J. Org. Chem. 1988, *53*, 4437–4442

Regioselective α-Lithiation of Unsymmetrical 1-(*tert*-Butoxycarbonyl)-1,4-dihydropyridines

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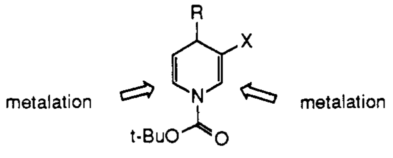
Received February 16, 1988

The α-lithiation–methylation of unsymmetrical C-3-substituted 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines was studied. The yield and regioselectivity, C-2 vs C-6, of the metalation was dependent upon the C-3 substituent, the metalation base, and the reaction conditions. When the C-3 substituent was a methyl or methoxy group, and mesityllithium was the base, C-6 lithiation–methylation occurred predominately. With a strongly ortho-directing C-3 substituent, i.e., Cl, Br, or OCONEt$_2$, metalation with phenyllithium occurred mainly at C-2. An α-amino alkoxide function at C-3 acted only as a blocking group, forcing lithiation to occur mainly at C-6. Two new trisubstituted pyridines, 3-[(*N*,*N*-diethylcarbamyl)oxy]-2,4-dimethylpyridine and 2,4-dimethyl-3-pyridinecarboxaldehyde, were prepared by aromatization of regioselectively alkylated 1,4-dihydropyridine intermediates with *o*-chloranil or sulfur in refluxing decalin, demonstrating a new approach to pyridine substitution.

We have described a convenient method for the preparation of 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines by regioselective addition of Grignard reagents to 1-acylpyridinium salts in the presence of a catalytic amount of cuprous iodide.[1] The potential of these heterocycles as synthetic intermediates[2] prompted us to develop methods for adding substitutents to the 1,4-dihydropyridine ring in a regioselective manner. β-Acylation[3] and β-formylation[4] of 1-acyl-1,4-dihydropyridines using the Friedel–Crafts and Vilsmeier–Haack reactions were previously reported. We have now found that regiospecific substitution at an α-position can be effected by using directed metalation. Symmetrical 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines are α-lithiated with *sec*-butyllithium in tetrahydrofuran and subsequently alkylated with electrophiles to give 2,4-disubstituted 1,4-dihydropyridines.[5] The 3-substituted 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine **1** has two different α-positions (C-2 and C-6) available for metalation.



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It seemed feasible that regioselective lithiation of dihydropyridines **1** might be achieved by proper choice of the metalation base and by modification of the C-3 substituent (X). By using a strongly ortho-directing C-3 substituent, lithiation–alkylation should occur at C-2. When a bulky, nondirecting substituent is at C-3, lithiation–alkylation at the C-6 position would be favored. In this paper we report our studies on the regioselective α-lithiation of various 3-substituted 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines.

Results and Discussion

The 3-substituted 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines **4** were prepared from 3-methyl-, 3-chloro-, 3-bromo-, 3-methoxy-, and 3-[(*N*,*N*-diethylcarbamyl)oxy]pyridine. The 3-substituted pyridines **2** were treated with phenyl chloroformate and methylmagnesium chloride in the presence of a catalytic amount of cuprous iodide to give the 1-(phenoxycarbonyl)-1,4-dihydropyridines **3**. Without purification, dihydropyridines **3** were converted to the 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines with potassium *tert*-butoxide in tetrahydrofuran (Table I).

Table I. Synthesis of 3-Substituted 1-(*tert*-Butoxycarbonyl)-1,4-dihydropyridines 4

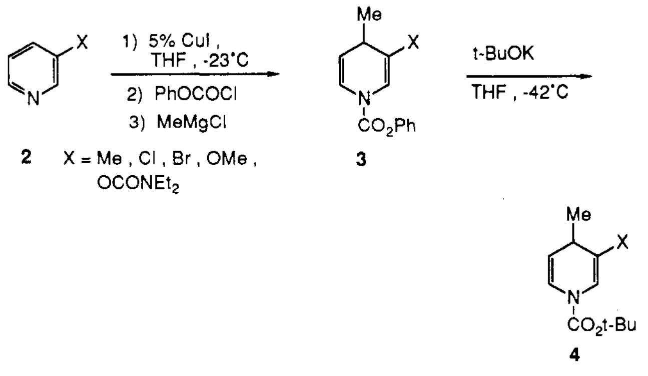
pyridine **2**[a]	X	yield of **3**,[b] %	yield of **4**,[c] %
a	Me	83	62
b	Cl	90	77
c	Br	85	73
d	OMe	92	68
e	OCONEt$_2$	87	64

[a] The reactions were generally performed on a 10-mmol scale in THF. [b] Yield of crude product, which was used directly in the next step. [c] Yield of purified product obtained from radial preparative-layer chromatography.

Table II. Lithiation–Methylation of 1,4-Dihydropyridine 4a

entry[a]	base[b]	metalation conditions[c]	yield of **5** and **6**,[d] %	ratio of **5** to **6**[f]
a	*n*-BuLi	−78 °C, 1 h	15[e]	84:16
b	PhLi/TMEDA	−78 °C, 6 h	25[e]	81:19
c	*sec*-BuLi	−78 °C, 1 h	70	48:52
d	*sec*-BuLi/TMEDA	−78 °C, 1 h	74	48:52
e	MesLi	−78 °C, 3 h	28[e]	93:7
f	MesLi	−60 °C, 3 h	60[e]	93:7
g	MesLi	−42 °C, 3 h	72	93:7

[a] The reactions were generally performed on a 2-mmol scale. [b] In all entries, 1.2 equiv of base was used. [c] THF was the solvent. After the indicated time, 3 equiv of methyl iodide was added. [d] Yield of isolated products **5** and **6** obtained as a mixture from radial preparative-layer chromatography. [e] Yield determined by ^{1}H NMR analysis. The reaction was incomplete, giving a considerable amount of starting material **4a** along with products **5** and **6**. [f] The product ratios were determined by ^{1}H NMR analysis.



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[1] Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315. Comins, D. L.; Mantlo, N. B. *J. Heterocycl. Chem.* **1983**, *20*, 1239. Comins, D. L.; Stroud, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151. Comins, D. L.; Smith, R. K.; Stroud, E. D. *Ibid.* **1984**, *22*, 339.

