A Facile Synthesis of 2-Hydroxy-3-Phenylquinoline Derivatives

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A mild and efficient way for the synthesis of 3-phenylquinoline-2-ol derivatives via chemo-selective reaction of substituted *O*-nitrobenzaldehyde and ethyl-2-phenylacetate catalyzed by Fe/HCl is described. The new procedure has the advantages of mild reaction conditions, high yields and one-pot manner with easy purification, and further characterised by NMR, FT-IR and HRMS spectral data.

Key words: Bechamp reduction, phenylethylacetate, 3-phenylquinoline-2-ol, chemo-selective, microwave

Received: July 2019; Accepted: October 2019

Phenylquinoline is a multipurpose bicyclic heterocyclic scaffold with immense therapeutic potential. Some of the compounds containing quinoline nucleus are agents of choice for the treatment of various ailments, particularly cancer and malaria [1-6]. Furthermore, several 3-phenylquininoline derivatives exhibit a broad spectrum anti-protozoal [7], antibacterial [8], anticancer and anti-asthmatic [9, 10] properties.

Although a number of useful synthetic procedures to prepare 3-aryl-4(1H)-quinoline derivatives have been developed, to the best of our knowledge, historically, phenylquinoline synthesis from corresponding aniline and 2-phenylethyl-acetoacate has been reported [11]. The classical Vilsmeier-Haack approach, N-2-diphenylacetamide is formulated into 2-chloro-3-phenylquinoline and 2-hydroxy-3-phenylquinoline in two steps under harsh acidic conditions in low yields [12, 13], Knorr reactions [14], arylation protocol of ethyl acetoacetate developed using hypervalent diaryliodonium salts under mild and metal-free conditions [15], and further novel metal-free trans annulation reaction of 2-nitroolefins with 2-substituted indoles in poly-phosphoric acid [16]. This acid facilitated torrent transformation runs mechanism and used in a grouping with the Fisher indole synthesis to offer a practical three-component hetero-annulation style to 2-quinolines from arylhydrazines, 2-nitroalkenes and acetophenone [17]. Recently, phenylquinoline has been synthesised from carbonylative cross-coupling reactions for iron and cobalt catalysed cross-coupling reactions in the company of quinoline and aryl magnesium reagents [18].

Over the past few years, iron (Fe) has emerged as a powerful catalyst for various organic transformations due to several advantages such as inexpensive, nontoxic and eco-friendly in nature. As a continuation of our research devoted to the development of new methods for the preparation of heterocycles via Bechamp reactions catalyzed by iron, herein, we would like to report the efficient one-pot synthesis of 2-hydroxy-3-phenylquinoline derivatives by a Bechamp reaction of 2-nitrobenzaldehyde and phenylethylacetate in ethanol catalyzed by iron and chemo-selectively marked bond formation process. This study reports a convenient and efficient synthesis of 2-hydroxy-3-phenylquinolines derivatives under microwave irradiation conditions.

MATERIAL AND METHODS

Column chromatography with Merck silica gel 60-120 mesh and hexane and ethylacetate as eluents, and thin layer chromatography silica with gel 200-400 mesh. All the basic chemicals were purchased from Merck and Avira chemical (India).

Analytical techniques

Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer as potassium bromide discs unless otherwise indicated, scanning 32 times from 4000 to 400 cm^{-1} at 4 cm^{-1} resolution. NMR spectra were obtained on a Brucker (500 MHz) instrument in $CDCl_3$ solutions using

