Green Chemistry Approach to the Synthesis of 2-Aryl-4-ferrocenyl-quinoline Derivatives under Microwave Irradiation

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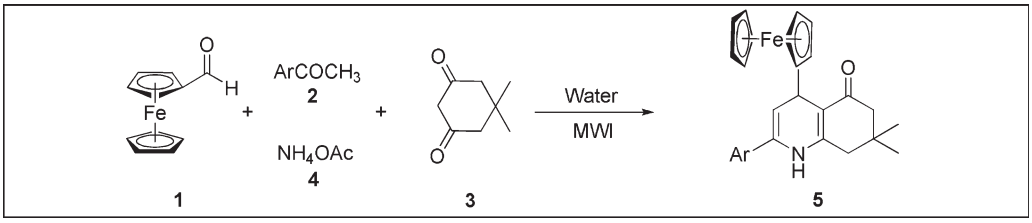

A clean and expeditious route for the synthesis of 2-aryl-4-ferrocenyl-quinoline derivatives through microwave-assisted multicomponent reaction of ferrocenecarboxaldehyde with ketone and dimedone in the presence of ammonium acetate using water as reaction media at 100°C is described. This procedure lends itself well to combinatorial methods, providing the target heteropolymetallic compounds in excellent yield.

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INTRODUCTION

The concept of ''green chemistry'' has been widely adopted to meet the fundamental scientific challenges of protecting human health and the environment while simultaneously achieving commercial viability [1]. The emerging area of green chemistry envisages minimum hazard as the performance criteria with designing new chemical processes. In essence, it prompts the chemical and pharmaceutical manufacturer to consider how human life is impacted after these chemicals are generated and introduced into their society [2]. By rethinking chemical design from the ground up, chemists are developing new ways to manufacture products that fuel the economy and lifestyles, without the damages to the environment that have become increasingly important in recent years.

The medicinal chemistry community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of drugs required by society in short periods of time. Because of high molecular complexity in drug discovery processes accompanied by time constraints, the primary driver of pharmaceutical green chemistry has become the development of efficient and environmentally benign synthetic protocols. This can be achieved through the proper choice of starting materials, atom economic methodologies with a minimum number of chemical steps, the appropriate use of greener solvents and reagents, and efficient strategies for product isolation and purification. Thus, green chemistry has emerged as a discipline that permeates all aspects of synthetic chemistry. A major goal of this endeavor must then be to simultaneously maximize the efficient use of safer raw materials and to reduce the waste produced in the process [3].

Ferrocene (Fig. 1) systems have been attractive candidates for studying mixed-valence behavior [4], as ferrocene has a well-developed organic chemistry, allowing attachment to a wide variety of bridges, high stability in both the oxidized and neutral states, and charge-transport ability. Many studies on linked bis-(ferrocenyl) compounds have been reported and have been comprehensively reviewed [5]. Compared with the classical heterocyclic compounds, incorporation of a ferrocene fragment into heterocycles often obtained unexpected biological activity [6] and has several applications in the field of material science, asymmetric catalysis [7], large scale olefin polymerization [8], and luminescent materials [9,10]. Furthermore, ferrocene has been studied extensively as it is thought to be responsible for a variety of biological stability and nontoxicity rendering such drugs compatible with other treatment [11–13]. The quinoline moiety has played a unique role in the design and synthesis of novel biologically active compounds serving as anti-inflammatory, antiasthmatic,

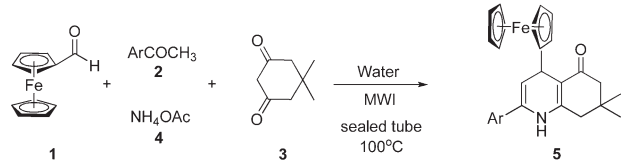
Figure 1. Structure of ferrocene.

antituberculosis, antibacterial, antihypertensive, antitumor, and, most notably, antimalarialm agents [14–17]. In the light of current studies, the combination of ferrocene units with quinoline derivatives offers a desired way to endow novel functional molecules [18–23]. Because of a range of biological activity they exhibited, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. Thus, the synthesis of these molecules has attracted considerable attention [24–28]. In our previous work, we had successfully induced ferrocene units to the 2 position of 4-aryl-2-ferrocenyl-quinoline derivatives [29]. As the continuation of this work and our research devoted to the development of green organic chemistry by performing reactions under using water conditions [30–34], in this article, we report a practical, inexpensive, rapid, and green microwave-promoted method for the synthesis of heterocyclic compounds containing ferrocene units in water (Scheme 1).

