A Convenient Method for the Regioselective Synthesis of 4-Alkyl(aryl)pyridines Using Pyridinium Salts

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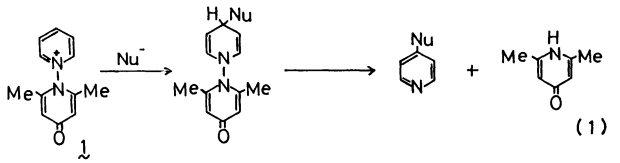
$RCu \cdot BF_3$ reacted with 1-ethoxycarbonylpyridinium chloride at the 4-position with almost complete regioselectivity (>99%) to afford the corresponding 1,4-dihydropyridine derivatives in high yields (81—94%). The dihydropyridines were oxidized by oxygen to give 4-alkyl(aryl)pyridines (38—68%). Grignard reagents also reacted with 1-*t*-butyldimethylsilylpyridinium triflate with almost complete regioselectivity (>99%) to afford the corresponding 1,4-dihydropyridines, which were easily oxidized by oxygen to give 4-substituted pyridines in higher yields than above (58—70%).

Considerable efforts have been directed at the introduction of substituents directly onto pyridine using organometallic reagents.[1] Organolithiums were shown to add to the 2-position selectively in high yields[2] and Grignard reagents to the 2- and 4-positions under forceful conditions in low yields.[3] 2-Lithio-1,3-dithiane adds to the 4-position and 4-formylpyridine is obtained after hydrolysis and air-oxidation.[4] However, it is necessary to activate pyridine as the pyridinium salt for facile reaction with organometalloids. Grignard and organocadmium reagents afford 2-substituted 1-acyl-1,2-dihydropyridines in good yields under mild conditions.[5]

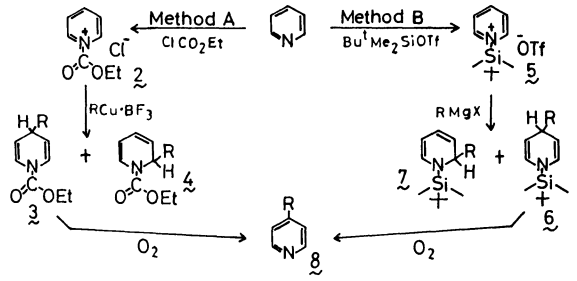
Lithium dialkylcuprate (I) is the only organometallic reagent known which adds to the 4-position of a pyridinium salt predominantly,[6] but one half of the alkyl group of the reagent is inevitably wasted. Therefore, it still remains to devise some pertinent method to introduce substituents selectively into the 4-position of pyridine. Recently, Katritzky and co-workers challenged this problem successfully and reported the synthesis of 4-substituted pyridines in good yields starting with 1-(2,6-dimethyl-4-oxo-1,4-dihydro-1-pyridyl)pyridinium salt (**1**), where the 2,6-positions of the pyridinium moiety is sterically shielded.[7]



In order to circumvent the preparation of the special starting material **1** and to start with pyridine itself, we investigated successfully the following two methods (Scheme 1) with the objective to, *i.e.*, i) use softer and maybe bulkier nucleophiles to increase the regioselectivity of attack at the 4-position of 1-ethoxycarbonylpyridinium chloride (Method A), ii) use the most versatile nucleophile, Grignard reagents, and choose bulky quaternizing reagents to shield the 2- and 6-positions sterically, which can readily be eliminated to give the pyridine nucleus (Method B).

Both methods showed better than a 99% selective nucleophilic attack at the 4-position relative to the 2-position.[8]

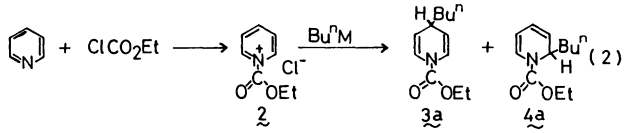
Quite recently after our research had been completed, we became aware of the results of Comins and Abdullah[9] which is closely related to Method A. This fact prompted us to publish our results in full.



Scheme 1.

Results and Discussion

Regioselective Synthesis of 4-Alkyl(aryl)pyridines by Method A. We examined the reaction of ethoxycarbonylpyridinium chloride with butylmagnesium bromide in tetrahydrofuran (THF) at 0 °C first in order to find a convenient procedure to convert the 1,2-dihydropyridine into the 2-substituted pyridine. While Fraenkel *et al.* obtained only 1,2-dihydropyridine (**4a**) in a moderate yield,[5a] a mixture (80% total yield) of 1,2-dihydropyridine (**4a**) and 1,4-dihydropyridine (**3a**) was obtained in a ratio of 65 to 35. A similar result was obtained with hexylmagnesium bromide. Furthermore, our result was confirmed recently by Comins *et al.*[9] and Yamaguchi *et al.*[10]



