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SYNTHESIS OF QUINOLINE-BEARING FERROCENE DERIVATIVES *VIA* FRIEDLÄNDER REACTION OF ACETYL- AND 1,1'-DIACETYL-FERROCENES WITH *o*-AMINO ARYL ALDEHYDES

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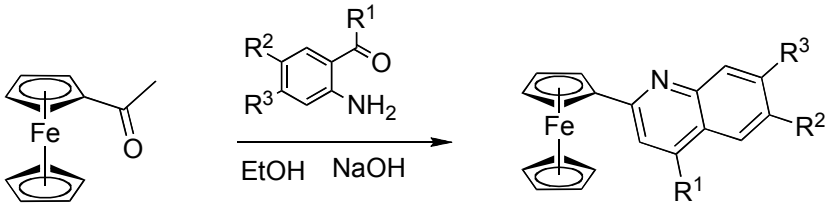
Abstract – A facile and convenient synthesis of quinolyl-substituted ferrocenes via Friedländer reaction of acetylferrocene or 1,1'-diacetylferrocene with 2-aminobenzaldehyde, 2-aminopiperonal, and (2-aminophenyl)(phenyl) methanone, respectively, with good yields is described.

Quinolines and their derivatives are receiving increasing importance due to their wide range of biological activities such as anti-malarial,[1,2] anti-hypertensive,[3-5] anti-parasitical,[6-10] anti-depression,[11] anti-bacterial,[12-20] anti-arrhythmic,[21] activity and as tyro-kinase PDGF-RTK inhibiting activity.[22,23] In addition, quinolines have also been employed in the study of bio-organic and bio-organometallic process.[24] Due to such a wide range of applicability in medicinal, bioorganic, industrial as well processes as in the fields of synthetic organic chemistry, there has been increasing interest in the development of efficient methodologies for the synthesis of quinolines.

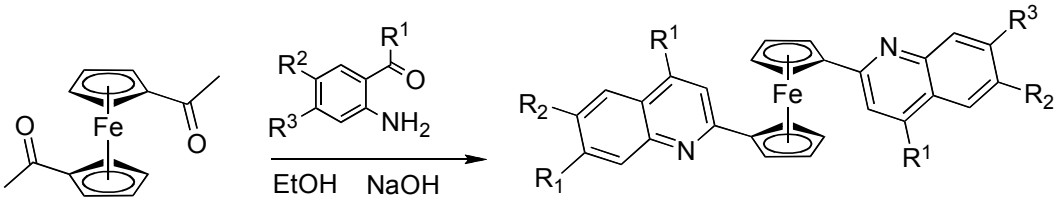
On the other hand, ferrocene is a compound with excellent stability. Unlike many other organometallic compounds, it is completely stable in water and air. Different ferrocenly compounds have wide applications in catalysis, in the design of new nonlinear opties materials, and in preparation of newly biological active compounds. It was reported that many ferrocenyl derivatives have good activity against several types of cancers.[25-30] Recently quinolinylferrocene derivatives were reported to display antimalarial, antitumor, fungicidal, anti-HIV and DNA cleaving activities.[31-34] The best example of this hydroxyferroquinoline derivatives, which is biologically active against HIV, SARS-CoV and expected to enter phase I clinical trials soon.[35] Therefore, the synthesis of ferrocene derivatives linked to a quinoline unit is of considerable interest since their properly substituted aryl quinolines are biologically active and exist in the structures of various antitumor agents. Previously, Gelin et al. reported on the Friedländer condensation of acetyl- and 1,l'-diacetylferrocene with unsubstituted 2-aminobenzaldehyde resulting in

the formation of the corresponding ferrocenyl quinolines.[36] Recently, Chupakhin et al. reported the synthesis of mono- and 1,1'-diquinolylferrocenes by the reactions of ferrocenyllithium with azaheterocycles.[37] More recently, Zora et al. have also reported the synthesis of quinolinyl ferrocenes involving iodine-catalyzed reactions of ferrocenylimines with enolizable aldehydes.[38] In this context, we wish to report, herein, the facile synthesis of quinolyl ferrocenes (**2a**-**4c**) by the Friedländer condensation reactions of acetylferrocene (**1**) or 1,1'-diacetylferrocene (**3**) with 2-aminobenzaldehyde, 2-aminopiperonal, and (2-aminophenyl)(phenyl)methane, respectively, as shown in Scheme 1 and Scheme 2. The yields and melting points of all the target compounds **2a-4c** were listed in Table 1.



