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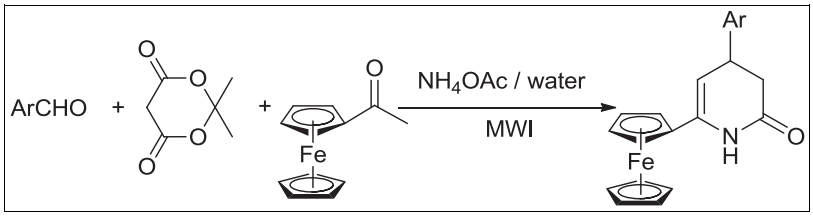

A clean and green method for synthesizing a series of new ferrocenyl pyridin-2(1*H*)-one derivative was developed via the one-pot reactions of aldehydes, Meldrum's acid, acetylferrocene, and ammonium acetate using high-temperature water as a solvent and microwave heating. This method had several advantages such as good yields, reduced environmental impact, and convenient procedure.

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INTRODUCTION

The similar polarity of classic organic solvents and high-temperature water has encouraged chemists to investigate the organic transformations in aqueous media [1]. In addition to being a safe, readily available, and environmentally friendly solvent, water has also been recognized as an effective reaction medium with unique properties and possibilities for many organic reactions [2]. Simultaneously, high density microwave (MW) irradiation has matured into a reliable and useful methodology for accelerated processing of small-scale reactions [3]. Thus, it has become clear that the combined approach of MW superheating and aqueous conditions offers a nearly synergistic strategy in the sense that the combination in itself offers greater potential than the two parts in isolation [4].

In modern drug discovery, a number of solutions to increase the output of unique chemical entities have been presented, for example, combinatorial synthesis, parallel synthesis, and automated library production [5]. Even though many of these small-scale techniques in themselves are productive, they generate significant quantities of chemical waste [6]. Overall, the development of new methods that reduce the environmental impact is of increasing importance, not only for pharmaceutical production but also in the medicinal or combinatorial chemistry research laboratory. The use of water as a nontoxic reaction medium, together with the employment of energy-efficient MW heating [7], must be considered to be both promising and enabling green alternatives.

Metallocenes are known to exhibit a wide range of biological activity [8]. Among them, ferrocene has attracted special attention because it is neutral, chemically stable, nontoxic, and able to cross cell membranes [9]. Recently, ferrocenyl derivatives were reported to display antimalarial [10], antitumor [11], and DNA cleaving [12] activities. For these reasons, the synthesis of these molecules containing ferrocene unit has attracted considerable attention [13]. On the other hand, the pyridin-2(1*H*)-one ring system and the corresponding dihydro and tetrahydro derivatives possess structural features found in a wide variety of naturally occurring alkaloids [14]. The pyridin-2(1*H*)-one derivatives have been found to exhibit interesting biological activities such as kappa opioid receptor agonists [15], antitumor agents [16], farnesyltransferase inhibitors [17], and cardiotonic agents [18]. It is now well established that the incorporation of ferrocene units in organic molecules introduces significant and new properties in these materials [19]. The introduction of ferrocenyl group on the 2(1*H*)-pyridone ring may lead to novel biological activities. However, the synthesis of these compounds with both ferrocene motif and pyridin-2(1*H*)-one motif was neglected all the time. Therefore, the synthesis of these compounds and development of more rapid and efficient entry to these heterocycles are strongly desired. Herein, we would like to report a rapid and efficient method for synthesizing ferrocenyl pyridin-2-one derivatives in high-temperature water using inexpensive reagents as starting materials and MW heating (Scheme 1).

RESULTS AND DISCUSSION

To explore the full scope and versatility of this method, various reaction conditions were investigated, including solvent, temperature, and volume of water variations. Highlighted in Table 1 for compound **4a**, for example, is the influence of solvents on the reaction yield. The MW

Scheme 1

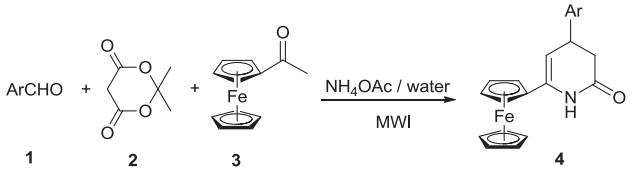


Table 1

Optimization of the solvents in the synthesis of compound **4a** at 100°C.

