SYNTHESIS OF 3-HALO- AND 3-FORMYL-4-ALKYLPYRIDINES

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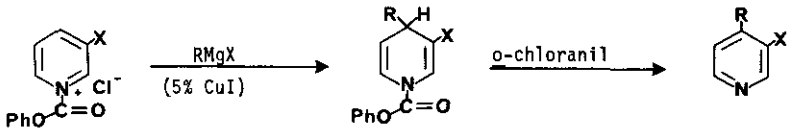
Abstract - In the presence of a catalytic amount of cuprous iodide, the addition of Grignard reagents to the 1-phenoxycarbonyl salts of 3-halopyridines gives 4-alkyl-3-halo-1-phenoxycarbonyl-1,4-dihydropyridines. The crude dihydropyridines were aromatized with o-chloranil to give 4-alkyl-3-halopyridines. Several 4-alkylnicotinaldehydes were synthesized in a similar manner from the cyclic acetal (1,3-dioxolane) of 3-pyridinecarboxaldehyde. After aromatization with sulfur, the crude acetals were hydrolyzed with oxalic acid to give the desired pyridinecarboxaldehydes.

We recently described a convenient method for the synthesis of 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines via the regioselective addition of Grignard reagents to 1-acylpyridinium salts in the presence of a catalytic amount of cuprous iodide.[1,2] The 1-acyldihydropyridines can be aromatized with hot sulfur or chloranil to provide substituted pyridines in moderate to good yield. We have been studying the scope of this pyridine synthesis with regard to what substituents can be present on the pyridine ring during the Grignard reaction. The 1-acylpyridinium salts are so reactive toward Grignard reagents that addition to the pyridine ring will occur in the presence of other reactive functional groups, such as esters.[3,4] Thus, 4-substituted methyl nicotinates can be prepared from methyl nicotinate using this two-step procedure.[4] Halopyridines have been reported to undergo metal-halogen exchange with aryl Grignard reagents;[5] however, we have shown that aryl Grignard reagents add readily to the 1-phenoxycarbonyl salt of 3-bromopyridine to give 4- and 6-aryl-3-bromopyridines after aromatization of the intermediate dihydropyridines.[2]

We have studied the copper-catalyzed Grignard reaction with the 1-phenoxycarbonyl salts of 3-chloro- and 3-bromopyridine (1). Nearly exclusive 1,4-addition results to give 4-alkyl-3-halo-1-phenoxycarbonyl-1,4-dihydropyridines **2**. The crude dihydropyridines were aromatized with o-chloranil[6] in toluene-acetic acid to give 4-alkyl-3-halopyridines **3** in moderate to good yield. The results are given in Table I.



1 X = Cl, Br

2 X = Cl, Br
R = alkyl, aryl

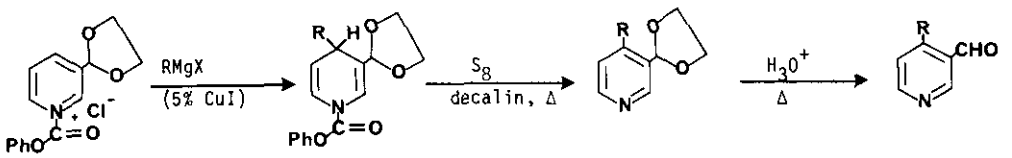
3 X = Cl, Br
R = alkyl, aryl

Table I. Synthesis of 4-Alkyl-3-halopyridines **3**

Starting Halopyridine[a]	RMgX	Product[b]	Overall Yield, %[c]	bp/mm, °C (ref)
3-bromopyridine	MeMgCl	3-bromo-4-methylpyridine	51	76-80/15 (8)
3-bromopyridine	EtMgCl	3-bromo-4-ethylpyridine	53	92-94/15 (9)
3-bromopyridine	n-BuMgCl	3-bromo-4-n-butylpyridine	68	99-103/1
3-bromopyridine	i-PrMgCl	3-bromo-4-i-propylpyridine	48	97-100/15
3-bromopyridine		3-bromo-4-cyclohexylpyridine	47	108-113/1.4
3-bromopyridine	t-BuMgCl	3-bromo-4-t-butylpyridine	37	100-114/15
3-chloropyridine	EtMgCl	3-chloro-4-ethylpyridine	58	89-91/15 (10)
3-chloropyridine	n-BuMgCl	4-n-butyl-3-chloropyridine	61	121-123/15 (11)
3-chloropyridine	i-PrMgCl	3-chloro-4-i-propylpyridine	51	100-101/15
3-chloropyridine		3-chloro-4-cyclohexylpyridine	45	150-152/15
3-chloropyridine	PhMgCl	3-chloro-4-phenylpyridine	55	120[d]/1 mp 35-37

