

SOLVENT AND TEMPERATURE EFFECTS ON THE NUCLEOPHILIC ADDITION OF ORGANOLITHIUMS TO 3-(4,4-DIMETHYLOXAZOLIN-2-YL)PYRIDINE.  
SYNTHESIS OF STABILIZED 1,2-, 1,4- AND/OR 1,6-DIHYDROPYRIDINES<sup>1</sup>

Sushil K. Dubey and Edward E. Knaus\*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada, T6G 2N8

Abstract - The reaction of 3-(4,4-dimethyloxazolin-2-yl)pyridine (1) with nucleophilic organolithium reagents afforded stabilized N-unsubstituted 1,2-, 1,4- and/or 1,6-dihydropyridines. Reaction of 1 with phenyllithium gave a mixture of 1,2- (2) and 1,4-dihydropyridines (3) whereas reaction with n-butyl- and methyllithium afforded a mixture of 1,2- (2), 1,4- (3) and 1,6-dihydropyridines (4). The regiochemistry of the nucleophilic substitution reaction was dependent upon reaction solvent, reaction temperature and the nature of the organolithium reagent. Reactions carried out using the less polar ether as solvent, provided higher yields of C-2 (2) and C-6 (4) substituted products, whereas reactions performed in tetrahydrofuran provided higher yields of C-4 substituted products (3). A decrease in reaction temperature, increased the yield of the 1,4-dihydro isomer (3) in both solvents. Reactions employing phenyllithium were more regioselective than those utilizing n-butyl- and methyllithium.

The development of methods for the introduction of substituents onto a pyridine ring has been an important synthetic goal. A variety of synthetic methods have been investigated, the most prominent of which was halogen-exchange reactions employing bromopyridines.<sup>2</sup> The direct metallation of pyridine was difficult, since most strong bases acted as nucleophiles, adding

across the electrophilic azomethine bond.<sup>3</sup> The directed (ortho) lithiation of substituted pyridines is a versatile method for effecting highly regioselective electrophilic heteroaromatic substitution and has been employed as a powerful synthetic tool.<sup>4,5</sup> Recent reports have demonstrated that pyridines activated by halogens,<sup>6</sup> oxazolines,<sup>4,5</sup> secondary or tertiary carboxamides,<sup>7,8</sup> esters<sup>9</sup> or ethers<sup>10</sup> can be effectively lithiated with complete regiochemical control and that the resulting lithiopyridines react smoothly with electrophiles. The direct metallation of pyridine using a complex of n-butyllithium and potassium t-butoxide in tetrahydrofuran and hexane has since been reported.<sup>11</sup>