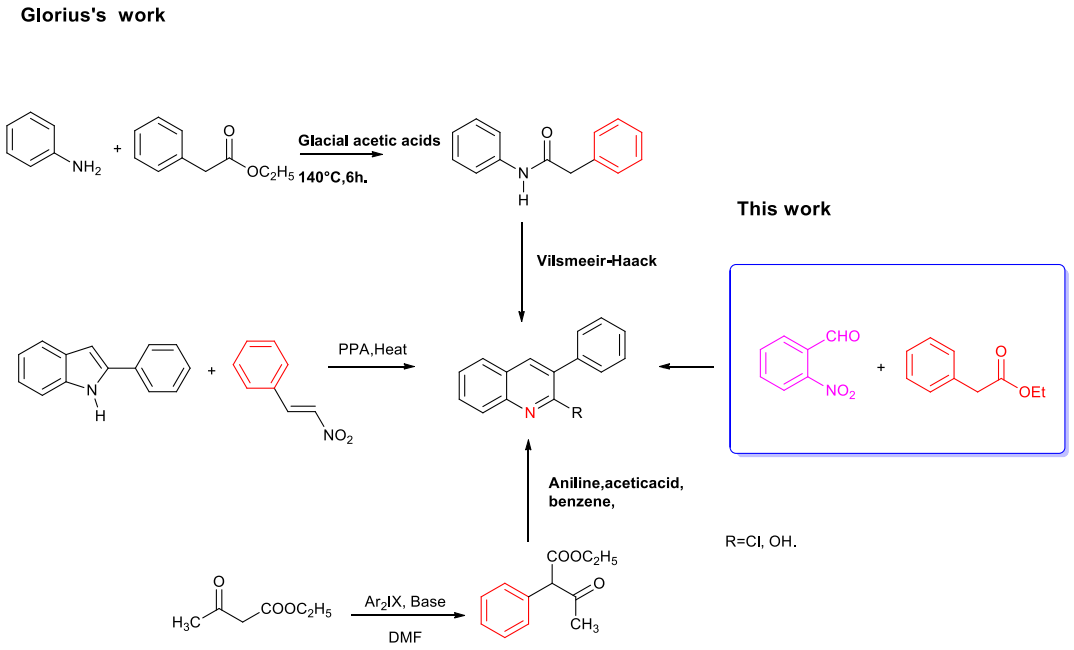


Figure 1. General procedure for synthesis route of 2-hydroxy-3-phenylquinoline.

tetramethylsilane as an internal standard. *J* values are given in Hz. Mass spectra were obtained at the Vellore Institute of Technology, Vellore, Tamil Nadu, India.

GC-MS information was obtained on Perkin-Elmer GC Clarus 680/Mass Spectrometer Clarus 600 (EI). The Clarus 680 GC used in the analysis employed a fused silica column, packed with Elite-5MS (5% biphenyl 95% dimethylpolysiloxane, 30 m × 0.25 mm ID × 250µm df) and the components were separated using helium as carrier gas at a constant flow of 1 ml/min. The injector temperature was set at 260°C during the chromatographic run. 1µL extract sample was injected into the instrument with the oven temperature as follows: 60°C (2 min); followed by 300°C at the rate of 10°C min^{-1}; and 300°C, where it was held for 6 min. The mass detector conditions were: transfer line temperature of 240°C; ion source temperature of 240°C; and ionization mode electron impact at 70 eV, a scan time of 0.2 sec and scan interval of 0.1 sec. The fragments were from 40 to 600. The spectra of the components were compared with the database of the spectra of known components stored in the GC-MS NIST (2008) library.

Typical experimental Procedure for the Synthesis of 3-phenylquinolin-2-ol derivatives (3)

A mixture of phenylethylacetate **1** (2.03 g, 0.1 mole) with *O*-nitrobenzaldehyde derivatives **2** (a-c) (0.1 mole) in dry ethanol (25 mL) was refluxed with added con HCl (0.5 mL), 20 negligible % iron powder (2 g) with careful monitoring of the progress of the used reaction by TLC. The precipitate was filtered off using distilled water and purified by chromatography.

Spectral Data of 3-phenylquinolin-2-ol **(3a),** Yellow crystal, m.p.:156˚C yield; 82%; IR (KBr, ν_{max}, cm^{-1}): 3397, 3053, 2924, 1678, 1619, 1560; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.30 (bs, 1H, quinoline-OH), 8.09 (s, 1H, quinoline-C_4-H), 7.99 (t, 1H, quinoline-C_6-H), 7.80 (d, 1H, *J* =15 quinoline C_5-H), 7.55-7.53 (m, 3H, phenyl,C_3-C_5-H), 7.49-7.46 (m, 2H, phenyl,C_2-C_6-H), 7.31 (t, 1H, quinoline, C_7-H), 6.69 (d, 1H,quinoline-C_8); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 152.0, 145.8, 139.1, 132.1, 130.4, 128.4, 122.6, 116.9, 111.8; GC-MS: m/z [M+1] 221.