Entry	Solvent	Power (W)	Time (min)	Yield (%)
1	Glycol	200	14	Trace
2	Water	200	8	64
3	HOAc	200	12	Trace
4	DMF	200	15	42
5	None	200	14	56

assisted reaction of 4-chlorobenzaldehyde (**1a**, 1.0 mmol), Meldrum's acid (**2**, 1.0 mmol), and acetylferrocene (**3**, 1.0 mmol) in the present of ammonium acetate (3.0 mmol) was examined using glycol, water, glacial acetic acid, and DMF as solvents (1.0 mL) and solvent-free at 100°C, respectively (Scheme 2). All the reactions were carried out at the maximum power of 200 W. The results were summarized in Table 1.

It was shown in Table 1 that the reaction using water as solvent resulted in good yield (Table 1, entry 2), whereas glycol, HOAc, DMF, or solvent-free did not give satisfactory result (Table 1, entries 1, 3, 4, and 5). So water was chosen as the reaction solvent.

To optimize the reaction temperature, the earlier reaction was carried out in water at temperatures ranging from 80°C to 130°C, with an increment of 10°C each time, using the maximum power of 200 W. (Table 2).

From Table 2, we found that the yield of product **4a** was improved and the reaction time was shortened as the temperature was increased from 80°C to 100°C (Table 2, entries 1–3). Because the reactions were carried out in a sealed tube under a pressurized atmosphere, the temperature could be increased beyond the boiling point of water

Scheme 2

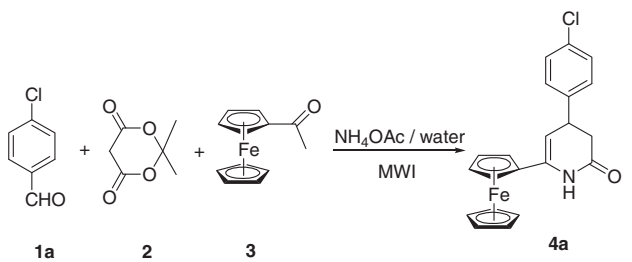


Table 2

Optimization of the temperatures in the synthesis of compound **4a** in water.

Entry	T/°C	Time/min	Yield/%
1	80	12	45
2	90	11	50
3	100	8	64
4	110	6	68
5	120	6	73
6	130	6	70

(100°C). When the temperature was increased from 100°C to 120°C (Table 2, entries 3–5), the yield of product **4a** was further increased. However, no significant increase in the yield of product **4a** was observed as the reaction temperature was raised to 130°C (Table 2, entry 6). Therefore, 120°C was chosen as the reaction temperature for all further MW-assisted reactions. Furthermore, the volume of water was found to be important in this reaction as well. When 1.0−1.5 mL of water was used as solvent, the reaction gave the best result.

These optimization results prompted us to select water as reaction solvent for further study. At the beginning of the search for the aldehyde substrate scope, Meldrum's acid and acetylferrocene were used as model substrates (Table 3, entries 1–9), and the results indicated that aromatic aldehydes bearing such functional groups as nitro, fluoro, chloro, bromo, or methoxyl were able to effect the synthesis of compound **4**. We have also observed delicate electronic effects, that is, aryl aldehydes with electron-withdrawing groups (Table 3, entries 1–5) reacted rapidly, whereas substitution of electron-rich groups (Table 3, entries 7–8) on the benzene ring decreased the reactivity, requiring longer reaction times. Moreover, the heterocyclic aldehyde such as thiophene-2-carbaldehyde (Table 3, entry 9) still displayed high reactivity and clean reaction under this standard condition.

For comparison, when the four-component reaction was carried out in a 10 mL sealed tube in water (1.0 mL) with

Table 3

Synthesis of **4** under microwave irradiation at 120°C in water.

