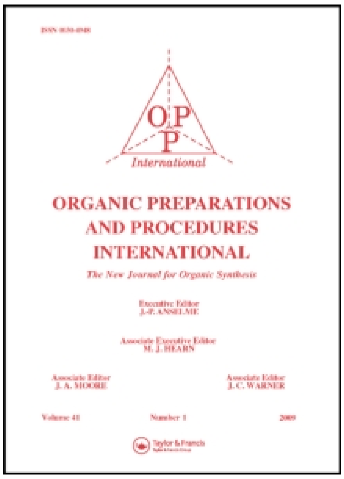

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SYNTHESIS OF METHOXYPYRIDYL PHENYL KETONES VIA PYRIDYLLITHIUM COMPOUNDS

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SYNTHESIS OF METHOXYPYRIDYL PHENYL KETONES VIA PYRIDYLLITHIUM COMPOUNDS

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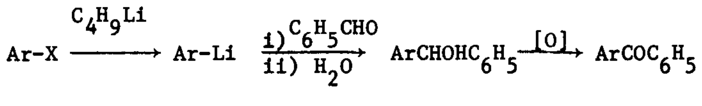
For the investigation of the photochemical reductions of some methoxypyridyl phenyl ketones, it was desirable to find a general method for the synthesis of these ketones. The Friedel-Crafts synthesis failed as the product from the reaction of 5-methoxypyridine-2-carboxylic acid chloride with benzene contained no methoxyl group. The Hammick reaction[1] was suitable for the synthesis of 2-pyridyl carbinols which were easily oxidized to the corresponding ketones, but could not be applied to the 3-pyridyl isomers. The best yields of both 2- and 3-pyridyl carbinols were obtained when corresponding pyridyllithium compounds were treated with benzaldehyde at low temperatures. The corresponding ketones were formed in quantitative yields by use of the Jones reagent[2]. The reaction sequence may be summarized as follows.



$$\text{Ar-X} \xrightarrow{C_4H_9Li} \text{Ar-Li} \xrightarrow[\text{ii) } H_2O]{\text{i) } C_6H_5CHO} \text{ArCHOHC}_6H_5 \xrightarrow{[O]} \text{ArCOC}_6H_5$$

where Ar = methoxypyridyl; and X = Br or I.

6-Methoxy-3-pyridyl and 3-methoxy-2-pyridyl phenyl ketones were synthesized.

EXPERIMENTAL

All melting points are uncorrected and were obtained using the Fischer-Johns melting block. Infrared spectra were recorded with a Beckman IR 8 spectrometer. NMR spectra were taken on a Varian model A-60 spectrometer; chemical shifts are reported in ppm (δ) from TMS as the internal standard. The mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6E spectrometer at 70 eV and 200°.

n-Butyllithium. The procedure of Gilman *et al.*[3] was used to prepare *n*-butyllithium from *n*-butyl bromide and lithium metal in the form of flattened wire. Yields of 80-90% were obtained when the reaction mixture was maintained at -20° to -30°.

6-Methoxy-3-pyridyl Phenyl Carbinol. A solution of *n*-butyllithium (0.6 mole) in 600 ml anhydrous ether was cooled to -40° under nitrogen in a flask equipped with a magnetic stirrer. A solution of 3-iodo-6-methoxypyridine[3] (50 g; 0.213 mole) in 200 ml ether cooled to -30° was added dropwise over a 15 min. period. The resulting yellow mixture was stirred at -40° to -50° for 15 min. Benzaldehyde (53 g; 0.5 mole) in 200 ml ether at -30° was added dropwise in 15 min. The clear yellow solution was stirred at -40° to -50° for 1 hr. It was allowed to warm up to -10° and 200 ml water was added to decompose the organolithium compounds. The ethereal layer was evaporated to half volume and shaken with 3 portions of 10% hydrochloric acid. The acidic extracts were filtered and made alkaline by the addition of solid sodium hydroxide. The oil that separated was extracted with three 100 ml portions of ether which were then combined and dried over "Drierite" (calcium sulfate). The solvent was removed by distillation. The remaining brown viscous liquid was distilled at 174-76° (3 mm). The carbinol (40 g; 0.19 mole) was obtained in 89% yield.

IR ($CHCl_3$): 3600 cm^{-1} (sharp,O-H); 3380 cm^{-1} (broad, bonded O-H).

NMR ($CDCl_3$): δ 3.85 (s, 3, $OC\underline{H}_3$), 4.3 (s, broad, 1, $O\underline{H}$), 5.7 (s, 1, Ar-$C\underline{H}$), 7.3 (m, 5, $C_6\underline{H}_5$), 6.5-8.2 (m, 3, pyridine protons).

