SYNTHESIS OF 1-ALKANOYL-1′-(TRIFLUOROACETYL)FERROCENES

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Dedicated to Professor Jaroslav Podlaha on the ocassion of his 70th birthday.

Synthesis of the first representatives of mixed acyl(perfluoroacyl)ferrocenes, 1-acetyl-1′-(trifluoroacetyl)ferrocene (**3a**) and 1-propionyl-1′-(trifluoroacetyl)ferrocene (**3b**), by stepwise Friedel–Crafts acylation is described. A comparison of redox potentials of acetylferrocene, (trifluoroacetyl)ferrocene, and **3a** as determined by cyclic voltammetry shows that the substitution effect is not purely additive.

Keywords: Ferrocenes; Metallocenes; Fluorous ferrocenes; Acylation; Trifluoroacetylation; Electrochemistry; Sandwich complexes; Electrophilic substitution.

Shortly after the discovery of ferrocene[1] and its aromatic nature, aromatic electrophilic substitution has become a powerful method for the preparation of its derivatives. Since ferrocene behaves like an electron-rich aromatic compound, Friedel–Crafts acylation is the method of choice for attaching various substituents to one or both cyclopentadienyl rings. The first diacylated derivative, 1,1′-diacetylferrocene, was prepared as early as in 1952 [2], followed by the first monoacylated analogue, acetylferrocene, in 1957 [3]. It was soon realized that the selective mono- and diacylation can be easily controlled by the amount of the added acylating agent and within a couple of years a number of variously mono- and disubstituted ferrocenes emerged[4]. Moreover, the selective monoacylation has opened an access to the synthesis of unsymmetrically 1,1′-substituted ferrocenes by stepwise acylation with two different acylating agents[5–10]. Later on, the preparation of various (perfluoroacyl)-[11,12] and (perfluoroaroyl)ferrocenenes[13] was re-

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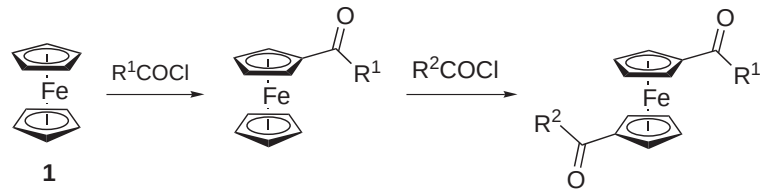
ported. In contrast to acylation, perfluoroacylation gives selectively monosubstituted products even with an excess of acylating agent. However, as it is accompanied by extensive decomposition, the yields of perfluoroacylated products usually do not exceed 30%. This situation changes upon introducing two[14] or more[15] methylene units as a spacer between the carbonyl and perfluoroalkyl groups; the spaced fluoroacyl halides give mono- and diacylated product depending on the reaction conditions. Interestingly, to the best of our knowledge, the preparation of mixed acyl-(perfluoroacyl)ferrocenes has not been yet reported.

Because of the general synthetic interest in the preparation of perfluoroalkyl-substituted cyclopentadienyl compounds[16–20] and the fact that ferrocene and its derivatives represent ideal model compounds to test the influence of the perfluoroalkyl groups on the properties of metallocenes, we decided to develop a method for the preparation of mixed acyl-(perfluoroacyl)ferrocenes (Scheme 1) and to check the substituent effect by electrochemical methods.



SCHEME 1
Stepwise acylation of ferrocene

EXPERIMENTAL

General

All reaction were run under Ar. Trifluoroacetic anhydride and aluminum chloride were purchased from Aldrich, ferrocene was purchased from Fluka. These chemicals were used as received. Dichloromethane was distilled from CaH_2 prior to use. Acetylferrocene (**2**) was prepared by the previously reported method[21]. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F (376 MHz) spectra were recorded on a Varian Unity Inova 400 spectrometer. The chemical shifts (δ, ppm) are given relative to internal tetramethylsilane (^{1}H and ^{13}C) and to external neat $CFCl_3$ (^{19}F), coupling constants (*J*) are given in Hz. Infrared spectra were recorded on a PE-640 Perkin–Elmer spectrometer. TLC was performed on Merck Silica Gel 60 F_{254} aluminium sheets, while column chromatography was performed on Fluka Silica Gel 60. Electrochemical measurements were performed under argon blanket with ca. 5×10^{-4} M dichloromethane solutions containing 0.05 M Bu_4NPF_6 as the supporting electrolyte. The

voltammograms were recorded at room temperature on a Multipurpose polarograph PA3 (Laboratorní přístroje, Prague), using a standard three-electrode cell consisting of a platinum disc (0.5 mm in diameter) working electrode, an Ag/AgCl reference electrode and a platinum sheet working electrode. The potential was scanned at 100 mV s^{-1}. The half-wave potentials (E^{FcH}) were determined as an average of the anodic and cathodic peak potentials (E^{FcH} = $1/2(E_{pa} + E_{pc})$) and are given relative to ferrocene/ferrocenium couple ($E^{o\prime}$ = +0.45 V under the conditions mentioned above).

