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AN IMPROVED SYNTHESIS OF 3-PHENYL- AND 3-METHOXYQUINALDINE

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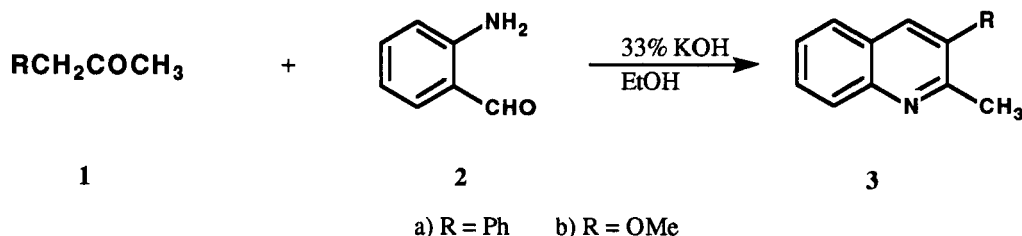
AN IMPROVED SYNTHESIS OF 3-PHENYL- AND 3-METHOXYQUINALDINE

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In connection with our ongoing program involving the design and synthesis of Hantzsch dihydropyridines as calcium channel antagonists, it became necessary to synthesize the title compounds (**3**) in large quantities. 3-Phenylquinaldine (**3a**) was synthesized by Glinka¹ *via* photocyclocondensation of (Z)- α -phenylbenzylideneacetone oxime, whereas de Mayo *et al.* prepared it by irradiation of *o*-styrylthioacetanilide.² In contrast, Gagan and Lloyd³ converted phenylacetone (**1a**) to β -chloro- α -phenylcrotonaldehyde which was then condensed with aniline to afford **3a** in 28% overall yield. 3-Methoxyquinaldine has been prepared⁴ by methylation of 3-hydroxyquinaldine with diazomethane. These syntheses either involve a multi-step reaction sequence or suffer from low yields. This communication describes a rapid one-step synthesis of the title compounds (**3**) using the Friedlander quinoline synthesis.⁵



Reaction of freshly prepared *o*-aminobenzaldehyde (**2**)⁶ with a substituted acetone (**1**) and 33% KOH in refluxing ethanol afforded 3-phenyl- and 3-methoxyquinaldine (**3a** and **3b**) in 81% and 76% yields respectively. Our initial attempts to perform this condensation using a catalytic amount of acetic acid resulted in a low yield of 3-phenylquinaldine (24%), whereas a similar reaction to prepare 3-methoxyquinaldine gave a complex mixture of products which did not contain the required product. When commercial *o*-aminobenzaldehyde was used, lower yields in the 40-50% range were consistently obtained.

EXPERIMENTAL SECTION

Methoxyacetone (**1b**) and phenylacetone (**1a**), were used as received from the Aldrich Chemical Co. and Terrochem Laboratories respectively. NMR spectra were recorded using a Bruker AM-300 spectrometer. ¹³C NMR spectra were determined using the J modulated spin echo technique where methyl and methine resonances appear as singlets, and methylene and quaternary carbon resonances appear as negative peaks. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected.

General Procedure.- A solution of *o*-aminobenzaldehyde (0.1 mol), the substituted acetone (0.1 mol) and 33% aqueous KOH (50 ml) in 95% ethanol (200 ml) was refluxed for 2 hrs. After cooling to 25°, the reaction mixture was neutralized with acetic acid, concentrated on a rotary evaporator, and extracted with ether. Removal of the solvent *in vacuo* and distillation of the product under reduced pressure gave the solid product which was recrystallized from hexane-ethyl acetate.

3-Phenylquinaldine (3a), bp. 140-142°/5mm, lit.³ bp. 207-209°. ¹H NMR (CDCl₃): δ 2.68 (s, 3H, -CH₃), 7.36-7.50 (m, 6H, phenyl hydrogens and quinolinyl H-6), 7.67 (d, J_{7,8} = 8.2 Hz of d, J_{6,7} = 6.7 Hz of d, J_{5,7} = 1.7 Hz, 1H, quinolinyl H-7), 7.73 (d, J_{5,6} = 8.0 Hz, 1H, quinolinyl H-5), 7.92 (s, 1H, quinolinyl H-4) and 8.08 (d, J_{7,8} = 8Hz, 1H, quinolinyl H-8). ¹³C NMR (CDCl₃): δ 24.27 (-CH₃), 125.64, 126.51 (phenyl C-1), 127.11, 127.23, 128.07, 128.19, 128.88, 128.94, 135.34 (C-10), 135.62 (C-4), 139.60 (C-3), 146.81 (C-9) and 156.91 (C-2).

3-Methoxyquinaldine (3b), bp. 85-90°/8mm, lit.⁴ 80-100°/10mm, mp. 34-35°, lit⁴ 34.5-35°. ¹H NMR (CDCl₃): δ 2.63 (s, 3H, -CH₃), 3.87 (s, 3H, -OCH₃), 7.19 (s, 1H, quinolinyl H-4), 7.40 (d, J_{5,6} = 8.0 Hz of d, J_{6,7} = 6.8 Hz, 1H, quinolinyl H-6), 7.48 (d, J_{7,8} = 8.2 Hz of d, J_{6,7} = 6.8 Hz, 1H, quinolinyl H-7), 7.63 (d, J_{5,6} = 8.0 Hz, 1H, quinolinyl H-5) and 7.95 (d, J_{7,8} = 8.2 Hz, 1H, quinolinyl H-8). ¹³C NMR (CDCl₃): δ 20.38 (-CH₃), 55.11 (-OCH₃), 110.61 (C-4), 125.89 (C-6), 126.15 (C-5), 126.31 (C-7), 128.19 (C-8), 128.31 (C-10), 142.53 (C-3), 152.00 (C-9) and 152.90 (C-2).

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