The Addition–Elimination Mechanism in the Nucleophilic Heteroaromatic Substitution of 3-(4',4'-Dimethyl-4',5'-dihydro-oxazol-2'-yl)pyridine. Solvent Effect on the Regiochemistry of the Addition Reaction [1]

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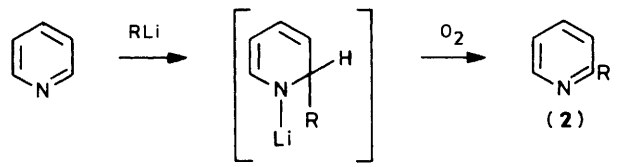
The nucleophilic heteroaromatic substitution of 3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)pyridine (**3**) with organolithium compounds has been studied. The reaction of (**3**) with butyl-lithium gave a mixture of the corresponding 2,3-, 3,4-, and 2,5-disubstituted pyridines; however, the predominant product was the 3,4-isomer (**5c**). With s-butyl-lithium, the 2,3- and 3,4-disubstituted pyridines were obtained; again, the 3,4-disubstituted derivative (**5d**) was the major isomer. With methyl-lithium or phenyl-lithium, the 3,4-isomer was also the predominant product. With t-butyl-lithium, the 3,4-compound was not isolated; instead only starting compound (**3**) was recovered. The substitution reactions proceed *via* an addition–elimination mechanism.

The regiochemistry of the nucleophilic substitution of (**3**) with butyl-lithium was found to be solvent dependent. Thus, when solutions of (**3**) in ether or tetrahydrofuran were treated with butyl-lithium, (**5c**) was the major product. When tetramethylethylenediamine was the solvent, the predominant product was 2-butyl-5-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)pyridine (**8**).

N-Lithiodihydropyridines can be conveniently aromatized *in situ* with oxygen to the corresponding substituted pyridines (**2**).[2] The isolation and characterization[3] of the reactive σ complex (**1**) clearly established the addition–elimination mechanism proposed[2,4] for the nucleophilic heteroaromatic substitution of pyridine derivatives. Previously, when a wide variety of 3-substituted pyridines were treated with strongly nucleophilic organolithium reagents, followed by oxidation and hydrolysis, the 2,3- and 2,5-disubstituted pyridines were obtained. The 2,3-isomer was usually predominant; however, the 2,5-isomer was prevalent in those cases involving steric interactions.[2] We have recently reported[5] that the reaction of 3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)pyridine (**3**) with organolithium compounds, followed by hydrolysis, affords the stable 1,4-dihydropyridines (**4**).† These dihydropyridines could be aromatized to



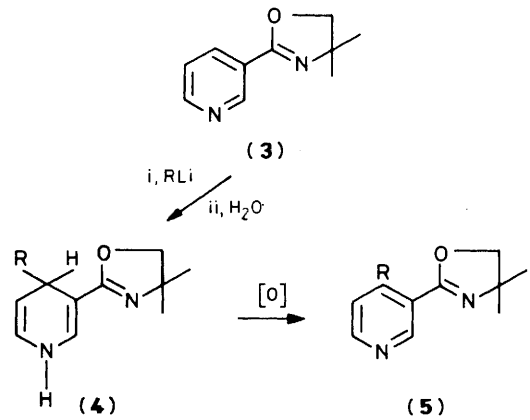
(**1**) (**2**)

the corresponding 3,4-disubstituted pyridines (**5**). However, little was known about the effects of solvent, temperature, and other reaction conditions upon the regiochemistry of the addition reaction.

