Synthesis, chemical reactivity and electrochemical behaviour of mono- and difluoro metallocenes

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ABSTRACT

We report the synthesis of mono- and 1,1′-difluoro-substituted metallocenes (ferrocene, ruthenocene) and of asymmetrical 1,1′-disubstituted ferrocenes with one substituent being fluorine. Lithiation of metallocenes and subsequent addition of the fluorinating agent NFSI gave the fluorinated metallocenes after optimization of the experimental conditions. All new compounds were comprehensively characterized and the cyclic voltammograms of fluoro- and 1,1′-difluoroferrocene were recorded and compared to other mono- and dihalogenated ferrocenes. Half-wave potentials of +106 mV and +220 mV vs. $FcH^{0/+}$ were obtained for monofluorinated species and difluorinated ferrocene, respectively. Both values are remarkably low compared to the other halogenated ferrocenes (Cl, Br, and I). Finally, 1-bromo-1'-fluoro-ferrocene turns out to be an ideal starting material for further fluoro-substituted ferrocene derivatives.

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1. Introduction

Metallocenes and their derivatives have attracted considerable attention over the past decades and are considered as valuable building blocks e.g. in medicinal chemistry or catalysis. Especially the halogenated ferrocenes ($Fe(C_5H_5)_2$ with $Cp = (C_5H_5)$) with chlorine, bromine, and iodine are well studied compounds [1–3]. In surprising contrast to this, metallocenes with one or multiple fluorine atoms attached to the Cp ring are not investigated in that extent.

Metallocenes containing fluorine atoms can be divided into two classes, i.e. metallocenes with fluorine atoms in side chains and metallocenes with fluorine atom(s) directly bound to the Cp ring [4–7]. The first group includes for example metallocenes with fluorinated alcohols or two metallocene moieties with a fluorinated bridging unit [8–12]. Such compounds were prepared and have been studied, e.g. for applications in tumor therapy [12,13]. The introduction of fluorine atom(s) directly to the Cp ring of the metallocene scaffold is quite challenging due to the redox properties of the metallocenes. These compounds are sensitive towards the strongly oxidizing and/or acidic reagents typically used for direct fluorination reactions, such as F_2 [14]. Consequently, very

little work has been done on this topic, whereas reactions for the incorporation of other halogen atoms (Cl, Br, I) in the metallocene scaffold have been investigated intensively. Halogenated metallocenes (with halogens ranging from Cl to I), on the other hand, are quite readily accessible [1–3]. In contrast, nearly nothing is known about the (physicochemical) properties of mono- and difluoroferrocenes.

Two different approaches for the synthesis of monofluoroferrocene (**1**) have been published so far. In 1971, Hedberg and Rosenberg synthesized monofluoroferrocene by using perchloryl fluoride. However, the yield was quite low (10%) and later the authors reported explosions during the synthesis [15]. Additionally, the oxidation potential of perchloryl fluoride is very high, which leads to decomposition of the oxidation-sensitive metallocene scaffold.

The second approach was an electrophilic fluorination performed by Lieb and coworkers [16]. FcHgCl was treated with N-fluoropyridinium tetrafluoroborate to yield monofluoroferrocene. Like in the first case, the desired compound was not fully characterized. Monofluoroferrocenes with other substituents at the Cp ring were synthesized by Sünkel and coworkers. 1-Fluoro-2-pyridyl-ferrocene was obtained by using a directed ortho metalation (DOM) reaction of pyridyl-ferrocene, which was treated with n-BuLi and subsequent addition of NFSI [17]. Englert first published this new method alongside with a report of fluorinated ruthenocenes [18].

Seppelt and coworkers tried to synthesize pentafluoro-substituted metallocenes. Their synthetic route involved the use of the pentafluoro cyclopentadienide anion, which was reacted with different metal halides such as $MnCl_2$ and $FeBr_2$, under various reactions conditions. However, none of these reactions were successful [19]. Very recently, Sünkel and coworkers achieved this by multiple fluorinations using NFSI after preceding lithiation [20]. Before this, the only pentafluoro-substituted metallocenes known was pentafluororuthenocene and 1,2,3,4,5-pentafluoro-pentamethyl-ruthenocene synthesized by Hitherto. Hughes and coworkers published a method using flash vacuum pyrolysis (FVP, approx. 750 °C, 10^{-4} Torr) of $Ru(C_5H_5)(OC_6F_6)$, which yields the afore mentioned pentafluororuthenocene [21,22]. Although the compound was isolated in 84% yield, this is clearly not a general synthetic entrance into this family of compounds [22].

