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Microwave-assisted rapid and straightforward synthesis of 2-aryl-4-quinolones from acylated 2′-aminoacetophenones

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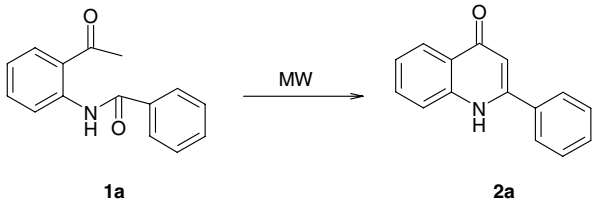
Abstract—The syntheses of a diverse set of 2-aryl-4-quinolone derivatives were achieved by exposing corresponding acylated 2′-aminoacetophenones to microwave irradiation in the presence of NaOH. The microwave accelerated cyclizations were complete within 10–22 min at 120 °C giving 57–95% isolated yields.

4-Quinolone derivatives are an important class of antibacterial agents. Numerous analogues have been synthesized to evaluate their antibacterial properties and antibacterial spectrum.[1] Recent studies also revealed that 2-aryl-4-quinolones possessed antitumor activities owing to their ability of inhibiting tubulin polymerization.[2] To construct this intriguing 2-aryl-4-quinolone scaffold, several synthesis methods have been developed from different starting materials.[3] Among them, cyclization of acylated 2′-aminoacetophenones attracts more attention because diverse starting materials are readily available and the reaction conditions are relatively mild, at 70–80 °C in the presence of potassium *tert*-butoxide (*t*-BuOK). However, long reaction time, 10–24 h, is always needed for reaction completion, and low yields are sometimes encountered.[4]

The introduction of microwave heating has greatly impacted many aspects of chemical synthesis. There are some excellent reviews and reports on the broad use of microwave irradiation in organic synthesis.[5] It has been demonstrated that the use of microwave heating can dramatically cut down reaction time, increase product purity and yields, and allow precise control of reaction conditions, all of which make it suited to meet the increased demands of high throughput chemistry. In this letter, we report an efficient and good yielding condition for synthesis of 2-aryl-4-quinolones from acylated 2′-aminoacetophenones with the aid of microwave irradiation. All microwave experiments were performed in a self-tuning single mode Biotage Initiator Microwave Synthesizer.[7]

To optimize the reaction conditions, cyclization of *N*-(2-acetyl-phenyl)-benzamide **1a** was selected as model reaction (Scheme 1). A mixture of **1a** and 5 equiv of *t*-BuOK in *t*-BuOH was initially exposed to microwave irradiation at 80 °C for 10 min. TLC test indicated the reaction as uncompleted. On increasing the temperature to 120 °C, the process of conversion of **1a** was completed giving 88% of desired product, 2-phenyl-4-quinolone **2a** (Table 1, entry 1). Under this condition, other four commonly used bases were employed to investigate their influence on the cyclization (Table 1, entries 2–5). Interestingly, 95% yield of product could be afforded under the effect of NaOH, whereas no product was detectable with K_2CO_3 due to its weak basicity. More experiments were carried out to evaluate the influence of temperature



1a **2a**

Scheme 1.

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Table 1. Reaction conditions on the cyclization of 2′-aminoacetophenone benzamide (Scheme 1)

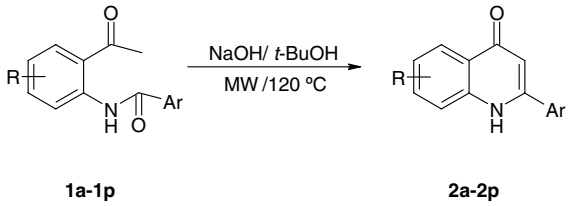
Entry	Microwave conditions	Conv.[a] (%)	Yields[a] (%)
1	*t*-BuOK, 120 °C, 10 min	100	88
2	NaOEt, 120 °C, 10 min	100	79
3	KOH, 120 °C, 10 min	100	82
4	NaOH, 120 °C, 10 min	100	95
5	K_2CO_3, 120 °C, 10 min	0	0
6	NaOH, 130 °C, 10 min	100	84
7	NaOH, 110 °C, 10 min	98	76
8	NaOH, 100 °C, 10 min	75	57
9	NaOH, 90 °C, 10 min	60	44
10	NaOH, 80 °C, 10 min	40	25

[a] Determined by HPLC at 215 nm and LC–MS.

on microwave assisted cyclization of benzamide **1a** (Table 1). With the decrease of the reaction temperature, both conversions and yields dropped (Table 1, entries 4 and 6–10). Although the starting material disappeared at 130 °C for 10 min, only 84% yield of expected product was gained, which possibly suggested that higher temperature might result in more by-products.