We now report a solvent effect causing an unexpected regiochemical effect on the addition reaction, as well as the direct preparation of the disubstituted pyridines (**5a**—**d**).[1]

Results and Discussion

Solutions of compound (**3**) in ether were treated dropwise with aliquots of a solution of phenyl-lithium in ether. Oxidation

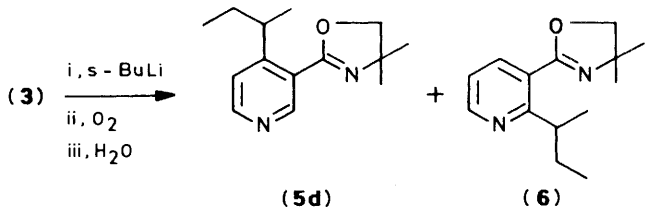


a ; R = Ph
b ; R = Me
c ; R = Bu^n
d ; R = Bu^s
e ; R = Bu^t

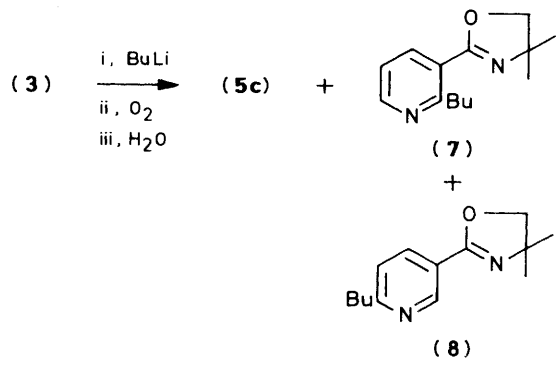
and hydrolysis of the reaction mixture gave 3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)-4-phenylpyridine (**5a**) as the major product. Similarly, when the reaction was conducted with methyl-lithium as the nucleophile, 3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)-4-methylpyridine (**5b**) was the major product. In addition to (**5b**), some starting material (**3**) was recovered. However, when t-butyl-lithium was employed as the nucleophile, only the starting material (**3**) was recovered. The desired 4-t-butyl-3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)-pyridine (**5e**) was not detected. This indicates that (**3**) is formed by the oxidative dealkylation of the *N*-lithio intermediate, since a similar reaction mixture gave 4-t-butyl-3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)-1,4-dihydropyridine (**4e**) upon hydrolysis.[1,5]

When solutions of (**3**) in ether were treated dropwise with a solution of s-butyl-lithium in cyclohexane and worked up, 4-s-butyl-3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)pyridine (**5d**) was the major product obtained, but 2-s-butyl-3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)pyridine (**6**) was also isolated.

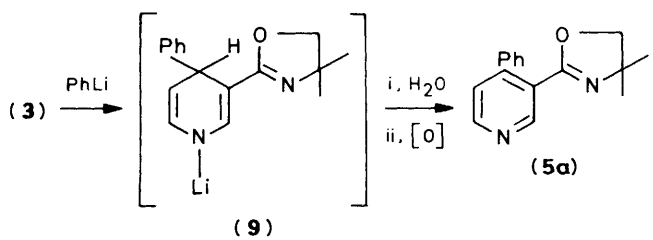
† E. E. Knaus has found that, under a different set of reaction conditions, the reaction of phenyl-lithium with (**3**) leads to the isolation of the 3-(4',4'-dimethyl-4',5'-dihydro-oxazol-2'-yl)-1,2-dihydro-2-phenylpyridine (personal communication).



Similarly, aliquots of a solution of butyl-lithium in hexane added dropwise to solutions of (**3**) in ether ultimately yielded 4-butyl-3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridine (**5c**) as the major product. 2-Butyl-3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridine (**7**) and 2-butyl-5-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridine * (**8**) were also isolated.



In order to observe whether these reactions proceeded *via* an addition–elimination mechanism, the reactions of (**3**) and phenyl-lithium were repeated in tetrahydrofuran (THF) instead of ether, so that a solution was obtained.[5] Examination of the red-brown solution by ^{1}H n.m.r. spectroscopy indicated that the 3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)-*N*-lithio-4-phenyl-1,4-dihydropyridine (**9**) was the intermediate in these reactions.[3a,6] The ^{1}H n.m.r. chemical shifts of the pyridine-ring protons of (**9**) are summarized in Table 1. Hydrolysis of these reaction mixtures with water afforded the dihydropyridine (**4a**), which could be oxidized to the disubstituted pyridine (**5a**).[5]