Syntheses

(Trifluoroacetyl)ferrocene (**4**). A suspension of anhydrous $AlCl_3$ (80 mmol, 10.67 g) in dry CH_2Cl_2 (60 ml) was treated dropwise at 0 °C with neat trifluoroacetic anhydride (40 mmol, 5.6 ml) and then with a solution of ferrocene (**1**; 40 mmol, 7.44 g) in dry CH_2Cl_2 (25 ml) over 2 h. The reaction mixture was stirred at the same temperature for another 4 h and then quenched by addition of ice-cold water (15 ml) and hexane (20 ml). The organic layer was separated and the aqueous layer was extracted with hexane (3 × 20 ml), the combined organic extracts were dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. Column chromatography on silica gel (hexane/Et_2O 9:1) afforded 3.42 g (30%) of the title compound as a cherry-red liquid. ^{1}H NMR (C_6D_6): 3.86 s, 5 H (C_5H_5); 4.11–4.13 m, 2 H and 4.72–4.75 m, 2 H (CH of C_5H_4). ^{13}C NMR (C_6D_6,): 71.34, 5 C (C_5H_5); 71.42 q, $^4J_{C\text{-}F}$ = 1.9, 2 C (CH of C_5H_4); 74.94, 2 C (CH of C_5H_4); 118.33 q, $^1J_{C\text{-}F}$ = 289 (CF_3); 186.43 q, $^2J_{C\text{-}F}$ = 34.5 (C=O); the C_{ipso} of C_5H_4 was not found. ^{19}F (376 MHz, C_6D_6, $CFCl_3$): –72.42 (CF_3). IR (KBr): 3095, 1686 (C=O), 1457, 1219, 1146, 1056, 825, 729, 485. R_F (hexane/Et_2O 9:1) 0.51.

1-Acetyl-1′-(trifluoroacetyl)ferrocene (**3a**). Acetyl chloride (5 mmol, 400 mg, 288 µl) was added slowly to a suspension of anhydrous $AlCl_3$ (5 mmol, 667 mg) in dry CH_2Cl_2 (5 ml) at 0 °C. After stirring at the same temperature for 1 h, a solution of (trifluoroacetyl)ferrocene (**4**; 1.4 mmol, 400 mg) in dry CH_2Cl_2 (5 ml) was introduced dropwise and the reaction mixture was stirred at 20 °C for 3 days. Then, it was quenched by ice-cold water (15 ml) and diluted with hexane (20 ml). The organic layer was separated and the aqueous layer was extracted with hexane (3 × 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel (hexane/EtOAc 4:1) afforded 60 mg (13%) of the title compound as a cherry-red liquid (additional purification of the product was achieved by column chromatography on aluminium oxide (benzene)). ^{1}H NMR (C_6D_6): 1.93 s, 3 H (CH_3); 3.93 dd, *J* = 2.0, 2.0, 2 H (CH of C_5H_4); 3.97 dd, *J* = 2.0, 2.0, 2 H (CH of C_5H_4); 4.41 dd, *J* = 2.0, 2.0, 2 H (CH of C_5H_4); 4.55–4.58 m, 2 H (CH of C_5H_4). ^{13}C NMR (C_6D_6): 27.21 (CH_3); 71.55, 2 C (CH of C_5H_4); 71.86 q, $^4J_{C\text{-}F}$ = 1.8, 2 C (CH of C_5H_4); 73.93, 2 C (CH of C_5H_4); 75.68, 2 C (CH of C_5H_4); 81.67 (C_{ipso} of C_5H_4); 117.18 q, $^1J_{C\text{-}F}$ = 290 (CF_3); 185.33 q, $^2J_{C\text{-}F}$ = 35.4 (CF_3**C**=O); 198.61 (CH_3**C**=O); the resonance due to C_{ipso} (C_5H_4) was not found. ^{19}F NMR ($CDCl_3$): –72.62 (CF_3). IR (KBr): 3103, 1685 (C=O), 1664 (C=O), 1457, 1279, 1190, 1040, 962, 856, 731, 494. MS (FAB^+), *m/z* (relative abundance): 324 (100, M^+), 182 (32, $[M - C_4H_3F_3O_2]^+$), 167 (38). R_F (hexane/EtOAc 4:1) 0.16.

