

Synthesis of Polysubstituted Analogues of the 4-Methyl-2-phenylquinoline

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A simple and convenient synthetic method for the direct synthesis of a series of polysubstituted analogues of the putative antifungal agent 4-methyl-2-phenylquinoline, a mimic of the natural bioactive 4-methoxy-2-phenylquinoline is reported.

Key Words: Quinolines, 2-Aminoacetophenone, 2-Hydroxyacetophenones, 2-(4-Methyl-2-quinolinyl)aniline.

INTRODUCTION

Quinolines are known to play an important and key role in pharmacologically active substances, clinical drugs and naturally occurring products¹. Quinolines either obtained from nature or synthesized have been reported to possess broad spectrum of biological activities including antimicrobial^{2,3}, anticancer^{4,5}, antimalarial^{6,7}, antiinflammatory⁸, antileishmanial^{9,10}, antiasthmatic¹¹, antiviral¹², antiamebic¹³ and tyrosine kinase inhibitor¹⁴ activities. In addition to wide applications in pharmaceuticals, quinolines are also used in electronics, photonic properties¹⁵ and bioorganometallic processes¹⁶. Owing to such a wide range of applications in various fields, considerable progress in synthetic methodology applicable to quinoline alkaloids have been made during the past decade¹⁷. Among various synthetic methods available in quinolines synthesis, Friedlander condensation is still one of the most convenient and most frequently used methods for the direct synthesis of quinolines¹⁸. Based on Friedlander annulation synthesis, several procedures have been reported to be effective for the synthesis of quinolines¹⁹.

2-Arylquinoline alkaloids are widely distributed in the plant family Rutaceae embodying about 160 genera with 1600 species. Varieties of quinoline alkaloids have been isolated from the plant species belonging to family Rutaceae²⁰. 2,4-Disubstituted quinolines specifically the 4-alkoxy-2-arylquinolines which are abundantly present in *Lunasia amara*^{20d,20e,20j} and *Galipea longiflora*^{20a} (family Rutaceae) have attracted considerable interest due to their important biological activities^{20a,20d,20j}. Recently some mimic derivatives based on 4-alkoxy-2-aryl quinolines were synthesized²¹ and reported to possess potent antiplatelet^{21a}, antiangiogenesis^{21c} and anti-

fungal activities^{21b,21d}. In particular, 4-methyl-2-phenylquinoline (1) and 6-bromo-4-methyl-2-(β -pyridyl)quinoline (2) (Fig. 1) showed highly potent antifungal activities against dermatophytes^{21b,21d}. However, perusal of literature reveals that only a limited number of methods are available for the synthesis of these compounds, which suffer several drawbacks such as multiple steps^{20e,22} and use of toxic reagents²³. In our continued interest on the synthesis of heterocyclic compounds²⁴ and considering the promising biological activities of 4-methyl-2-phenyl quinolines^{21b,21d}, in this paper, we describe the synthesis of 4-methyl-2-phenyl quinoline derivatives **4**, **4a** and **7a-g**.

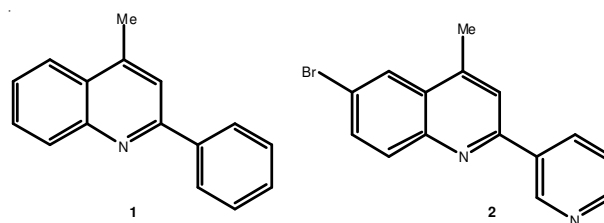


Fig. 1. Structure of 2-arylquinolines reported as antifungal agent

EXPERIMENTAL

Melting points were determined on a Gallen Kamp melting point apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded with a JEOL ECP-400 spectrophotometer. The NMR samples were prepared in CDCl₃ with tetramethylsilane (TMS) as an internal standard. The chemical shifts and coupling constants (*J*) were expressed in δ and Hz, respectively. MS spectra were recorded on Shimadzu QP5050A GC/MS system. The thin layer chromatography (TLC) was carried out on pre-coated Silica gel 60 F₂₅₄ (0.2 mm, Merck) plates and compounds were detected by UV light.