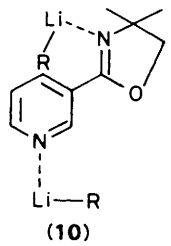


These results support the involvement of the addition–elimination mechanism in the nucleophilic heteroaromatic substitutions leading to the 4-substituted 3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridines (**5**). The formation of the 4- rather than the 2- or 6-substituted product may be due to co-ordination between the nitrogen atoms of (**3**) and the organolithium compounds. The two tertiary amine functions in (**3**) are both capable of involvement in complex formation[7] with the lithium reagents. A complex formed between the organolithium compounds and the oxazole nitrogen of (**3**) may be orientated in such a way as to facilitate the nucleophilic addition to the 4-position of the pyridine ring. Such an orientation may be used to account for the observed regiochemistry of the additions in these reactions. Furthermore, complexation of the pyridine nitrogen of (**3**) would also facilitate nucleophilic attack, as this would increase the susceptibility of the pyridine ring to nucleophilic attack at the 4-position, as well as at the 2- and 6-position. A complex in which both nitrogen atoms of (**3**) are complexed, complex (**10**), may account for the observed regiochemical outcome of these reactions. Haglid[8] has proposed a similar complex in the reactions of methyl-lithium with nicotine.

Table 1. ^{1}H N.m.r. chemical shifts of the pyridine-ring protons of 3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)-*N*-lithio-4-phenyl-1,4-dihydropyridine (**9**)

Position	δ[a]	
C-2	6.94	
C-4	4.52	$J_{4,5}$ 4.6 Hz
C-5	4.31	$J_{4,5}$ 4.6, $J_{5,6}$ 7.0 Hz
C-6	6.11	$J_{5,6}$ 7.0 Hz

[a] In THF relative to external $SiMe_4$.



(10)

Since the reaction of butyl-lithium with (**3**) gave all three substitution products, this system was used to investigate the factors affecting the yields of the 4-substituted 3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridine. The effect of varying reaction temperature, solvent, reactant ratio, and reaction period on the yields of 4-butyl-3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridine (**5c**) were investigated.

Solutions of (**3**) in THF were stirred in test tubes at temperatures of −78, −38, 0, 25 (room temperature), and 50 °C. An equimolar portion of a solution of butyl-lithium in hexane was added to each test tube. The reaction mixtures were stirred at various temperatures (Table 2) for 1 h. The contents of the test tubes were brought to 0 °C and the oxygen was bubbled through the solutions under anhydrous conditions. The reaction mixtures were hydrolysed and analysed by gas chromatography (g.c.) and the results are summarized in Table 2. The yields of (**5c**) decreased as the reaction temperature was increased, and an increase in side reaction was evidenced by an increased amount of unidentified high boiling compounds in the g.c. analysis. When the reaction mixtures were oxidized and hydrolysed at −78 °C, there was no significant change in the product mixture, indicating that the products were thermodynamically controlled.

Solutions of (**3**) in ether, THF, and *NNN′N′*-tetramethylethylenediamine (TMEDA) were stirred in test tubes at −38 °C. Aliquots of a solution of butyl-lithium in hexane were added to each test tube. The bright yellow reaction mixtures were stirred at −38 °C for 1 h. The mixtures were oxidized as described above, hydrolysed, and analysed by g.c. The results

* This product result from 1,6-addition to (**3**), and similar 2,5-isomers have been named as the 3,6-isomers.

Table 2. Effects of reaction temperature on the yields of (**5c**)

Temperature (°C)	% Yield[a] of (**5c**)
−78	78
−38	60
0	57
25 (room temp.)	53
50	47

[a] Yields are based on starting amounts of (**3**). We thank Mr. Marcel Sweers for performing low-temperature experiments which confirmed that the products were thermodynamically controlled.