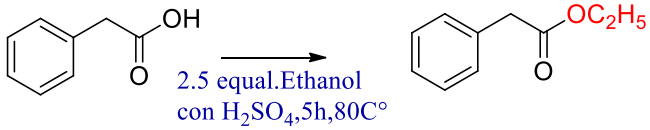
5-fluoro-3-phenylquinolin-2-ol **(3b),** Red crystal, m.p.:146˚C yield; 59 %; IR (KBr, ν_{max}, cm^{-1}): 3440, 3300, 3057, 2918, 1655, 1554; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.30 (bs,1H, quinoline-OH), 8.69 (bs, 1H, quinoline-C_4-H), 8.16-8.14 (d, 1H, *J* = 8.5 quinoline, C_8-H), 8.02-8.00 (d, 1H, *J* = 8.0 quinoline-C_7-H), 8.0 (s, 1H, quinoline-C_5-H), 7.54 (m, 3H, phenyl (C_2-H,C_5-H), quinoline (C_6-H)); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 147.3, 138.8, 133.3, 130.7, 129.9, 129.6, 129.5, 129.0, 128.9, 128.5, 128.3, 128.1, 126.6, 124.4, 116.8; GC-MS: m/z [M+1] 239.

3-phenylquinoline-2,5-diol **(3c),** Yellow, m.p.:176, 59% yield; IR (KBr, ν_{max}, cm^{-1}): 3800, 3716, 3440, 3082, 3058, 1655, 1585, 1495, 776; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.10 (bs, 1H, quinoline C_2-OH), 8.29 (s, 1H, quinoline-C_5-H), 7.82 (t, 1H, quinoline-C_7-H), 7.51-7.48 (2d, 2H, phenyl-C_3 and C_5-H), 7.34 (t, 1H, aromatic C_3-H), 7.50 (t, quinoline C_7-H), 5.50 (bs, 1H, quinoline C_5-OH); ^{13}C NMR (120 MHz, $CDCl_3$): δ 178.9, 149.5, 146.5, 139.5, 139.1, 137.4, 137.3, 135.4, 134.8, 130.8, 130.6, 129.6, 129,4, 128.9, 128.4, 127.5, 123.5, 120.8, 116.0; GC-MS: m/z [M+1] 238.

RESULTS AND DISCUSSIONS

Synthesis and characterization

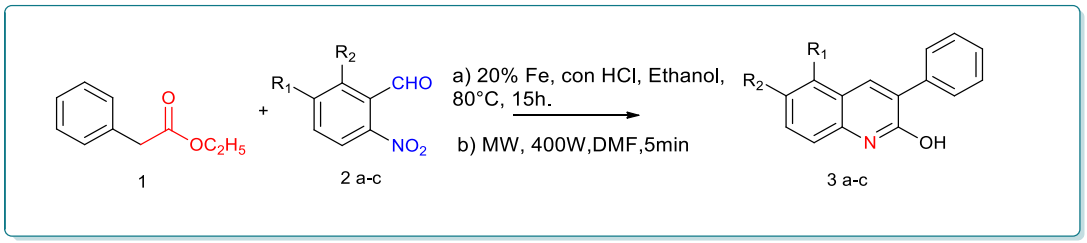
1-phenylethylacetate **1** was chosen as a starting precursor since its synthesis has been clearly described in our previous reports [13, 19-22].



Scheme 1. Synthesis of ethylphenylacetate

The treatment of 1-phenylethylacetate **1** and *O*-nitrobenzaldehyde **2** a-c in ethanol in the presence of 20% Fe powder / con HCl at reflux condition afforded the corresponding 2-hydroxy-3-phenylquinoline derivatives **3** a-c in high yields (Scheme 2).

After usual work-up, followed by column chromatography purification with the mobile phase of petroleum ether and ethyl acetate (10:90), 75% yield of 3-phenyl-2-hydroxyquinoline derivatives, as a yellow powder, was obtained. For the synthesis responsible for compounds 3 (a-c), the FT-IR spectrum of aromatic OH stretching appeared at 3550-3200 cm-1, the 1H-NMR spectrum of characteristic chemical showed a shift at δ 12.00 observed for quinoline C2- hydroxyl hydrogen bored singlet and multiplet for aromatic protons at 6.72–8.09. The 13C-NMR spectrum further supported the unique structure; the ester carbon at δ 180-190 disappeared and finally the mass spectrum confirmed compounds 3 (a-c).