[2] For a review on dihydropyridines, see: Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223–243.

[3] Comins, D. L.; Mantlo, N. B. *Tetrahedron Lett.* **1983**, *24*, 3683.

[4] Comins, D. L.; Herrick, J. J. *Heterocycles* **1987**, *26*, 2159.

[5] Comins, D. L. *Tetrahedron Lett.* **1983**, *24*, 2807.

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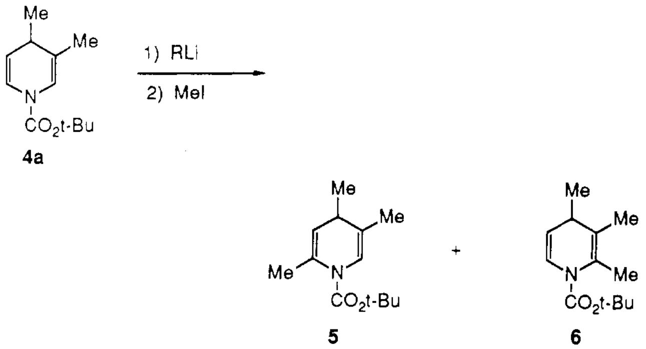
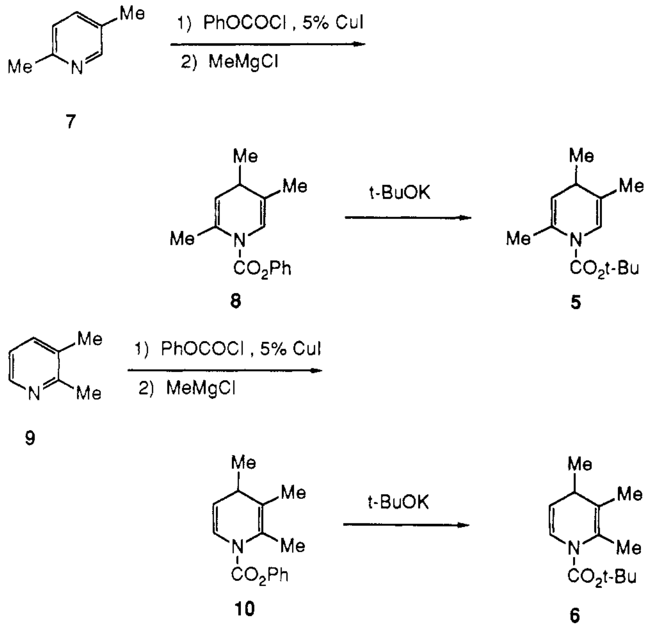
The initial metalation studies were performed on 1-(*tert*-butoxycarbonyl)-3,4-dimethyl-1,4-dihydropyridine (**4a**). As shown in Table II, several metalation conditions were explored. The reaction time, temperature, and type of metalation base were varied. When *sec*-butyllithium was used as the base, methylation with methyl iodide gave a good yield of dihydropyridines **5** and **6** in a ratio of 48:52 (entry c). Lithiation with *n*-butyllithium or phenyllithium



and methylation gave dihydropyridine **5** as the major product in low yield (entries a and b). The best conditions found for regioselective metalation–alkylation used mesityllithium[6,7] (MesLi) as the base (entry g). The high degree of regioselectivity undoubtedly results from the steric interaction of the C-3 methyl group and the bulky base, which inhibits lithiation at C-2. The structures and ratios of dihydropyridines **5** and **6** were confirmed by comparison to those of authentic samples prepared from 2,5-dimethylpyridine (**7**) and 2,3-dimethylpyridine (**9**) via dihydropyridines **8** and **10**.



To determine if regioselective C-2 lithiation could be achieved by modifying the C-3 substituent, we studied the metalation of 3-chloro-4-methyl-1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine (**4b**). It was anticipated that the electron-withdrawing chlorine substituent would lower the acidity of the C-2 hydrogen considerably,[8] allowing for a highly regioselective metalation to occur at C-2. However, as is shown in Table III, the regioselectivity is highly dependent upon the structure and quantity of the metalation base. When 1.2 equiv of base was utilized, alkyllithiums and mesityllithium led to mixtures of C-2 and C-6 methylated products, whereas use of phenyllithium at −42 °C (entry g) gave the C-2 methylated product exclusively. When 0.9 equiv of *sec*-butyllithium is used as the base, anion equilibration occurs at −42 °C to give the C-2 lithiated intermediate, which affords solely dihydropyridine **11** on methylation (entry d). The regioselectivity obtained in the phenyllithium reaction appears to be due to anion equilibration only to a small extent (entries h and i). The effectiveness of phenyllithium may be due to its lower basicity, which induces preferential deprotonation at the more acidic C-2 position.

Table III. Lithiation–Methylation of 1,4-Dihydropyridine 4b

entry[a]	base[b]	metalation conditions[c]	yield of **11** and **12**,[d] %	ratio of **11** to **12**[e]
a	*n*-BuLi	−78 °C, 1 h	55[f]	85:15
b	*sec*-BuLi	−78 °C, 1 h	82	57:43
c	*sec*-BuLi	−78 °C, 1 h; −42 °C, 1 h	85	53:47
d	*sec*-BuLi[g]	−78 °C, 1 h; −42 °C, 1 h	80[f]	100:0
e	*t*-BuLi	−78 °C, 1 h	68[f]	43:57
f	PhLi	−42 °C, 1 h	92	98:2
g	PhLi	−42 °C, 2 h	87	100:0
h	PhLi	−78 °C, 1 h	40[f]	95:5
i	PhLi	−78 °C, 3 h	51[f]	100:0
j	MesLi	−78 °C, 1 h	83	58:42

[a] The reactions were generally performed on a 2-mmol scale. [b] Unless indicated, 1.2 equiv of base was used. [c] THF was the solvent. After the indicated time, 3 equiv of methyl iodide was added. [d] Yield of isolated products **11** and **12** obtained as a mixture from radial preparative-layer chromatography. [e] The product ratios were determined by ^{1}H NMR analysis. [f] Yield determined by ^{1}H NMR analysis. The reaction was incomplete giving a significant amount of starting material **4b** along with products **11** and **12**. [g] This reaction was carried out with 0.9 equiv of base.

