3 H), 2.7 (m, $CH_2C$=N, 2 H), 2.37 (m, $CH_2C$—O, 2 H), 1.73 (m, $CH_2$, 4 H); $^{13}C$ NMR ($CDCl_3$) δ 1.73.34 (s, C=O), 158.81 (s, C=N), 51.48 (q, $OCH_3$), 33.22 (t, CC=O), 24.76 (t, CC—N), 23.92 (t, CCC—O), 23.10 (t, CCC—N).

The same product was also obtained from the reaction of 4-(methoxycarbonyl)pentanehydroximoyl chloride (**10**) with 1 molar equiv of pyridine and sulfur dioxide in methylene chloride solution.

**5-[ω-(Methoxycarbonyl)hexyl]-1,3,2,4-dioxathiazole *S*-Oxide[11] (15).** Similarly 2,2-dimethoxycyclooctanone oxime (5.02 g, 25 mmol) was converted to the sulfur dioxide complex **15**: 4.5 g (72.6% yield). $^1H$ NMR ($CDCl_3$) δ 3.67 (s, $OCH_3$, 3 H), 2.67 (m, $CH_2C$=N, 2 H), 2.33 (m, $CH_2C$=O, 2 H), 1.47 (m, $CH_2$, 8 H); $^{13}C$ NMR ($CDCl_3$) δ 173.87 (s, C=O), 159.17 (s, C=N), 51.37 (q, $OCH_3$), 33.80 (t, CC=O), 28.38 (t, CCCCC=N), 25.14 (t, CCC=O), 24.62 (t, CC—N), 23.23 (t, CCC=N).

**Methyl 5-Isocyanatovalerate (16).** The sulfur dioxide complex of 5-(methoxycarbonyl)pentanenitrile oxide (**14**) was refluxed in cyclohexane until sulfur dioxide evolution ceased.[11] Evaporation of the cyclohexane gave about a 60% yield of methyl 5-isocyanatovalerate (**16**): bp 50 °C (0.4 mm); $^1H$ NMR ($CDCl_3$) δ 3.67 (s, $OCH_3$, 3 H), 3.33 (m, $CH_2N$, 2 H), 2.37 (m, $CH_2CO$, 2 H), 1.67 (m, $CH_2$, 4 H). A small sample of the isocyanate was treated with aniline to give the *N*-phenyl-*N'*-[(4-methoxycarbonyl)butyl]urea: mp 106–108 °C (ethyl acetate); $^{13}C$ NMR ($CDCl_3$) δ 173.91 (s, C=O), 156.85 (s, NCN), 139.19 (s, N—$C(CH_2)_5$), 51.49 (q, $OCH_3$), 39.69 (t, CN), 33.56 (t, CC=O), 29.60 (t, CCN), 22.13 (t, CCC=O). Anal. ($C_{13}H_{18}N_2O_3$): C, H, N.

**Methyl 7-isocyanatoheptanoate (17)** was prepared in a manner similar to that above: $^1H$ NMR ($CDCl_3$) δ 3.67 (s, $OCH_3$, 3 H), 3.33 (m, $CH_2N$, 2 H), 2.33 (m, $CH_2C$=O, 2 H), 1.43 (m, $CH_2$, 8 H); $^{13}C$ NMR ($CDCl_3$) δ 173.87 (s, C=O), 122.6 (s, NCO), 51.36 (q, $OCH_3$), 43.12 (t, CN) 33.91 (t, CC=O), 31.34 (t, CCN), 28.63 (t, CCCC=O), 26.42 (t, CCCN), 24.98 (t, CCC=O).

**Reaction of 2,2-Dimethoxycyclohexanone oxime (1) with Chlorine in the Presence of Pyridine.** A solution of 2,2-dimethoxycyclohexanone oxime (**1**; 8.65 g, 50 mmol) in dry methylene chloride (50 mL) and pyridine (3.95 g, 50 mmol) was treated with chlorine (3.55 g, 50 mmol) over 1.2 h at 15 °C. After being stirred for 2 h at room temperature, the solution was washed three times with equal volumes of cold water and evaporated. There was obtained 9.8 g of yellow liquid which, according to the mass spectrum was a mixture of 5-(methoxycarbonyl)valeronitrile, 5-methoxycarbonyl)valeronitrile oxide (**9**), 4-methoxycarbonyl)-pentanehydroximoyl chloride (**10**), 4,5-bis[4-(methoxycarbonyl)butyl]furoxan (**11**), and the corresponding furazan.

**2-Chloro-5-(methoxycarbonyl)valeronitrile (18).** To a solution of 2,2-dimethoxy-3-chlorocyclohexanone oxime (**2**; 1 g, 4.8 mmol) in 10 mL of dry methylene chloride was added a solution of ethyldimethoxycarbonium tetrafluoroborate (0.5 mmol) in 2 mL of the same solvent dropwise at room temperature, causing an exothermic reaction. After being stirred for 30 min, the reaction mixture was worked up to give methyl 2-chloro-5-cyanovalerate (**18**).

**Acknowledgment.** We thank Miss Barbara J. Rutt for her valuable assistance in all phases of this work. We are also indebted to the staff of our Analytical Sciences Laboratories for their analytical services.

**Registry No.** **1**, 52540-36-0; **2**, 58700-10-0; **3**, 52841-56-2; **4**, 58158-90-0; **5**, 81617-18-7; **6**, 81617-19-8; **7**, 81617-20-1; **8**, 81617-21-2; **9**, 81617-22-3; **10**, 81617-23-4; **11**, 81617-24-5; **12**, 64950-92-1; **13**, 81617-25-6; **14**, 81617-26-7; **15**, 81617-27-8; **16**, 70288-68-5; **17**, 64054-33-7; **18**, 58700-11-1; 2,2-dimethoxy-5-*tert*-butylcyclohexanone oxime, 68226-32-4; 2,2-dimethoxy-3-chloro-5-*tert*-butylcyclohexanone oxime, 70165-53-6; 2,2-dimethoxy-3-chlorocyclooctanone oxime, 70165-52-5; 2,2-dimethoxy-3-chlorocyclododecanone oxime, 81617-28-9; 2,2-dimethoxycyclododecanone oxime, 68226-33-5; 3-oximido-4,4-dimethoxy-5-chloroheptane, 70165-56-9; 3-oximido-4,4-dimethoxyheptane, 68226-61-9; 2,2-dimethoxy-3-bromocyclohexane oxime, 70165-54-7; 2,2-dimethoxy-3-bromocyclooctanone oxime, 70165-55-8; 5-methoxycarbonylvaleronitrile, 3009-88-9.

