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Synthesis and electrochemical properties of a series of ferrocene-containing alcohols

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Abstract

A series of primary ferrocenylalcohols, Fc–$(CH_2)_m$–OH with m = 1–4 and Fc = ferrocenyl, was synthesised by reduction of the appropriate ferrocenylcarboxylic acids, Fc–$(CH_2)_n$–COOH (n = 0–3) and the ester methyl 4-ferrocenylbutanoate with $LiAlH_4$, the reduction of the γ-ketoacid ferrocylpropanoic acid, Fc–CO–$(CH_2)_2$–COOH, with $AlCl_3/LiAlH_4$, and the reduction of ferrocenylcarboxaldehyde, FcCHO, with $NaBH_4$. The secondary ferrocenyl alcohols $CpFe(C_5H_4–CH(OH)–CH_3)$ and $Fe(C_5H_4–CH(OH)–CH_3)_2$ were obtained by $NaBH_4$ reduction of acetyl and diacetyl ferrocene. The different reduction methods are compared. The electrochemistry of the alcohols was studied by cyclic voltammetry in CH_3CN/0.1 M $N(^nBu)_4PF_6$ utilising a platinum working electrode. The ferrocenyl group showed reversible electrochemistry with the formal reduction potential ($E^{o'}$ versus Fc/Fc^+) of the ferrocenyl group inversely proportional to side chain length. The influence of the side chain length on $E^{o'}$ was more pronounced for the acids because the electron-withdrawing properties of the carbonyl group is stronger than that of the alcohol group. Ion pairing was found to play a major role in the electrochemical behaviour of ferrocenylmethanol, Fc–CH_2–OH.

Keywords: Synthesis; Ferrocene; Alcohol; Carboxylic acid; Electrochemistry; Cyclic voltammetry

1. Introduction

The synthesis of ferrocenylmethanol via the reduction of ferrocenecarboxaldehyde or by trimethylamine displacement from the methyl iodide salt of dimethylaminomethylferrocene by –OH [1], and of 2-ferrocenylethanol from acetyl ferrocene via the intermediate ferrocenylacetic acid [2] have been described. We have reported on the use of 4-ferrocenylbutanol as precursor for introducing the ferrocenyl group as high-burning rate catalyst in solid propellants for the rocket industry [3]. These three alcohols are members of a series of ferrocenyl-containing alcohols where the OH group is separated from the ferrocenyl (Fc) group by alkyl chains, –$(CH_2)_m$–, of increasing chain length. In a related series of carboxylic acids, Fc–$(CH_2)_n$–COOH, we have previously demonstrated that the antineoplastic properties of the ferrocenyl group changes with increasing value of "n" [4]. In particular, more beneficial cytotoxic properties for potential cancer treatment were identified for compounds with the largest n-value. The explanation for this observation was related to the formal reduction potential of the ferrocenyl group, which became smaller with increasing chain length. In our ongoing research on the cytotoxic properties of ferrocene-containing compounds, it became important to establish how the formal reduction potential of the ferrocenyl group change by a systematic increase in alkyl chain length between the Fc and OH moieties in the alcohol series Fc–$(CH_2)_m$–OH. In this regard, we were surprised about the limited amount of physical studies that were performed on alcohol derivatives of ferrocene. We report with this paper the results of an electrochemical study

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of the alcohol series Fc–$(CH_2)_m$–OH with $m = 1$–4, Fc–CH(OH)–CH_3 and $Fe(C_5H_4$–CH(OH)–$CH_3)_2$. Results are expressed relative to ferrocene itself and are compared with the related acid series, Fc–$(CH_2)_n$–COOH, $n = 0$–3.

