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Note

1,1′-Bis(3-hydroxypropyl)ferrocene: Preparation and substitution with polyfluoroalkyl groups

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Abstract

$SiMe_3CH_2CH_2$ was demonstrated as a robust and convenient OH protecting group in the preparation of 1,1′-bis(3-hydroxypropyl)ferrocene (**1**). The OH groups were used to introduce polyfluorinated alkyl chains by acylation of **1** with $(C_2F_5CO)_2O$ and alkylation with $CF_3(CF_2)_6CH_2OH$ under Mitsunobu reaction conditions. This demonstrates a new method for introduction of an ω-hydroxyalkyl group to the Cp unit as a synthetic handle for modification of molecular properties.

Keywords: Ferrocene; Mitsunobu reaction; Fluorinated ether; Fluorinated ester

1. Introduction

The design and synthesis of polysubstituted and polyfunctionalized metallocenes, especially ferrocenes [1], has been of increasing interest in recent years. For instance, a tetraalkenyl derivative of ferrocene was used in the synthesis of polynuclear organometallic complexes [2]. Other examples include pentakis(carbomethoxy) derivative of a Mn complex [3], ω-Ph_3Sn- [4] and ω-carboxamide [5] functionalized alkylmetallocenes, ω-$(OEt)_3Si$-alkyl- [6], ω-(phosphanyl)alkyl- [7], and polyfluoalkyl- [8–10] substituted ferrocene. In spite of these reports, complexes containing more than one functional group per Cp group (i.e. other than a hydrocarbon) are rare.

Our current project in molecular materials requires organometallic complexes containing a pentasubstituted Cp ligand in which the groups can be chemically modified to induce hydrophilic, hydrophobic, fluorophilic or aurophilic properties in the alkyl chains. Therefore, we have focused on the ω-hydroxyalkyl substituent in which the OH group provides a convenient synthetic handle for conversion to other functional groups through standard methods [11]. We selected the 3-hydroxypropyl substituent, which can be alkylated or acylated with appropriately functionalized reagents. Alternatively, the OH group can be converted into a leaving group and reacted with nucleophiles.

The introduction of substituents to the Cp ligand can be accomplished in two ways: by substitution of a metallocene or by using the appropriately substituted Cp for the preparation of a metallocene (Fig. 1). The latter method is used more frequently and often involves alkylation of cyclopentadiene [12–14]. However, pentasubsuituted Cp's are difficult to obtain by alkylation [15,16], and therefore two other methods were developed [17,18] for the preparation of such ligands **II** and their complexes **I** with $n = 5$ (Fig. 1). These methods require a substituent X that is stable under nucleophilic conditions for the preparation of **II** and subsequent formation of the complex **I**. We have envisioned the introduction of the 3-hydroxypropyl group with the protected OH functionality which latter will be unmasked after metal complex formation. We chose the $SiMe_3CH_2CH_2$ group as a robust protecting group, which can be removed with F^- under mild conditions.

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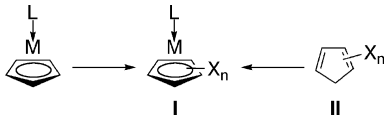
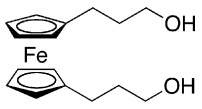


Fig. 1. Two general ways for introduction of substituents X to complex **I**.

In this report, we demonstrate the principle of our strategy for introduction of the 3-hydroxypropyl group to a metallocene using the known ferrocene diol **1** [19] as a convenient model. We describe the preparation of **1** and its two simple transformations, which introduce fluorinated alkyl chains.



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2. Results and discussion

The dihydroxy derivative **1** was obtained in three steps starting from 3-(2-trimethylsilylethoxy)propyl bromide (**2**). Alkylation of cyclopentadiene with bromide **2** gave the monosubstituted derivative **3** in 87% yield as a mixture of isomers (Scheme 1). ^{1}H NMR analysis revealed that the mixture consists almost exclusively of two isomers substituted at the sp^2 carbon in an approximate ratio of 4:3. This observation is consistent with other reports for similar compounds [5,10]. Subsequent reaction of **3** with iron(II) chloride in dry DMSO in the presence of sodium hydride led to the formation of ferrocene derivative **4** which was isolated in 84% yield. Deprotection of the hydroxy groups in **4** and the formation of diol **1** was accomplished using $LiBF_4$ according to a general literature procedure [20]. Other reagents, such as $BF_3 \cdot Et_2O$ [21] or Bu_4NF, were ineffective and starting **4** was fully recovered. The overall yield of **1** was 45% for the three steps based on the starting bromide **2**. In comparison, the overall yield in the published three-step preparation of **1** was lower (32%), and neither of the two intermediates were isolated due to the sensitivity of the THP group used to protect the OH [19].

