Indian Journal of Chemistry
Vol. 46B, July 2007, pp. 1203-1207

Note

Microwave-assisted solvent-free synthesis of 4-methyl-2-hydroxy- and 2-methyl-4-hydroxyquinolines

V Nadaraj & S Thamarai Selvi*

Department of Chemistry (PG & Research) Kongunadu Arts and Science College, G.N. Mills Post, Coimbatore 641 029, India

E-mail: thamaraimohan@yahoo.co.in

Received 14 September 2006; accepted (revised) 9 March 2007

Rapid and efficient microwave-assisted synthesis of 4-methyl-2-hydroxy- and 2-methyl-4-hydroxyquinolines from anilines and ethyl acetoacetate under different conditions is described.

Keywords: 4-Methyl-2-hydroxyquinolines, 2-methyl-4-hydroxyquinolines, microwave irradiation, solvent-free synthesis, quinolines

Reaction between different aromatic amines and ethyl acetoacetate is well explored. Attack of amine on the ketone carbonyl is favoured when the initial reaction is carried out at RT in an acidic medium, while attack of amine on the ester function, which is thermodynamically favoured, occurs when the reaction is carried out at 110-40°C (**Scheme I**).

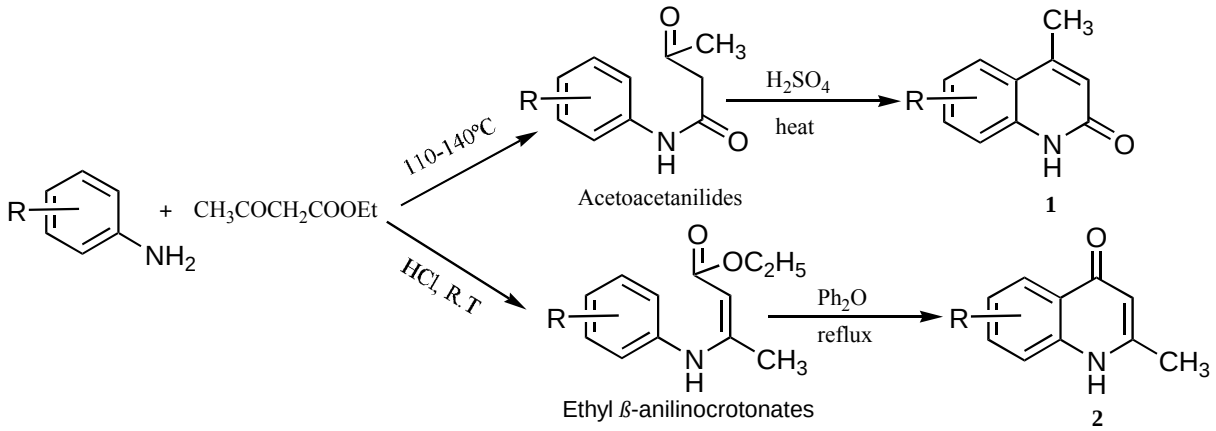
Hence the synthesis of 2(4)-methyl-4(2)-hydroxyquinolines is a two step process based on the above reaction sequence. Though the synthesis of these quinolines has been well documented with a variety of reaction conditions being available, many of these have limitations in their general application[1-6]. For example, hazardous acidic condition is required in the second step of the synthesis of 4-methyl-2-hydroxyquinolines and the preparation of 2-methyl-4-hydroxyquinolines involves cyclisation of ethyl β-anilinocrotonates in high boiling solvents like diphenyl ether, Dowtherm or paraffin oil.

Microwave irradiation has opened up new possibilities in synthetic organic chemistry, not only in terms of yield and selectivity, but also in ease of the reaction conditions[7-11]. Microwave heating in dry media is especially appealing for providing an environmentally benign system[12,13]. The synthesis of 4-methyl-2-hydroxy- and 2-methyl-4-hydroxyquinolines is important because of their applications as synthons in various heterocyclic synthesis and chemical transformations[14-20]. Herein is reported an easy, efficient, solvent-free, one pot synthesis of 4-methyl-2-hydroxyquinolines under mild acidic conditions and solvent-free, uncatalysed synthesis of 2-methyl-4-hydroxyquinolines.