1 **2a-c**

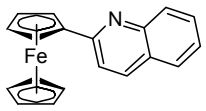
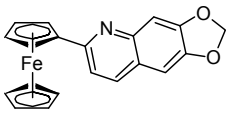
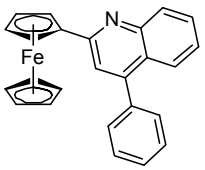
Scheme 1. Synthetic route of the title compounds **2a-c**



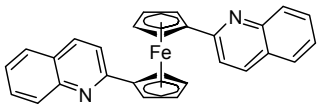
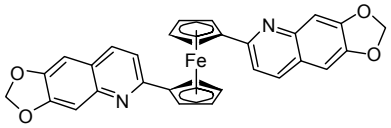
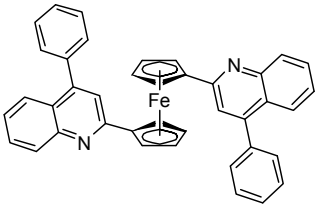
3 **4a-c**

Scheme 2. Synthetic route of the title compounds **4a-c**

Table 1. Synthesis of the quinolyl ferrocenes (**2a**-**4c**)

Entry	Product		Time (h)	Yield (%)[a]	Mp (°C)
1		**2a**	19	79 lit.[36]: 53	137-139 lit.[36]: 130-133
2		**2b**	17	72	152-153
3		**2c**	20	75	>300

Continued (Table 1)

Entry	Product		Time (h)	Yield (%)[a]	Mp (°C)
4		**4a**	20	73 lit.[36]: 75	206-208 lit.[36]:209-210
5		**4b**	23	69	227-229
6		**4c**	23	71	>300

[a]Isolated yield.

In fact, the reaction of acetylferrocene (**1**) with 2-aminobenzaldehyde was initially performed under standard Friedländer conditions,[39] namely using sodium ethoxide as catalyst and absolute enthanol as solvent. But the TLC showed that the reaction proceeded not very well due to the occurrence of some by-reactions. After purification by flash chromatography, the product **2a** was obtained in a low yield of 45%. Thus, we turned our attention to other catalysts, such as sodium hydroxide, potassium carbonate, or pyrrolidine as shown in Table **2**. The results showed that the best results could be achieved when using 2.0 equivalent of sodium hydroxide as catalyst and the product was obtained in 79% yield (Entry 1, Table **2**). In addition, we also attempted to other solvents such as MeOH, THF, MeCN, 50% EtOH. But the results showed in Table **3** that the yield could not be improved further.

Table 2. Catalyst optimization for the synthesis of **2a**

Entry	Base	Time (h)	Yield (%)
1	sodium hydroxide	20	79
2	potassium carbonate	20	67
3	pyrrolidine	20	65

Table 3. Yields of compound **2a** in different solvents

Entry	Solvent	Time (h)	Yield (%)
1	MeOH	20	60
2	THF	20	35
3	MeCN	20	57
4	50% aq. EtOH	20	67

Similarly, under the optimized reaction conditions, the reaction of acetylferrocene (**1**) with 2-aminopiperonal and (2-aminophenyl)(phenyl)methanone afforded the corresponding (6,7-methylenedioxyquinolin-2-yl)ferrocene (**2b**) and (4-phenylquinolin-2-yl)ferrocene (**2c**) in good yields of 72% and 75%, respectively (Entries 2 and 3, Table **1**). Then the above-mentioned method was further extended to the Friedländer condensation reaction of 1,1'-diacetylferrocene (**2**) with 2-aminobenzaldehyde, 2-aminopiperonal, and (2-aminophenyl)(phenyl)methanone as shown in Scheme 2. To our delight, in all these cases, the reactions proceeded smoothly and gave the corresponding 1,1'-bis(quinolin-2-yl)ferrocenes **4a-c** in 69%-73% yields (Entries 4-6, Table **1**). All the synthesized products except compounds **2a** and **4a** are novel and their structures have been characterized by IR, ^{1}H NMR spectra and elemental analyses.