# Substitutions on Pyridines Activated by Oxazolines via Nucleophilic Additions or Metalation–Alkylation

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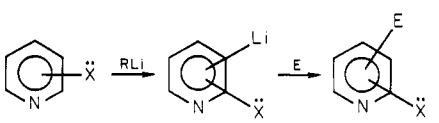
*Received January 13, 1982*

Pyridyloxazolines, derived from nicotinic acid or isonicotinic acid, have been shown to metalate at the 4- and 3-positions, respectively. These react with a variety of electrophiles to provide 4- and 3-substituted pyridines in good yield. Alternatively, 3-pyridyloxazolines, when treated with organolithium or Grignard reagents, give addition to the 4-position and provide a series of 4-substituted 1,4-dihydropyridines.

Substitution on the pyridine ring has long been an important synthetic goal, and a variety of methods have been described, the most prominent of which is halogen–metal exchange on bromopyridines.[1] The direct metalation of pyridines has, until recently, been precluded from the arsenal of substitution methods mainly because most strong bases act as nucleophiles and add across the C=N link.[2] However, in the last few years a number of elegant techniques[3] have been reported which allow direct removal

Scheme I




X = $CO_2Et$, $CONR_2$

of a ring proton by organolithium bases, provided an adjacent electron withdrawing group, also capable of lithium

(1) Schofield, K. "Heteroaromatic Nitrogen Compounds. Pyrroles and Pyridines"; Plenum Press: New York, 1967; pp 162–163, 379–384. Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 285. Klingsberg, E. "Heterocyclic Compounds, Pyridine and Its Derivatives Part II"; Interscience: New York, 1961.

(2) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: New York, 1974.

(3) (Aminocarbonyl)pyridines have been metalated at the 2-, 3-, and 4-positions: Epsztajn, J.; Berski, Z.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1980**, 4739. Katritzsky, A. R.; Rahimi-Rastgoo, S.; Ponkshe, N. K. *Synthesis* **1981** 127. Nicotinate esters have also been metalated and alkylated: Ferles, M.; Silhanova, A. *Collect. Czech. Chem. Commun.* **1979**, *44*, 3137. Metalation of chloropyridines: Gribble, G.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, 4137.

0022-3263/82/1947-2633$01.25/0 

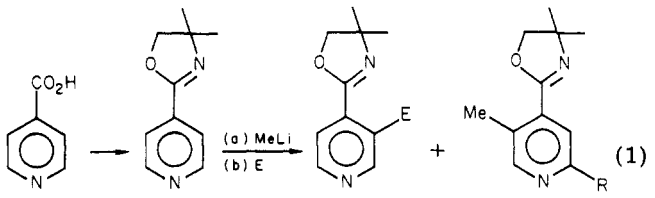
Table I. Alkylation of 1 with Methyllithium and Electrophiles

| electrophile | E for 3 | % yield[a] |
|---|---|---|
| $D_2O$ | D | 79 |
| MeI | Me | 63 |
| EtI | Et | 56 |
|  |  | 54 |
| PhCHO |  | 83 |
| $Et_2C{=}O$ |  | 76 |
| $Me_2NCHO$ | CHO | 52 |
| $O_2$ | OH | 27 |

[a] Yields are for pure isolated products (purified via preparative TLC).

chelation, is present (Scheme I). In 1978, we reported,[4] in preliminary form, studies in progress which indicated that the oxazoline moiety, already established as a strong activating group for metalation on benzene derivatives,[5,6] likewise activated pyridines toward proton removal. We now describe the full account of pyridine-containing oxazolines and their reactions with various organometallic reagents which, under certain conditions, not only metalate the pyridine ring but also conjugatively add to furnish stable 1,4-dihydropyridines.[7]

2-(4-Pyridyl)-4,4-dimethyl-2-oxazoline (1) was prepared in 81% yield from isonicotinic acid and subjected to a series of organolithium bases in an effort to metalate the 3-position of the pyridine ring. The use of *n*-butyllithium or *sec*-butyllithium at temperatures between −78 and −20 °C in THF gave mixtures, after addition of methyl iodide, of **3** and **4**. Thus, addition of the lithium species to the C=N was competing with proton abstraction, and **4** arises by alkylation of the *N*-lithio intermediate. This has previously been observed by Giam and co-workers.[8] Use of lithium diisopropylamide followed by methyl iodide gave only a 9% yield of **3**, the remainder of the material being recovered as starting **1**. However, when methyllithium was employed as the base (eq 1), clean metalation occurred

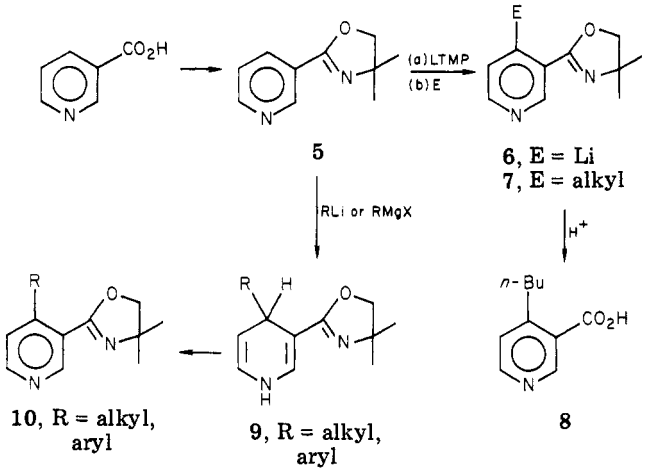


(1)