1-Propionyl-1′-(trifluoroacetyl)ferrocene (**3b**). Propionyl chloride (5 mmol, 463 mg, 435 µl) was added slowly to a suspension of anhydrous $AlCl_3$ (5 mmol, 667 mg) in dry CH_2Cl_2 (6 ml) at 0 °C. After stirring at the same temperature for 1 h, a solution of (trifluoroacetyl)ferrocene (**4**; 3.8 mmol, 1100 mg) in dry CH_2Cl_2 (5 ml) was introduced dropwise and the reaction mixture was stirred at 20 °C for 3 days. Then, it was quenched by ice-cold water (30 ml) and

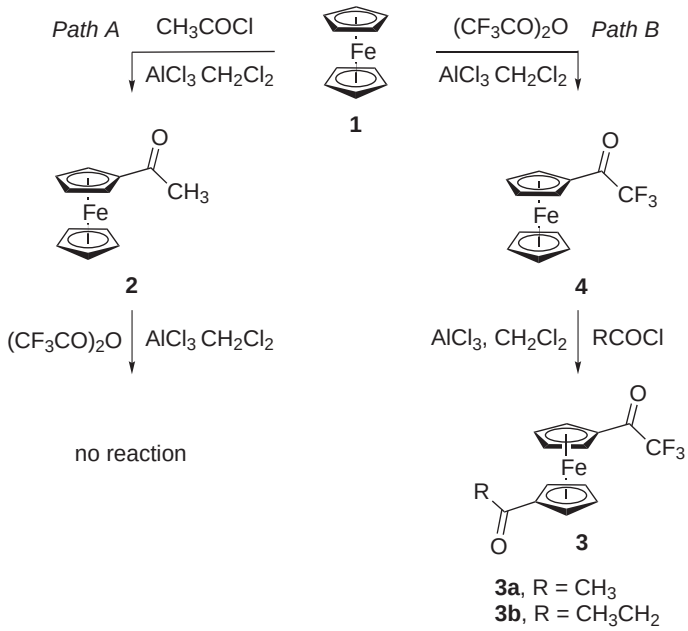
diluted with hexane (30 ml). The organic layer was separated and the aqueous layer was extracted with hexane (4 × 20 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel (hexane/EtOAc 9:1) afforded 120 mg (9%) of the title compound as a cherry-red liquid (additional purification of the product was achieved by column chromatography on aluminium oxide (benzene)). ^{1}H NMR (C_6D_6): 1.12 t, J = 7.2, 3 H (CH_3); 2.24 q, J = 7.2, 2 H (CH_2); 3.97 dd, J = 2.0, 2.0, 2 H (CH of C_5H_4); 4.03 dd, J = 2.0, 2.0, 2 H (CH of C_5H_4); 4.49 dd, J = 2.0, 2.0, 2 H (CH of C_5H_4); 4.59–4.61 m, 2 H (CH of C_5H_4). ^{13}C NMR (C_6D_6): 8.08 (CH_3); 32.96 (CH_2); 71.26, 2 C (CH of C_5H_4); 71.83 q, $^4J_{C\text{-}F}$ = 1.8, 2 C (CH of $C_5H_4C(O)CF_3$); 73.79, 2 C (CH of C_5H_4); 75.65, 2 C (CH of C_5H_4); 81.67 (C_{ipso} of $C_5H_4C(O)Et$); 117.21 q, $^1J_{C\text{-}F}$ = 291 (CF_3); 185.41 q, $^2J_{C\text{-}F}$ = 35.4 (CF_3C=O); 201.63 (EtC=O); the resonance due to C_{ipso} (C_5H_4) was not found. ^{19}F NMR ($CDCl_3$): –72.62 (CF_3). IR (KBr): 3103, 1694 (C=O), 1682 (C=O), 1456, 1246, 1220, 1189, 1147, 1057, 1033, 962, 856, 729, 527, 482. MS (EI$^+$), *m/z* (relative abundance): 338 (100, M^+), 309 (38, $[M - Et]^+$), 167 (62). R_F (hexane/EtOAc 9:1) 0.22.

