Synthesis of Perfluoroalkylthio-Substituted Ferrocenes

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Abstract: Mono- and bis(trifluoromethylthio)-substituted and perfluoroalkanesulfonylferrocene derivatives were prepared by nucleophilic substitution reactions on the ferrocene core. Thus, Hg(SCF₃)₂ was activated in situ by Cu and used for nucleophilic displacement reactions of bromide. Trifluoromethylsulfonylferrocene was not accessible by this method. The reaction of lithioferrocene with trifluoromethylsulfonyl chloride gave chloroferroocene in small yield, presumably due to the high lattice energy of solid LiF. On the other hand, the known trifluoromethylferrocene was obtained as the only isolable compound from the photochemical reaction of CF₃SCF₃ with ferrocene. The same product was detected in small amounts in the reaction of chloromercuryferrocene with trifluoromethylsulfonyl chloride. It thus appears that most established methods for trifluoromethylation of purely organic compounds fail for ferrocene due to concurring redox reactions. The new compounds have been comprehensively characterized by elemental analyses, NMR and IR spectroscopy, mass spectrometry, and electrochemistry. The SCF₃ group appears to be almost as electron-withdrawing as a trifluoromethyl group on the ferrocene core.

Key words: electrochemistry, ferrocene, fluoro compounds, trifluoromethyl

Fluorine substitution has become an important tool to optimize the pharmacokinetic and pharmacodynamic properties of drug candidates with only very small structural changes. Because of the similarity in size to hydrogen (van der Waals radii: F = 1.35 Å; H = 1.2 Å), about one third of all newly approved active substances in the last twenty years contained at least one fluorine atom, usually in the form of fluoro or trifluoromethyl groups. Actually 20–25% of all drugs in the pharmaceutical pipeline contain at least one fluorine atom.¹ Today, as many as 30–40% of agrochemicals and 20% of pharmaceuticals on the market are estimated to contain fluorine, including three of the top eight drugs sold in 2007.²

By comparison, fluorine-substituted compounds are surprisingly rare in organometallic chemistry. This is exemplified by fluorinated or trifluoromethylated ferrocenes which are barely known in the literature,³⁴ despite the enormous amount of work on almost all other classes of ferrocene derivatives.³ This is presumably due to the sensitivity of the ferrocene core against oxidizing processes, which occur in most fluorinating reactions. Therefore, the only pathways for generating such fluorinated species are nucleophilic substitution reactions or photochemical trifluoromethylation.³ Perfluoroalkylthio substitution is a viable alternative to arrive at fluorinated ferrocene derivatives. Hence, we were interested in synthesizing new perfluoroalkylthio-substituted ferrocenes as potential starting materials, for example, for ferrocene peptides or PNA.⁶–⁸

Following recently published procedures for the selective lithiation of ferrocene,⁹ we could generate selectively mono- and dilithiated ferrocenes, which served as starting materials directly or were brominated with dibromotetrafluoroethane in good yield.¹⁰ Thus, appropriate starting materials are available for further exchange reactions.

Parallel to the bromination of monolithiated ferrocene, we reacted trifluoromethylsulfonyl chloride with this intermediate, aiming to obtain trifluoromethylsulfonylferrocene as a new compound. Surprisingly, we obtained the well-known chloroferroocene as the only product in 5% yield (Scheme 1). Due to its high lattice energy, LiF seems to be the favored leaving group in this reaction and was indeed observed in the solid residue from the reaction. The product chloroferroocene was easily identified by its mass and NMR spectra, which are identical to those published.¹¹

Based on the above observation, perfluoroalkanesulfonyl fluoride was chosen to react with monolithiated ferrocene, which yielded the expected 1-perfluoroalkanesulfonylferrocene, albeit in low yield (Scheme 2).

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tivity of ferrocene. Several photochemical procedures for the introduction of trifluoromethyl groups by using CF₃X (X = Br, I) into aromatic ring systems are known from the literature. In a related fashion, a mixture of ferrocene and CF₃SCF₃ was irradiated in acetonitrile for six hours. Interestingly, and in contrast to the reaction products with benzene or toluene that cleanly generated the CF₃S derivatives, we obtained trifluoromethylferrocene in ca. 5% yield along with elemental sulfur, but no CF₃S analogue (Scheme 3). Physical data of the obtained ferrocene product were identical to those reported, and S₈ was readily identified by mass spectrometry.