Table IV. Lithiation–Methylation of 1,4-Dihydropyridine 4c

entry[a]	base[b]	metalation conditions[c]	yield **13**, **14**, **15**,[d] %	ratio of **13** to **14**[f]	ratio of (**13** + **14**) to **15**[f]
a	*n*-BuLi	−78 °C, 1 h	59	73:27	43:57
b	*sec*-BuLi/ TMEDA	−78 °C, 1 h	46	47:63	75:25
c	*t*-BuLi	−78 °C, 1 h	43	88:12	40:60
d	PhLi	−78 °C, 1 h	50[e]	93:7	96:4
e	PhLi	−42 °C, 1 h	87	100:0	100:0

[a] The reactions were generally performed on a 2-mmol scale. [b] In all examples, 1.2 equiv of base was used. [c] THF was the solvent. After the indicated time, 3 equiv of methyl iodide was added. [d] Yield of isolated products **13**, **14**, and **15** obtained as a mixture from radial preparative-layer chromatography. [e] Yield determined by ^{1}H NMR analysis. The reaction was incomplete, giving a significant amount of starting material **4c** along with products **13**, **14**, and **15**. [f] The product ratios were determined by ^{1}H NMR analysis.

The 3-bromo-1,4-dihydropyridine **4c** behaved in a similar manner to that of **4b**, except in some cases lithium–halogen exchange competed with α-lithiation to give the 3,4-dimethyl-1,4-dihydropyridine **15** in significant quantities (Table IV). The use of phenyllithium as the base in tetrahydrofuran at −42 °C gave regiospecific lithiation at C-2, which allowed for the synthesis of **13** in high yield (entry e).

The 3-methoxy-1,4-dihydropyridine **4d** exhibited a preference for lithiation at C-6 (Table V). Metalation with mesityllithium in tetrahydrofuran at −42 °C and subsequent methylation gave an 85% yield of dihydropyridines

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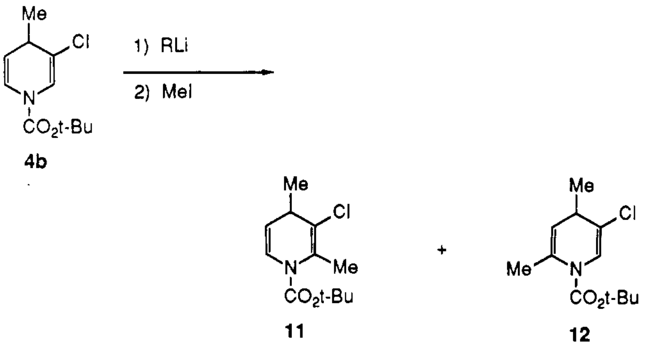
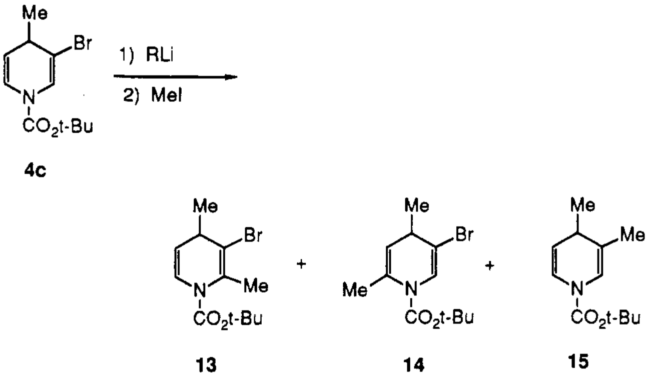
(6) Mesityllithium has been reported to ortho-lithiate 2-, 3-, and 4-methoxypyridine. Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.

(7) The mesityllithium used in this study was prepared from bromomesitylene and 1 equiv of *n*-butyllithium. For larger scale reactions, it may be more convenient to prepare mesityllithium from bromomesitylene and lithium metal. Rausch, M. D.; Tibbetts, F. E. *Inorg. Chem.* **1970**, *9*, 512.

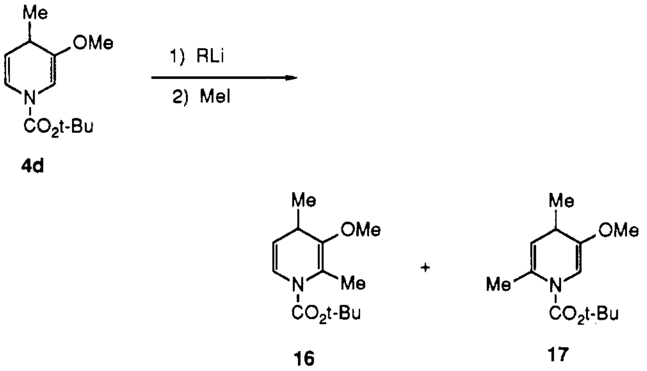
(8) Gschwend, H. W.; Rodriquez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, 1–360.





16 and 17 in a ratio of 13:87 (entry f).

In contrast, the 3-(carbamyloxy)-1,4-dihydropyridine 4e showed a tendency to lithiate predominately at C-2 (Table VI). Although alkyllithiums led to mixtures of C-2 and C-6 alkylation, the use of phenyl- or mesityllithium gave the C-2 methylated product 18 with a high degree of regioselectivity (entries f–h). Although some equilibration is possible at −42 °C (entries c and d), it is not substantial enough to explain the high regioselectivity observed when phenyl- or mesityllithium is used as the base. The high degree of regioselectivity found in entries f–h must be mainly due to preferential kinetic deprotonation at C-2. Aromatization of 18 with o-chloranil in toluene/acetic acid gave 2,4-dimethyl-3-[(N,N-diethylcarbamyl)oxy]pyridine (20). This methodology is tantamount to the disubstitution of the pyridinol synthon 21 and complements the C-4 lithiation–alkylation of 3-[(N,N-diethylcarbamyl)oxy]pyridine developed by Sniekus and co-workers.[9]