Table 3. Solvent effect on the reaction of (**3**) with butyl-lithium at −38 °C

	% Yield[a]		
Product	Ether	THF	TMEDA
(**5c**)	31	53	20
(**7**)	14	2	2
(**8**)	6	22	42
(**3**)	1	11	4

[a] Yields are based on starting amount of (**3**).

Table 4. Effects of reactant ratios on the product yields at −78 °C

	% Yield[a]		
Mol ratio (**3**):Bu^{n}Li	(**5c**)	(**7**)	(**8**)
1:1	73	0.9	21
1:2	67	1.0	17
1:3	70	0.7	11
1:4	67	0.7	11
2:1	32	*b*	8

[a] Yields are based on starting amount of (**3**). [b] The starting oxazole (**3**) (209.8 mg, 49.6%) was also present.

Table 5. Effect of reaction time at −78 °C on product yields

	% Yield[a]			
Reaction time (h)	(**5c**)	(**7**)	(**8**)	Total
0.5	51	0.7	9.5	62
1.0	66	1.4	14	81
1.5	64	0.9	14	79
2.0	63	1.3	17	81
3.0	65	1.2	16	82

[a] Yields are based on starting amounts of (**3**).

are summarized in Table. 3. The results in Table 3 indicate that the regiochemistry of this reaction is solvent dependent. When ether or THF is the reaction solvent, the 4-butyl isomer (**5c**) is the major product, with THF providing this isomer in greatest yield. In ether the major by-product (**7**) resulted from 1,2-addition, and in THF the major by-product (**8**) resulted from 1,6-addition. While the product of 1,4-addition, (**5c**), was the major product in these ether solvents, the product of 1,6-addition, (**8**), was found to be the major product in the more polar TMEDA. This latter result supports the involvement of the complex (**10**) in these reactions, since the tertiary amino functions of TMEDA may compete with those of (**3**) for complexation of the lithium reagent.

The choice of solvent also had an effect upon the overall yield of the butylated 3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)-pyridines (**5c**), (**7**), and (**8**). The combined yields of these disubstituted pyridines are in the order: THF > TMEDA > ether. Since THF afforded the highest yield of products, this solvent was used in subsequent investigations.

Experiments using various molar ratios of (**3**) and butyl-lithium were studied to optimize the yield of (**5c**). Solutions of (**3**) in THF were placed in test tubes and stirred at −78 °C. The solutions were stirred with butyl-lithium for 1 h. The test tubes were warmed to 0 °C, and the contents were oxidized as before. The mixtures were hydrolysed and analysed by g.c. The results are summarized in Table 4.

The above experiments indicated that the total yield of (**5c**), (**7**), and (**8**) decreased with increasing ratio of reactants [(**3**) and BuLi] from 1:1 to 1:4; however, the ratio of the amount of (**5c**) to that of the total product suggested preferential addition at the 4-position. This result also supports the formation of a complex such as (**10**), since the amount of 4-substituted product obtained would be expected to increase with concentration of lithium reagent. As the ratio of butyl-lithium to (**3**) was increased, an increase in unidentified by-products was also observed.

The effect of reaction time on product formation was also studied. The results are summarized in Table 5. The optimum time was found to be approximately 1 h [66% yield of (**5c**)]. There were no significant differences in the yields of (**5c**) in reactions lasting between 1 and 3 h; however, as the reaction time increased, the yield of undesirable by-products detected during the gas chromatographic analyses also increased.

Conclusions

In the nucleophilic heteroaromatic substitutions of 3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridine with organolithium compounds in ether, except that with t-butyl-lithium, the predominant product was the 3,4-disubstituted pyridine. With t-butyl-lithium large amounts of the starting 3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridine were recovered. The expected 4-substituted addition product might have been formed, but there was evidence that it was dealkylated to the starting compound.[5c]

The substitutions probably proceed *via* an addition–elimination mechanism. The evidence for this mechanism includes the ^{1}H n.m.r. spectra of the THF reaction solutions of the *N*-lithio-1,4-dihydropyridines. Oxidation and hydrolysis of the adducts gave the corresponding disubstituted pyridines.

