in vacuo gave an oil which was chromatographed with 150 g of acid-washed CC-4 silica gel. Elution with hexane–EtOAc (3:1) gave 0.464 g of **10**, TLC (hexane–EtOAc, 4:1, containing 1% HOAc) R_f 0.28. A portion of **10** (0.291 g, 0.56 mmol) was hydrolyzed with stirring in 12 mL of HOAc–H_2O–THF (20:10:3) at 45 °C for 2 h. The solvents were removed in vacuo to afford 0.253 g of crude product. This material as chromatographed by LPLC (two Lobar B columns connected in series) with $CHCl_3$–MeOH–HOAc (1000:50:5) to yield 0.058 g of **6a** (4*E* isomer) and 0.108 g of **6** (4*Z* isomer), both as viscous colorless oils. TLC in $CHCl_3$–MeOH–HOAc (15:1:0.15) gave R_f 0.31 for **6a** and R_f 0.24 for **6**: ^{1}H NMR ($CDCl_3$; the spectra of **6a** and **6** were very similar) δ 5.70 (br s, OH's), 5.51 (m, 2 H), 5.17 (m, 1 H), 4.30–3.50 (m, 2 H), 2.75–1.10 (m, 23 H), 0.88 (t, 3 H); IR (film; the spectra of **6a** and **6** were identical) 3300–2800 (br, s), 1705, 1120, 975 cm^{-1}; mass spectrum (Me_3Si derivative), *m/e* 566 (M^+); calcd for $C_{30}H_{58}O_4Si_3$ *m/e* 566.3643, found 566.3622 (**6a**), 566.3639 (**6**).

By use of the exact same procedure as described above, reaction of **8** with (4-carboxy-*n*-butyl)triphenylphosphonium bromide gave **7a** (5*E* isomer) and **7** (5*Z* isomer). TLC in $CHCl_3$–MeOH–HOAc (9:1:0.2) gave R_f 0.52 for **7a** and R_f 0.49 or **7**: ^{1}H NMR ($CDCl_3$) for **7a** δ 6.62 (br s, OH's), 5.47 (m, 2 H), 5.10 (m, 1 H), 4.25–3.50 (m, 2 H), 2.80 (m, 25 H), 0.88 (t, 3 H); for **7** δ 6.85 (br s, OH's), 5.50 (m, 2 H), 5.12 (m, 1 H), 4.20–3.60 (m, 2 H), 2.75–1.10 (m, 25 H), 0.88 (t, 3 H); IR (film; the spectra of **7a** and **7** were identical) 3300–2800 (br, s), 1705, 1120, 970 cm^{-1}; mass spectrum (Me_3Si derivative), *m/e* 570 (M^+, weak); calcd for $C_{30}H_{57}O_4Si_3$ ($M^+ - CH_3$) *m/e* 565.3364, found 565.3550 (**7a**), 565.3552 (**7**).

Registry No. **6**, 82933-66-2; **6** TMS, 82933-67-3; **6a**, 82977-35-3; **6a** TMS, 82977-36-4; **7**, 71934-99-1; **7** TMS, 82933-68-4; **7a**, 71963-53-6; **7a** TMS, 82977-37-5; **8**, 82933-69-5; **9**, 82933-70-8; **9** TMS, 82933-71-9; (*E*)-**10**, 82933-72-0; (*Z*)-**10**, 82977-38-6; (*E*)-**11**, 82933-73-1; (*Z*)-**11**, 82977-39-7; **12**, 37435-65-7; **13**, 82933-74-2; **14**, 82933-75-3; **15**, 82933-76-4; **16**, 82933-77-5; **17**, 82951-10-8; **18**, 82933-78-6; **18** (9β epimer), 82977-40-0; **18** benzenesulfonate, 82933-79-7; **19**, 82951-11-9; **20**, 82933-80-0; **21**, 82933-81-1; (3-carboxypropyl)triphenylphosphonium bromide, 17857-14-6; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6.