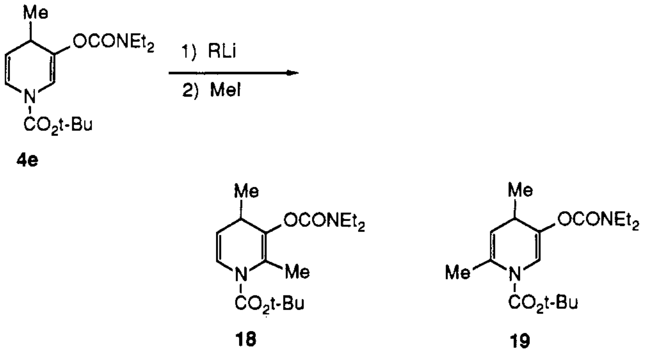


Table V. Lithiation–Methylation of 1,4-Dihydropyridine 4d

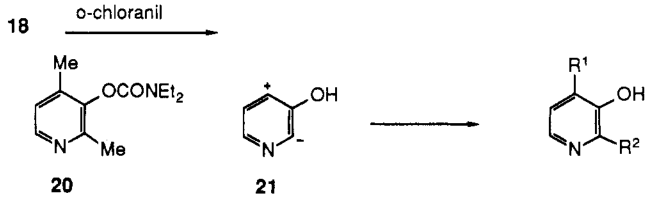
entry^a	base^b	metalation conditions^c	yield of 16 and 17,^{d} %	ratio of 16 to 17^f
a	n-BuLi	−78 °C, 1 h	30^e	41:59
b	PhLi	−78 °C, 1 h	10^e	25:75
c	MesLi	−78 °C, 1 h	30^e	13:87
d	MesLi	−60 °C, 1 h	40^e	22:78
e	MesLi	−42 °C, 2 h	72	13:87
f	MesLi	−42 °C, 3 h	85	13:87

^{a}The reactions were generally performed on a 2-mmol scale. ^{b}In all examples, 1.2 equiv of base was used. ^{c}THF was the solvent. After the indicated time, 3 equiv of methyl iodide was added. ^{d}Yield of isolated products 16 and 17 obtained as a mixture from radial preparative-layer chromatography. ^{e}Yield determined by ^{1}H NMR analysis. The reaction was incomplete, giving a significant amount of starting material 4d along with products 16 and 17. ^{f}The product ratios were determined by ^{1}H NMR analysis.

Table VI. Lithiation–Methylation of 1,4-Dihydropyridine 4e

entry^a	base^b	metalation conditions^d	yield of 18 and 19,^{e} %	ratio of 18 to 19^f
a	n-BuLi	−78 °C, 1 h	55	83:17
b	sec-BuLi	−78 °C, 1 h	68	61:39
c	sec-BuLi/ TMEDA	−78 °C, 1 h	76	54:46
d	sec-BuLi/ TMEDA^c	−78 °C, 1 h; −42 °C, 3 h	58	78:22
e	t-BuLi	−78 °C, 1 h	75	56:44
f	PhLi	−78 °C, 1 h	70^g	98:2
g	PhLi	−42 °C, 1 h	48	98:2
h	MesLi	−42 °C, 1 h	77	94:6

^{a}The reactions were generally performed on a 2-mmol scale. ^{b}Unless indicated, 1.2 equiv of base was used. ^{c}This reaction was carried out with 0.9 equiv of base. ^{d}THF was the solvent. After the indicated time, 3 equiv of methyl iodide was added. ^{e}Yield of isolated products 18 and 19 obtained as a mixture from radial preparative-layer chromatography. Unless indicated, the starting material 4e was completely consumed. In some cases decomposition occurred during metalation causing lower yields. ^{f}The product ratios were determined by ^{1}H NMR analysis. ^{g}Yield determined by ^{1}H NMR analysis. The reaction was incomplete, giving a small amount of starting material 4e along with products 18 and 19.



Lithiation of a 1,4-Dihydropyridine Directed by α-Amino Alkoxides. The addition of aromatic aldehydes to certain lithium dialkylamides gives α-amino alkoxides that can be ring lithiated with alkyllithiums. Alkylation and hydrolysis on workup provides o-substituted aryl aldehydes via a one-pot reaction.[10] This methodology works well for the one-pot substitution of heterocyclic aromatic aldehydes[11] as well as for benzaldehyde derivatives.[10] To determine if 1,4-dihydropyridine-3-carboxaldehydes could

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(9) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.

(10) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. Comins, D. L.; Brown, J. D. *Ibid.* **1983**, *24*, 5465. Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.

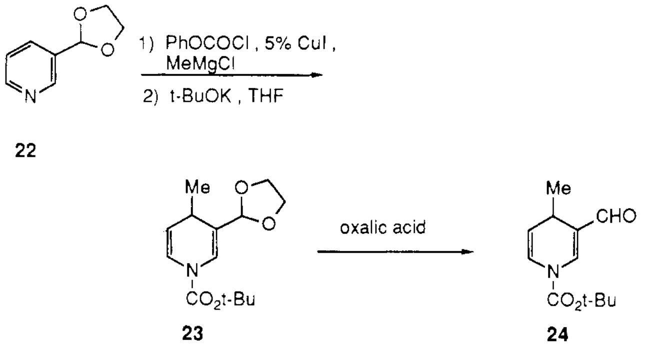
(11) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.

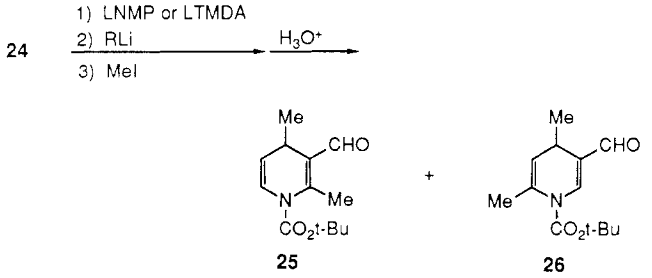
Table VII. α-Amino Alkoxide Directed Lithiation of 1,4-Dihydropyridine 24

entry[a]	lithium amide[b]	metalation base	metalation conditions[c]	yield of 25, 26, 24,[d] %	ratio of 25 to 26[e]	ratio of (25 + 26) to 24[e]
a	LNMP	1.2 *sec*-BuLi	−78 °C, 2 h	66	27:73	60:40
b	LNMP	1.2 PhLi	−42 °C, 3 h	77	30:70	80:20
c	LNMP	1.2 MesLi	−42 °C, 3 h	64	19:81	80:20
d	LNMP	2.0 MesLi	−42 °C, 3 h	82	8:92	100:0
e	LTMDA	1.2 MesLi	−42 °C, 4 h	73	27:73	80:20
f	LDA	1.5 MesLi	−42 °C, 3 h	70	30:70	75:25