Entry	**4**	R	Time/min	Yield/%	Mp/°C
1	**4a**	4-ClC_6H_4	6	73	274–276
2	**4b**	4-BrC_6H_4	6	80	254–256
3	**4c**	4-FC_6H_4	8	75	250–252
4	**4d**	3,4-$Cl_2C_6H_3$	6	79	189–191
5	**4e**	4-$NO_2C_6H_4$	4	81	217–218
6	**4f**	C_6H_5	8	68	247–249
7	**4g**	4-$CH_3OC_6H_4$	10	70	210–211
8	**4h**	3,4-$OCH_2OC_6H_3$	9	74	206–207
9	**4i**	2-thiophenyl	10	72	200–202

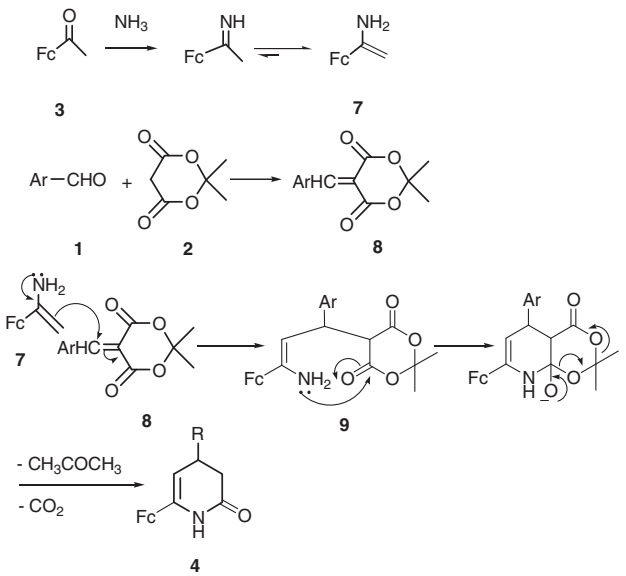
1a (1.0 mmol), **2** (1.0 mmol), and **3** (1.0 mmol) in the present of ammonium acetate (3.0 mmol) under classical heating conditions at 120°C, the product **4a** failed to be obtained after 2 h. The results indicated (Table 3, entry 1) that there is a clear advantage in terms of reaction time and yield when working under MW conditions. Therefore, the reaction was efficiently promoted by MW irradiation.

All these new products were characterized by IR spectra, ^{1}H NMR data, and elemental analyses. In the IR spectra of compound **4g** showed strong absorptions at 3204 cm^{-1} because of NH group, and at 1682 cm^{-1} because of C═O group. The ^{1}H NMR spectrum of **4g** showed a singlet at δ 3.73 because of OCH_3, a singlet at δ 4.18 and 4.28 because of ferrocenyl-H, and a singlet at δ 9.12 because of NH proton (exchanged with D_2O).

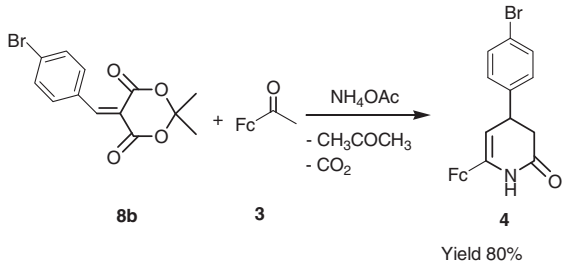
It is well known that the pK_a value of Meldrum's acid is lower than those of acetylferrocene, so the aldehydes were first condensed with Meldrum's acid. Although the detailed mechanism of the earlier reaction remains to be fully clarified, the formation of **4** was expected to proceed via initial condensation of acetylferrocene **2** with amine from ammonium acetate to afford 1-ferrocenylethenamine **7**, which further underwent *in situ* Michael addition reaction with compound **8** to yield intermediate **9**. The intermediate **9** then cyclized and subsequently lost a carbon dioxide and an acetone molecule to afford the product **4** (Scheme 3).

In order to support the proposed mechanism, the compound **8b** was prepared independently from *p*-bromobenzaldehyde **1b** and Meldrum's acid **2** and then employed in a three-component reaction with acetylferrocene **3** and ammonium acetate to afford product **4b** in 80% yield (Scheme 4). When *p*-bromobenzaldehyde **1b** was first condensed with acetylferrocene **3** to afford chalcones **9**,

Scheme 3



Scheme 4



which was followed by reaction with Meldrum's acid **2** and ammonium acetate, product **4b** was given in 45% yield (Scheme 5). The fact was further supported proposed mechanism.

