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Tetrahedron
Tetrahedron 63 (2007) 892–897

Microwave-assisted solvent-free synthesis of substituted 2-quinolones

Cheng-Sheng Jia,[a] Ya-Wei Dong,[a] Shu-Jiang Tu[b] and Guan-Wu Wang[a,*]

[a]*Hefei National Laboratory for Physical Sciences at Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, PR China*
[b]*Department of Chemistry and Key Laboratory of Biotechnology for Medicinal Plants, Xuzhou Normal University, Xuzhou, Jiangsu 221116, PR China*

Received 5 September 2006; revised 10 November 2006; accepted 13 November 2006
Available online 27 November 2006

Abstract—A rapid and efficient method for the preparation of a variety of substituted 2-quinolones has been developed through the reactions of *o*-aminoarylketones with ester compounds containing a reactive α-methylene moiety in the presence of a catalytic amount of cerium chloride heptahydrate under solvent-free conditions in high yields. The rate and yield of the reaction are considerably improved by employing microwave irradiation.
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1. Introduction

The 2-quinolone (carbostyril) skeleton is an important structural moiety present in a large number of alkaloids[1–3] and in biologically active compounds.[1–8] Some of them exhibit, for example, antioxidative activity,[1] nitric oxide production inhibitory activity,[2] and cytotoxicity against human tumor cell lines.[3] Some of them are angiotensin II receptor antagonist,[4] glycine NMDA receptor antagonists,[5] endothelin receptor antagonist,[6] antiplatelet agents,[7] and antitumor agents.[8] 2-Quinolones are also valuable intermediates in organic synthesis.[9] The classic methods for the synthesis of 2-quinolones involve acid-catalyzed cyclization of acylacetoanilides (the Knorr synthesis),[10] Heck reaction,[11] and cyclization/rearrangement.[12] The Knorr synthesis stands out as the most general method. The growing importance of these compounds has led to the development of new methods for their synthesis, including solid-phase synthesis,[13] microwave-enhanced synthesis,[14] acylation/cyclodehydration of anilines[15] and *o*-aminobenzophenones,[16] palladium-catalyzed carbonylative annulation of alkynes,[17] palladium-catalyzed amidation of *o*-carbonyl-substituted aryl halides,[18] palladium-catalyzed Ullmann cross-coupling of 1-bromo-2-nitroarenes with α-halo-esters,[19] electrocyclic reaction of *o*-isocyanatostyrenes,[20] cyclization of Baylis–Hillman adducts,[21] and cyclization of *o*-amino-functionalized benzoyl acetates.[22] However, most of these synthetic methods for 2-quinolones have their own drawbacks such as difficulties in obtaining the starting materials, expensive catalysts, low yields, prolonged reaction time, and/or drastic reaction conditions. Thus, development of simple, convenient, and efficient methods for the preparation of these important molecules still continues to be an interesting and attractive area of research in synthetic organic chemistry.

In recent years, microwave-assisted reactions have attracted much research interest because of the simplicity in operation, enhanced reaction rates, and great selectivity. Thus, microwave irradiation, which has become a powerful synthetic tool for the rapid synthesis of a variety of biologically active compounds, is used to enhance the rates of classical organic reactions.[23]

Cerium chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) has emerged as a potentially useful Lewis acid, and imparts high regio- and chemoselectivity in various chemical transformations. It is also a cheap, non-toxic, and water-tolerant catalyst. Due to its unique catalytic properties, $CeCl_3 \cdot 7H_2O$ has been extensively used for a plethora of organic transformations such as hydrooxacyclization of unsaturated 3-hydroxy esters,[24] Michael addition,[25] dihydroxylation of unreactive olefins,[26] and Julia olefination of cyclopropyl carbinols.[27] Recently, Bose and Kumar developed the $CeCl_3 \cdot 7H_2O$-catalyzed Friedländer condensation of *o*-aminoarylketones with α-methylene ketones at ambient temperature in acetonitrile solutions to afford quinoline derivatives.[28] To the best of our knowledge, there has been no report on its use for the 2-quinolone synthesis. Although the synthesis of 2-quinolones from *o*-aminoarylketone and β-ketoester[29] or ethyl cyanoacetate[30] or ethyl malonyl chloride[9a]/diethyl malonate[9b]/malonic acid[13b] has been reported, it is limited to a substantial extent due to operational difficulties,