General procedure for the preparation of the quinoline derivatives **4**, **4a** and **7a-g**

Compounds **4 and **4a**:** In a 100 mL conical flask, 2-aminoacetophenone (1 g, 7.4 mmol), one drop of diluted hydrochloric acid and 0.8 g of silica gel were shaken well and then subjected to microwave irradiation at 440 watt for 0.5 h. The reaction flask was taken out of the microwave oven and allowed to cool down at room temperature. The cooled reaction mixture was dissolved in chloroform, silica gel was filtered off and the filtrate was evaporated under vacuum. The resulting oily material was digested with ethanol and cooled down to give compound **4**. The latter compound was refluxed with a mixture of 5 mL acetic acid and 0.2 mL acetic anhydride for 2 h. Crushed ice was added to the reaction mixture and the resulting solid was filtered and washed with cold water to obtain **4a**.

Compounds **7a-g:** To a mixture of 2-aminoacetophenone (1 g, 7.4 mmol) and the appropriate 2-hydroxyacetophenone derivative (8.148 mmol) in 100 mL conical flask, one drop of diluted hydrochloric acid and 0.8 g of silica gel were added and the reaction flask was shaken well and subjected to microwave irradiation at 600 watt for 1 h. The reaction flask was taken out of the microwave oven and allowed to cool down at room temperature. The cooled reaction mixture was dissolved in chloroform and filtered with chloroform washing to isolate organic material from silica gel. The chloroform soluble material was concentrated and the resulting solid was recrystallized from ethanol to give the quinoline derivatives **7a-g**.

Spectral data for compounds

2-(2'-Aminophenyl)-4-methylquinoline^{25,26} (4**):** Pale yellow powder; m.p. 58-59 °C; ¹H NMR (400 MHz, CDCl₃): δ 2.74 (s, 3H), 6.10 (brs, 2H), 6.81 (m, 2H), 7.20 (m, 1H), 7.53 (t, 1H, *J* = 8.06 Hz), 7.66 (s, 1H), 7.69 (t, 1H, *J* = 8.06 Hz), 7.70 (m, 1H), 7.96 (d, 1H, *J* = 8.06 Hz), 8.08 (d, 1H, *J* = 8.06 Hz). ¹³C NMR (100 MHz, CDCl₃): 19.2, 117.5, 117.7, 121.2, 121.8, 123.7, 126.1, 126.6, 129.3, 129.5, 129.9, 130.3, 145.1, 146.6, 147.3, 158.9. MS: *m/z* (%) 235 (M⁺), 233, 219, 109.

2-(2'-Acetamidophenyl)-4-methylquinoline (4a**):** White fine crystal; m.p. 120 °C; ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3H), 2.79 (s, 3H), 7.20 (m, 1H), 7.44 (m, 1H), 7.61 (t, 1H, *J* = 8.06 Hz), 7.72 (s, 1H), 7.77 (t, 1H, *J* = 8.06 Hz), 7.81 (m, 1H), 8.02 (d, 1H, *J* = 8.06 Hz), 8.04 (d, 1H, *J* = 8.06 Hz), 8.60 (m, 1H), 12.92 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 19.3, 25.4, 121.5, 123.4, 124.0, 125.1, 126.8, 126.9, 128.8, 129.3, 130.2, 130.6, 138.5, 143.9, 145.6, 146.9, 157.4, 168.8. MS: *m/z* (%) 276 (M⁺), 261, 233, 217, 115.

2-(2'-Hydroxyphenyl)-4-methylquinoline (7a**):** Brown yellow powder; m.p. 70 °C; ¹H NMR (400 MHz, CDCl₃): δ s, 3H), 6.92 (t, 1H, *J* = 8.06 Hz), 7.08 (d, 1H, *J* = 8.06 Hz), 7.31 (t, 1H, *J* = 8.06 Hz), 7.53 (m, 1H), 7.69 (m, 1H), 7.80 (s, 1H), 7.88 (d, 1H, *J* = 8.06 Hz), 7.92 (m, 1H), 7.98 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): MS: *m/z* (%) 235 (M⁺), 220, 207, 181, 102, 90, 63.