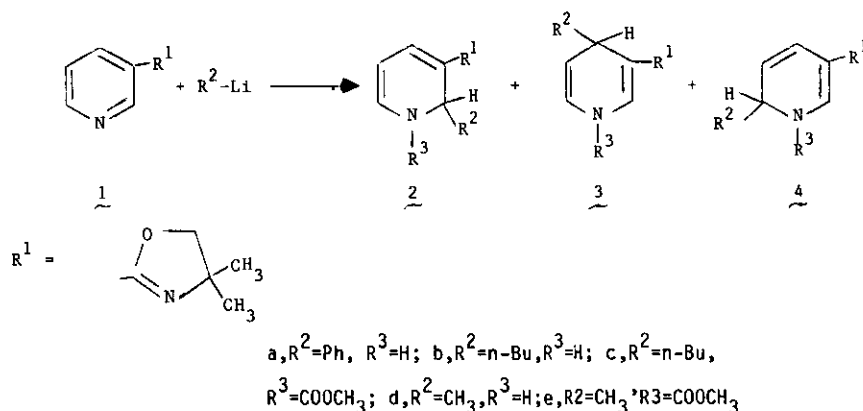
It is well documented that electron-attracting substituents, capable of resonance interaction, such as COOH, COMe, CO<sub>2</sub>Me, CONH<sub>2</sub>, NO<sub>2</sub>, CN and oxazolin-2-yl in the C-3 and C-5 positions, stabilize dihydropyridines by extending the conjugation.<sup>1,4b,12,13</sup> Reaction of 3-cyanopyridine with alkyllithiums gave a mixture of 1,2- and 1,4-dihydropyridines, whereas similar reactions of 3-diethylamino- and 3-methoxycarbonylpyridine yielded a mixture of 1,4- and 1,6-dihydropyridines.<sup>14</sup> The position of the oxazolin-2-yl substituent is crucial, since treatment of 4-(4,4-dimethyloxazolin-2-yl)pyridine with alkyllithiums, such as n-butyl- and sec-butyllithium in tetrahydrofuran at low temperature afforded products resulting from both C-3 metallation and addition to the C=N moiety, whereas reaction with methylithium gave exclusive C-3 metallation. On the other hand, reaction of 3-(4,4-dimethyloxazolin-2-yl)pyridine with methylithium under similar conditions gave a quantitative yield of the 1,4-dihydropyridine analog.<sup>4b</sup> In related studies, the reaction of 3-(4,4-dimethyloxazolin-2-yl)pyridine with organolithiums has been shown to yield predominantly 1,4-dihydropyridine intermediates, which on oxidation, provide a facile route to 3,4-disubstituted pyridines.<sup>13</sup> Previously, we reported<sup>1</sup> in preliminary form, the synthesis of stabilized N-unsubstituted 3-(4,4-dimethyloxazolin-2-yl)-1,2-, 1,4- and/or 1,6-dihydropyridines. We now describe the full account of the effect of solvent and temperature upon the regioselective nucleophilic addition of organolithiums to 3-(4,4-dimethyloxazolin-2-yl)pyridine (1).

## RESULTS AND DISCUSSION

The effect of solvent and temperature upon regiochemistry was investigated by <sup>1</sup>H nmr spectrometry since it was considered to be the most precise procedure for determination of the ratio of dihydropyridine products. The dihydropyridines 2-4 were required for use as medicinal synthons in our drug design research.<sup>15</sup> Furthermore, oxidation of the dihydropyridine intermediates, obtained on quenching the reaction with water, to the disubstituted pyridines may not reflect the true isomeric ratio of products initially present. The reaction of 3-(4,4-dimethyloxazolin-2-yl)pyridine 1 with phenyllithium, n-butyllithium and methylithium in diethyl ether and tetrahydro-

furan at 25°, 0° and -78°C was investigated, respectively. A solution of the organolithium reagent (1 equivalent) was added dropwise to a solution of 1, and the reaction mixture was hydrolyzed with water after 30 min (see Scheme 1).

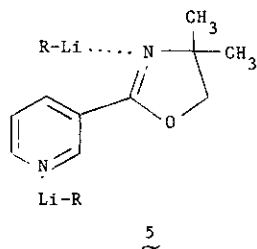
Reaction of phenyllithium with 1 in ether at 25°C afforded a mixture of 2a and 3a in a ratio of 4:1 as determined from the <sup>1</sup>H nmr integrals of H-2 at 5.68 and H-6 at 6.2 for the respective isomers. Sublimation of this mixture afforded the stable 2-phenyl-3-(4,4-dimethyloxazolin-2-yl)-1,2-dihydropyridine (2a) in 55.7% yield. In contrast, reaction of phenyllithium with 1 in tetrahydrofuran at 25°C afforded a mixture of the 1,2-dihydro (2a) and 1,4-dihydro (3a) isomers (16:84) with the 1,4-dihydro isomer (3a) predominating. Reaction of phenyllithium with 1 at 0° and -78°C in ether and tetrahydrofuran was also investigated, and the results are summarized in Table 1. The relative ratio of 1,4-dihydro isomer (3a), to 1,2-dihydro isomer (2a), increased as the temperature was decreased in both solvents. Thus, reaction of phenyllithium with 1 in tetrahydrofuran at -78°C afforded the 1,4-dihydro isomer (3a) in quantitative yield. No product 4a, resulting from attack at the C-6 position of 1, irrespective of solvent or temperature, was observed.