Regioselective Addition of Grignard Reagents to 1-Acylpyridinium Salts. A Convenient Method for the Synthesis of 4-Alkyl(aryl)pyridines

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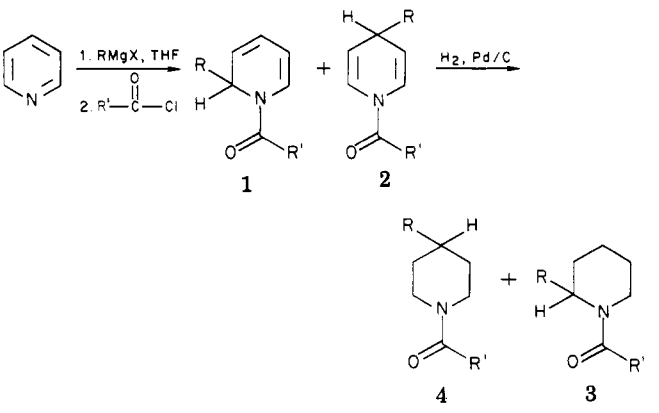
Received April 22, 1982

The addition of Grignard reagents to 1-acylpyridinium salts afforded 1-acyl-2-alkyl(aryl)-1,2-dihydropyridines and 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines. The regioselectivity of this reaction, 1,2- vs. 1,4-addition, was examined and found to be dependent upon the structures of the Grignard reagent and the 1-acyl group. Pyridine, 2-picoline, and 3-picoline were studied, and in most cases, significant amounts of 1,4-addition occurred. When a catalytic amount of cuprous iodide was present, nearly exclusive 1,4-addition resulted. The crude 1,4-dihydropyridines were aromatized by heating with sulfur to provide 4-substituted pyridines and picolines in good yield and high isomeric purity.

The synthesis of substituted pyridines by the reaction of Grignard reagents and pyridine is not a practical method due to the strenuous conditions required for addition, the low yields obtained, and frequent lack of regioselectivity.[1] To obtain high yields of addition with Grignard reagents, activation of the pyridine ring is necessary. Fraenkel and co-workers[2] reported that the pyridine ring could be readily attacked by Grignard reagents in the presence of ethyl chloroformate to provide 2-substituted 1-(ethoxycarbonyl)-1,2-dihydropyridines. Lyle and co-workers[3] elaborated on this method by demonstrating that acid chlorides (e.g., acetyl chloride and benzoyl chloride) are also effective in activating the pyridine ring toward attack by Grignard and organocadmium reagents. The intermediate 1,2-dihydropyridines can be readily oxidized by heating with sulfur to provide 2-substituted pyridines in good yield.[4] The reaction of Grignard reagents with 1-acylpyridinium salts appeared from examination of the literature to form preferentially 1,2-dihydropyridines by attack at the 2-position of the pyridine ring. However, the degree of regioselectivity was unclear since 4-alkylpyridines, in which the 4-position is blocked, were used as starting material in most of the reactions studied thus far.[2-4] It was therefore of interest to study the regioselectivity of this reaction with regard to how the structures of the acyl halide and Grignard reagent influence the de-

Scheme I



(1) (a) Goetz-Luthy, N.; *J. Am. Chem. Soc.* **1949**, *71*, 2254. (b) Bryce-Smith, D.; Morris, P. J.; Wakefield, B. J. *Chem. Ind. (London)* **1964**, 495. (c) Doering, W. v. E.; Pasternak, V. Z. *J. Am. Chem. Soc.* **1950**, *72*, 143. (d) Benkeser, R. A.; Holton, D. S. *Ibid.* **1951**, *73*, 5861.

(2) Fraenkel, G.; Cooper, J. W.; Fink, C. M. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 523.

(3) Lyle, R. E.; Marshall, J. L.; Comins, D. L. *Tetrahedron Lett.* **1977**, 1015.

(4) Lyle, R. E.; Comins, D. L. *J. Org. Chem.* **1976**, *41*, 3250.

