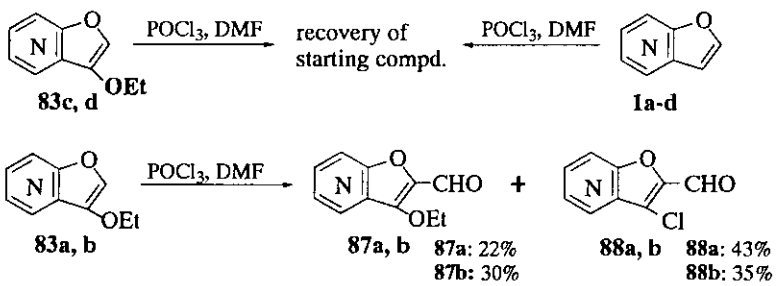
The bromination of 3-ethoxyfuropyridines (**83a-d**) with 1 equivalent mole of bromine in chloroform (commercial reagent grade, containing ethanol (ca. 1%) as stabi- lizer) or with 3 moles in dry chloroform yielded the corresponding 2-bromo-3-ethoxy derivatives (**84a-d**). While, the bromination with 3-moles of bromine in commercial reagent grade chloroform afforded somewhat complicated results as shown in the Scheme below.[35]





c) Vilsmeier reaction[35]

The Vilsmeier reaction of the parent furopyridines and the 3-ethoxy derivatives of isoquinoline isosteres with phosphoryl chloride and DMF resulted in complete recovery of the starting compound, while the 3-ethoxy derivatives of quinoline isosteres (**83a**) and (**83b**) yielded the corresponding 3-ethoxy-2-aldehyde (**87a**) and (**87b**) and 3-chloro-2-aldehyde (**88a**) and (**88b**). The 3-chloro-2-aldehydes would be formed by the nucleophilic substitution of the ethoxy group with chloride anion, which was facilitated by the formyl group at 2-position.

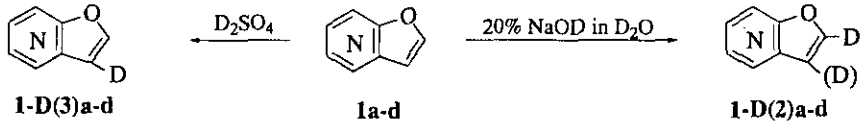


McFarland reported[38] that attempts at acetylation of furo[3,2-*c*]pyridine (**1d**) with acetyl chloride-aluminum chloride and acetic anhydride-boron trifluoride etherate, and sulfonation of **1d** with concentrated sulfuric acid or pyridine-sulfur trioxide were unsuccessful and/or resulted in recovery of the starting compound.

d) H-D exchange[37]

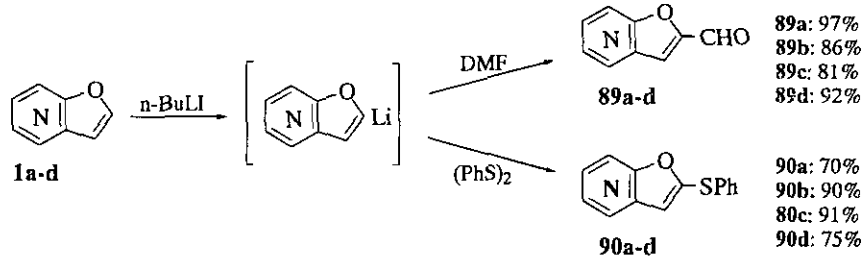
The H-D exchange reaction of the parent compounds (**1a-d**) in 96% sulfuric acid-d_2 at 85°C, the simplest electrophilic reaction, was followed by ^{1}H-NMR technique. After 9 hours, 54% of H-3 of **1a**, 70% of H-3 of **1b**, 95% of H-3 of **1c** and 87% of H-3 of **1d** were exchanged without any noticeable change of the intensity of the H-2 or other ring proton signal. The H-D exchange reactions of **1a-d** with 20% sodium deuterioxide in methanol-d_4 at 55°C were also studied. After 1.5 hours, 61%, 68%, 90% and 68% of H-2 were exchanged accompanying the exchange of 5%, 10%, 20% and 5% of H-3,

respectively.



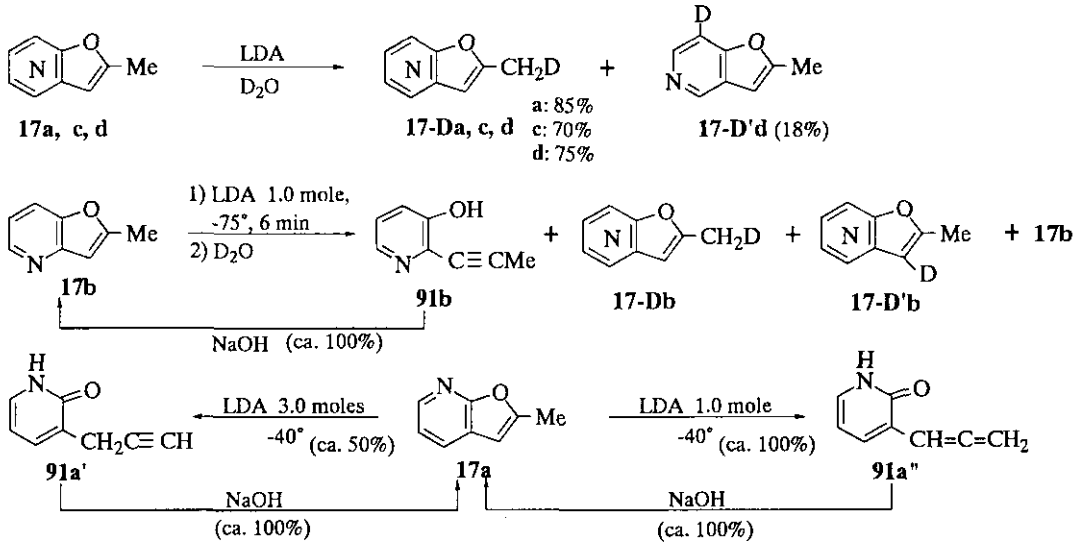
e) Lithiation of the parent and 2-methyl compounds[10,39-41]

Lithiation of the parent furopyridines (**1a-d**) with *n*-butyllithium or LDA, in THF at -75°C, yielded exclusively 2-lithio intermediate. The subsequent treatment of the 2-lithio intermediate with DMF and diphenyl disulfide gave the corresponding 2-formyl (**89a-d**)[10,39] and 2-phenylthio derivatives (**90a-d**)[40] in excellent yield. Under these conditions, addition of BuLi to the heterocyclic nitrogen was not observed, which was discussed by Klemm for thieno[2,3-*b*]pyridine[42] and by Gronowitz and Sandberg for thieno[2,3-*c*]- and -[3,2- *c*]pyridine.[43]

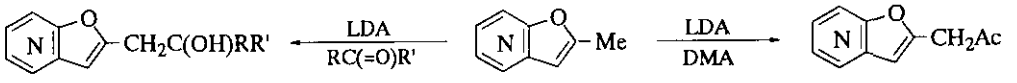


Reaction of 2-methylfuropyridines (**17a-d**) with LDA gave somewhat complicated results. When 2-methylfuro[2,3-*b*]- (**17a**) and -[2,3-*c*]pyridine (**17c**) were reacted with 1.0 eq. of LDA at -75°C and then treated with D_2O, the corresponding 2-monodeuteriomethylfuropyridines (**17-Da**) and (**17-Dc**) were obtained in excellent yield. While, the same reaction of 2-methylfuro[3,2-*b*]pyridine (**17b**) yielded a mixture of 2-monodeuteriomethyl compound (**17-Db**), 2-methyl-3-deuteriofuro[3,2-*b*]pyridine (**17-D'b**), 2-(1-propynyl)pyridin-3-ol (**91b**) and (**17b**) (40:25:25:10). The same reaction of 2-methylfuro[3,2-*c*]pyridine (**17d**) gave a mixture of the 2-monodeuteriomethyl compound (**17-Dd**) and 2-methyl-7-deuteriofuro[3,2-*c*]pyridine (**17-D'd**). Interestingly, the reaction of **17a** with 1.0 eq. of LDA at -40°C afforded 3-(1,2-propadienyl)pyridin-2-ol (**91'a**), with 3.0 eq. of LDA a mixture of **91'c** and 3-(2-propynyl)pyridin-2-ol (**91"a**) (1:1). The reaction of **17b** with 1.0 eq. of LDA at -40°C gave a mixture of **91b** and **17-Db** (1:1). The allene compound (**91"a**) and the acetylenic compounds (**91'a**) and (**91b**) were recyclized to the corre-

sponding furopyridine by treatment with sodium hydroxide or by heating above 150°C.[41]