Scheme 1

The two tertiary nitrogens in 1 are both capable of forming chelates (complexes) with the organolithium reagent. A complex formed between the organolithium reagent, and the oxazoline nitrogen of 1 may be orientated in such a way as to direct nucleophilic addition to either the C-2 or C-4 position of the pyridine ring. Complexation with the pyridine nitrogen atom would be expected to increase the probability of attack at C-2 and/or C-6 as well as the C-4 position. A complex where both nitrogen atoms are chelated such as 5 is also possible. A similar complex has been postulated for the reaction of methyllithium with nicotine.<sup>16</sup>

The polarity of the solvent has a distinct effect on the regiochemistry of the reaction of



phenyllithium with 1. In weakly polar solvents such as diethyl ether, complexation of the pyridine nitrogen atom with the organolithium reagent appears to direct attack to C-2. A similar effect has been observed in the metallation of pyridine.<sup>11</sup> In the more polar tetrahydrofuran, the nucleophilic addition may be more dependent upon the resonance and inductive effects of the pyridine nitrogen atom and the oxazoline substituent. Steric effects do not appear to be important, since no C-6 substituted product 4a was detected in these reactions. Equilibration between isomers was not evident once the addition had taken place.

Table 1. Isomeric ratios (%) as determined from <sup>1</sup>H nmr integrals<sup>a</sup>

R <sup>2</sup> -Li	Solvent	Temp., °C	1,2-Isomer ( <u>2</u> )	1,4-Isomer ( <u>3</u> )	1,6-Isomer ( <u>4</u> )
PhLi	Et O	25	80	20	-
PhLi	Et O	0	75	25	-
PhLi	Et O	-78	5	95	-
PhLi	THF	25	16	84	-
PhLi	THF	0	8	92	-
PhLi	THF	-78	-	100	-
n-BuLi	Et O	25	50	40	10
n-BuLi	Et O	0	44.4	44.4	11.1
n-BuLi	Et O	-78	15	70	15
n-BuLi	THF	25	11	55	34
n-BuLi	THF	0	3.5	62	34.5
n-BuLi	THF	-78	-	88.5	11.5
MeLi	Et O	25	67	25	8
MeLi	Et O	0	63	32	5
MeLi	Et O	-78	40	54	6
MeLi	THF	25	17	50	33
MeLi	THF	0	10	60	30
MeLi	THF	-78	-	>95	<5

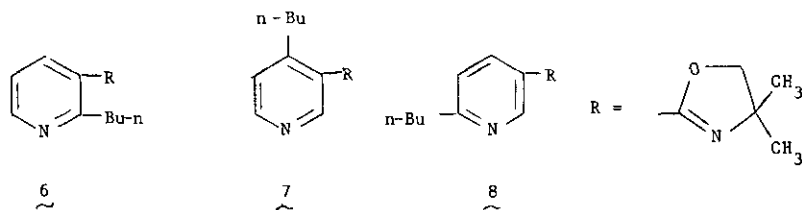
<sup>a</sup>The ratio was calculated from the integrals for H-4, H-2 and H-2 of 2, 3 and 4 respectively.

The reaction of n-butyllithium with 1 was also investigated. Thus, reaction at 25°C in ether gave a mixture of 1,2-dihydro (2b), 1,4-dihydro (3b) and 1,6-dihydro (4b) isomers in a ratio of 50:40:10. A similar reaction in tetrahydrofuran yielded 2b, 3b and 4b in a ratio of 11:55:34. In tetrahydrofuran, attack at C-4 was favored at all temperatures, whereas attack at C-2 and C-6

was predominant in ether at 0° and 25°C. The percentage of 1,4-dihydro product (3b) increased while that of the 1,2-dihydro isomer (2b) decreased in both solvents as the temperature was reduced. These reactions differed from those employing phenyllithium, since the 1,6-dihydro isomer (4b), resulting from attack at C-6, was also formed. These results indicate that n-butyllithium is less regioselective than phenyllithium which may be due, at least in part, to differences in nucleophilicity. The ratio of the isomeric dihydropyridines (2b-4b) was determined from the <sup>1</sup>H nmr integrals (CDCl<sub>3</sub>) of H-4,

H-2 and H-2 at 6.8, 6.92 and 7.2 δ for the 1,2-dihydro, 1,4-dihydro and 1,6-dihydro isomers, respectively. The dihydropyridines (2b and 4b), which were difficult to obtain as pure products, were characterized as their N-methoxycarbonyl derivatives (2c and 4c) obtained by treatment of the N-lithio intermediates with methyl chloroformate.<sup>3</sup> Purification was effected on preparative silica gel G plates (0.5 mm) with ether:hexane (6:4 v/v) as development solvent.

