Synthesis and physical properties of the six furylpyridines

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Received April 6, 1982[2]

PIERRE RIBEREAU and GUY QUEGUINER. Can. J. Chem. **61**, 334 (1983).

The 3-step synthesis of furylpyridines is described, using ethyl pyridinoylacetates as starting materials for 2-furyl compounds and chloroacetylpyridines for 3-furyl isomers. Furthermore, thesc last compounds were prepared by a convenient new method for 3-substituted furan synthesis. This synthesis starts from bromopyridines and proceeds through the key intermediates (2,2-diethoxyacetyl)pyridines and methyl 2-(*x*-pyridyl)-4,4-diethoxy-2-methoxy-2-butenoates. The physical properties of the furylpyridines have been determined. Structures and interactions between furan and pyridine rings have been discussed by comparing their uv spectra, basicity constants, and dipole moments with those of phenyl and thienylpyridines.

PIERRE RIBEREAU et GUY QUEGUINER. Can. J. Chem. **61**, 334 (1983).

Nous décrivons la synthèse des furylpyridines en trois étapes à partir des pyridoylacétates d'éthyle pour les dérivés en 2 du furanne et à partir des chloroacétylpyridines dans le cas des isomères en 3. Nous décrivons une nouvelle voie d'accès aux dérivés du furanne substitué en 3. La synthèse est réalisée à partir de bromopyridines et procède par l'intermédiaire des (diéthoxy-2,2 acétyl)pyridines et pyridyl-2 diéthoxy-4,4 méthoxy-2 butène-2 oates de méthyle. Les propriétés physiques des furylpyridines ont été déterminées. Leur structure et l'intéraction entre les cycles furanne et pyridine sont discutées en comparant leurs spectres uv, constantes de basicité et moments dipolaires avec ceux des phényl et thiénylpyridines.

In the last decade much interest has focussed on the properties and reactivity of biheterocycles which result from linking of "electrophilic" and "nucleophilic" rings (1).

A 2-(3-furyl)pyridine derivative was prepared as precursor in the synthesis of nupharamine (2). Derivatives of such naturally occurring compounds isolated from Nuphar and Castoreum (3) have been employed in pharmaceutical preparations (4). Furthermore, a methiodide derivative of 4-(3-furyl)pyridine has been found to display hypoglycemic activity (5). However, only a small number of papers dealing with the synthesis and the properties of furylpyridines have been published. Most routes adopted for the preparation of 3-(2-furyl)pyridine (6−10), 2-(2-furyl)pyridine (11), and 4-(3-furyl)pyridine (5) were either the construction of the nitrogen ring starting from furan derivatives, or the linkage of the two heterocycle units. But these syntheses gave rather low yields or can only be used for the preparation of one isomer. It seemed of interest to prepare furylpyridines by an improved general method. The synthesis of these compounds will be described, using a pyridine derivative as a substrate through the construction of the oxygen ring, as reported in a previous paper (12).

Furthermore, we describe a new synthetic procedure for 3-substituted furans, which are compounds of interest in the field of natural products but not easily accessible.

Synthesis of x-*(2-furyl)pyridines*

These have been prepared according to the method established by Lions and Ritchie (6) for the synthesis of 3-(2-pyrrolyl)pyridine. The cyclization step was modified to improve the yield of furyl derivative. Finally, the best yields of furan esters **3** were obtained when ethyl pyridoylacetates **1** were treated with 1,2-dichloroethyl acetate and 10% aqueous ammonia. In fact, thermolysis of the first reaction product was necessary in order to aromatize the compound. The intermediate product **2** was isolated under mild conditions and its structure was inferred from the spectral analyses. Its ir spectrum exhibits the characteristic absorption bands of the alcohol function at 3140 and 1100 cm $^{-1}$. The ^{1}H nmr spectrum presents a deshielded doublet of doublets at δ 5.37 ppm (J = 4 and 5.5 Hz) which is the resonance of a proton attached to an hydroxyl-bearing carbon of dihydrofuran (13, 14). The ^{13}C nmr spectrum of compound **2** presents no cyclic hemiacetal type carbon (about 100 ppm). In view of these observations, we identified compound **2** as ethyl 5-(*x*-pyridyl)-3-hydroxy-2,3-dihydro-4-furoate. Formation of this nondehydrated precursor of the furyl ring can be explained by a ketolization reaction between ketoester **1** and chloroacetaldehyde resulting from the hydrolysis of 1,2-dichloroethyl acetate. Subsequent cyclization gives a dihydrofuran derivative **2**. Thermolysis of this compound produced furan ester **3**. After saponification of the ester and decarboxylation of the acid **4** at 160−220°C the furylpyridine **5** was obtained. By this route 2-, 3-, and 4-(2-furyl)-pyridines were prepared in satisfactory overall yields, namely 40%, 50%, and 34%, respectively. These results compare favorably with the yields of the syntheses previously described (6, 11).

Synthesis of x-*(3-furyl)pyridines by cyclization of epoxyalkyne*

Among the several methods described in the literature to achieve the synthesis of 3-substituted furan, the only one which offered some interest was the route proceeding through an epoxide according to the sequence established by Miller (15) for the preparation of 3-phenylfuran. Following this method, chloroacetylpyridine hydrochlorides **6** (16) react with ethynylmagnesium bromide in tetrahydrofuran and give chlorhydrins **7**. The reaction of these compounds with sodium hydroxide proceeds smoothly to give the corresponding 3,4-epoxy-3-(*x*-pyridyl)-1-butynes **8**. Because of their instability, compounds **7** and **8** were not purified. They exhibited spectral data in accordance with their structural assignments and they were shown to have a purity of at least 95% by nmr.

When acetylenic α,β-epoxides **8***b* and **8***c* were heated with 2 *N* sulfuric acid containing a catalytic amount of mercuric

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[2]Revision received October 5, 1982.