2-(5'-Fluoro-2'-hydroxyphenyl)-4-methylquinoline (7b**):** Grey crystal; m.p. 76 °C; ¹H NMR (400 MHz, CDCl₃): δ s, 3H), 6.98 (d, 1H, *J* = 8.80 Hz), 7.02 (dd, 1H, *J* = 8.80 and 2.93 Hz), 7.48 (d, 1H, *J* = 2.93 Hz), 7.51 (t, 1H, *J* = 8.06 Hz), 7.60 (s, 1H), 7.67 (t, 1H, *J* = 8.06 Hz), 7.87 (d, 1H, *J* = 8.06

Hz), 7.91 (d, 1H, *J* = 8.06 Hz). ¹³C NMR (100 MHz, CDCl₃): MS: *m/z* (%) 253 (M⁺), 220, 207, 181, 102, 90, 63.

2-(5'-Chloro-2'-hydroxyphenyl)-4-methylquinoline (7c**):** Orange crystal; m.p. 150 °C; ¹H NMR (400 MHz, CDCl₃): δ s, 3H), 6.98 (d, 1H, *J* = 8.80 Hz), 7.21 (dd, 1H, *J* = 8.80 and 2.20 Hz), 7.54 (m, 1H), 7.68 (s, 1H), 7.70 (m, 1H), 7.78 (d, 1H, *J* = 2.20 Hz), 7.91 (m, 1H), 7.97 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): MS: *m/z* (%) 269 (M⁺), 254, 204, 102, 63.

2-(5'-Bromo-2'-hydroxyphenyl)-4-methylquinoline (7d**):** Brown crystal; m.p. 154 °C; ¹H NMR (400 MHz, CDCl₃): δ s, 3H), 6.98 (d, 1H, *J* = 8.80 Hz), 7.35 (dd, 1H, *J* = 8.80 and 2.20 Hz), 7.59 (m, 1H), 7.75 (m, 1H), 7.77 (s, 1H), 7.97 (d, 1H, *J* = 2.20 Hz), 7.99 (m, 1H), 8.07 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): MS: *m/z* (%) 314 (M⁺), 313, 298, 204, 191, 117, 102, 63.

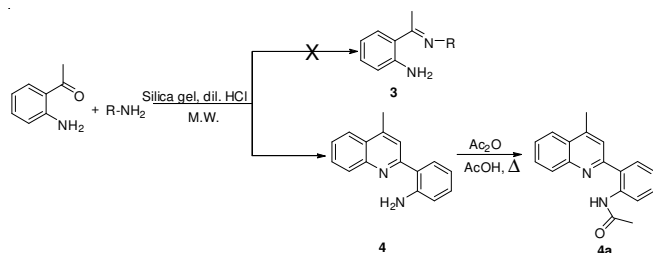
2-(2'-Hydroxy-5'-methoxyphenyl)-4-methylquinoline (7e**):** Brown crystal; m.p. 98 °C; ¹H NMR (400 MHz, CDCl₃): δ s, 3H), 3.82 (s, 3H), 6.93 (dd, 1H, *J* = 8.80 and 2.93 Hz), 6.99 (d, 1H, *J* = 8.80 Hz), 7.35 (d, 1H, *J* = 2.93 Hz), 7.50 (m, 1H), 7.66 (m, 1H), 7.69 (s, 1H), 7.88 (m, 1H), 7.94 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): MS: *m/z* (%) 265 (M⁺), 250, 194, 168, 115, 102, 63.

2-(3',5'-Dichloro-2'-hydroxyphenyl)-4-methylquinoline (7f**):** Brown crystal, m.p. 205 °C; ¹H NMR (400 MHz, CDCl₃): δ s, 3H), 7.41 (d, 1H, *J* = 2.93 Hz), 7.63 (m, 1H), 7.75 (d, 1H, *J* = 2.93 Hz), 7.76 (s, 1H), 7.79 (m, 1H), 8.00 (m, 1H), 8.10 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): MS: *m/z* (%) 304 (M⁺), 303, 288, 204, 115, 102, 63.