* Corresponding author. E-mail: gwang@ustc.edu.cn

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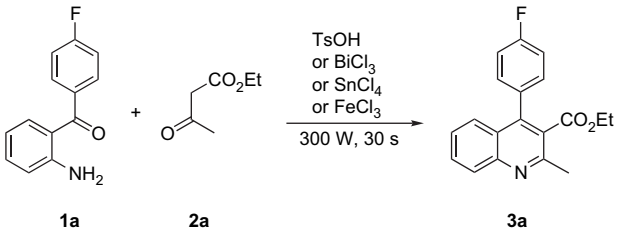
doi:10.1016/j.tet.2006.11.030

prolonged reaction time, and drastic reaction conditions. In continuation of our interest in solvent-free organic reactions,[31] herein we report a simple and facile approach to the preparation of substituted 2-quinolones using catalytic amount of $CeCl_3 \cdot 7H_2O$ under solvent-free conditions by microwave-promoted reactions of *o*-aminoarylketones with various ester compounds containing a reactive α-methylene moiety.

2. Results and discussion

Recently, we reported the synthesis of substituted quinolines through Friedländer condensation by both microwave irradiation and conventional heating under solvent-free conditions.[31e] Various catalysts were screened for the Friedländer condensation of 2-amino-4′-fluorobenzophenone (**1a**) with ethyl acetoacetate (**2a**) under microwave conditions (300 W, 30 s, SANYO EM-350S microwave oven) in order to find the best catalyst. The use of equivalent TsOH, $BiCl_3$, $SnCl_4 \cdot 5H_2O$, and $FeCl_3 \cdot 6H_2O$ afforded only quinoline derivative **3a** in over 80% yield after irradiation at 300 W for 30 s (Scheme 1).[31e]



Scheme 1.

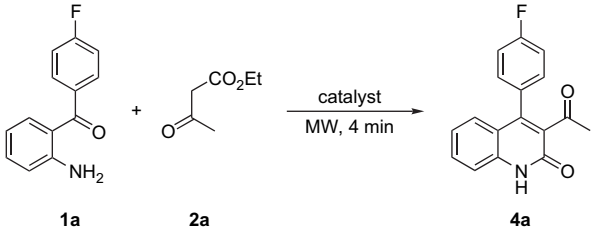
However, when equivalent $CuSO_4 \cdot 5H_2O$, CuCl, and $CuCl_2 \cdot 2H_2O$ were used as the catalysts, the reaction didn't proceed efficiently at 300 W for 30 s, and just furnished quinoline **3a** in lower yields, i.e., 35%, 50%, and 48%, respectively.[31e] In addition, when 0.2 equiv of the catalyst, higher irradiation power (450 W), and longer reaction time (4 min) were employed for the reaction, another major product was formed besides quinoline **3a**, which was obtained in 24%, 36%, and 35% yields, respectively. This compound turned out to be another type of product, i.e., 2-quinolone derivative (**4a**) and was obtained in 68%, 42%, and 46% yields with $CuSO_4 \cdot 5H_2O$, CuCl, and $CuCl_2 \cdot 2H_2O$ as the catalysts, respectively (entries 2–4 in Table 1). To achieve the highest yield of 2-quinolone **4a** from the reaction of **1a** with **2a** (Scheme 2), other catalysts were examined under the microwave conditions to sort out which one had the most effective catalytic activity.

Typically, a mixture of **1a** (1.0 mmol) and **2a** (1.0 mmol), and the desired amount of catalysts was subjected to irradiation in a SANYO EM-350S microwave oven at a given power for 4 min. Subsequent work-up afforded **4a**. The yields, microwave irradiation powers, and amounts of the catalyst used for the reaction of **1a** with **2a** are listed in Table 1.