Results and Discussion

Microwave assisted condensation between aniline and ethyl acetoacetate under neat condition has been tried. The reaction failed because trace amount of acid was absent, which is required for the formation of either *β*-anilinocrotanate or acetoacetanilide.

Hence, the same reaction has been tried with *p*-toluenesulphonic acid as a catalyst, which afforded a colourless solid, the structure of which was assigned as 4-methyl-2-hydroxyquinoline **1a** on the basis of spectral and analytical data. Thus, IR spectrum of the



Scheme I

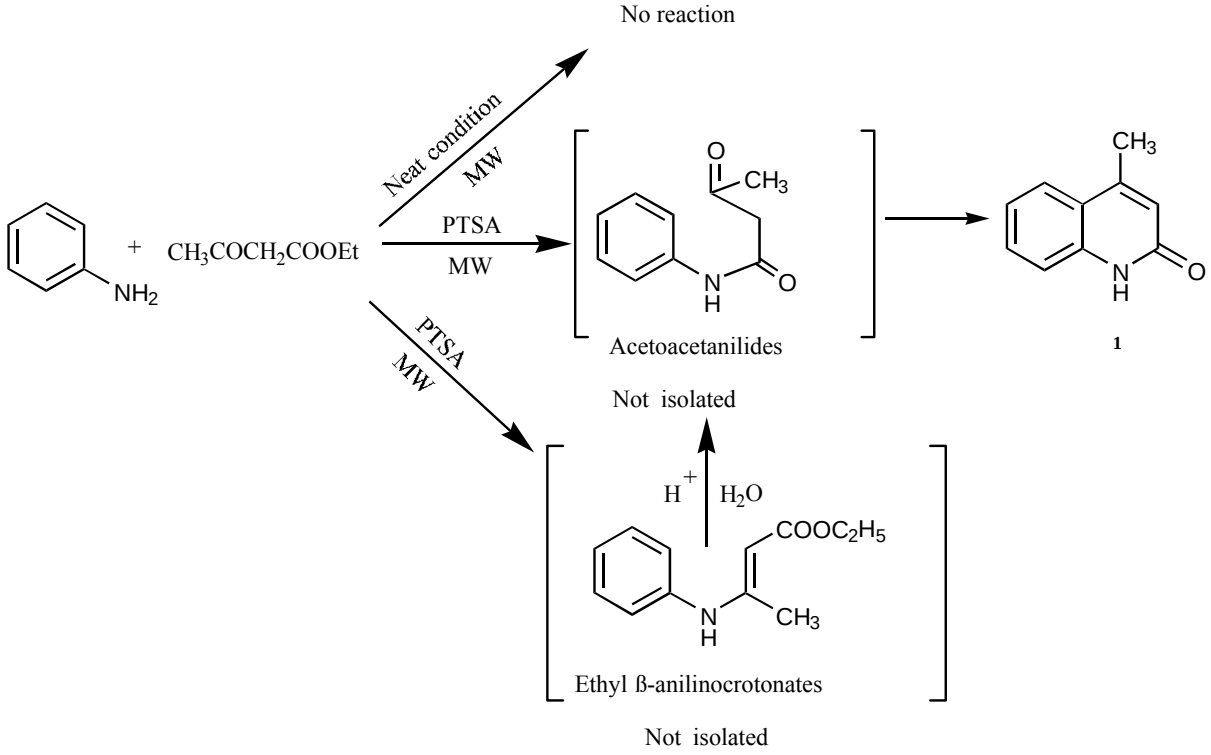
solid showed absorption bands at 1660 cm^{-1} and 3000-3300 cm^{-1} attributable to 2-quinolinone and NH stretching vibrations respectively. The ^1H NMR spectrum represented a singlet at δ 2.41 for the C_4-CH_3 protons, singlet at δ 6.21 for the C_3-H, multiplet in the region δ 7.35-8.18 for aromatic protons and a singlet at δ 11.68 for NH proton. Mass spectrum showed a molecular ion peak at *m/z* 159 ($M^{+\cdot}$, 15%) and elemental analysis corroborated the proposed molecular formula $C_{10}H_9NO$. Found: C, 75.40; H, 5.69; N, 8.78. Calcd.: C, 75.43; H, 5.70;N, 8.80%. Moreover the m.p. of the solid is consistent with Lit.[21] m.p. of 4-methyl-2-hydroxyquinoline as 224°C.

