Regioselective Nucleophilic Addition of Organolithium Compounds to 3-(4,4-Dimethyloxazolin-2-yl)pyridine [1]

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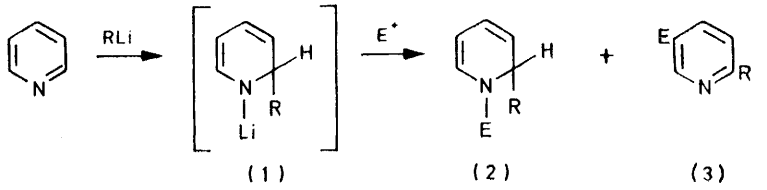
The nucleophilic heteroaromatic addition reactions of 3-(4,4-dimethyloxazolin-2-yl)pyridine (8) with organolithium compounds as nucleophilic reagents have been investigated. Strongly nucleophilic reagents have been observed to add preferentially to the γ- rather than the α-position of the pyridine ring. Stable crystalline 4-substituted 3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridine addition products have been isolated in good yields. Further, the dihydropyridines could be oxidized to the corresponding 3,4-disubstituted pyridines by a variety of oxidizing agents. Interesting oxidative dealkylations of the 4-t-butyl-1,4-dihydropyridine (9e) have been observed, and they may account for the anomalous ratio of aromatized products.

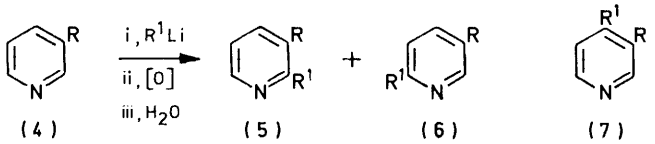
ZIEGLER and Zeiser [2] first reported that alkyl- and aryllithium compounds add to the α-position of the pyridine nucleus, followed by elimination of lithium hydride to give the corresponding α-substituted pyridines. An addition–elimination mechanism was proposed and confirmed [3] including the actual isolation and characterization [3c] of the reactive σ complex (1) (see Scheme 1).

The mode of addition of organolithium compounds to 3-substituted pyridines provides information on the steric and electronic effects of substituents upon the addition of these nucleophiles to the pyridine nucleus. Both electronic and steric factors influence the attack; however, the primary directive influence appears to be



SCHEME 1

due to the inductive effect of the pyridine ring nitrogen atom rather than the substituent.[4,5] When a variety of 3-substituted pyridines [3-4,6] were treated with alkyl- and aryl-lithium compounds, followed by oxidation and hydrolysis, the predominant mode of addition was found to be 1,2-, affording the 2,3-disubstituted pyridines (5). The minor mode of addition was 1,6- giving the corresponding 2,5-disubstituted pyridines (6) (Scheme 2).



SCHEME 2

In spite of careful analysis, no products resulting from 1,4-addition (7) could be detected.

There are a few reports of the addition of organolithium compounds to the 4-position of the pyridine nucleus, but they involved weaker nucleophilic reagents. Thus, benzyl-lithium reacted with 3-picoline and pyridine to give 4-benzyl-3-picoline [7] and 4-benzylpyridine,[7,8] respectively. Other examples of 1,4-addition to the pyridine nucleus include the additions of triphenylsilyllithium [9] and 2-lithio-2-alkyl-1,3-dithianes [10] to pyridine. To date there have been no reports of the 1,4-addition of stronger nucleophilic organolithium compounds, such as phenyl-lithium or alkyl-lithium to the 4-position of a 3-substituted pyridine.

The study of the nucleophilic heteroaromatic substitution of pyridine derivatives by organolithium compounds has been limited mainly to pyridines with electron-releasing substituents. While there have been studies of the reaction of Grignard or metallohydride reagents [11] with substituted pyridines containing electron-withdrawing substituents, only one example of the reaction of an organolithium compound with an electronegatively substituted pyridine has been reported.[5]

We sought to extend the investigation of the reaction of organolithium compounds to pyridines containing electron-withdrawing substituents, such as pyridine-3-carboxylic acid or its derivatives. Carboxylic acid functions can be converted into oxazoline derivatives which are more appropriate because they are inert to organolithium reagents.[12] In order to study the mode of

TABLE 1

4-Substituted 3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridines (9a—e); % yields and elemental analyses

		Elemental analysis (%)					
		Found			Required		
Compd.	Yield [a]	C	H	N	C	H	N
(9a)	78.6	75.3	7.05	10.75	75.76	7.13	11.01
(9b)	69.3	69.0	8.25	14.3	68.72	8.39	14.57
(9c)	78.6	72.1	9.25	12.0	71.76	9.46	11.95
(9d)	74.2	71.95	9.3	12.05	71.76	9.46	11.95
(9e)	75.7	71.85	9.4	11.8	71.76	9.46	11.95

[a] Yields are based on 3-(4,4-dimethyloxazolin-2-yl)pyridine.