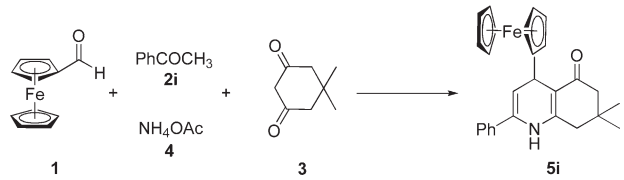
RESULTS AND DISCUSSION

Our strategy synthesizing the 2-aryl-4-ferrocenyl-quinolines was that ferrocenecarboxaldehyde was examined as starting material to react with ketones, dimedone, and ammonium acetate under microwave heating. Initially, we screened various conditions for the one-pot, four-component reaction of ferrocenecarboxaldehyde with acetophenone, dimedone, and ammonium acetate at 100°C without any catalyst under microwave irradiation (Scheme 2 and Table 1). Among various solvents tested, glacial acetic acid (HOAc), glycol, *N*,*N*-dimethylformamide (DMF), and solvent-free gave poor or moderate yields of the expected product (Table 1, entries 1–4). The best solvent was found to be water. In this solvent, 7,7-dimethyl-2-phenyl-4-ferrocenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (**5i**) was obtained with the best yield (Table 1, entry 5). To further optimize the reaction conditions, the reaction was carried out at temperatures ranging from 70 to 130°C, with an increment of 10°C

Scheme 1



Scheme 2



each time. The yield of product **5i** was increased and the reaction time was shortened as the temperature was increased from 70 to 130°C (Table 1, entries 5–11). However, further increase of the temperature to 130°C failed to improve the yield of product **5i** (Table 1, entry 9–11). Therefore, 100°C was chosen as the reaction temperature for all further microwave-assisted reactions.

The use of these optimal microwave experimental conditions [Water, 100°C] to the reactions of different ketones afforded good yields of 4-ferrocenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-ones, with ferrocene groups presenting in positions 4 of the quinoline nucleus. To test the scope of ketones, ferrocenecarboxaldehyde, dimedone, and ammonium acetate were used as model substrates, and the results (Table 2, entries 1–9) indicated that ketones bearing functional groups such as chloro, bromo, or methyl are suitable for the reaction. We have also observed electronic effects, that is, ketones with electron-withdrawing groups reacted rapidly, while electron-rich groups decreased the reactivity, requiring longer reaction times.

The use of water in these reactions avoids the use of volatile and toxic organic solvents. In addition to the often referred advantages of using water as solvent, this procedure has following remarkable features when compared to conventional method: (1) short reaction time, (2) clean reaction protocol, and (3) high yielding.

The formation of **5** is expected to proceed via initial condensation of ferrocenecarboxaldehyde **1** with dimedone **3** to afford **6**, which further undergoes *in situ* Michael addition with **7**, obtained by treating ketones **2**

Table 1

Optimization for the synthesis of **5i** under microwave irradiation.

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)
1	HOAc	80	12	Trace
2	Glycol	80	15	32
3	DMF	80	9	41
4	None	80	10	17
5	Water	80	15	59
6	Water	70	20	44
7	Water	90	12	77
8	Water	100	10	92
9	Water	110	9	78
10	Water	120	7	60
11	Water	130	8	48

Table 2

Synthesis of compound **5** under microwave irridiation.

Entry	5	Ar	Time (min)	Yield (%)	Mp (°C)
1	**5a**	4-FC_6H_4	10	92	203–206
2	**5b**	4-ClC_6H_4	9	93	209–212
3	**5c**	4-BrC_6H_4	9	90	229–230
4	**5d**	4-$CH_3C_6H_4$	12	91	189–192
5	**5e**	4-$NO_2C_6H_4$	12	78	219–222
6	**5f**	3-$NO_2C_6H_4$	13	79	205–207
7	**5g**	2,4-$Cl_2C_6H_3$	12	75	216–218
8	**5h**	4-OHC_6H_4	10	86	204–207
9	**5i**	C_6H_5	10	92	230–233

with ammonia from ammonium acetate **4**, to yield intermediate **8**, which is then cyclized to afford the products **5** (Scheme 3).

In this study, all the products were characterized by melting point, IR, and ^{1}H-NMR spectral data, and HRMS (ESI).

