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Unexpected synthesis of novel aza-[3]-ferrocenophanes

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Abstract—An unexpected reactivity of ferrocenedicarboxaldehydes **1** and **2** with primary amines in classical reductive amination conditions gives two new *N*-(substituted)-2-aza-[3]-ferrocenophanes in 1,1′ and in 1,2 series.

Malaria is an infectious disease caused by obligated protozoa of genus Plasmodium. Unfortunately, falciparum malaria is frequently resistant to drugs and is becoming more common in high elevation areas of Africa, and in portions of Asia. Until an effective vaccine is developed, malaria control will largely be dependent on the research of new antimalarial agents. So, exploiting the crucial role played by metallodrugs,[1] our laboratories have developed a new strategy based upon incorporation of the ferrocenyl moiety into current antimalarial drugs.[2] Since the discovery of ferroquine (FQ, Fig. 1),[3] considerable effort continues to be focused on introduction of the hydrophobic ferrocenyl groups into the molecular structure of different blood schizontocides.[4,5]

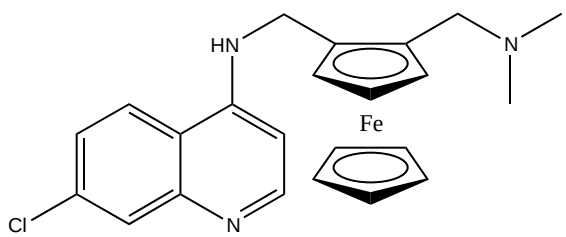

Figure 1. Ferroquine (FQ).

During a program directed toward the search of new organometallic analogues of FQ: cheap to prepare and easily accessible, we investigated the reactivity of 1,2- and 1,1′-ferrocenedicarboxaldhyde **1**[6] and **2**[7] with different aminoquinolines and obtained the unexpected cyclic compounds **3** and **4** instead of the intended diaminomethylferrocenes. Previously, aza-[3]-1,1′-ferrocenophanes were synthesized by Lorkowski starting from ferrocene 1,1′-dimethanol and an aryl isocyanate.[8,9] Thereafter Sakano has optimized the synthesis using $RuCl_2(PPh_3)_3$ as catalyst.[10] Other teams have also worked on the synthesis of such compounds,[11,12] but to our knowledge, this constitutes the first report of aza-[3]-1,2-ferrocenophane.

Our chosen synthetic route to **3** and **4** was based on a simple method of consecutive reductive amination of **1** and **2** with the aminoquinolines bearing spacers of varying length ($n=2$–4 and 6) (Scheme 1). These primary amines were obtained by direct condensation of the 4,7-dichloroquinoline with the corresponding diamine used as solvent at 85°C.[13] The cyclic aminodimethylferrocenes **3** and **4** were obtained, in unoptimized yields (32 and 34%, respectively), after 12 days of reaction of **1** and **2** in dried methanol in the presence of $NaBH_3CN$. The course of the reaction was monitored by thin layer chromatography until no ferrocenedicarboxaldehyde could be detected. The reaction was marked by a change of the colored mixture from red to dark. An excess (4 equiv.) of the reducing agent did not improve the yield of the reaction. The low yield obtained for **3** and **4** could be attributed to the formation of uncharacterized by-products due to the long reaction period. Indeed when the reaction was

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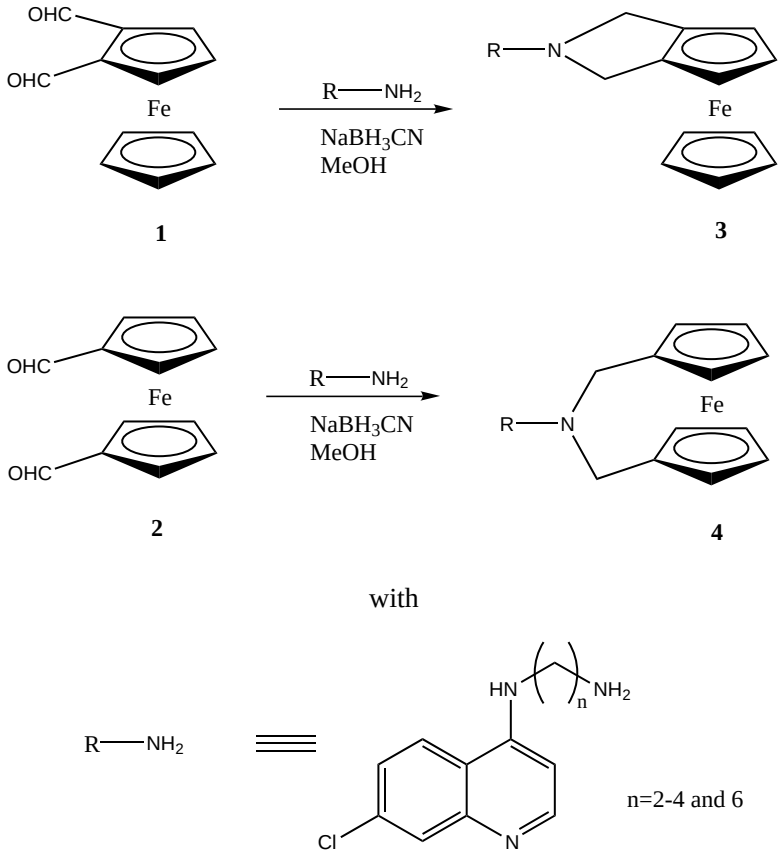