Increasing reaction periods, changes in reaction temperatures, and varying molar ratios of reactants [3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)pyridine to organolithium compound] did not significantly affect the yield or isomer ratio of the products. However, the regiochemistry of the nucleophilic additions, and therefore that of the substitution products, was found to be solvent dependent.*

We are currently investigating the chemical and biological properties of the compounds reported in this research.

Experimental

Equipment and Materials.—All m.p.s were taken on a Büchi melting-point apparatus and are uncorrected. I.r. spectra were recorded by using a Beckman IR-18 spectrophotometer. All ^{1}H n.m.r. spectra were taken on a Varian Model HA-100 n.m.r. spectrometer. All ^{13}C n.m.r. spectra were obtained in $CDCl_3$

* E. E. Knaus has found that under a different set of reaction conditions, the reaction of phenyl-lithium with (**3**) leads to the isolation of the 3-(4′,4′-dimethyl-4′,5′-dihydro-oxazol-2′-yl)-1,2-dihydro-2-phenylpyridine (personal communication).

solution with a JEOL PFT-100 spectrometer system operating at 25.0344 MHz (proton resonance frequence 99.5388 MHz) and equipped with a Nicolet 1081 Fourier Transform accessory. Chemical shifts are reported on the δ scale in p.p.m. relative to Me_4Si for all spectra. All solvent evaporations were done in a rotary evaporator. Analytical and preparative g.c. analyses were done on a 10 ft × 1/4 in stainless steel 3% OV-1 on a Gas Chrom Q (100—120 mesh) column unless noted otherwise. The g.c. used was a Varian Aerograph Model 1520B equipped with a dual thermal conductivity detector. Elemental analyses were performed by the Centre for Trace Characterization, Texas A & M University, College Station, Texas.

All organolithium additions were carried out under dry nitrogen in round-bottomed flasks or 15 × 200 mm serum-capped test tubes equipped with a stirring bar, nitrogen inlet, and an oil bubbler. Ether and THF were heated over lithium aluminum hydride (LAH) and distilled from LAH under nitrogen just prior to use. *NNN'N'*-Tetramethylethylenediamine (TMEDA) was distilled from KOH and stored over KOH under nitrogen. 3-(4',4'-Dimethyl-4',5'-dihydro-oxazol-2'-yl)pyridine (**3**) was prepared as described earlier.[5b] Butyl-lithium in hexane, s-butyl-lithium in cyclohexane, and methyl-lithium in ether were obtained from Ventron. t-Butyl-lithium in pentane was obtained from the Aldrich Chemical Co. Phenyl-lithium in ether was prepared from lithium wire (Ventron) and bromobenzene (Eastman).

General Procedure for Reaction of 3-(4',4'-*Dimethyl*-4',5'-*dihydro-oxazol-2'-yl*)*pyridine* (**3**) *with Organolithium Compounds.*—In a dry-nitrogen-flushed 100 ml round-bottomed flask equipped with a magnetic stirrer and a dropping funnel sealed with a rubber septum was placed a colourless solution of the dihydro-oxazole (**3**) (1.0 equiv.) in anhydrous ether (or THF). A solution of the organolithium compound (1.0 equiv.) was placed in the dropping funnel *via* a transfer needle. The organolithium compound was added dropwise to the stirred solution of (**3**). Any excess of pressure was released *via* an oil bubbler. After the addition was complete the reaction mixture was stirred at room temperature for 1 h. The mixture was cooled in an ice–water bath and oxygen was bubbled through the solution. The reaction mixture was then treated with water (10 ml). The organic layer was separated and the basic aqueous layer was extracted with ether (3 × 10 ml). The combined organic layers were dried (Na_2SO_4), and the solvent removed under reduced pressure. The residue was purified by distillation and/or preparative g.c. The products were characterized by a combination of spectral (^1H and ^{13}C n.m.r. and i.r.) and analytical data. The method of purification, boiling and/or melting points, yields, i.r., ^1H n.m.r., ^{13}C n.m.r., and analytical data are given below.