Scheme 2. The reaction of **1, 2** a-c**.**

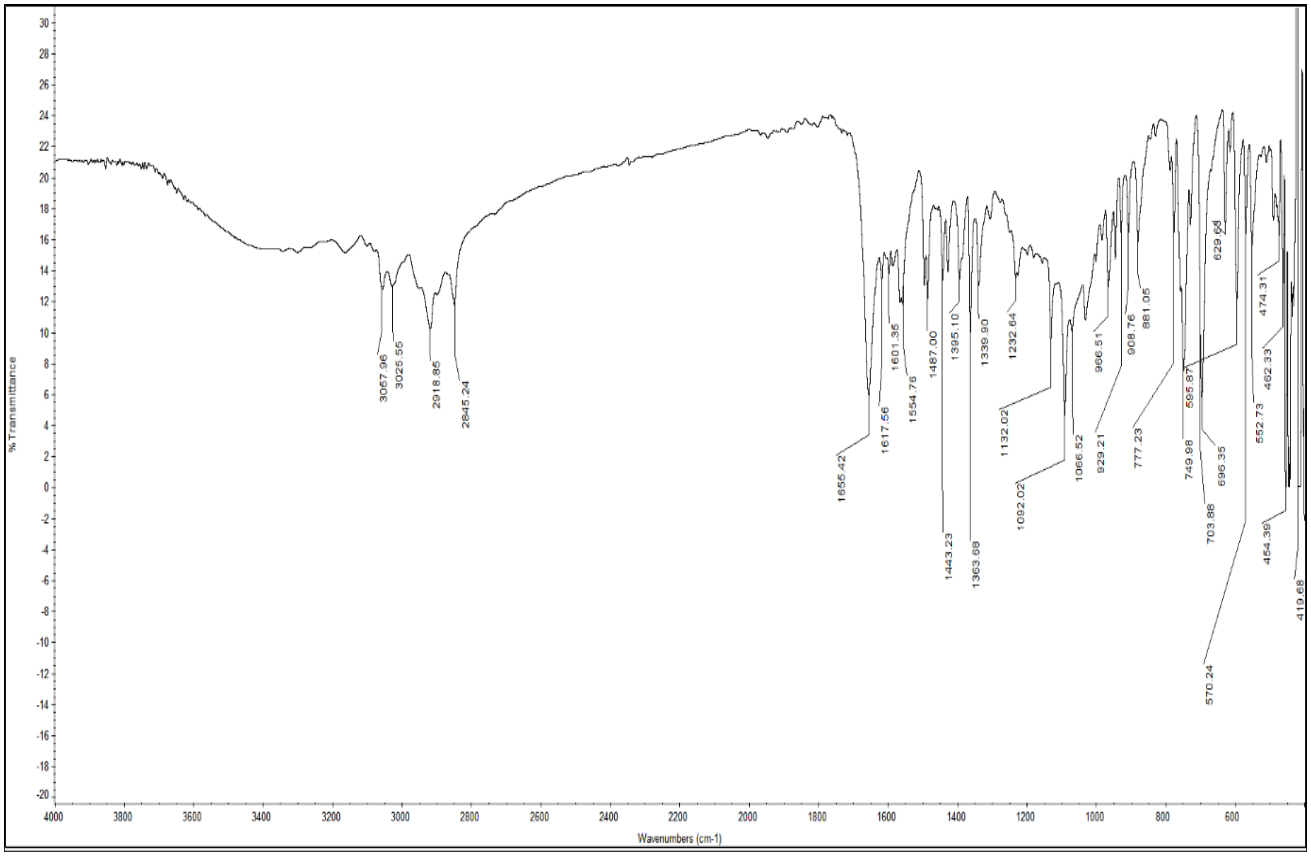


Figure 2. FT-IR Spectrum of 3-phenylquinolin-2-ol (3a).