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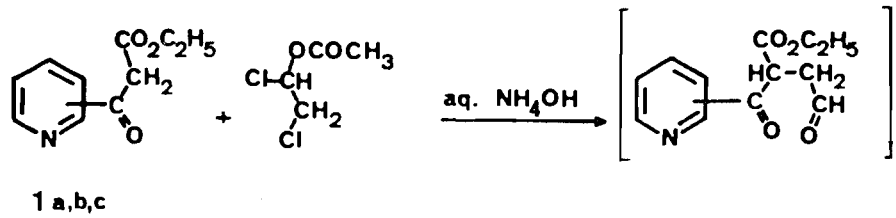
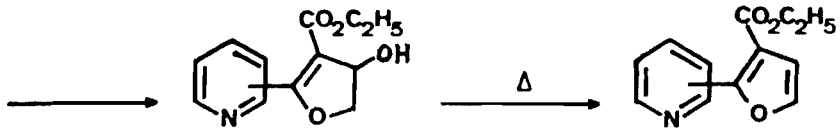


1 a,b,c



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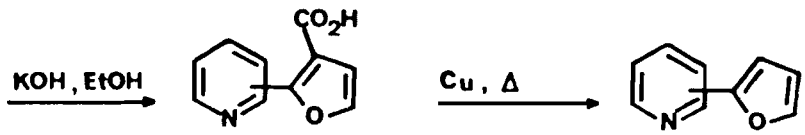
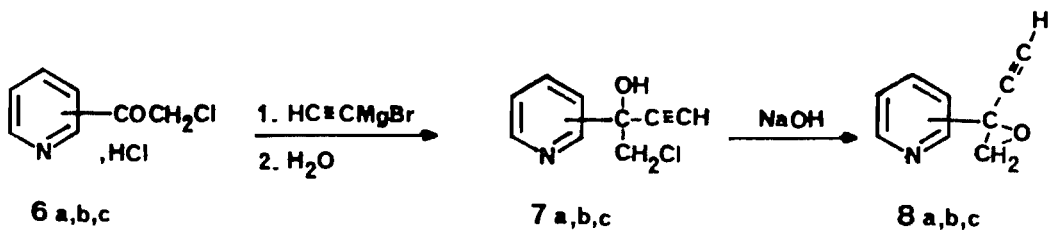