3-(4',4'-*Dimethyl*-4',5'-*dihydro-oxazol-2'-yl*)-4-*phenyl-pyridine* (**5a**) * (61% yield), δ_C 161.2 (oxazole C-2), 151.1 (pyridine C-6), 150.5 (pyridine C-2), 149.0 (phenyl C-1), 138.1 (pyridine C-4), 128.5 (phenyl C-4), 128.2 and 128.0 (phenyl C-2 and -3), 124.1 (pyridine C-3), 123.8 (pyridine C-5), 79.4 (oxazole C-5), 67.8 (oxazole C-4), and 27.9 p.p.m. (CH_3).

3-(4',4'-*Dimethyl*-4',5'-*dihydro-oxazol-2'-yl*)-4-*methyl-pyridine* (**5b**)* (76.2% yield), δ_C 160.3 (oxazole C-2), 150.7 and 150.4 (pyridine C-2 and -6), 147.7 (pyridine C-4), 125.7 (pyridine C-5), 124.0 (pyridine C-3), 78.5 (oxazole C-5), 68.1 (oxazole C-4), 28.4 (geminal CH_3), and 21.1 p.p.m. (pyridine 4-CH_3).

4-*Butyl*-3-(4',4'-*dimethyl*-4',5'-*dihydro-oxazol-2'-yl*)*pyridine* (**5c**)* (63.8% yield), δ_C 160.1 (oxazole C-2), 152.1 (pyridine C-4), 150.8 (pyridine C-2 and -6), 124.8 (pyridine C-5), 123.7 (pyridine C-3), 78.5 (oxazole C-5), 68.0 (oxazole C-4), 33.4 (pyridine 4-CH_2), 32.7 (CH_2), 28.3 (geminal CH_3), 22.6 (CH_2), and 13.9 p.p.m. (CH_3).

4-*s*-*Butyl*-3-(4',4'-*dimethyl*-4',5'-*dihydro-oxazol-2'-yl*)-*pyridine* (**5d**),* purified by g.c. with a 5 ft × 1/4 in column, 10% FFAP on 60/80 Chrom W; 150 °C; 60 ml min^{-1}; [83.4% yield of (**5d**) and (**6**)]; (79.6%), δ_C 160.7 (oxazole C-2), 156.7 (pyridine C-4), 151.0 (pyridine C-6), 150.6 (pyridine C-2), 124.3 (pyridine C-3), 120.9 (pyridine C-5), 78.9 (oxazole C-5), 68.2 (oxazole C-4), 36.2 (CH), 30.5 ($3H_2$), 28.3 (geminal CH_3), 20.4 (CH_3), and 12.0 p.p.m. (CH_3).

2-*s*-*Butyl*-3-(4',4'-*dimethyl*-4',5'-*dihydro-oxazol-2'-yl*)-*pyridine* (**6**), retention time (R_t) 14 min; (20.4%), b.p. 35.5—36 °C at 0.20 Torr; $\nu_{max.}$(neat) 2 963, 1 621, 1 436, 1 059, and 1 029 cm^{-1}; $\delta_H(CDCl_3)$ 8.60 (1 H, dd, $J_{4,6}$ 1.9, $J_{5,6}$ 4.9 Hz, pyridine 6-H), 7.91 (1 H, dd, $J_{4,5}$ 8.0, $J_{4,6}$ 1.9 Hz, pyridine 4-H), 7.04 (1 H, dd, $J_{4,5}$ 4.9 Hz, pyridine 5-H), 4.04 (2 H, s, oxazole 5-H_2), 3.67 (1 H, hex, CH), 1.72 (2 H, c m, CH_2), 1.37 (6 H, s, geminal CH_3), 1.30 (3 H, d, CH_3), and 0.80 (3 H, t, CH_3); δ_C 165.7 (pyridine C-2), 161.8 (oxazole C-2), 150.7 (pyridine C-6), 137.4 (pyridine C-4), 123.9 (pyridine C-3), 120.1 (pyridine C-5), 79.1 (oxazole C-5), 68.1 (oxazole C-4), 39.2 (CH), 29.9 (CH_2), 28.3 (geminal CH_3), 20.1 (CH_3), and 12.3 p.p.m. (CH_3) (Found: C, 72.6; H, 8.7; N, 12.25. Calc. for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06%).