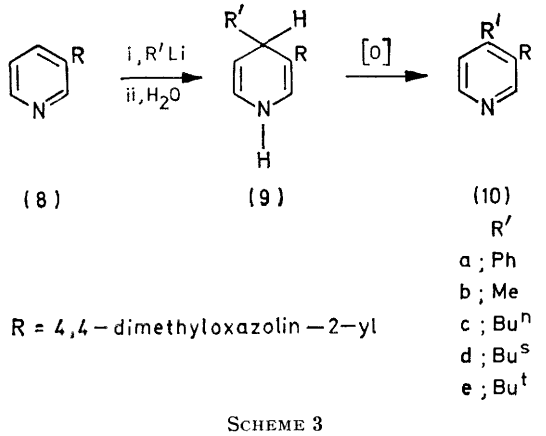
the nucleophilic addition, *i.e.* 1,2-, 1,4-, or 1,6-addition of organolithium compounds to nicotinic acid derivatives, we prepared 3-(4,4-dimethyloxazolin-2-yl)pyridine (8). We now report the unexpected alkylation and arylation at the 4-position of (8) by the more strongly nucleophilic organolithium compounds, and also the isolation of a group of stable 1,4-dihydropyridines.

RESULTS AND DISCUSSION

3-(4,4-Dimethyloxazolin-2-yl)pyridine (8) was obtained by heating methyl nicotinate at reflux with 2-amino-2-methylpropan-1-ol. When a solution of phenyl-lithium in diethyl ether was added dropwise to a solution of compound (8) in diethyl ether at room temperature a dark precipitate formed. When tetrahydrofuran (THF) was used as the solvent no precipitate was formed, but the reaction product was the same as that obtained in the ethereal solution. Hydrolysis of the reaction mixture gave a bright yellow precipitate, 3-(4,4-dimethyloxazolin-2-yl)-4-phenyl-1,4-dihydropyridine (9a). Similarly, treatment of ethereal solutions of compound (8) with other organolithium compounds, followed by hydrolysis, gave the corresponding dihydropyridines (9b—e) (Table 1). Structural assignments for these 1,4-dihydropyridines are based on their ^1H and ^{13}C n.m.r. spectra, u.v.–visible spectra, i.r. spectra, and their aromatization to the corresponding 3,4-disubstituted pyridines (10).

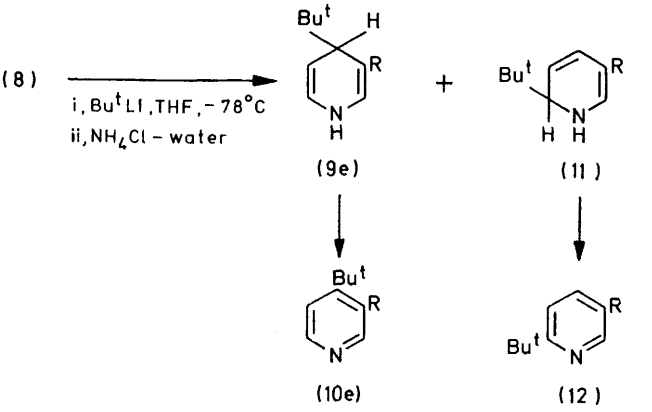
The reaction of compound (8) in diethyl ether with t-butyl-lithium at 0 °C to room temperature, followed by hydrolysis, gave good yields of the 4-t-butyl-1,4-dihydropyridine (9e) (76% isolated yield).

Aliquots of a solution of t-butyl-lithium in n-pentane were added dropwise to solutions of compound (8) in THF at −78 °C for 1 h and warmed to 0 °C. Hydrolysis with saturated aqueous ammonium chloride afforded the 6-t-butyl-1,6-dihydropyridine (11). Work-up of the mother liquors afforded the 4-t-butyl-1,4-dihydropyridine (9e). The total isolated yield of dihydropyridines was 88%. The isomer ratio (9e) : (11) was 61 : 39 indicating that 1,4-addition was again the predominant mode of attack. Meyers and Gabel [13] had informed us that they had observed similar products but more (11) than (9e) in similar studies. This may be attributed to the preferential dealkylation of (9e) over (11) which is discussed later.