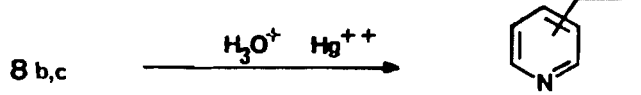
4 a,b,c 5 a,b,c

a: 2-pyridyl, b: 3-pyridyl, c: 4-pyridyl

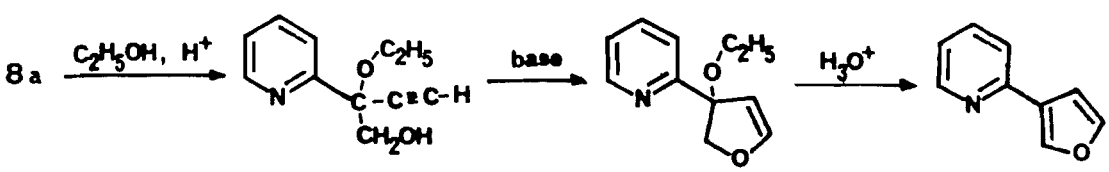
SCHEME 1



6 a,b,c 7 a,b,c 8 a,b,c



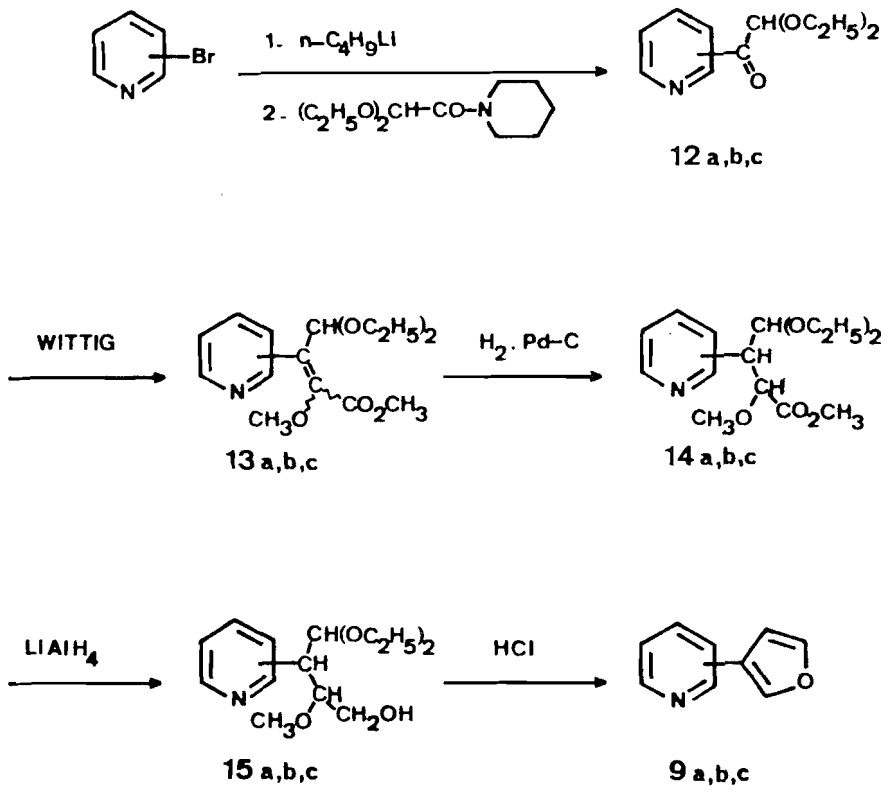
8 b,c 9 b,c



8 a 10 11 9 a

a: 2-pyridyl, b: 3-pyridyl, c: 4-pyridyl

SCHEME 2



SCHEME 3

sulfate, cyclization occurred and gave furylpyridines **9***b* and **9***c* in rather low yields, 15% and 21%, respectively, from the corresponding chloroketones **6**. However under the same conditions, cyclization failed with the 2-pyridyl derivative. The acetylenic epoxide **8***a* also reacted but no 2-(3-furyl)pyridine could be isolated. Alternatively, this compound was prepared by a base-induced cyclization. The epoxide ring of compound **8***a* was opened with perchloric acid in ethanol to give 3-ethoxy-3-(2-pyridyl)-1-butyn-4-ol **10**. The structure was deduced from spectroscopic data similar to those of 3-ethoxy-3-phenyl-1-butyn-4-ol (15). Treatment of alcohol **10** with sodium ethoxide at 80°C gave the cyclized product **11** whose ir spectrum showed no hydroxy or acetylenic functions. The ^{1}H nmr spectrum exhibited two doublets at δ 6.70 and 5.21 ppm (J = 2.5 Hz) which were assigned to H-5 and H-4. The two protons on carbon 2 appeared as two singlets at δ 4.59 and 4.61 ppm. A base-induced intramolecular attack of oxygen on the acetylenic bond can easily explain this result. Such a reaction was previously used for cyclization of acetylenic diols (17) and enyne alcohols (18). Subsequent treatment of dihydrofuran derivative **11** with acid gave the expected 2-(3-furyl)pyridine (**9***a*) in a very low overall yield (9%) from chloroketone **6***a*. Since this method necessitates the prior synthesis of hard-to-obtain chloroacetylpyridines and since the yields were low, we sought another route to *x*-(3-furyl)pyridines. This new synthetic procedure was carried out using bromopyridines as starting material.

Synthesis of x-*(3-furyl)pyridines by cyclization of hydroxyacetal*

Lithiopyridines (19) were obtained from bromopyridines and n-butyllithium. The subsequent reaction with 1-(2,2-diethoxyacetyl)piperidine (20) at −70°C yields diethoxyacetylpyridines **12**. When methyl diethoxyphosphinylmethoxyacetate (21) was used in the Wittig–Horner reaction with ketones **12**, equivalent amounts of geometrical isomers of esters **13** were formed (nmr). The ethoxymethoxy series was chosen here because it offered the advantage of simple interpretation of nmr spectra of intermediates in the synthesis. Reduction of the ethylenic double bond with hydrogen and palladium catalyst provided the desired saturated esters **14**. The carbethoxy group was reduced to the hydroxymethyl group with lithium aluminium hydride. Finally, treatment of the alcohols **15** with hydrochloric acid in toluene gave the *x*-(3-furyl)pyridines. These compounds were obtained with an overall yield of 49%, 40%, and 42% from ketoacetals **12**. This easy access to the 3-furyl compounds offers an interesting potential entry to products of interest in biological or pharmaceutical problems.

Physical properties of furylpyridines

Because reactions carried out on these compounds gave results somewhat different from those obtained with analogues like thienyl and phenylpyridines (1), we have made some physical studies to clarify the interactions between the two rings.

The ultraviolet spectra of furylpyridines were obtained with absolute ethanol solution (see Table 1). 2-(2-Furyl)pyridine displays an absorption maximum at a longer wavelength than the other isomers, indicating that conjugation should be greater in this compound. From earlier studies (22–24), there is evidence that the differences between the characteristic spectral behaviour of arylpyridines and those of the corresponding pyridinium ions are related to the electronic interaction between the two rings. When the higher maximum wavelength of furyl, thienyl, and phenylpyridines (23) is compared with that of their

TABLE 1. Acidity constants, ultraviolet spectral data, and dipole moments of furylpyridines **5***a*–*c* and **9***a*–*c* and (thienyl-2)-2-pyridine **16**

		Ultraviolet		Dipole moment		
					μ^d	
Compounds	pK_a[a]	Solvent[b]	λ max, nm (log ε)	μ[c]	α = 0	α = 180
5*a*	4.18±0.05[e]	A	303 (4.16), 270 (4.12)	1.37±0.05	2.46	1.30
		B	332 (4.27)			
5*b*	4.62±0.06[f]	A	283 (4.21), 236 (3.72)	2.42±0.02	2.94	2.02
		B	290 (4.29), 236 (4.00)			
5*c*	5.60±0.08	A	294 (4.37), 235 (3.94)	3.04±0.08	2.94	
		B	332 (4.41), 237 (3.84)			
9*a*	4.65±0.03	A	285 (3.74), 255 (3.77) 227 sh[g]	2.27±0.02	2.50	1.80
		B	307 (3.99), 245 (3.86)			
9*b*	4.93±0.04	A	257 (3.86), 225 sh	2.23±0.03	2.45	1.68
		B	243 (4.03)			
9*c*	5.72±0.03	A	270 (4.01), 223 sh	2.35±0.03	2.09	
		B	304 (3.98), 250 sh, 239 (3.98)			
16	3.797±0.012[h]			2.06±0.02	2.49	1.42

[a]The acidity constants have been determined by spectrophotometry in water (I = 0.1, $NaClO_4$; 25°C).
[b]A, solution in absolute ethanol, B, solution in aqueous 0.01 M $HClO_4$, 0.1 M $NaClO_4$, and at 25°C.
[c]Dipole moments are measured in benzene solutions at 25°C.
[d]Calculated dipole moments respectively with the dihedral angle α between the planes of the two rings.
[e]Reference 8, pK_a = 4.17 ± 0.04.
[f]Reference 8, pK_a = 4.59 ± 0.011.
[g]sh, shoulder.
[h]Reference 25.

NOTE: 3-(2-Thienyl)pyridine: pK_a = 4.515; 4-(2-thienyl)pyridine: pK_a = 5.591; 2-(3-thienyl)pyridine: pK_a = 4.776; 3-(3-thienyl)pyridine: pK_a = 4.920; 4-(3-thienyl)pyridine: pK_a = 5.712; 2-phenylpyridine: pK_a = 4.735; 3-phenylpyridine: pK_a = 4.924; 4-phenylpyridine: pK_a = 5.488 (25); pyridine: pK_a = 5.33 (8).

protonated species, a bathochromic shift is apparent: 18 to 31 nm, −14 to 9 nm, and 32 to 40 nm for 2-, 3-, and 4-pyridyl derivatives respectively. These results show, as expected, that the interaction between the pyridine nuclei and the other aryl ring is weaker in the case of 3-substituted pyridines.