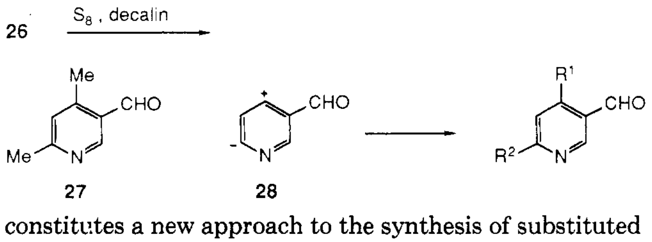
[a] The reactions were generally performed on a 2-mmol scale. [b] The α-amino alkoxides were prepared from 1.1 equiv of lithium *N*-methylpiperazide (LNMP), lithiated *N,N,N′*-trimethylethylenediamine (LTMDA), or lithium diisopropylamide (LDA). [c] THF was the solvent. After the indicated time, 3 equiv of methyl iodide was added. [d] Yield of isolated products **25** and **26** and recovered starting material **24** obtained as a mixture from radial preparative-layer chromatography. [e] The product ratios were determined by ^{1}H NMR analysis.

be substituted in this manner, we prepared dihydropyridine **24**. The 1,3-dioxolane **22** was converted to the 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine **23** by using the copper-catalyzed Grignard procedure. Treatment of crude **23** with oxalic acid in tetrahydrofuran afforded aldehyde **24** in 63% overall yield. The metalation studies were performed by first adding lithium *N*-methylpiperazide (LNMP), or lithiated *N,N,N′*-trimethylethylenediamine (LTMDA), to form an α-amino alkoxide in situ, which was metalated and methylated to give substituted dihydropyridines **25** and **26** on aqueous workup.

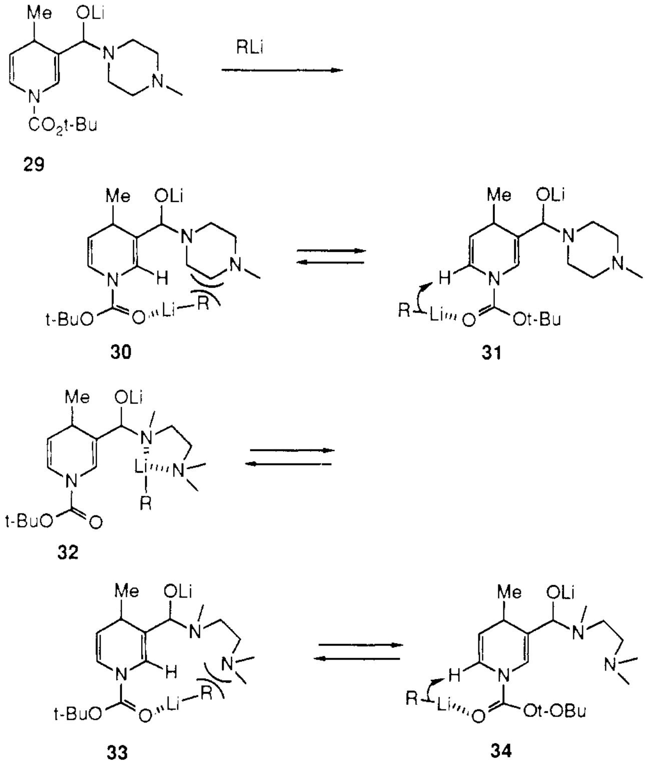




The results of this study are given in Table VII. Lithiation of the α-amino alkoxide formed in situ from **24** and LNMP was anticipated to occur at C-6, for an α-amino alkoxide group derived from *N*-methylpiperazine is bulky and not a strong directing group. In this manner, with mesityllithium as the base, an 82% yield of products **25** and **26** could be obtained in a ratio of 8:92 (entry d). Aromatization of **26** with sulfur in refluxing decalin gave 2,4-dimethyl-5-pyridinecarboxaldehyde (**27**). This sequence constitutes a new approach to the synthesis of substituted 3-pyridinecarboxaldehydes that is equivalent to the bis-substitution of synthon **28**. Interestingly, the α-amino alkoxide derived from **24** and LTMDA also gave mainly C-6 lithiation (entry e), even though an α-amino alkoxide group derived from *N,N,N′*-trimethylethylenediamine is a strong ortho director.[10,11]



These results provide evidence that complexation of the metalating base with the carbonyl oxygen of the *N*-acyl group occurs prior to lithiation of the dihydropyridine ring. Metalation via complex **31** is favored over reaction via complex **30** due to the steric interaction of the complexed alkyllithium in **30** with the bulky α-amino alkoxide group. Metalation via complex **32**, which would lead to C-2 substitution, apparently is less favored than metalation via complexes **33** and **34**. Complex **34** reacts at a faster rate than **33** for steric reasons, thus lithiation occurs mainly at C-6. This type of complexation has been suggested to play an important role in the *N*-methyl lithiation of amides to give dipole-stabilized carbanions.[12,13]



Conclusion

The α-lithiation of unsymmetrical 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines has considerable potential for the regioselective synthesis of highly substituted 1,4-dihydropyridines. By proper choice of the C-3 substituent, the metalation base, and reaction conditions, either C-2

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(12) Beak, P.; Zajdel, W. J. *Chem. Rev.* **1984**, *84*, 471–523.
(13) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363.

or C-6 substitution can be effected with a high degree of regioselectivity. The metalation likely occurs via a complex induced proximity effect,[13] where the organolithium base complexes to the carbamate carbonyl oxygen prior to kinetic removal of an α-proton. The C-3 substituent affects the regiochemistry through electronic or steric effects. Although methyl iodide was used as the trapping agent in these studies, other electrophiles are effective as has been previously demonstrated.[5] Mesityllithium was an effective base for many of the metalation reactions studied, and should prove useful for lithiation of other heterocyclic systems.[6] On oxidation, these heterocycles are converted to substituted pyridines that may be difficult to prepare by classical methods. Although 1-acyl-1,4-dihydropyridines have not been utilized for the synthesis of natural products to the degree that 1-acyl-1,2-dihydropyridines have, the ability to prepare highly substituted 1,4-dihydropyridines in a regioselective manner will make these heterocycles more attractive as synthetic intermediates. The studies presented in this paper should be considered as progress toward that goal.