**1** **2**, E = Li; **3**, E = Me, R **4**, R = *n*-Bu, *sec*-Bu

(confirmed by $D_2O$ quenching) with no evidence of addition to the C=N link of the pyridine nucleus. A series of electrophiles was examined by treating the 3-lithio derivative **2** in THF at −78 °C and allowing to warm to ambient temperature. In no instance was any other product, other than starting material, observed (Table I). With the exception of the oxygenation of the lithiopyridine **2**, all the electrophiles reacted in good yield. This low conversion probably reflects the poorly electrophilic nature of oxygen and concomitant radical reactions. Hydrolysis of the elaborated pyridines to remove the oxazoline moiety was accomplished in aqueous acid, and for **3** (E = $C(OH)Et_2$) the lactone **14** was directly formed in 76% yield.

Scheme II



**5** **6**, E = Li; **7**, E = alkyl **8** **9**, R = alkyl, aryl **10**, R = alkyl, aryl

Table II. Addition of Organometallics to 5 and Oxidation to Pyridines 10

| organometallic | R for 9 | % yield of 9 | R for 10 | % yield of 10 |
|---|---|---|---|---|
| MeLi | Me | 100 | Me | 73 |
| *n*-BuLi | *n*-Bu | 99 | *n*-Bu | 90 |
| EtMgBr | Et | 99 | Et | 99 |
| PhLi | Ph | 100 | Ph | 88 |
| PhMgBr | Ph | 56 | Ph | 88 |
| $LiCH_2CN$ | $NCCH_2$ | 32 | $NCCH_2$ | 71 |

In view of the successful metalation of **1**, the study turned to the pyridyloxazoline derived from nicotinic acid (**5**). The latter was prepared in 67% yield and subjected to organometallic bases. It is to be noted that oxazoline **5** has two favored sites for metalation (2- and/or 4-position). When optimum conditions for metalation of **1** were employed (MeLi, −78–0 °C, THF; Scheme II) and the reaction quenched with $D_2O$, no deuterium incorporation was observed, but we obtained instead a quantitative yield of the 1,4-dihydropyridine **9** (R = Me). The deuterium presumably present on the pyridine nitrogen was exchanged during aqueous workup. The dihydropyridine thus produced was a stable solid which could be readily crystallized from hexane and stored for an indefinite time in an inert atmosphere. The absence of ring metalation by methyllithium and its clean conjugative addition to form **9** are somewhat reminiscent of the Grignard addition to 3-acylpyridines to give 4-substituted 3-acyl-1,4-dihydropyridines. However, this process is only partially successful and requires bulky acyl groups (duryl, mesityl).[9]

Although metalation of **5** was not successful, oxidation of the addition product **9** (air, 25 °C) smoothly gave the aromatized product **10** which is tantamount to metalation and alkylation with electrophiles, albeit in a nucleophilic process. This addition process was repeated with a number of organolithium and Grignard reagents, and all gave generally good yields of 4-substituted 1,4-dihydropyridines.

(4) (a) Meyers, A. I.; Gabel, R. A. *Tetrahedron Lett.* **1978**, 227. (b) *Heterocycles* **1978**, *11*, 133.

(5) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158. Gschwend, H. W.; Hamdam, A. *J. Org. Chem.* **1975**, *40*, 2008. Meyers, A. I.; Lutomski, K. A. *Ibid.* **1979**, *44*, 4464. Beak, P.; Brown, R. A. *Ibid.* **1979**, *44*, 4463. Meyers, A. I.; Avila, W. B. *Ibid.* **1981**, *46*, 3881.

(6) Metalation of thiophene oxazolines has also been reported: Dellavecchia, L.; Vlattas, I. *J. Org. Chem.* **1977**, *42*, 2649.

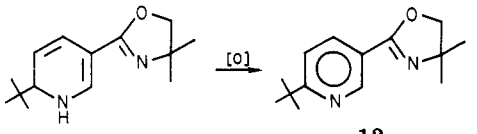
(7) A similar study on additions to pyridine–oxazolines to give 1,4-dihydropyridines has been reported: Hauck, A. E.; Giam, C. S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2070. A preliminary report from this laboratory has also appeared (see ref 4b).

(8) Giam, C. S.; Knaus, E. E.; Pasutto, F. M. *J. Org. Chem.* **1974**, *39*, 3565.

(9) Lyle, R. E.; Nelson, D. A. *J. Org. Chem.* **1963**, *28*, 169. Fuson, R. C.; Miller, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 3477.

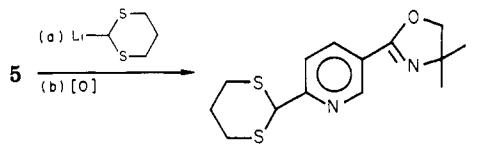
Oxidation of the latter with either air, quinones, or permanganate furnished the substituted pyridines in good yield (Table II). The facile route to 4-phenyl-1,4-dihydropyridines has additional significance due to the recent surge of interest in these systems as potent calcium antagonists.[10] This method could provide a wide variety of 4-aryl derivatives for this purpose.