From Table 1, it is obvious that the reaction could proceed to a certain extent in all cases, even in the absence of catalyst. $CeCl_3 \cdot 7H_2O$ demonstrated superior catalytic activity and

Table 1. The reaction conditions and yields for the synthesis of 2-quinolone **4a** with different catalysts

Entry	Catalyst	Equivalent	Power (W)	Yield (%)
1	None	—	450	51
2	$CuSO_4 \cdot 5H_2O$	0.20	450	68
3	CuCl	0.20	450	42
4	$CuCl_2 \cdot 2H_2O$	0.20	450	46
5	$Cu(OAc)_2 \cdot H_2O$	0.20	450	25
6	NH_4Cl	0.20	450	72
7	NH_4OAc	0.20	450	58
8	$CeCl_3 \cdot 7H_2O$	0.10	450	79
9	$CeCl_3 \cdot 7H_2O$	0.15	450	85
10	$CeCl_3 \cdot 7H_2O$	0.20	450	90
11	$CeCl_3 \cdot 7H_2O$	0.25	450	90
12	$CeCl_3 \cdot 7H_2O$	0.50	450	91
13	$CeCl_3 \cdot 7H_2O$	0.20	300	62
14	$CeCl_3 \cdot 7H_2O$	0.20	600	88
15	$CeCl_3 \cdot 7H_2O$	0.20	700	85



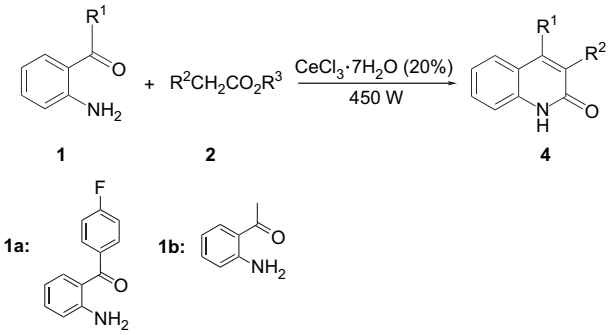
Scheme 2.

appeared to be the best catalyst among the examined catalysts. When the amount of $CeCl_3 \cdot 7H_2O$ was increased to 0.2 equiv, the yield was increased up to 90% at 450 W (entry 10 vs entries 8 and 9). More than 0.2 equiv of $CeCl_3 \cdot 7H_2O$ did not improve the yields significantly (entries 11 and 12). The power level of 450 W was found to be the most appropriate one (entry 10) as lower power level gave lower yield (entry 13) and higher power likewise resulted in a slightly lower yield (entries 14 and 15). These optimization results prompted us to employ 0.2 equiv of $CeCl_3 \cdot 7H_2O$ and 450 W of irradiation power for the further library synthesis of 2-quinolones **4** from **1a** or 2-aminoacetophenone (**1b**) and various ester compounds containing a reactive α-methylene moiety (**2a–m**).

The reaction times, yields, and melting points for the reactions of *o*-aminoarylketones **1a** and **b** with ester compounds **2a–m** are summarized in Table 2.

As shown in Table 2, the scope and generality of this protocol is illustrated with respect to *o*-aminoarylketones (**1a**,**b**) and a wide variety of ester compounds containing a reactive α-methylene group such as β-ketoesters (**2a–e**), ethyl cyanoacetate (**2f**), and diethyl malonate (**2g**). Good to excellent isolated yields were obtained for all of the employed substrates. The reaction process was solvent-free and thus environmentally benign, only catalytic amount of $CeCl_3 \cdot 7H_2O$ was required, and the experimental procedure was very simple. All of the products were isolated in practically pure form by simple filtration and washing, and, in most cases, no further purification was needed. The current method is fairly general, clean, rapid, and efficient, thus providing an expeditious access to the preparation of various 2-quinolones **4a–m**.

Table 2. Reaction times, yields, and melting points of 2-quinolones **4a–m** by the $CeCl_3$-catalyzed reaction under microwave irradiation conditions