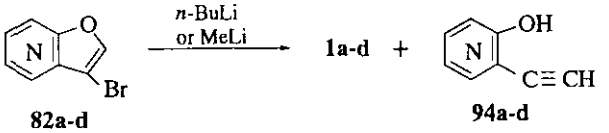
The lithio intermediate from these 2-methylfuropyridines (**17a-d**) afforded the corresponding secondary or tertiary alcohols (**92a-d**) by treatment with aldehydes or ketones, and the acetonyl compounds (**93a-d**) with *N*,*N*-dimethylacetamide.[41]



	R	R'	yield (%)		R	R'	yield (%)
	Ph	H	95		Ph	H	94
a:	Et	H	74	c:	Et	H	90
	Me	Me	71		Me	Me	95
	Ph	H	10		Ph	H	95
b:	Et	H	-	d:	Et	H	88
	Me	Me	21		Me	Me	95

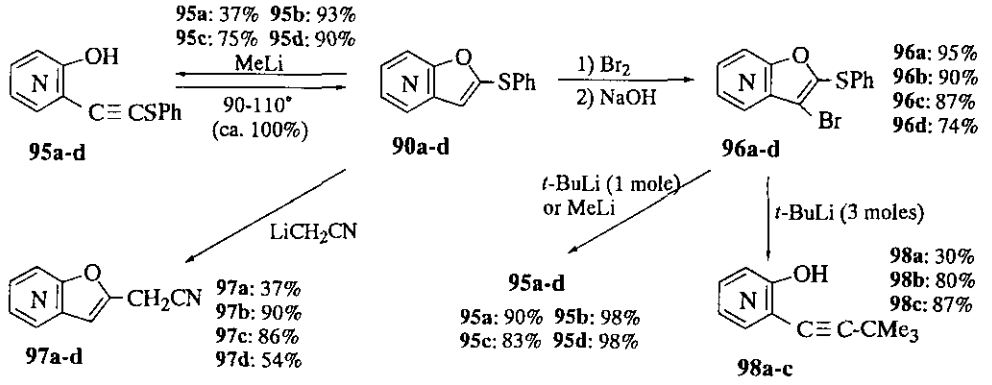
f) Reaction of 3-bromo compounds with alkyllithium[40]

When 3-bromofuropyridines (**82a-d**) reacted with *n*-butyllithium or methyllithium, a mixture of the corresponding parent furopyridine (**1a** (38%), **1b** (56%), **1c** 58%) and **1d** (35%)) and the *o*-ethynylpyridinol (**94a** (57%), **94b** (36%), **94c** (38%) and **94d** (55%)), were obtained, respectively.



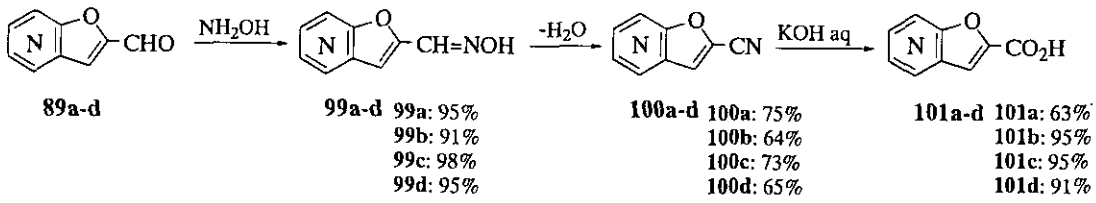
The 2-phenylthiofuropyridines (**90a-d**) reacted with methyllithium to give the *o*-phenylthioethynylpyridinols (**95a-d**) which were recyclized to yield **90a-d** by heating at 110°C. The phenylthio group of 2-phenylthiofuropyridines (**90a-d**) was substituted by cyanomethyl group by the reaction with lithioacetonitrile to give compounds (**97a-d**).

Reaction of 2-phenylthio-3-bromofuropyridines (**96a-d**) with methyllithium (3 eq.) or *t*-butyllithium (1.2 eq) afforded the phenylthioethynylpyridinols (**95a-d**). When 3 eq. of *t*-butyllithium was used, compounds (**96a-c**) afforded ethynylpyridinol compounds (**98a-c**) in which the phenylthio group was replaced with *t*-butyl group.

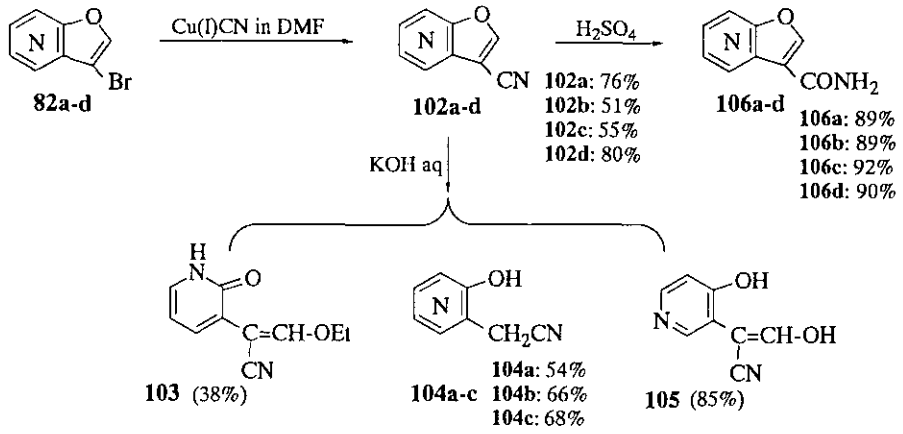


g) Preparation and hydrolysis of 2- and 3-cyanofuropyridines[10,39]

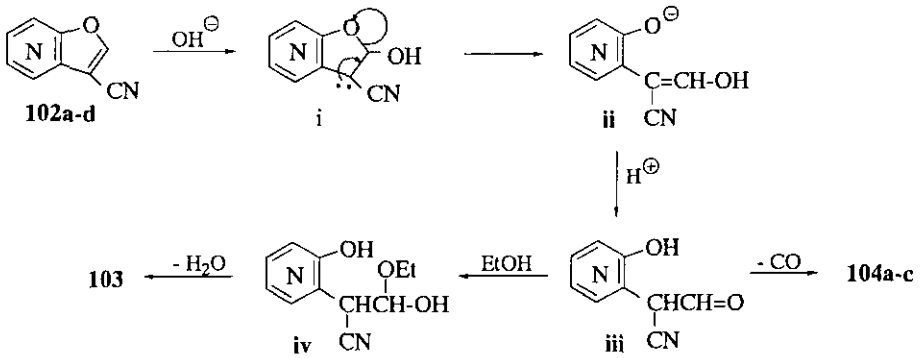
The 2-cyano derivatives (**100a-d**) were prepared by dehydration of the oximes (**99a-d**) of 2-aldehydes (**89a-d**). The bromine of 3-bromo compounds (**82a-d**) was substituted with a cyano group by heating with Cu(I)CN in DMF to give 3-cyano derivatives (**102a-d**).[10,39]



The cyano group of 2-cyano compound was hydrolyzed with potassium hydroxide to give the 2-carboxylic acid (**101a-d**), while the hydrolysis of 3-cyano group of **102a-d** with potassium hydroxide yielded a mixture of 1-[3-(1-hydroxypyridyl)]-2-ethoxyacrylonitrile (**103**) and 3-cyanomethylpyridin-2-ol (**104a**) from **102a**, 2-cyanomethylpyridin-3-ol (**104b**) from **102b**, 4-cyanomethylpyridin-3-ol (**104c**) from **102c** and 1-[3-(4-hydroxypyridyl)]-2-hydroxyacrylonitrile (**105**) from **102d**.[10,39]



These unexpected results would be interpreted as follows. The carbon at 2-position of **102a-d** is highly reactive for nucleophilic attack due to the electron withdrawing effect of the 3-cyano group and the ring oxygen. Therefore, the intermediate (**i**) is easily formed by attack of hydroxide anion. Cleavage of the 1-2 bond of (**i**) yields intermediate (**ii**) which gives compound (**104**) through isomerization to intermediate (**iii**) and decarbonylation. Attack of ethanol molecule at the carbonyl carbon or (**iii**) gives intermediate (**iv**) from which compound (**103**) is formed by dehydration.[10,39]