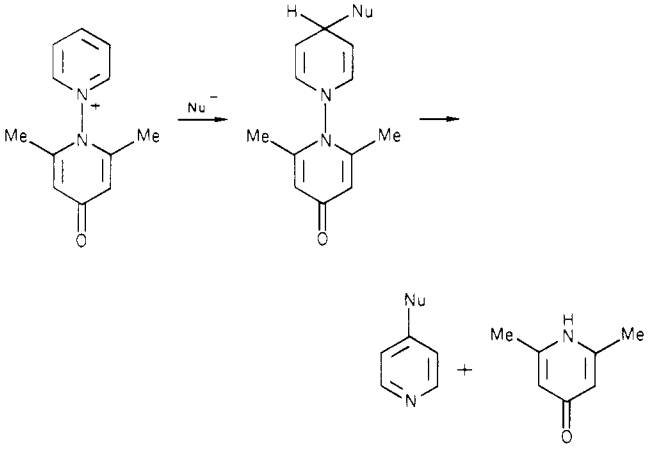
0022-3263/82/1947-4315$01.25/0

gree of 1,2- vs. 1,4-addition. We also studied the effect of a catalytic amount of cuprous iodide on the regioselectivity, since Piers and Soucy[5] (1974) reported that lithium dialkylcuprates and pyridine in the presence of methyl chloroformate gave mainly 1,4-dihydropyridines.

Results and Discussion

The 1-acyldihydropyridines **1** and **2** were prepared by the reaction of a Grignard reagent and pyridine (1.5 equiv) in the presence of an acyl chloride in tetrahydrofuran (THF) at −20 °C. The reaction could be performed by adding the acyl chloride to a mixture of the Grignard reagent and pyridine in THF (method A) or the Grignard reagent could be added dropwise to the preformed 1-acylpyridinium salt in THF (method B). The reaction of pyridine with an acyl chloride is very rapid and allows for the use of method A without significant competition from the reaction of the Grignard reagent and the acyl chloride.[3] The crude dihydropyridines **1** and **2** were immediately reduced to their piperidine derivatives **3** and **4** via catalytic hydrogenation and the ratio of isomers were determined by GC (see Scheme I). The results of this study are given in Table I.

With the exception of two examples, entries d and e, significant amounts of 1,4-addition occurred. The amount of attack at the 4-position is clearly dependent upon the degree of steric hindrance at the 2-position. The larger the N-substituent and Grignard reagent, the more 1,4-addition occurs. This is consistent with previous findings in the literature. For example, Katritzky and co-workers[6] recently reported that the 1-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salt **5** is attacked at the 4-position by Grignard reagents and other nucleophiles. The nitrogen substituent sterically shields the 2-position while activating the 4-position to nucleophilic attack.



Our results show that due to a lack of regioselectivity the reacton of Grignard reagents with 1-acylpyridinium chlorides is limited in scope with regard to the synthesis of 2-alkylpyridines. However, the method may be valuable for the preparation of 2-arylpyridines since aryl Grignard reagents appear to have a greater preference for attack at the 2-position than their aliphatic counterparts. The method is useful for the preparation of 2-substituted 4-alkylpyridines where the 4-position of the original pyridine is blocked to attack.[4] This preparation has some advantages over the synthesis of 2-substituted pyridines via the addition of lithium reagents to pyridines. The Grignard reagents are more conveniently prepared from their halide precursors, and often in higher yield, than the corresponding lithium reagents. In addition, the strong basic and nucleophilic properties of lithium reagents limit the variety of functionality that can be present on the pyridine ring during the reaction. In the reaction utilizing Grignard reagents and 1-acylpyridinium salts, the pyridine ring is so activated that addition to the ring will occur in the presence of other reactive functional groups such as ketones[3] and esters.[7] For example, treatment of the ethoxycarbonyl salt of **6** with *o*-tolylmagnesium bromide, followed by aromatization of the intermediate dihydropyridine with sulfur, gave pyridine **7** in 68% yield. The product's (**7**) isomeric purity was greater than 95%, thus demonstrating regioselectivity as well as chemeoselectivity in the addition step.[7]

Table I. Conversion of Pyridine to Piperidine Derivatives 3 and 4

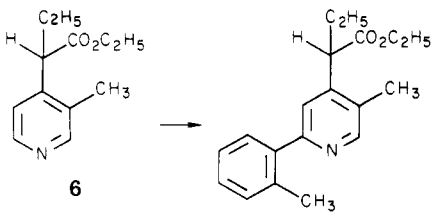
entry	RMgX	acyl chloride (R′)	overall yield,[a] %	ratio (3/4)[b]
a	C_2H_5MgBr	CH_3	76	70:30
b	C_2H_5MgBr	C_2H_5O	73	64:36
c	C_2H_5MgBr	$(CH_3)_3C$	73	52:48
d	C_6H_5MgCl	CH_3	70	93:7
e	C_6H_5MgCl	C_2H_5O	80	93:7
f	C_6H_5MgCl	C_6H_5	77	73:27
g	C_6H_5MgCl	$(CH_3)_3C$	66	52:48
h	$(CH_3)_2CHMgCl$	CH_3	56	51:49
i	$(CH_3)_2CHMgCl$	C_2H_5O	82	41:59
j	$(CH_3)_2CHMgCl$	$(CH_3)_3C$	80	13:87