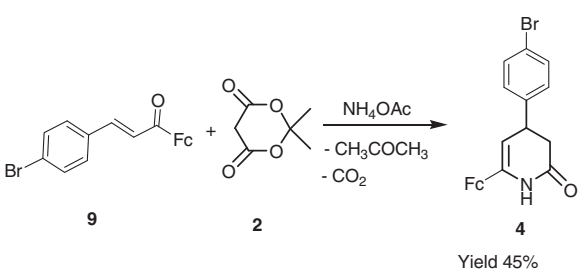
In summary, we have accomplished the synthesis of highly functionalized ferrocenyl pyridin-2(*1H*)-one derivatives of potentially biological importance using high-temperature water as a solvent and MW heating. It is availably expanded the scope of the class of organic synthesis in aqueous media. In addition, it is possible to apply the tenets of green chemistry to the generation of interesting products using aqueous media methods that are less expensive and less toxic than those with organic solvents. Moreover, the procedure offers several advantages including operational simplicity, clean reactions, increased safety for small-scale high-speed synthesis, and minimal environmental impact that make it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

Microwave syntheses were carried out on MW oven Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FTIR-tensor 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analyses were determined by using a Perkin–Elmer 240c elemental analysis instrument.

Sample experimental. All MW-assisted reactions were performed in Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Typically, in a 10-mL Emrys™ reaction vial, aromatic aldehyde (1.0 mmol), acetylferrocene (1.0 mmol),

Scheme 5



Meldrum's acid (1.0 mmol), ammonium acetate (3.0 mmol), and water (1.0 mL) were mixed and then capped. The mixture was irradiated by MW at 200 W and at 120°C for a given time. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and washed with 2 mL ether, filtered to give the crude products, which were further purified by recrystallization from 95% EtOH. The analytical data of new products are the following:

4-(4-Chlorophenyl)-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4a). Brown solid; IR (KBr): ν 3208, 3097, 1673, 1644, 1498, 1375, 1091, 817 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H, NH), 7.41 (d, J = 8.4 Hz, 2H, ArH), 7.32 (d, J = 8.4 Hz, 2H, ArH), 5.38 (d, J = 4.4 Hz, 1H, CH), 4.72 (d, J = 7.6 Hz, 2H, ferrocenyl), 4.29 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 3.79–3.76 (m, 1H, CH), 2.73 (dd, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 1H, CH_2), 2.48 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, CH_2); *Anal*. Calc. for $C_{21}H_{18}ClFeNO$: C, 64.40; H, 4.63; N, 3.58; found C, 64.56; H, 4.54; N, 3.49 %.

4-(4-Bromophenyl)-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4b). Brown solid; IR (KBr): ν 3208, 3099, 1672, 1647, 1482, 1376, 1074, 914, 816 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H, NH), 7.54 (d, J = 8.4 Hz, 2H, ArH), 7.27 (d, J = 8.4 Hz, 2H, ArH), 5.38 (d, J = 4.4 Hz, 1H, CH), 4.73 (d, J = 7.6 Hz, 2H, ferrocenyl), 4.28 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 3.77–3.76 (m, 1H, CH), 2.76 (dd, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 1H, CH_2), 2.47 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, CH_2); *Anal.* Calc. for $C_{21}H_{18}BrFeNO$: C, 57.83; H, 4.16; N, 3.21; found: C, 57.74; H, 3.31; N, 3.14 %.

4-(4-Fluorophenyl)-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4c). Brown solid; IR (KBr): ν 3205, 3098, 1671, 1647, 1508, 1370, 1223, 1075, 1007, 821, 793 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H, NH), 7.35–7.32 (m, 2H, ArH), 7.20–7.153 (m, 2H, ArH), 5.39 (d, J = 4.0 Hz, 1H, CH), 4.73 (d, J = 9.6 Hz, 2H, ferrocenyl), 4.29 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 3.81–3.76 (m, 1H, CH), 3.70–3.68 (m, 1H, CH), 2.78–2.72 (m, 1H, CH_2), 2.49–2.46 (m, 1H, CH_2); *Anal*. Calcd for $C_{21}H_{18}FFeNO$: C, 67.22; H, 4.84; N, 3.73; found C, 67.35; H, 4.68; N, 3.65%.