Experimental Section

Reactions involving organometallic reagents were performed in oven-dried glassware under a N_2 or Ar atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. Diisopropylamine, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), *N,N,N′*-trimethylethylenediamine, and *N*-methylpiperazine were distilled from calcium hydride and stored over 4-Å molecular sieves under N_2. Other solvents and reagents from commercial sources were generally used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in ppm relative to Me_4Si (δ 0), and coupling constants are in hertz. ^{13}C NMR spectra are reported in ppm relative to the $CDCl_3$ absorption (77.0 ppm). Radial preparative-layer chromatography (radial PLC) was carried out by using a Chromatotron (Harrison Associates, Palo Alto, CA). Elemental analyses were carried out by M-H-W laboratories, Phoenix, AZ. Due to their instability,[14] several of the dihydropyridines were not submitted for elemental analysis.

1-(*tert*-Butoxycarbonyl)-3,4-dimethyl-1,4-dihydropyridine (4a). General Procedure for the Synthesis of 1,4-Dihydropyridines 4a–e. To a 250-mL one-neck flask was added cuprous iodide (0.19 g, 1.0 mmol), anhydrous THF (15 mL), and methyl sulfide (4 mL). After the mixture was stirred at room temperature for 15 min, 80 mL of THF and 1.94 mL (20.0 mmol) of 3-picoline were added, and the solution was cooled to −23 °C (CCl_4/CO_2). Phenyl chloroformate (2.51 mL, 20 mmol) was added slowly dropwise with stirring to form a thick brown precipitate. After stirring for 15 min, methylmagnesium chloride in THF (6.66 mL, 20 mmol) was added to the heterogeneous mixture, which turned homogeneous on complete addition of the Grignard reagent. The reaction was stirred for 20 min at −23 °C and then at room temperature for an additional 20 min, followed by addition of aqueous 20% NH_4Cl (50 mL). To this solution was added 100 mL of ether, and the organic layer was washed with 20-mL portions of 20% NH_4Cl/NH_4OH (50:50), water, 10% HCl, water, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give 3.79 g (83%) of the crude intermediate **3a** as a yellow oil.

To 1.56 g (6.80 mmol) of crude **3a** in 15 mL of THF at −42 °C was added dropwise a solution of potassium *tert*-butoxide (1.53 g, 13.6 mmol) in 30 mL of anhydrous THF. The resulting heterogeneous orange mixture was stirred for 30 min at −42 °C and for an additional 10 min at room temperature. Water (15 mL) and 40 mL of ether were added, and the aqueous layer was extracted with ether. The combined ether extracts were washed with cold 1 N NaOH (2 × 20 mL), water (2 × 20 mL), and brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give 1.07 g (75%) of the crude product. Purification by radial PLC (silica gel, EtOAc/hexanes) gave 880 mg (62%) of **4a** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 and 6.63 (pair of d due to rotamers, 1 H, *J* = 8.5 Hz), 6.61 and 6.45 (pair of s due to rotamers, 1 H), 4.90–4.70 (m, 1 H), 2.85 (m, 1 H), 1.66 (s, 3 H), 1.50 (s, 9 H), 1.11 (d, 3 H, *J* = 7.0 Hz).

^{1}H NMR Spectral Data. 4b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 and 6.85 (pair of s due to rotamers, 1 H), 6.76 and 6.61 (pair of d due to rotamers, 1 H, *J* = 7.5 Hz), 4.95–4.75 (m, 1 H), 3.17 (m, 1 H), 1.51 (s, 9 H), 1.24 (d, 3 H, *J* = 7.0 Hz).

4c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 and 6.98 (pair of s due to rotamers, 1 H), 6.78 and 6.62 (pair of d due to rotamers, 1 H, *J* = 8.5 Hz), 4.95–4.75 (m, 1 H), 3.21 (m, 1 H), 1.51 (s, 9 H), 1.24 (d, 3 H, *J* = 7.0 Hz).

4d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 and 6.66 (pair of d due to rotamers, 1 H, *J* = 8.0 Hz), 6.32 and 6.13 (pair of s due to rotamers, 1 H), 4.90–4.70 (m, 1 H), 3.58 (s, 3 H), 3.11 (m, 1 H), 1.51 (s, 9 H), 1.16 (d, 3 H, *J* = 7.0 Hz).

4e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 and 6.71 (pair of s due to rotamers, 1 H), 6.77 and 6.61 (pair of d due to rotamers, 1 H, *J* = 8.0 Hz), 4.95–4.75 (m, 1 H), 3.50–3.20 (m, 5 H), 1.49 (s, 9 H), 1.16 (m, 6 H), 1.14 (d, 3 H, *J* = 7.0 Hz).

1-(*tert*-Butoxycarbonyl)-2,4,5-trimethyl-1,4-dihydropyridines (5). To a solution of bromomesitylene (0.20 mL, 1.32 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (0.73 mL, 1.32 mmol). After 30 min, the mesityllithium was added via a double-tipped needle to a solution of dihydropyridine **4a** (231 mg, 1.10 mmol) in 10 mL of THF at −42 °C (CH_3CN/CO_2). The mixture was stirred at −42 °C for 3 h. Methyl iodide (0.21 mL, 3.3 mmol) was added, and stirring was continued at −42 °C for 1 h and at room temperature for 30 min. Addition of water (10 mL), extraction with ether, washing the combined organic layers with brine, drying ($MgSO_4$), and concentration gave the crude product. Purification by radial PLC (silica gel, hexanes–10% EtOAc/hexanes) gave 177 mg (72%) of **5** as a light yellow oil that was identical with an authentic sample prepared from 2,5-dimethylpyridine. This product contained approximately 7% of isomer **6** as determined by NMR analysis.

