A facile and green preparation of 2,4-diarylpolyhydroquinolines

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An efficient and environmentally benign procedure for the preparation of 2,4-diarylpolyhydroquinoline derivatives from 5,5-dimethylcyclohexane-1,3-dione, chalcones and ammonium acetate under microwave irradiation in a solvent-free manner is described in this paper.

Keywords: 2,4-diarylpolyhydroquinolines, green chemistry

The polyhydroquinoline moiety is present in various natural products, and many polyhydroquinoline derivatives exhibit a broad range of biological activities.[1] In particular, it has been reported that 4-arylpolyhydroquinolines play an important role in medical chemistry serving as vasodilators and antihypertensive agents.[2] Therefore, it is not surprising that many synthetic methods towards polyhydroquinoline derivatives have already been developed.[3] Nevertheless, these methods often involved harsh conditions, long reaction time, and large amount of conventional organic solvents, which are usually volatile, flammable, toxic and thus environmentally hazardous. Consequently, there have been always needs for the development of more efficient and greener procedures for the preparation of polyhydroquinolines as well as, of course, other kinds of organic compounds.

In recent years, the utilisation of microwave irradiation in chemical transformations has attracted considerable interests[4] and is of significant importance in search of green synthesis and sustainable chemistry. It is due to the fact that compared with conventional heating, not only can microwave irradiation save energy and time, but also in most cases avoid the use of expensive and toxic solvents. Moreover, many microwave-assisted reactions also demonstrate advantages as better yields and higher selectivity compared to conventional methods. As continuation of our interest in the area of clean synthesis, we report a very convenient and green procedure for the preparation of 2,4-diarylpolyhydroquinoline derivatives (**3**, Scheme 1) through a three-component coupling reaction of chalcones (**1**), 5, 5-dimethylcyclohexane-1, 3-dione (**2**), and ammonium acetate under microwave irradiation in the absence of any solvents.

Results and discussion

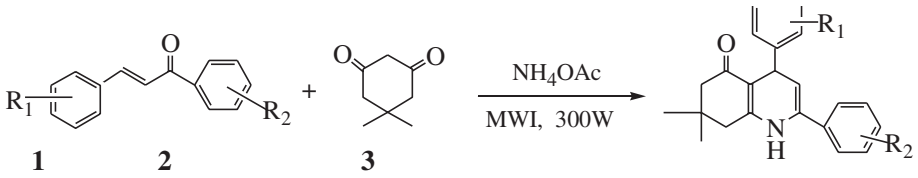
The feasibility of the present procedure was first examined by using 1,3-diphenyl-2-propen-1-one (**1a**) as a model substrate. Firstly, **1a**, **2** and ammonium acetate were mixed together and subjected to microwave irradiation (300 W) for several minutes. Unfortunately, subsequent TLC analyses indicated that it had resulted in a complicated mixture, from which, the desired product was obtained with a mere 30% yield. As an alternative, firstly, **2** and ammonium acetate was mixed together and then treated under microwave irradiation (300 W) for 2 min. TLC analysis showed that **2** was consumed completely and the corresponding enamine intermediate was formed. Then **1a** was added and the mixture was exposed to microwave irradiation at 300 W for 5 min. Then, TLC analysis showed that a new compound was formed in the mean time, but part of the enamine intermediate still remained intact. Our next try by having the mixture of the enamine intermediate and **1a** under MW irradiation for 10 min gave a much more improved result but the reaction was still uncompleted. Finally, when the irradiation period was prolonged to 15 min, a complete conversion was observed and the desired product **3a** was obtained in 80% yield (Table 1, Entry 1).