We then examined the reaction of **2** with butyllithium in ether, in which case the corresponding dihydropyridine was not obtained but the original pyridine was recovered. On the other hand, the reaction of **2** with $Bu^nLi \cdot BBu^n_3$ in ether afforded a mixture of **3a** and **4a** in a ratio of 75 to 25 with a total yield of 42%. Accordingly, we investigated the reaction of $Bu^nMgBr \cdot BBu^n_3$, Bu^nCu, and $Bu^nCu \cdot BF_3$[11] with **2** and the results are summarized in Table 1. Exclusive attack at the 4-position was achieved with Bu^nCu and $Bu^nCu \cdot$

Table 1. Reaction of various organometallic reagents with **2**

Nucleophile		Yield of **3a** and **4a**(%)[3]	Ratio=1,4-(**3a**)/1,2-(**4a**)[4]	Solvent
Bu^nMgBr		80	35/65	THF
HexMgBr		90	30/70	THF
Bu^nLi		0	—	ether
$Bu^nLi \cdot BBu^n_3$ [1]		42	75/25	ether
$Bu^nMgBr \cdot BBu^n_3$ [1]		58	62/38	THF
Bu^nCu	(Bu^nLi+CuI)	35	—	ether
	(Bu^nMgBr+CuI)	78	99.5/0.5	THF
$Bu^nCu \cdot BF_3$ [2]	(Bu^nLi+CuI)	48	98.0/2.0	ether
	(Bu^nMgBr+CuI)	59	99.2/0.8	ether
	(Bu^nMgBr+CuI)	89	99.5/0.5	THF

1) Tributylborane complex was prepared by addition of the borane to Bu^nLi or Bu^nMgBr at −78 °C. 2) This reagent was prepared following the procedure of Maruyama and Yamamoto.[11] 3) Isolated yield by Kugelrohr distillation. 4) Product ratio was determined by GLC analysis (5% Apiezon Grease L on Chromosorb WAW DMCS, 100 °C→230 °C).

Table 2. Regioselective synthesis of **3** and **8**

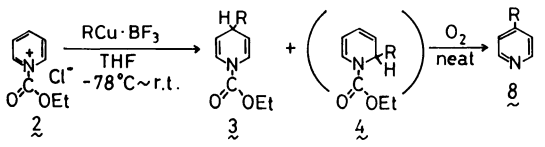
	R	Total yield of **3** and **4**[1](%)	Ratio: 1,4-(**3**)/1,2-(**4**)[2]	Oxidation time (h)	Yield of **8**[3] (%)	Overall yield from Py (%)
a	$CH_3(CH_2)_3$-	89	99.5/0.5	1	68	61
b	$CH_3(CH_2)_5$-	85	99.7/0.3	1	66	56
c	$PhCH_2CH_2$-	81	100/0	19	55[4]	45
d	$CH_3CH_2\diagdown CH-\ CH_3\diagup$	83	99.7/0.3	7	38[4]	32
e	Ph-	94	99.0/1.0	12	59	55

1) Isolated yield by Kugelrohr distillation. Satisfactory IR and ^1H NMR data were obtained for these compounds and satisfactory MS data was obtained for **3a**. 2) By GLC analysis (5% Apiezon Grease L on Chromosorb WAW DMCS, 100 °C⟶230 °C). 3) Isolated yield by Kugelrohr distillation. Identified by IR and ^1H NMR spectroscopy and MS. 4) Lower yields may be due to over-oxidation.

BF_3 in high yield in THF (**3a**:**4a**=~99.5:~0.5). The total yields were about 10% higher with $Bu^nCu \cdot BF_3$ than with Bu^nCu under the same conditions as shown in Table 1. This can probably be ascribed to the relative stability of the copper reagents.

It was also found that the yield of **3a** was higher when butylmagnesium bromide was used as a source of organocopper reagent compared with that using butyllithium.

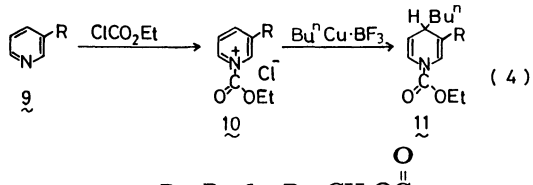
Therefore, we examined the reaction of various $RCu \cdot BF_3$ reagents with **2** in THF and some of the results are summarized in Table 2. Evidently this method is superior to that with lithium dialkylcuprate (I),[6] because one equivalent of an alkyl group is transferred to the pyridine nucleus stoichiometrically. Moreover, the ratio (99.0:1.0) remains high even with $PhCu \cdot BF_3$, whereas it lowered to 90:10 with lithium diphenylcuprate (I).