Procedure for Varying Reaction Temperature to Optimize the Yields of (**5c**).—Solutions of (**3**) [(450.7 mg, 2.6 mmol), (499.8 mg, 2.6 mmol), (437.8 mg, 2.5 mmol), (479.3 mg, 2.7 mmol), and (476.6 mg, 2.7 mmol), respectively], in THF (5 ml) were stirred in nitrogen-flushed test tubes capped with rubber septums. To each of the test tubes [at −78, −38, 0, 25 and 50 °C, respectively] was added a solution of butyl-lithium in hexane (1 equiv.). The contents of each test tube were stirred for 1 h. The reaction mixtures were brought to 0 °C, and oxygen was bubbled through the solutions for 3 h. The contents of each tube were hydrolysed with water (5 ml). The organic layer was separated and the basic aqueous layer extracted with ether (2 × 5 ml). The combined organic layers were dried (Na_2SO_4). After removal of the solvents the residues were analysed by g.c. The results are summarized in Table 2.

Procedure for Studying the Solvent Effect on the Reaction of (**3**) *with Butyl-lithium.*—A solution of (**3**) (449.8 mg, 2.6 mmol) in THF (5 ml) was stirred in a test tube at −38 °C. A solution of butyl-lithium in hexane (1.0 equiv.) was added to the solution. The mixture was stirred at −38 °C for 1 h. The mixture was oxidized at −38 °C, hydrolysed, worked up, and analysed as described earlier for the temperature-effect experiments.

The procedure for the reactions in ether or TMEDA was similar to that described above except that dry ether or TMEDA was used instead of THF. The results are summarized in Table 3.

The combined reaction mixtures were subjected to preparative g.c. on a 10% Carbowax 20M on Gas Chrom Q (100/120) column, operated at 210 °C, with a 52 ml min^{-1} helium flow-rate. Four products, (**3**), (**7**), (**5c**), and (**8**) were collected.

3-(4',4'-*Dimethyl*-4',5'-*dihydro-oxazol-2'-yl*)*pyridine* (**3**), R_t 12—16 min, colourless oil.

2-*Butyl*-3-(4',4'-*dimethyl*-4',5'-*dihydro-oxazol-2'-yl*)*pyridine* (**7**), R_t 24—31 min, odourless oil; $\nu_{max.}$(neat) 2 963, 1 644, 1 447, 1 063, and 1 028 cm^{-1}; $\delta_H(CDCl_3)$ 8.56 (1 H, dd, $J_{4,6}$ 2.2, $J_{5,6}$ 4.8 Hz, pyridine 6-H), 7.98 (1 H, dd, $J_{4,5}$ 8.0, $J_{4,6}$ 2.2 Hz, pyridine 4-H), 7.12 (1 H, dd, $J_{4,5}$ 8.0, $J_{5,6}$ 4.8 Hz, pyridine 5-H), 4.08 (2 H,

* The method of purification and i.r. and ^1H n.m.r. data are presented in ref. 5c, and will not be duplicated here. Acceptable analyses were obtained for these compounds and are also reported in ref. 5c.

s, oxazole 5-H_2), 3.17 (2 H, t, CH_2), 1.62 (4 H, m, CH_2CH_2), 1.39 (6 H, s, geminal CH_3), and 0.93 (3 H, t, CH_3); δ_C 162.4 (pyridine C-2), 161.4 (oxazole C-2), 150.5 (pyridine C-6), 137.6 (pyridine C-4), 123.5 (pyridine C-3), 120.4 (pyridine C-5), 79.0 (oxazole C-5), 68.1 (oxazole C-4), 36.5 (pyridine 2-CH_2), 32.0 (CH_2), 28.3 (geminal CH_3), 22.8 (CH_2), and 13.9 p.p.m. (CH_3) (Found: C, 72.2; H, 8.7; N, 11.95. Calc. for $C_{14}H_{20}N_2O$: C, 72.28; H, 8.68; N, 12.06%).