The unexpected formation of 4-methyl-2-hydroxyquinoline can be explained by the reaction of aniline and ethyl acetoacetate to give acetoacetanilide at high temperature which further underwent cyclisation to give **1a** in the presence of *p*-toluenesulphonic acid in a single step with quantitative yield (91%). β-Anilinocrotanate formation is also possible in the presence of acid at high temperature. However, it may be converted into anilide in the presence of acid and water, which is indeed formed during the course of reaction, as both crotonate and anilide formations are reversible[22] (**Scheme II**). Hence, the formation of 4-methyl-2-hydroxyquinoline as the exclusive product. The reaction was very well generalised with different aromatic amines and ethyl acetoacetate, which afforded corresponding 4-methyl-2-hydroxyquinolines **1b-i** (**Scheme III**) in good to excellent yield with shorter reaction times (**Table I**).

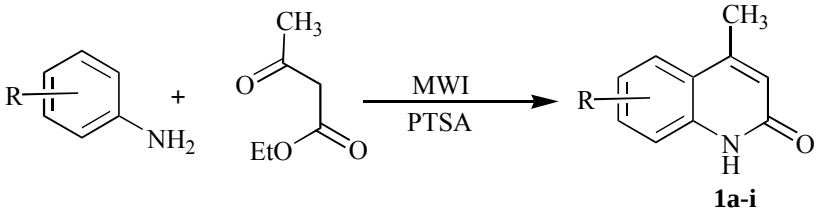
The use of other acidic catalysts like acetic acid, silica gel, acidic alumina and montmorillonite K_{10} clay gave poor results with lesser yield and mixture of products as compared to *p*-toluenesulphonic acid (**Table II**).

In another exploration of the pursuit of microwave irradiation, it was desired to generalize a solvent-free synthetic route for 2-methyl-4-hydroxy quinolines as they are very good intermediates for the synthesis of some other heterocycles[14,15,20]. Thus, ethyl β-anilinocrotonate was prepared[23] from aniline and ethyl acetoacetate at RT and irradiated under microwaves in the absence of any solvent and catalyst. The product 2-methyl-4-hydroxy quinoline was formed within 2.0 min and the structure of the compound was assigned using m.p., (Lit. m.p. 234°C)(Ref. 23), m.p., IR, ^1H NMR and mass spectral data. This methodology was extended to the synthesis of other derivatives **2b-i** (**Scheme IV**). In all the cases reaction proceeded successfully with good yields of the end product (**Table I**).

In conclusion, a simple, fast, solvent-free, solid based and efficient method has been formulated for



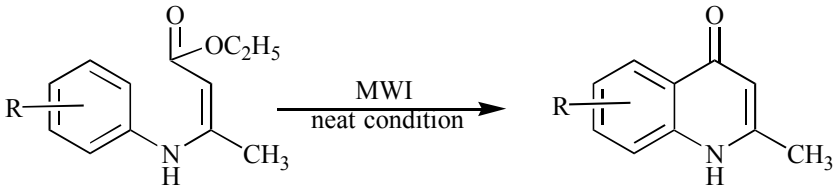
Scheme II



1a-i

1a: R = H **1b**: R = 6-CH_3 **1c**: R = 8-CH_3 **1d**: R = 6-OCH_3 **1e**: R = 8-OCH_3
1f: R = 6-Cl **1g**: R = 6-Br **1h**: R = 8-NO_2 **1i**: R = 8-OH

