SYNTHESIS OF 4-SUBSTITUTED 3-PYRIDYL KETONES

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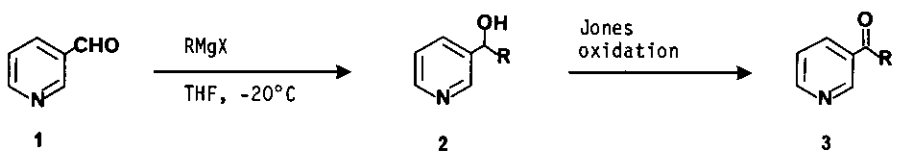
Abstract - In the presence of a catalytic amount of cuprous iodide, the addition of Grignard reagents to the 1-phenoxycarbonyl salts of 3-acylpyridines gives 3-acyl-4-alkyl-1-phenoxycarbonyl-1,4-dihydropyridines. The crude dihydropyridines were aromatized with hot sulfur to give 4-substituted 3-pyridyl ketones.

The copper-catalyzed regioselective addition of Grignard reagents to 1-acylpyridinium salts is a convenient method for the synthesis of 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines. The 1-acyldihydropyridines can be aromatized with hot sulfur or chloranil to provide 4-substituted pyridines in moderate to good yield.[1,2] 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.[1,2d] Various 4-substituted methyl nicotinates can be prepared from methyl nicotinate using this two-step procedure. Halopyridines have been reported to undergo metal-halogen exchange with aryl Grignard reagents;[3] however, we have shown that Grignard reagents in the presence of a catalytic amount of cuprous iodide add readily to the 1-phenoxycarbonyl salt of 3-bromo- or 3-chloropyridine to give 4-substituted 3-halopyridines after aromatization of the intermediate dihydropyridines.[2c,e]

Since 4-substituted 3-acylpyridines are difficult to prepare,[4] we initiated a study on the copper-catalyzed addition of Grignard reagents to the 1-phenoxycarbonyl salts of 3-pyridyl ketones. The 3-pyridyl ketones **3** were purchased commercially or prepared[5] from 3-pyridinecarboxaldehyde (**1**) as shown in Scheme 1.

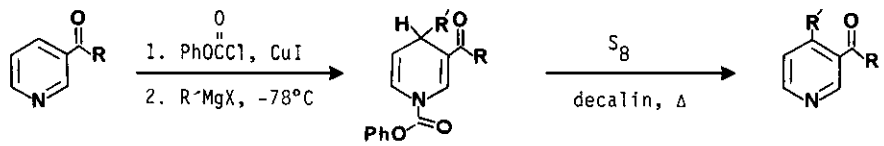
SCHEME 1



1 **2** **3**

The 1-acylpyridinium salts of **3** were prepared in tetrahydrofuran (-78°C) containing a catalytic amount of cuprous iodide. Grignard reagents were added to this mixture to provide the crude 1,4-dihydropyridines **4**, which were aromatized with hot sulfur to give the desired 4-substituted 3-pyridyl ketones **5** as shown in the Table. Surprisingly, the regioselectivity (80-90%) of the copper-catalyzed Grignard addition was not as high as the analogous reactions with methyl nicotinate.[2d] The 4-substituted 3-pyridyl ketones **5** were easily purified by chromatography on silica gel. This method is convenient and compliments our earlier synthesis of 3-acylpyridines utilizing a Friedel-Crafts reaction.[2b]

TABLE



3 4 5

R[a]	R'	Overall Yield of 5, %[4b,c]	mp, °C (picrate)
CH_3	C_3H_7	36	126.0-127.0
CH_3	n-C_6H_{13}	37	97.5- 98.5
CH_3	C_6H_{11}	34	172.0-173.0
CH_3	Ph	38	166.5-167.5
Ph	n-C_3H_7	28	111.0-112.0
Ph	n-C_6H_{13}	26	111.5-112.5
Ph	C_6H_{11}	19	124.0-125.0
Ph	Ph	41	169.5-170.5
n-C_6H_{13}	n-C_3H_7	30	106.0-107.0
n-C_6H_{13}	n-C_6H_{13}	30	106.0-107.0
n-C_6H_{13}	C_6H_{11}	28	119.0-120.0
n-C_6H_{13}	Ph	40	101.5-102.5
C_6H_{11}	n-C_3H_7	35	112.0-113.0
C_6H_{11}	n-C_6H_{13}	19	92.0- 93.0
C_6H_{11}	C_6H_{11}	37	163.0-164.0
C_6H_{11}	Ph	38	130.5-131.5

[a]Reactions were performed on a 20-mmol scale. [b]All products gave the expected IR and ^1H NMR spectra. New products (5) gave satisfactory analytical data (±.4% C,H,N). [c]Yields are for isolated, pure material obtained from radial preparative layer chromatography (silica gel, acetone-hexane).