Preparation of 5 from 2,5-Dimethylpyridine (7). This compound was prepared on a 10-mmol scale from 2,5-dimethylpyridine, cuprous iodide, phenyl chloroformate, methylmagnesium chloride, and potassium *tert*-butoxide by the method described for the preparation of **4a**. Purification by radial PLC (silica gel, 10% EtOAc/hexanes) gave 1.08 g (48% overall) of **5** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (br q, 1 H, *J* = 1.0 Hz), 4.71 (br dq, 1 H, *J* = 5.0 Hz and *J* = 1.0 Hz), 2.70 (br dq, 1 H, *J* = 7.0 Hz and *J* = 5.0 Hz), 2.12 (pair of d due to rotamers, 3 H, *J* = 1.0 Hz), 1.66 (m, 3 H), 1.50 (s, 9 H), 1.05 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 151.2, 132.2, 120.6, 119.7, 113.9, 81.3, 32.9, 28.3, 22.3, 21.0, 18.3; IR (neat) 2990, 1700, 1660, 1460, 1310, 1280 cm^{-1}.

Preparation of 6 from 2,3-Dimethylpyridine (9). This compound was prepared on a 10-mmol scale from 2,3-dimethylpyridine as described above for the preparation of **5** from 2,5-dimethylpyridine (**7**). Purification by radial PLC (silica gel, 10% EtOAc/hexanes) gave 1.03 g (46% overall) of **6** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, 1 H, *J* = 7.0 Hz), 5.04 (dd, 1 H, *J* = 7.0 Hz and *J* = 5.0 Hz), 2.58 (br dq, 1 H, *J* = 7.0 Hz and *J* = 5.0 Hz), 2.02 (br s, 3 H), 1.68 (br s, 3 H), 1.51 (s, 9 H), 1.03 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 151.6, 126.6, 126.1, 121.0, 113.6, 81.0, 34.6, 28.3, 20.8, 17.7, 17.4; IR (neat) 2980, 2880, 1700, 1640, 1450, 1340 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.84; H, 9.49; N, 6.37.

1-(*tert*-Butoxycarbonyl)-3-chloro-2,4-dimethyl-1,4-dihydropyridine (11). To a solution of bromobenzene (0.32 mL, 3.05 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (1.69 mL, 3.05 mmol). After 30 min, the phenyllithium was added via a double-tipped needle to a solution of dihydropyridine **4b** (583 mg, 2.54 mmol) in 10 mL of THF at −42 °C (CH_3CN/CO_2). The mixture was stirred at −42 °C for 1 h. Methyl iodide (0.47 mL, 7.62 mmol) was added, and stirring was continued at −42 °C for 1 h and at room temperature for 30 min. Addition of water (10 mL), extraction with ether, washing the combined organic layers with brine, drying ($MgSO_4$), and concentration gave 662 mg of

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[14] Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.

the crude product as an oil. Purification by radial PLC (silica gel, 25% EtOAc/hexanes) gave 570 mg (92%) of **11** as a clear oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.75 (d, 1 H, J = 8.0 Hz), 4.98 (dd, 1 H, J = 8.0 Hz and J = 5.0 Hz), 3.03 (br dq, 1 H, J = 7.0 Hz and J = 5.0 Hz), 2.20 (pair of s due to rotamers, 3 H), 1.51 (s, 9 H), 1.18 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 151.0, 129.6, 125.3, 121.8, 111.6, 82.1, 36.8, 28.2, 21.1, 18.8; IR (neat) 2980, 1710, 1680, 1630, 1450, 1330 cm^{-1}.

3-Bromo-1-(*tert*-butoxycarbonyl)-2,4-dimethyl-1,4-dihydropyridine (13). This compound was prepared on a 1.71-mmol scale from dihydropyridine **4c**, phenyllithium, and methyl iodide as described above for the preparation of **11**. Purification by radial PLC (silica gel, 25% EtOAc/hexanes) gave 429 mg (87%) of **13** as a light yellow oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.75 (d, 1 H, J = 7.5 Hz), 4.97 (dd, 1 H, J = 7.5 Hz and J = 5.0 Hz), 3.14 (br dq, 1 H, J = 6.5 Hz and J = 5.0 Hz), 2.24 (pair of s due to rotamers, 3 H), 1.51 (s, 9 H), 1.18 (d, 3 H, J = 6.5 Hz); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 150.8, 131.3, 125.4, 114.5, 111.9, 82.1, 39.0, 28.2, 21.7, 21.6; IR (neat) 2995, 1710, 1690, 1615, 1425, 1310 cm^{-1}. Anal. Calcd for $C_{12}H_{18}BrNO_2$: C, 50.01; H, 6.30; N, 4.86. Found: C, 50.16; H, 6.34; N, 4.76.

1-(*tert*-Butoxycarbonyl)-2,4-dimethyl-5-methoxy-1,4-dihydropyridine (17). This compound was prepared on a 4.58-mmol scale from dihydropyridine **4d**, mesityllithium, and methyl iodide as described for the preparation of **5** from **4a**. Purification by radial PLC (silica gel, hexanes–10% EtOAc/hexanes) gave 929 mg (85%) of a clear oil, which contained **17** and isomer **16** in a ratio of 87:13: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.32 (s, 1 H), 4.74 (m, 1 H), 3.57 (s, 3 H), 2.94 (m, 1 H), 2.13 (pair of d due to rotamers, 3 H), 1.52 (s, 9 H), 1.10 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 151.4, 147.6, 132.2, 113.2, 101.7, 81.4, 55.0, 32.3, 28.4, 22.3, 20.6; IR (neat) 2980, 2940, 1705, 1645, 1450, 1340 cm^{-1}.

1-(*tert*-Butoxycarbonyl)-3-[(*N*,*N*-diethylcarbamyl)oxy]-2,4-dimethyl-1,4-dihydropyridine (18). This compound was prepared on a 1.36-mmol scale from dihydropyridine **4e**, mesityllithium, and methyl iodide as described above for the preparation of **17**. Purification by radial PLC (silica gel, hexanes–30% EtOAc/hexanes) gave 340 mg (77%) of **18** as a clear oil. This product contained 6% of the C-6 isomer **19**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.77 (d, 1 H, J = 8.0 Hz), 4.95 (dd, 1 H, J = 8.0 Hz and J = 4.0 Hz), 3.34 (m, 4 H), 3.17 (m, 1 H), 2.02 (pair of s due to rotamers, 3 H), 1.50 (s, 9 H), 1.17 (m, 6 H), 1.09 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 153.2, 151.2, 136.4, 128.0, 125.0, 111.7, 81.7, 42.1, 41.7, 31.6, 28.2, 20.2, 14.9, 14.4, 13.5; IR (neat) 2980, 1710, 1640, 1340, 1280 cm^{-1}.