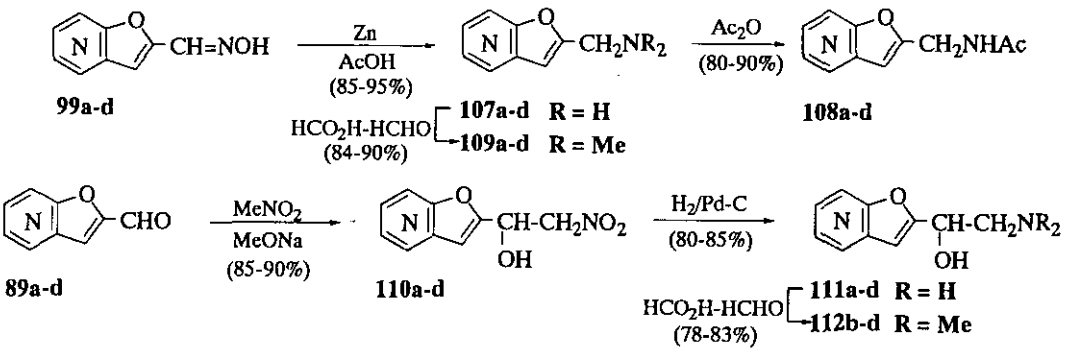


Hydrolysis of the 3-cyano compounds with diluted sulfuric acid yielded the amides (**106a-d**).[10,39]

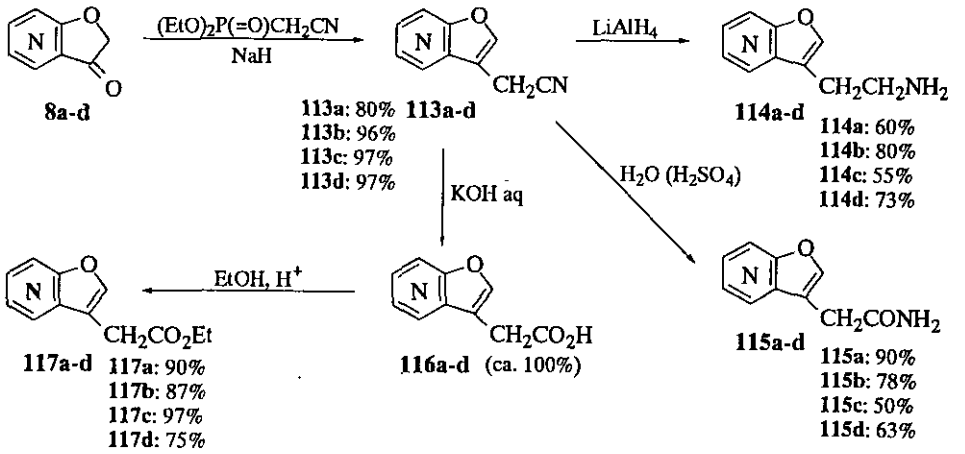
h) Preparation of some derivative having a carbon-substituent at 2- or 3-position[44,45]

With the aim of determining the pharmacological activities, some 2-aminoalkyl derivatives and derivatives having a carbon-substituent at 3-position were prepared.

Reduction of the oximes (**99a-d**) by heating with zinc in acetic acid afforded 2-aminomethyl compounds (**107a-d**), from which the *N*-acetyl (**108a-d**) and *N*,*N*-dimethyl derivatives (**109a-d**) were prepared. Condensation of the aldehydes (**99a-d**) with nitromethane afforded the corresponding nitroethanols (**110a-d**). The nitro group was catalytically reduced, followed by methylation with formaldehyde and formic acid to give the *N*,*N*- dimethyl derivatives (**112a-d**).[44]

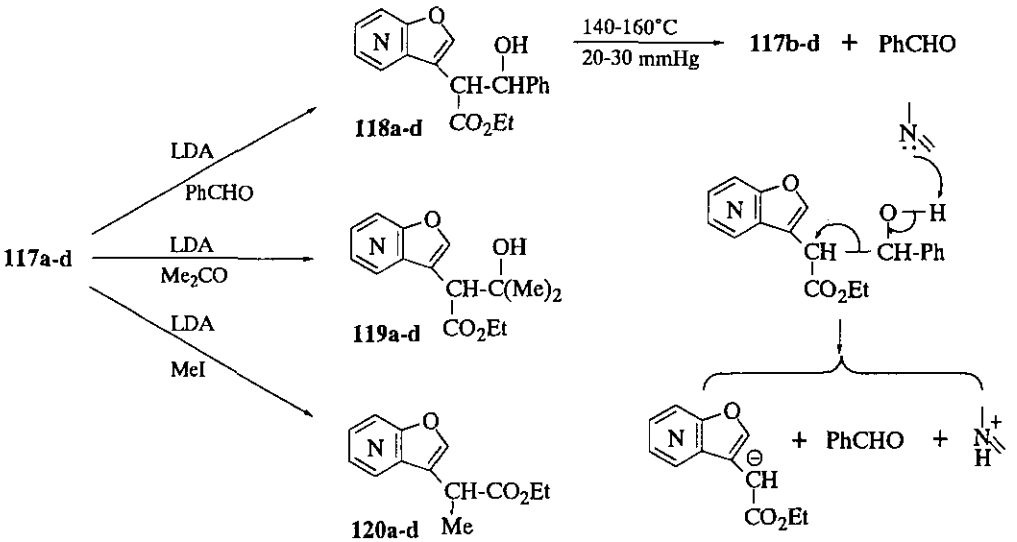


Cyanomethylation of furopyridin-3(2*H*)-ones (**8a-d**) by Wittig-Horner reaction with diethyl cyanomethylphosphonate yielded the corresponding 3-cyanomethyl derivatives (**113a-d**). The cyanomethyl derivatives were converted to the 3-aminoethyl compounds (**114a-d**) by reduction with $LiAlH_4$, to the amides (**115a-d**) by hydrolysis with 95%-H_2SO_4 and the ethoxycarbonylmethyl compound (**117a-d**) by alkaline hydrolysis and the subsequent esterification.[45]



The esters (**117a-d**) were lithiated with 1.2 eq. of LDA and then treated with benzaldehyde, acetone and iodomethane, by which the corresponding alcohols (**118a-d**), (**119a-d**) and

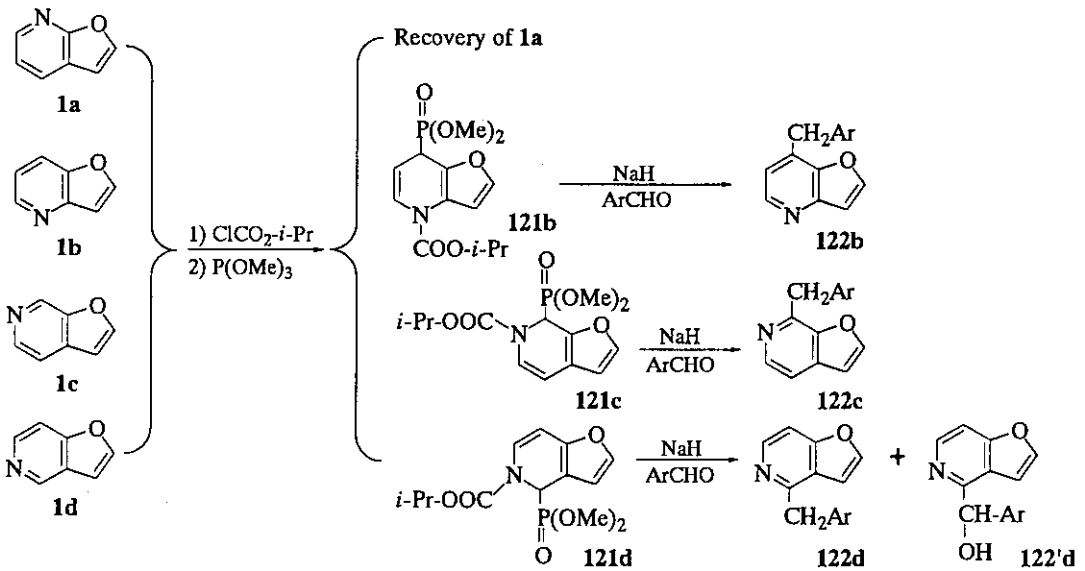
the methylated products (**120a-d**) were prepared in fairly good yields. In contrast, the reaction with *N*,*N*-dimethylacetamide, a weak electrophile, resulted in complete recovery of the starting ester. It is of interest that the secondary alcohols (**118b-d**) were decomposed to the ethoxycarbonylmethyl compounds (**117b-d**) and benzaldehyde by heating at 140-160 °C under reduced pressure in almost quantitative yield, while compounds (**118a**) and (**119a-d**) were stable at this temperature and could be distilled without any decomposition; moreover, none of these compounds (**118a-d**) and (**119a-d**) yielded any dehydrated olefinic product by refluxing with hydrochloric acid. These unexpected results can be interpreted as follows. The hydroxyl proton of **118b-d** is drawn to the ring nitrogen of furopyridine intermolecularly, and the electrons at the O-H bond are transferred to from the C=O double bond and subsequently the C-C bond is cleaved, which assisted by the conjugation effect of the phenyl group as depicted in the Scheme below. In the case of **118a**, the hydroxy proton would not be drawn by ring nitrogen of furo[2,3-*b*]pyridine, a very weak base, intermolecularly. The inductive effect of the methyl group of **119a-d** would prevent formation of the C=O double bond.[45]



III-2. Reaction of the pyridine ring of furopyridines

a) Wittig-Horner reaction of a phosphonate of Reissert analogue[46]

N-Isopropoxycarbonylfuropyridinium chlorides were formed from the parent furopyridines (**1b-d**), except from **1a**, with isopropyl chloroformate, which were converted to the dimethylphosphonyl derivatives (**121b-d**) with trimethyl phosphite. Wittig-Horner reaction of **121b-d** with several *p*-substituted benzaldehydes afforded compounds having an arylmethyl group at the α-position to the ring nitrogen from **1c** and **1d**, and γ-position from **1b** as the final products (**122b-d**). In the case of **121d**, however, 4-(1-hydroxyphenylmethyl) derivatives (**122'd**) were also formed.