6-Methoxy-3-pyridyl Phenyl Ketone. The carbinol (5 g; 0.023 mole) was dissolved in 20 ml reagent grade acetone and the "Jones reagent" (prepared by dissolving 26.7 g chromium trioxide in a solution of 23 ml. conc. sulfuric acid in 40 ml water, then diluted to 100 ml) was added dropwise with manual agitation until a pale red color persisted in the solution. A greenish residue was also formed. The mixture was diluted with 25 ml water and made basic by the addition of sodium hydroxide pellets. It was extracted with three 50 ml portions of ether which were combined and dried over potassium hydroxide. Evaporation of the solvent gave a yellow oily liquid. Since its nmr spectrum showed the presence of about 5% starting material, it was redissolved in acetone and oxidized again by the Jones reagent. Upon workup as above, 4.7 g (0.022 mole; 96%) of 6-methoxy-3-pyridyl phenyl ketone was obtained (m.p. 47-49°). Recrystallization from benzene resulted in 4 g of colorless needles (m.p. 54°).

IR ($CHCl_3$): carbonyl band at 1625 cm^{-1} (strong).

NMR ($CDCl_3$): δ 4.0 (s, 3, $OC\underline{H}_3$), 6.7-6.9 (m, 1, pyridine-5 proton), 7.3-7.9 (m, 6, $C_6\underline{H}_5$ and pyridine-4 proton), 8.15 (m, 1, pyridine-2 proton).

Mass spectrum: m/e and relative abundance - 51(29.7), 77(58.3), 105(41.9), 136(86.8), 183(14.6), 212(56.4), 213(100.0), 214(15.1).

Anal. Calc'd for $C_{13}H_{11}NO_2$: C, 73.24; H, 5.16; Found: C, 72.95; H, 5.31.

2-Bromo-3-methoxypyridine. A solution of 10 g (0.065 mole) of 2-nitro-3-methoxypyridine[4] in 250 ml ethyl alcohol was hydrogenated in the presence of 10% palladium on carbon catalyst at low pressure (below 50 psi). The solution was filtered and turned dark on exposure to air. The crude amine (7.8 g; 0.063 mole) was obtained by removal of the solvent at reduced pressure. It melted at 68-69° and was obtained in a 97% yield. Its structure as 2-amino-3-methoxypyridine was confirmed by its nmr spectrum ($CDCl_3$) δ 3.7 (s, 3, $OC\underline{H}_3$), 5.25 (broad, 2, $N\underline{H}_2$), 6.5-7.7 (m, 3, pyridine protons). The amine (7.5 g; 0.06 mole) was diazotized in hydrobromic acid solution in the presence of bromine according to the procedure reported by Allen and Thirtle[5]. After the workup, 8.5 g (0.045 mole, 75%) of 2-bromo-3-methoxypyridine (m.p. 38°) was obtained.

NMR ($CDCl_3$): 3.85 (s, 3, $OC\underline{H}_3$), 7.1-7.9 (m, 3, pyridine protons).

Anal. Calc'd for C_6H_6BrNO: C, 38.32; H, 3.22; N, 7.45; Found: C, 38.12; H, 3.15; N, 7.53.

3-Methoxy-2-pyridyl Phenyl Carbinol. The carbinol was obtained in 85% yield by treatment of 2-bromo-3-methoxypyridine with *n*-butyllithium and benzaldehyde as described under 6-methoxy-3-pyridyl phenyl carbinol. The pure compound (pale yellow crystals) melted at 116.5°

IR ($CHCl_3$): 3400 cm^{-1} (broad, bonded O-H)

NMR ($CDCl_3$): δ 3.7 (s, 3, $OC\underline{H}_3$), 5.5 (broad, 1, O$\underline{H}$), 5.9 (s, 1, Ar-C$\underline{H}$), 7-7.5 (m, 7, $C_6\underline{H}_5$ and pyridine protons), 8.2 (m, 1, pyridine-2 proton).

Mass spectrum: m/e 215 (100%, base peak)

Anal. Calc'd for $C_{13}H_{13}NO_2$: C, 72.57; H, 6.05; N, 6.51.
Found: C, 72.80; H, 6.13; N, 6.61.

3-Methoxy-2-pyridyl Phenyl Ketone. By the treatment of 3-methoxy-2-pyridyl phenyl carbinol with the Jones Reagent as described under 6-methoxy-3-pyridyl phenyl ketone, 3-methoxy-2-pyridyl phenyl ketone was obtained in 90% yield as a colorless liquid, b.p. 174-75° (3 mm). On prolonged standing, it solidified to form colorless crystals, m.p. 34-35°.

IR ($CHCl_3$): carbonyl band at 1665 cm^{-1} (strong).

NMR ($CDCl_3$): δ 3.8 (s, 3, $OC\underline{H}_3$), 7.4 (m, 5, $C_6\underline{H}_5$), 7.9-8.2 (m, 3, pyridine protons).

Mass spectrum: m/e and relative abundance - 51(33), 77(100), 105(96), 155(13.5), 184(69), 185(35.5), 212(19), 213(16).

Anal. Calc'd for $C_{13}H_{11}NO_2$: C, 73.24; H, 5.16; N, 6.57

Found: C, 73.03; H, 4.97, N, 6.47

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