[a] Yield of purified product mixtures isolated by bulb-to-bulb distillation. All product mixtures exhibited the expected ^1H NMR and IR spectra as compared to authentic samples prepared by standard methods. [b] Ratio determined by GC analysis.

Table II. The Effect of 5% CuI on the Grignard Reaction (See Scheme I)

RMgX[a]	acyl chloride (R′)	overall yield,[b] %	ratio (3/4)[c]
C_6H_5MgCl	CH_3	65	0:100
C_2H_5MgBr	C_2H_5O	79	5.3:94.7
C_2H_5MgBr	C_6H_5	30	0:100
$(CH_3)_2CHMgCl$	C_2H_5O	62	1.6:98.4

[a] The reactions were performed on a 20-mmol scale, using method B (inverse addition). [b] Yield of purified product mixtures isolated by bulb-to-bulb distillation. [c] Ratio determined by GC.



Synthesis of 4-Substituted Pyridines. As mentioned earlier, the work of Piers and Soucy[5] with lithium dialkylcuprates prompted us to examine the effect of CuI on the regioselectivity of the Grignard addition step. The reactions were performed the same as in the previous study

(5) Piers, E.; Soucy, M. *Can. J. Chem.* **1974**, *52*, 3563.
(6) (a) Katritzky, A. R.; Beltrami, H.; Keay, J. G., Rogers, D. N.; Sammes, M. P.; Leung, C. W. G.; Lee, C. M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 792. (b) Katritzky, A. R.; Keay, J. G.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 668. (c) See ref 18b.
(7) Comins, D. L. Ph.D. Thesis, University of New Hampshire, Durham NH, 1977.

Table III. A Convenient Synthesis of 4-Substituted Pyridines 10a (See Scheme II)

R'MgX	overall yield,[a] %	ratio (10a:11a)[e]	obsd bp/mm or mp, °C	lit. bp/mm or mp, °C	ref
n-C_4H_9MgCl	62[c]	99.1:0.9	bp 88-91/16, picrate mp 112-113	bp 98/20, picrate mp 112.8-113.8	14, 15
$C_6H_{11}MgCl$	77[c]	100:0	bp 130-132/16, picrate mp 152-153	picrate mp 154-155	16
C_6H_5MgCl[b]	62[d]	100:0[f]	mp 73-74	mp 69-70	12

[a] The reactions were performed on a 0.1-mol scale, using ethyl chloroformate and method B unless indicated. [b] Trimethylacetyl chloride and method A were utilized. [c] Yield of purified product isolated by distillation. [d] Purified by recrystallization from hexane. [e] Ratio determined by GC. [f] GC analysis was performed on recrystallized product.

Table IV. Synthesis of 4-Substituted 2-Picolines 10b (See Scheme II, R=CH_3)

entry	R'MgX	overall yield,[a] %	ratio (10b/11b)[c]	obsd bp/mm or mp, °C	lit. bp/mm or mp, °C	ref
a	C_2H_5MgCl	12[b]	91:9	b		
b	C_2H_5MgCl (5% CuI)	27	100:0	66-69/16, picrate mp 142-143	bp 179-180, picrate mp 141-142	17
c	$(CH_3)_2CHMgCl$	43[b]	95:5	b		
d	$(CH_3)_2CHMgCl$ (5% CuI)	41	100:0	74-78/16, picrate mp 129-130	98-99/40, picrate mp 131-132	18
e	C_6H_5MgCl	16[b]	49:51	b		
f	C_6H_5MgCl (5% CuI)	55	98.8:1.2	bp 150-155/16, mp 49-50, picrate mp 219-220	bp 280, mp 48, picrate mp 210-213	19

[a] The reactions were performed on a 0.1-mol scale, using method B, and the products were isolated by distillation unless indicated. [b] The reactions were performed on a 20-mmol scale and the product mixtures were isolated by bulb-to-bulb distillation. [c] Ratio determined by GC.