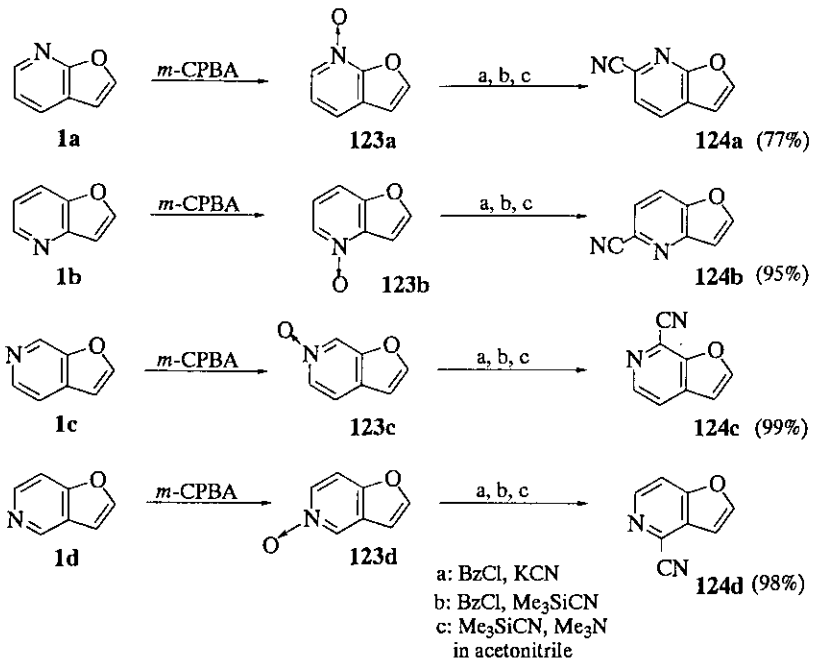


Ar = Ph, *p*-$MeOC_6H_4$, *p*-NCC_6H_4

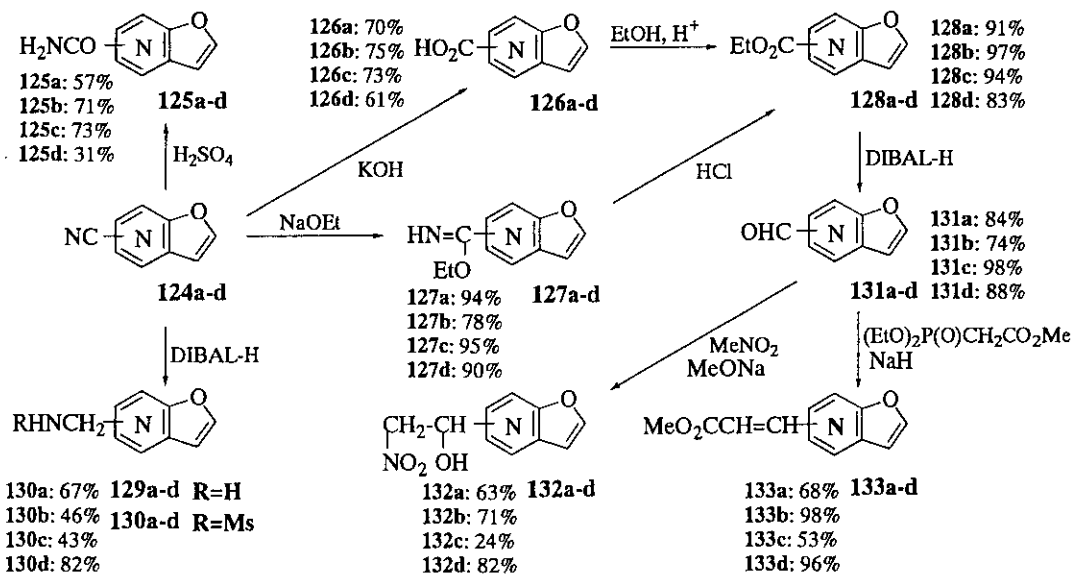
	Ph	*p*-$MeOC_6H_4$	*p*-NCC_6H_4
122b:	73%	73%	73%
122c:	84%	98%	90%
122d:	5%	10%	21%
122'd:	50%	50%	29%

b) Cyanation of *N*-oxides[47-49]

The *N*-oxides (**123a-d**) of furopyridines were cyanated by Reissert-Henze method using benzoyl chloride and potassium cyanide or benzoyl chloride and trimethylsilyl cyanide in dichloromethane, and by the method of Vorbruggen using trimethylsilyl cyanide and trimethylamine in acetonitrile. Though these methods afforded the same derivatives (**124a-d**) cyanated at the α-position to the ring nitrogen (7-position in **1c** and 4- in **1d**) for each furopyridine, the last method gave the best results in yield and purity of the product.[47,48]



The cyano compounds were derived to the corresponding amides (**125a-d**), carboxylic acids (**126a-d**), iminoesters (**127a-d**) and esters (**128a-d**) in good yields. Reduction of the cyano group with DIBAL-H yielded the aminomethyl compounds (**129a-d**), while the reduction of the esters (**128a-d**) with 2-eq. of DIBAL-H gave the corresponding aldehydes (**131a-d**). The aldehydes were converted to the nitroethanol compounds (**132a-d**) with nitromethane, and to the methyl acrylate compounds (**133a-d**) by Wittig-Horner reaction



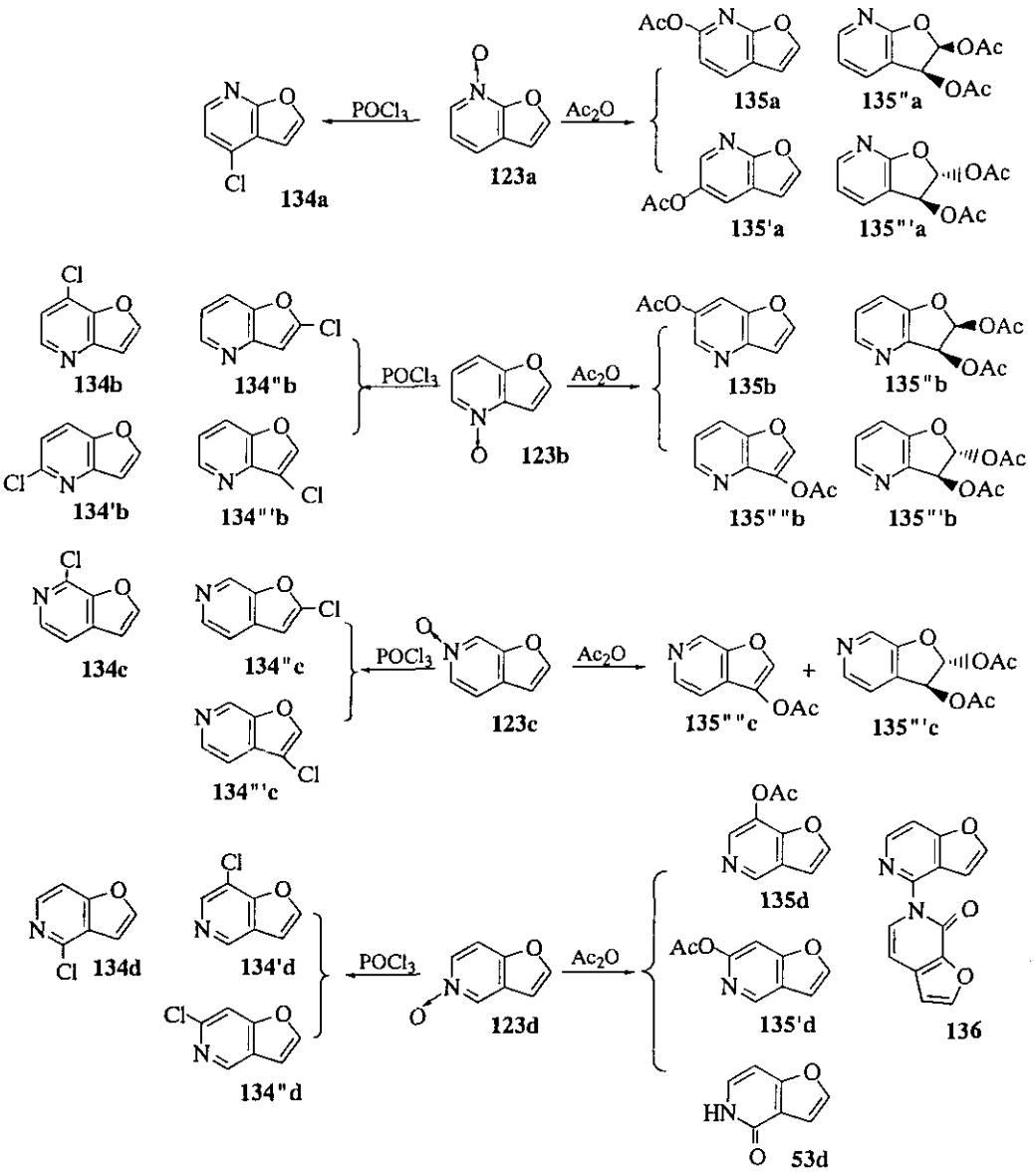
with methyl diethoxyphosphonoacetate.[47,49]