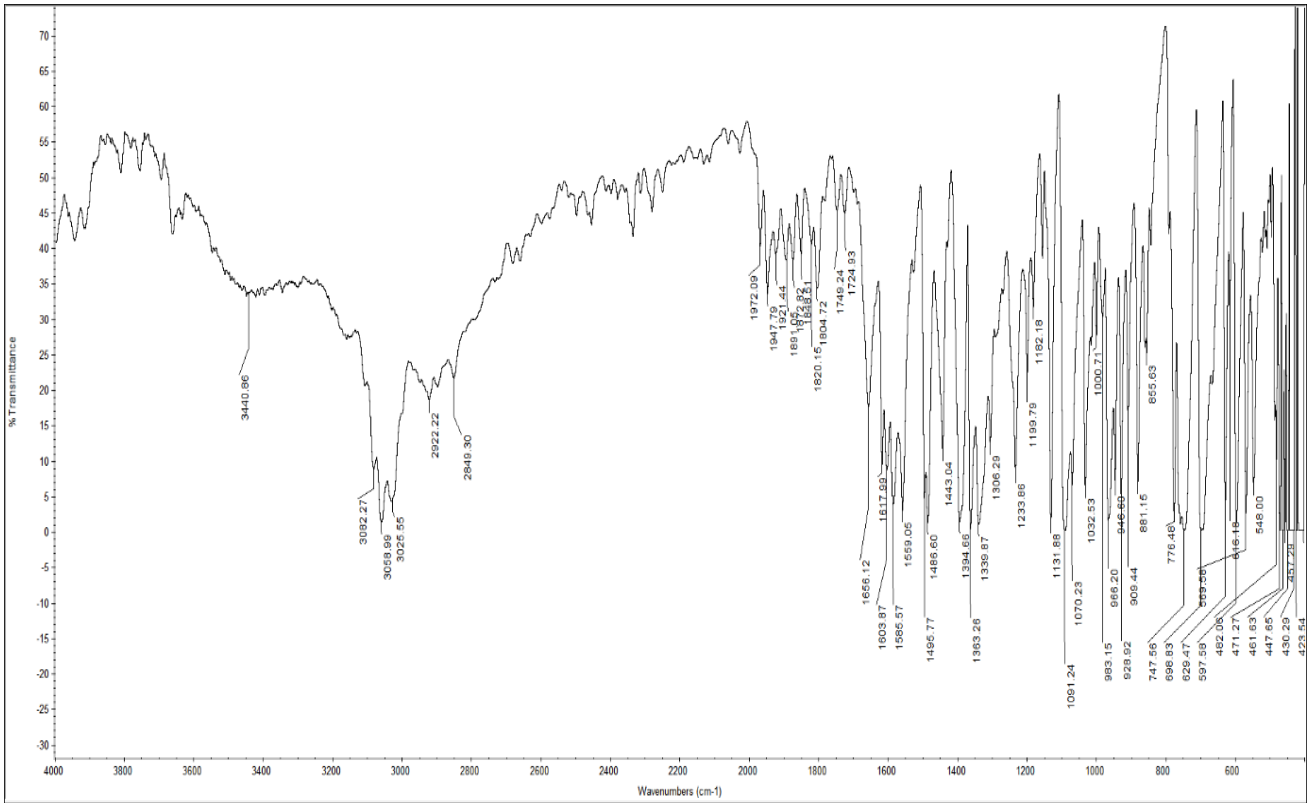


Figure 3. FT-IR Spectrum of 5-fluoro-3-phenylquinolin-2-ol (3b).