![Scheme 3](image)

Scheme 3 Photochemical synthesis of trifluoromethylferrocene

We subsequently decided to explore nucleophilic exchange reactions. In particular, the substitution of ring-bound bromine through a CF₃S group was attempted by stirring bromoferrocene with Hg(SCF₃)₂ in hexane. Because we did not observe any changes in the reaction mixture even after heating for two days, we added some freshly generated copper bronze. From the literature it is known that this increases the nucleophilic strength because of in situ formation of CuSCF₃, and indeed, trifluoromethyliodoferrocene 2 was finally obtained in good yield (Scheme 4, top). By a similar reaction sequence, 1,1’-bis(trifluoromethylthio)ferrocene (3) was obtained in moderate yield from 1,1’-dibromoferrocene (Scheme 4, bottom).

![Scheme 4](image)

Scheme 4 Syntheses of mono- (top) and 1,1’-bis(trifluoromethylthio)-substituted ferrocene (bottom)

First attempts to lithiate ferrocene followed by bromination yielded mixtures of mono- and dibromoferrocene depending on the presence of N,N,N’N’-tetramethylethane-1,2-diamine (TMEDA). Reacting this mixture with the above-mentioned nucleophiles in turn generated mixtures of mono- and bis(trifluoromethylthio)-substituted ferrocenes. Because of their physical properties being very similar, compounds 2 and 3 could not be separated using standard methods like distillation, recrystallization, or chromatography. To avoid product mixtures, it is therefore mandatory to start with clean mono- or dibrominated starting materials. Chemically, these two compounds show different behavior, for example, only the mono-substituted ferrocene reacts with benzoyl chloride under Friedel–Crafts conditions.

Because of the sensitivity of ferrocene against oxidizing agents, the standard procedure to oxidize the sulfur in trifluoromethylthio ligands to a sulfonyle group is not possible. Several attempts were thus made to generate a CF₃SO₂-containing ferrocene by nucleophilic replacement. As mentioned above, the reaction between lithiated ferrocene and trifluoromethylsulfonyl chloride generated the chlorinated ferrocene. We therefore synthesized the chloromercuryferrocene, ferrocene-HgCl₂, as an alternative starting material for nucleophilic substitution. By reacting this compound with CF₃SO₂Cl, a small amount (<5%) of trifluoromethylferrocene was detected by ¹⁹F NMR spectroscopy and GC-MS, accompanied by unsubstituted ferrocene, but no CF₃SO₂-containing moieties (Scheme 5).

![Scheme 5](image)

Scheme 5 Reaction of chloromercuryferrocene with CF₃SO₂Cl

Activated copper powder was added to increase the nucleophilicity, but this only led to complete conversion into pure ferrocene. It seems that the reduction process with elimination of mercury and formation of amalgam is the main reaction under these conditions.

All new compounds gave satisfactory elemental analyses and were comprehensively characterized spectroscopically (see experimental section). The fluoroalkyl groups are strongly electron-withdrawing in general. This is demonstrated by the electrochemistry of the new compounds. Cyclic voltammetry of the bis(trifluoromethylthio)ferrocene 3 in MeCN shows a reversible oxidation wave with E₁/₂ = 0.561 V vs. FeCl₃/FcH⁺. 1,1’-Bis(trifluoromethylthio)ferrocene was shown to have an E° of 0.640 V while the E₁/₂ of bis(pentafluorophenyl)iron (CF₃)Fe was determined to be 0.345 V relative to FeCl₃/FcH⁺. This means that the CF₃S group exerts quite a strong electron-withdrawing influence, similar to CF₃ groups. Mass spectra of the new compounds showed the expected patterns, with the typical elimination of CF₃ groups from the molecule as a prominent fragmentation pattern.

This work presents the synthesis of perfluoroalkylthio-substituted ferrocenes. It is interesting to note that standard electrophilic replacement procedures, which work well for aromatic organic compounds, do not proceed as expected with ferrocene. Also, photochemical reactions did not furnish the expected perfluoroalkylthio products. For ferrocene, only nucleophilic reactions seem to give the desired products. Electrochemical data on the new
perfluoroalkylthioferrocenes confirm the strongly electron-withdrawing nature of this class of derivatives. Experiments for further functionalization of such ferrocene derivatives for use in bioconjugates are under way in our laboratory.