c) Chlorination and acetoxylation of *N*-oxides[47,50,51]

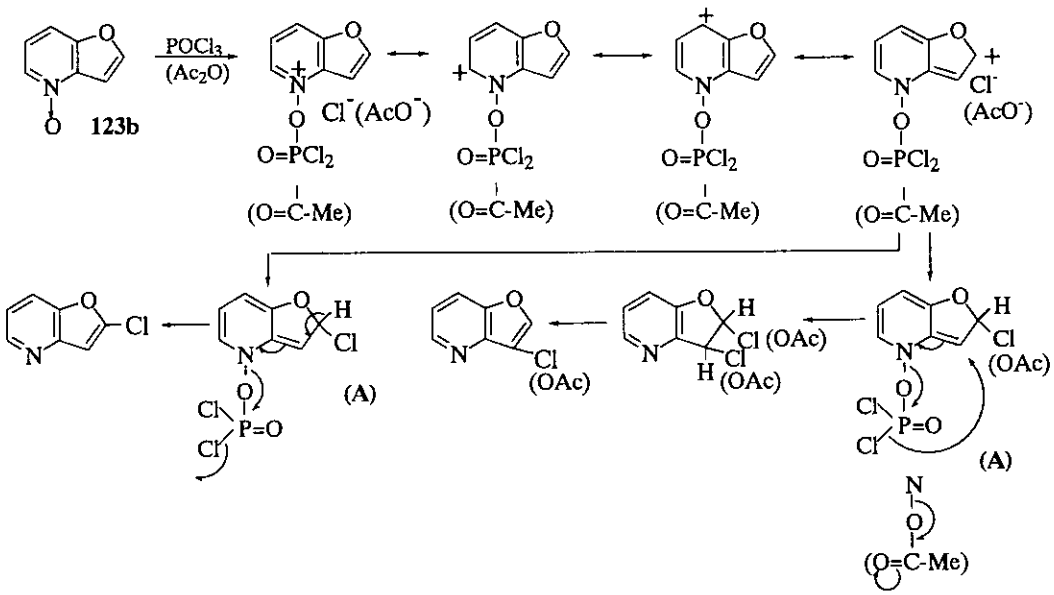
Chlorination of *N*-oxides (**123a-d**) with phosphorus oxychloride gave somewhat complex results. The chlorination of **123a** yielded 4-chloro derivative (**134a**, 65%). From the crude reaction product of **123b**, four monochloro derivatives, 7-chloro (**134b**, 47%), 5-chloro (**134'b**, 17%), 2-chloro (**134"b**, 3%) and 3-chloro derivative (**134'''b**, 13%) were isolated. The chlorination of **123c** yielded afforded three monochloro derivatives, 7-chloro (**134c**, 30%), 2-chloro (**134"c**, 5.5%) and 3-chloro compound (**134'''c**, 3%). The chlorination of (**123d**) yielded three monochloro derivatives, 4-chloro (**134d**, 65%), 7-chloro (**134'd**, 7%) and 6-chloro (**134"d**, 2%).[49,51]

Acetoxylation of *N*-oxides (**123a-d**) with acetic anhydride resembles the chlorination with phosphorus oxychloride. *N*-Oxide (**123a**) afforded four compounds, 6-acetoxy (**135a**, 50%), 5-acetoxy (**135'a**, 15%), *cis*-2,3-diacetoxy-2,3-dihydro (**135"a**, 3%) and *trans*-2,3-diacetoxy-2,3-dihydro compound (**135'''a**, 20%). *N*-Oxide (**123b**) gave four compounds, 6-acetoxy- (**135b**, 4%), *cis*-2,3-diacetoxy-2,3-dihydro- (**135"b**, 21%), *trans*-2,3-diacetoxy-2,3-dihydro- (**135'''b**, 33%) and 3-acetoxyfuro[3,2-*b*]pyridine (**135""b**, 4%). *N*-Oxide (**123c**) yielded two compounds, *trans*-2,3-diacetoxy-2,3-dihydro- (**135"**, 1%) and 3-acetoxyfuro[2,3-*c*]pyridine (**135""c**, 40%). *N*-Oxide (**123d**) gave four compounds, 7-acetoxy- (**135d**, 10%), 6-acetoxyfuro[3,2-*c*]pyridine (**135'd**, 4%), furo[3,2-*c*]pyridin-4(5*H*)-one (**53d**, 41%) and 5-(4'-furo[3,2-*c*]pyridyl)furo[3,2-*c*]pyridin-4(5*H*)-one (**136**, 30%).[50]

These results indicated that *N*-oxides of furopyridines having the furan oxygen at the β-position to the pyridine nitrogen, (**123b** and **123c**), yield compounds having chlorine or acetoxy substituent at the furan carbon. Formation of compound having a chlorine or an acetoxy group at the pyridine carbon, furopyridinone (**53**) and dimeric compound (**135"d**) from **123d** is interpreted by the well known mechanism for the chlorination and acetoxylation of *N*-oxides of pyridine, quinoline and isoquinoline.[52] However, formation of compounds having a chlorine or an acetoxy group at the furan carbon and diacetoxy derivatives was unexpected. These results can be interpreted as follows. The electron withdrawing effect of the phosphonated of acetoxylated pyridinium cation in the intermediate is efficiently exerted upon the carbon at the 2-position in furo[3,2-*b*]- and -[2,3-*c*]pyridine; that is the resonance form having a positive charge on C-2 is possible



for the intermediates from **123b** and **123c**, and impossible for **123a** and **123d**. Accordingly, in the cases of **123b** and **123c**, the first attack of the chloride or the acetoxy anion occurs at C-2 to form intermediate (A) and the successive attack of the anion at C-3, followed by concerted release of the phosphate or acetoxy group from the ring nitrogen to give 2,3-disubstituted-2,3-dihydro derivative. Dehydrochlorination or dehydroacetoxylation from the disubstituted derivative yields 3-substituted furopyridine. Deprotonation and the concerted release of the phosphate group from (A) would give 2-chloro compound.[50,51]