It is noteworthy that 1,4-dihydropyridines (**3**) can be obtained pure and stable by distillation with quick work-up in the air. 1,4-Dihydropyridines (**3**) were fully characterized as described in Experimental Section. The ^1H NMR of **3a** in $CDCl_3$ (δ) showed the 4-H at 2.72—3.10 as a multiplet, the 3-H and 5-H at 4.77 as a broad double of doublet (J=8 and 3 Hz), and the 2-H and 6-H at 6.79 as a broad doublet (J=8 Hz). The characteristic ^1H NMR signals are almost identical to all **3**.

On the other hand, it is well known that dihydropyridine derivatives are susceptible to oxidation and a small amount of oxidized product **8** was often detected by ^1H NMR. Therefore, oxidation of **3a** in solution (CH_2Cl_2 and THF) was effected by bubbling dry air or oxygen during 10—15 h, but the yield of **8a** was 40—50%. The product **8a** was obtained in 68% yield by oxidation of the neat liquid **3a** under an oxygen atmosphere with stirring for 1 h followed by distillation. Others were oxidized similarly as shown in Table 2. Oxidation of **3e** proceeds sluggishly. The lower yield of **8c** and **8d** may be ascribed to overoxidation. Other oxidations of **3a** were less successful, *i.e.*, i) with H_2O_2–NaOH in THF for 3 d at r.t., 24%; ii) with MCPBA in CH_2Cl_2 for 12 h at r.t., 9%; iii) MCPBA in CH_2Cl_2 for 3 h at reflux, 10%; iv) with *p*-benzoquinone in CH_2Cl_2 at r.t., no reaction took place and at reflux for 3 h, only a tarry residue was obtained. Although oxidation of **3a** to **8a** was performed with silver nitrate in THF at r.t. in 67% yield and that with sulfur has been reported,[12] we adopted the above mentioned procedure mainly due to its simplicity.

We next demonstrated the utility of this method to some of substituted pyridines to investigate the limitation of this method. First, reaction of the 3-bromopyridinium salt (**10a**) with $Bu^nCu \cdot BF_3$ was carried out by the same procedure as described above where 3-bromo-4-butyl-1-ethoxycarbonyl-1,4-dihydropyridine (**11a**) was obtained in 42% yield after Kugelrohr distillation. In a similar manner, reaction of the 3-methoxycarbonylpyridinium salt (**10b**) was tried, however, the reaction mixture was very complicated. Purification of the mixture by flash column chromatography afforded 4-butyl-1-ethoxycarbonyl-3-methoxycarbonyl-1,4-dihydropyridine (**11b**, 19%) and its oxidized product, 4-butyl-3-methoxycarbonylpyridine (12%).



(4)

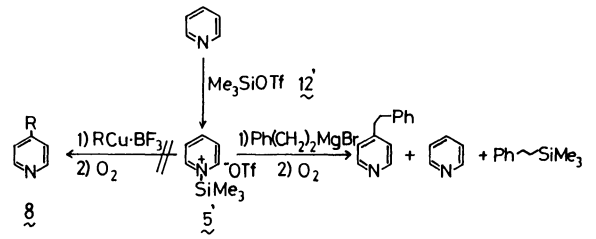
9 10 11

a: R=Br, **b**: R=CH_3OC(=O)-

On the other hand, when α-picoline was used the desired product was not obtained because the α-picolinium salt was not prepared in a pure state at 0 °C with or without solvent and a dark brown viscous oil was gradually produced. It was reported that the α-picolinium salt can be prepared below −20 °C and used for the reaction with a Grignard reagent in the presence of CuI, although the yields were low.[9]

Regioselective Synthesis of 4-Alkylpyridines by Method B. In the regioselective synthesis of 4-alkylpyridines *via* Method A, the total yield was not so high as desired due to the moderate yield in the oxidation step. We now describe a more facile and handy method for the regioselective synthesis of 4-alkylpyridines using Grignard reagents as the nucleophile and a silyl triflate as a quaternizing reagent. The silyl group is electron-donating and the resulting 1,4-dihydropyridines can be oxidized more easily.