In conclusion, we have demonstrated that water is a convenient, inexpensive, nontoxic, and recyclable reaction medium for the efficient synthesis of 2-aryl-4-ferrocenyl-quinoline derivatives. Interestingly, we found a new multicomponent reaction of ferrocenecarboxaldehyde with ketones, dimedone, and ammonium acetate in water, which provides a rapid and efficient route for the construction of quinolines skeleton.

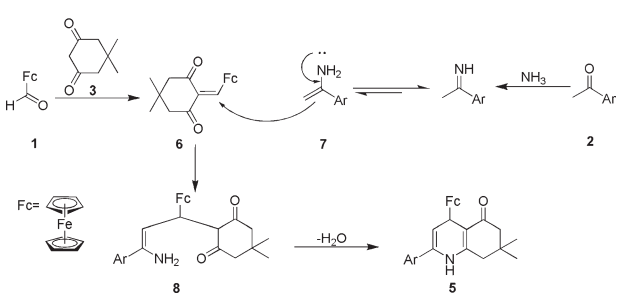
This protocol offers a rapid and clean alternative and reduces reaction time. The media makes reaction economically and potentially viable for commercial applications.

EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in XT5 apparatus and are uncorrected. IR spectra were recorded on a FTIR-Tensor 27 spectrometer. ^{1}H-NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-d_6 as solvent and TMS as internal standard. HRMS (ESI) was determined by using micrOTOF-QII HRMS/MS instrument (BRUKER).

General procedure for the synthesis of compounds 5 with microwave irradiation. Typically, in a 10 mL Emrys™ reaction vial, aromatic ferrocenecarboxaldehyde **1** (1 mmol), ketones **2** (1 mmol), dimedone **3** (1 mmol), ammonium acetate **4** (2.5 mmol), and water (2.0 mL) were mixed and then capped. The mixture was irradiated for a given time at 100°C under microwave irradiation (initial power 100 W and maximum power 250 W). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was filtered to give the crude product and purified by recrystallization from EtOH (95%) to give rise to the pure product **5**. All the products were characterized by IR, ^{1}H-NMR, and HRMS.

Scheme 3



2-(4-Fluorophenyl)-7,7-dimethyl-4-ferrocenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5a). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.70 (s, 1H, NH), 7.64 (dd, J_1 = 5.6 Hz, J_2 = 8.4 Hz, 2H, ArH), 7.32 (t, J = 8.8 Hz, 2H, ArH), 5.41 (d, J = 6.0 Hz, 1H, CH), 4.29 (d, J = 6.0 Hz, 1H, ferroceneyl), 4.18 (s, 1H, CH), 4.14 (s, 5H, ferroceneyl), 4.02 (s, 1H, ferroceneyl), 3.96 (s, 1H, ferroceneyl), 3.80 (s, 1H, ferroceneyl), 2.42 (d, J = 16.8 Hz, 1H, CH_2), 2.30 (d, J = 17.2 Hz, 1H, CH_2), 2.16 (d, J = 16.0 Hz, 1H, CH_2), 2.01 (d, J = 16.0 Hz, 1H, CH_2), 1.01 (s, 3H, CH_3), 0.89 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3303, 3094, 2947, 2868, 1616 , 1591, 1484, 1388, 1236, 1157, 1054, 816, 761, 575. HRMS (ESI) *m*/*z*: calc. for: 455.1348 $[M+H]^+$, found: 455.1333 $[M+H]^+$.

2-(4-Chlorophenyl)-7,7-dimethyl-4-ferrocenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5b). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.69 (s, 1H, NH), 7.64 (d, J = 8.4 Hz, 2H, ArH), 7.54 (d, J = 8.4 Hz, 2H, ArH), 5.48 (d, J = 6.0 Hz, 1H, CH), 4.30 (d, J = 6.0 Hz, 1H, CH), 4.18 (s, 1H, ferroceneyl), 4.13 (s, 5H, ferroceneyl), 4.02 (s, 1H, ferroceneyl), 3.96 (s, 1H, ferroceneyl), 3.78 (s, 1H, ferroceneyl), 2.42 (d, J = 16.8 Hz, 1H, CH_2), 2.31 (d, J = 17.2 Hz, 1H, CH_2), 2.16 (d, J = 16.0 Hz, 1H, CH_2), 2.02 (d, J = 16.4 Hz, 1H, CH_2), 1.01 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3288, 3097, 2954, 2870, 1615 , 1590, 1488, 1385, 1266, 1153, 1053, 812, 751, 574. HRMS (ESI) *m*/*z*: calc. for: 471.1052 $[M+H]^+$, found: 471.1050 $[M+H]^+$.