Scheme III



Ethyl ß-anilino crotonates

2a-i

2a: R = H **2b**: R = 6-CH_3 **2c**: R = 8-CH_3 **2d**: R = 6-OCH_3 **2e**: R = 8-OCH_3
2f: R = 6-Cl **2g**: R = 6-Br **2h**: R = 8-NO_2 **2i**: R = 8-OH

Scheme IV

Table I — Physical data of compounds **1a-i** and **2a-i**

Compd	Time (min)	Yield (%)	m.p. (Lit. m.p.) °C	Compd	Time (min)	Yield (%)	m.p. (Lit. m.p.) °C
1a	2.00	91	224-25 (223) (Ref. 21)	**2a**	3.00	92	234-45 (234) (Ref. 23)
1b	2.30	97	190-91	**2b**	2.30	96	283-84 (280) (Ref. 24)
1c	2.35	99	184-86	**2c**	3.00	90	262-64
1d	2.30	93	168-67	**2d**	2.00	92	201-02
1e	3.00	99	158-60	**2e**	3.00	89	218-20
1f	4.00	76	195-97	**2f**	4.00	77	>300 (320) (Ref. 25)
1g	4.30	91	203-05 (292) (Ref. 19)	**2g**	3.30	74	280-82 (>300) (Ref. 25)
1h	4.00	63	154-55	**2h**	4.00	80	223-24
1i	3.00	89	196-98 (190) (Ref. 6)	**2i**	3.00	90	265-66

the construction of 4-methyl-2-hydroxy- and 2-methyl-4-hydroxyquinolines from anilines and ethyl acetoacetate under different conditions.

Experimental Section

Melting points were recorded on Boetieus micro-heating table and are uncorrected. IR (KBr) spectra were recorded on a Shimadzu-8201 FT spectrometer. ^{1}H NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference, and mass spectra were recorded at 70 eV on a Jeol JMS-D-300 instrument. The reactions were carried out in a domestic microwave oven (KENSTAR-OM-20ESP, 2450 MHz).

Table II — Effect of different acid catalyst for the synthesis of **1a** under microwave irradiation (power = 160 W)

Catalyst	Time (min)	Yield (%)
None	30	Nil
Silica gel	15	45.0
Acidic alumina	13.5	72.7
K10	22	55.2
AcOH	20	63.0

Table III — Spectral characterization and elemental analysis data of compounds **1a-i** and **2a-i**