Acidity constants of furylpyridines are reported in Table 1. 4-Arylpyridines have similar pK_a and they are stronger bases than pyridine. This first result suggests that the mesomeric effect (+M) for all furyl, thienyl, and phenyl groups makes electrons available in the same order of magnitude. 3-Arylpyridines are slightly weaker bases than pyridine. This can be explained by the lack of conjugative interaction for the 3-substituted pyridines and by the weak electron-withdrawing due to the inductive effect of the aryl groups. For all the 2-substituted pyridines, the basicity is weaker than that of pyridine. It is evident that the +M effect of the aryl group is diminished by its greater hindrance and by the increased importance of its inductive effect. The pK_a values of 2-(3-furyl), 2-(3-thienyl), and 2-phenylpyridines are similar (24, 25), indicating that steric hindrance of the aryl groups is about the same because, as we have seen above, the mesomeric and inductive effects are of the same order of magnitude. 2-(2-Furyl)pyridine is a stronger base than 2-(2-thienyl)pyridine (**16**) and, apart from the −I effect which is presumed to be more important for oxygen than for sulfur, other parameters must influence the stability of the protonated species (coordination of the proton by the oxygen of the furyl compound may increase the stability of the protonated form).

The experimental dipole moments of furylpyridines are reported in Table 1. Ultraviolet spectra and basicity studies have shown that electron displacements within the molecules are similar in furyl, thienyl, and phenylpyridines. Thus there are good reasons to believe that the mesomeric moment induced in the furyl or thienyl groups by the primary moment associated with the pyridine ring is not so different from the dipole moment induced in the phenyl group of phenylpyridines (26). From the dipole moments of the unsubstituted parent compounds (26, 27) and the mesomeric moments deduced from phenylpyridine studies (26), we have determined, by vector analysis, a calculated moment for *trans*-planar (α = 0°) and *cis*-planar (α = 180°) conformations of furylpyridines (Table 1).

4-(2-Furyl)pyridine and 4-(3-furyl)pyridine yield calculated moments irrespective of the angle between the planes of the two rings and consistent with the experimentally determined values. These results show that the use of mesomeric moments of phenylpyridines is significant in the case of furylpyridines. 2-(2-Furyl)pyridine shows an experimental dipole moment in good agreement with the calculated value for the *trans*-planar geometry. The most preferred conformation of this compound is thus presumed to be planar. The other isomers of the series do not exhibit such an agreement. For these substances, the experimental dipole moments lie between the values calculated for *s-cis* and *s-trans* conformations, and suggest that the two rings are not coplanar. On the basis of the calculated and measured values of the dipole moment, 2-(2-thienyl)pyridine also appears to have a twisted equilibrium conformation (28), an indication of the difference between this compound and the corresponding furan derivative, as already implied from pK_a measurement. These physical properties of furylpyridines

TABLE 2. Yield, analytical, ^{1}H nmr, and infrared data for compounds **3***a*–*c* and **4***a*–*c*

Compounds	Boiling point (°C/Torr) *Melting point* (°C)	Yield %	Analysis (%) calcd. found			^{1}H nmr[a]														Infrared (cm^{-1})[b]	
			C	H	N	Pyridyl H-2	H-3	H-4	H-5	H-6	$J_{2,3}$ $5,6$	$J_{2,4}$ $4,6$	$J_{2,5}$ $3,6$	$J_{3,4}$ $4,5$	Furyl H-4	H-5	$J_{4,5}$	Others CH_2	CH_3	J	ν(C=O)	ν(O—H)
3*a*	128/0.3	82	48.44	3.16	12.55	—	8.22	7.76	7.26	8.68	4.8	2.0	1.0	8.0	6.86	7.52	2.0	4.31	1.32	7	1709	—
			48.9	3.3	12.4		dt	td	ddd	ddd					d	d		q	t			
3*b*	120/0.1	60	48.44	3.16	12.55	9.12	—	8.35	7.36	8.58	4.8	2.0	1.0	8.0	6.87	7.48	1.8	4.31	1.32	7	1718	—
	27		48.3	3.2	12.4	dd		dt	ddd	dd					d	d		q	t			
3*c*	130/0.5	51	48.44	3.16	12.55	8.67	7.94	—	7.94	8.67	4.8		1.5		6.87	7.47	1.8	4.32	1.33	7	1721	—
	65		48.3	2.9	12.4	dd	dd		dd	dd					d	d		q	t			
4*a*	*170*	71	63.49	3.73	7.40	—	8.15	8.15	7.65	8.78	4.8	2	1	8	7.01	8.00	1.8				1701	3436
			63.6	3.5	7.2		m	m	m	m					d	d						
4*b*	229	93	63.49	3.73	7.40	9.10	—	8.30	7.50	8.63	4.8	2.0		8.0	6.89	7.83	1.8				1701	3486
			63.3	3.6	7.1	d		dt	dd	dd		1.8			d	d						
4*c*	*260*	80	63.49	3.73	7.40	8.63	7.92	—	7.92	8.63	4.5		1.5		6.91	7.82	1.8				1698	3436
			63.4	3.4	7.2	dd	dd		dd	dd					d	d						

[a]Abbreviations: d doublet, dd doublet of doublets, t triplet, q quartet, m multiplet. Solvent: compounds **3***a*–*c* in $CDCl_3$; compounds **4***a*–*c* in Me_2SO-d_6.
[b]In KBr except for compound **3***a*: neat.

show that interaction between the two rings is mainly inductive and steric in nature.

All of the furylpyridines show very similar mass spectra, with an intense peak for the molecular ion m/e = 145 and the same degradation fragments. Hydrogen abstraction leads to a fragmentation peak $M - 1$ with an intensity of 29% in the spectrum of 2-(2-furyl)pyridine and of only 10% in the case of 2-(3-furyl)pyridine (the results are somewhat different in the thiophene series (29)).

