Synthesis of 4-Alkyl-3-pyridinols from 3-Benzyloxypyridine

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The addition of Grignard reagents to the 1-phenoxycarbonyl salt of 3-benzyloxypyridine and a catalytic amount of cuprous iodide afforded 4-alkyl-3-benzyloxy-1-phenoxycarbonyl-1,4-dihydropyridines in good yield. The crude dihydropyridines were aromatized with *o*-chloranil to give 4-alkyl-3-benzyloxypyridines, which were debenzylated with hydrogen and 10% palladium on carbon to provide 4-alkyl-3-pyridinols.

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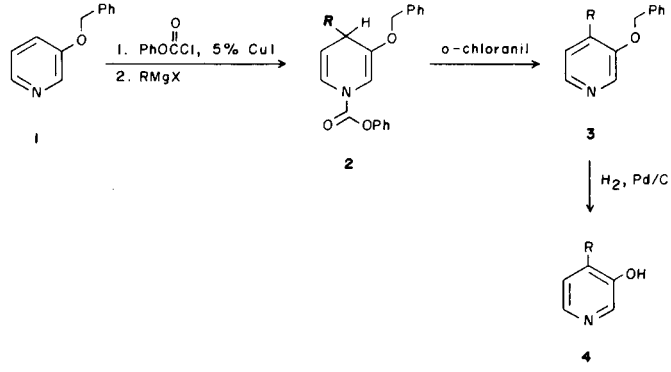
The copper-catalyzed reaction of Grignard reagents with 1-acylpyridinium salts has been utilized for the synthesis of 4-alkyl(aryl)pyridines [1a], 4-aryl-3-bromopyridines [1b], 4-alkyl-3-halopyridines [1c], 4-substituted methyl nicotinates [1d], 4-alkyl-3-pyridinecarboxaldehydes [1c], 4-alkyl-3-acylpyridines [1e], and 2,4-disubstituted pyridines [1f]. To determine if the scope of this pyridine synthesis could be expanded to include the preparation of substituted pyridinols, we investigated the copper-catalyzed Grignard addition to the 1-phenoxycarbonyl salt of 3-benzyloxypyridine.

Although 3-benzyloxypyridine (**1**) can be prepared from 3-pyridinol [2], we found it more convenient to treat 3-chloropyridine with the sodium salt of benzyl alcohol (2 equivalent) in dimethylsulfoxide at 125° for 3 hours to give **1** in 77% yield [4]. Addition of Grignard reagents to the 1-phenoxycarbonyl salt of **1** and 5% cuprous iodide in tetrahydrofuran (−23°) gave 1,4-dihydropyridines **2** in good yield. The reaction is regiospecific [5]. The crude dihydropyridines **2** were aromatized with *o*-chloranil in toluene to give 4-alkyl-3-benzyloxypyridines **3** in moderate yield. Hydrogenolysis of pyridines **3** gave the desired 4-alkyl-3-pyridinols in good yield as shown in Table I.



EXPERIMENTAL

Reactions involving organometallic reagents were performed in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. Cuprous iodide was obtained from the Fisher Scientific Co. and activated at 135° for 10 hours. 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. The ^{1}H-nmr spectra were recorded on a Varian EM-360 spectrometer.

Table I

Synthesis of 4-Alkyl-3-pyridinols **4**

Entry	R	Yield, % **3**	Yield, % **4**	Mp, °C **4**	Empirical Formula (**4**)	Elemental Analysis % Found (Calcd.) C	H	N
a	CH_3	56	79	117-119 (lit [3] 120-121)				
b	C_2H_5	48	91	93.5-95	C_7H_9NO	68.30 (68.23)	7.33 (7.31)	11.36 (11.38)
c	n-C_4H_9	36	92	71.5-72.5 (picrate)	$C_9H_{13}NO$	71.35 (71.54)	8.51 (8.60)	9.22 (9.27)
d	i-C_3H_7	50	80	162.5-163.5	$C_8H_{11}NO$	70.08 (70.10)	7.93 (8.03)	10.19 (10.21)
e	C_6H_{11}	37	86	189-190	$C_{11}H_{15}NO$	74.73 (74.60)	8.72 (8.50)	7.94 (7.91)
f	C_6H_5	41	91	125-126	$C_{11}H_9NO$	77.11 (77.21)	5.32 (5.26)	8.05 (8.18)