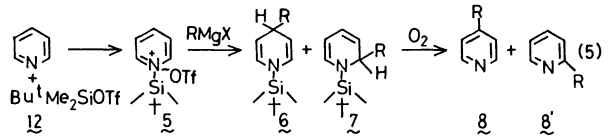
The reaction of pyridine with trimethysilyl chloride was carried out first, however, the corresponding pyridinium salt was not obtained under several conditions since the chloride anion seemed to attack the silicon to dissociate the pyridinium salt. Trimethylsilyl trifluoromethanesulfonate (**12'**) was then used as a quaternizing reagent because trifluoromethanesulfonate anion has a low nucleophilicity. The reaction of pyridine with **12'** in CH_2Cl_2 at 0 °C afforded the trimethylsilylpyridinium triflate (**5'**) as a white solid after removal of the solvent. When **5'** was allowed to react with a couple of $RCu \cdot BF_3$ in THF, no desired product was obtained after the oxidation procedure and pyridine was recovered. This result suggests that the trimethylsilyl group does not activate the pyridinium moiety sufficiently, compared to the ethoxycarbonyl group, for $RCu \cdot BF_3$ to add to **5'**. Phenethylmagnesium bromide in THF was then added to a suspension of **5'** in THF at room temperature. After oxidative work-up phenethylpyridine was obtained in 29% yield where the ratio of the 4- to 2-derivative was 99 to 1. Trimethylphenethylsilane and pyridine were the major products.



8 5'

Scheme 2.

Since reaction of *t*-butyldimethylsilyl chloride with nucleophiles is 10^4 times slower relative to trimethylsilyl chloride,[13] we used *t*-butyldimethylsilyl triflate (**12**) as a quaternizing reagent. When *t*-butyldimethylsilylpyridinium triflate (**5**), prepared from **12** and pyridine, was reacted with phenethylmagnesium bromide followed by oxidation of **6** and **7** using oxygen, 4- and 2-phenethylpyridines were obtained (67%, **8c**:**8'c**= 98.9:1.1). The reaction of various Grignard reagents with **5** was attempted and some of results are summarized in Table 3.



12 5 6 7 8 8'

When the entire process is carried out in one-pot, *i.e.*, oxygen was bubbled through a mixture of THF and aq $NaHCO_3$ solution, the yields of 4-alkylpyridines were 10—20% lower than the results shown in Table 3.

It should be noted that there is definitely a limitation to this method depending on the nature of the nucleophiles. When butyllithium was used instead of butylmagnesium bromide, the total yield of butylpyridine was 58% according to the standard procedure and the ratio of 4- to 2-substitution was 85 to 15, showing poorer selectivity. The lithium enolate of acetophe-

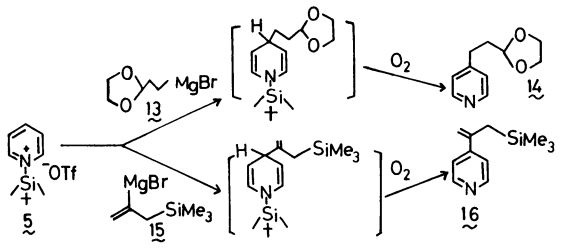
Table 3. Regioselective synthesis of 4-alkylpyridines (**8**)

	R	Yield (%)	Ratio (**8** : **8'**)[4]
a	$CH_3(CH_2)_3$-	68[1] (79)[3]	99.6 : 0.4
b	$CH_3(CH_2)_5$-	62[1] (72)[3]	99.5 : 0.5
c	$PhCH_2CH_2$-	64[2] (71)[3]	98.9 : 1.1
d	CH_3CH_2(CH$_3$)CH-	58[1] (72)[3]	98.8 : 1.2
e	Ph-	59[2] (73)[3]	99.7 : 0.3
f	$CH_3(CH_2)_2$-	61[1] (78)[3]	99.4 : 0.6
g	CH_3(CH_3)CH-	65[1] (73)[3]	99.0 : 1.0
h	$CH_3(CH_2)_4$-	63[1] (75)[3]	99.5 : 0.5
i	$CH_3(CH_2)_7$-	69[1] (78)[3]	99.7 : 0.3

1) Isolated yield based on pyridine after Kugelrohr distillation. 2) Isolated yield after TLC (SiO_2, $MeCO_2Et$) purification. 3) Yield after ether extraction (pure by ^1H NMR). 4) Determined by GLC (5% Apiezon Grease L on Chromosorb WAW DMCS, 150—200 °C).

none and Grignard type reagent of 2-mercaptoacetate attacked the silicon of **5** almost exclusively. On the other hand, no reaction took place with **5** when dibutylboron enolate and trimethylsilyl enol ether of acetophenone and the Reformatzky reagent of ethyl bromoacetate were used.