4-(3,4-Dichlorophenyl)-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4d). Brown solid; IR (KBr): ν 3205, 3096, 1673, 1650, 1467, 1366, 1007, 817 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H, NH), 7.63 (d, J = 8.4 Hz, 1H, ArH), 7.55 (s, 1H, ArH), 7.32 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, ArH), 5.41 (d, J = 4.8 Hz, 1H, CH), 4.75 (d, J = 7.6 Hz, 2H, ferrocenyl), 4.30 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 3.83–3.73 (m, 1H, CH), 2.79 (dd, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 1H, CH_2), 2.48 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, CH_2); *Anal*. Calcd for $C_{21}H_{17}Cl_2FeNO$: C, 59.19; H, 4.02; N, 3.29; found C, 59.08; H, 3.94; N, 3.37%.

4-(4-Nitrophenyl)-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4e). Red solid; IR (KBr): ν 3203, 3107, 1682, 1651, 1596, 1520, 1346, 1104, 855, 812, 754 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H, NH), 8.23 (d, J = 8.4 Hz, 2H, ArH), 7.58 (d, J = 8.4 Hz, 2H, ArH), 5.42 (d, J = 4.4 Hz, 1H, CH), 4.75 (d, J = 7.6 Hz, 2H, ferrocenyl), 4.30 (s, 2H, ferrocenyl), 4.19 (s, 5H, ferrocenyl), 3.97–3.95 (m, 1H, CH), 2.84 (dd, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 1H, CH_2), 2.51 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, CH_2); *Anal*. Calcd for $C_{21}H_{18}FeN_2O_3$: C, 62.71; H, 4.51; N, 6.96; found C, 62.91; H, 4.60; N, 6.87%.

4-Phenyl-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4f). Red solid; IR (KBr): ν 3201, 3080, 1668, 1650, 1371, 1075, 820, 763 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H, NH), 7.36–7.30 (m, 4H, ArH), 7.26–7.24 (m, 1H, ArH), 5.41 (d, J = 4.4 Hz, 1H, CH), 4.73 (d, J = 7.6 Hz, 2H, ferrocenyl), 4.29 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 3.78–3.75 (m, 1H, CH), 2.76 (dd, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 1H, CH_2), 2.49 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, CH_2); *Anal*. Calcd for $C_{21}H_{19}FeNO$, C, 70.61; H, 5.36; N, 3.92; found C, 70.84; H, 5.39; N, 3.79%.

4-(4-Methoxyphenyl)-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4g). Red solid; IR (KBr): ν 3204, 3102, 3028, 1682, 1596, 1519, 1346, 854, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H, NH), 7.21 (d, J = 8.4 Hz, 2H, ArH), 7.04 (d, J = 8.4 Hz, 2H, ArH), 5.38 (d, J = 4.4 Hz, 1H, CH), 4.72 (d, J = 7.6 Hz, 2H, ferrocenyl), 4.28 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 3.73 (s, 3H, OCH_3), 3.70 3.68 (m, 1H, CH), 2.73 (dd, J_1 = 16.0 Hz, J_2 = 6.8 Hz, 1H, CH_2), 2.44 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, CH_2); *Anal*. Calcd for $C_{22}H_{21}FeNO_2$: C, 68.23; H, 5.47; N, 3.62; Found C, 68.41; H, 5.39; N, 3.58%.

4-(Benzo[d][1,3]dioxol-5-yl)-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4h). Red solid; IR (KBr): ν 3230, 3084, 2901, 1665, 1488, 1440, 1374, 1036, 813 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H, NH), 6.88–6.86 (m, 2H, ArH), 6.76 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, ArH), 5.97 (s, 2H, CH_2), 5.37 (d, J = 4.4 Hz, 1H, CH), 4.72 (d, J = 10.0 Hz, 2H, ferrocenyl), 4.28 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 3.69–3.67 (m, 1H, CH), 2.72 (dd, J_1 = 16.0 Hz, J_2 = 6.8 Hz, 1H, CH_2), 2.47 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, CH_2); *Anal.* Calcd for $C_{22}H_{19}FeNO_3$: C, 65.86; H, 4.77; N, 3.49; found C, 65.67; H, 4.84; N, 3.56%.