Substrate **1**	Substrate **2**			2-Quinolone **4**[a]			Time (min)[b]	Yield (%)[c]	Mp (lit.) (°C)
	R^2	R^3		R^1	R^2				
1a	CH_3CO	Et	**2a**	*p*-FC_6H_4	CH_3CO	**4a**	4	90	250–251
1a	*n*-PrCO	Et	**2b**	*p*-FC_6H_4	*n*-PrCO	**4b**	5	91	216–218
1a	*i*-PrCO	Me	**2c**	*p*-FC_6H_4	*i*-PrCO	**4c**	5	86	232–234
1a	*c*-PrCO	Et	**2d**	*p*-FC_6H_4	*c*-PrCO	**4d**	6	89	264–265 (263.0–264.5)[32]
1a	PhCO	Et	**2e**	*p*-FC_6H_4	PhCO	**4e**	6	95	222–224
1a	CN	Et	**2f**	*p*-FC_6H_4	CN	**4f**	5	82	308–310
1a	CO_2Et	Et	**2g**	*p*-FC_6H_4	CO_2Et	**4g**	6	89	204–205 (204–206)[9a]
1b	CH_3CO	Et	**2a**	CH_3	CH_3CO	**4h**	5	88	278–280
1b	*n*-PrCO	Et	**2b**	CH_3	*n*-PrCO	**4i**	6	85	208–209
1b	*i*-PrCO	Me	**2c**	CH_3	*i*-PrCO	**4j**	6	89	226–228
1b	*c*-PrCO	Et	**2d**	CH_3	*c*-PrCO	**4k**	5	85	188–189
1b	PhCO	Et	**2e**	CH_3	PhCO	**4l**	5	91	262–264
1b	CN	Et	**2f**	CH_3	CN	**4m**	6	86	>300 (320)[30]

[a] All products were fully characterized by HRMS, ^1H NMR, ^{13}C NMR, and IR spectra.
[b] Reaction time for each product was optimized from several comparative runs.
[c] Isolated yield.

In order to draw a direct comparison between microwave irradiation and conventional heating, a few selected reactions were carried out at an identical temperature in a monomodal Emrys™ Creator microwave synthesizer as well as in a thermostated oil bath. The results are collected in Table 3.

Table 3. Synthesis of 2-quinolones **4** catalyzed by $CeCl_3\cdot 7H_2O$ at 160 °C[a] under microwave irradiation using a monomodal Emrys™ Creator and conventional heating in a thermostated oil bath

1	**2**	**4**	Microwave irradiation		Conventional heating	
			Time (min)[b]	Yield (%)	Time (min)[b]	Yield (%)
1a	**2a**	**4a**	5	89	35	61
1a	**2e**	**4e**	8	93	50	65
1b	**2a**	**4h**	6	87	50	52
1b	**2e**	**4l**	9	90	60	58

[a] Reaction temperature was optimized based on the results in an oil bath.
[b] Time at which the maximum yield was obtained.

By comparison of the data in Table 3, it is obvious that the microwave irradiation protocol resulted in much faster reactions and significantly higher yields than the thermal heating process at the same temperature, reflecting the specific non-thermal effects under microwave irradiation conditions. Furthermore, under thermal heating conditions the reactions produced quinoline derivatives as the side products besides 2-quinolones, thus resulting in lower yields. It should be noted that while our work was in process Bose and Kumar reported the $CeCl_3\cdot 7H_2O$-catalyzed Friedländer condensation of *o*-aminobenzophenone with α-ketoesters in solutions affording quinoline derivatives in high yields.[28] However, our solvent-free reactions of *o*-aminoarylketones with α-ketoesters gave selectively quinolone derivatives under microwave irradiation conditions or preferentially quinolone derivatives under thermal heating conditions, reflecting different reaction mechanism under solvent-free conditions.

For the microwave-assisted reactions in a SANYO E-350S microwave oven (Table 2), the required reaction time could be even shorter than that in a monomodal Emrys™ Creator. One possible reason is that the microwave output power (450 W) in a SANYO E-350S microwave oven was higher than the power (300 W) in an Emrys™ Creator. It can be seen from the results in Tables 2 and 3 that good yields in a commercially available and cheap SANYO E-350S domestic microwave oven could be reproduced in a monomodal Emrys™ Creator and thus could be transferred to a more modern microwave synthesizer.

3. Conclusion

We have developed a novel and efficient approach for the rapid synthesis of various substituted 2-quinolones using $CeCl_3\cdot 7H_2O$ as an inexpensive catalyst. The notable features of this procedure are mild and solvent-free reaction conditions, operational simplicity, improved yields, and enhanced reaction rates, which make it an attractive protocol to synthesize polysubstituted 2-quinolones of biological importance.

4. Experimental

4.1. General

Melting points were determined on an XT-4 apparatus and were uncorrected. IR spectra were taken on a Bruker Vector-22 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were recorded at 300 MHz on a Bruker Avance-300 spectrometer in $CDCl_3$ and DMSO-d_6 with chemical shifts (δ) given in parts per million relative to TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance-300 (75.5 MHz) spectrometer with complete proton decoupling; chemical shifts are reported in parts per million relative to the solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm; DMSO-d_6, δ 39.52 ppm). All intensities in the ^{13}C NMR spectral data are 1C except where indicated. High-resolution mass spectra (HRMS) were obtained on a Micromass GCT mass spectrometer with positive EI mode.