Here we present our results on the synthesis and purification of mono- and difluorometallocenes, along with a number of 1,1′-substituted derivatives which can be used as building-blocks for further applications. Besides the synthesis and the full characterization of these compounds, their electrochemical properties were investigated by cyclic voltammetry.

2. Experimental

2.1. General remarks

Unless noted otherwise, all syntheses were carried out under an inert atmosphere of argon or N_2 using standard Schlenk techniques. All reagents and anhydrous solvents were purchased from commercial sources and used as received unless stated/noted otherwise. 1,1′-Dibromo- and 1,1′-diiodoferrocene were synthesized by modifying the literature procedure of Long and coworkers [23]. NMR spectra were recorded at ambient temperature on a Bruker DPX 250 spectrometer (^1H: 250 MHz, ^{19}F: 235 MHz and ^{13}C: 63 MHz). $CFCl_3$ and TMS were used as internal standards. The ^{13}C and ^{19}F NMR spetra were run with ^1H decoupling ($^{13}C\{^1H\}$ and $^{19}F\{^1H\}$). Chemical shifts (δ) are reported in parts-per-million (ppm) vs. solvent signals as secondary standards. Coupling constants (J) are quoted in Hertz as absolute values and were partially determined with the global spectral deconvolution (GSD) function of MestReNova (Ver. 7.0.1–8414). App. signifies apparent multiplets, br. signifies broad signals. HPLC runs were performed on a Varian Prostar instrument using an HIBAR Lichrospher 100 RP-18e reversed phase column (Merck, 250 × 25 mm, flow rate: 19 ml/min, UV = 254 nm). IR spectra were recorded on a Bruker Tensor 27 spectrometer with an ATR unit as solid samples, wavelengths of absorption are given in cm^{-1}. GC/MS spectra were recorded on a Shimadzu GCMS-QP2010. Elemental analyses of compounds were carried out at the RUBiospek Bio-spectroscopy Department, Ruhr-Universität Bochum.

2.2. General synthesis of monofluorinated metallocenes **1** (starting from Fc) and **6**

Under a positive pressure of argon, the respective metallocene (1 equiv.) and potassium *tert*-butoxide (0.125 equivalents) were dissolved in dry tetrahydrofuran (1 mmol in 10 ml). The solution of the metallocene was cooled to −78 °C and the solution of *tert*-butyllithium in n-heptane (1.6 M, 2 equivs.) was added slowly, ensuring that the temperature did not exceed −70 °C. Stirring was continued for 60 min at −78 °C. After that, the suspension was transferred into a solution of NFSI (2.5 equivs.) in dry diethylether (7 ml per 1 mmol) at −20 °C. Then, the reaction mixture was directly subjected to a water-cooled column containing neutral alumina gel (activity III, diameter 2 cm, length 25 cm). The column was eluted with hexanes until the eluent was colorless (for **1**) or

approx. four times (for **6**), in order to remove excess NFSI and other polar byproducts. The solvent was removed *in vacuo*.

2.3. Monofluoroferrocene (**1**)

A: From ferrocene: Synthesis according to the general procedure mentioned above. The product is obtained with a purity >95%, containing traces of ferrocene and difluoroferrocene as indicated by ^1H NMR. If necessary these can be removed by HPLC.

HPLC: CH_3CN/H_2O (60/40; isocratic). Orange solid (490 mg, 2.4 mmol, 42%);

B: From bromoferrocene:

Under a positive pressure of argon, freshly sublimated mono-bromoferrocene (300 mg, 1.14 mmol) was dissolved in dry tetrahydrofuran (20 ml) and the resulting yellow solution was cooled to −78 °C. Over a period of 5 min n-butyllithium in n-hexane (0.5 ml, 1.25 mmol, 2.5 M) was added, ensuring that the temperature does not exceed −70 °C. After stirring for 2 h at −5 °C, the suspension of NFSI (4.3 g, 14 mmol) in diethylether (50 ml) was added at once. Subsequently, the reaction mixture was directly subjected to water-cooled column (20 mm Ø) containing neutral alumina (Activity III). The column was washed with hexanes until the eluate was colorless. The organic solvents were removed under reduced pressure and the product was obtained as an orange solid.