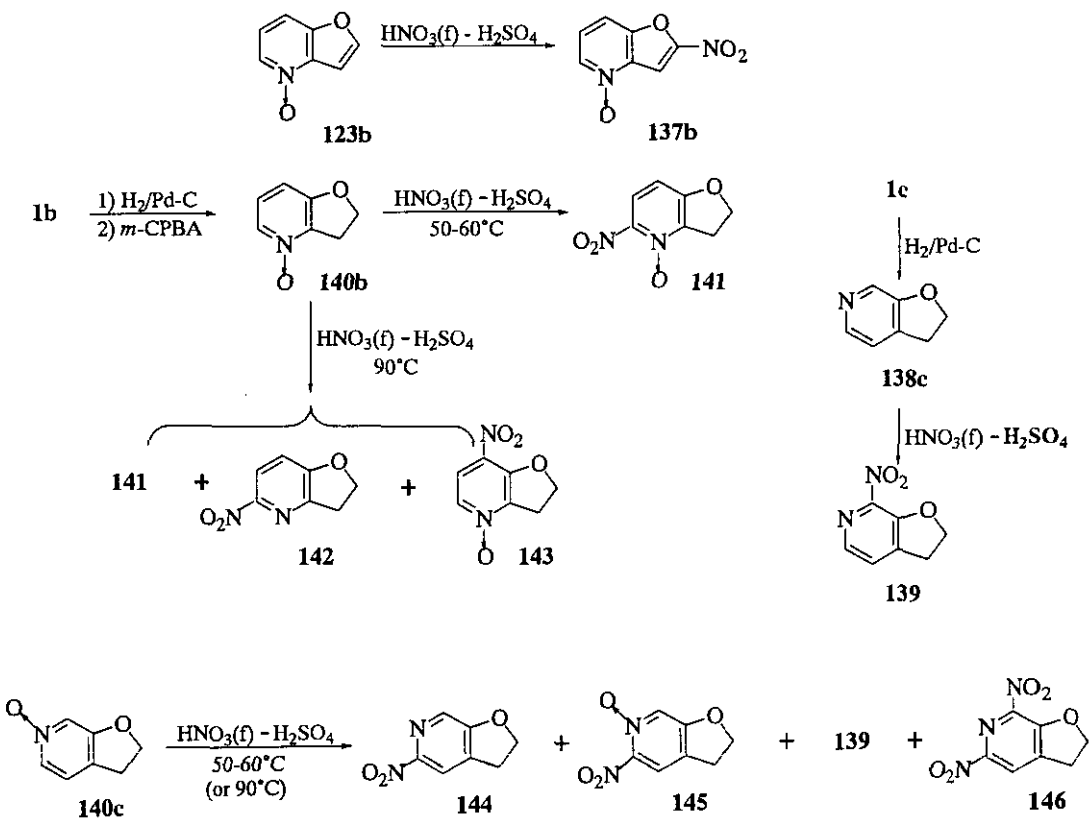


d) Nitration, chlorination, acetoxylation and cyanation of 2,3-dihydrofuropyridine *N*-oxides[53]

Treatment of furo[3,2-*b*]pyridine *N*-oxide (**123b**) with a mixture of fuming nitric acid and sulfuric acid yielded no compound nitrated at the pyridine ring but 2-nitro derivative (**137b**) in low yield. Though nitration of 2,3- dihydrofuro[2,3-c]pyridine (**138c**) afforded 7-nitro compound (**139**) in excellent yield, trials to obtain the pyridine-nitro derivatives by nitration of 2,3-dihydrofuropyridines (**138a**, **b** and **d**) with fuming nitric acid and sulfuric acid again yielded insufficient results.

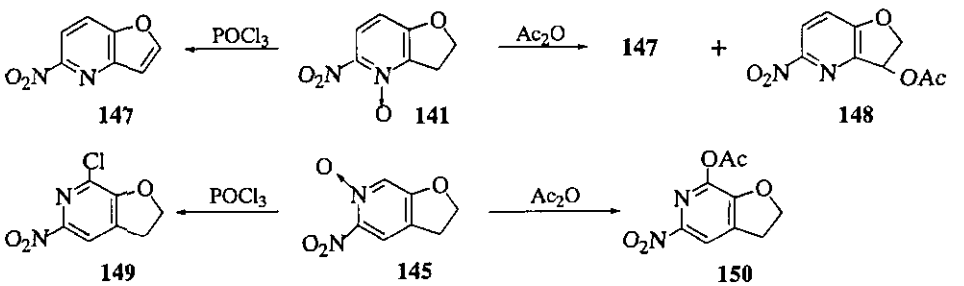
Nitration of 2,3-dihydrofuropyridine *N*-oxides (**140a** and **d**) with fuming nitric acid and sulfuric acid yielded no nitro compound. In contrast, nitration of the *N*-oxides (**140b** and **c**) gave compounds nitrated at the pyridine ring. The nitration of **140b** at 60°C yielded 5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine *N*-oxide (**141**, 90%) and the reaction at 90°C gave a mixture of **141** (44%), 5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine (**142**, 2%), 7-nitro-2,3-dihydrofuro[3,2-*b*]pyridine *N*-oxide (**143**, 15%). The nitration of **140c** at 60°C yielded a mixture of 5-nitro- (**144**, 5%), 7-nitro- (**139**, 2%), 5,7-dinitro-2,3-dihydrofuro[2,3-*c*]- pyridine (**146**, 5%) and *N*-oxide (**145**, 32%) of **144**.

These results indicated that the reactivity of the α- and γ-positions to the ring nitrogen for nitration is apparently affected by the electron donating mesomeric effect of the ring oxygen. In the cases of **140b** and **140c**, in which the ring oxygen is at the β-position to the ring nitrogen, the mesomeric effect and the back-donating effect of the *N*-oxide oxygen

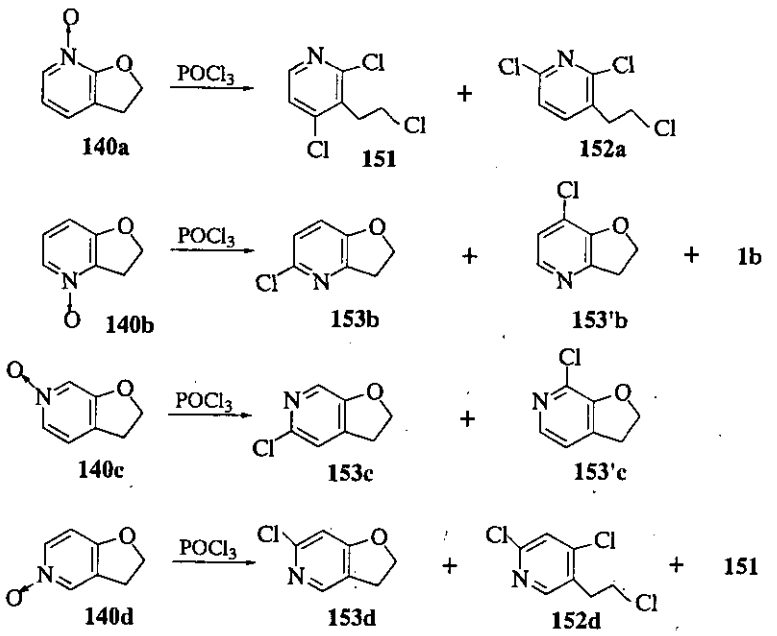


efficiently enhance the electrophilic reactivity of the α- and γ-positions to the ring nitrogen. While, in **140a** and **140d**, the mesomeric effect and the back-donating effect counteract each other at the α- and γ-position to the ring nitrogen.

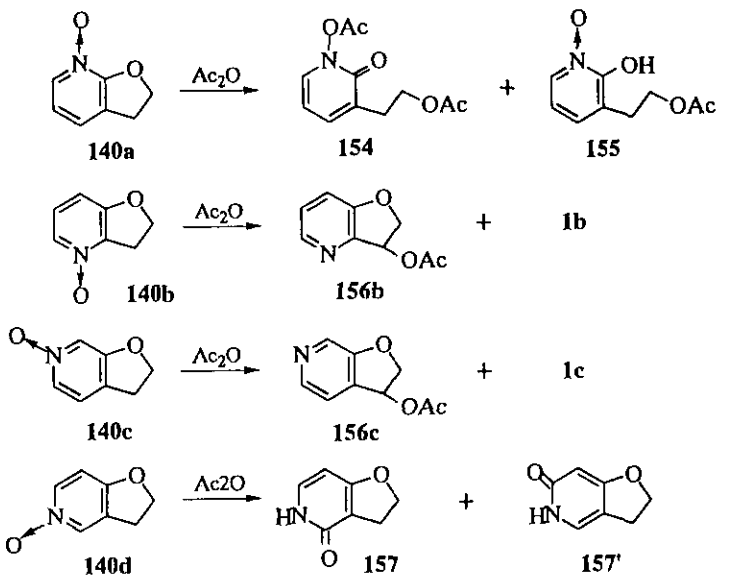
Interestingly, treatment of the 5-nitro *N*-oxide (**141**) with phosphorus oxychloride gave the dehydrogenated compound, *5-nitrofuro[3,2-b]pyridine* (**147**, 65%). The same reaction of 5-nitro *N*-oxide (**145**) afforded 5-nitro-7-chloro-2,3-dihydrofuro[2,3-*c*]pyridine (**149**, 99%). The acetoxylation of **141** yielded **147** (24%) and 3-acetoxy-2,3-dihydro compound (**148**, 33%). The acetoxylation of **145** gave 5-nitro-7-acetoxy-2,3-dihydro compound (**150**, 99%).