EXPERIMENTAL

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 idoide (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. ^1H NMR spectra were recorded on Varian EM-360 or JEOL FX-90-Q spectrometers. IR spectra were recorded on a Perkin-Elmer 710B spectrometer. Radial preparative layer chromatography was carried out by using a Chromatotron (Harrison Assoc., Palo Alto, CA). Combustion anaylses were performed by M. H. W. Laboratories, Phoenix, AZ.

3-Acetyl-4-n-propylpyridine. General Procedure. A solution of 3-acetylpyridine (2.67 g, 22 mmol), 400 mg of CuI, and 3.0 ml of methyl sulfide in 60 ml of dry THF was cooled to -78°C

(dry ice/acetone). Phenyl chloroformate (2.7 ml, 22 mmol) was added dropwise to the vigorously stirred solution. After 10 min, a solution of n-propylmagnesium chloride (20 mmol) in 10 ml of THF (or ether) was added dropwise. The mixture was stirred for 20 min at -78°C, allowed to come to room temperature, and quenched with 20 ml of aqueous 20% NH_4Cl solution. Ether (25 ml) was added and the organic layer was washed with 25-ml portions of 20% NH_4Cl/NH_4OH (50:50), water, 10% HCl, water and brine. After drying ($MgSO_4$), the solution was concentrated to give the crude dihydropyridine as a viscous oil.

The crude dihydropyridine was treated with 700 mg (22 mmol) of sublimed sulfur in refluxing decalin (50 ml) for 7h under a N_2 stream. After cooling to room temperature, ether (30 ml) and Norite (3 g) were added and the mixture was stirred for 15 min. The mixture was filtered through celite and the filtrate was extracted with aqueous 10% HCl (5 x 25 ml). The combined acid extracts were cooled, made basic with 25% NaOH and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (K_2CO_3), and concentrated. The crude product was isolated from the residue by Kugelrohr distillation and purified by radial preparative layer chromatography (silica gel, 20% acetone-hexane) to give 1.18 g (36%) of 3-acetyl-4-n-propylpyridine as a clear oil: picrate mp 126-127°C; ^1H NMR (CCl_4) δ 9.07 (s, 1H), 8.65 (d, 1H, J = 6 Hz), 7.25 (d, 1H, J = 6 Hz), 3.1-2.5 (m containing a singlet at 2.65, 5H), 2.0-1.2 (m, 2H), 0.95 (t,3H); IR (neat) 1680, 1590, 1265 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.64; H, 7.97; N, 8.58. Found: C, 73.49; H, 8.03; N, 8.57.

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REFERENCES

1. D. L. Comins and A. H. Abdullah, J. Org. Chem., 1982, 47, 4315.
2. (a) D. L. Comins, Tetrahedron Lett., 1983, 24, 2807. (b) D. L. Comins and N. B. Mantlo, ibid., 1983, 24, 3683. (c) D. L. Comins and N. B. Mantlo, J. Heterocycl. Chem., 1983, 20, 1239. (d) D. L. Comins, E. D. Stroud, and J. J. Herrick, Heterocycles, 1984, 22, 151. (e) D. L. Comins, R. K. Smith, and E. D. Stroud, ibid., 1984, 22, 339. (f) D. L. Comins and E. D. Stroud, J. Heterocycl. Chem., 1985, 22, 1419.
3. H. H. Paradies and M. Gorbing, Angew. Chem., 1969, 81, 293.
4. R. A. Abramovitch and J. G. Saha in "Advances in Heterocyclic Chemistry", Vol. 6, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, N.Y., 1966, p. 229.
5. E. V. Brown in "Pyridine and Its Derivatives", Vol. 14, Part 4, E. Klingsberg, Ed., Wiley, New York, 1964, p. 11.

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