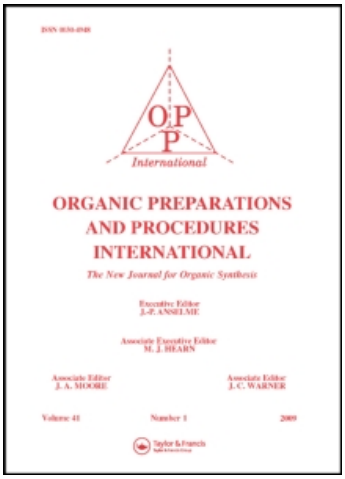


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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

M. R. Akula[a]; M. W. Wolowyk[a]; E. E. Knaus[a]
[a] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, CANADA

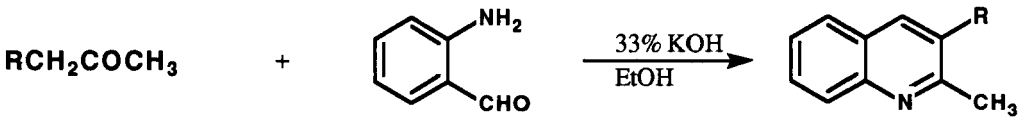
To cite this Article Akula, M. R. , Wolowyk, M. W. and Knaus, E. E.(1991) 'AN IMPROVED SYNTHESIS OF 3-PHENYL- AND 3-METHOXYQUINALDINE', Organic Preparations and Procedures International, 23: 3, 386 — 387
To link to this Article: DOI: 10.1080/00304949109458217
URL: http://dx.doi.org/10.1080/00304949109458217

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

Submitted by (12/04/90) M. R. Akula, M. W. Wolowyk and E. E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences
University of Alberta
Edmonton, Alberta, CANADA T6G 2N8

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 Glinka[1] *via* photocyclocondensation of (Z)–α-phenylbenzylideneacetone oxime, whereas de Mayo et al. prepared it by irradiation of *o*-styrylthioacetanilide.[2] In contrast, Gagan and Lloyd[3] 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 prepared[4] 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]



1 **2** **3**

a) R = Ph b) R = OMe

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. ^{13}C 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°. ^{1}H NMR ($CDCl_3$): δ 2.68 (s, 3H, -CH_3), 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). ^{13}C NMR ($CDCl_3$): δ 24.27 (-CH_3), 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°, lit[4] 34.5-35°. ^{1}H NMR ($CDCl_3$): δ 2.63 (s, 3H, -CH_3), 3.87 (s, 3H, -OCH_3), 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). ^{13}C NMR ($CDCl_3$): δ 20.38 (-CH_3), 55.11 (-OCH_3), 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).

Acknowledgement.- We are thankful to the Medical Research Council of Canada (Grant MA-8892) for financial support of this research.

REFERENCES

1. J. Glinka, Pol. J. Chem., 53, 2143 (1979).

2. P. de Mayo, L. K. Sydnes and G. Wenska, J. Org. Chem., 45, 1549 (1980).

3. J. M. F. Gagan and D. Lloyd, J. Chem. Soc. (C), 2488 (1978).

4. K. Eiter and M. Nagi, Monatsh Chem., 80, 607 (1949).

5. C. C. Cheng and S. J. Yan, Org. Reactions, 28, 37 (1982).

6. L. I. Smith and J. W. Opie, Org. Synth., 28, 11 (1948).

****