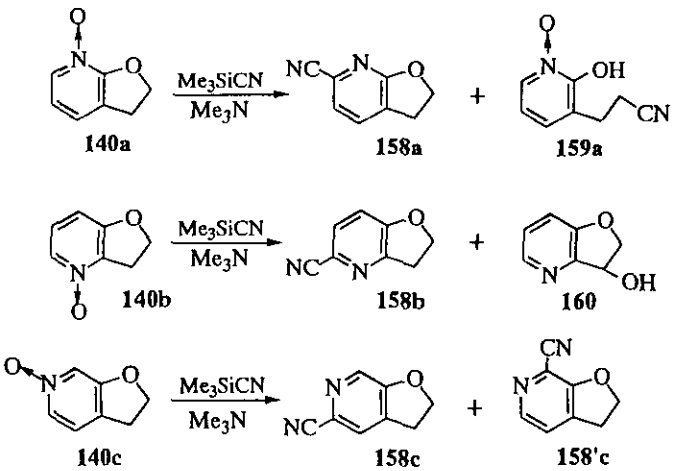
Chlorination of 2,3-dihydrofuro[2,3-*b*]pyridine *N*-oxide (**140a**) with phosphorus oxychloride gave a complex mixture of products, from which 2,4-dichloro-3-(2-chloroethyl)pyridine (**151**, 1.3%) and 2,6-dichloro-3-(2-chloroethyl)pyridine (**152a**, 6.5%) were isolated. Chlorination of 2,3-dihydrofuro[3,2-*c*]pyridine *N*-oxide (**140d**) with phosphorus oxychloride yielded 6-chloro-2,3-dihydrofuro[3,2-*c*]pyridine (**153d**, 6%), 2,4-dichloro-5-(2-chloroethyl)pyridine (**152d**, 10%) and **151** (12%). On the other hand, the chlorination of -[3,2-*b*]- *N*-oxide (**140b**) and -[2,3-*c*]- *N*-oxide (**140c**) afforded the pyridine chlorinated 2,3-dihydrofuropyridines, 5-chloro- (**153b**, 9%) and 7-chloro-2,3-dihydro[3,2-*b*]pyridine (**153'b**, 26%) accompanying formation of the parent compound (**1b**, 16%) from **140b**, and 5-chloro- (**153c**, 36%) and 7-chloro-2,3-dihydrofuro-[2,3-*c*]pyridine (**153'c**, 37%) from **140c**.

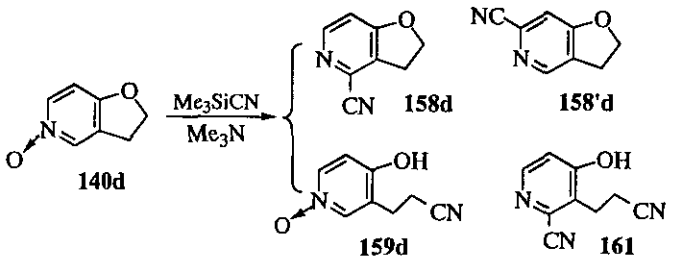


Acetoxylation of **140a** with acetic anhydride also afforded a complex mixture of products, from which β-acetoxypyridine compounds (**154a**, 6%) and (**155a**, 49%) were isolated. From the crude product of **140d**, 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-one (**157**, 10%) and 2,3-dihydrofuro[3,2-*c*]pyridin-6(5*H*)-one (**157'**, 6.5%) were isolated. Under the similar condition, the dihydro *N*-oxides (**140b**) and (**140c**) gave the furan acetoxylated compounds (**156b**, 59%) and (**156c**, 41%), and the parent furopyridine (**1b**, 9%) and (**1c**, 29%).



The results of cycnation of the dihydro *N*-oxides with Me_3SiCN in acetonitrile also varied from system to system of furopyridine. Compound (**140a**) yielded 6-cyano-2,3-dihydrofuro[2,3-*b*]pyridine (**158a**, 40%) and 3-(2'cyanoethyl)-2-pyridinol *N*-oxide (**159a**, 19%). Cyanation of **140b** yielded 5-cyano- (**158b**, 18%) and 3-hydroxy-2,3-dihydrofuro[3,2-*b*]pyridine (**160**, 19%) and the parent compound (**1b**, 18%). Compound (**140c**) afforded 5-cyano- (**158c**, 34%) and 7-cyano-2,3-dihydrofuro[2,3-*c*]pyridine (**158'c**, 63%). Compound (**140d**) yielded 4-cyano- (**158d**, 22%) and 6-cyano-2,3-dihydrofuro[3,2-*c*]pyridine (**158'd**, 27%), 3-(2'-cyanoethyl)-4-pyridinol *N*-oxide (**159d**, 15%) and 2-cyano-3-(2'- cyanoethyl)-4-pyridinol (**161**, 33%).



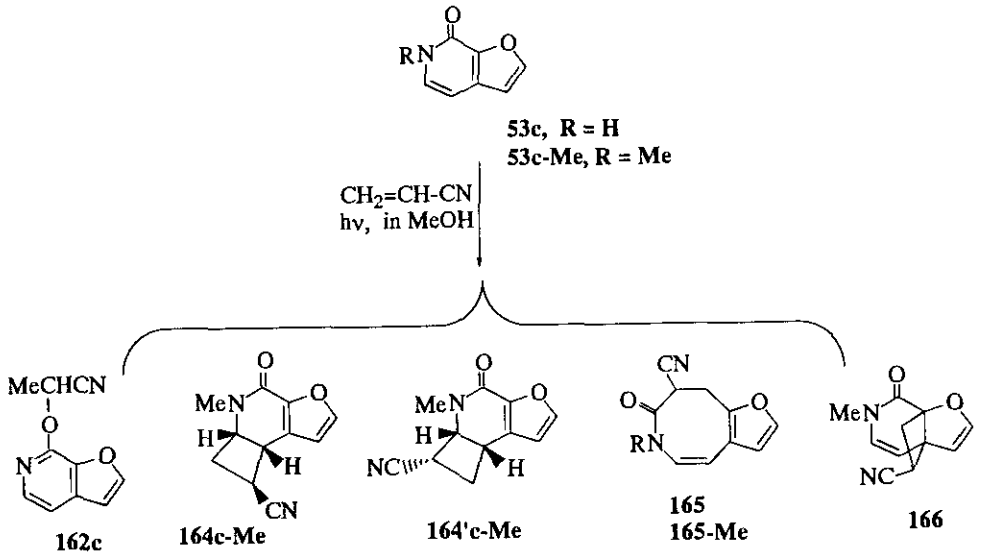


Chlorination, acetoxylation and cyanation of 2,3-dihydrofuropyridine *N*-oxides (**140a-d**) afforded the pyridine-substituted products in considerably lower yield than these reactions of full aromatic furopyridine *N*-oxides, with a few exception. Moreover, compound (**140a**) and (**140d**), in which the ring oxygen is at α- and γ-position to the ring nitrogen, afforded products formed through fission of the 1-2 bond, and compound (**140b**) and (**140c**), in which the ring oxygen is at β-position to the ring nitrogen, accompanied formation of 3-substituted compounds. These results suggested that the nucleophilic reactivity at the α- and γ-positions of the *N*-phosphonate, *N*-acetoxylated or *N*-siloxylated ammonium cation is much reduced by the electron donating mesomeric effect of the ring oxygen. In the cases of **140b** and **140c**, the electron withdrawing effect of the ammonium cation would affect at C-3 through C-3a-C-3 bond. Thus, by comparing the results of chlorination, acetoxylation and cyanation of **140a-d** with those of full aromatic furopyridine *N*-oxides (**123a-d**) it would be concluded that the electronic effect of the ring oxygen of 2,3-dihydrofuropyridine *N*-oxide upon the pyridine ring is mesomeric and electron donating and that of furopyridine *N*-oxide is rather electron withdrawing.

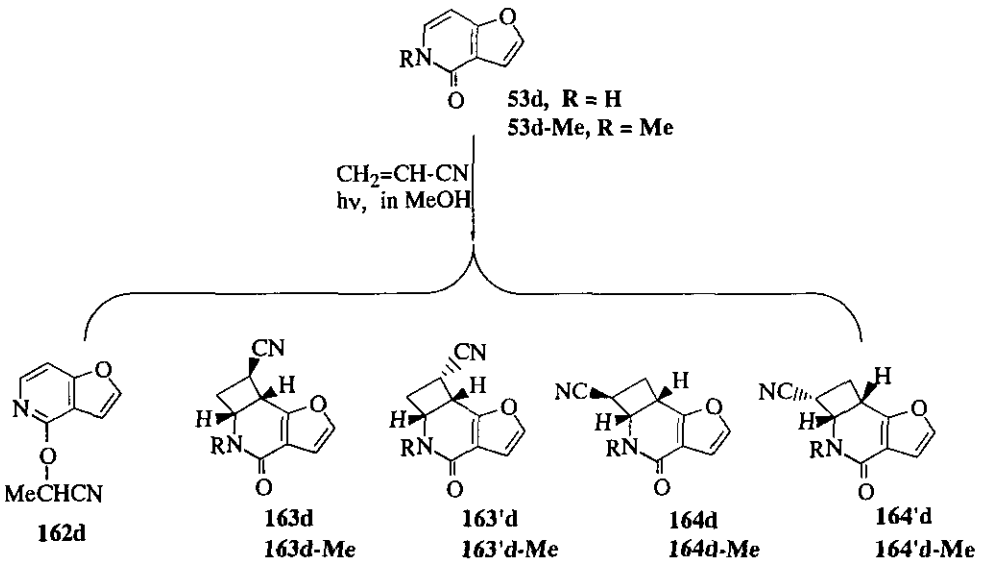
e) Photo[2+2]cycloaddition of furo[2,3-c]pyridin-7(6*H*)-one and furo[3,2-c]pyridin-4(5*H*)-one and their *N*-methyl derivatives [54,55]