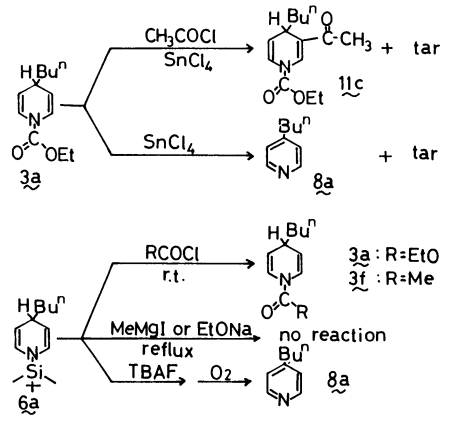
We also applied this reaction to introduce functional groups other than alkyl and aryl groups into the 4-position of the pyridine ring. First, the reaction of **5** with the Grignard reagent **13**, prepared from 2-bromopropionaldehyde ethylene acetal, afforded 3-(4-pyridyl)propionaldehyde ethylene acetal (**14**) in 50% yield after oxidation under a stream of oxygen followed by purification. In a similar fashion, **5** reacted with 1-(trimethylsilylmethyl)vinylmagnesium bromide[14] (**15**) to give **16** in 38% yield after standard work-up. Thus, it was demonstrated that almost any Grignard reagent containing some functional group can be introduced selectively at the 4-position of pyridine.



Scheme 3.

Attempted Reactions of 1,4-Dihydropyridines as Enamines. Since 1-ethoxycarbonyl-1,4-dihydropyridines (**3**) can be obtained easily after distillation and 1-*t*-butyldimethylsilyl-1,4-dihydropyridines (**6**) can be generated *in situ* in high yield, we investigated their use as enamines to introduce a second substituent into the 3-position. There is only one such a report by Shōno *et al.* where the Vilsmeier reaction of 1-methoxycarbonyl-1,4-dihydropyridine gave 3-formyl-1-methoxycarbonyl-1,4-dihydropyridine in 75% yield.[15] When acetylation of **3a** was carried out in dichloromethane at −78 °C in the presence of a ten molar excess of acetyl chloride and tin tetrachloride, the expected **11c** was obtained in 21% yield after separation by flash column chromatography. Although **11c** gave correct ^{1}H NMR and IR spectra, it gradually deteriorated under careful handling. At r.t., **3a** was oxidized by tin tetrachloride to **8a** in low yield (*ca.* 30%) together with tarry material.

Since the silyl group is electron-donating, acylation of **6a** generated *in situ* by Method B was attempted. However, exchange of the silyl group for the acyl group occurred unexpectedly in moderate yield (R=EtO, 57%; R=Me, 65%).[16] Although the mechanism of this exchange is not clear, electron transfer from **6a** to the acylating reagent may take place at the initial stage of the reaction, because nucleophilic attack at the N–Si bond should not take place due to the steric effects of the silyl group as exemplified by the inertness of the bond to methylmagnesium iodide and sodium ethoxide. Desilylation by TBAF (tetrabutylammonium fluoride) took place to give **8a** in high yield after usual work-up in the air.



Scheme 4.

Experimental

Infrared spectra were recorded with a Hitachi 215 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian T-60 spectrometer and chemical shifts (δ) were reported in ppm using internal tetramethylsilane. Mass spectra were measured with a Hitachi RMU-6L spectrometer. Boiling points quoted for products distilled in a Kugelrohr apparatus refer to the oven temperature. Melting points were measured using a Yanagimoto micro melting point apparatus and are uncorrected. GLC was performed with a Yanagimoto gas chromatograph G-180 equipped with a 3.0 m×4 mm column, packed with 5% Apiezon Grease L on Chromosorb WAW DMCS. Merck 230—400 mesh silica gel (art 9385) was used for flash column chromatography. All reactions were carried out under a nitrogen atmosphere using syringe and septum techniques.[17] THF and diethyl ether were freshly distilled from Na/benzophenone. Pyridine, α-picoline, and alkyl halides were distilled from CaH_2 under nitrogen. Ethyl chloroformate and boron trifluoride etherate were used after simple distillation under nitrogen. Trimethylsilyl chloride was used after distillation in the presence of a small amount of quinoline. Trimethylsilyl triflate and *t*-butyldimethylsilyl triflate were prepared according to the literature.[18] Butyllithium in hexane was carefully standardized prior to use.

Preparation of 4-Alkyl-1-ethoxycarbonyl-1,4-dihydropyridines (3) by the Reaction of 1-Ethoxycarbonylpyridinium Chloride (2) with RCu·BF$_3$. Method A. 4-Butyl-1-ethoxycarbonyl-1,4-dihydropyridine (3a). General Procedure: Butylmagnesium bromide, prepared from butyl bromide (1.90 ml, 17.6 mmol) and magnesium (0.43 g, 17.6 mmol) in THF (30 ml), was added to a suspension of CuI (3.36 g, 17.6 mmol) in THF (60 ml) at −20 °C under nitrogen through a double-ended needle and the mixture was stirred for 10 min at that temperature. The mixture was then cooled to −78 °C and $BF_3 \cdot OEt_2$ (2.17 ml, 17.6 mmol) was added slowly. After stirring for 10 min at −78 °C, the resulting dark brown mixture was transferred through a double-ended needle to a suspension of the pyridinium salt, which was prepared from pyridine (1.22 ml, 15.0 mmol) and ethyl chloroformate (1.44 ml, 15.0 mmol) in THF (60 ml) at 0 °C, and the mixture was allowed to warm to room temperature with stirring. The color changed from dark brown to dark gray. After the reaction mixture was stirred for 3 h at room temperature, aq 5% $NaHCO_3$ (100 ml) was added and the THF was evaporated under reduced pressure. The following procedure must be carried out quickly because the 1,4-dihydropyridine is easily oxidized. The product was extracted with ether (30 ml×3) and the solvent was evaporated under reduced pressure after drying ($MgSO_4$). The