The use of *tert*-butyllithium as a base to metalate **5** also gave addition rather than the desired metalation. However, addition under the conditions examined (THF, −78 °C) gave mainly the 6-*tert*-butyl derivative **11** in 87% yield along with 13% of the 4-*tert*-butyl system, **9** (R = *t*-Bu). Giam and Hauck reported in their recent study[7] that *tert*-butyllithium in ether gave mainly the 4-*tert*-butyl derivative **9** in 53% yield and the 6-*tert*-butyl derivative **11** in 35% yield. We repeated this experiment and obtained a mixture containing 31% **10**, 12% **12**, and 31% dealkylated pyridine **5**, after oxidation to the pyridine (eq 2). Thus, ether changes the mode of *tert*-butyllithium




11 12

addition to a product mixture containing mainly the 4-*tert*-butyl product. The significant amount of dealkylated product **5** undoubtedly arises from loss of the *tert*-butyl cation during the aromatization step.[8] The use of *tert*-butylmagnesium bromide in ether or THF resulted only in recovery of starting material, **5**. Another example wherein 6-substitution was the primary mode of addition involved the lithiodithiane addition to **5** (eq 3). The only

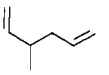
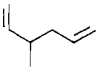



13

product recovered, in 32% isolated yield, was the 6-(dithianyl)pyridine **13**, after aromatization. The addition of *tert*-butyl- and dithianyllithium reagents to the 6-position indicates that bulky reagents appear to kinetically favor addition to the more accessible carbon adjacent to the pyridine nitrogen. Attempts to allow equilibration of the intermediate lithio adducts to either the 4- or 6-position failed to support any reversal once the addition had taken place.

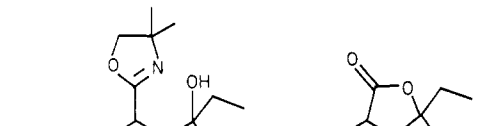
The search for a suitable base that would metalate the 2- or 4-position in **5** was finally ended when the latter was treated with lithium 2,2,6,6-tetramethylpiperidide (LTMP). Metalation of the 4-position occurred exclusively at 0 °C in THF to give **6**, and addition of various electrophiles then produced **7**. As seen from Table III, only highly electrophilic reagents gave good yields whereas alkyl halides, possessing $\alpha$-protons adjacent to the pyridine ring gave products of sequential metalation. The kinetic acidities of the $\alpha$-methylene groups inserted into the 4-position were undoubtedly sufficient for reaction with the 4-lithiated species **6**. From Table III (entries 4–6), the products are those derived from further metalation and

Table III. Alkylation of 5 with LTMP and Electrophiles

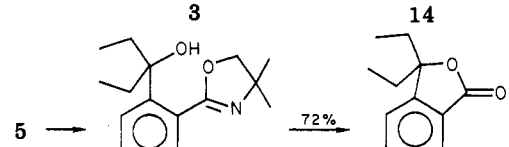
| entry | electrophile | E for 7 | % yield[a] |
|---|---|---|---|
| 1 | $D_2O$ | D | 70 |
| 2 | PhCHO |  | 50 |
| 3 | $Et_2C{=}O$ |  | 52 |
| 4 |  |  | 39 |
| 5 |  |  | 72 |
| 6 | MeI[c] | Et | 80 |
| 7 | *n*-BuI | Bu | 9 |

[a] Yields are for pure, chromatographed materials. [b] 1.0 equiv of LTMP and 1.0 equiv of allyl bromide were used. [c] 2.0 equiv of alkylhalide and 2.0 equiv of LTMP were used.

alkylation. This process can be made quite efficient if excess base and electrophile are present in the reaction. However, bulkier alkyl halides (e.g., *n*-butyl iodide) reacted poorly (entry 7). Acidic hydrolysis of **7** or **10** gave the expected 4-substituted nicotinic acid **8**. Furthermore, acidic hydrolysis of **7** (entry 3) gave the lactone **15**, isomeric with **14** obtained from metalation of **1** (eq 4 and 5). The




3 14




7 15

above methodology relating to substituent introduction into the pyridine nucleus shows considerable versatility when a variety of electrophilic or nucleophilic reagents are used. This, coupled with the ready removal of the oxazoline to the carboxylic acid and other functional groups, should allow access to a wide variety of pyridines.

## Experimental Section

**2-(4-Pyridyl)-4,4-dimethyl-2-oxazoline (1).** Isonicotinic acid (10.0 g, 0.08 mol) was added to 30 mL of thionyl chloride and stirred 24 h. The excess thionyl chloride was removed by distillation (the last traces removed by vacuum) to give the acid chloride hydrochloride as a solid. It was slowly added to a solution of 21.7 g (0.24 mol) of 2-amino-2-methyl-1-propanol in 200 mL of methylene chloride at 0 °C. After the addition, the mixture was stirred at 25 °C for 48 h. It was then filtered, and the amine hydrochloride was washed with methylene chloride. The combined filtrate and washings were concentrated to give the amide. Any excess amino alcohol was removed by vacuum distillation [60 °C (0.05 mm)]. (The amide is very water soluble and any aqueous workup results in significant loss.)

Thionly chloride (25 mL) was then added to the solid amide (9.7 g, 0.05 mol) and stirred 30 min after all the amide was in solution. The thionyl chloride solution was added dropwise to an excess of 20% NaOH cooled in an ice bath (a very vigorous reaction takes place). On a large scale, the excess thionyl chloride can be removed under vacuum. The aqueous solution was ex-

(10) Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 762.

(11) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879. This work describes the conversion of aryloxazolines to primary alcohols in chiral binaphthyl systems.

tracted with ether (5 × 50 mL), and the ether was washed with brine, dried over potassium carbonate, and rotoevaporated to give 1: 7.16 g (81%); mp 52–53 °C (sublimed); IR (film) 1640, 1585, 1295, 680 $cm^{-1}$. NMR ($CCl_4$) δ 8.57–8.73 (m, 2), 7.60–7.77 (m, 2), 4.03 (s, 2), 1.33 (s, 6). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86. Found: C, 67.87; H, 6.64.

**2-(3-Pyridyl)-4,4-dimethyl-2-oxazoline (5).** By use of the above procedure for **1**, 10.0 g of nicotinic acid was converted into 5: 5.92 g (67%); bp 80 °C (0.5 mm); IR (neat) 1655, 1080, 1021, 170 $cm^{-1}$; NMR ($CCl_4$) δ 9.05 (dd, $J$ = 0.9, 2.1 Hz, 1), 8.62 (dd, $J$ = 2.0, 5.0 Hz, 1), 8.13 (ddd, $J$ = 2.0, 2.1, 8.0 Hz, 1), 7.25 (ddd, $J$ = 0.9, 5.0, 8.0 Hz, 1), 4.05 (s, 2), 1.33 (s, 6). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86. Found: C, 68.09; H, 6.84.