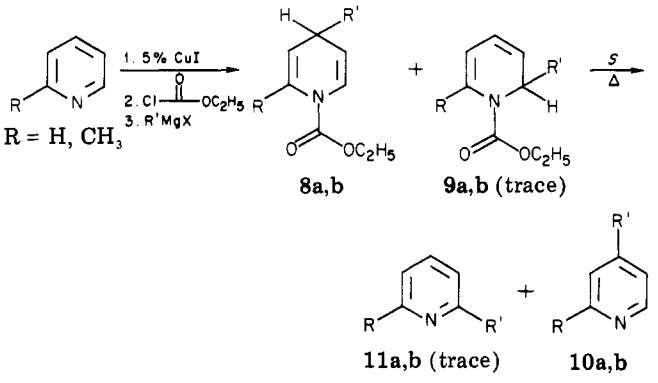
(Scheme I) except 5 mol % of CuI was added. The results are shown in Table II.

Initially method A, in which the acyl chloride was added dropwise to pyridine, Grignard reagent, and CuI in THF, was utilized. However, this method was only successful for phenylmagnesium chloride and failed with aliphatic Grignard reagents. We reasoned that the failure was probably due to the instability of the intermediate organocopper species. We circumvented this problem by utilizing method B; the Grignard reagent was added dropwise to the preformed acylpyridinium salt and CuI in THF, which allowed the organocopper intermediate to react with substrate as soom as it was formed. This procedure gave good yields with all Grignard reagents studied particularly when ethyl chloroformate was used as the acyl chloride. The added catalytic amount of CuI had a major effect on the regioselectivity, causing nearly exclusive attack at the 4-position. This result prompted us to develop a convenient synthesis of 4-substituted pyridines via the route depicted in Scheme II.

The reactions were performed on a 0.1-mol scale, using ethyl chloroformate and method B. The crude intermediate dihydropyridines **8a** and **9a** were not purified but were immediately aromatized with hot sulfur. After purification the substituted pyridines were analyzed by GC and the results are shown in Table III. These results clearly demonstrate a highly efficient and practical synthesis of 4-substituted pyridines. The experimental process is convenient and amenable to large-scale preparation. During the course of this study a communication appeared reporting a similar synthesis utilizing stoichiometric organocopper reagents (e.g., RCu, RCu·BF_3).[8]

The success of the above method encouraged us to examine the analogous reactions with 2-picoline and 3-picoline. The results of a study of the Grignard reaction with 2-picoline (Scheme II, R=CH_3), with and without added CuI, are given in Table IV. The overall yields were somewhat lower than the corresponding reactions with

Scheme II



pyridine, but the degree of regioselectivity when 5% CuI was present is virtually 100%. Since 2-picoline has one less reactive α position than pyridine, one would anticipate, based on a probability factor, a higher ratio of 4-substituted product for those reactions performed in the absence of CuI. Comparison of the data in Table IV (entries a, c, and e) with the analogous examples in the pyridine series (Table I, entries b, e, and h) shows that this is indeed the case.

The 3-picoline series is partiularly interesting in that three regioisomers are formed, and 2-, 6-, and 4-isomers (see Scheme III), and the ratio of those isomers (**12**/**13**/**14**) gives an indication of the degree that the 3-methyl group directs the nucleophilic attack. The directing ability of a 3-methyl group on a pyridine ring is well-established. The usual orientation of addition of organometallics to a 3-alkylpyridine is at the 2-position and not at the less hindered 6-position. The reactions of phenyllithium with 3-picoline,[9] 3-alkyl-1-ethoxypyridinium bromides with

(8) Akiba, K-Y.; Iseki, Y.; Wada, M. *Tetrahedron Lett.* **1982**, 429.