2. Experimental

2.1. Equipment and materials

Ferrocene (**1**, Strem), $LiAlH_4$ (Merck), $AlCl_3$ and other solid reagents (Aldrich) were used without further purification. Dry acetonitrile was obtained by refluxing under nitrogen over CaH_2, distilled onto alumina for storage, and redistilled just prior to use. THF and ether was dried by refluxing under a nitrogen atmosphere over sodium wire and distilled directly before use. Organic solvents were distilled prior to use, water was double distilled. Ferrocene carboxylic acids **2**–**5** [5], **6** [3], the ester **7** [3] and the aldehyde, **8** [6] were synthesised as described before and used as precursors to the alcohols **9**–**12**, Scheme 1. Alcohol **9** was synthesised by $NaBH_4$ reduction of **8** in 90% yield as described by Broadhead [1] but on a 10 times larger scale. The secondary alcohols 1-hydroxyethylferrocene (**13**) and 1,1′-bis(hydroxyethyl)ferrocene (**14**) Fig. 1, was obtained utilising the literature methods [3]. Chromatography was performed on Fluka silica gel 60 grade 60741. The electrolyte tetrabutylammonium tetrakis(pentafluorophenyl)borate was prepared as described [7]. Melting points were determined with a Reichert Thermopan Microscope with a Koffler hot-stage and are uncorrected. ^1H NMR spectra at 20 °C were recorded on a Bruker Advance DPX 300 NMR spectrometer at 300 MHz with chemical shifts presented as δ values referenced to $SiMe_4$ at 0.00 ppm utilising $CDCl_3$ that was made acid free by passing it through basic alumina immediately before use. IR spectra (cm^{-1}) were recorded on a Hitachi spectrophotometer Model 270-50 with data processor. For solid state spectra a KBr matrix was used, while NaCl plates were used for thin films of liquid samples. Elemental analysis was conducted by the Canadian Microanalytical Service, Ltd.

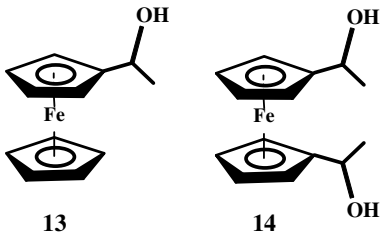
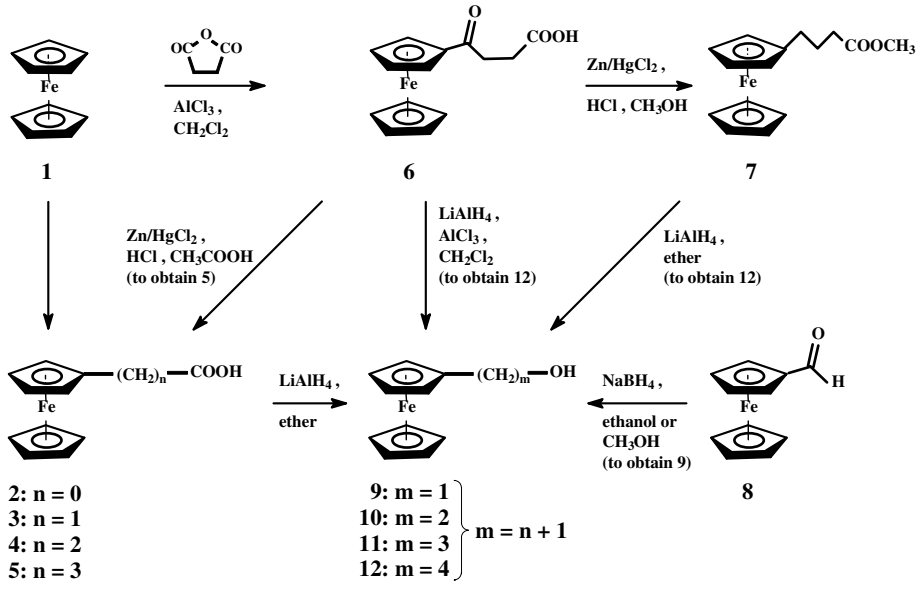


Fig. 1. Structures of secondary alcohols **13** and **14**.

2.2. Synthesis

2.2.1. Fc–$(CH_2)_m$–OH, with m = 1 (9), 2 (10), 3 (11) and 4 (12), utilising $LiAlH_4$ reduction of acids 2–5

The synthesis of 3-ferrocenylpropanol (**11**) may serve as an example. To a $LiAlH_4$ suspension in dry ether (3.42 g, 90 mmol in 100 cm^3) was slowly added a solution of 3-ferrocenylpropanoic acid (**4**, 3 g, 12.6 mmol) in dry ether (110 cm^3) while slight boiling was maintained. After refluxing the mixture for 13 h at 50 °C, a 1:1 ethanol:ether mixture (50 cm^3) was very carefully added to destroy the excess $LiAlH_4$. The reaction mixture was slowly poured into an excess of ice cold 2 M



Scheme 1. Different routes that may be followed to obtain ferrocene-containing alcohols **9**–**12**.