RESULTS AND DISCUSSION

Although the preparation of mixed acyl(perfluoroacyl)ferrocenes could be a priori considered a rather easy task, the absence of any literature data concerning the preparation of such substituted ferrocene derivatives indicated the real situation to be different. Generally, we envisaged that there were two approaches to the target compound: the first was based on perfluoroacetylation of acylferrocene, while the second one comprised identical steps but in the reverse order, i.e. on perfluoroacetylation of ferrocene followed by acylation. Since acylferrocenes are easily accessible in high yield by the Friedel–Crafts reaction of acyl chlorides with ferrocene[21], we decided to check the former approach. Thus, acetylation of ferrocene (**1**) under previously reported conditions afforded acetylferrocene (**2**), which was subjected to perfluoroacetylation with trifluoroacetic anhydride in the presence of $AlCl_3$ (Scheme 2, path A). Although we observed the consumption of the starting material, the target compound **3a** was not detected in the reaction mixture. Instead, most of the starting material was converted into tar-like products.

The starting point of the second approach was perfluoroacetylation of ferrocene with trifluoroacetic anhydride (Scheme 2, path B). The acylation reaction proceeded well, affording (trifluoroacetyl)ferrocene (**4**) as a cherry-red viscous liquid in a reasonable yield of 30%. Notably, this yield ranges at the upper limit of the yields usually attained in these reactions[11,12]. In the following step, acylation of **4** with acetyl chloride and propionyl chloride in the presence of $AlCl_3$ afforded the desired 1-acetyl-1′-(trifluoroacetyl)ferrocene (**3a**) and 1-propionyl-1′-(trifluoroacetyl)ferrocene (**3b**) in 13 and 9%

yield, respectively. Both products were unstable dark cherry-red liquids. Similarly to path A, the last step was accompanied by extensive degradation of the reactants into a dark, tarry material.



SCHEME 2
Preparation 1-alkanoyl-1′-(trifluoroacetyl)ferrocenes **3**

The compounds **2**, **3a**, and **4** were characterized by standard spectral methods and further studied by cyclic voltammetry on a platinum disc electrode in dichloromethane solutions. All the compounds display reversible, one-electron redox waves attributable to chemically and electrochemically reversible oxidation of the ferrocene moiety to the corresponding ferrocenium (Fig. 1, Table I). The ferrocene/ferrocenium redox potentials are more positive than those for the ferrocene reference due to the presence of electron-withdrawing groups at the ferrocene unit. Although the potentials follow the trend expected for a combined influence of the substituents, **2** < **4** < **3a**, the individual values apparently indicate that the overall substituent effect is not purely additive within the series. Considering a strict additivity of the substituent effects for ferrocene compounds and E^{FcH} values as their measure, one would expect the redox potential of **3a** to be as

high as ca. 0.69 V (0.25 V + 0.44 V), which is significantly higher than the observed value. On the other hand, the difference between the measured and calculated values is rather small (~10%) to indicate existence of any unusual structural effects.

CONCLUSION

In summary, we have synthesized the first mixed acyl(perfluoroacyl)ferrocenes **3**, showing the order of sequential acylation reactions to be important factor for their successful synthesis. The electrochemical data indicate a synergic but not purely additive influence of the substitutents at the ferrocene unit on ferrocene/ferrocenium redox potential. This deviation, however, can be accounted for by electron-buffering effect of the electron rich ferrocene framework, particularly in the monosubstituted derivatives.

TABLE I
Electrochemical data for ferrocenes **2**, **3a**, and **4**[a]

Compound	E^{FcH}, V	ΔE_p, V
2	0.25	80
4	0.44	90
3a	0.64	85

[a] Data from cyclic voltammetry on a platinum electrode at 100 mV s^{-1} with dichloromethane solutions. The formal redox potentials were calculated from the anodic and cathodic peak potentials as follows: $E^{FcH} = 1/2(E_{pa} + E_{pc})$, relative to ferrocene/ferrocenium standard. ΔE_p is the separation of the cyclovoltammetric counterpeaks, $\Delta E_p = E_{pa} - E_{pc}$. All redox waves exhibit limiting current ratios (i_{pa}/i_{pc}) of unity.

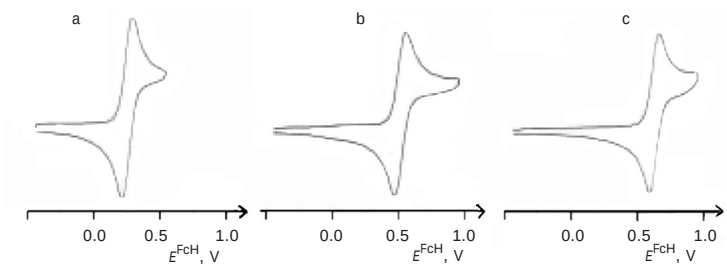


FIG. 1
Cyclic voltamograms of **2** (a), **3a** (b), and **4** (c)

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