The reaction mixtures containing 2b-4b, obtained from the reaction of n-butyllithium with 1 in tetrahydrofuran at 25°, 0° and -78°C were oxidized using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), potassium permanganate or oxygen.<sup>17</sup> These experiments were performed to determine the stability of the isomeric products 2b-4b toward the oxidation agents and to correlate, if possible, the ratio of the oxidation products 6-8 with the initial ratio of 2b-4b as determined from <sup>1</sup>H nmr integrals. The reaction mixture, obtained after reaction of n-butyllithium with 1 at 25°C in tetrahydrofuran and hydrolysis with water, was oxidized with DDQ. Preparative silica gel G tlc afforded the pure 4-butyl isomer (7) but the 2-butyl (6) and 6-butyl (8) products were not resolved as indicated by <sup>1</sup>H nmr. On the other hand, oxidation of the reaction mixture, obtained from reaction of n-butyllithium with 1 in tetrahydrofuran at 0°C and hydrolysis with water, with potassium permanganate afforded 7 and 8 in a ratio of 7:1 after tlc separation relative to 62:35 as indicated by <sup>1</sup>H nmr integrals for the original reaction mixture. The 1,2-dihydro isomer (2b) decomposed during the oxidation reaction since no trace of 6 was evident in the unpurified oxidation reaction mixture. Oxidation of the reaction mixture, obtained by treatment of 1 with n-butyllithium in tetrahydrofuran at -78°C, with potassium permanganate or oxygen yielded 7 and 8



in ratios of 83:17 and 81:19 respectively as indicated by the  $^1\text{H}$  nmr integrals. These studies indicate that the 1,2-isomer (2b) undergoes appreciable decomposition during oxidation and the total yield of products is low.

The ratio of isomeric 1,2-dihydro (2d), 1,4-dihydro (3d) and 1,6-dihydro (4d) products, obtained from reaction of 1 with methyl lithium was qualitatively similar to those observed upon reaction with n-butyllithium with respect to solvent and temperature (see Table 1). The percentage of 1,2-dihydro isomer (2d) was increased while that of the 1,4-dihydro isomer (3d) was decreased (methyl lithium) relative to that of the 1,2-dihydro isomer (2b) and 1,4-dihydro isomer (3b)(n-butyllithium), respectively. There appears to be little difference in regioselectivity between n-butyllithium and methyl lithium. The dihydropyridine isomers (2d-4d) were characterized as their N-methoxycarbonyl derivatives (2e-4e), as described previously.

#### CONCLUSIONS

The reaction of 3-(4,4-dimethyloxazolin-2-yl)pyridine (1) with phenyl-, n-butyl- and methyl lithium is a useful method for the synthesis of stabilized N-unsubstituted 1,2-dihydro, 1,4-dihydro and/or 1,6-dihydropyridines (2-4). The 3-(4,4-dimethyloxazolin-2-yl) substituent is inert, and does not induce ortho-metallation, and confers a stabilizing effect by extending the conjugation.<sup>1,4b,12,13</sup> The regiochemistry of the nucleophilic addition reaction is solvent and temperature dependent. Reactions performed in the less polar solvent such as diethyl ether afforded higher yields of C-2 (2) and C-6 (4) substituted products than those reactions carried out in the more polar tetrahydrofuran which yielded predominantly C-4 (3) substituted products at similar temperatures. A decrease in reaction temperature reduced the proportion of the C-2 (2) substituted product and increased the amount of the C-4 (3) substituted product. The reactions of phenyllithium with 1 were more selective than those employing n-butyl- or methyl lithium, since the former afforded only 1,2-dihydro (2) and 1,4-dihydro (3) products, whereas the latter yielded all three isomeric products (2-4). Reaction of phenyllithium with 1 in tetrahydrofuran at  $-78^\circ\text{C}$  gave a quantitative yield of the 1,4-dihydro product (3a). The ratio of isomeric products 2-4 obtained upon reaction of 1 with n-butyllithium was qualitatively similar to those obtained upon reaction with methyl lithium. Reaction of the intermediate N-lithio dihydropyridines (2-4) ( $\text{R}^3=\text{Li}$ ) with electrophiles such as methyl chloroformate, provides a facile route to stabilized N-substituted dihydropyridines 2-4 ( $\text{R}^3=\text{CO}_2\text{Me}$ ).