It is accepted that both thermal effect and specific microwave effect may induce the acceleration of some reactions somehow on irradiating with microwave. In order to testify if the microwave speeds up the cyclization, the model reaction was conducted in a sealed thick-walled tube under an identical condition but instead heating in an oil bath. The time course results are plotted in Figure 1. Microwave heated reactions could produce, through all the way of the reactions' process, higher conversion of the starting material and higher yield of the product than when heated in traditional oil bath (Fig. 1A and B). The differences are especially significant within 5 min, 90% conversions for microwave but only 50% for oil-bath heating. And to complete the cyclization, it takes only 10 min by microwave heating (Fig. 1A), while normally 10–24 h by previously reported method. These results may elucidate that microwave effect might play a certain role in the cyclization.

To expand the scope of this chemistry to more 2-aryl-4-quinolone derivatives syntheses, a diverse set of substrates **1a**–**p** were selected and exposed to the irradiation



Scheme 2.

of microwave under the condition described above (Scheme 2). Because *t*-BuOK and NaOH exhibited similar catalytic character (Fig. 1), and NaOH is cheaper and easily obtainable, reactions listed in Table 2 were carried out using NaOH as the base. The desired products **2a**–**p** could be precipitated in water at pH 5–6, and collected by filtration followed by washing with water and a cold mixture of acetone and dichloromethane.[8] Good to excellent isolated yields, 57–95%, were gained, which are summarized in Table 2. In general, R1 substituent produced minor influence on the microwave assisted cyclization (Table 2, entries a–c, g–k, and n–p), but there was still a vague case that 4,5-dimethoxy substituted substrates afforded relatively lower yields even exposed to irradiation for a prolonged period (Table 2, entries l and m). In contrast, the properties of R displayed prominent effect on the isolated yields. *para*-Chloro substituted benzamides (Table 2, entries b, i, and o) always afforded lower yields when compared with benzamides (Table 2, entries a, h, and n) and substituted benzamides containing electron-donating groups (Table 2, entries c, d, j, and p). However again a vague case was observed in which a low yield was produced from 3,4,5-trimethoxy-benzamide cyclization (Table 2, entry e). Heterocyclic acylated substrates (Table 2, entries f, g, k, and m) could not afford as much product as benzamides (Table 2, entries a, h, and n).

In summary, a rapid and straightforward method was developed for the synthesis of 2-aryl-4-quinolone derivatives from acylated 2′-aminoacetophenones under the irradiation of microwave and in the presence of NaOH. The reaction time was dramatically reduced from 10 to 24 h by traditional oil bath heating to 10–22 min. A diverse range of 2-aryl-4-quinolone derivatives were synthesized to demonstrate that the reported method

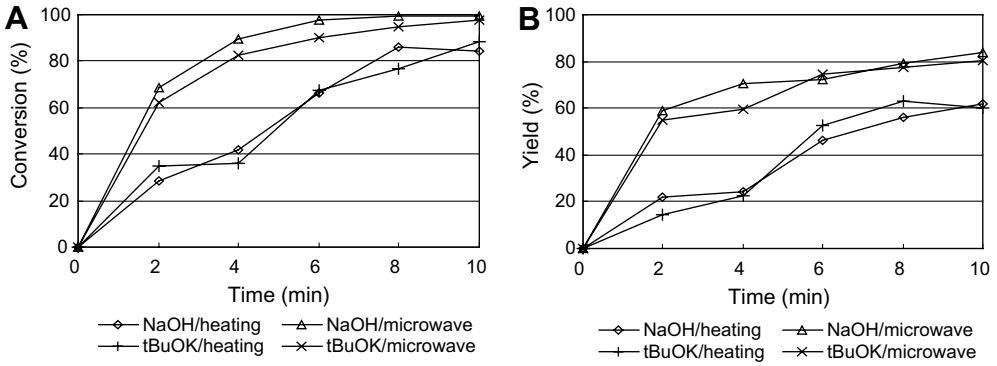


Figure 1. Comparison of the effect of microwave and oil-bath heating on the cyclization: (A) kinetic curves of conversion and (B) kinetic curves of yield.