4-(Thiophen-2-yl)-6-ferrocenyl-3,4-dihydropyridin-2(1H)-one (4i). Red solid; IR (KBr): ν 3208, 3098, 1669, 1645, 1447, 1368, 1257, 997, 819, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H, NH), 7.37 (d, J = 4.8 Hz, 1H, thiophenyl-H), 7.00 6.95 (m, 2H, thiophenyl-H), 5.49 (d, J = 4.8 Hz, 1H, CH), 4.72 (d, J = 6.0 Hz, 2H, ferrocenyl), 4.29 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 4.06 4.02 (m, 1H, CH), 2.85 (dd, J_1 = 16.0 Hz, J_2 = 6.8 Hz, 1H, CH_2), 2.52 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, CH_2); *Anal*. Calcd for $C_{19}H_{17}FeNOS$, C, 62.82; H, 4.72; N, 3.86; S, 8.83 found C, 62.74; H, 4.64; N, 3.97; S, 8.94%.

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REFERENCES AND NOTES

[1] (a) Sinou, D. Top Curr Chem 1999, 41, 206; (b) Strauss, C. R.; Trainor, R. W. Aust J Chem 1995, 48, 1665; (c) An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. J Org Chem 1997, 62, 2505; (d) Beletskaya, I. P.; Cheprakov, A. V. In Organic Synthesis in Water; Grieco, P. A., Ed.; Blackie: London, 1998, 141–222; (e) Arvela, R. K.; Leadbeatera, N. E.; Collins, M. J. Tetrahedron 2005, 61, 9349; (f) Wu, X.; Larhed, M. Org Lett 2005, 7, 3327; (g) Kormos, C. M.; Leadbeater, N. E. Tetrahedron 2006, 62, 4728; (h) Arvela, R. K.; Leadbeater, N. E. J Org Chem 2005, 70, 1786.

[2] (a) Li, C.-J. Chem Rev 2005, 105, 3095; (b) Li, C. J. Handbook of Green Chemistry, Volume 5: Reactions in Water; Wiley-VCH: Weinheim, Germany, 2010, pp 427; (c) Li, C.-J. Acc Chem Res 2010, 43, 581; (d) Basle, O.; Li, C.-J. Green Chem 2007, 9, 1047; (e) Li, C.-J.; Chen, L. Chem Soc Rev 2006, 35, 68; (f) Li, C.-J. Acc Chem Res 2002, 35, 533; (g) Li, C.-J. Chem Rev 2007, 107, 2546.

[3] (a) Larhed, M.; Moberg, C.; Hallberg, A. Acc Chem Res 2002, 35, 717; (b) Kappe, C. O. Angew Chem Int Ed 2004, 43, 6250; (c) Olofsson,

K.; Larhed, M. In Microwave Assisted Organic Synthesis; Tierney, J. P.; Lidström, P., Eds.; Blackwell: Oxford, 2005, 23–43; (d) Kappe, C. O.; Dallinger, D. Nat Rev Drug Discovery 2006, 5, 51.

[4] (a) Wu, X.; Ekegren, J. K.; Larhed, M. Organometal 2006, 25, 1434; (b) Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G. Green Chem 2010, 12, 1357.

[5] Dolle, R. E. J Comb Chem 2004, 6, 623.

[6] (a) Sheldon, R. A. Chemtech 1994, 24, 38; (b) Roberts, B. A.; Strauss, C. R. Acc Chem Res 2005, 38, 653.

[7] (a) Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. Org Process Res Dev 2005, 9, 516; (b) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. J Org Chem 1999, 64, 3885; (c) Leadbeater, N. E.; Marco, M. Org Lett 2002, 4, 2973; (d) Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. J Org Chem 1996, 61, 7355.

[8] Farrell, N. Transition Metal Complexes as Drugs and Therapeutic Agents; Kluwer Academic: Dordrecht, Germany, 1989.

[9] Dombrowski, K. E.; Baldwin, W.; Sheats, J. E. J Organomet Chem 1986, 302, 281.

[10] (a) Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S. J Med Chem 1997, 40, 3715; (b) Itoh, T.; Shirakami, S.; Ishida N.; Yamashita, Y.; Yoshida, T.; Kim, H.-S.; Wataya, Y. Bioorg Med Chem Lett 2000, 10, 1657.

[11] (a) Köpf-Maier, P.; Köpf, H. Drugs Future 1986, 11, 297; (b) Köpf-Maier, P.; Köpf, H.; Neuse, E. W. Angew Chem 1984, 96, 446.