**General Procedure for the Treatment of 1 with Methyllithium and an Electrophile. Preparation of 3.** To 0.176 g (1.00 mmol) of **1** in 5 mL of dry THF at −78 °C was added 0.74 mL (1.00 mmol) of MeLi, and the yellow solution was stirred 1 h. The solution was then allowed to warm to 0 °C for 1 h. The dark solution was then cooled to −78 °C, the electrophile was added, and the mixture was allowed to warm to 25 °C and stirred the prescribed length of time (see below for individual times of reaction). The reaction mixture was poured into saturated ammonium chloride solution and extracted with ether. The ether was washed twice with water and once with saturated brine and dried over potassium carbonate. The ether was removed by rotoevaporation and the crude product purified by PTLC (ethyl acetate).

**3 (R = D)**: reaction quenched after 30 min; 0.17 g (96%); NMR spectrum showed 80% D incorporation.

**3 (R = Me)**: 3 mmol of methyl iodide, 2 h, three elutions on silica gel (ethyl acetate/hexane, 4:1); 0.12 g (63%); bp 80 °C (0.05 mm); IR (neat) 1654, 1595, 1304, 775, 694, 674 $cm^{-1}$; NMR ($CCl_4$) δ 8.40 (s, 1), 8.37 (d, $J$ = 5 Hz, 1), 7.52 (d, $J$ = 5 Hz, 1), 3.96 (s, 2), 2.55 (s, 3), 1.33 (s, 6). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42. Found: C, 69.37; H, 7.43.

**3 (R = Et)**: 3 mmol of ethyl iodide, 4.5 h, two elutions with ethyl acetate/hexane (9:1); 56%; bp 65 °C (0.1 mm); IR (neat) 1650, 1590, 1070, 1045, 690, 670 $cm^{-1}$; NMR ($CCl_4$) δ 8.42 (s, 1), 8.38 (d, $J$ = 5 Hz, 1), 7.49 (d, $J$ = 5 Hz, 1), 3.97 (s, 2), 3.03 (q, $J$ = 7 Hz, 2), 1.33 (s, 6), 1.20 (t, $J$ = 7 Hz, 3). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90. Found: C, 70.78; H, 7.81.

**3 (R = allyl)**: 2 mmol of allyl bromide, 2.5 h, two elutions with ethyl acetate/hexane (9:1); 54%; bp 80 °C (0.1 mm); IR (neat) 1640, 1590, 1070, 840, 690 $cm^{-1}$; NMR ($CCl_4$) δ 8.42 (s, 1), 8.41 (d, $J$ = 5 Hz, 1), 7.53 (d, $J$ = 5 Hz, 1), 5.58–6.33 (m, 1), 4.73–5.20 (m, 2), 3.97 (s, 2), 3.67–4.03 (m, 2), 1.33 (s, 6). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46. Found: C, 71.96; H, 7.92.

**3 (R = CH(OH)Ph)**: 2 mmol of benzaldehyde, 4 h, two elutions with ethyl acetate/hexane (9:1); 83%; bp 125 °C (0.05 mm); IR (neat) 3250 (br), 1640, 1580, 1064, 770, 745, 680 $cm^{-1}$; NMR ($CCl_4$) δ 8.54 (d, $J$ = 5 Hz, 1), 8.50 (s, 1), 7.56 (d, $J$ = 6 Hz, 1), 7.18 (s, 5), 6.75 (d, $J$ = 8 Hz, 1), 5.88 (d, $J$ = 8 Hz, collapses to singlet with $D_2O$, 1), 3.90 (s, 1), 3.87 (s, 1), 1.27 (s, 3), 0.93 (s, 3). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43. Found: C, 71.59; H, 6.61.

**3 (R = C(OH)Et$_2$)**: 3 mmol of 3-pentanone, 3 h, two elutions with ethyl acetate/hexane (9:1); 76%; mp 84.5–85 °C; IR (film) 3300 (br), 1690, 1055, 945, 840, 680 $cm^{-1}$; NMR ($CCl_4$) δ 8.63 (d, $J$ = 5 Hz, 1), 8.53 (s, 1), 7.59 (d, $J$ = 5 Hz, 1), 3.32 (s, 2), 2.93 (br s, 1), 2.04 (q, $J$ = 7 Hz, 2), 1.99 (q, $J$ = 7 Hz, 2), 1.32 (s, 6), 0.75 (t, $J$ = 7 Hz, 6). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45. Found: C, 68.44; H, 8.36.

**3 (R = CHO)**: 2 mmol of dimethylformamide, 2 h; product unstable to silica gel (ethyl acetate); yield of crude product prior to chromatography 0.16 g (52%); NMR ($CCl_4$) δ 10.75 (s, 1), 8.28–9.33 (m, 2), 7.28–7.77 (m, 1), 4.10 (s, 2), 1.38 (s, 6).

**3 (R = OH)**: oxygen bubbled through solution at −78 °C, 2 h, elution with ethyl acetate/hexane (9:1); 27%; mp 78–79 °C (hexane); IR (film) 2400–3200, 1640, 1355, 1090, 960, 795, 697, 590 $cm^{-1}$; NMR ($CCl_4$) δ 11.20 (br s, 1), 8.37 (s, 1), 8.09 (d, $J$ = 5 Hz, 1), 7.34 (d, $J$ = 5 Hz, 1), 4.13 (s, 2), 1.47 (s, 6). Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29. Found: C, 62.72; H, 6.21.