4-*Butyl*-3-(4′,4′-*dimethyl*-4′,5′-*dihydro-oxazol*-2′-*yl*)*pyridine* (**5c**),* R_f 38—48 min, colourless oil.

2-*Butyl*-5-(4′,4′-*dimethyl*-4′,5′-*dihydro-oxazol*-2′-*yl*)*pyridine* (**8**), R_f 51—56 min, colourless oil; $\nu_{max.}$(neat) 2 954, 1 650, 1 313, 1 074, and 1 019 cm^{-1}; $\delta_H(CDCl_3)$ 9.02 (1 H, d, $J_{4,6}$ 2.2 Hz, pyridine 6-H), 8.11 (1 H, dd, $J_{3,4}$ 8.4, $J_{4,6}$ 2.2 Hz, pyridine 4-H), 7.15 (1 H, d, $J_{3,4}$ 8.4 Hz, pyridine 3-H), 4.09 (2 H, s, oxazole 5-H_2), 2.84 (2 H, t, CH_2), 1.69 (4 H, m, CH_2CH_2), 1.38 (6 H, s, geminal CH_3), and 0.93 (3 H, t, CH_3); δ_C 165.4 (pyridine C-2), 160.4 (oxazole C-2), 149.0 (pyridine C-6), 135.9 (pyridine C-4), 122.1 (pyridine C-3), 121.6 (pyridine C-5), 79.2 (oxazole C-5), 67.7 (oxazole C-4), 38.2 (pyridine 2-CH_2), 31.9 (CH_2), 28.4 (geminal CH_3), 22.4 (CH_2), and 13.9 p.p.m. (CH_3) (Found: C, 72.7; H, 8.5; N, 12.2. Calc. for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06%).

Procedure for Varying the Ratio of Reactants to Optimize Yields of (**5c**).—Solutions of (**3**) [(421.6 mg, 2.4 mmol), (409.8 mg, 2.3 mmol), (426.6 mg, 2.4 mmol), (455.1 mg, 2.6 mmol), and (470.9 mg, 2.7 mmol)] in THF (5 ml) were stirred in test tubes at −78 °C. To each of the test tubes was added a solution of butyl-lithium in hexane (2.3M) [(0.5 ml, 1.2 mmol), (1.0 ml, 2.3 mmol), (2.1 ml, 4.8 mmol), (3.4 ml, 7.8 mmol), and (4.6 ml, 10.6 mmol)], respectively. The reaction mixtures were stirred at −78 °C for 1 h. The reaction mixtures were then oxidized, hydrolysed, worked up, and analysed as described earlier for the temperature-effect experiments. The results are summarized in Table 4.

Procedure for Studying the Effect of Reaction Period on Yields of (**5c**).—Solutions of (**3**) [(486.1 mg, 2.8 mmol), (504.6 mg, 2.9 mmol), (483.2 mg, 2.7 mmol), (476.9 mg, 2.7 mmol), and (480.7 mg, 2.7 mmol)] in THF (5 ml) were stirred in test tubes at −78 °C. A solution of butyl-lithium in hexane (1 equiv.) was added to each test tube. The reaction mixtures were stirred at −78 °C for 0.5 h, 1.0 h, 1.5 h, 2.0 h, and 3.0 h, respectively. Each reaction mixture was oxidized, hydrolysed, worked up, and analysed as described earlier for the temperature-effect experiments. The results are summarized in Table 5.

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