HPLC: CH_3CN/H_2O (60/40; isocratic). Orange solid (204 mg, 1.0 mmol, 79%);

^1H NMR ($CDCl_3$): δ 4.30 (dt, $J_{HH, HF}$ = 3.0, 2.0 Hz, 2H, CpH), 4.26 (s, 5H, CpH), 3.79 (td, $J_{HH, HF}$ = 2.1, 1.3 Hz, 2H, CpH). ^{13}C NMR ($CDCl_3$): δ 135.8 (d, $^1J_{CF}$ = 268 Hz, C_1), 69.4 (s, $C_{1'-5'}$), 61.2 (d, $^3J_{CF}$ = 3.8 Hz, $C_{3,4}$), 56.2 (d, $^2J_{CF}$ = 15.2 Hz, $C_{2,5}$). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ −189 (s). IR (solid): cm^{-1} 3098 (w), 1467 ν(C-$C_{aromatic}$, vs); 1239 ν(C−F, m), 1103 (m), 803 (vs), 632 (m). MS (EI): m/z 204 $[M]^+$, 128 $[Cp_2]^+$, 121 $[CpFe]^+$; calcd for $C_{10}H_9FFe$ 204. Anal. Calcd for $C_{10}H_9FFe$: C, 58.87; H, 4.45. Found: C, 58.65; H, 4.24.

2.4. 1,1′-Difluoroferrocene (**2**)

1,1′-Dibromoferrocene [23] (300 mg, 0.87 mmol) was dried for 3 h at 2 * 10^{-2} mbar in a Schlenk flask. Afterwards, it was dissolved in dry diethylether (2 ml) forming a clear yellow solution. In a separate Schlenk flask diethylether (4 ml) was cooled to −78 °C and *tert*-butyllithium in n-hexane (2.3 ml, 3.66 mmol, 1.6 M) was added. The dissolved 1,1′dibromoferrocene was added dropwise to the *tert*-butyllithium solution over a period of 5 min. The resulting mixture was stirred at −78 °C for 1 h. In an additional Schlenk flask NFSI (1.15 g, 3.66 mmol), which had been dried for 3 h *in vacuo*, was dissolved in tetrahydrofurane (6 ml). The NFSI solution was added to the reaction mixture within 2 min. Directly after the addition the solution was quenched with $NaBH_4$ and 20 ml 0.1 M $Ca(OH)_2$. Pentane (50 ml) was added and the two-phase system was stirred for 1 h. The organic phase was separated and washed 3 times with water. All solvents were carefully removed *in vacuo*. The crude product was filtered through alumina (Activity III, diameter 2 cm, length 25 cm) with pentane as mobile phase. After evaporation of the solvent, the crude product was purified by HPLC (CH_3CN/H_2O (70:30); isocratic). The HPLC fractions were extracted with pentane (4 × 20 ml). The organic phase was dried with $MgSO_4$ and carefully evaporated *in vacuo* (the product is volatile!). The product was obtained as a yellow solid.

HPLC: CH_3CN/H_2O (70:30; isocratic). Yellow solid (20 mg, 0.09 mmol, 10%);

^1H NMR ($CDCl_3$): δ 4.39 (app. q, $J_{HH, HF}$ = 2.2 Hz, 4H, CpH), 3.91–3.89 (app. m, 4H, CpH). ^{13}C NMR ($CDCl_3$): δ 135.9 (d, $^1J_{CF}$ = 269 Hz, $C_{1,1'}$), 62.5 (d, $^3J_{CF}$ = 3.8 Hz, $C_{3,3',4,4'}$), 57.5 (d, $^2J_{CF}$ = 15.1 Hz, $C_{2,2',5,5'}$). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ −189 (s). IR (solid):