crude product was purified by Kugelrohr distillation to afford 4-butyl-1-ethoxycarbonyl-1,4-dihydropyridine (2.80 g) in 89% yield. bp 125—135 °C/1.0 mmHg (by Kugelrohr distillation); ^{1}H NMR ($CDCl_3$) δ=0.60—1.50 (m, 12H), 2.72—3.10 (m, 1H), 4.19 (q, 2H, J=7 Hz), 4.77 (br. dd, 2H, J=8, 3 Hz), and 6.79 (br. d, 2H, J=8 Hz); IR (neat) 2940, 1720, 1690. 1635, 1470, 1415, 1400, 1375, 1335, 1310, 1210, 1120, 970, 950, 760, and 740 cm^{-1}; MS (m/z) 209 (M^+, 14.7%), 152 (100), 135 (32.2), 108 (58.0), and 83 (76.7); Ratio: **3a**/**4a**=99.5/0.5 (by GLC analysis); Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69%; Found: C, 68.60; H, 9.45; N, 6.61%.

*1-Ethoxycarbonyl-4-hexyl-1,4-dihydropyridine (**3b**).* Yield 81%; bp 140—165 °C/0.15 mmHg (by Kugelrohr distillation); ^{1}H NMR ($CDCl_3$) δ=0.90—1.70 (m, 16H), 2.76—3.10 (m, 1H), 4.11 (q, 2H, J=7 Hz), 4.81 (br. dd, 2H, J=8, 3 Hz), and 6.74 (br. d, 2H, J=8 Hz); IR (neat) 2930, 1720, 1690, 1635, 1465, 1415, 1395, 1375, 1335, 1310, 1205, 1110, 955, 760, 740 cm^{-1}; Ratio: **3b**/**4b**=99.7/0.3 (by GLC analysis).

*1-Ethoxycarbonyl-4-phenethyl-1,4-dihydropyridine (**3c**).* Yield 81%; bp 140—150 °C/0.50 mmHg (by Kugelrohr distillation); ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7 Hz), 1.50—1.90 (m, 2H), 2.40—2.80 (m, 2H), 2.80—3.20 (m, 1H), 4.22 (q, 2H, J=7 Hz), 4.84 (br. dd, 2H, J=8, 3 Hz), 6.79 (br. d, 2H, J=8 Hz), and 7.17 (s, 5H); IR (neat) 2940, 1730, 1635, 1400, 1380, 1340, 1315, 1215, 1120, 960, 740, and 700 cm^{-1}; Ratio: **3c**/**4c**=100/0 (by GLC analysis).

*4-s-Butyl-1-ethoxycarbonyl-1,4-dihydropyridine (**3d**).* Yield 83%; bp 115—125 °C/0.35 mmHg (by Kugelrohr distillation); ^{1}H NMR ($CDCl_3$) δ=0.60—1.60 (m, 12H), 2.85—3.13 (m, 1H), 4.21 (q, 2H, J=7 Hz), 4.77 (br. dd, 2H, J=8, 3 Hz), and 6.80 (br. d, 2H, J=8 Hz); IR (neat) 2950, 1720, 1690, 1635, 1465, 1415, 1330, 1310, 1210, 1110, 975, 760, and 730 cm^{-1}; Ratio: **3d**/**4d**=99.7/0.3 (by GLC analysis).

*1-Ethoxycarbonyl-4-phenyl-1,4-dihydropyridine (**3e**).* Yield 94%; bp 185—195 °C/0.70 mmHg (by Kugelrohr distillation); ^{1}H NMR ($CDCl_3$) δ=1.29 (t, 3H, J=7 Hz), 4.25 (q, 2H, J=7 Hz), 4.10—4.30 (m, 1H), 4.89 (br. dd, 2H, J=8, 3 Hz), 6.85 (br. d, 2H, J=8, 3 Hz), and 7.10—7.60 (m, 5H); IR (neat) 2980, 1720, 1690, 1630, 1415, 1375, 1335, 1310, 1205, 1115, 980, 840, 725, and 695 cm^{-1}; Ratio: **3e**/**4e**=99.0/1.0 (by GLC analysis).