Compd	^{1}H NMR (DMSO-d_6) (δ, ppm)	Found (Calcd) C	H	N	MS (70 eV) $M^{+\cdot}$ (*m/z*)
1a	2.41 (s, 3H, C_4-CH_3), 6.21 (s, 1H, C_3-H), 7.35-8.18 (m, 4H, Ar-H), 11.68 (s, 1H, NH)	75.40 (75.43	5.69 5.70	8.78 8.80)	159
1b	2.42 (s, 3H, C_4-CH_3), 2.44 (s, 3H, C_6-CH_3), 6.23 (s, 1H, C_3-H), 7.36-8.21 (m, 3H, Ar-H), 11.65 (s, 1H, NH)	76.25 (76.26	6.39 6.40	8.05 8.08)	173
1c	2.41 (s, 3H, C_4-CH_3), 2.43 (s, 3H, C_8-CH_3), 6.24 (s, 1H, C_3-H), 7.30-8.19 (m, 3H, Ar-H), 11.65 (s, 1H, NH)	76.24 (76.26	6.37 6.40	8.06 8.08)	173
1d	2.41 (s, 3H, C_4-CH_3), 3.98 (s, 3H, C_6-OCH_3), 6.23 (s, 1H, C_3-H), 7.30-8.23 (m, 3H, Ar-H), 11.70 (s, 1H, NH)	69.75 (69.80	5.79 5.86	7.36 7.40)	189
1e	2.43 (s, 3H, C_4-CH_3), 3.99 (s, 3H, C_8-OCH_3), 6.24 (s, 1H, C_3-H), 7.26-8.28 (m, 3H, Ar-H), 11.66 (s, 1H, NH)	69.73 (69.80	5.77 5.86	7.38 7.40)	189
1f	2.42 (s, 3H, C_4-CH_3), 6.20 (s, 1H, C_3-H), 7.30-8.41 (m, 3H, Ar-H), 11.69 (s, 1H, NH)	62.00 (62.01	4.44 4.46	7.20 7.23)	193
1g	2.43 (s, 3H, C_4-CH_3), 6.22 (s, 1H, C_3-H), 7.35-8.26 (m, 3H, Ar-H), 11.65 (s, 1H, NH)	50.40 (50.42	3.35 3.38	5.83 5.88)	237
1h	2.41 (s, 3H, C_4-CH_3), 6.22 (s, 1H, C_3-H), 7.35-8.30 (m, 3H, Ar-H), 11.70 (s, 1H, NH)	58.78 (58.80	3.92 3.95)	13.70 13.72)	204
1i	2.42 (s, 3H, C_4-CH_3), 6.23 (s, 1H, C_3-H), 7.26-8.39 (m, 3H, Ar-H), 11.70 (s, 1H, NH), 12.06 (s, 1H, OH)	68.55 (68.57	5.13 5.14	7.98 8.00)	175
2a	2.33 (s, 3H, C_2-CH_3), 6.02 (s, 1H, C_3-H), 7.40-8.20 (m, 4H, Ar-H), 11.70 (s, 1H, NH)	75.42 (75.43	5.67 5.70	8.76 (8.80)	159
2b	2.34 (s, 3H, C_2-CH_3), 2.44 (s, 3H, C_6-CH_3), 6.05 (s, 1H, C_3-H), 7.36-8.23 (m, 3H, Ar-H), 11.71 (s, 1H, NH)	76.22 (76.26	6.37 6.40)	8.05 (8.08)	173
2c	2.34 (s, 3H, C_2-CH_3), 2.42 (s, 3H, C_8-CH_3), 6.06 (s, 1H, C_3-H), 7.40-8.25 (m, 3H, Ar-H), 11.70 (s, 1H, NH)	76.23 (76.26	6.39 6.40	8.04 (8.08)	173
2d	2.33 (s, 3H, C_2-CH_3), 3.97 (s, 3H, C_6-OCH_3), 6.02 (s, 1H, C_3-H), 7.40-8.23 (m, 3H, Ar-H), 11.70 (s, 1H, NH)	69.74 (69.80	5.80 5.86	7.37 7.40)	189
2e	2.32 (s, 3H, C_2-CH_3), 3.99 (s, 3H, C_8-OCH_3), 6.02 (s, 1H, C_3-H), 7.46-8.30 (m, 3H, Ar-H), 11.66 (s, 1H, NH)	69.77 (69.80	5.79 5.86	7.39 7.40)	189
2f	2.31 (s, 3H, C_2-CH_3), 6.00 (s, 1H, C_3-H), 7.42-8.26 (m, 3H, Ar-H), 11.70 (s, 1H, NH)	62.00 (62.01	4.43 4.46)	7.25 7.23)	193
2g	2.33 (s, 3H, C_2-CH_3), 5.96 (s, 1H, C_3-H), 7.40-8.21 (m, 3H, Ar-H), 11.65 (s, 1H, NH)	50.41 (50.42	3.37 3.38	5.85 5.88)	237
2h	2.36 (s, 3H, C_2-CH_3), 6.06 (s, 1H, C_3-H), 7.45-8.30 (m, 3H, Ar-H), 11.72 (s, 1H, NH)	58.78 (58.8	3.94 3.95	13.70 13.72)	204
2i	2.35 (s, 3H, C_2-CH_3), 6.00 (s, 1H, C_3-H), 7.46-8.29 (m, 3H, Ar-H), 11.70 (s, 1H, NH), 12.05 (s, 1H, OH)	68.55 (68.57	5.13 5.14	7.98 8.00)	175