4.2. General procedure for the synthesis of compounds 4 with microwave irradiation in a SANYO EM-350S microwave oven

o-Aminoarylketone (**1a/1b**) (1 mmol) and an ester compound (**2a–g**) (1 mmol) were mixed with a given amount of $CeCl_3 \cdot 7H_2O$ or other catalyst, and introduced into a test tube (10 mL). The mixture was subjected to microwave irradiation at an output of 450 W or other designated output power for a given time (monitored by TLC). After it was cooled to room temperature, water (5 mL) was added to the reaction mixture. Then the mixture was stirred for 5 min and the solid was collected by Büchner filtration, washed with H_2O (5 mL×3) and ethyl acetate–petroleum ether (1:4, 3 mL×3), and air-dried to give the product as white powder. The product was further purified by recrystallization from ethanol when necessary. For the reactions affording low to moderate product yields in Table 1, column separation on a silica gel column was employed to get pure **4a**.

4.2.1. 3-Acetyl-4-(4-fluorophenyl)-2(1*H*)-quinolinone (4a). Mp 250–251 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 7.13–7.26 (m, 4H), 7.29–7.35 (m, 2H), 7.45 (d, J=7.8 Hz, 1H), 7.56 (ddd, J=8.3, 6.8, 1.5 Hz, 1H), 12.44 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 31.40, 115.46 (d, $^2J_{C-F}$=22.0 Hz, 2C), 115.64, 118.93, 122.34, 126.95, 130.46 (d, $^4J_{C-F}$=3.3 Hz), 131.02 (d, $^3J_{C-F}$=8.3 Hz, 2C), 131.21, 133.58, 138.44, 146.16, 159.23, 162.12 (d, $^1J_{C-F}$= 245.9 Hz), 201.63; FTIR (KBr) 3449, 2995, 2846, 1701, 1648, 1602, 1551, 1509, 1497, 1478, 1431, 1377, 1280, 1225, 1158, 1075, 826, 761, 653, 644 cm^{-1}; HRMS (+EI) calcd for $C_{17}H_{12}FNO_2$ (M^+): 281.0852, found: 281.0854.

4.2.2. 3-Butyryl-4-(4-fluorophenyl)-2(1*H*)-quinolinone (4b). Mp 216–218 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J=7.4 Hz, 3H), 1.52 (sextet, J=7.3 Hz, 2H), 2.55 (t, J=7.2 Hz, 2H), 7.13–7.26 (m, 4H), 7.29–7.36 (m, 2H), 7.42 (d, J=7.8 Hz, 1H), 7.55 (ddd, J=8.3, 7.0, 1.5 Hz, 1H), 12.25 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.15, 15.90, 45.04, 115.38 (d, $^2J_{C-F}$=21.7 Hz, 2C), 115.63, 118.94, 122.36, 126.84, 130.23 (d, $^4J_{C-F}$=3.0 Hz), 131.17, 131.28 (d, $^3J_{C-F}$=8.4 Hz, 2C), 133.62, 138.42, 146.00, 159.25, 162.13 (d, $^1J_{C-F}$=245.6 Hz), 203.69; FTIR (KBr) 3406, 2968, 2875, 1713, 1646, 1606, 1553, 1501, 1482, 1435, 1381, 1281, 1226, 1159, 1099, 996, 916, 846, 806, 768, 641, 585 cm^{-1}; HRMS (+EI) calcd for $C_{19}H_{16}FNO_2$ (M^+): 309.1165, found: 309.1159.