[a]Reactions were performed on a 50- or 20-mmol scale. [b]All products gave the expected IR and ^{1}H NMR spectra. New products gave satisfactory analytical data (±.4% C,H,N). [c]Yields are for isolated pure material obtained from vacuum distillation. [d]Oven temperature during Kugelrohr distillation.

Synthesis of 4-Alkyl-3-pyridinecarboxaldehydes. An aldehyde is too reactive and will not survive the Grignard-acylpyridinium salt reaction. In order to prepare 4-alkyl-3-pyridinecarboxyaldehydes from nicotinaldehyde, the formyl group must be protected as an acetal. The copper-catalyzed Grignard addition to the 1-phenoxycarbonylpyridinium salt **4** is again regioselective giving the 4-alkyl-1,4-dihydropyridines **5** in high yield (80-90%). The crude dihydropyridines were aromatized with sulfur[7] in refluxing decalin. The crude acetals **6** were hydrolyzed with oxalic acid to give the desired 4-alkyl-3-pyridinecarboxaldehydes **7** in moderate overall yield as shown in Table II.



4 **5** **6** **7**

Table II. Synthesis of 4-Alkyl-3-pyridinecarboxaldehydes **7** from **4**

RMgX[a]	Product[b]	Overall Yield, %[c]	^{1}H NMR (CCl_4) δ(aldehyde proton and aromatic protons at C_2, C_6, C_5)
MeMgCl	4-methyl-3-pyridinecarboxaldehyde	30	10.3(s), 8.94(s), 8.65 (d, J=5 Hz), 7.23 (d, J=5 Hz)
n-BuMgCl	4-n-butyl-3-pyridinecarboxaldehyde	33	10.35(s), 8.96(s), 8.68(d, J=5 Hz) 7.25(d, J=5 Hz)
n-PrMgCl	4-n-propyl-3-pyridinecarboxaldehyde	45	10.37(s), 8.97(s), 8.7(d, J=5 Hz) 7.26(d, J=5 Hz)
i-PrMgCl	4-i-propyl-3-pyridinecarboxaldehyde	39	10.35(s), 8.93(s), 8.72(d, J=5 Hz) 7.28(d, J=5 Hz)
	4-cyclohexyl-3-pyridinecarboxaldehyde	44	10.33(s), 8.92(s), 8.68(d, J=5 Hz) 7.33(d, J=5 Hz)
PhMgCl	4-phenyl-3-pyridinecarboxaldehyde	62	10.17(s), 9.18(s), 8.87(d, J=5 Hz) 7.4(d, J=5 Hz)

[a]Reactions were performed on a 20-mmol scale. [b]All products gave the expected IR and ^{1}H NMR spectra. New products gave satisfactory analytical data (± .4% C, H,N). [c]Yields are for isolated pure material obtained from radial preparative layer chromatography (silica gel, ethyl acetate-hexanes).

In summary, the copper-catalyzed reaction of Grignard reagents with 1-phenoxycarbonylpyridinium chlorides has been examined as a method for preparing 4-substituted 3-halo- and 3-formylpyridines. Despite the moderate overall yields, this two- or three-step process is convenient, practical, and amenable to large-scale preparation of these functionalized 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. Toluene was dried over 3A molecular sieves. Cuprous iodide (CuI), ultrapure, was obtained from Alfa Products. 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 NMR spectra were recorded on a Varian EM-360 spectrometer. Gas-liquid chromatography (GC) was performed with a Hewlett-Packard 5830A gas chromatograph equipped with a 30 m x 0.25 mm FSOT column packed with OV-101.