SCHEME 3

The ^1H n.m.r. spectrum of 3-(4,4-dimethyloxazolin-2-yl)-4-t-butyl-1,4-dihydropyridine (9e) is representative of those obtained for the other dihydropyridines (9). It showed a doublet of doublets at δ 7.09 (1H) assigned to the pyridine 2-H, a complex multiplet at δ 6.16 (1H) assigned to the pyridine 6-H, a broad absorption at δ 5.81 (1 H) assigned to the pyridine *N*-H, a doublet of doublets at 4.94 (1 H) assigned to the pyridine 5-H, an AX pattern at δ 3.85 (2 H) assigned to the oxazoline 5-H, a doublet of doublets at δ 3.22 (1 H) assigned to the pyridine 4-H, two singlets at 1.27 (3 H) and 1.26 (3 H) assigned to the geminal methyl groups at C-4 of the oxazoline ring, and a singlet at 0.83 (9 H) assigned to the t-butyl group. A summary of the ^1H n.m.r. chemical shifts of the pyridine-ring protons for all 1,4-dihydropyridines (9) is given in Table 2. The deuterium-exchange experiments were particularly useful during the analysis of the ^1H n.m.r. spectra of the dihydropyridines. The addition of deuterium oxide to the sample eliminated coupling between the *N*-H and pyridine-ring protons at positions 2, 5, and 6. As expected for 1,4-dihydropyridines, with no substituent on the pyridine nitrogen,[14] there was no long-range coupling between the *N*-H and pyridine-ring protons at position 4.



SCHEME 4

The chemical shifts (Table 2) observed for 3-(4,4-dimethyloxazolin-2-yl)-6-t-butyl-1,6-dihydropyridine

TABLE 2

^1H N.m.r. chemical shifts [a] of the pyridine-ring protons of the substituted 3-(4,4-dimethyloxazolin-2-yl)-1,4- and -1,6-dihydropyridines

Compd.	H-1	H-2	H-4	H-5	H-6
(9a)	5.75	7.08	4.74	4.94	6.18
(9b)	6.50	6.79	3.32	4.58	5.88
(9c)	6.56	6.85	3.33	4.55	5.92
(9d)	5.22	6.97	3.49	4.73	6.07
(9e)	5.81	7.09	3.22	4.94	6.16
(11)	4.71	7.39	6.42	5.09	4.50

[a] In $CDCl_3$, relative to TMS.

(11) indicate that the proton attached to the sp^3 hybridized carbon is located α to the pyridine-ring nitrogen atom.[15] The deuterium exchange experiments were also useful in elucidating the structure of compound (11).

Recently, ^{13}C n.m.r. spectral analysis has become an important tool for the structural elucidation of NAD and NADH,[16] as well as for distinguishing between 1,4- and 1,6-dihydropyridines.[17] Analysis of the ^{13}C n.m.r. spectra of compounds (9a—e) and (11) (Table 3) provided *good evidence* for the 1,4-dihydropyridine structures. The spectral assignments for these dihydropyridines are in agreement with the chemical shifts reported for other dihydropyridines.[16,17]

TABLE 3

^{13}C N.m.r. chemical shifts at 25.034 4 MHz of the pyridine-ring and oxazoline-ring carbons of the substituted 3-(4,4-dimethyloxazolin-2-yl)-1,4- and -1,6-dihydropyridines

Compd.[a]	C-2	C-3	C-4	C-5	C-6	C-2′	C-4′	C-5′
(9a)	132.3	97.8	97.8	103.4	124.3	161.2	66.3	77.2
(9b)	132.2	99.2	27.3	104.5	124.2	161.2	66.2	76.9
(9c)[b]	132.7	99.8	36.7	104.6	124.0	162.5	66.6	77.8
(9d)	135.6	99.9	[c]	103.1	125.2	162.1	67.4	78.3
(9e)	134.0	95.9	42.0	99.8	126.4	163.1	66.3	77.3
(11)	140.8	91.4	123.4	111.2	60.8	160.6	65.6	77.4

[a] In $(CD_3)_2SO$, relative to $SiMe_4$. [b] In $CDCl_3$, relative to $SiMe_4$. [c] Not observed.

Before the advent of n.m.r. spectroscopy, u.v. and visible spectroscopy was the most useful technique for the identification of dihydropyridines. For our purposes, it is still an important diagnostic tool.[18] Dihydropyridines containing an electron-withdrawing substituent at the three position display u.v. absorption spectra characteristic of the 1,2- and 1,4-, and 1,6-dihydropyridine chromophores. The extended dienamine chromophores of 1,2-dihydropyridines absorb at longer wavelengths (>350 nm) than the corresponding 1,4-isomers or the cross-conjugated 1,6-dihydropyridines. A band at 250—300 nm is frequently observed for 1,2- or 1,6-dihydropyridines and has been used to distinguish these isomers from the 1,4-dihydropyridine. The exact wavelength of these absorption bands is dependent upon several factors,[19] including the nature of the 3-substituent, the presence of other substituents, the solvent, and the nature of the substitution at the pyridine-ring nitrogen.

Compounds (9a—e) all displayed one strong absorption between 300 and 350 nm characteristic of 1,4-dihydropyridines. However, compound (11) displayed two strong absorptions and a shoulder. The possibility of a 1,2-dihydropyridine was ruled out, since none of the absorptions displayed by compound (11) was greater than 350 nm. Consequently, the spectrum of compound (11) was thought to arise from the 1,6-dihydropyridine chromophore. The u.v.–visible spectral data for these dihydropyridines is summarized in Table 4.