4.2.3. 4-(4-Fluorophenyl)-3-isobutyryl-2(1*H*)-quinolinone (4c). Mp 232–234 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (d, J=7.0 Hz, 6H), 2.67 (heptet, J=7.0 Hz, 1H), 7.04–7.23 (m, 2H), 7.33–7.43 (m, 4H), 7.56 (t, J=7.7 Hz, 1H), 7.64–7.73 (m, 1H), 12.20 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 17.90 (2C), 41.21, 115.97 (d, $^2J_{C-F}$=21.8 Hz, 2C), 116.36, 119.50, 123.33, 127.50, 130.65 (d, $^4J_{C-F}$=3.2 Hz), 132.08, 132.12 (d, $^3J_{C-F}$= 8.2 Hz, 2C), 133.46, 138.82, 147.26, 160.10, 163.09 (d, $^1J_{C-F}$=247.2 Hz), 208.59; FTIR (KBr) 3382, 2972, 2838, 1699, 1639, 1604, 1548, 1509, 1497, 1479, 1433, 1378, 1275, 1224, 1156, 1095, 1038, 1003, 822, 800, 762, 654, 560 cm^{-1}; HRMS (+EI) calcd for $C_{19}H_{16}FNO_2$ (M^+): 309.1165, found: 309.1162.

4.2.4. 3-Cyclopropanecarbonyl-4-(4-fluorophenyl)-2(1*H*)-quinolinone (4d). Mp 264–265 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02–1.08 (m, 2H), 1.27–1.32 (m, 2H), 2.16–2.24 (m, 1H), 7.12–7.22 (m, 2H), 7.28–7.41 (m, 4H), 7.41 (d, J=7.8 Hz, 1H), 7.55 (ddd, J=8.2, 7.1, 1.2 Hz, 1H), 12.15 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 11.18 (2C), 22.72, 115.08 (d, $^2J_{C-F}$=21.5 Hz, 2C), 115.52, 118.83, 122.15, 126.78, 130.46 (d, $^4J_{C-F}$=3.4 Hz), 131.10, 131.25 (d, $^3J_{C-F}$=8.2 Hz, 2C), 133.95, 138.51, 146.09, 159.08, 162.06 (d, $^1J_{C-F}$=245.8 Hz), 203.28; FTIR (KBr) 3004, 2850, 1688, 1644, 1605, 1499, 1385, 1225, 1162, 1043, 993, 773, 575 cm^{-1}; HRMS (+EI) calcd for $C_{19}H_{14}FNO_2$ (M^+) 307.1009, found: 307.1006.

4.2.5. 3-Benzoyl-4-(4-fluorophenyl)-2(1*H*)-quinolinone (4e). Mp 222–224 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (t, J=8.2 Hz, 2H), 7.15 (t, J=8.2 Hz, 1H), 7.21–7.32 (m, 4H), 7.38 (t, J=7.8 Hz, 2H), 7.46–7.55 (m, 2H), 7.82 (d, J=8.3 Hz, 2H), 12.37 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 115.27 (d, $^2J_{C-F}$=21.7 Hz, 2C), 115.76, 119.04, 122.38, 126.80, 128.70 (2C), 128.84 (2C), 130.10 (d, $^4J_{C-F}$=3.4 Hz), 131.20 (d, $^3J_{C-F}$=9.2 Hz, 2C), 131.26, 131.42, 133.61, 136.41, 138.79, 147.46, 159.53, 162.56 (d, $^1J_{C-F}$=246.4 Hz), 194.19; FTIR (KBr) 3434, 2850, 1678, 1651, 1607, 1556, 1508, 1498, 1479, 1377, 1240, 1159, 826, 757, 687 cm^{-1}; HRMS (+EI) calcd for $C_{22}H_{14}FNO_2$ (M^+): 343.1009, found: 343.1001.

4.2.6. 4-(4-Fluorophenyl)-2(1*H*)-quinolinone-3-carbonitrile (4f). Mp 308–310 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.34 (m, 3H), 7.40 (d, J=7.9 Hz, 1H), 7.47–7.51 (m, 2H), 7.62 (d, J=8.0 Hz, 1H), 7.70 (t, J=7.4 Hz, 1H), 12.73 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 106.42, 115.26, 115.89 (d, $^2J_{C-F}$=21.9 Hz, 2C), 116.17, 117.97, 123.02, 127.86, 130.05 (d, $^4J_{C-F}$=3.2 Hz), 131.11 (d, $^3J_{C-F}$= 8.7 Hz, 2C), 133.80, 139.78, 158.39, 159.38, 162.83 (d, $^1J_{C-F}$=247.5 Hz); FTIR (KBr) 3482, 2991, 2851, 2231, 1673, 1602, 1500, 1481, 1378, 1281, 1233, 1159, 842, 766 cm^{-1}; HRMS (+EI) calcd for $C_{16}H_9FN_2O$ (M^+): 264.0699, found: 264.0690.