2-(2'-Hydroxy-6'-methoxyphenyl)-4-methylquinoline (7g**):** Dark brown powder; m.p. 115 °C; ¹H NMR (400 MHz, CDCl₃): δ s, 3H), 3.91 (s, 3H), 6.50 (d, 1H, *J* = 8.06 Hz), 6.74 (d, 1H, *J* = 8.06 Hz), 7.22 (t, 1H, *J* = 8.06 Hz), 7.51 (m, 1H), 7.64 (m, 1H), 7.90 (m, 1H), 7.98 (m, 1H), 8.28 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): MS: *m/z* (%) 265 (M⁺), 250, 234, 144, 115, 102, 63.

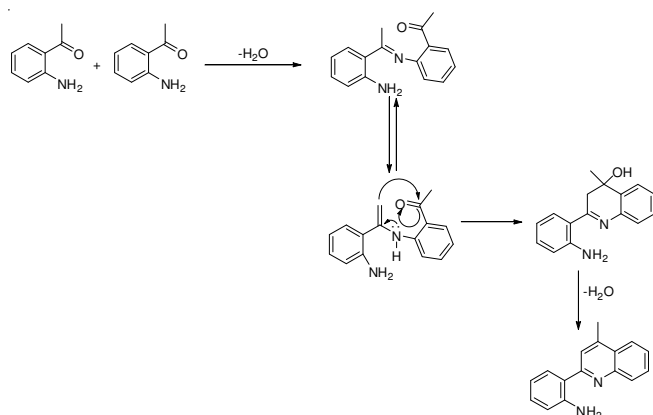
RESULTS AND DISCUSSION

In a previous study^{24d}, we prepared a series of imine derivatives (Schiff bases) from the reaction of 2-hydroxyacetophenones with alkyl amines under microwave irradiation. However, when the same reaction was carried out using 2-aminoacetophenones with alkyl amines under the same conditions, the reaction did not proceed and we obtained only starting materials even after heating the reaction mixture for long periods of time. In order to obtain an appropriate reaction condition for the synthesis of the desired imine derivatives, we examined the reaction of 2-aminoacetophenones with amino derivatives in the presence of silica gel and a drop of diluted hydrochloric acid which upon purification led to the formation of a light yellow powder, that turned out not to be the expected schiff base **3** (Scheme-I). Analysis of the spectral data (MS, ¹H and ¹³C NMR) of the product ruled out the possible formation of the schiff base **3**. The structure features of the product confirmed the formation of 2-(2'-aminophenyl)-4-methylquinoline (**4**) (Scheme-I). This reaction was repeated many times with and without amine derivatives and found that the formation of the quinoline derivative **4** was not affected by the presence of the amines. Quinoline moiety **4**



Scheme-I

seems to be formed *via* dimerization of 2-aminoacetophenone (Scheme-II). The success encountered in the formation of quinoline moiety prompted us to generalize the reaction condition by preparing a series of novel quinoline derivatives **7a-g** from the reaction of 2-aminoacetophenone and substituted 2-hydroxyacetophenones (Table-1).



Scheme-II

TABLE-1
SILICA GEL HYDROCHLORIC ACID CATALYZED
SYNTHESIS OF QUINOLINE DERIVATIVES

Entry	R ₁	R ₂	R ₃	Product ^a	Yield ^b (%)
1	H	H	H	7a	51
2	H	F	H	7b	36
3	H	Cl	H	7c	39
4	H	Br	H	7d	41
5	H	OMe	H	7e	34
6	Cl	Cl	H	7f	45
7	H	H	OMe	7g	30

^aIdentified by ¹H, ¹³C, EI-MS and by comparison of their spectral data with those of related compounds. ^bIsolated yield.

Conclusion

We have developed a convenient, safe and efficient one step procedure for the direct synthesis of biologically important polysubstituted quinolines. Synthetic methods for the construction of putative antifungal 4-methyl-2-phenylquinoline, mimics of natural bioactive 4-methoxy-2-phenyl quinoline are very rare^{21b-21d, 25,26} and to the best of our knowledge this is the first time when direct synthesis of polysubstituted 4-methyl-

2-phenylquinolines are being prepared *via* dimerization of 2-aminoacetophenones.

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