Irradiation of furo[2,3-c]pyridin-7(6*H*)-one (**53c**) and its *N*-methyl derivative (**53c-Me**) in methanol containing large excess of acrylonitrile by high pressure mercury lamp gave a mixture of addition products. From the crude product of **53c**, an addition product (**162c**, 4.3%) at the carbonyl oxygen and an ethylene inserted product (**165**, 13%) at the 7- and 7a-position were isolated. From the reaction product of **53c-Me**, two cyclobutane-fused adducts (**164c-Me**, 1.1% and **164'c-Me**, 4.5%) with the acrylonitrile group incorporated at 6- and 7-position, and at the 2a- and 7a-position (**166**, 6.5%), and an ethylene inserted product at the 7- and 7a-position (**165-Me**, 25%) were isolated by

column chromatography.[54]



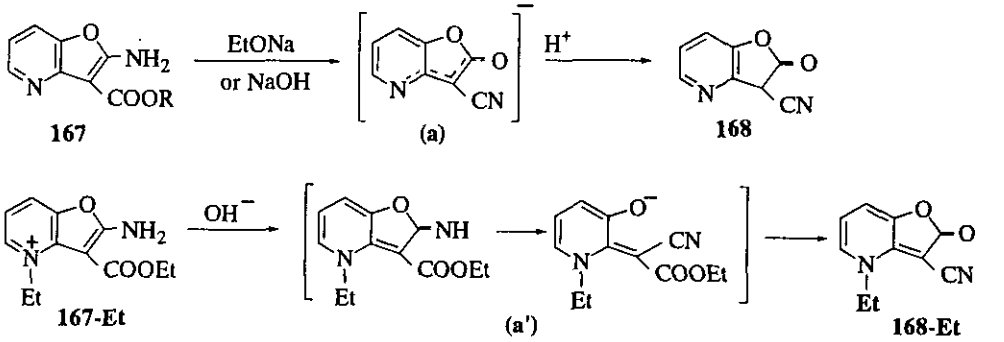
Photocycloaddition of compound (**53d**) and its *N*-methyl derivative (**53d-Me**) under the same conditions again afforded a complex mixture of addition products from which an addition product at the carbonyl oxygen (**162d**, 4.7%) and four isomers (**163d**, 15%) (**163d-Me**, 15%), (**163'd**, 19%) (**163'd-Me**, 20%), (**164d**, 3%) (**164d-Me**, 7%) and (**164'd**,12%) (**164'd-Me**, 20%) of a cyclobutane-fused adduct with acrylonitrile incorporated at the 6- and 7-position, were isolated.[55]



It had been reported that in the photocycloaddition to monosubstituted olefin, isoquinolone-1 and/or its *N*-substituted derivatives afforded 1-substituted cyclobut[*c*]isoquinolones as the major products.[56] Thus, these results for furopyridones may be interpreted by the low energy difference between the possible biradical intermediates by the electron donating effect of the furan oxygen. The products (**162c**) and (**162d**) may be afforded by the addition at the carbonyl group in the excited state. Formation of such an addition at the carbonyl group in pyridones, quinolones and isoquinolones had not yet been reported.

f) Others

Rearrangement of ethyl 2-aminofuro[3,2-*b*]pyridine-3-carboxylate (**167**) or its *p*-nitrophenyl ester (**167'**) and 2-amino-3-carbethoxy-4-ethylfuro[3,2-*b*]pyridinium cation (**167-Et**) to the corresponding 2-oxo-3-cyano-3*H*-furo[3,2-*b*]pyridine (**168**) and its *N*-methyl derivative (**168-Et**) by sodium ethoxide or sodium hydroxide was studied in detail by Stein *et al.*[57] They suggested the rearrangement would occur through formation of an intermediate (**a**) or (**a'**).



IV. MISCELLANEOUS

a) Basicity[37]

Ionization constants of the protonated parent furopyridines are listed in the Table below, which were determined by titration or UV absorption method. It should be pointed out

that the quinoline isosteres are weaker in basicity than pyridine and quinoline, and isoquinoline isosteres are stronger than pyridine and isoquinoline. Furthermore, the basicity of fur [2,3-b]pyridine (**1a**) is extremely weak, which may be caused by the steric repulsion of the lone-pair electrons of the nitrogen and oxygen, and instability of the protonated ammonium ion in water.

Table. Ionization Constants of Furopyridines

Compound		pKa/20°C
Furo[2,3-*b*]pyridine	(**1a**)	0.87
-[3,2-*b*]-	(**1b**)	4.11
-[2,3-*c*]-	(**1c**)	5.43
-[3,2-*c*]-	(**1d**)	5.79
3-Br-[2,3-*b*]-	(**82a**)	-0.23
3-Br-[3,2-*b*]-	(**82b**)	4.54
3-Br-[2,3-*c*]-	(**82c**)	4.93
3-Br-[3,2-*c*]-	(**82d**)	6.41

b) NMR spectra

The ^{1}H-NMR spectra of the parent furopyridines and their derivatives have been reported in the papers which reported the synthesis and/or formation of the compounds. Gronowitz discussed ^{1}H-NMR spectra of the parent compound, 5-methyl and 5-carboxyl derivatives of furo-, thieno- and selenolo[3,2-b]pyridine, and pointed out that the 7-proton signals for the fused pyridine derivatives are systematically shifted to lower field on going from the furan-fused to the selenophene-fused systems and that the order O>S>Se is the same as that of the electron donating mesomeric effect of the hetero-atoms.[22]

The ^{13}C-NMR spectra of the parent furopyridines and derivatives having a substituent at C-2 or C-3 were also reported.[58] In that paper Shiotani pointed out that the difference of C-2 chemical shift of each parent furopyridine (+3.78, +2.88, +0.47 and -0.31 ppm for **1b**, **1c**, **1d** and **1a**) to that (δ 144.72) of benzo[*b*]furan reflect the difference in chemical shift of C-3a but not C-7a by change of the annelation (C-3a (δ 147.31) of **1b**

corresponds to the α-carbon of pyridine, **1c** (δ 133.39) to the γ-carbon, **1d** (δ 124.34) and **1a** (δ 118.93) to the β-carbon), and that there is good correlation between the chemical shift of C-2 of furopyridines and the electron density (q_r) (0.938, 0.940, 0.964 and 0.67 for C-2 of **1b**, **1c**, **1d** and **1a**) which also correlates to q_r of C-3a (0.979, 0.998, 1.035 and 1.036 for **1b**, **1c**, **1d** and **1a**) calculated using simple HMO method,[57] the lower chemical shift and electron density of C-2 corresponds to the lower chemical shift and electron density of C-3a. These facts imply that the electronic effect of the pyridine ring upon C-2 is exerted mainly through the C-3 - C-3a link, as in the case of benzo[*b*]furan.[60]

Actually, acetylation of lithio intermediate of 2-methylfuro[2,3-*c*]pyridine with DMA resulted in recovery of the starting compounds and alkylation of lithio intermediate of ethyl 2-(3-furo[2,3-*c*]pyridyl)acetate with acetone did not occur at 2-position but at the α-carbon, while the analogues of other furopyridines yielded the expected results.[39,43] These results could be interpreted by the postulation in the above: the electron withdrawing effect of the ring nitrogen of furo[2,3-c]pyridine is efficiently exerted upon 2-methyl and C-2 through C-3 - C-3a bond.

V. CONCLUSION

In this review the author has focused on syntheses and chemical properties of furopyridines, *N*-oxide of furopyridines, *N*-oxide of 2,3-dihydrofuropyridines and their derivatives. From the results described in this review it is apparent that the reactions of these furopyridines are considerably affected by the mode of annelation of the furopyridines. Thus, the reactions of these furopyridines are divided into three types; type (1): reactions afforded the similar results for the four furopyridines, type (2): yielded the similar results for the quinoline isosteres which are different from those for the isoquinoline isosteres, and type (3): yielded the similar results for furopyridines having the ring oxygen at the β-position to the ring nitrogen which are different from those for furopyridines having the ring oxygen at the α- or γ-position.

The use of these bicyclic heteroaromatics as precursors for many purposes awaits further systematic development. The author hopes that this review will provide an incentive for further studies.

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