4.2.7. Ethyl 4-(4-fluorophenyl)-2(1*H*)-quinolinone-3-carboxylate (4g). Mp 204–205 °C; ^1H NMR (300 MHz,

$CDCl_3$) δ 1.04 (t, J=7.1 Hz, 3H), 4.15 (q, J=7.1 Hz, 2H), 7.14–7.28 (m, 4H), 7.36–7.41 (m, 2H), 7.45 (d, J=8.0 Hz, 1H), 7.56 (ddd, J=8.3, 6.9, 1.3 Hz, 1H), 12.14 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.93, 61.55, 115.66 (d, $^2J_{C-F}$=21.7 Hz, 2C), 117.10, 119.56, 123.14, 126.66, 127.39, 130.66 (d, $^4J_{C-F}$=3.5 Hz), 130.90 (d, $^3J_{C-F}$= 8.2 Hz, 2C), 131.77, 138.60, 149.61, 161.22, 163.15 (d, $^1J_{C-F}$=249.0 Hz), 165.60; FTIR (KBr) 3436, 2984, 2852, 1732, 1651, 1608, 1557, 1500, 1434, 1391, 1381, 1291, 1245, 1159, 1133, 1087, 766, 592 cm^{-1}; HRMS (+EI) calcd for $C_{18}H_{14}FNO_3$ (M^+): 311.0958, found: 311.0960.

4.2.8. 3-Acetyl-4-methyl-2(1*H*)-quinolinone (4h). Mp 278–280 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.66 (s, 3H), 7.28–7.34 (m, 2H), 7.56 (ddd, J=8.3, 7.1, 1.2 Hz, 1H), 7.78 (dd, J=7.8, 1.0 Hz, 1H), 11.54 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 15.11, 31.29, 115.60, 119.14, 122.28, 125.62, 131.09, 132.88, 138.02, 143.65, 159.52, 203.50; FTIR (KBr) 3435, 2930, 2849, 1693, 1661, 1604, 1547, 1505, 1484, 1432, 1390, 1345, 1283, 1220, 1139, 1107, 1031, 906, 872, 750, 663 cm^{-1}; HRMS (+EI) calcd for $C_{12}H_{11}NO_2$ (M^+): 201.0790, found: 201.0788.

4.2.9. 3-Butyryl-4-methyl-2(1*H*)-quinolinone (4i). Mp 208–209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J=7.4 Hz, 3H), 1.81 (sextet, J=7.3 Hz, 2H), 2.45 (s, 3H), 2.95 (t, J=7.3 Hz, 2H), 7.27 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 7.39 (dd, J=8.2, 0.8 Hz, 1H), 7.55 (ddd, J=8.3, 7.2, 1.2 Hz, 1H), 7.76 (dd, J=8.2, 0.9 Hz, 1H), 12.72 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.59, 15.15, 16.52, 45.04, 115.60, 119.16, 122.27, 125.53, 131.02, 132.82, 138.02, 143.54, 159.58, 205.82; FTIR (KBr) 3442, 2923, 2846, 1684, 1656, 1606, 1555, 1503, 1485, 1434, 1389, 1273, 1198, 1084, 1033, 986, 904, 875, 743 cm^{-1}; HRMS (+EI) calcd for $C_{14}H_{15}NO_2$ (M^+): 229.1103, found: 229.1112.

4.2.10. 3-Isobutyryl-4-methyl-2(1*H*)-quinolinone (4j). Mp 226–228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J=7.0 Hz, 6H), 2.44 (s, 3H), 3.38 (heptet, J=7.0 Hz, 1H), 7.25–7.34 (m, 2H), 7.55 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 7.76 (d, J=7.9 Hz, 1H), 11.96 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 15.56, 17.53 (2C), 40.28, 115.60, 119.15, 122.25, 125.55, 131.01, 132.25, 138.05, 144.22, 159.72, 209.35; FTIR (KBr) 3430, 2971, 2852, 1703, 1645, 1609, 1559, 1506, 1485, 1433, 1393, 971, 749, 667, 600 cm^{-1}; HRMS (+EI) calcd for $C_{14}H_{15}NO_2$ (M^+): 229.1103, found: 229.1106.