As a whole, the ^1H and ^{13}C n.m.r. spectra and u.v.–visible spectra unambiguously demonstrate that compounds (9a—e) are the 1,4-dihydropyridines and that compound (11) is the 1,6-isomer. The oxidation of

TABLE 4

U.v.–visible spectral data for compounds (9a—e) and (11) [a]

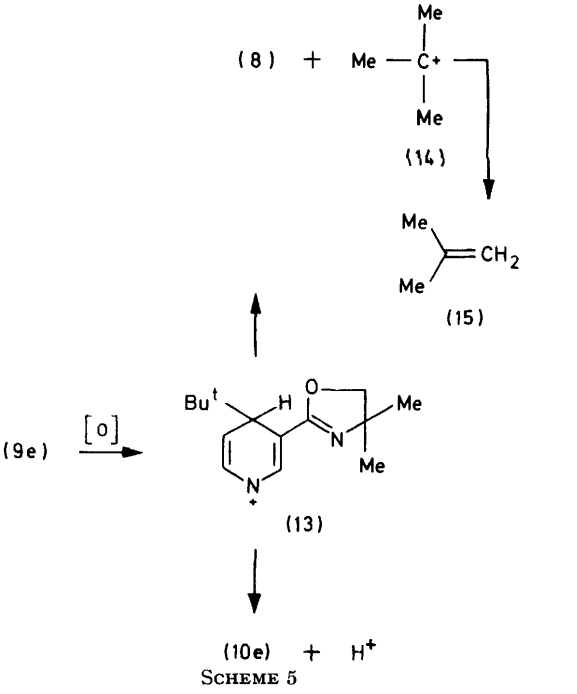
Compd.	Chromophore	$\lambda_{max.}$/nm	ε/mol l^{-1} cm^{-1}	log ε
(9a)	1,4-	332	2 416	3.383
(9b)	1,4-	328	9 257	3.967
(9c)	1,4-	329	6 913	3.840
(9d)	1,4-	329	9 205	3.964
(9e)	1,4-	318	6 246	3.796
(11)	1,6-	339	9.832	3.977
		277 [b]	28 376	4.435
		267	32 298	4.509

[a] In absolute ethanol. [b] Shoulder.

these stable dihydropyridine addition products to the corresponding disubstituted pyridine derivatives provides unequivocal structural proof. The stability of the 1,4-dihydropyridines required that strong oxidizing agents be employed in these aromatizations. The resulting disubstituted pyridines were easily characterized on the basis of their ^1H and ^{13}C n.m.r. and i.r. spectra.

Dihydropyridines (9a—c) were aromatized, by potassium permanganate in acetone [20] or 5% palladium on charcoal in toluene containing glacial acetic acid,[21] to the desired 3,4-disubstituted pyridines (10a—c). All the dihydropyridines were oxidized by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene [22] to the corresponding disubstituted pyridines; however, the aromatization of (9e) was accompanied by dealkylative oxidation to give the oxazoline (8). Compounds (9b) and (9e) were oxidized with oxygen [23] while the 1,6-dihydropyridine (11) in chloroform slowly aromatized in the air. The results of these aromatizations are summarized in Table 5.

The aromatization of dihydropyridines usually proceeds *via* dehydrogenation and occasionally by the loss of a substituent. Dealkylative oxidation is parti-



SCHEME 5

TABLE 5

Oxidation of compounds (9a—e) and (11) to the corresponding disubstituted pyridines

Method	Compd.	Product	% Yield [a]	Elemental analysis (%) Found C	H	N	Required C	H	N
A [b]	(9a)	(10a)	41.3						
B [c]	(9a)	(10a)	48.1	76.2	6.35	11.05	76.17	6.39	11.10
C [d]	(9a)	(10a)	50.3						
A	(9b)	(10b)	48.7						
B	(9b)	(10b)	27.5	69.65	7.35	14.5	69.45	7.42	14.72
C	(9b)	(10b)	24.8						
D [e]	(9b)	(10b)	52.3						
A	(9c)	(10c)	45.3						
B	(9c)	(10c)	44.6	72.5	8.65	12.15	72.38	8.68	12.06
C	(9c)	(10c)	83.2						
C	(9d)	(10d)	55.3	72.7	8.55	11.85	72.38	8.68	12.06
C	(9e)	(10e)	71.1	72.25	8.9	11.9	72.38	8.68	12.06
D	(9e)	(10e)	19.4						
C	(11)	(12)	80.2	72.45	8.55	12.35	72.38	8.68	12.06

[a] Yields are based on the starting dihydropyridines. [b] $KMnO_4$–acetone, 25 °C. [c] 5% Palladium on carbon in toluene–glacial acetic acid at reflux. [d] DDQ in benzene, 25 °C. [e] Oxygen, 25 °C.

cularly favoured when the substituent lost is capable of forming a stable carbonium ion assisted by relief of steric strain.[24] Thus, we observed that oxidation of 3-(4,4-dimethyloxazolin-2-yl)-4-t-butyl-1,4-dihydropyridine (9e) was often accompanied by loss of the t-butyl group (Table 6). The thermal oxidation of (9e) also resulted in a mixture of products (10) and (8).