**Lactone 14.** Oxazoline **3** [R = C(OH)Et$_2$); 0.09 g, 0.33 mmol] was heated at reflux in 5 mL of 4.5 N HCl for 18 h. The solution was cooled, the pH was adjusted to 3.5, a solid precipitated which was filtered, and the filtrate was extracted with ether. The ether was washed, dried, and rotoevaporated. The precipitate was washed and dried to give **14**: combined yield 0.05 g (76%); mp 62 °C (petroleum ether); IR (film) 1770, 1080, 805, 705 $cm^{-1}$; NMR ($CCl_4$) δ 8.76 (d, $J$ = 5 Hz, 1), 8.70 (s, 1), 7.67 (d, $J$ = 5 Hz, 1), 1.93 (q, $J$ = 7 Hz, 2), 2.16 (q, $J$ = 7 Hz, 2), 1.23 (t, $J$ = 7 Hz, 6). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 68.85; H, 6.69.

**General Procedure for the Reaction of 5 with Nucleophiles.** To 0.18 g (1.00 mmol) of **5** in 6 mL of dry THF at −78 °C was added 1.00 mmol of of the organolithium or Grignard reagent, and the yellow solution was stirred 1 h. The solution was then allowed to warm to 0 °C and stirred one 1 h. A standard workup as for **1** gave the crude dihydropyridine which was recrystallized from hexane. Analyses were performed on the aromatized product, **10**, whose physical data follows after each individual dihydropyridine.

**9 (R = Me)**: yield 100%; mp 124–126 °C; IR (film) 3100–3500, 1642, 1615, 1030 $cm^{-1}$; NMR ($CDCl_3$) δ 6.85 (s, $J$ = 5 Hz, 1), 6.27 (br s, 1), 5.93 (dd, $J$ = 4, 7 Hz, 1), 4.63 (ddd, $J$ = 2, 5, 7 Hz, 1), 3.85 (s, 2), 3.42 (dq, $J$ = 2, 7 Hz, 1), 1.28 (s, 3), 1.25 (s, 3), 1.14 (d, $J$ = 7 Hz, 3).

**10 (R = Me).** To 0.19 g (1.00 mmol) of **9** (R = Me) in 10 mL of dry ether was added 0.25 g (1.00 mmol) of chloranil, and the mixture was stirred 30 min. The pyridyloxazoline was extracted into 1 N HCl and then neutralized with 30% NaOH. Etheral extraction gave 0.05 g (28%) **10**. When **9** was dissolved in ether–THF and air bubbled in, the yield was 73%: bp 60 °C (0.3 mm); IR (neat) 1645, 1040, 746 $cm^{-1}$; NMR ($CCl_4$) δ 8.88 (s, 1), 8.45 (d, $J$ = 5 Hz, 1), 7.08 (d, $J$ = 5 Hz, 1), 4.00 (s, 2), 2.53 (s, 3), 1.38 (s, 6). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42. Found: C, 69.34; H, 7.59.

**9 (R = *n*-Bu).** With *n*-butyllithium, the yield was 99%: mp 112–114 °C; IR (film) 3150–3500, 1645, 1610, 1070, 725 $cm^{-1}$; NMR ($CDCl_3$) δ 6.82–7.03 (m, 1), 5.85–6.17 (m, 2), 4.65 (dd, $J$ = 5, 9 Hz, 1), 3.87 (s, 2), 3.30–3.63 (m, 1), 1.28 (s, 6), 0.67–1.67 (m, 9).

**10 (R = *n*-Bu).** To 0.07 g (0.27 mmol) of **9** in 10 mL of toluene was added 0.07 g (0.28 mmol) of chloranil, and the mixture was stirred for 2 h. The solution was then extracted with 12% NaOH until colorless (5 × 10 mL). The toluene was washed with water, dried over potassium carbonate, and rotoevaporated to give **10**: 0.06 g (90%); bp 80 °C (0.25 mm); IR (neat) 1650, 1034 $cm^{-1}$; NMR ($CCl_4$) δ 8.87 (s, 1), 8.43 (d, $J$ = 5 Hz, 1), 7.07 (d, $J$ = 5 Hz, 1), 4.02 (s, 2), 3.06 (t, $J$ = 7 Hz, 2), 1.32–1.77 (m, 5), 1.35 (s, 6), 0.83–1.13 (m, 3). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68. Foundb C, 72.46; H, 8.82.

**9 (R = Et).** Use of ethylmagnesium bromide in THF gave a 99% yield: mp 111–112 °C; IR (film) 3400 (br), 1645, 1605, 1200, 1040, 760, 725 $cm^{-1}$; NMR ($CDCl_3$) δ 6.88–7.08 (m, 1), 5.93–6.33 (m, 2), 4.62 (dd, $J$ = 5, 9 Hz, 1), 3.87 (s, 2), 3.48 (q, $J$ = 6 Hz, 1), 1.27 (s, 6), 1.33–1.67 (m, 2), 0.87 (t, $J$ = 7 Hz, 3).

**10 (R = Et).** Dihydropyridine **9** was allowed to stand at room temperature for 1 month. A quantitative air oxidation occurred to give **10**: bp 75 °C (0.4 mm); IR (neat) 1650, 1400, 1260, 800 $cm^{-1}$; NMR ($CCl_4$) δ 8.88 (s, 1), 8.44 (d, $J$ = 5 Hz, 1), 7.09 (d, $J$ = 5 Hz, 1), 4.00 (s, 2), 3.09 (q, $J$ = 7 Hz, 2), 1.34 (s, 6), 1.23 (t, $J$ = 7 Hz, 3). Anal. Calcd for $C_{11}H_{16}N_2O$: C, 70.56; H, 7.90. Found C, 70.59; H, 7.73.

**9 (R = Ph).** Phenyllithium was used to give a 100% yield: mp 182–184 °C (ethyl acetate–hexane); IR (nujol) 3400 (br), 1645 $cm^{-1}$; NMR ($CDCl_3$) δ 6.83–7.66 (m, 6), 5.90–6.33 (m, 1), 5.20–5.83 (m, 2), 4.50–5.00 (m, 2), 3.77 (s, 2), 1.25 (s, 3), 1.10 (s, 3). When **5** was treated with phenylmagnesium chloride, 56% of **10** was obtained.