2-(4-Bromophenyl)-7,7-dimethyl-4-ferrocenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5c). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.68 (s, 1H, NH), 7.68 (d, J = 9.2 Hz, 2H, ArH), 7.56 (d, J = 8.4 Hz, 2H, ArH), 5.48 (d, J = 6.0 Hz, 1H, CH), 4.29 (d, J = 5.6 Hz, 1H, CH), 4.18 (s, 1H, ferroceneyl), 4.13 (s, 5H, ferroceneyl), 4.02 (s, 1H, ferroceneyl), 3.96 (s, 1H, ferroceneyl), 3.78 (s, 1H, ferroceneyl), 2.42 (d, J = 17.2 Hz, 1H, CH_2), 2.31 (d, J = 17.2 Hz, 1H, CH_2), 2.16 (d, J = 16.4 Hz, 1H, CH_2), 2.02 (d, J = 15.6 Hz, 1H, CH_2), 1.01 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3303, 3097, 2954, 2870, 1615, 1590, 1488, 1385, 1266, 1153, 1053,

812, 751, 574. HRMS (ESI) *m/z*: calc. for: 515.0547 $[M+H]^+$, found: 515.0529 $[M+H]^+$.

2-(4-p-Tolylphenyl)-7,7-dimethyl-4-ferrocenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5d). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.60 (s, 1H, NH), 7.54 (d, J = 8.4 Hz, 2H, ArH), 7.03 (d, J = 8.4 Hz, 2H, ArH), 5.34 (d, J = 5.6 Hz, 1H, CH), 4.28 (d, J = 5.6 Hz, 1H, CH), 4.17 (s, 1H, ferroceneyl), 4.13 (s, 5H, ferroceneyl), 4.01 (s, 1H, ferroceneyl), 3.95 (s, 1H, ferroceneyl), 3.87 (s, 1H, ferroceneyl), 3.80 (s, 3H, CH_3), 2.41 (d, J = 16.8 Hz, 1H, CH_2), 2.31 (d, J = 16.8 Hz, 1H, CH_2), 2.16 (d, J = 16.0 Hz, 1H, CH_2), 2.01 (d, J = 16.0 Hz, 1H, CH_2), 1.01 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3297, 3097, 2951, 2868, 1619, 1590, 1487, 1397, 1252, 1153, 1061, 826, 791, 542. HRMS (ESI) *m/z*: calc. for: 452.1671 $[M+H]^+$, found: 452.1614 $[M+H]^+$.

7,7-Dimethyl-2-(4-nitrophenyl)-4-ferrocenylquinolin-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5e). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.50 (s, 1H, NH), 8.34 (d, J = 8.0 Hz, 2H, ArH), 7.89 (d, J = 8.8 Hz, 2H, ArH), 5.72 (d, J = 5.6 Hz, 1H, CH), 4.34 (d, J = 6.0 Hz, 1H, CH), 4.19 (s, 1H, ferroceneyl), 4.15 (s, 5H, ferroceneyl), 4.04 (s, 1H, ferroceneyl), 3.97 (s, 1H, ferroceneyl), 3.79 (s, 1H, ferroceneyl), 2.45 (d, J = 17.2 Hz, 1H, CH_2), 2.34 (d, J = 16.8 Hz, 1H, CH_2), 2.18 (d, J = 16.0 Hz, 1H, CH_2), 2.04 (d, J = 16.4 Hz, 1H, CH_2), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3295, 3082, 2958, 2887, 1611, 1588, 1490, 1344, 1252, 1155, 1056, 815, 757, 596. HRMS (ESI) *m/z*: calc. for: 482.1293 $[M+H]^+$, found: 482.1282 $[M+H]^+$.