*The Conversion of **3** into 4-Alkylpyridine (**8**). 4-Butylpyridine (**8a**). General Procedure*: The dihydropyridine (**3a**: 0.338 g, 1.62 mmol) was placed in a flask under an atmosphere of oxygen without solvent. Stirring was continued until TLC analysis indicated that the starting material was consumed (*ca.* for 6 h). Aqueous 5 M HCl (1 M=1 mol dm^{-3}) was added to the mixture until a pH of 2 was obtained and the organic layer was extracted with water (20 ml×3). The acidic solution was then treated with aqueous 3M NaOH until a pH of 11 was obtained. The product was extracted with CH_2Cl_2 (50 ml×2) and the extracts were dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and distilled by Kugelrohr to give 0.149 g (68%) of 4-butylpyridine (**8a**), which gave correct elemental analysis. Bp 90—100 °C/12 mmHg (lit,[20] bp 98 °C/20 mmHg).

*4-Hexylpyridine (**8b**).* Yield 66%; bp 120—140 °C/18 mmHg (by Kugelrohr distillation) (lit,[9] bp 130—132 °C/16 mmHg).

*4-Phenethylpyridine (**8c**).* Yield 55%; mp 68.5—70.0 °C (from hexane); (lit,[21] mp 70—71 °C).

*4-s-Butylpyridine (**8d**).* Yield 38%; bp 125—145 °C/25 mmHg (by Kugelrohr distillation) (lit,[22] bp 90—150 °C/20 mmHg; bp 194—195 °C/740 mmHg).

*4-Phenylpyridine (**8e**).* Yield 59%; mp 75.5—76 °C (lit,[9]mp 73—74 °C).

*Preparation of 4-Alkylpyridines (**8**) by the Reaction of the N-Silylpyridinium Salts (**5**) with Grignard Reagent: Method B. 4-Butylpyridine (**8a**). General Procedure*: A solution of pyridine (0.38 ml, 4.70 mmol) in CH_2Cl_2 (5 ml) was cooled to 0 °C and *t*-butyldimethylsilyl triflate (**12**) (1.24 ml, 4.69 mmol) was added. After stirring for 5 min, the solvent was evaporated under reduced pressure to give the pyridinium salt as a white solid. The pyridinium salt can be also prepared without solvent. THF (7 ml) was added to the pyridinium salt and then cooled to ice bath temperature. Butylmagnesium bromide, prepared from butyl bromide (0.62 ml, 5.77 mmol) and magnesium (0.14 g, 5.76 mmol) in THF (20 ml), was added to a suspension of the pyridinium salt and the mixture was stirred for 2—3 h at room temperature under a nitrogen atmosphere. The crude product, which contained 20—40% of 4-butylpyridine due to air-oxidation, was obtained by ether extraction (15 ml×3) after quenching the mixture with 5% aq $NaHCO_3$ (30 ml). The mixture of crude product was placed in a flask and stirred for 3 h under an atmosphere of oxygen. The method of purification was the same as described for the synthesis of 4-alkylpyridine from 4-alkyl-1-ethoxycarbonyl-1,4-dihydropyridine (**3**). 4-Butylpyridine was obtained in 68% yield (**8a**:**8′a**=97.6:0.4, by GLC analysis). Overall yields of 4-alkylpyridines and ratios (4-alkylpyridine/2-alkylpyridine) were

*Hexylpyridine (**8b**).* :62% :99.5/0.5
*Phenethylpyridine (**8c**).* :64% :98.9/1.1
*s-Butylpyridine (**8d**).* :58% :98.8/1.2
*Phenylpyridine (**8e**).* :59% :99.7/0.3
*Propylpyridine (**8f**).* :61% :99.4/0.6

bp 70—85 °C/18 mmHg (by Kugelrohr distillation) (lit,[20] bp 80 °C/20 mmHg).

*s-Propylpyridine (**8g**).* :65% :99.0/1.0

bp 170 °C (by Kugelrohr distillation) (lit,[23] bp 173 °C).

*Pentylpyridine (**8h**).* :63% :99.5/0.5

bp 110—122 °C/15 mmHg (by Kugelrohr distillation) (lit,[20] bp 114 °C/20 mmHg).

*Octylpyridine (**8i**).* :69% :99.7/0.3

bp 103—115 °C/1 mmHg (by Kugelrohr distillation) (lit,[20] bp 91 °C/0.1 mmHg).

*3-(4-Pyridyl)propionaldehyde Ethylene Acetal (**14**).* Yield 50%; ratio: 4-substituted pyridine (**14**)/2-substituted pyridine (**14′**)=98.3/1.7; ^{1}H NMR (CCl_4) δ=1.69—2.12 (m, 2H), 2.52—2.88 (m, 2H), 3.68—4.03 (m, 4H), 4.76 (t, 1H, J=4.5 Hz), 7.01 (dd, 2H, J=4, 2 Hz), and 8.33 (dd, 2H, J=4, 2 Hz); IR (neat) 1605, 1410, 1135, and 1025 cm^{-1}.