TABLE 6

Oxidation of the dihydropyridine (9e)

Oxidation method [a]	% Yield [b] (10e)	(8)
A		90.2
C	71.1	27.4
D	19.4	79.5
E [c]	12.1	85.9

[a] See Table 5. [b] Yields are based on compound (12e). [c] Thermal oxidation at 350 °C

Examination of the space-filling molecular models representing the dihydropyridine (9e) and the 3,4-disubstituted pyridine (10e) indicates that a large amount of steric hindrance is generated during the conversion of (9e) into (10e). Indeed, there can be practically no rotation about the single bonds between the substituents and the pyridine ring in (10e). Under the oxidation conditions the t-butyl cation, a relatively stable carbonium ion, can be lost and deprotonated to yield isobutene (15). Indeed, the dihydropyridine (9e) when pyrolysed [2,*] gave isobutene (15) (Scheme 5). The dealkylative oxidation of (9e) is facilitated by the loss of a stable carbonium ion (14) and the relief of steric strain to give compound (8) rather than (10e). Thus, while there are more 4- than 6-substituted dihydropyridines, under certain oxidation conditions, the ratio of the 4- and 6-aromatized products can be reversed.

EXPERIMENTAL

Equipment and Materials.—All m.p.s were taken on a Büchi melting-point apparatus and are uncorrected. I.r. spectra were recorded using a Beckman IR-8 spectrometer, and are reported as cm^{-1}. U.v.–visible spectra were recorded using a Cary 118C ultraviolet–visible spectrophotometer. All ^1H n.m.r. spectra were taken using either a Varian Model T-60 or a Varian Model HA-100 n.m.r. spectrometer. All ^{13}C n.m.r. spectra were taken using a JEOL PFT 100 spectrometer equipped with a Nicolet 1080 Fourier Transform accessory. All solvent evaporations were done on a rotary evaporator. Analytical and preparative gas chromatographic (g.c.) analyses were done on a 10 ft × 1.4 in stainless steel 3% OV-1 on Gas Chrom Q (100/120) column unless noted otherwise. The gas chromatograph used was a Varian Aerograph Model 1520B equipped with a dual thermal conductivity detector. Elemental analyses were performed by the Center for Trace Characterization, Texas A & M University, College Station, Texas.

All organolithium additions were carried out under nitrogen in a round-bottomed flask equipped with stirring bar, serum-capped addition funnel, nitrogen inlet, and an oil bubbler. Diethyl ether and tetrahydrofuran (THF) were heated over lithium aluminium hydride (LAH) for a period of time and distilled from LAH under nitrogen just prior to use. n-Butyl-lithium in n-hexane, s-butyl-lithium in cyclohexane, and methyl-lithium in diethyl ether were obtained from Ventron. t-Butyl-lithium in n-pentane was obtained from Aldrich or Ventron. Phenyl-lithium in diethyl ether was prepared from lithium wire and bromobenzene. Throughout, ether refers to diethyl ether.

3-(4,4-*Dimethyloxazolin*-2-*yl*)*pyridine* (8).—Methyl nicotinate (50 g, 365 mmol) and 2-amino-2-methylpropan-1-ol (49g, 548 mmol) were heated at reflux for 2.5 h. The clear orange mixture was cooled and the methanol removed under aspiration. The excess of amino-alcohol was removed by vacuum distillation (48—58 °C/1.55—1.8 Torr). The crude oxazoline (8) was collected as a colourless liquid (100—123 °C/1.2—1.45 Torr). A brown-white solid remained in the distillation pot. The crude solid, nicotinic acid, was recrystallized from ethanol to give a white powder; purified yield 3.88 g (8.6%), m.p. 232—235 °C; mixed m.p. (undepressed) 231.5—234.5 °C.

3-(4,4-Dimethyloxazolin-2-yl)pyridine (8) was fractionated through a 10-cm Vigreaux column to give a colourless liquid; isolated and purified yield 48.80 g (75.9%), b.p. 89—91 °C (0.65 Torr); i.r. (neat) 2 971, 1 644, 1 355, 1 032, and 812 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 9.15 (d, $J_{2.}$ 2.1 Hz, 1 H, pyridine 2-H), 8.67 (dd, $J_{4.6}$ 2.1 Hz and $J_{5.6}$ 4.9 Hz,

* We thank Mr. David Wisdom for carrying out the gas-phase pyrolysis of compound (9e) and for his helpful comments.