This three-component condensation reaction was then extended to other chalcone derivatives (**1b–j**) and the results were summarised in Table 1. It showed that in general a wide range of chalcones could react with **2** and ammonium acetate smoothly and gave **3** in good to excellent yields (Table 1, entries 1–9). It is also notable that the electronic property of the aromatic ring of chalcones has some effects on the rate of the condensation process. Generally speaking, shorter reaction time was needed for the substrates bearing electron-withdrawing groups on the aromatic rings (Table 1, entries 2, 3, 5, 6, 8, 9). On the other hand, while substrates bearing electron-donating groups can afford the corresponding products with almost equally satisfactory yields, a little bit

Table 1 Preparation of **3** under microwave irradiation in the absence of solvent[a]

Entry	Substrates	R_1	R_2	Products	Time /min	Yields /%[b]
1	**1a**	H	H	**3a**	15	80
2	**1b**	H	*p*-NO_2	**3b**	11	84
3	**1c**	H	*p*-Br	**3c**	12	83
4	**1d**	*p*-CH_3	H	**3d**	16	77
5	**1e**	*p*-Cl	*p*-NO_2	**3e**	10	86
6	**1f**	*m*-NO_2	*p*-Cl	**3f**	10	85
7	**1g**	*p*-OCH_3	H	**3g**	16	75
8	**1h**	*p*-Cl	H	**3h**	13	82
9	**1i**	H	*p*-Cl	**3i**	12	80

[a]Irradiated at 300W; [b]Isolated yields.



1 2 3

Scheme 1

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longer reaction period was necessary to complete the reaction (Table 1, entries 1, 4, 7).

In summary, an application of microwave irradiation without any solvent in the preparation of polyhydroquinoline derivatives from a variety of chalcones, dimedone and ammonium acetate is described in this paper. With its operational simplicity, good yields, short reaction time as well as clean nature, this procedure may provide a novel alternative for the preparation of polyhydroquinoline derivatives.

Experimental

Melting points were measured by a Kofler micro-melting point apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC 400 spectrometer as DMSO solutions. Chemical shifts (δ) were expressed in ppm downfield from the internal standard tetramethylsilane and coupling constants *J* were given in Hz. Mass spectra were recorded on a HP-5989B mass spectrometer. Elemental analyses were performed on a PE-2400 CHN elemental analyzer.

General procedure for the preparation of 2,4-diaryl-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives

5,5-dimethylcyclohexane-1,3-dione **2** (1mmol) and ammonium acetate (2.5 mmol) were mixed together in a 10 ml open flask. The flask was then placed in a domestic microwave oven (Galanz WD750S) and was exposed to microwave irradiation (300 W) for 2 min. Then, **1** (1mmol) was added and the mixture was allowed to be irradiated at 300 W for a certain period of time as required to complete the reaction (monitored by TLC). At completion, the reaction mixture was allowed to reach room temperature and ethanol (95%) was added to the mixture. The solid precipitated was collected by suction and recrystallised from ethanol (95%) to give products **3** (shown in Table 1).

7,7-Dimethyl-5-oxo-2,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline (**3a**): M.p. 193–195 °C (lit[3f]. 206–208 °C); ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.94 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.98 (d, 1H, *J* = 16 Hz, CH_2), 2.15 (d, 1H, *J* = 16 Hz, CH_2), 2.47 (s, 2H, CH_2), 4.55 (d, 1H, *J* = 5.6 Hz, CH), 5.18 (d, 1H, *J* = 5.6 Hz, =CH), 7.05–7.10 (m, 1H, ArH), 7.18–7.21 (m, 4H, ArH), 7.30–7.37 (m, 3H, ArH), 7.46 (d, 2H, *J* = 7.2Hz, Ar H), 8.51 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3286, 3075, 2959, 1658, 1623, 1591, 1493, 1393, 848, 767, 699; MS (70eV), *m/z* (%): 330 (M + 1), 329 (M^+), 252, 207, 168, 115, 77, 28.

7,7-Dimethyl-2-(4-nitrophenyl)-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (**3b**): M.p. 224–226 °C; ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.94 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.99 (d, 1H, *J* = 16 Hz, CH_2), 2.16 (d, 1H, *J* = 16 Hz, CH_2), 2.52 (s, 2H, CH_2), 4.57 (d, 1H, *J* = 5.6 Hz, CH), 5.47 (d, 1H, *J* = 5.6Hz, = CH), 7.07–7.11 (m, 1H, ArH), 7.19–7.24 (m, 4H, ArH), 7.74 (d, 2H, *J* = 8.8 Hz, ArH), 8.20 (d, 2H, *J* = 8.8 Hz, ArH), 8.76 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3262, 3075, 2970, 1649, 1559, 1490, 1393, 1340, 851, 752, 700; MS (70eV), *m/z* (%): 374 (M^+), 371, 342, 316, 281, 241, 207, 139, 28. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.68; H, 5.87; N, 7.56.