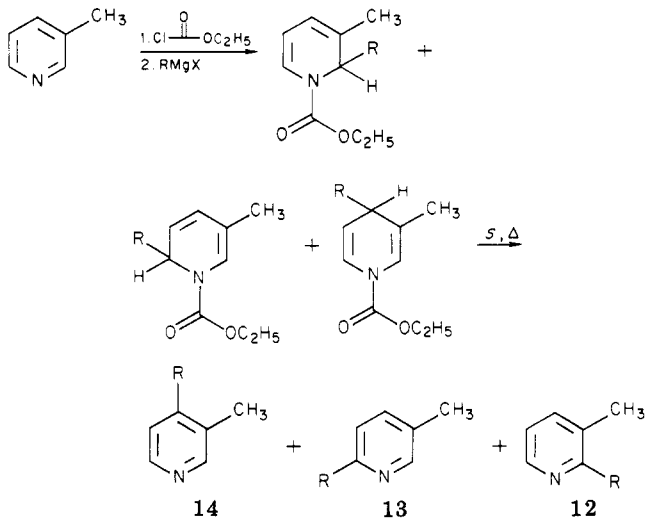
(9) (a) Abramovitch, R. A.; Singer, G. M. "Pyridine and its Derivatives"; Abramovitch, R. A., Ed.; Wiley-Interscience: New York, 1974; Vol. 14, Part 1, p 50. (b) Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, *6*, 229. (c) Abramovitch, R. A.; Giam, C. S. *Can. J. Chem.* **1969**, *42*, 1627.

Table V. Synthesis of 4-Substituted 3-Picolines (See Scheme III)

entry	RMgX	overall yield,[a] %	ratio (12/13/14)[c]	obsd bp/mm or mp, °C	lit. bp/mm or mp, °C	ref
a	C_2H_5MgCl	49[b]	40:7:53	b		
b	C_2H_5MgCl (5% CuI)	68	2:1:97	bp 77–78/16, picrate mp 144–145	bp 192–193, picrate mp 144–145	20
c	$(CH_3)_2CHMgCl$	59[b]	2:3:95	b		
d	$(CH_3)_2CHMgCl$ (5% CuI)	60	0.2:0.5:99.3	bp 85–88/16, picrate mp 117–118, d	picrate mp 107–108	18b
e	C_6H_5MgCl	74[b]	19:66:15	b		
f	C_6H_5MgCl (5% CuI)	67	3:5:92	bp 144–146/16, picrate mp 162–163, d	bp 195–198/60, picrate mp 167–168	18b, 21

[a] The reactions were performed on a 0.1-mol scale, using method B, and the products were isolated by distillation unless indicated. [b] The reactions were performed on a 20-mmol scale and the product mixtures were isolated by bulb-to-bulb distillation. [c] Ratio determined by GC. [d] ^1H NMR spectrum was identical with the reported spectrum of this compound.[18b]

Scheme III



Grignard reagents,[10] and 3,4-lutidine methiodide with benzylmagnesium chloride[11] all give mainly or exclusively 2-substitution. This "ortho" effect is probably related to London forces.[9] The results of our study with 3-picoline are given in Table V. The example where ethylmagnesium chloride was utilized (entry a) clearly shows an "ortho" effect. The ratio of α to γ substitution was 47:53 with the ratio of α-substituted products, the 2- and 6-isomers (**12** and **13**), being 86:14 in favor of the more hindered 2-substituted isomer (**12**). When larger Grignard reagents were utilized, e.g., isopropyl- and phenylmagnesium halides, 6-substitution predominated over 2-substitution. This is in agreement with the results reported for the reaction of aryl Grignard reagents with 1-alkoxycarbonyl salts of 3,4-lutidine.[4] The ratio of α to γ substitution with phenylmagnesium chloride (entry e) was 85:15, thus demonstrating again the affinity of phenylmagnesium halide for the α position of the pyridine ring. In the presence of 5% CuI, all examples (entries b, d, and f) gave 4-substituted 3-picolines of high isomeric purity.

In summary, the addition of Grignard reagents to 1-acylpyridinium chlorides as a route for preparing substituted pyridines has been examined in detail. With the possible exception of preparing 2-arylpyridines, the method is not practical for the synthesis of most 2-substituted 4-unsubstituted pyridines due to the poor regioselectivity of this reaction. The addition of a catalytic amount of CuI has a pronounced effect on the regioselectivity in that exclusive or nearly exclusive 4-addition occurs. Subsequent aromatization of the crude 1,4-dihydropyridines produced gives 4-substituted pyridines of high isomeric purity. This two-step process is convenient, practical, and amenable to large-scale preparation of 4-substituted pyridines.