All manipulations were carried out under N₂ atmosphere. Melting points are uncorrected. All reagents were purchased from commercial sources and used as received. Solvents were distilled over molecular sieves (CH₂Cl₂, MeOH, hexane, MeCN) or taken from the solvent purification system MBrAUS SPS (THF). Glassware was used oven dry. NMR spectra were recorded on a Bruker DPX 250 (250 MHz) spectrometer at r.t. The 1H NMR chemical shifts (δ) are reported in ppm relative to the residual proton chemical shifts of the deuterated solvent as secondary standard, set relative to external TMS. The absolute values of coupling constants are given in Hz. Microanalysis was performed on a Analytik Jena Multi EA 3100 and on a CE-Instruments EA 1110. GC/MS spectra were recorded on a Shimadzu GCMS-QP2010 and IR spectra on a Bruker Tensor 27 with an ATR optical system.

NOTE: Caution must be exercised when handling volatile and toxic organomercury compounds, which should only be handled by experienced persons!

1-Perfluoroocatanesulfonylferrocene (1)

In a two-neck Schlenk flask, ferrocene (1 g, 5.38 mmol) was dissolved in of hexane (60 mL) and TMEDA (2 mL) was added. This mixture was treated with n-BuLi (2.5 M solution in hexane, 5 mL, 5.81 mmol) under N₂ at 0 °C and stirred at r.t. for 3 h. After this, 1-perfluoroocatanesulfonyl fluoride (2.7 g, 5.4 mmol) was added dropwise at –78 °C by a syringe. The mixture was stirred for 10 h. By adding H₂O (100 mL), the product precipitated as a finely dispersed powder. The pale brown precipitate was collected by filtration after standing for 2 d and dried in vacuo. It turned out to be analytically pure; yield: 0.21 g (0.31 mmol, 6%); mp >220 °C.

1H NMR (250 MHz, CDCl₃): δ = 4.80 (s, 2 H, Cp), 4.70 (s, 2 H, Cp), 4.52 (s, 5 H, Cp).

19F NMR (235 MHz, CDCl₃): δ = –80.7 (s, CF₃), –112.9 (m, 2-CF₂), –119.8 (m, 4,5,6-CF₂), –122.6 (m, 7-CF₂), –126.1 (m, SO₂CF₂).

MS (EI): m/z (%) = 667 (66, [M⁺]), 185 (100, [Fe⁺]).

Anal. Calcd for C₁₁H₉F₃FeS: C, 46.18; H, 1.37. Found: C, 45.84; H, 1.51.

Trifluoromethylthioferrocene (2)

Compound 2 was synthesized as described below for 3 starting with bromoferrocene (0.3 g, 1.13 mmol). The reaction yielded 0.28 g (0.93 mmol, 82%) of trifluoromethylthioferrocene as a yellow oil.

IR (ATR): 2965, 1367, 1200 (SO₂), 1147 (C–F), 1105 (C–F), 1030, 815, 733, 707 cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 4.80 (s, 2 H, Cp), 4.70 (s, 2 H, Cp), 4.52 (s, 5 H, Cp).

19F NMR (235 MHz, CDCl₃): δ = –80.7 (s, CF₃), –112.9 (m, 2-CF₂), –119.8 (m, 4,5,6-CF₂), –122.6 (m, 7-CF₂), –126.1 (m, SO₂CF₂).

MS (EI): m/z (%) = 286 (100, [M⁺]), 217 (84, [M – CF₃⁺]).

Anal. Calcd for C₁₁H₇F₃FeS: C, 56.54; H, 2.00. Found: C, 57.1; H, 2.04.

1,1'-Bis(trifluoromethyloxy)ferrocene (3)

1,1'-Dibromoferrocene (0.2 g, 0.582 mmol) was dissolved in hexane (50 mL) in a two-neck Schlenk flask. Freshly sublimed Hg(SCF₂̋̋)₂ (1.0 g, 2.48 mmol) and Cu bronze (1 g) were added to the solution. This mixture was refluxed overnight while stirring. After this, the formation of a green solid (Cu-amalgam) indicated the end of the reaction. The solid was filtered off and the solvent was removed in vacuo. The product was isolated as a yellow oil (0.08 g 36%); mp 22–20 °C.

IR (ATR): 1417, 1095 (C–F), 1023 (C–F), 897, 823, 756, 644 cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 4.58–4.55 (m, 4 H, Cp), 4.48–4.45 (m, 4 H, Cp).

13C NMR: Identical with 2.

19F NMR (235 MHz, CDCl₃): δ = –45.1.

MS (EI): m/z (%) = 386 (100, [M⁺²]), 317 (49, [M – CF₂⁺]), 248 (28, [M – 2 CF₂⁺]).


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