1 H, pyridine 6-H), 8.20 (dt, $J_{2,4}$ 2.1 Hz, $J_{4,5}$ 8.3 Hz and $J_{4,6}$ 1.8 Hz, 1 H, pyridine 4-H), 7.30 (m, $J_{4,5}$ 8.3 Hz and $J_{5,6}$ 4.9 Hz, 1 H, pyridine 5-H), 4.10 (s, 2 H, oxazoline 5-H), and 1.30 (s, 6 H, oxazoline geminal CH_3) (Found: C, 67.9; H, 6.8; N, 15.65. $C_{10}H_{12}N_2O$ requires C, 68.16; H, 6.86; N, 15.90%.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*phenyl*-1,4-*dihydropyridine* (9a).—To a solution of compound (8) (4.0 g, 22.7 mmol) in ether (25 ml) was added dropwise a solution of phenyl-lithium in ether (1.0M; 24 ml; 22.7 mmol); addition was complete after 10 min. A dark brown solid was formed. The flask was shaken intermittently for 1 h at room temperature. Hydrolysis with water (10 ml) afforded a yellow solid. The solid was filtered off and washed with ether (2 × 5 ml). The basic aqueous layer was extracted with ether (8 × 10 ml). The combined ether extracts were dried (Na_2SO_4). The solvent was removed *in vacuo*, leaving an orange solid. The crude product obtained, (9a), was recrystallized from benzene to give a white powder, yield 4.54 g (78.6%); m.p. 184—186 °C (C_6H_6), 169—172 °C (subl.); i.r. (KBr) 2 946, 1 661, 1 597, 1 241, and 1 163 cm^{-1}.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*methyl*-1,4-*dihydropyridine* (9b).—To a solution of (8) (2.0 g, 11.3 mmol) in ether (25 ml) was added dropwise a solution of methyl-lithium in ether (2.0M; 5.7 ml; 11.3 mmol). Addition was complete after 10 min. The red-brown solution was stirred at room temperature for 1 h. Hydrolysis with water afforded a yellow solution. The ether layer was separated. The basic aqueous layer was extracted with ether (3 × 10 ml) and the combined ether layers were dried (Na_2SO_4). The solvent was removed *in vacuo*, leaving a yellow solid. The crude product obtained, (9b), was sublimed to give white granules: isolated yield 1.51 g (69.3%); m.p. 139—141 °C; i.r. (KBr) 2 962, 1 616, 1 602, 1 249, and 1 169 cm^{-1}.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*n-butyl*-1,4-*dihydropyridine* (9c).—Similarly, a solution of compound (8) (2.0 g, 11.3 mmol) in ether (25 ml) was treated with a solution of n-butyl-lithium in n-hexane (2.0M; 5.7 ml; 11.3 mmol). Hydrolysis with water (10 ml), and work-up, *vide supra*, afforded a yellow solid. The crude product obtained, (9c), was recrystallized from benzene and then linearly sublimed to give a white powder; isolated yield 2.08 g (78.5%), m.p. 122—123 °C; i.r. (KBr) 2 964, 1 670, 1 605, 1 245, and 1 170 cm^{-1}.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*s-butyl*-1,4-*dihydropyridine* (9d).—As described above, compound (8) (5.54 g, 31.46 mmol) in ether and s-butyl-lithium in cyclohexane (1.2M; 26.5 ml, 31.5 mmol) followed by hydrolysis with water (10 ml) afforded a white solid which was filtered off and washed with ether (2 × 10 ml). The crude product obtained, (9d), was recrystallized from benzene and linearly sublimed to give white granules; isolated yield 5.47 g (74.2%), m.p. 118—120 °C; i.r. (KBr) 2 962, 1 671, 1 602, 1 241, and 1 174 cm^{-1}.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*t-butyl*-1,4-*dihydropyridine* (9e).—To a solution of compound (8) (5.37 g, 30.4 mmol) in ether (25 ml) stirred at 0 °C was added dropwise a solution of t-butyl-lithium in n-pentane (1.3M; 23.5 ml; 30.4 mmol). Addition was complete after 10 min. The mixture was stirred at 0 °C for 30 min. The orange-brown suspension was warmed to room temperature for 1 h. Hydrolysis with water (10 ml) afforded a bright yellow solid which was filtered off and washed with ether (3 × 10 ml). The crude product obtained, (9e), was linearly sublimed to give white granules; isolated yield 5.37 g (75.7%), m.p. 147—149 °C; i.r. (KBr) 2 958, 1 658, 1 602, 1 247, and 1 162 cm^{-1}.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-6-*t-butyl*-1,6-*dihydropyridine* (11).—To a solution of compound (8) (2.40 g, 13.6 mmol) in THF cooled to −78 °C was added dropwise a solution of t-butyl-lithium in n-pentane (1.3M; 10.5 ml, 13.6 mmol). Addition was complete after 8 min. The yellow solution was stirred at −78 °C for 1 h and then warmed to 0 °C. Hydrolysis with a saturated ammonium chloride solution (10 ml) afforded a white solid which was filtered off. The crude product obtained, (11), was linearly sublimed to give white flakes; isolated yield 1.10 g (34.5%), m.p. 117—119 °C; i.r. (KBr) 2 958, 1 647, 1 605, 1 245, and 1 191 cm^{-1} (Found: C, 71.4; H, 9.35; N, 11.85. $C_{14}H_{22}N_2O$ requires C, 71.76; H, 9.46; N, 11.95%).