Experimental

Boiling points are uncorrected. Infrared (ir) spectra were determined on a Beckman IR 4250 grating infrared spectrometer. Ultraviolet (uv) spectra were obtained on a Beckman DK-2 spectrophotometer. Proton nuclearmagnetic resonance (^{1}H nmr) spectra were recorded using a Varian A 60 spectrometer and chemical shifts are reported as δ values in ppm relative to Me_4Si as internal standard; ^{13}C nmr spectra were obtained on a Brucker WH 90 spectrometer at 22.69 MHz and chemical shifts are reported in ppm downfield from internal Me_4Si. Mass spectra were recorded on a JEOL JMS D 100 spectrometer.

*Preparation of ethyl 2-(*x*-pyridyl)-3-furoates (**3**a–c)*

To a stirred and cooled (−5 to 0°C) solution of 116 g (0.6 mol) of ethyl 3-(*x*-pyridyl)-3-oxopropanoate (30) in 1 L of CH_2Cl_2 was added 300 mL of 10% aqueous ammonia. A solution of 100 g (0.64 mol) of 1,2-dichloroethyl acetate in 200 mL of CH_2Cl_2 was added over a 30 min period. The reaction mixture was stirred for an additional 2 h at 0°C and then allowed to come to room temperature overnight. After acidification with concentrated hydrochloric acid, the aqueous layer was extracted with $CHCl_3$. After removal of the solvents, the resulting oil was distilled, giving compounds **3***a*–*c* (Table 2).

*Ethyl 5-(3-pyridyl)-3-hydroxy-2,3-dihydro-4-furoate (**2**b)*

A solution of ketoester **1***b* was treated as described above in the preparation of compounds **3**. Decantation of the organic layer and removal of the solvent, at a temperature below 40°C to avoid dehydration, gave a residue which was recrystallized in CCl_4, giving 65 g (46%) of white crystals, mp 116°C; ir (KBr): 3140 (OH), 1690 (C=O), 1415, 1290, 1100 (OH) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.12 (t, 3H, CH_3), 4.0 (m, 1H, OH), 4.11 (q, 2H, CH_2), 4.52 (d, 1H, J = 4 Hz, one H of CH_2—O), 4.53 (d, 1H, J = 5.5 Hz, one H of CH_2—O), 5.37 (2 doublets, 1H, HC(OH)), 7.25 (m, 1H, pyridyl H-5), 7.7 (m, 2H, pyridyl H-3 and H-4), 8.6 (m, 1H, pyridyl H-6); ^{13}C nmr ($CDCl_3$) δ: 13.7 (CH_3), 59.9 (CH_2—O), 73.5 (C—OH), 77.2 (ring CH_2—O), 122.2 (pyridyl C-5), 136.7 (pyridyl C-4), 149.9 (pyridyl C-2), 150.9 (pyridyl C-6). *Anal.* calcd. for $C_{12}H_{13}NO_4$: C 61.28, H 5.53, N 5.95; found: C 61.5, H 5.3, N 6.1.

*Preparation of 2-(*x*-pyridyl)-3-furoic acids (**4**a–c)*

To a stirred solution of 72 g (0.78 mol) of KOH in 300 mL of ethanol was added 70 g (0.32 mol) of ester **3**. The mixture was heated at 80°C for 16 h. After removal of the solvent the residue was dissolved in a minium quantity of water. The aqueous solution was washed with ether and then acidified to pH 4 with an aqueous solution of HCl. The precipitate was filtered, washed with cold water, and recrystallized from ethanol affording acids **4***a*–*c* (Table 2).

Preparation of x*-(2-furyl)pyridines (**5**a–c)*

A 10 g sample of **4** was mixed thoroughly with 10 g of red copper and the mixture was heated from 160°C to 220°C at reduced pressure (12 Torr). The resulting oil was dissolved in ether. The ether solution was washed with a 10% aqueous NaOH solution, then with water, and finally worked up as usual. Distillation offered compounds **5***a*–*c* (Table 3).

*2-(2-Chloroacetyl)pyridine hydrochloride (**6**a)*

A solution of 19.6 g (0.16 mol) of picolinic acid in 120 mL of freshly distilled sulfinyl chloride was heated at 80°C for 2 h. The excess of sulfinyl chloride was distilled off and, after addition of 20

mL of dry benzene, the solvents were removed under reduced pressure. A suspension of the residue in 100 mL of dry benzene was introduced in portions to a cooled (0–5°C) and stirred solution of about 22.5 g (0.54 mol) of diazomethane in 1.2 L of diethyl ether (dried 2 h on KOH pellets). The mixture was stirred and allowed to come to room temperature overnight. The solution was then filtered. In one run the solvent was removed using a rotary evaporator. Distillation of the residue afforded 20.7 g (88%) of 2-pyridyldiazoketone: bp 82°C/0.3 Torr; ir (CCl_4): 2110 (N_2), 1640 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 6.7 (s, 1H, CHN_2), 7.4 (m, 1H, C-5 H), 7.6–8.1 (m, 2H, C-3 H and C-4 H), 8.5 (dd, 1H, C-2 H). The cooled (0°C) and stirred solution of diazo ketone in ether was treated by a dry stream of hydrogen chloride. The precipitate was filtered and washed with dry ether. Drying under reduced pressure afforded 28.9 g of hydrochloride **6***a* (94%): ^1H nmr (DMSO-d_6) δ: 5.15 (s, 2H, CH_2Cl), 7.6 (m, 1H, C-5 H), 7.8–8.0 (m, 2H, C-3 H and C-4 H), 8.6 (m, 1H, C-6 H), 12.6 (m, 1H, N^+H). *Anal.* calcd. for C_7H_8NOCl: C 43.54, H 3.69, N 7.45; found: C 43.4, H 3.8, N 7.3.