**10 (R = Ph).** Dihydropyridine **9** (0.14 g, 0.53 mmol) was dissolved in 15 mL of toluene, 0.14 g (0.55 mmol) of chloranil was added, and the solution was heated at reflux for 2 h. Workup gave **10**: 0.12 g (88%); mp 84.5–85 °C (sublimed); IR (film) 1650, 1030, 750, 700 $cm^{-1}$; NMR ($CCl_4$) δ 8.83 (s, 1), 8.52 (d, $J$ = 5 Hz, 1), 7.29 (s, 5), 7.14 (d, $J$ = 5 Hz, 1), 3.72 (s, 2), 1.20 (s, 6). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39. Found: C, 75.71; H, 6.38.

**9 (R = CH$_2$CN).** Lithioacetonitrile (from lithium isopropylamide and acetonitrile, THF, −78 °C) was used and gave **9**: 32% yield; mp 124–125 °C; IR (film) 3400 (br), 1670, 1620 (br), 1500, 1170, 1060, 768 $cm^{-1}$; NMR ($CDCl_3$) δ 7.06 (dd, $J$ = 1, 5 Hz, 1), 6.77 (br s, 1), 6.22 (ddd, $J$ = 1, 5, 8 Hz, 1), 470 (ddd, $J$ = 1, 5, 8 Hz, 1), 3.90 (s, 2), 3.75–4.03 (**ABX**, 1), 2.17–3.17 (**ABX**, 2), 1.28 (s, 3), 1.22 (s, 3).

**10 (R = $CH_2CN$).** Oxidation of **9** with chloranil as above gave a 71% yield of **10**: mp 90–91 °C (sublimed); IR (film) 1650, 1090, 1050, 740 $cm^{-1}$; NMR ($CCl_4$–$CDCl_3$) $\delta$ 9.03 (s, 1), 8.68 (d, $J$ = 5 Hz, 1), 7.55 (d, $J$ = 5 Hz, 1), 4.34 (s, 2), 4.05 (s, 2), 1.36 (s, 6). Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09. Found: C, 66.72; H, 6.04.

**Reaction of 5 with *tert*-Butyllithium.** By use of the general procedure for addition of organometallics to **5**, a 95% yield of material was isolated, showing a mixture of **9**, **11**, and **5**. No attempt was made the purify the dihydropyridines, and they was carried directly to the oxidation step. To the crude mixture in 10 mL of toluene was added 0.23 g (1.00 mmol) of DDQ, and the mixture was stirred 30 min. Workup as above gave **12**: 0.08 g (59%); mp 57–58 °C (sublimed); IR (film) 1650, 1600, 1485, 710 $cm^{-1}$; NMR ($CCl_4$) 8.88 (br d, $J$ = 2 Hz, 1), 8.07 (dd, $J$ = 2, 8 Hz, 1), 7.28 (br d, $J$ = 8 Hz, 1), 4.02 (s, 2), 1.33 (s, 6), 1.34 (s, 9). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.78. Found: C, 72.28; H, 8.77.

Also isolated were 29% **5** (from loss of *tert*-butyl during oxidation) and 10% **10** (R = *t*-Bu): IR (neat) 1655, 1585, 1040, 710 $cm^{-1}$; NMR ($CCl_4$) 8.41 (d, $J$ = 5 Hz, 1), 8.37 (br s, 1), 7.20 (d, $J$ = 5 Hz, 1), 3.98 (br s, 2), 1.40 (s, 9), 1.37 (s, 3), 1.34 (s, 3).

When oxazoline **5** in ether was added to *tert*-butyllithium in ether at −78 °C, a mixture of dihydropyridines was again obtained. Oxidation as above gave 12% **12**, 31% **10** (R = *t*-Bu), and 31% **5**. Oxidation with potassium permanganate in acetone at 25 °C for 3 has also performed. Excess oxidizing agent was destroyed with sodium sulfite and the mixture filtered through Celite. The acetone was concentrated and the residue extracted with ether, yielding 16% **12** and 73% **5**.

**Dithiane–pyridine 13.** By use of 1-lithio-1,3-dithiane according to the general procedure, addition to **5** gave 61% **13**, mp 122–124 °C (sublimed). Due to rapid oxidation, the intermediate dihydropyridine was not found, only the pyridine **13**: IR (film) 1650, 1076, 704 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 9.08 (d, $J$ = 2 Hz, 1), 8.27 (dd, $J$ = 2, 9 Hz, 1), 7.55 (d, $J$ = 9 Hz, 1), 5.39 (s, 1), 4.06 (s, 2), 2.87–3.23 (m, 4), 2.00–2.33 (m, 2), 1.38 (s, 6). Anal. Calcd for $C_{14}H_{18}N_2OS_2$: C, 57.11; H, 6.16. Found: C, 57.13; H, 6.30.

**General Procedure for the Reaction of 5 with LTMP and Electrophiles.** Lithium 2,2,6,6-tetramethylpiperidide (LTMP, 1.10 mmol) was prepared from *n*-BuLi and 2,2,6,6-tetramethylpiperidine in THF at 0 °C. Oxazoline **5** (0.18 g, 1.00 mmol) in 6 mL of dry THF was added and stirred 1 h at 0 °C. The electrophile was then added, and the solution was allowed to warm to 25 °C and stirred the specified length of time (as given below). A standard workup as for **1** gave the indicated product.

**7 (E = D)**: excess $D_2O$, 30 min; 84% yield; 84% D incorporation, (by NMR); NMR $\delta$ 9.03 (s, 1), 8.59 (d, $J$ = 5 Hz, 1), 7.26 (d, $J$ = 5 Hz, 1), 4.05 (s, 2), 1.33 (s, 6).