4.2.11. 3-Cyclopropanecarbonyl-4-methyl-2(1*H*)-quinolinone (4k). Mp 188–189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08–1.17 (m, 2H), 1.33–1.38 (m, 2H), 2.42–2.51 (m, 1H), 2.48 (s, 3H), 7.27 (ddd, J=8.1, 7.1, 0.9 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.55 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 7.77 (d, J=8.1 Hz, 1H), 12.07 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 11.29 (2C), 15.47, 22.75, 115.55, 119.10, 122.20, 125.57, 131.01, 132.84, 138.12, 143.64, 159.52, 205.05; FTIR (KBr) 3442, 2954, 2873, 1697, 1659, 1602, 1502, 1429, 1385, 1370, 1268, 1080, 991, 909, 885, 751, 638 cm^{-1}; HRMS (+EI) calcd for $C_{14}H_{13}NO_2$ (M^+): 227.0946, found: 227.0938.

4.2.12. 3-Benzoyl-4-methyl-2(1*H*)-quinolinone (4l). Mp 262–264 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 7.18–7.29 (m, 2H), 7.48 (t, J=8.1 Hz, 3H), 7.61 (ddd, J=8.0, 6.8, 1.2 Hz, 1H), 7.74 (d, J=8.1 Hz, 1H), 7.98 (d, J=6.9 Hz, 2H), 11.81 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 15.61, 115.73, 119.15, 122.30, 125.36, 128.88 (2C), 129.05 (2C), 130.85, 131.10, 133.96, 136.50, 138.32, 144.63, 159.72, 195.74; FTIR (KBr) 3442, 2944, 2848, 1688, 1641, 1561, 1502, 1483, 1433, 1386, 1370, 1312, 1282, 1245, 1153, 925, 899, 820, 750, 689, 580 cm^{-1}; HRMS (+EI) calcd for $C_{17}H_{13}NO_2$ (M^+): 263.0946, found: 263.0945.

4.2.13. 4-Methyl-2(1*H*)-quinolinone-3-carbonitrile (4m). Mp>300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (s, 3H), 7.33–7.39 (m, 2H), 7.68 (ddd, J=8.4, 7.1, 1.3 Hz, 1H), 7.80 (d, J=8.7 Hz, 1H), 10.98 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 18.22, 105.99, 115.61, 116.12, 118.08, 122.99, 126.53, 133.78, 138.97, 158.47, 158.80; FTIR (KBr) 3447, 3147, 3013, 2894, 2854, 2222, 1660, 1602, 1504, 1475, 1430, 1389, 1368, 1275, 1246, 1162, 1123, 863, 842, 756, 673, 663 cm^{-1}; HRMS (+EI) calcd for $C_{11}H_8N_2O$ (M^+): 184.0637, found: 184.0636.

4.3. General procedure for the synthesis of compounds 4 with microwave irradiation in a monomodal Emrys™ Creator microwave synthesizer

The experiments were carried out in a monomodal Emrys™ Creator from Personal Chemistry (Uppsala, Sweden). The reactions were performed in sealed microwave process vials utilizing the standard level (300 W maximum power). Reaction times under microwave irradiation conditions reflected the time that the reaction mixture was kept at the designated temperature (fixed hold time). Typically, a mixture of *o*-aminoarylketone (**1a/1b**) (1 mmol), ethyl acetoacetate (**2a**)/ethyl benzoylacetate (**2e**) (1 mmol), and $CeCl_3\cdot 7H_2O$ (0.2 mmol) in a sealed 10-mL Emrys™ reaction vial was irradiated at 160 °C for a given time, then the sample was cooled using compressed air. The work-up procedure followed was the same as that in a SANYO EM-350S microwave oven.

4.4. General procedure for the synthesis of compounds 4 with conventional heating

A mixture of *o*-aminoarylketone (**1a/1b**) (1 mmol), ethyl acetoacetate (**2a**)/ethyl benzoylacetate (**2e**) (1 mmol), and $CeCl_3\cdot 7H_2O$ (0.2 mmol) was introduced into a test tube (10 mL) and stirred at 160 °C (oil bath temperature) for the designated time. After the reaction was completed (monitored by TLC), the reaction mixture was separated by column chromatography to give the pure product.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (Nos. 20125205 and 20321101) and Anhui Provincial Bureau of Human Resources (2001Z019).

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