General procedure for synthesis of 4-methyl-2-hydroxyquinolines, 1a-i

Respective anilines (0.01 mol), ethyl acetoacetate (0.01 mol) and *p*-toluenesulphonic acid (120 mg) were taken in 100 mL beaker, mixed well and irradiated in a microwave oven at the power of 320 W for the specified time (**Table I**). The progress of the reaction was monitored after every 30s by TLC. After irradiation, 10 mL of petroleum ether (60-80ºC) was added. The product was collected by suction and purified by recrystallisation from DMF-water. The spectral and analytical data of the compounds are shown in **Table III**.

General procedure for synthesis of 2-methyl-4-hydroxyquinolines, 2a-i

Ethyl β-anilinocrotonate (1g) was taken in a beaker and irradiated in a microwave oven, at the power of 320 W for the specified time (**Table I**). The progress of the reaction was monitored after every 30s by TLC. After completion of the reaction, 10 mL of petroleum ether (60-80ºC) was added. The solid obtained was further washed with benzene and dried. The product

was purified by recrystallisation from hot ethanol-water. The spectral and analytical data of the compounds are shown in **Table III**.

References

1 Knorr, *Ber,* 16, **1883**, 2593.
2 Conrand & Limpach, *Ber,* 20, **1887**, 944.
3 Cavalito & Haskell, *J Am Chem Soc,* 66, **1944**, 1166.
4 Kaslow & Marsh, *J Org Chem*, 12, **1947**, 456.
5 Deshmukh M B & Chavan P B, *J Indian Chem Soc*, 68, **1991**, 573.
6 Deshmukh M B, Desai S D & Chavan S S, *Indian J Chem*, 44B, **2005**, 1659.
7 Caddick S, *Tetrahedron,* 51, **1995**, 10403.
8 Mogailaiah K & Vasudeva Reddy N, *Indian J Chem*, 42B, **2003**, 2124.
9 Surayaprakash Rao H & Senthil Kumar S P, *J Chem Soc,* 116, **2004**, 163.
10 Thamarai Selvi S, Nadaraj V, Mohan S, Sasi R & Hema M, *Bioorg & Med Chem,* 14, **2006**, 3896.
11 Nadaraj V, Thamarai Selvi S & Sasi R, *Arkivoc*, X, **2006**, 82.
12 Kidwai M & Misra P, *Synth Commun*, 29, **1999**, 3237.
13 Palle L, Jason T, Bernard W & Jacob W, *Tetrahedron,* 57, **2001**, 9225.
14 Thamarai Selvi S & Mohan P S, *Indian J Chem*, 39B, **2000**, 703.
15 Thamarai Selvi S & Mohan P S, *Heterocyclic Commun*, 5, **1999**, 533.
16 Nandhakumar R, Suresh T & Mohan P S, *Indian J Chem*, 42B, **2003**, 2069.
17 Polt K T, Bhattacharya J, Smith S L, Ihring A M & Girard C A, *J Org Chem*, 37, **1927**, 4410.
18 Kidwai M, Goel Y & Kumar R *Indian J Chem*, 37B, **1998**, 174.
19 Davis S E, Rauckman B S, Chan J H & Roth B, *J Med Chem,* 32, **1989**, 1936.
20 Dhanabal T, Sangeetha R & Mohan P S, *Tetrahedron*, 62, **2006**, 6258.
21 Vidya D G, Jyothi B S, Santosh G T & Raghao S M, *J Chem Res (s),* 10, **2003**, 628.
22 Hauser C R & Reynolds G A, *J Am Chem Soc*, 70, **1948**, 2402.
23 Reynolds G A & Hauser C R, in *Organic Synthesis* edited by E C Hornig (John Wiley and Sons, New York) Coll Vol 3, **1995**, 593.
24 Geissman T A, Schlatter M J, Webb I D & Roberts J D, *J Org Chem,* 11, **1946**, 741.
25 Kermack W O & Weatherhead A P, *J Chem Soc*, **1939**, 563.