*3-(2-Chloroacetyl)pyridine hydrochloride (**6**b)*

A solution of 41 g (0.33 mol) of nicotinic acid in 240 mL of sulfinyl chloride was heated at 80°C for 2 h. The excess of sulfinyl chloride was distilled and after addition of 20 mL of dry benzene the solvents were removed under reduced pressure. To the residue was added 32 g of freshly distilled pyridine. The mixture was distilled and the fraction collected at 91–95°C/13 Torr was redistilled offering 40 g of nicotinoyl chloride (85%), bp 90°C/12 Torr. A solution of 38.2 g (0.27 mol) of acid chloride in 100 mL of dry benzene was added dropwise to a cooled solution (0–5°C) of about 22.5 g (0.54 mol) of diazomethane in 1.2 L of ether (dried 2 h on KOH pellets). The mixture was treated as described above in the preparation of **6***a*. By this method was obtained 49 g of hydrochloride **6***b* (94%); ^1H nmr (DMSO-d_6) δ: 5.3 (s, 2H, CH_2Cl), 7.9 (ddd, 1H, J_{5-2} = 1 Hz, J_{5-4} = 8 Hz, J_{5-6} = 5 Hz, C-5 H), 8.7 (ddd, 1H, J_{4-2} = 2.5 Hz, J_{4-6} = 1.5 Hz, C-4 H), 9.0 (dd, 1H, C-6 H), 9.3 (dd, 1H, C-2 H), 11.4 (m, 1H, N^+H). *Anal.* calcd. for $C_7H_8NOCl_2$: C 43.54, H 3.69, N 7.45; found: C 43.7, H 3.6, N 7.3.

*4-(2-Chloroacetyl)pyridine hydrochloride (**6**a)*

According to the above method, the following were obtained from isonicotinic acid: 39 g (83%) of isonicotinoyl chloride, bp 81°C/13 Torr, and then 29 g (95%) of compound **6***c*: ^1H nmr (DMSO-d_6) δ: 5.45 (s, 2H, CH_2Cl), 8.3 (dd, 2H, J_{3-2} = 6.5 Hz, J_{5-2} = 1.5 Hz, C-3 H and C-5 H), 9.2 (dd, 2H, C-2 H and C-6 H), 11.2 (m, 1H, N^+H). *Anal.* calcd. for $C_7H_8NOCl_2$: C 43.54, H 3.69, N 7.45; found: C 43.6, H 3.5, N 7.2.

*Preparation of 4-chloro-3-(x-pyridyl)-1-butyn-3-ols (**7**a–c)*

Ethyl magnesium bromide, prepared in tetrahydrofuran (100 mL) from 35 g (0.32 mol) of ethyl bromide and 8 g (0.33 mol) of magnesium, was converted into ethynylmagnesium bromide by dropwise addition during 1 h to a saturated solution of acetylene in 100 mL of THF, while acetylene was passed continuously through the mixture. A suspension of 57.6 g (0.3 mol) of compound **6***a–c* in 250 mL of THF was added in portions to the Grignard reagent at 0–5°C. The mixture was stirred for 14 h at 20°C, cooled to 0–5°C, decomposed by addition of 16 mL of saturated aqueous ammonium chloride solution, and extracted with ether. Removal of the solvents left a dark oil which was used without further purification (Table 4).

*Preparation of 3,4-epoxy-3-(x-pyridyl)-1-butynes (**8**a–c)*

To a solution of compound **7***a–c* in 100 mL of dry ether was added 40 g of powdered sodium hydroxide. The mixture was stirred for 14 h, filtered, and the solvent removed. The residual oil was used without further purification (Table 4).

*3-(3-Furyl)pyridine (**9**b)*

A solution of 1.6 g of mercuric sulphate in 40 mL of 2 *N* sulphuric acid was added to a solution of compound **8***b* in 100 mL of 2 *N* sulphuric acid. The mixture was stirred 1 h at 90°C, cooled to 20°C,

TABLE 3. Yield, analytical, and ^1H nmr data for furylpyridines **5***a–c* and **9***a–c*

Compounds	Boiling point (°C/Torr)	Yield (%)	Analysis (%) found[a]			^1H nmr															
						Pyridyl								Furyl							
			C	H	N	H-2	H-3	H-4	H-5	H-6	$J_{2,3}$ $_{5,6}$	$J_{2,4}$ $_{4,6}$	$J_{2,5}$ $_{3,6}$	$J_{3,4}$ $_{4,5}$	H-2	H-3	H-4	H-5	$J_{2,3}$ $_{3,5}$	$J_{3,4}$	$J_{4,5}$	$J_{2,5}$
5*a*	58/0.3	80	74.4	4.9	9.8	—	7.58	7.58	7.05	8.56	4.5	1.2	1.2	8.0	—	7.03	6.48	7.48	0.8	3.3	1.8	
							m	m	m	dt						dd	dd	dd				
5*b*	67/0.4	86	74.4	4.9	9.8	8.91	—	7.79	7.25	8.45	4.9	1.9	1.0	8.0	—	6.65	6.50	7.43	0.8	3.5	1.9	
						dd		dt	ddd	dd						dd	dd	dd				
5*c*	110/0.6	83	74.5	4.8	9.6	8.60	7.47	—	7.47	8.60	4.5		1.5			6.83	6.48	7.52	0.8	3.5	1.8	
	69[b]					dd	dd		dd	dd						dd	dd	dd				
9*a*	112/13	84	74.6	4.9	9.6	—	7.2–7.7		7.10	8.56	4.7	2.0	1.0	6.7	7.96	—	6.82	7.32	0.8		1.8	1.5
							m		m	ddd	$J_{3,5}$ = 1.9				dd		dd	dd				
9*b*	120/13	83	74.6	5.0	9.5	8.76	—	7.68	7.20	8.48	4.7	2.0	0.8	8.0	7.72	—	6.66	7.46	0.8		1.8	1.6
						dd		dt	ddd	dd		1.7			dd		dd	dd				
9*c*	122/14	86	74.7	4.9	9.4	8.52	7.33	—	7.33	8.52	4.5		1.3		7.86	—	6.72	7.50	0.8		1.7	1.5
						dd	dd		dd	dd					dd		dd	dd				

[a]Analysis calculated for C_9H_7NO: C 74.47, H 4.86, N 9.65.
[b]Melting point (°C).