The stabilized dihydropyridines 2-4 are useful medicinal synthons which are being used in our drug design program.

## EXPERIMENTAL

EQUIPMENT and MATERIALS - Melting points were determined with a Buchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in deuteriochloroform with tetramethylsilane as an internal standard with a Bruker AM-300 or Varian EM-360 spectrometer. Infrared spectra were recorded on a Nicolet 5DX FT or Perkin Elmer 267 spectrometer. Mass spectra were determined with an AEI MS-50 mass spectrometer.

All organolithium reactions were performed under dry nitrogen. Ether and tetrahydrofuran were refluxed over lithium aluminum hydride from which it was distilled just prior to use. 3-(4,4-Dimethyloxazolin-2-yl)pyridine was prepared according to the literature.<sup>4b</sup> All products described gave rise to a single spot on tlc using a solvent system of low, medium and high polarity. No residue remained after combination of the products.

3-(4,4-Dimethyloxazolin-2-yl)-2-phenyl-1,2-dihydropyridine (2a).

A solution of 1 (1.056 g, 6 mmol) in dry diethylether (20 ml) was added dropwise to a solution of phenyllithium (6 mmol) in dry ether (30 ml) with stirring at 25°C under a nitrogen atmosphere. The reaction was allowed to proceed at 25°C for 30 min, and the mixture was cooled to 0°C and then water (10 ml) was added dropwise. The ethereal fraction was separated, and the aqueous layer was extracted with ether (2 x 20 ml). The combined ethereal extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed in vacuo to yield a solid residue. This residue was sublimed to give 2a as a yellow solid (0.85 g, 55.7%), mp 169-170°C; ir(KBr), 3240 and 1640 cm<sup>-1</sup>; <sup>1</sup>H nmr (DMSO-d<sub>6</sub> and CDCl<sub>3</sub>) δ, 7.16-7.66 (m, 5H, Ph), 6.9 (d, J<sub>4,5</sub>=6.5Hz, 1H, H-4), 6.48 (d, J<sub>5,6</sub>=6Hz of d, J<sub>NH,6</sub>=6Hz, 1H, H-6; collapses to a d, J<sub>5,6</sub>=6Hz after deuterium oxide exchange), 5.68 (d, J<sub>NH,2</sub>=3Hz, 1H, H-2), 4.85 (d, J<sub>4,5</sub>=6.5Hz of d, J<sub>5,6</sub>=6Hz of d, J<sub>NH,5</sub>=1.5Hz, 1H, H-5; br s, 1H, NH, exchanges with deuterium oxide), 3.9 (s, 2H, OCH<sub>2</sub>), 1.3 and 1.18 (two s, 3H each, CH<sub>3</sub>); C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O requires C, 75.59; H, 7.08; N, 11.02). (Found: C, 75.73; H, 7.07, N, 10.98).

The reactions of 1 with phenyl-, n-butyl- and methyl lithium was also carried out at 25°, 0° and -78°C in ether and tetrahydrofuran (see Table 1) using this general procedure. The physical data (mp, ir, <sup>1</sup>H nmr) for 3a, 3b and 3c were identical to those previously reported<sup>13b</sup> except that the mp of 3a was 184-186°C rather than 169-172°C. The mp of 2a is 169-172°C.