Table 2. Preparation of 2-aryl-4-quinolones (Scheme 2)

Entry	R	Ar	Time (min)	Yield[a] (%)	Mp (°C)	Ref.
a	H	Phenyl	10	85	251–253	3b
b	H	4-Chlorophenyl	10	67	252–254	3b
c	H	4-Methoxyphenyl	10	81	292–294	6
d	H	2-Methoxyphenyl	10	81	234–235	—
e	H	3,4,5-Trimethoxyphenyl	10	63	232–234	3b
f	H	4-Chloro-3-pyridyl	10	69	282–284	—
g	H	2-Thiophene	12	74	>300	—
h	4-Chloro	Phenyl	10	87	>300	3c
i	4-Chloro	4-Chlorophenyl	10	64	>300	—
j	4-Chloro	4-Methoxyphenyl	10	79	>300	—
k	4-Chloro	2-Thiophene	10	73	>300	—
l	4,5-Dimethoxy	4-Methoxyphenyl	22	57	271–273	—
m	4,5-Dimethoxy	2-Thiophene	18	63	286–289	—
n	3,4,5-Trimethoxy	Phenyl	10	84	216–218	4c
o	3,4,5-Trimethoxy	4-Chlorophenyl	10	65	257–260	—
p	3,4,5-Trimethoxy	4-Methoxyphenyl	10	95	213–216	—

[a] Isolated yields.

provided an opportunity to acquire many other analogues.

Acknowledgements

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7. *General experimental procedure*: The preparation of **2p** is representative for all synthesis. A 10 mL Biotage vial containing a magnetic stirring bar was charged with compound **1p** (107.4 mg, 0.3 mmol), NaOH (60 mg, 1.5 mmol) and 1.5 mL *t*-BuOH. The vial was sealed and the resulting suspension was heated in the Biotage Initiator Synthesizer under selected microwave conditions. The conversion was monitored by HPLC and the product analyzed by LC–MS. The reaction mixture was cooled and poured onto 8 mL of water and adjusted to pH 5–6. The solution was concentrated under reduced pressure until copious solid appeared. The solid was collected and washed successively with water and a cold mixture of acetone and dichloromethane to give the pure product.
8. All products were characterized by NMR, MS, and IR spectroscopy. The following spectral data are representative: Compound **2d**: white solid; yield 81%; mp: 234–235 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.90$ (s, 3H), 7.23–7.26 (m, 1H), 7.29 (s, 1H), 7.34–7.36 (m, 1H), 7.67–7.71 (m, 2H), 7.76–7.80 (m, 1H), 8.03–8.07 (m, 1H), 8.14–8.16 (m, 1H), 8.34–8.36 (m, 1H); IR (KBr): 3425, 2941, 1639, 1599, 1496, 1456, 1365, 1248 cm^{-1}. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 56.1$, 107.2, 112.4, 119.9, 120.0, 121.0, 121.2, 123.6, 127.2, 131.1, 133.4, 134.4, 139.6, 152.4, 156.8, 170.2. MS (EI): $m/z = 251$ (M^+), 236, 120. HRMS (EI): m/z calcd for $C_{16}H_{13}NO_2$ [M^+]: 251.0946; found: 251.0947. Compound **2o**: white solid; yield 65%; mp: 257–260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.81$ (s, 3H), 3.85 (s, 3H), 3.94 (s, 3H), 6.75 (s, 1H), 7.34 (s, 1H), 7.70 (d, 2H, $J = 8.0$ Hz), 7.93 (d, 2H, $J = 8.0$ Hz). IR (KBr): 3377, 2933, 1630, 1603, 1568, 1527, 1477, 1408, 1265 cm^{-1}. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 55.8$, 61.1, 61.9, 95.9, 108.4, 114.2, 128.9 (2C), 129.1 (2C), 132.5, 135.1, 138.7, 139.5, 146.2, 152.1, 156.2, 176.2. MS (EI): $m/z = 347$, 345 (M^+), 330, 315, 302, 287, 272. HRMS (EI): m/z calcd for $C_{18}H_{16}NClO_4$ [M^+]: 345.0768; found: 345.0755. Compound **2p**: white solid; yield: 95%; mp: 213–216 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.81$ (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.94 (s, 3H), 6.73 (s, 1H), 7.17–7.20 (m, 2H), 7.38 (s, 1H), 7.86–7.89 (m, 2H). IR (KBr): 3435, 2941, 2837, 1610, 1517, 1400, 1255 cm^{-1}. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 55.6$, 56.2, 61.1, 62.1, 96.9, 105.0, 111.4 (2C), 114.7, 124.6, 129.3 (2C), 139.6, 140.3, 150.0, 150.7, 157.4, 161.8, 172.0. MS (EI): $m/z = 341$ (M^+), 326, 315, 298, 283, 268. HRMS (EI): m/z calcd for $C_{19}H_{19}NO_5$ [M^+]: 341.1263; found: 341.1268.