TABLE 4. ^{1}H nmr and infrared data for compounds **7***a*–*c* and **8***a*–*c*

Compounds	^{1}H nmr: Pyridyl H-2	H-3	H-4	H-5	H-6	$J_{2,3\ 5,5}$	$J_{2,4\ 4,6}$	$J_{2,5\ 3,6}$	$J_{5,4}$	Others: CH_aH_b	J_{ab}	≡CH	Infrared (cm^{-1}): ν(≡C—H)	ν(C≡C)
7*a*	—	7.7–7.9 m		7.3 m	8.5 m					3.90 s		2.70 s	3300	2120
7*b*	8.8 m	—	7.9 m	7.6 m	8.6 m					3.75 s		2.73 s	3300	2120
7*c*	8.6 dd	7.6 dd	—	7.6 dd	8.6 dd	4.8		1.5		3.75 s		2.75 s	3300	2120
8*a*	—	7.7 m		7.23 m	8.60 dt	4.8	1.8		8.5	3.43 s		2.62 s	3300	2120
8*b*	8.75 dd	—	7.75 dt	7.30 ddd	8.57 dd	4.8	2.0	1.0	8.0	3.05d 3.47d	6	2.60 s	3300	2120
8*c*	8.60 dd	7.40 dd	—	7.40 dd	8.60 dd	4.8		1.5		2.98d 3.48d	6	2.60 s	3300	2120

basified with $NaHCO_3$, and extracted with ether. Distillation afforded 7.2 g (15%) of **9***b*, bp 72°C/0.2 Torr.

*4-(3-Furyl)pyridine (**9**c)*

It was prepared as compound **9***b*. Distillation afforded 9.1 g (21%) of **9***c*, bp 80°C/0.3 Torr.

*3-Ethoxy-3-(2-pyridyl)-1-butyn-4-ol (**10**)*

To a solution of epoxide **8***a* in 50 mL of ethanol was added 0.5 mL of 70% perchloric acid. The mixture was stirred 1 h at 80°C, cooled, and treated with anhydrous sodium carbonate. After filtration, removal of the solvent left an oil which was used without further purification: ir (neat): 3650 and 3300 (O—H), 3310 (≡C—H), 2125 (C≡C) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.1 (t, 3H, J = 6.5 Hz, CH_3—CH_2), 2.55 (s, 1H, ≡C—H), 3.1 (q, 2H, J = 6.5 Hz, CH_2—CH_3), 3.8 (s, 2H, CH_2), 4.0 (m, 1H, HO, signal disappeared on deuteriation), 7.2 (m, 1H, C-5 H), 7.8–7.6 (m, 2H, C-3 H and C-4 H), 8.5 (m, 1H, C-6 H).

*3-Ethoxy-3-(2-pyridyl)-4,5-dihydrofuran (**11**)*

A solution of sodium ethoxide (from 0.6 g of sodium in 150 mL of ethanol) was added to a solution of compound **10** in 50 mL of ethanol. The mixture was stirred at 80°C during 6 h. The solvent was removed and the residue was extracted with ether. Evaporation of the ether afforded an oil **11**: ^{1}H nmr ($CDCl_3$) δ: 1.20 (t, 3H, J = 6.5 Hz, CH_3—CH_2), 3.47 (q, 2H, J = 6.5 Hz, CH_2—CH_3), 4.60 and 4.58 (2s, 2H, furyl C-2 H_2), 5.21 (d, 1H, J = 2.5 Hz, furyl C-4 H), 6.70 (d, 1H, J = 2.5 Hz, furyl C-5 H), 7.10 (m, 1H, pyridyl C-5 H), 7.7–7.5 (m, 2H, pyridyl C-3 H and C-4 H), 8.53 (m, 1H, pyridyl C-6 H).

*2-(3-Furyl)pyridine (**9**a)*

A solution of compound **11** in 50 mL of 2 *N* sulphuric acid was stirred 1 h at 90°C, cooled to 20°C, treated with $NaHCO_3$, and extracted with ether. Distillation afforded 4.2 g (9.6%) of **9***a*, bp 68°C/0.2 Torr.

*2-(2,2-Diethoxyacetyl)pyridine (**12**a)*

A solution of 88.4 g (0.56 mol) of 2-bromopyridine in 100 mL of dry ether was added dropwise during 1 h to a cold (−20°C) and stirred solution of 450 mL (0.675 mol) of 1.5 *N* n-butyllithiun in hexane and 1.1 L of dry ether. The mixture was stirred for an additional 0.5 h and cooled to −25°C. A solution of 120.3 g (0.56 mol) of 1-(2,2-diethoxyacetyl)piperidine in 80 mL of dry ether was added during 1 h. The mixture was stirred at −25°C for 2 h and then allowed to come to room temperature overnight. A saturated aqueous solution of NH_4Cl (100 mL) was added slowly. Ether extraction followed by distillation of the residue afforded 98 g (84%) of ketone **12***a*, bp 95°C/0.03 Torr.

*3-(2,2-Diethoxyacetyl)pyridine (**12**b)*

A solution of 3-bromopyridine was treated according to the preparation of **12***a*, but at −70°C. By that method was obtained 91 g (78%) of ketone **12***b*, bp 90°C/0.05 Torr.

*4-(2,2-Diethoxyacetyl)pyridine (**12**c)*

A freshly prepared solution of 4-bromopyridine was treated as described above in the preparation of **12***b*. By this method was obtained 91.6 g (78.5%) of ketone **12***c*, bp 82°C/0.04 Torr.

*Preparation of methyl 3-(2-pyridyl)-4,4-diethoxy-2-methoxy-2-butenoates (**13**a–c)*

A stirred suspension of 3.0 g (0.126 mol) of sodium hydride (mineral oil free) in 120 mL dry THF was treated during 0.5 h with the dropwise addition of 30.2 g (0.126 mol) of methyl diethoxyphosphinylmethoxy acetate. Following the addition, the reaction mixture was stirred for an additional 0.5 h. After cooling to 0°C, a solution of 20.9 g (0.1 mol) of ketone **12***a*–*c* in 50 mL of dry THF was added dropwise to this solution over a 30 min period. Near the end of the addition, a gummy precipitate was formed. The reaction mixture was stirred overnight at 25°C and then treated with 75 mL of water. Benzene extraction, including an aqueous ammonium chloride wash, followed by distillation of the residue afforded a mixture (1:3) of unsaturated esters **13***a*–*c* (Table 5).