General Procedure for the Preparation of 1-Methoxycarbonyl Derivatives of 1,2- (2), 1,4- (3) and 1,6-Dihydropyridines (4) - A solution of 1 (1.056 g, 6 mmol) in dry tetrahydrofuran (20 ml) was added dropwise to a solution of n-butyllithium (6 mmol) in dry tetrahydrofuran (30 ml) with stirring in a nitrogen atmosphere at 25°C. The reaction was allowed to proceed for 30 min at 25°C, and the mixture was cooled to -78°C. A solution of methyl chloroformate (0.5 ml, 6 mmol)

in dry tetrahydrofuran (5 ml) was added dropwise with stirring. The reaction mixture was allowed to warm to 25°C and then water (10 ml) was added. Extraction with ether (3 x 25 mL), drying ( $\text{Na}_2\text{SO}_4$ ) and removal of the solvent *in vacuo* gave a mixture of 2c, 3c and 4c in quantitative yield. This mixture was separated on silica gel G plates, 0.5 mm in thickness, using ether:hexane (6:4 v/v) as a development solvent. The products were characterized by ir,  $^1\text{H}$  nmr and high-resolution mass spectrometry data as illustrated below.

2-n-Butyl-3-(4,4-dimethyloxazolin-2-yl)-1-methoxycarbonyl-1,2-dihydropyridine (2c).  $\cdot$   $\ast R_f$  0.55; oil, 7.1% yield; ir (neat), 1735, 1670, 1644 and 1620  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$ , 0.98 (t,  $J=7\text{Hz}$ , 3H,  $-\text{CH}_2\text{CH}_3$ ), 1.1-1.88 (m, 12H,  $-(\text{CH}_2)_3\text{CH}_3$ , geminal  $\text{CH}_3$ ), 3.92 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.06 (s, 2H,  $-\text{CH}_2-$ ), 5.32-5.72 (m, 2H, H-2 and H-5), 6.8 (d,  $J_{5,6}=5.5\text{Hz}$ , 1H, H-6), 7.06 (d,  $J_{4,5}=9.75\text{Hz}$ , 1H, H-4). Exact Mass calcd. for  $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3$ : 292.1787; found (high-resolution ms): 292.1785.

4-n-Butyl-3-(4,4-dimethyloxazolin-2-yl)-1-methoxycarbonyl-1,4-dihydropyridine (3c).  $\ast R_f$  0.6; oil, 20.1% yield; ir (neat), 1745, 1700 and 1650  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$ , 1.0 (t,  $J=7\text{Hz}$ , 3H,  $\text{CH}_2\text{CH}_3$ ), 1.2-1.7 (m, 12H,  $\{\text{CH}_2\}_3\text{CH}_3$ , geminal  $\text{CH}_3$ ), 3.58 (m, 1H, H-4), 3.96 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.02 (s, 2H,  $\text{OCH}_2$ ), 5.15 (d,  $J_{5,6}=8\text{Hz}$  of d,  $J_{4,5}=5\text{Hz}$ , 1H, H-5), 6.93 (d,  $J_{5,6}=8\text{Hz}$ , 1H, H-6), 7.7 (s, 1H, H-2). Exact Mass calcd. for  $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3$ : 292.1787; found (high-resolution ms): 292.1778.

6-n-Butyl-3-(4,4-dimethyloxazolin-2-yl)-1-methoxycarbonyl-1,6-dihydropyridine (4c).  $\ast R_f$  0.4; mp 65-67°C; 17.3% yield; ir (KBr), 1735, 1670, 1640 and 1600  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$ , 0.94 (t,  $J=7\text{Hz}$ , 3H,  $\text{CH}_2\text{CH}_3$ ), 1.1-1.7 (m, 12H,  $\{\text{CH}_2\}_3\text{CH}_3$ , geminal  $\text{CH}_3$ ), 3.88 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.03 (s, 2H,  $\text{OCH}_2$ ), 4.84 (m, 1H, H-6), 5.72 (d,  $J_{4,5}=9.75\text{Hz}$  of d,  $J_{5,6}=5.5\text{Hz}$ , 1H, H-5), 6.5 (d,  $J_{4,5}=9.75\text{Hz}$ , 1H, H-4), 7.57 (s, 1H, H-2). Exact Mass calcd. for  $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3$ : 292.1787; found (high-resolution ms): 292.1783.

The 1,2- (2e), 1,4- (3e) and 1,6-dihydropyridines (4e) were prepared by the reaction of 1 with methyl lithium using the general procedure described above.