EXPERIMENTAL

Melting points (uncorrected) were determined by using WRS-1B melting points apparatus. The ^{1}H NMR (400 MHz) spectra were recorded on a Brucker AVANCE 400 NMR spectrometer at 400 MHz using TMS as internal standard. The Mass spectra were determined using a MSD VL ESI1 spectrometer. The elemental analyses was performed for C, H using an Elementar Vario EL-III element analyzer and found within ±0.4%. The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel GF254 using ethyl acetate/petroleum ether (1/3) as eluent. Acetylferrocene and 1,1'-diacetylferrocene were prepared by acylation of ferrocene with a acetic acid/phosphorus trichloride/aluminum trichloride combination according to known literature procedures.[40]

General procedure for the synthesis of quinolinyl ferrocenes 2a-c and 4a-c. To a solution of acetylferrocene **1** or 1,1'-diacetylferrocene **2** (0.50 mmol) and 2-aminobenzaldehyde, (2-aminophenyl) (phenyl)methanone or 2-aminopiperonal (0.60 mmol or 1.20 mmol) in 3 mL of EtOH was added sodium

hydroxide (40.03 mg, 1 mmol). The resulting mixture was then heated at reflux for 17-23 h. After the reaction was complete, the mixture was cooled to room temperature, and then poured into some water, filtered to give the crude products, which were further purified by recrystallization. The reaction time, yields and melting points are listed in Table 1.

(Quinolin-2-yl)ferrocene (2a). This compound was obtained as red solid from EtOAc, IR (KBr) ν/cm^{-1}: 3091, 3060, 2924, 1599, 1556, 1510, 1423, 1280, 1128, 1104, 1009, 907, 820, 757; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.03 (d, *J*=8.5 Hz, 2H, ArH), 7.74 (dd, *J*=1.3 Hz, 1.5 Hz, 1H, ArH), 7.67-7.64 (m, 1H, ArH), 7.57 (d, *J*=8.5 Hz, 1H, ArH), 7.47-7.44 (m, 1H, ArH), 5.07 (t, *J*=1.9 Hz, 2H, ferrocenyl), 4.47 (t, *J*=1.9 Hz, 2H, ferrocenyl), 4.06 (s, 5H, ferrocenyl); MS (ESI, *m/z*): 314.08 $(M+H)^+$; Anal. Calcd for $C_{19}H_{15}FeN$: C, 72.87; H, 4.83; N, 4.47. Found: C, 72.91; H, 4.78; N, 4.51. The spectral data are in agreement with the literature.[36]

(6,7-Methylenedioxyquinolin-2-yl)ferrocene (2b). This compound was obtained as red solid from EtOAc, IR (KBr) ν/cm^{-1}: 3055, 2962, 2924, 1589, 1546, 1495, 1443, 1243, 1092, 1029, 915, 813, 762 ,697; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.10 (d, *J*=8.10 Hz, 1H, ArH), 7.82 (d, *J*=15.0 Hz, 1H, ArH), 7.66 (t, *J*=13.2 Hz, 12.0 Hz, 1H, ArH), 7.55(d, *J*=12.5 Hz, 5H, ArH), 7.50(s, 1H, ArH), 7.41(t, *J*=13.0 Hz, 12.0Hz, 1H, ArH), 5.08 (s, 2H, ferrocenyl), 4.47 (s, 2H, ferrocenyl), 4.08 (s, 5H, ferrocenyl); MS (ESI, *m/z*): 390.06 $(M+H)^+$; Anal. Calcd for $C_{25}H_{19}FeN$: C, 77.14; H, 4.92; N, 3.60. Found: C, 77.21; H, 4.98, N, 3.71.