7,7-Dimethyl-2-(3-nitrophenyl)-4-ferrocenylquinolin-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5f). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.88 (s, 1H, NH), 8.26 (s, 1H, ArH), 8.42 (d, J = 8.0 Hz, 1H, ArH), 8.08 (d, J = 8.0 Hz, 1H, ArH), 7.78 (t, J = 8.0 Hz, 1H, ArH), 5.65 (d, J = 5.6 Hz, 1H, CH), 4.32 (d, J = 6.0 Hz, 1H, CH), 4.18 (s, 1H, ferroceneyl), 4.15 (s, 5H, ferroceneyl), 4.03 (s, 1H, ferroceneyl), 3.96 (s, 1H, ferroceneyl), 3.80 (s, 1H, ferroceneyl), 2.43 (d, J = 16.8 Hz, 1H, CH_2), 2.32 (d, J = 17.2 Hz, 1H, CH_2), 2.16 (d, J = 16.4 Hz, 1H, CH_2), 2.02 (d, J = 16.0 Hz, 1H, CH_2), 1.01 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3298, 3080, 2945, 2897, 1621, 1583, 1490, 1345, 1262, 1147, 1061, 815, 758, 591. HRMS (ESI) *m/z*: calc. for: 482.1293 $[M+H]^+$, found: 482.1290 $[M+H]^+$.

2-(2,4-Dichlorophenyl)-7,7-dimethyl-4-ferrocenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5g). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.75 (s, 1H, NH), 7.76 (s, 1H, ArH), 7.61–7.52 (m, 3H, ArH), 5.15 (d, J = 5.6 Hz, 1H, CH), 4.32 (d, J = 6.0 Hz, 1H, CH), 4.18 (s, 1H, ferroceneyl), 4.13 (s, 5H, ferroceneyl), 4.03 (d, J = 5.6 Hz, 2H, ferroceneyl), 3.98 (s, 1H, ferroceneyl), 2.29 (d, J = 16.8 Hz, 1H, CH_2), 2.17 (d, J = 17.2 Hz, 1H, CH_2), 2.13 (d, J = 16.0 Hz, 1H, CH_2), 1.99 (d, J = 16.0 Hz, 1H, CH_2), 0.97 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3300, 3082, 2957, 2863, 1622, 1597, 1468, 1380, 1240, 1137, 1076, 817, 765, 576. HRMS (ESI) *m/z*: calc. for: 505.0663 $[M+H]^+$, found: 505.0659 $[M+H]^+$.

2-(4-Hydroxyphenyl)-7,7-dimethyl-4-ferrocenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5h). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.30 (s, 1H, OH), 8.51 (s, 1H, NH), 8.21 (d, J = 8.0 Hz, 2H, ArH), 7.74 (d, J = 8.8 Hz, 2H, ArH), 5.16 (d, J = 5.6 Hz, 1H, CH), 4.29 (d, J = 6.0 Hz, 1H, CH), 4.14 (s, 1H, ferroceneyl), 4.10 (s, 5H, ferroceneyl), 4.02 (s, 1H, ferroceneyl), 3.91 (s, 1H, ferroceneyl), 3.79 (s, 1H, ferroceneyl), 2.18 (d, J = 18 Hz, 1H, CH_2), 2.03 (d, J = 18.8 Hz, 1H, CH_2), 1.77 (d, J = 14.0 Hz, 1H, CH_2), 1.61 (d, J = 14.4 Hz, 1H, CH_2), 0.97 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3424, 3303, 3088, 2960, 2867, 1625, 1582, 1473, 1370, 1258, 1161, 1064, 816, 747, 569. HRMS (ESI) *m/z*: calc. for: 453.1391 $[M+H]^+$, found: 453.1381 $[M+H]^+$.

7,7-Dimethyl-2-phenyl-4-ferrocenyl–4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5i). ^{1}H-NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.58 (s, 1H, NH), 7.49–7.47 (m, 2H, ArH), 7.40–7.34 (m, 3H, ArH), 5.21 (d, J = 6.0 Hz, 1H, CH), 4.56 (d, J = 5.2 Hz, 1H, CH), 4.28 (s, 1H, ferroceneyl), 4.23 (s, 5H, ferroceneyl), 4.11 (s, 1H, ferroceneyl), 4.04 (s, 1H, ferroceneyl), 3.88 (s, 1H, ferroceneyl), 2.47 (d, J = 16.8 Hz, 1H, CH_2), 2.31 (d, J = 16.8 Hz, 1H, CH_2), 2.17 (d, J = 16.0 Hz, 1H, CH_2), 2.01 (d, J = 16.0 Hz, 1H, CH_2), 1.03 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3292, 3094, 2947, 2867, 1616, 1590, 1485, 1384, 1274, 1153, 1033, 821, 760, 568. HRMS (ESI) *m/z*: calc. for: 438.1515 $[M+H]^+$, found: 438.1495 $[M+H]^+$.

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