3-(4,4-Dimethyloxazolin-2-yl)-1-methoxycarbonyl-2-methyl-1,2-dihydropyridine (2e).  $\ast R_f$  0.6; oil; 12.8% yield; ir (neat), 1740, 1670 and 1620  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$ , 1.2 (d,  $J_{\text{Me},\text{H}-2}=6\text{Hz}$ ,  $\text{CH}_3-\text{C}-2$ ), 1.32 (s, 6H, geminal  $\text{CH}_3$ ), 3.86 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.02 (s, 2H,  $\text{OCH}_2$ ), 5.2-5.72 (m, 2H, H-2, H-5), 6.72 (d,  $J_{5,6}=6\text{Hz}$ , 1H, H-6), 7.0 (d,  $J_{4,5}=8\text{Hz}$ , 1H, H-4). Exact Mass calcd. for  $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3$ : 250.1318; found (high-resolution ms): 250.1310.



3-(4,4-Dimethyloxazolin-2-yl)-1-methoxycarbonyl-4-methyl-1,4-dihydropyridine (3e). \*R<sub>f</sub> 0.7; oil; 36.6% yield; ir (neat), 1750, 1700, 1650 and 1635 cm<sup>-1</sup>; <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ, 1.3 (d, J<sub>Me,H-4</sub>=6.5Hz, CH<sub>3</sub>-C-4), 1.36 (s, 6H, geminal CH<sub>3</sub>), 3.48 (ddd, J<sub>Me,H-4</sub>=6.5Hz of d, J<sub>4,5</sub>=5Hz, 1H, H-4), 3.92 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.0 (s, 2H, OCH<sub>2</sub>), 5.12 (d, J<sub>5,6</sub>=8Hz of d, J<sub>4,5</sub>=5Hz, 1H, H-5), 6.8 (d, J<sub>5,6</sub>=8Hz, 1H, H-6), 7.6 (s, 1H, H-2). Exact Mass calcd. for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: 250.1318; found (high-resolution ms): 250.1312.

3-(4,4-Dimethyloxazolin-2-yl)-1-methoxycarbonyl-6-methyl-1,6-dihydropyridine (4e). \*R<sub>f</sub> 0.4; oil; 22.1% yield; ir (neat), 1740, 1670, 1640 and 1600 cm<sup>-1</sup>; <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ, 1.27 (d, J<sub>Me,H-6</sub>=6Hz, 3H, CH<sub>3</sub>-C-6), 1.4 (s, 6H, geminal CH<sub>3</sub>), 3.92 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.08 (s, 2H, OCH<sub>2</sub>), 4.92 (ddd, J<sub>Me,H-6</sub>=6Hz of d, J<sub>5,6</sub>=5.5Hz, 1H, H-6), 5.7 (d, J<sub>4,5</sub>=9.75Hz of d, J<sub>5,6</sub>=5.5Hz, 1H, H-5), 6.5 (d, J<sub>4,5</sub>=9.75 Hz, 1H, H-4), 7.56 (s, 1H, H-2). Exact Mass calcd. for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: 250.1318; found (high-resolution ms): 250.1316.

4-n-Butyl-3-(4,4-dimethyloxazolin-2-yl)pyridine (7) and 6-n-Butyl-3-(4,4-dimethyloxazolin-2-yl)pyridine (8). - The reaction mixture, obtained from reaction of 1 (6 mmol) with n-butyllithium (6 mmol) at 0°C in tetrahydrofuran as described previously, was dissolved in acetone (50 ml). A solution of potassium permanganate in acetone (5% w/v) was added dropwise with stirring until the purple color persisted and then isopropyl alcohol (10 ml) was added to reduce excess potassium permanganate present. The reaction mixture was filtered, and the residue was washed with acetone (3 x 10 ml). Removal of the solvent from the combined filtrates in vacuo gave a mixture which was purified on silica gel G plates, 0.5 mm in thickness, using ethyl acetate as a development solvent. Extraction of the product bands with methanol yielded 7 (0.38 g, 27.5%)<sup>13b</sup> and 8 (0.11 g, 7.8%)<sup>13c</sup> which were identical (ir, <sup>1</sup>H nmr) with literature data.

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