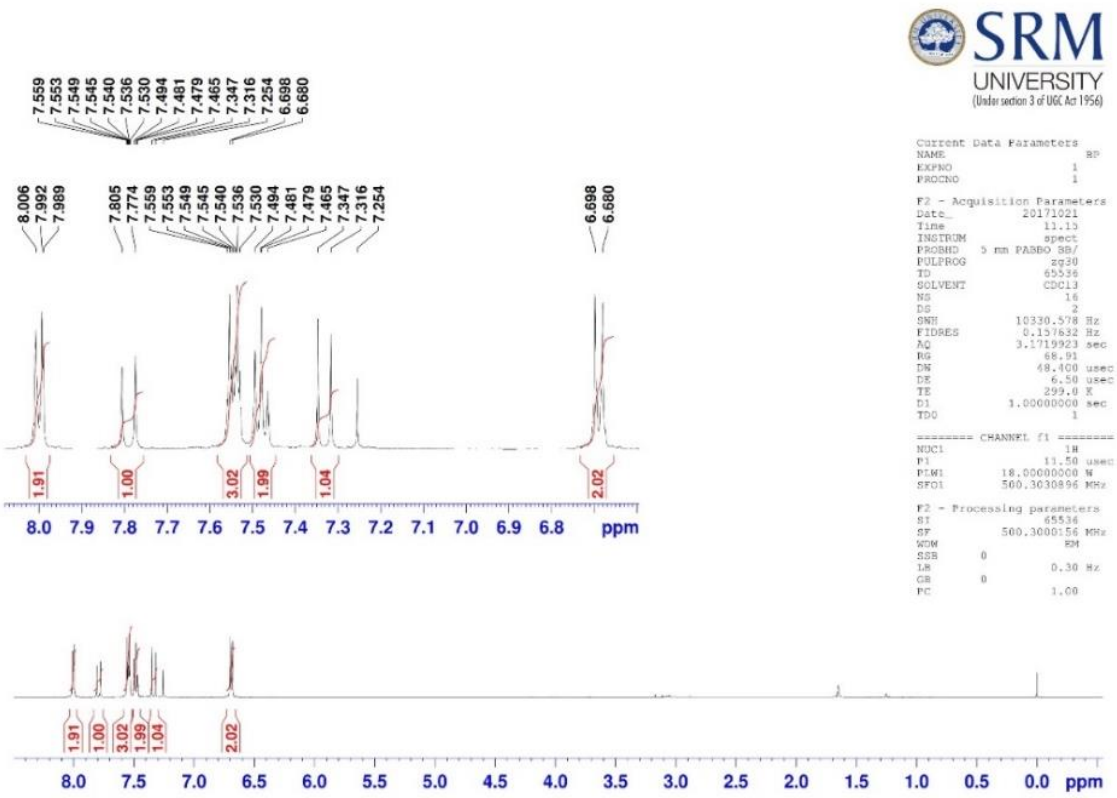


Figure 4. ^{1}H-NMR Spectrum of 3-phenylquinolin-2-ol (3a).

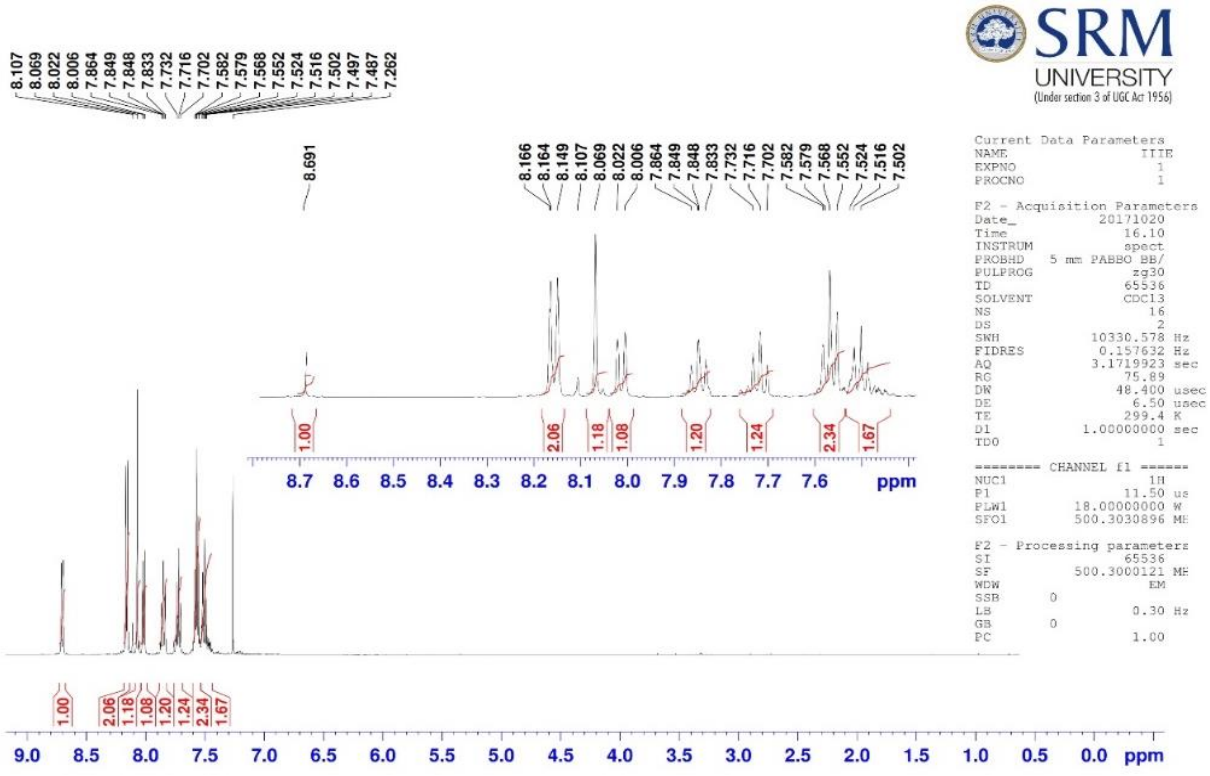


Figure 5. [1]H-NMR Spectrum of 5-fluoro-3-phenylquinolin-2-ol (3b).