(4-Phenylquinolin-2-yl)ferrocene (2c). This compound was obtained as red solid from EtOAc, IR (KBr) ν/cm^{-1}: 3079, 2957, 2917, 1617, 1579, 1525, 1455, 1236, 1172, 1103, 1035, 933, 861, 710; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.84 (d, *J*=10.0 Hz, 1H, ArH), 7.42 (d, *J*=15.0 Hz, 1H, ArH), 7.34 (s, 1H, ArH), 7.00 (s, 1H, ArH), 6.07 (s, 2H, -OCH_2O-), 5.00 (t, *J*=5 Hz, 2H, ferrocenyl), 4.42 (t, *J*=5 Hz, 2H, ferrocenyl), 4.04 (s, 5H, ferrocenyl); MS (ESI, *m/z*): 358.05 $(M+H)^+$; Anal. Calcd for $C_{20}H_{15}FeNO_2$: C, 67.25; H, 4.23; N, 3.92. Found: C, 67.34; H, 4.27; N, 4.01.

1,1'-Bis(quinolin-2-yl)ferrocene (4a). This compound was obtained as red solid from EtOAc, IR (KBr) ν/cm^{-1}: 3096, 3056, 2924, 1600, 1557, 1513, 1425, 1282, 1127, 1093, 1028, 910, 820, 750; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.86 (d, *J*=10.5 Hz, 2H, ArH), 7.59 (t, *J*=2.0 Hz, 4.5Hz, 2H, ArH), 7.39 (t, *J*=4.0 Hz, 1.5Hz, 4H, ArH), 7.23 (d, *J*=11.0 Hz, 2H, ArH), 7.00 (d, *J*=10.5 Hz, 2H, ArH), 5.04 (t, *J*=2.5 Hz, 2.0Hz, 4H, ferrocenyl), 4.42 (t, *J*=2.0, 2.5 Hz, 4H, ferrocenyl); MS (ESI, *m/z*): 441.06 $(M+H)^+$; Anal. Calcd for $C_{28}H_{20}FeN_2$ C, 76.38; H, 4.58; N, 6.36. Found: C, 76.42; H, 4.59; N, 6.41. The spectral data are in agreement with the literature.[36]

1,1'-Bis(6,7-methylenedioxyquinolin-2-yl)ferrocene (4b). This compound was obtained as red solid from EtOAc, IR (KBr) ν/cm^{-1}: 3071, 2924, 2852, 1592, 1546, 1496, 1413, 1307, 1098, 1031, 917, 828, 767, 701; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.78 (d, *J*=14.0 Hz, 2H, ArH), 7.63 (d, *J*=13.5 Hz, 2H, ArH), 7.48

(dd, *J*=10.5 Hz, 5.5Hz, 8H, ArH), 7.35-7.31 (m, 8H, ArH), 5.00 (s, 4H, ferrocenyl), 4.43 (d, *J*=2.5 Hz, 4H, ArH); MS (ESI, *m/z*): 593.06 $(M+H)^+$; Anal. Calcd for $C_{40}H_{28}FeN_2$ C, 81.08; H, 4.76; N, 4.73. Found: C, 81.10; H, 4.82; N, 4.75.

1,1'-Bis(4-Phenylquinolin-2-yl)ferrocene (4c). This compound was obtained as red solid from dioxane, IR (KBr) ν/cm^{-1}: 3080, 2959, 2901, 1618, 1581, 1527, 1458, 1239, 1176, 1078, 1039, 934, 859, 725; ^1H NMR ($CDCl_3$) δ (ppm): 7.22 (s, 2H, ArH), 6.99 (s, 2H, ArH), 6.94 (d, *J*=14.0 Hz, 2H, ArH), 6.70 (s, 2H, ArH), 6.08 (s, 4H, 2-OCH_2O-), 4.97 (s, 4H, ferrocenyl), 4.40 (d, *J*=2.5 Hz, 4H, ferrocenyl); MS (ESI, *m/z*): 529.03 $(M+H)^+$; Anal. Calcd for $C_{30}H_{20}FeN_2O_4$ C, 68.20; H, 3.82; N, 5.30. Found: C, 68.25; H, 3.87; N, 5.35.

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