*2-(4-Pyridyl)-3-trimethylsilyl-1-propene (**16**).* Yield 38%; ^{1}H NMR (CCl_4) δ=−0.07 (s, 9H), 1.98 (s, 2H), 4.95 (d, 1H, J=1 Hz), 5.25 (d, 1H, J=1 Hz), 7.17 (dd, 2H, J=5, 1.5 Hz), and 8.43 (dd, 2H, J=5, 1.5 Hz); IR (neat) 2960, 1595, 1405, 1245, 845, and 825 cm^{-1}.

Introduction of a Butyl Group into the 4-Position of 3-Substiteud Pyridines (3-Bromopyridine, Methyl nicotinate). The procedure for the synthesis of these compounds was the same as described above in the synthesis of 4-alkylpyridines by Method A.

*3-Bromo-4-butyl-1-ethoxycarbonyl-1,4-dihydropyridine (**11a**).* Attempts to purify **11a** by Kugelrohr distillation was not so successful as much residue was produced by polymerization during distillation. Almost pure **11a** was obtained after extraction as indicated by ^{1}H NMR in which case the yield was about 80%.

Yield 42%; bp 150—160 °C/0.5 mmHg (by Kugelrohr distillation); ^{1}H NMR ($CDCl_3$) δ=0.70—1.72 (m, 12H), 3.04—3.36 (m, 1H), 4.22 (q, 2H, J=7 Hz), 4.77 (dd, 1H, J=8, 4 Hz), 6.73 (d, 1H, J=8 Hz), and 7.07 (s, 1H).

*4-Butyl-1-ethoxycarbonyl-3-methoxycarbonyl-1,4-dihydropyridine (**11b**).* A portion of **11b** was oxidized to 4-butyl-3-methoxycarbonylpyridine during purification by flash

† 1 mm Hg≈133.322 Pa.

column chromatography.

Yield 19% (purified by flash column chromatography, SiO_2: hexane/AcOEt=9/1): ^1H NMR ($CDCl_3$) δ=0.65—1.90 (m, 12H), 3.04—3.36 (m, 1H), 3.77 (s, 3H), 4.34 (q, 2H, J=7 Hz), 5.10 (dd, 1H, J=8, 5 Hz), 6.87 (d, 1H, J=8 Hz), and 7.95 (s, 1H); IR (neat) 2960, 1730, 1710, 1625, 1470, 1400, 1375, 1330, 1230, 1175, 765, and 735 cm^{-1}.

4-Butyl-3-methoxycarbonylpyridine. Yield 12% (purified by flash column chromatography, SiO_2: hexane/AcOEt=9/1): ^1H NMR ($CDCl_3$) δ=0.75—1.85 (m, 7H), 2.98 (t, 2H, J=8 Hz), 3.94 (s, 3H), 7.17 (d, 1H, J=5 Hz), 8.42 (d, 1H, J=5 Hz), and 8.88 (s, 1H); IR (neat) 2950, 1720, 1585, 1275, and 1100 cm^{-1}.

*Reaction of 4-Butyl-1-t-butyldimethylsilyl-1,4-dihydropyridine (**6a**) with Acetyl Chloride and Ethyl Chloroformate. 1-Acetyl-4-butyl-1,4-dihydropyridine (**3f**)*: To the reaction mixture containing **6a**, prepared from **5** (2.47 mmol) and butylmagnesium bromide, was added acetyl chloride (0.23 ml, 3.23 mmol) at room temperature with stirring. After stirring for 2 h, the reaction mixture was quenched with 20 ml of 5% aqueous sodium hydrogencarbonate. The crude product was extracted with ether (15 ml×3), dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Flash column chromatography (SiO_2, hexane/AcOEt=9/1) afforded 1-acetyl-4-butyl-1,4-dihydropyridine (**3f**) in a 65% yield (0.288 g). This compound is susceptible to be oxidized by oxygen.

^1H NMR (CCl_4) δ=0.87—1.55 (m, 9H), 2.11 (s, 3H), 2.80—3.07 (m, 1H), 4.60—5.00 (m, 2H), 6.30—6.60 (m, 1H), and 6.87—7.17 (m, 1H); IR (neat): 2920, 1670, 1375, 1325, and 1310 cm^{-1}.

*4-Butyl-1-ethoxycarbonyl-1,4-dihydropyridine (**3a**).* Yield 57% (flash column chromatography: SiO_2 hexane/AcOEt=9/1), spectral data were identical to those described before.

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