Table II

Compound No.	NMR (δ carbon tetrachloride) Protons at C_2, C_6, C_5 and benzylic
3a	8.23 (s, 1H), 8.15 (d, 1H), 7.0 (d, 1H), 5.12 (s, 2H)
3b	8.25 (s, 1H), 8.2 (d, 1H), 7.06 (d, 1H), 5.13 (s, 2H)
3c	8.22 (s, 1H), 8.15 (d, 1H), 7.03 (d, 1H), 5.13 (s, 2H)
3d	8.28 (s, 1H), 8.2 (d, 1H), 7.08 (d, 1H), 5.1 (s, 2H)
3e	8.28 (s, 1H), 8.2 (d, 1H), 7.07 (d, 1H), 5.12 (s, 2H)
3f	8.43 (s, 1H), 8.34 (d, 1H), 7.24 (d, 1H), 5.1 (s, 2H)
4a	8.3 (s, 1H), 8.1 (d, 1H), 7.23 (d, 1H)
4b	8.33 (s, 1H), 8.07 (d, 1H), 7.16 (d, 1H)
4c	8.33 (s, 1H), 8.1 (d, 1H), 7.2 (d, 1H)
4d	8.4 (s, 1H), 8.18 (d, 1H), 7.3 (d, 1H)
4e	8.4 (s, 1H), 8.17 (d, 1H), 7.28 (d, 1H)
4f	8.58 (s, 1H), 8.25 (d, 1H), 7.4 (d, 1H)

General Procedure.

To a solution of 3-benzyloxypyridine (1.0 ml, 6.0 mmoles) in 70 ml of dry THF under nitrogen was added 60 mg of cuprous iodide and methyl sulfide (3 ml). The mixture was stirred at room temperature until it became homogeneous and then cooled to −23° (dry ice/carbon tetrachloride). Phenyl chloroformate (0.8 ml, 6.6 mmoles) was added dropwise and the mixture was stirred at −23° for 10 minutes. A solution of the Grignard reagent (6.6 mmoles) in THF was added dropwise. The mixture was stirred at −23° for 15 minutes, allowed to come to room temperature, and quenched with 15 ml of 20% ammonium chloride solution. Ether (25 ml) was added and the organic layer was washed with 20-ml portions of 20% aqueous ammonium chloride/ammonium hydroxide (50/50), water, 10% hydrochloric acid, water, and brine. After drying (magnesium sulfate), the solution was concentrated to give the crude dihydropyridine as a viscous oil, which was used directly in the next step.

To the crude dihydropyridine in dry toluene (30 ml) was added dropwise *o*-chloranil (1.5 g, 6.6 mmoles) in 10 ml of toluene. The mixture was stirred at room temperature overnight (10-15 hours). An aqueous solution of 10% sodium hydroxide (20 ml) was added and the mixture was stirred for 10 minutes at room temperature. After adding ether (20 ml), the organic layer was washed with 20-ml portions of 10% sodium hydroxide and water, then extracted with 10% hydrochloric acid (4 × 25 ml). The combined acid extracts were cooled, made basic with 25% sodium hydroxide, and extracted wtih methylene chloride (4 × 25 ml). The combined organic layer was washed with brine, dried (potassium carbonate), and concentrated. The crude product **3** was isolated from the residue by Kugelrohr distillation and purified by radial preparative layer chromatography (30% acetone/hexane). See Table I for yields and Table II for nmr spectral data. The purified pyridine **3** was used directly in the next step.

A solution of **3** in 20 ml of absolute ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 100 mg of 10% palladium on carbon until hydrogen uptake stopped. Removal of catalyst, concentration of filtrate, and purification by radial preparative layer chromatography (40% acetone/hexane) gave the desired 4-alkyl-3-pyridinol **4**. Analytical samples were prepared by recrystallization from hexane. The yields, melting points, elemental analyses, and nmr spectral data are given in Tables I and II.

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[4] The distilled 3-benzyloxypyridine prepared in this manner is greater than 98% pure by gc analysis. No isomeric benzyloxypyridines were detected, indicating the absence of a benzyne intermediate.

[5] The ^{1}H nmr analysis of intermediate dihydropyridine **2** (R = n-C_3H_7) showed the regioselectivity of the copper-catalyzed Grignard addition to be greater than 95%. In the absence of cuprous iodide, the analogous reaction gave a mixture of isomers containing mainly 1,2-dihydropyridines and approximately 10% of the 1,4-dihydropyridine **2** (R = n-C_3H_7).