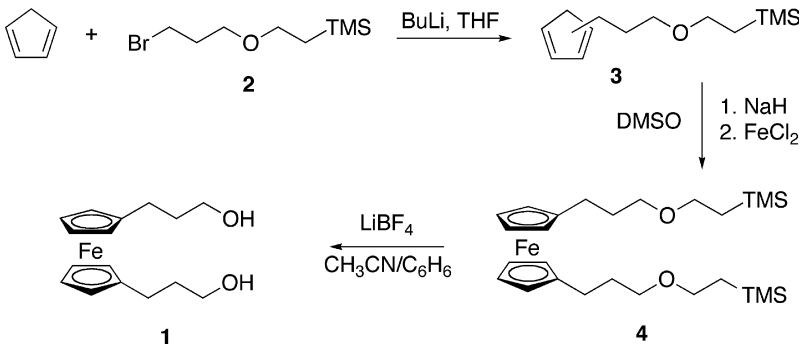
The required bromide **2** was prepared in two steps from 3-bromo-1-propanol. The alcohol was converted to chloromethyl ether **5** according to a general literature procedure [22] and subsequently reacted with (trimethylsilyl)methylmagnesium chloride to give **2** in 50% overall yield (Scheme 2).

Substitution of diol **1** with fluorinated alkyl groups was accomplished in two ways; by formation of an ester or ether (Scheme 3). The former method is simple and involves acylation of the hydroxyl functionality with a perfluoroalkanoic anhydride. Thus, a reaction of **1** with pentafluoropropionic anhydride in ether gave the expected diester **6**, which was isolated in 81% yield (or 90% per OH group) by chromatography on silica. No other products were detected in the reaction mixture by TLC. Attempted separation of **6** on alumina led to complete hydrolysis of the ester, and diol **1** was the only isolated product.

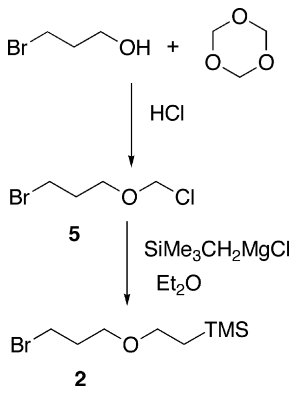
The formation of ether **7** with a partially fluorinated alkyl group was accomplished using the Mitsunobu reaction following a general literature procedure [23] (Scheme 3). The reaction conditions were optimized for the intermediate acidity of the fluoroalcohols R_fCH_2OH, and Bu_3P and 1,1′-(azodicarbonyl)dipiperidine (ADDP) were found to be far more effective than the typical reagents (Ph_3P/DEAD) [23].

A Williamson-type alkylation of **1** with $C_6F_{13}CH_2CH_2I$ in the presence of sodium hydride in either THF or DMSO led to decomposition of the iodide presumably by elimination of HI.

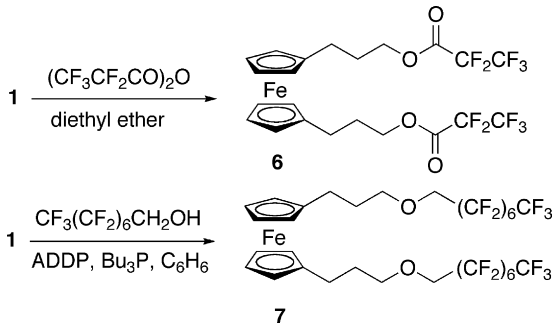
The above experiments demonstrate reactions of diol **1** as a nucleophile (ester **6**) and electrophile formed *in situ* in the Mitsunobu reaction (ether **7**). The electrophilic triflate of **1** was also reported in the literature [19]. The first type of reaction is preferred for derivatives with multiple hydroxy groups, since few, if any, side reactions of the alcohol functionality can occur. Indeed, ester **6** was obtained in high purity and high isolated yield of 90% per OH group. The second process, in which the alcohol is converted to an electrophile, is synthetically much more valuable, but it can also lead to a number of side reactions, such as elim-



Scheme 1.



Scheme 2.



Scheme 3.

ination. As a consequence, lower overall yields and difficulties with separation of the substitution products can be expected. In the case of the present Mitsunobu reaction (compound **7**) the yield is 73% per OH group. The yields of individual steps become particularly important for polyols, which are being currently pursued in our laboratory.