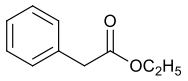
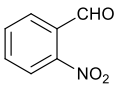
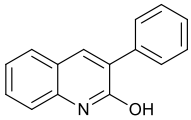
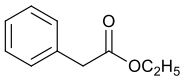
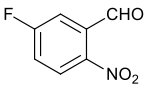
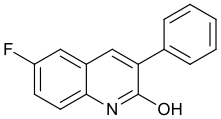
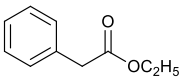
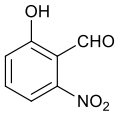
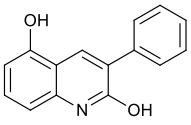
Using the conversion of 1-phenylethylacetate **1** and *O*-nitrobenzaldehyde **2a** as a model, several parameters were explored as shown in Table 1. **4a** was not detected by TLC at room temperature and reflux in the absence of iron (Table 1, Entries 1 and 2), but much greater in the presence of various quantities of iron (Fe), reaching a maximum of 83% yield with 20 mol% Fe powder (Table 1, entries 5-7). The yield of **4a** was also dependent on temperature (entries 3~5), proceeding smoothly at reflux in high yields. Different solvents were also tested, and C_2H_5OH appeared to be the best medium for this transformation (entry 5 vs. 8-11).

Reagents and conditions: phenylethyl-acetate **1** (2.03g, 0.1 mole), *O*-nitrobenzaldehyde **2a** (0.1 mole), solvent (10 mL).

Table 1. Synthesis results of 4a under different reaction reagents and conditions.

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	-	C_2H_5OH	r.t.	12	0
2	-	C_2H_5OH	Reflux	12	0
3	Fe (5%)	C_2H_5OH	r.t.	12	Trace
4	Fe (5%)	C_2H_5OH	50	12	48
5	Fe (5%)	CH_3OH	Reflux	6	80
6	Fe (10%)	CH_3OH	Reflux	6	82
7	Fe (20%)	CH_3OH	Reflux	6	83
8	Fe (5%)	CH_3CN	Reflux	6	60
9	Fe (5%)	Benzene	Reflux	6	56
10	Fe (5%)	DMF	Reflux	6	31
11	Fe (20%)	$CHCl_3$	Reflux	6	45
12	Fe (20%)	DMF	400w	5 min	92

Table 2. Synthesis results of 3a-c catalyzed by iron.

Entry	1-phenylethylacetate 1	O-nitrobenzaldehyde 2	Product 3	Yields %
1		 2a	 3a	80
2		 2b	 3b	68
3		 2c	 3c	57

[a] Reagents and conditions: phenylethylacetate **1** (2.03g, 0.1 mole), *O*-nitrobenzaldehyde **2a** (0.1mole), ethanol solvent (10 mL). [b] Isolated yields.

These optimized conditions were applied to the conversion of various kinds of O-nitro-benzaldehyde 2a-c into the corresponding 2,4-dihydroxy-3-phenylquinoline 3. Reactions using aldehydes containing electron-withdrawing groups (F, NO2, Br) on 2-nitrobenzaldehyde proceeded smoothly within a few hours, giving 4a-l in high yields. It should be noted that only 2,4-dihydroxy-3-phenylquinoline 3 was obtained in high chemo-selective and then products were still isolated in moderate to good yields (56%–85%).

CONCLUSIONS

In conclusion, we found a mild and efficient method for the synthesis of 2-hydroxy-3-phenylquinoline derivatives via single step Bechamp reduction reactions of 2-nitrobenzaldehyde and phenylethyl-acetate catalysed by iron. The features of this procedure are mild reaction conditions, high yields, operational simplicity, one-pot and metal-free catalyst.

ACKNOWLEDGEMENTS

The author gratefully acknowledges the Laboratory support from Annai Group of Institution, Kumbakonam, India for this work.

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