4-n-Butyl-3-chloropyridine. General Procedure. In a 500-ml three-necked flask equipped with an overhead stirrer were placed 3-chloropyridine (4.8 ml, 0.05 mol), CuI (476mg, 2.5 mmol), methyl sulfide (12 ml), and 125 ml of THF under N_2. The solution was cooled to -20°C and 6.4 ml (0.05 mol) of phenyl chloroformate was added via syringe with stirring. After 5 min, n-butylmagnesium chloride (0.05 mol) in 25 ml of THF 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, followed by the addition of aqueous 20% NH_4Cl solution (75 ml). Ether (100 ml) was added and the organic layer was washed with 25-ml portions of 20% NH_4Cl/NH_4OH (50/50) (2x), water, 10% HCl (2x), water and brine. After drying ($MgSO_4$), the solution was filtered and concentrated to yield 15.4 g of crude 3-chloro-1-phenoxycarbonyl-4-n-butyl-1,4-dihydropyridine as a light yellow oil.

To the crude dihydropyridine in dry toluene (50 ml) was added dropwise o-chloranil (12.3g, 0.05 mol) in 35 ml of acetic acid. The mixture was stirred at room temperature for 8 h and concentrated. Toluene (50 ml), ether (50 ml), 10 g of celite, and 10% NaOH (100 ml) were added. The mixture was stirred for 15 min and filtered through celite. The dark organic layer was washed with 25-ml portions of 10% NaOH and water, then extracted with 4 x 25 ml of 10% HCl. The combined acid extracts were concentrated (roto-vap) to approximately 50 ml, cooled, made basic with 20% NaOH, and extracted with methylene chloride (3 x 50 ml). The combined organic layer was washed with brine, dried (K_2CO_3), and concentrated to yield the crude product as a dark oil. Purification by vacuum distillation gave 5.16 g (61%) of 4-butyl-3-chloropyridine as

a clear oil: bp 121-123°C (15 mm); GC purity >95%; ^{1}H NMR (CCl_4) δ 8.58 (s, 1H), 8.38 (d, 1H, J=5 Hz), 7.14(d, 1H, J=5 Hz), 2.72 (t, 2H), 0.7-1.9 (bm, 7 H); IR (neat) 2950, 1580, 1400, 1090, 1025 cm^{-1}. Anal. Calcd for $C_9H_{12}ClN$: C, 63.72; H, 7.13; N, 8.26. Found: C, 63.88; H, 6.98; N, 8.35.

4-Cyclohexyl-3-pyridinecarboxaldehyde. General Procedure. To a solution of 2-(3'-pyridyl)-1,3-dioxolane (3.0g, 20 mmol) in 40 ml of dry THF under N_2 was added CuI (200 mg) and methyl sulfide (3 ml). The mixture was stirred at room temperature until it became homogeneous and then cooled to -20°C (dry ice/CCl_4). Phenyl chloroformate (2.6 ml, 20 mmol) was added dropwise and the mixture was stirred at -20°C for 10 min. A solution of cyclohexylmagnesium chloride (20 mmol) in 10 ml of THF was added dropwise. The mixture was stirred at -20°C for 15 min, allowed to come to room temperature, and quenched with 50 ml of aqueous 20% NH_4Cl solution. Ether (75 ml) was added and the organic layer was washed with 20-ml portions of 20% NH_4Cl/NH_4OH (50/50), water, 10% HCl (2x), water, and brine. After drying ($MgSO_4$), the solution was concentrated to give the crude dihydropyridine as a viscous oil.

The crude dihydropyridine was aromatized with sulfur (800 mg) in refluxing decalin (40 ml, 3h) under N_2. After cooling, ether (50 ml) was added and the mixture was extracted with 5x 25-ml portions of 10% HCl. The acid extracts were concentrated (roto-vap) in a 250 ml flask to give a brown oil. Oxalic acid (2.5 g) and 30 ml of water were added, then the mixture was heated at reflux for 1 h. The mixture was made basic with Na_2CO_3 and extracted with methylene chloride (3 x 50 ml). The organic layer was washed with brine, dried (K_2CO_3), and concentrated to give a tan oil (2.8 g). Purification by radial preparative layer cromatography (EtOAc-hexanes) gave 1.68 g (44%) of 4-cyclohexyl-3-pyridinecarboxaldehyde as a clear oil: GC purity > 95%; ^{1}H NMR (CCl_4) δ 10.33(s, 1 H), 8.92 (s,1 H), 8.68 (d, 1 H, J=5 Hz), 7.33 (d, 1H, J=5 Hz), 3.6 (bs, 1 H), 1.0-2.1 (bm, 10 H). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.98 H, 7.95; N, 7.33.

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