[12] (a) Frühauf, H.-H. Chem Rev 1997, 97, 523; (b) Lautens, M.; Tam, W. Chem Rev 1996, 96, 49; (c) Dell, C. P. Curr Med Chem 1998, 5, 179; (d) Saito, S.; Yamamoto, Y. Chem Rev 2000, 100, 2901.

[13] (a) Jones, T. H.; Blum, M. S. In Alkaloids: Chemical and Biological Perspectives; Pelletier, S. W., Ed.; Wiley: New York, 1983; 1, 33–84; (b) Fodor, G. B.; Colasanti, B. In Alkaloids: Chemical and Biological Perspectives; Pelletier, S. W., Ed.; Wiley: New York, 1985; 3, 1–90; (c) Balasubramanian, M.; Deay, J. G. In Comprehensive Heterocyclic Chemistry II; Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: New York, 1996; 5, 245; (d) Zhuang, Q. Y.; Jia, R. H.; Tu, S. J.; Zhang, J. Y.; Jiang, B.; Zhang, Y.; Yao, C. S. J Heterocycl Chem 2007, 44, 895; (e) Tu, S. J.; Yan, S.; Cao, X. D.; Wu, S. S.; Zhang, X. H.; Hao, W. J.; Han, Z. G.; Shi, F. J Organomet Chem 2009, 694, 91.

[14] (a) Fujita, R.; Watanabe, K.; Ikeura, W.; Ohtake, Y.; Hongo, H. Heterocycles 2000, 53, 2607; (b) Casamitjana, N.; Lopez, V.; Jorge, A.; Bosch, J.; Molins, E.; Roig, A. Tetrahedron 2000, 56, 4027; (c) Grundon, M. F. Nat Prod Rep 1989, 6, 523; (d) Elbein, A. D.; Molyneux, R. J. In Alkaloids: Chemical and Biological Perspectives; Pelletier, S. W., Ed.; Wiley: New York, 1981; 5, 1–54; (e) Lin, C. H.; Tsai, M. R.; Wang, Y. S.; Chang, N. C. J Org Chem 2003, 68, 5688; (f) Sutherland, A.; Gallagher, T. J Org Chem 2003, 68, 3352.

[15] Cocco, M. T.; Congiu, C.; Onnis, V. Eur J Med Chem 2003, 38, 37.

[16] (a) Li, Q.; Claiborne, A.; Li, T.; Hasvold, L.; Stoll, V. S.; Muchmore, S.; Jakob, C. G.; Gu, W.; Cohen, J.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. Bioorg Med Chem Lett 2004, 14, 5367; (b) Hasvold, L. A.; Wang, W. B.; Gwaltney, S. L.; Rockway, T. W.; Nelson, L. T. J.; Mantei, R. A.; Fakhoury, S. A.; Sullivan, G. M.; Li, Q.; Lin, N. H.; Wang, L.; Zhang, H.Y.; Cohen, J.; Gu, W. Z.; Marsh, K.; Bauch, J.; Rosenberg, S.; Sham, H. L. Bioorg Med Chem Lett 2003, 13, 4001; (c) Lobell, R. B.; Omer, C. A.; Abrams, M. T.; Bhimnathwala, H. G.; Brucker, M. J.; Buser, C. A.; Davide, J. P.; DeSolms, S. J.; Dinsmore, C. J.; Ellis-Hutchings, M. S.; Kral, A. M.; Liu, D. M.; Lumma, W. C.; Machotka, S. V.; Rands, E.; Williams, T. M.; Graham, S. L.; Hartman, G. D.; Oliff, A. I.; Heimbrook, D. C.; Kohl, N. E. Cancer Res 2001, 61, 8758.

[17] El-Kemary, M.; Organero, J. A.; Douhal, A. J Med Chem 2006, 49, 3086.

[18] Astruc, D. Electron Transfer and Radical Processes in Transition-Metal Chemistry; Verlag Chemie: New York, 1995.

[19] (a) Lakshmi, V.; Santosh, G.; Ravikanth, M.J Organomet Chem 2011, 696, 925; (b) Fukino, T.; Fujita, N.; Aida, T. Org Lett 2010, 12, 3074; (c) Carr, J. D.; Coles, S. J.; Hursthouse, M. B.; Tucker, J. H. R. J Organomet Chem 2001, 304, 637; (d) Lindner, E.; Zong, R.; Eichele, K.; Ströbele, M. J Organomet Chem 2002, 660, 78.