**7 (E = PhCH(OH))**: 3.0 mmol of benzaldehyde, 5 h; 50% yield; bp 100 °C (0.35 mm); IR (neat) 3200 (br), 1645, 1035 (br), 700, 604 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 8.97 (s, 1), 8.54 (d, $J$ = 5 Hz, 1), 7.23 (s, 5), 7.02 (d, $J$ = 5 Hz, 1), 6.67–7.00 (m, 1), 5.77–6.03 (m, 1), 4.02 (s, 2), 1.37 (s, 3), 1.10 (s, 3). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43. Found: C, 71.98; H, 6.56.

**7 (E = $Et_2COH$)**: 3.0 mmol of 3-pentanone, 4.5 h; 52% yield; bp 85 °C (0.25 mm); IR (neat) 3350 (br), 1690 (br), 1690 (br), 1600, 1050 (br), 835, 735, 610 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 8.94 (d, $J$ = 0.8 Hz, 1), 8.61 (d, $J$ = 5 Hz, 1), 7.09 (dd, $J$ = 0.8, 5 Hz, 1), 3.32 (s, 2), 2.78 (br s, 1), 1.68–2.22 (m, 4), 1.30 (s, 6), 0.72 (t, $J$ = 8 Hz, 6). Analyses were performed on lactone **15**.

**Lactone 15**: Oxazoline **7** (E = $Et_2(OH)$) was heated to reflux with 4.5 N HCl for 18 h and allowed to cool before the pH was adjusted to 3–4. A solid appeared which was collected by filtration while the filtrate was extracted with ether, washed, and concentrated. The combined material was recrystallized from petroleum ether: mp 78.5–79.0 °C; IR (film) 1755, 1610, 1073, 1030 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 9.07 (d, $J$ = 0.8 Hz, 1), 8.80 (d, $J$ = 5 Hz, 1), 7.34 (dd, $J$ = 0.8, 5 Hz, 1), 2.02 (q, $J$ = 8 Hz, 2), 2.07 (q, $J$ = 8 Hz, 2), 0.70 (t, $J$ = 8 Hz, 6). Anal. Calcd for $C_{11}H_{13}NO_2$: C. 69.09; H, 6.85. Found: C, 68.55; H, 6.59.

**4-*n*-Butylnicotinic Acid (8).** The oxazoline **7** (R = *n*-Bu, 70 mg) was heated with 4.5 N HCl to reflux for 18 h. On when the mixture cooled, the pH was adjusted to 5, and the solid (40 mg, 82%) was collected, dried, and sublimed: mp 107 °C; IR (film) 2300–3600, 1710, 1600, 1380, 1275 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 11.0 (br s, 1), 9.13 (br s, 1), 8.43–8.70 (m, 1), 7.16–7.40 (m, 1), 2.83–3.23 (m, 2), 0.67–2.00 (m, 7). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02 H, 7.31. Found: C, 67.01; H, 7.82.

**7 (E = 1,2,5,6-Hexadien-3-yl).** Use of 2.20 mmol of LTMP and 7.00 mmol of allyl bromide gave, after 5 h, **7**: 72% yield; bp 85° C (0.30 mm); IR (neat) 1643, 1037, 918 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 8.87 (s, 1), 8.38 (d, $J$ = 5 Hz, 1), 7.21 (d, $J$ = 5 Hz, 1), 5.35–6.23 (m, 2), 4.70–5.33 (m, 5), 4.02 (s, 2), 2.45 (br t, 2), 1.36 (s, 6). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86. Found: C, 75.44; H, 8.01.

**7 (E = Et).** Use of 2.2 mmol of LIMP and 5.0 mmol of methyl iodide gave **7** in 60% yield, which was identical in all respects with **10** (R = Et). No detectable amount of **7** (R = Me) could be found.

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**Registry No.** **1**, 66464-33-3; **3** (R = D), 66464-34-4; **3** (R = Me), 66464-36-6; **3** (R = Et), 66464-35-5; **3** (R = allyl), 66464-37-7; **3** (R = CH(OH)Ph), 66464-38-8; **3** (R = $C(OH)Et_2$), 66464-39-9; **3** (R = CHO), 66464-40-2; **3** (R = OH), 81603-46-5; **5**, 68981-86-2; **7** (E = D), 70646-96-7; **7** (E = PhCH(OH)), 70646-97-8; **7** (E = $Et_2C(OH)$), 70646-98-9; **7** (E = 1,2,5,6-hexadien-3-yl), 81603-47-6; **8**, 81603-48-7; **9** (R = Me), 68981-79-3; **9** (R = *n*-Bu), 68981-80-6; **9** (R = Et), 70647-00-6; **9** (R = Ph), 68981-78-2; **9** (R = $CH_2CN$), 81603-49-8; **10** (R = Me), 68981-84-0; **10** (R = *n*-Bu), 68981-83-9; **10** (R = Et), 70647-02-8; **10** (R = Ph), 68981-85-1; **10** (R = $CH_2CN$), 81603-50-1; **10** (R = *t*-Bu), 68981-82-8; **11**, 70647-01-7; **12**, 70647-03-9; **13**, 81603-51-2; **14**, 66464-41-3; **15**, 70646-99-0; isonicotinic acid, 55-22-1; isonicotinoyl chloride hydrochloride, 39178-35-3; 2-amino-2-methyl-1-propanol, 124-68-5; *N*-(2-hydroxy-1,1-dimethylethyl)isonicotinamide, 81603-52-3; nicotinic acid, 59-67-6; $D_2O$, 7789-20-0; MeI, 74-88-4; EtI, 75-03-6; allyl bromide, 106-95-6; PhCHO, 100-52-7; $Et_2C{=}O$, 96-22-0; $Me_2NCHO$, 68-12-2; $O_2$, 7782-44-7; MeLi, 917-54-4; BuLi, 109-72-8; EtBr, 74-96-4; PhLi, 591-51-5; PhBr, 108-86-1; $LiCH_2CN$, 55440-71-6; 1,3-dithian-2-yllithium, 75953-31-0; BuI, 542-69-8; *t*-BuLi, 594-19-4; lithium 2,2,6,6-tetramethylpiperidide, 38227-87-1.