Experimental Section

Reactions involving organometallic reagents were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. Cuprous iodide (CuI) was obtained from the Fisher Scientific Co. and activated at 135 °C for 10 h. 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. ^1H NMR spectra were recorded on a Varian EM-360 spectrometer. Gas–liquid chromatography (GC) was performed with a Hewlett-Packard Model 5830 A gas chromatograph equipped with a 30 m × 0.25 mm FSOT column packed with 3555 OV-101.

1-Acyl-2- and -4-alkyl(aryl)piperidines (3 and 4). A solution of pyridine (30 mmol) in 30 mL of dry THF under N_2 was cooled in a dry ice/CCl_4 bath (−20 °C). A Grignard reagent (20 mmol) in THF or ether was added via syringe followed by the dropwise addition of the acyl chloride (20 mmol) in 4 mL of THF. The mixture was stirred at −20 °C for 15 min and then at room temperature for 15 min. Water (20 mL) was added followed by extraction with three 25-mL portions of ether. The combined organic phase was washed with 20-mL portions of saturated $CuSO_4$ solution, water, saturated $NaHCO_3$, and brine and then was dried ($MgSO_4$). The solution was filtered and concentrated to provide the crude 1,2- and 1,4-dihydropyridines **1** and **2** as a yellow oil. A solution of the crude oil in 50 mL of absolute ethanol was hydrogenated at room temperature and 45 psi in the presence of 0.5–2 g of 10% palladium on carbon for 8–10 h. Removal of catalyst, concentration of filtrate, and Kugelrohr distillation provided the piperidine derivatives **3** and **4**. The ratio of **3**/**4** was determined by GC analysis (see Table I). Authentic samples of **3** and **4** were prepared from the appropriate 2- or 4-substituted piperidines and acyl chlorides by standard methods.

4-Phenylpyridine. Method A. To a solution of pyridine (12.1 mL, 0.15 mol) in 200 mL of THF under N_2 was added CuI (952 mg, 5 mmol) and the mixture was stirred at room temperature until it became homogeneous. After the mixture cooled to −20 °C (dry ice/CCl_4), phenylmagnesium chloride (0.1 mol) in 50 mL of THF was added via syringe. Trimethylacetyl chloride (12.3 mL, 0.1 mol) in 10 mL of THF was added dropwise over 5 min. The mixture was stirred at −20 °C for 15 min and then at room temperature for 15 min followed by the addition of aqueous 20% NH_4Cl solution (75 mL). Ether (200 mL) was added and the organic layer was washed with 50-mL portions of 20% NH_4Cl/NH_4OH (50:50), water, 10% HCl, water, and brine. After drying ($MgSO_4$), the solution was filtered and evaporated to yield 24 g of a yellow solid. The crude yellow solid was treated with sublimed sulfur (3.2 g, 0.1 mol) at 190–200 °C for 45 min under N_2. The

(10) Cervinka, O. *Chem. Ind. (London)* **1960**, 1482.
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reaction mixture was cooled, dissolved in 150 mL of ether, and extracted with four 50-mL portions of 10% HCl. The acid extracts were washed with 50 mL of ether and concentrated under reduced pressure. The residue was treated with 100 mL of saturated K_2CO_3 solution and extracted with ether. The combined organic layer was dried (K_2CO_3/Norite), filtered, and concentrated to give 12.2 g of a light-yellow solid. The solid was recrystallized from 100 mL of hexane to provide 9.6 g (62%) of 4-phenylpyridine as white crystals: mp 73–74 °C (lit.[12] mp 69–70 °C); the NMR spectrum was identical with the published spectrum of authentic 4-phenylpyridine.[13]

4-Butylpyridine. Method B. General Procedure. In a 1-L flask equipped with an overhead stirrer were placed pyridine (12.1 mL, 0.15 mol), CuI (952 mg, 5 mmol), and 250 mL of THF under N_2. The solution was cooled to −20 °C and ethyl chloroformate (9.6 mL, 0.1 mol) was added via syringe with stirring. After 5 min, butylmagnesium bromide (0.1 mol) in 80 mL of ether was added dropwise over 10 min. The mixture was stirred for 15 min at −20 °C and then at room temperature for another 15 min. The isolation of the crude dihydropyridine intermediate was the same as described above for 4-phenylpyridine (method A). The crude dihydropyridine was aromatized with sulfur as described above except that volatiles (EtOH) were distilled from the reaction as it proceeded. The crude product (10.4 g) was vacuum distilled to give 8.4 g (62%) of 4-butylpyridine as a clear oil: bp 88–91 °C (16 mm); picrate mp 112–113 °C [lit.[14] bp 98 °C (20 mm); lit.[15] picrate mp 112.8–113.8 °C].