*Preparation of methyl 3-(x-pyridyl)-4,4-diethoxy-2-methoxy-butanoates (**14**a–c)*

To a solution of 11.8 g (0.04 mol) of the esters **13***a*–*c* in 50 mL of absolute ethanol was added 1.1 g of 10% palladium-on-carbon catalyst. The mixture was stirred under a hydrogen atmosphere until uptake of hydrogen ceased. The time required was approximately 20 min. Then the catalyst was removed by centrifugation and washed with ethanol. The organic fractions were combined and the solvent was evaporated. Distillation of the residue afforded esters **14***a*–*c* (Table 5).

*Preparation of 3-(x-pyridyl)-4,4-diethoxy-2-methoxy-1-butanols (**15**a–c)*

To a vigorously stirred suspension of 1.82 g (0.048 mol) of lithium aluminium hydride in 120 mL of dry THF was added 11.9 g (0.04 mol) of esters **14***a*–*c* in 30 mL of dry THF over a one-hour period. Following the addition, the reaction mixture was stirred for an additional hour before the excess hydride was destroyed by addition

TABLE 5. Yield, analytical, ^{1}H nmr, and infrared data for compounds **12***a*–*c*, **13***a*–*c*, **14***a*–*c*, and **15***a*–*c*

Compounds	Boiling point (°C/Torr)	Yield (%)	Analysis (%) calcd. found			^{1}H nmr															Infrared (cm^{-1}) ν(C=O) ν(O—H)
						Pyridyl								Acetal			Others				
			C	H	N	H-2	H-3	H-4	H-5	H-6	$J_{2,3}$ $J_{5,6}$	$J_{2,4}$ $J_{4,6}$	$J_{2,5}$ $J_{3,6}$	$J_{3,4}$ $J_{4,5}$	CH	CH_2	CH_3	CH_3—O	CH_3—O—CO	C—CH	CH_2	
12*a*	95/0.03	84	63.14 62.9	7.23 7.3	6.69 6.8	—	7.6–8.2 m		7.43 ddd	8.70 m	4.5	1.5	$J_{3,5}$ =2.5	6.5	6.17 s	3.75 dq	1.17 t					1725
12*b*	90/0.05	78	63.14 62.9	7.23 7.05	6.69 6.9	9.18 dd	—	8.31 dt	7.28 ddd	8.61 dd	4.5	2.0	1.0	7.0	4.95 s	3.69 m	1.21 t					1697
12*c*	82/0.04	78.5	63.14 63.2	7.23 7.1	6.69 6.8	8.58 dd	7.83 dd	—	7.83 dd	8.58 dd	4.5		1.5		4.95 s	3.65 m	1.18 t					1704
13*a*	120/0.04	87	61.00 60.8	7.17 7.0	4.74 4.8	—	7.3–7.7 m		7.0 m	8.4 m	4.5	1.5		6.5	5.58s 5.70s	3.6 m	1.1 m	3.47 s	3.62 2s			1735
13*b*	132/0.05	75	61.00 60.7	7.17 7.2	4.74 4.9	8.3 m	—	7.55 m	7.1 m	8.3 m	4.5	2.0	1.0	7.0	5.47s 5.50s	3.5 m	1.11 m	3.38 s	3.62 s			1733
13*c*	133/0.06	75	61.00 60.9	7.17 7.0	4.74 5.0	8.41 m	7.2 2dd	—	7.2 2dd	8.41 m	4.5		1.5		5.41s 5.51s	3.5 m	1.11 m	3.38 s	3.62 s			1733
14*a*	122/0.05	80	60.59 60.8	7.80 7.7	4.71 4.9	—	6.9–7.7 m			8.36 m					4.90d 5.02d	3.5 m	1.00 dt	3.17 s	3.57 s	4.1 m		1758
14*b*	120/0.03	87	60.59 60.9	7.80 7.9	4.71 4.5	8.45 m	—	7.7 dt	7.15 m	8.45 m		2.0	1.0	7.5	4.86d 4.95d	3.5 m	1.1 m	3.40 s	3.54 s	4.1 m		1768
14*c*	118/0.03	90	60.59 60.5	7.80 8.0	4.71 4.8	8.39 m	7.12 m	—	7.12 m	8.39 m	4.5		1.5		4.79d 4.88d	3.5 m	1.1 m	3.34 s	3.46 s	4.1 m		1755
15*a*	115/0.02	83	62.43 62.6	8.61 8.9	5.20 5.4	—	6.9–7.7		m	8.37 ddd	4.5	2.0		6.5	4.98d 4.99d	3.4 m	1.05 m	3.30 s	—	3.5 m	3.4 m	3400
15*b*	133/0.05	74	62.43 62.4	8.61 8.3	5.20 5.4	8.37 dd	—	7.70 dt	7.15 ddd	8.42 m	4.5	2.0	1.0	7.5	4.83 d	3.5 m	1.1 m	3.37 s	—	3.5 m	3.5 m	3400
15*c*	134/0.05	73	62.43 62.2	8.61 8.5	5.20 5.0	8.42 dd	7.28 dd	—	7.28 dd	8.42 dd	4.5		1.5		4.85 d	3.5 m	1.1 m	3.37 s	—	3.5 m	3.5 m	3300

of ethyl acetate. After work-up according to Fieser and Fieser (31) and benzene extraction, distillation afforded alcohols **15***a*–*c* (Table 5).

Preparation of x-*(3-furyl)pyridine (***9**a–c*) from compounds* ***15***a–c

To a stirred solution of 5.4 g (0.02 mol) of alcohols **15***a*–*c* in 150 mL of dry toluene was added 15 mL of a 1.6 *N* solution of hydrogen chloride in ether. The mixture was heated at 120°C for 24 h. After cooling, the mixture was base washed and distillation afforded compounds **9***a*–*c* (Table 3).

Acknowledgement

We wish to thank Professor Mollier (Université de Caen) for the dipole moments measurements.

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