1-(*tert*-Butoxycarbonyl)-3-formyl-4-methyl-1,4-dihydropyridine (24). The intermediate 1,4-dihydropyridine **23** was prepared on a 20-mmol scale from 2-(3′-pyridyl)-1,3-dioxolane (**22**) by the general procedure described for the preparation of **4a**, except the 10% HCl wash was omitted. In this manner, dihydropyridine **23** was isolated as a light yellow oil (84%). The crude material was used directly in the next step.

To the acetal **23** (1.45 g, 5.42 mmol) in 15 mL of THF at 0 °C was added 3 mL of saturated aqueous oxalic acid. The mixture was stirred at 0 °C for 15 min and then extracted with ether. The combined extracts were washed with water and brine, dried (MgSO$_4$), and concentrated to give 1.24 g of an oil. Purification by radial PLC (silica gel, 20% EtOAc/hexanes) gave 909 mg (75%) of **24** as a light yellow oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.34 (s, 1 H), 7.56 (br s, 1 H), 6.70 (m, 1 H), 5.10 (m, 1 H), 3.36 (m, 1 H), 1.56 (s, 9 H), 1.16 (d, 3 H, J = 7.0 Hz); IR (neat) 2980, 2720, 1720, 1665, 1610, 1350 cm^{-1}.

1-(*tert*-Butoxycarbonyl)-2,4-dimethyl-5-formyl-1,4-dihydropyridine (26). To a solution of 0.64 mL (5.81 mmol) of *N*-methylpiperazine in 15 mL of THF at −23 °C was added 2.55 mL (5.81 mmol) of *n*-BuLi dropwise. After 20 min, this solution was added via a double-tipped needle to a solution of aldehyde **24** (1.18 g, 5.28 mmol) in 30 mL of THF at −42 °C (CH$_3$CN/CO$_2$). The mixture was stirred at −42 °C for 20 min, and then mesityllithium (10.56 mmol) in 20 mL of THF (−78 °C) was added dropwise. After the mixture was stirred at −42 °C for 3 h, methyl iodide (1.64 mL, 26.40 mmol) was added, and stirring was continued at −42 °C for 1 h and then at room temperature for 15 min. The mixture was poured into cold, vigorously stirred aqueous 20% NH$_4$Cl solution and extracted with ether. The combined ether extracts were washed with water and brine, dried (MgSO$_4$), and concentrated to give 2.64 g of an orange oil. Purification by radial PLC (silica gel, hexanes–30% EtOAc/hexanes) gave 1.02 g (82%) of **26** as a light yellow oil. This product contained approximately 8% of the isomer **25**. Spectral data for **26**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.36 (s, 1 H), 7.67 (s, 1 H), 4.94 (d, 1 H, J = 5.0 Hz), 3.26 (br dq, 1 H, J = 7.0 Hz and J = 5.0 Hz), 2.15 (s, 3 H), 1.57 (s, 9 H), 1.09 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 190.8, 150.1, 144.8, 131.5, 125.0, 115.7, 84.0, 28.0, 25.9, 22.1, 21.9; IR (neat) 2980, 2740, 1725, 1670, 1620, 1455, 1325 cm^{-1}.

3-[(*N*,*N*-Diethylcarbamyl)oxy]-2,4-dimethylpyridine (20). To a solution of dihydropyridine **18** (1.35 g, 4.17 mmol) in 10 mL of dry toluene was added dropwise *o*-chloranil (1.13 g, 4.59 mmol) in 10 mL of glacial acetic acid. The mixture was stirred at room temperature for 12 h and concentrated. Toluene (10 mL), ether (10 mL), Celite (2 g), and 20 mL of 10% NaOH were added. The mixture was stirred at room temperature for 15 min and filtered through Celite. The dark organic layer was washed with water and then extracted with 3 × 20 mL of 10% HCl. The combined acid extracts were washed with ether and concentrated. The residue was cooled, made basic with 25% NaOH, and extracted with methylene chloride (3 × 20 mL). The combined organic extracts were washed with brine, dried (K$_2$CO$_3$), and concentrated to yield the crude product (426 mg) as a yellow oil. Purification by radial PLC (silica gel, 50–80% EtOAc/hexanes) gave 357 mg (39%) of **20** as a clear oil: mp picrate 148–149 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.20 (d, 1 H, J = 5.0 Hz), 7.00 (d, 1 H, J = 5.0 Hz), 3.50 (q, 2 H, J = 7.0 Hz), 3.40 (q, 2 H, J = 7.0 Hz), 2.42 (s, 3 H), 2.20 (s, 3 H), 1.30 (t, 3 H, J = 7.0 Hz), 1.21 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 152.5, 151.5, 145.4, 145.3, 139.7, 123.6, 42.3, 41.9, 19.4, 15.9, 14.3, 13.4; IR (neat) 2980, 2940, 1710, 1600, 1420, 1280 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.65; H, 8.29; N, 12.43.

2,4-Dimethyl-5-pyridinecarboxaldehyde (27). Sublimed sulfur (159 mg, 4.97 mmol) was added to a solution of 983 mg (4.14 mmol) of dihydropyridine **26** in 30 mL of decalin. The mixture was refluxed under argon for 3 h with an air condenser and cooled to room temperature, and 30 mL of ether was added. The mixture was filtered through Celite, and the filtrate was extracted with 4 × 20-mL portions of 10% HCl. The combined acid extracts were washed with ether and cooled to 0 °C, and methylene chloride (30 mL) was added. The mixture was made basic with 25% NaOH and extracted with methylene chloride (3 × 20 mL). The combined organic phase was washed with brine, dried (K$_2$CO$_3$), and concentrated to give 477 mg of crude product. Purification by radial PLC (silica gel, 50% EtOAc/hexanes) gave 395 mg (71%) of **27** as a clear oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.22 (s, 1 H), 8.81 (s, 1 H), 7.09 (s, 1 H), 2.64 (s, 3 H), 2.60 (s, 3 H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 191.6, 163.4, 154.3, 149.3, 127.7, 126.2, 24.7, 19.6; IR (neat) 2970, 2860, 1690, 1600, 1550, 1450 cm^{-1}. Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.93; H, 6.95; N, 10.50.

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) for financial support of this research. The 300-MHz NMR spectra were recorded on a Varian XL-300 spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant CHE-8417529).