The THF layer was separated from the basic aqueous layer. The aqueous layer was extracted with ether (2 × 10 ml) and the combined ether and THF layers were dried (Na_2SO_4). The solvents were removed *in vacuo* leaving a bright yellow solid. The crude solid obtained, (9e), was linearly sublimed to give white granules; isolated yield 1.70 g (53.3%).

General Procedure for Potassium Permanganate Oxidation of Dihydro-pyridines (9a—c).—A solution of the dihydropyridine in acetone (50 ml) was treated with a mixture of potassium permanganate (5 g) in acetone (100 ml). The addition was terminated when the purple colour remained. The excess of potassium permanganate was reduced by stirring with isopropyl alcohol. The brown precipitate was filtered off and the filtercake was washed with acetone (5 × 10 ml). The solvent was removed *in vacuo* from the filtrate and the residues were subjected to preparative t.l.c. on silica gel (ethyl acetate) or filtration through a neutral alumina column (ethyl acetate). Boiling and/or melting points, yields, i.r., and ^1H n.m.r. data are given below.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*phenylpyridine* (10a), b.p. 75—82 °C (0.025 Torr), m.p. 83.5—85 °C; 41.3% yield; i.r. (KBr) 2 974, 1 652, 1 777, 1 088, and 1 034 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 8.92 (s, 1 H, pyridine 2-H), 8.68 (d, $J_{5,6}$ 5.8 Hz, 1 H, pyridine 6-H), 7.40 (s, 5 H, phenyl H), 7.29 (d, $J_{5,6}$ 5.8 Hz, 1 H, pyridine 5-H), 3.84 (s, 2 H, oxazoline 5-H), and 1.30 (s, 6 H, oxazoline geminal CH_3).

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*methylpyridine* (10b), b.p. 70—71 °C (0.10 Torr); 48.7%; i.r. (neat) 2 971, 1 644, 1 192, 1 086, and 1 041 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 8.94 (s, 1 H, pyridine 2-H), 8.45 (d, $J_{5,6}$ 5.0 Hz, 1 H, pyridine 6-H), 7.09 (d, $J_{5,6}$ 5.0 Hz, 1 H, pyridine 5-H), 4.05 (s, 2 H, oxazoline 5-H), 2.58 (s, 3 H, CH_3), and 1.37 (s, 6 H, oxazoline geminal CH_3).

4-*n-Butyl*-3-(4,4-*dimethyloxazolin*-2-*yl*)*pyridine* (10c), b.p. 49.5 °C (0.015 Torr); 46.3%; i.r. (neat) 2 959, 1 644, 1 309, 1 074, and 1 032 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 8.93 (s, 1 H, pyridine 2-H), 8.48 (d, $J_{5,6}$ 5.0 Hz, 1 H, pyridine, 6-H), 7.10 (d, $J_{5,6}$ 5.0 Hz, 1 H, pyridine 5-H), 4.02 (s, 2 H, oxazoline 5-H), 2.99br (t, 2 H, CH_2), 1.48 (cm, 4 H, CH_2CH_2), 1.34 (s, 6 H, oxazoline geminal CH_3), and 0.91br (t, 3 H, CH_3).

General Procedure for 5% Palladium on Carbon Oxidation of Dihydropyridines (9a—c).—A mixture of the dihydropyridine and 5% palladium on carbon (36.3 : 1, mmol : mg) was covered with toluene and glacial acetic acid (mmol dihydropyridine : ml acid, 1.2 : 1). The mixture was heated at reflux and filtered hot. The resulting solution

was washed with water (3 × 5 ml), 10% $NaHCO_3$ (3 × 5 ml), and water (3 × 5 ml). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residues were subjected to filtration through a neutral alumina column (ethyl acetate). Each product was characterized by a combination of spectral (i.r. and ^1H and ^{13}C n.m.r.) data. The periods of reflux and yields are given below.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*phenylpyridine* (10a), 48 h; 48.1% yield.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*methylpyridine* (10b), 42 h; 27.5% yield.

4-*n*-*Butyl*-3-(4,4-*dimethyloxazolin*-2-*yl*)*pyridine* (10c), 36 h; 44.6% yield.

General Procedure for DDQ Oxidation of Dihydropyridines (9a—e) *and* (11).—A suspension of the dihydropyridine (1.0 mol equiv.) in benzene was treated with DDQ (1.0 mol equiv.) and the mixture was stirred at room temperature; it was then filtered through a neutral alumina column (ethyl acetate). The products were purified by filtration through a neutral alumina column or preparative g.c. Each product was characterized by a combination of spectral (i.r. and ^1H and ^{13}C n.m.r.) data. The reaction periods, methods of purification, and yields are given below:

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*phenylpyridine* (10a), 3 h, column, 50.3% yield.