3. Conclusions

Results show that the $SiMe_3CH_2CH_2$ group serves as a robust protecting group for the OH functionality in the preparation of functionalized ferrocenes. It can be removed under neutral conditions giving a hydroxyalkylferrocene derivative in high yields. Two effective ways to append perfluoroalkyl chain were demonstrated. The ester group, however, appears to have limited stability especially under even weakly basic conditions. This methodology can, in principle, be expanded to other ω-hydroxyalkyl substituents and it is promising for introduction of multiple hydroxyalkyl groups to the Cp ligand and subsequent substitution with perfluoroalkyl chains.

4. Experimental

4.1. General procedures, materials, and solvents

All reagents were obtained commercially and used as received. All solvents were dried over appropriate reagents. Manipulations that needed inert conditions were carried out under an atmosphere of nitrogen by use of standard techniques. NMR spectra were recorded in $CDCl_3$ (TMS-free) and referenced to the solvent.

4.2. 1,1′-Bis(3-hydroxypropyl)ferrocene (*1*) [19]

A 1 M solution of $LiBF_4$ in MeCN (14.8 mL, 14.8 mmol) was added to a solution of ferrocene **4** (375 mg, 0.74 mmol) in MeCN/benzene mixture (10 mL, 1:1) and the mixture was stirred for 48 h at 65 °C. Solvents were evaporated, water was added followed by Zn powder (0.1 g) and a drop of concentrated HCl. After 25 min. the resulting yellow mixture was extracted (CH_2Cl_2), dried (Na_2SO_4), and solvents evaporated. The residue was purified by column chromatography (SiO_2, EtOAc) to give 161 mg (72% yield) of diol **1** as an orange oil with spectroscopic data identical to that reported in the literature [19].

4.3. 1-Bromo-3-(2-trimethylsilylethoxy)propane (*2*)

A solution of $SiMe_3CH_2Cl$ (11.02 g, 90 mmol) in dry Et_2O (100 mL) was added dropwise to magnesium turnings (2.16 g, 90 mmol) and the mixture was stirred for 30 min. The resulting solution of the Grignard reagent was added dropwise to a solution of chloro ether **5** (11.32 g, 60 mmol) in dry Et_2O (100 mL) under inert atmosphere at 0 °C (exothermic effect was observed). The reaction mixture was stirred overnight at room temperature to form a white precipitate. It was quenched with water, extracted (CH_2Cl_2), dried ($MgSO_4$), and the solvent evaporated. The crude product was distilled (83–84 °C/7 mm Hg) to give 10.32 g (72% yield) of **2** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.92 (t, $J = 8.2$ Hz, 2H), 2.09 (quint, $J = 6.2$ Hz, 2H), 3.504 (t, $J = 7.0$ Hz, 2H), 3.507 (t, $J = 6.5$ Hz, 2H), 3.510 (t, $J = 7.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.4, 18.1, 30.8, 33.0, 67.5, 68.2; MS, *m/z* 195 and 197 (1.5%, 1:1), 73 (100%). *Anal.* Calc. for $C_8H_{19}BrOSi$: C, 40.17; H, 8.01. Found: C, 40.33; H, 8.12%.

4.4. 3-(2-Trimethylsilylethoxy)propylcyclopentadiene (*3*)

A 2.5 M solution of BuLi (6 mL, 15 mmol) was added to a solution of freshly cracked cyclopentadiene (1.98 g, 2.5 mL, 30 mmol) in THF (20 mL) at −78 °C under inert atmosphere. The resulting mixture was stirred for 30 min and than it was warmed up to room temperature. Bromide **2** (2.39 g, 10 mmol) was added at 0 °C and stirring was continued overnight at room temperature. Solvents were evaporated, the residue was passed through a silica gel plug (CH_2Cl_2), and subsequently purified by column chromatography (CH_2Cl_2/hexane, 1:2) to give 1.97 g (87% yield) of **3** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.94 (t, $J = 8.2$ Hz, 2H), 1.75–1.88 (m, 2H), 2.43 and 2.48 (two td, $J_1 = 7.7$ Hz, $J_2 = 1.5$ Hz and $J_1 = 7.9$ Hz, $J_2 = 0.9$ Hz, 2H), 2.89 and

2.95 (two dm, $J = 1.2$ Hz, 4:3 ratio, 2H), 3.407 and 3.413 (two t, $J = 6.6$ Hz, 3:4 ratio, 2H), 3.51 (t, $J = 8.2$ Hz, 2H), 5.58–6.46 (m, 3H); MS, *m/z* 224 (0.1%, M−1), 73 (100%).