2-(4-Bromophenyl)-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (**3c**): M.p. 234–236 °C (lit[3f]. 264–266 °C); ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.94 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.98 (d, 1H, *J* = 16 Hz, CH_2), 2.14 (d, 1H, *J* = 16 Hz, CH_2), 2.48 (s, 2H, CH_2), 4.53 (d, 1H, *J* =5.6 Hz, CH), 5.23 (d, 1H, *J* = 5.6 Hz, = CH), 7.05–7.09 (m, 1H, ArH), 7.19–7.23 (m, 4H, ArH), 7.42 (d, 2H, *J* = 8.4 Hz, ArH), 7.54 (d, 2H, *J* = 8.4 Hz, ArH), 8.52 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3233, 3073, 2970, 1667, 1592, 1502, 1386, 1327, 831, 696; MS (70eV), *m/z* (%): 409 (M+1), 408 (M^+), 407, 362, 330, 276, 242, 208, 167, 119, 73, 51.

7,7-Dimethyl-4-(4-methylphenyl)-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (**3d**): M.p. 186–188 °C; ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.92 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.95 (d, 1H, *J* = 16Hz, CH_2), 2.14 (d, 1H, *J* = 16Hz, CH_2), 2.19 (s, 3H, CH_3), 2.47 (s, 2H, CH_2), 4.48 (d, 1H, *J* = 5.6Hz, CH), 5.15 (d, 1H, *J* = 5.6Hz, = CH), 7.00 (d, 2H, *J* = 8.0Hz, ArH), 7.07 (d, 2H, *J* = 8.0Hz, ArH), 7.29–7.37 (m, 3H, ArH), 7.44 (d, 2H, *J* = 6.8Hz, ArH), 8.55 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3234, 3050, 2953, 1662, 1585, 1494, 1386, 1332, 811, 770, 699; MS (70eV), *m/z* (%): 344 (M+1), 343 (M^+), 340, 281, 252, 207, 133, 73, 28. Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.79; H, 7.46; N, 3.96.

4-(4-Chlorophenyl)-7,7-dimethyl-2- (4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**3e**): M.p. 242–244 °C; ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.93 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.00 (d, 1H, *J* = 16Hz, CH_2), 2.16 (d, 1H, *J* = 16Hz, CH_2), 2.47 (s, 2H, CH_2), 4.60 (d, 1H, *J* = 4.8Hz, CH), 5.43 (d, 1H, *J* = 4.8Hz, =CH), 7.21 (d, 2H, *J* = 8.0Hz, ArH), 7.27 (d, 2H, *J* = 8.0Hz, ArH), 7.75 (d, 2H, *J* = 8.0Hz, ArH), 8.20 (d, 2H, *J* = 8.0Hz, ArH), 8.74 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3332, 3085, 2955, 1659, 1589, 1489, 1391, 850, 753; MS (70eV), *m/z* (%): 408 (M+1), 407 (M^+), 405, 376, 350, 315, 281, 241, 207, 133, 73, 28. Anal. Calcd for $C_{23}H_{21}ClN_2O_3$: C, 67.56; H, 5.18; N, 6.85. Found: C, 67.65; H, 5.11; N, 6.88.