3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*methylpyridine* (10b), 1 h, column, 24.8% yield.

4-*n*-*Butyl*-3-(4,4-*dimethyloxazolin*-2-*yl*)*pyridine* (10c), 4.5 h, column, 83.2% yield.

4-*s*-*Butyl*-3-(4,4-*dimethyloxazolin*-2-*yl*)*pyridine* (10d), 2 h; g.c., 5 ft × 1/4 in 10% FFAP on 60/80 Chrom W, room temp. (170 °C, 60 ml/min) 28 min; 49—50 °C (0.015 Torr); 55.3% yield; i.r. (neat) 2 972, 1 641, 1 192, 1 089, and 1 032 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 8.86 (s, 1 H, pyridine 2-H), 8.53 (d, $J_{5,6}$ 5.9 Hz, 1 H, pyridine 6-H), 7.18 (d, $J_{5,6}$ 5.9 Hz, 1 H, pyridine 5-H). 4.04 (s, 2 H, oxazoline 5-H), 3.68 (sextet, 1 H, CH), 1.60 (cm, 2 H, CH_2), 1.32 (s, 6 H, oxazoline geminal CH_3), 1.23 (d, 3 H, CH_3), and 0.83 (t, 3 H, CH_3).

4-*t*-*Butyl*-3-(4,4-*dimethyloxazolin*-2-*yl*)*pyridine* (10e), 30 min; g.c., 10 ft × 1/4 in 3% OV-1 on 100/120 Gas Chrom Q, 150 °C, 50 ml/min; 98.1% yield of two products.

(8): room temp. 4 min 42 s; 27.4%.

(10e): room temp. 13 min 22 s; 71.1%, i.r. (neat) 2 972, 1 664, 1 587, 1 188, and 1 040 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 8.53 (d, $J_{5,6}$ 5.8 Hz, 1 H, pyridine 6-H), 8.51 (s, 1 H, pyridine 2-H), 7.33 (d, $J_{5,6}$ 5.8 Hz, 1 H, pyridine 5-H), 4.13 (s, 2 H, oxazoline 5-H), 1.42 (s, 15 H, oxazoline geminal CH_3 and t-butyl CH_3).

2-*t*-*Butyl*-5-(4,4-*dimethyloxazolin*-2-*yl*)*pyridine* (12), 30 min; linear sublimation; 58—59 °C; 80.2% yield; i.r. (KBr) 2 971, 1 649, 1 130, 1 069, and 1 015; ^1H n.m.r. ($CDCl_3$) δ 9.07 (d, $J_{2,4}$ 2.3 Hz, 1 H, pyridine 6-H), 8.12 (dd, $J_{2,4}$ 2.3 Hz and $J_{3,4}$ 8.5 Hz, 1 H, pyridine 4-H), 7.32 (d, $J_{3,4}$ 8.5 Hz, 1 H, pyridine 3-H), 4.06 (s, 2 H, oxazoline 5-H), 1.36 (s, 15 H, oxazoline geminal CH_3 and t-butyl CH_3).

Reaction of 3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*methyl*-1,4-*dihydropyridine* (9b) *with Oxygen*. A solution of compound (9b) (2.06 g, 10.7 mmol) in benzene (75 ml) was stirred at room temperature. Oxygen was bubbled through the solution for 10 h. The mixture was then filtered through a 2 × 10 cm neutral alumina column (ethyl acetate). The solvents were removed *in vacuo*; isolated yield 1.07 g (52.3%).

Reaction of 3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*t*-*butyl*-1,4-*dihydropyridine* (9e) *with Oxygen*.—A suspension of compound (9e) (23.4 mg, 0.1 mmol) in chloroform (2 ml) was treated with oxygen at room temperature. The reaction was monitored by ^1H n.m.r. spectroscopy. There was no change in the spectrum after 1, 3, or 8 h. After 17, 24, and 32 h the spectrum indicated a mixture of aromatic compounds. The solvent was removed *in vacuo* leaving a yellow oil, 23.2 mg (99.9%).

A quantitative analysis of the residue by g.c. (3% OV-1, 179 °C, 50 ml/min) gave 14.0 mg (79.5%) of compound (8) (room temp. 2 min 30 s) and 4.5 mg (19.4%) of (10e) (room temp. 5 min 20 s), respectively.

Thermal Oxidation of 3-(4,4-*Dimethyloxazolin*-2-*yl*)-4-*t*-*butyl*-1,4-*dihydropyridine* (9e).—A test tube containing (9e) (35.2 mg, 0.15 mmol) was heated in a sand-bath at 350 °C for 10 min. The mixture was cooled giving a yellow oil, 34.4 mg (98.7%).

A quantitative analysis of the residue by g.c. (3% OV-1, 180 °C, 50 ml/min) gave 22.7 mg (85.9%) of compound (8) (room temp. 2 min 26 s) and 4.2 mg (12.1%) of compound (10e) (e.r. 5 min 21 s), respectively.

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