Scheme 1.

stopped earlier the purification through column chromatography was complicated by the presence of the intermediate iminium species (**1a**). The analytical and spectroscopic data reported herein for **3** and **4** unequivocally revealed their proposed structure.[14]

A typical procedure was as follows: A mixture of N^1-(7-chloro-4-quinolyl)-1,2-ethanediamine (450 mg, 2 mmol), 1,2-ferrocenedicarboxaldehyde (**1**, 484 mg, 2 mmol) and $NaBH_3CN$ (284 mg, 4.5 mmol) in dried methanol (20 mL) was stirred at ambient temperature for 12 days. The solution was concentrated under vacuum and the residue was dissolved in CH_2Cl_2. The crude solution was filtered through a layer of Celite, concentrated (2 mL) and then chromatographed on silica using Et_2O/petroleum ether/Et_3N (6:1:3) as eluent to give *N*-{*N*′-[2-(7-chloro-4-quinolyl)amino]ethyl}-2-aza-[3]-1,2-ferrocenophane as a yellow solid (294 mg, 0.68 mmol, 34% yield).

The formation of compounds **3** and **4** could be explained using the mechanism proposed by Boga for the preparation of 2,5-dimethylpyrrolidines and 2,6-piperidines.[15] In the first step condensation of **1** (or **2**) lead to an aminoaldehyde which is in equilibrium with a cyclic amino alcohol followed by an iminium ion **1a**. In the second step, the ionic specie led to the corresponding aza-[3]-ferrocenophane **3** (or **4**) (Scheme 2).

In conclusion, we showed an unexpected reactivity of the 1,1′-ferrocenedicarboxaldehyde leading to the formation of *N*-substituted-2-aza-[3]-1,1′-ferrocenophane in a one step reaction. This simple methodology enabled the synthesis of compounds that were previously inaccessible: the *N*-substituted-2-aza-[3]-1,2-ferrocenophane. Further investigations aimed at optimization of the reaction are in progress and the antimalarial activity of these compounds will be reported in due course.

Acknowledgements

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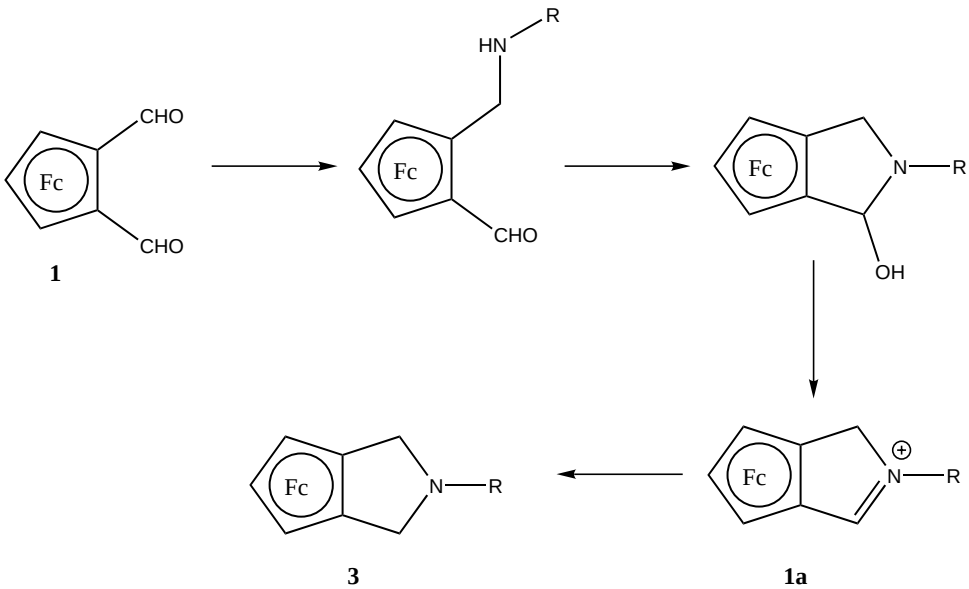

Scheme 2.

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14. Selected data for *N*-{*N*′-[2-(7-chloro-4-quinolyl)amino]-ethyl}-2-aza-[3]-1,2-ferrocenophane **3**: yellow solid; mp 192–193°C; ^{1}H NMR ($CDCl_3$): δ 8.57 (d, $J=5.31$ Hz, 1H); 7.96 (d, $J=2.13$ Hz, 1H), 7.77 (d, $J=8.94$ Hz, 1H), 7.31 (dd, $J=6.75$ and 2.16 Hz, 1H), 6.43 (d, $J=5.35$ Hz, 1H), 6.25 (m, 1H), 4.10 (m, 7H), 4.04 (m, 1H), 3.89 (d, $J=10.19$ Hz, 2H), 3.39 (m, 2H), 3.20 (s, $J=10.22$ Hz, 2H), 3.18 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 152.3, 149.9, 142.2, 135.0, 129.0, 125.6, 121.1, 117.5, 99.4, 90.4, 70.0, 69.0, 60.2, 54.0, 53.7, 40.9; MS MALDI TOF (thap): 432.3 (MH^+ ^{35}Cl), 434.3 (MH^+ ^{37}Cl), 398.3. Anal. calcd for $C_{23}H_{22}ClFeN_3$: C, 63.96; H, 5.10; N, 9.73. Found: C, 63.51; H, 5.27; N, 9.83.
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