4.5. 1,1′-Bis[3-(2-trimethylsilylethoxy)propyl]ferrocene (4)

To a suspension of NaH (60% in oil, 330 mg, 8.25 mmol) in dry DMSO (10 mL), cyclopentadiene **3** (1.20 g, 5.36 mmol) was added under a nitrogen atmosphere. After 30 min, a solution of anhydrous $FeCl_2$ (750 mg, 5.89 mmol) in DMSO (10 mL) was added. The reaction mixture was stirred at room temperature overnight, poured into water, filtered through Celite®, and extracted (EtOAc). The Celite was washed with EtOAc (3×30 mL), the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed. The resulting crude product was purified by chromatography (Al_2O_3, CH_2Cl_2/hexane 1:1) to give 1.13 g (84% yield) of ferrocene **4** as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 18H); 0.93 (t, $J = 8.3$ Hz, 4H), 1.74 (quint, $J = 7.2$ Hz, 4H), 2.36 (t, $J = 7.8$ Hz, 4H), 3.37 (t, $J = 6.5$ Hz, 4H), 3.47 (t, $J = 8.3$ Hz, 4H), 3.96 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.4, 18.2, 26.0, 31.3, 67.8, 67.9, 68.6, 69.9, 88.6. *Anal.* Calc. for $C_{26}H_{46}FeO_2Si_2$: C, 62.13; H, 9.22. Found: C, 62.23; H, 9.32%.

4.6. 1-Bromo-3-(chloromethoxy)propane (5) [24]

Trioxane (2.85 g, 32 mmol) was dissolved in 3-bromo-1-propanol (12.0 g, 87 mmol). The solution was cooled and HCl was bubbled through for 2 h at 0 °C. The resulting biphasic mixture was stirred overnight at room temperature. The organic layer was separated and dried ($CaCl_2$). The crude product was distilled through a short Vigreux column (63–65 °C/6.5 mm Hg; literature [25] 78–80 °C/15 mm Hg) to give 11.32 g (70% yield) of **5** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (quint, $J = 6.1$ Hz, 2H), 3.49 (t, $J = 6.6$ Hz, 2H), 3.83 (t, $J = 5.8$ Hz, 2H), 5.50 (s, 2H).

4.7. 1,1′-Bis[3-(2,2,3,3,3-pentafluoropropionyloxy)propyl]ferrocene (6)

A solution of pentafluoropropionic anhydride (451 mg, 1.45 mmol) in dry Et_2O (25 mL) was added dropwise to a solution of diol **1** (199 mg, 0.66 mmol) in dry Et_2O (5 mL) at ice bath temperature 0 °C under an inert atmosphere. After 30 min, the ice bath was removed and vigorous stirring was continued overnight. Than solvent was removed and the resulting product was purified by chromatography (SiO_2, hexane/CH_2Cl_2, 2:1) to give 316 mg (81% yield) of pure ester **6** as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (quint, $J = 7.0$ Hz, 4H), 2.42 (t, $J = 7.5$ Hz, 4H), 3.97 (t, $J = 1.6$ Hz, 4H), 4.03 (t, $J = 1.6$ Hz, 4H), 4.37 (t, $J = 6.3$ Hz, 4H); IR (neat) ν 1779 (C=O), 1216, 1150, 1029 (C–O) cm^{-1}. *Anal.* Calc. for $C_{22}H_{20}F_{10}FeO_4$: C, 44.47; H, 3.39. Found: C, 45.06; H, 3.51%.

4.8. 1,1′-Bis[3-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)-propyl]ferrocene (7)

$CF_3(CF_2)_6CH_2OH$ (445 mg, 1.11 mmol), ADDP (140 mg, 0.55 mmol), and Bu_3P (0.14 mL, 112 mg, 0.55 mmol) were added to a solution of diol **1** (42 mg, 0.14 mmol) in benzene (3 mL) at room temperature. The reaction mixture was stirred at 60 °C for 48 h, and the solvent was evaporated. The residue was purified by chromatography (hexanes followed by hexane/CH_2Cl_2, 2:1) to give 80 mg (54% yield) of ferrocene **7** as a light-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (quint, $J = 6.9$ Hz, 4H), 2.41 (t, $J = 7.6$ Hz, 4H), 3.59 (t, $J = 6.2$ Hz, 4H), 3.92 (t, $J = 13.9$ Hz, 4H), 3.97 (s, 4H), 4.00 (s, 4H). *Anal.* Calc. for $C_{32}H_{24}F_{30}FeO_2$: C, 36.04; H, 2.27. Found: C, 36.43; H, 2.31%.

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