2- (4-Chlorophenyl)-7,7-dimethyl-4- (3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**3f**): M.p. 237–239 °C; ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.93 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.00 (d, 1H, *J* = 16Hz, CH_2), 2.17 (d, 1H, *J* = 16Hz, CH_2), 2.47 (s, 2H, CH_2), 4.74 (d, 1H, *J* = 5.2Hz, CH), 5.26 (d, 1H, *J* = 5.2Hz, =CH), 7.42 (d, 2H, *J* = 8.8Hz, ArH), 7.51 (d, 2H, *J* = 8.8Hz, ArH), 7.55 (d, 1H, *J* = 8.0Hz, ArH), 7.68 (d, 1H, *J* = 8.0Hz, ArH), 7.97 (d, 1H, *J* = 8.0Hz, ArH), 8.02 (s, 1H, ArH), 8.74 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3235, 3076, 2968, 1664, 1587, 1531, 1491, 1349, 827; MS (70eV), *m/z* (%): 408 (M+1), 407 (M^+), 406, 376, 350, 327, 281, 253, 207, 133, 73, 28. Anal. Calcd for $C_{23}H_{21}ClN_2O_3$: C, 67.56; H, 5.18; N, 6.85. Found: C, 67.67; H, 5.21; N, 6.88.

7,7-Dimethyl-4-(4-methoxyphenyl)-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (**3g**): M.p. 192–194 °C; ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.93 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.96 (d, 1H, *J* = 16Hz, CH_2), 2.13 (d, 1H, *J* = 16Hz, CH_2), 2.47 (s, 2H, CH_2), 3.66 (s, 3H, OCH_3), 4.48 (d, 1H, *J* = 5.2Hz, CH), 5.16 (d, 1H, *J* = 5.2Hz, =CH), 6.77 (d, 2H, *J* = 8.4Hz, ArH), 7.11 (d, 2H, *J* = 8.4Hz, ArH), 7.31–7.37 (m, 3H, ArH), 7.46 (d, 2H, *J* = 7.2Hz, ArH), 8.48 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3245, 3071, 2978, 2953, 1660, 1585, 1495, 1370, 823, 769, 691; MS (70eV), *m/z* (%): 360 (M+1), 359 (M^+), 358, 357, 314, 281, 252, 207, 121, 73, 28. Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.12; H, 7.05; N, 3.78.

4-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (**3h**): M.p. 202–204 °C (lit[3f]. 224–226 °C); ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.92 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.98 (d, 1H, *J* = 16Hz, CH_2), 2.15 (d, 1H, *J* = 16Hz, CH_2), 2.47 (s, 2H, CH_2), 4.56 (d, 1H, *J* = 5.2Hz, CH), 5.16 (d, 1H, *J* = 5.2Hz, =CH), 7.21 (d, 2H, *J* = 8.4Hz, ArH), 7.26 (d, 2H, *J* = 8.4Hz, ArH), 7.31–7.42 (m, 3H, ArH), 7.46 (d, 2H, *J* = 8.0Hz, ArH), 8.57 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3278, 3076, 2957, 1661, 1595, 1489, 1392, 828, 723; MS (70eV), *m/z* (%): 365 (M+1), 364 (M^+), 363, 318, 281, 252, 207, 168, 73, 28.

2-(4-chlorophenyl)-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (**3i**): M.p. 231–233 °C (lit[3f]. 250–252 °C); ^1H NMR (DMSO, 400 MHz), δ (ppm): 0.92 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.99 (d, 1H, *J* = 16Hz, CH_2), 2.14 (d, 1H, *J* = 16Hz, CH_2), 2.47 (s, 2H, CH_2), 4.54 (d, 1H, *J* = 5.2Hz, CH), 5.20 (d, 1H, *J* = 5.2Hz, =CH), 7.10–7.15 (m, 1H, ArH), 7.20–7.25 (m, 4H, ArH), 7.44 (d, 2H, *J* = 8.4Hz, ArH), 7.53 (d, 2H, *J* = 8.4Hz, ArH), 8.59 (s, 1H, NH); IR (KBr), ν (cm^{-1}): 3273, 3070, 2958, 1661, 1594, 1491, 1393, 835, 731; MS (70eV), *m/z* (%): 365 (M+1), 364 (M^+), 363, 315, 281, 252, 207, 168, 77, 28.

This work was financially supported by the National Natural Science Foundation of China under NSFC grant No. 20372018 and Excellent Young Teacher Research Foundation of Henan Normal University under grant No. 0307032.

Received 17 April 2005; accepted 16 June 2005
Paper 05/3184

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