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Registry No. 3a, 3433-40-7; **3b**, 82902-42-9; **3c**, 82902-43-0; **3d**, 32245-98-0; **3e**, 82902-44-1; **3f**, 82902-45-2; **3g**, 82902-46-3; **3h**, 82902-47-4; **3i**, 82902-48-5; **3j**, 82902-49-6; **4a**, 82902-50-9; **4b**, 82902-51-0; **4c**, 82902-52-1; **4d**, 32245-87-7; **4e**, 82902-53-2; **4f**, 82902-54-3; **4g**, 82902-55-4; **4h**, 82902-56-5; **4i**, 82902-57-6; **4j**, 82902-58-7; **10a** (R^1 = Bu), 5335-75-1; **10a** (R^1 = Bu) picrate, 82902-59-8; **10a** (R^1 = C_6H_{11}), 13669-35-7; **10a** (R^1 = C_6H_{11}) picrate, 13742-76-2; **10a** (R^1 = Ph), 939-23-1; **10b** (R^1 = Et), 536-88-9; **10b** (R^1 = Et) picrate, 5933-90-4; **10b** (R^1 = *i*-Pr), 13854-03-0; **10b** (R^1 = *i*-Pr) picrate, 13896-39-4; **10b** (R^1 = Ph), 15032-21-0; **10b** (R^1 = Ph) picrate, 15032-22-1; **12** (R = Et), 56986-88-0; **12** (R = *i*-Pr), 72693-04-0; **12** (R = Ph), 10273-90-2; **13** (R = Et), 18113-81-0; **13** (R = *i*-Pr), 6343-58-4; **13** (R = Ph), 27012-22-2; **14** (R = Et), 20815-29-6; **14** (R = Et) picrate, 76833-16-4; **14** (R = *i*-Pr), 76160-91-3; **14** (R = *i*-Pr) picrate, 82902-60-1; **14** (R = Ph), 2052-92-8; **14** (R = Ph) picrate, 1689-41-4; CH_3COCl, 75-36-5; EtOCOCl, 541-41-3; *t*-BuCOCl, 3282-30-2; EtMgBr, 925-90-6; PhMgCl, 100-59-4; *i*-PrMgCl, 1068-55-9; EtMgCl, 2386-64-3; BuMgCl, 693-04-9; $C_6H_{11}MgCl$, 931-51-1; 2-picoline, 109-06-8; cuprous iodide, 7681-65-4; pyridine, 110-86-1; 3-picoline, 108-99-6.

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Oxazolines. 3.[1] Regioselective Synthesis of 2-(Monosubstituted phenyl) and/or Unsymmetrically 2-(Disubstituted phenyl) 2-Oxazolines by Cross-Coupling Grignard Reagents to (Haloaryl)-2-oxazolines

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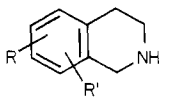
2-(Monosubstituted phenyl) 2-oxazoline **5** (R = H) and unsymmetrically 2-(disubstituted phenyl) 2-oxazolines **5** have been prepared by cross-coupling alkyl and aryl Grignard reagents to 2-(mono- and dihalogenated phenyl) 2-oxazolines **2** and **3** (X = halogen), respectively, under nickel–phosphine complex catalysis. Regioselective cross-coupling was observed with 2-(dihalogenated phenyl) 2-oxazolines **3** (X = halogen) when a halogen was ortho to the 2-oxazolinyl moiety.

We have ongoing in this laboratory an effort to develop a two-step (reduction–cyclization)[1] synthesis of pharmalogically active[2,3] unsymmetrically disubstituted tetrahydroisoquinolines **1** using unsymmetrically 2-(disubstituted phenyl) 2-oxazolines **5** as key intermediates. Con-



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