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THE SYNTHESIS AND REACTIVITY OF (FERROCENYLOXY)-2-TETRAHYDROPYRAN *

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Summary

Ferrocenylboronic acid was prepared in good yield via the base hydrolysis of ferrocenylboron dibromide. The ferrocenylboronic acid was converted into hydroxyferrocene which was treated with 2,3-dihydropyran to give (ferrocenyl oxy)-2-tetrahydropyran. Lithiation of this pyran gave the corresponding 2-lithiated ferrocene, which was used to prepare some 1,2-disubstituted ferrocenes including 1-carboxy-2-acetoferrocene ("ferrocenyl-aspirin").

Introduction

Phenol is important commercially and its chemistry has been investigated thoroughly [2]. However, the corresponding ferrocene derivative, hydroxyferrocene, has received little attention. Two possible reasons for this are (i) hydroxyferrocene is oxidatively unstable, and (ii) hydroxyferrocene has been difficult to obtain easily in reasonable quantities. Thus hydroxyferrocene is prepared usually from ferroceneboronic acid [3], via ferrocenylacetate, which is obtained in relatively low yields from ferrocene [4].

We required some 2-substituted hydroxyferrocenes as part of an investigation into ferrocene derivatives which were potentially pharmacologically active [5]. Previously 2-substituted ferrocenes have been prepared in good yields via the metallation of dimethylaminomethylferrocene and related compounds [6]. However, the lithiation of ferrocenyl ethers and related compounds with an oxygen atom attached directly to one of the cyclopentadienyl rings has received little attention, although phenyl ethers have been more thoroughly investigated [7]. Nesmeyanov et al. have reported the metallation of methoxyferrocene with n-butyllithium [8]. Lithiation occurred next to the oxygen atom, and condensa-

* Some of these results have been presented in a preliminary form [1].

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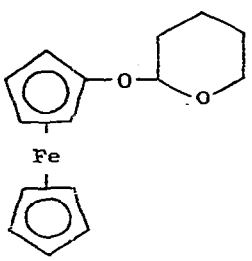
tion of the lithio intermediate with electrophiles gave 2-substituted methoxyferrocenes.

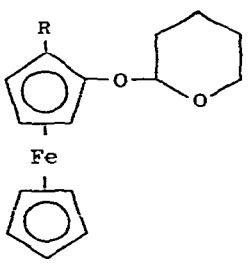
Preliminary experiments [9] indicated that the direct lithiation of hydroxyferrocene with n-butyllithium was not a good route to 2-substituted hydroxyferrocenes. This conclusion parallels that of Gilman et al., who found that the direct metallation of phenol gave only low yields of ring-metallated products [10]. However, protection of the hydroxyl group by treatment with 2,3-dihydropyran, followed by metallation, reaction with a given electrophile and acid cleavage of the pyranyl group provided a satisfactory route to 2-substituted phenols [11]. The reaction of hydroxyferrocene with 2,3-dihydropyran to give (ferrocenyloxy)-2-tetrahydropyran, and the lithiation of this compound are the subjects of this report.

Results and discussion

Ferrocenylboron dibromide was prepared by the direct reaction of ferrocene with boron tribromide [12]. Base hydrolysis of the dibromide [13] gave ferrocenylboronic acid in good yield. This route made it possible to prepare hydroxyferrocene in sufficient quantities for our work. The ferrocenylboronic acid was converted into hydroxyferrocene, via ferrocenylacetate [3], which on treatment with 2,3-dihydropyran in the presence of acid gave the air stable acetal I [11]. The acetal I was stable to base hydrolysis, but treatment with dilute hydrochloric acid easily regenerated hydroxyferrocene.



(I)



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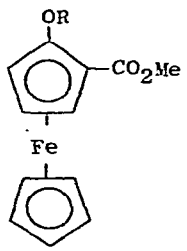

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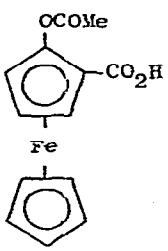

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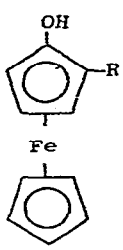

(V)

TABLE 1

THE USE OF 2-ACETOXYFERROCENE CARBOXYLIC ACID (FERROCENYL-ASPIRIN) IN THE CARRAGEENAN-INDUCED PAW OEDEMA TEST IN THE RAT

Results are expressed as means ± standard deviations with 5 rats per group apart from the higher dose of ferrocenyl-aspirin where one rat died.

	Dosage (mg/kg)	Increase in paw volume (% increase of the zero time value)				
		1 h	2 h	3 h	4 h	5 h
Control		19 ± 2	78 ± 11	93 ± 9	82 ± 9	92 ± 11
Aspirin	200	5 ± 5[a]	33 ± 15[a]	62 ± 12[a]	71 ± 24	77 ± 22
Aspirin	50	11 ± 4[a]	54 ± 8[a]	80 ± 16	91 ± 12	94 ± 13
Ferrocenyl-aspirin	200	17 ± 9	61 ± 14	88 ± 9	84 ± 15	81 ± 4
Ferrocenyl-aspirin	50	19 ± 5	76 ± 3	92 ± 4	85 ± 8	86 ± 7

[a] Indicates a significant reduction in paw volume as compared with the control value.

Treatment of the ferrocenylacetal I with n-butyllithium at room temperature gave the corresponding 2-lithiated derivative II (R = Li), which on condensation with carbon dioxide gave the ferrocene carboxylic acid II (R = CO_2H). Treatment of this acid with hydrochloric acid at room temperature gave 1-carboxy-2-hydroxyferrocene, the analogue of salicyclic acid. The reaction of this acid with an excess of diazomethane produced the ester III (R = H), which on further treatment with diazomethane gave the methoxy ester III (R = OMe). This ester was prepared also from methoxyferrocene [14], and this confirmed the 1,2-orientation of the substituents in the compounds prepared from the pyran I via lithiation. The ester III (R = H) was prepared also by treatment of the ferrocene acid II (R = CO_2H) with diazomethane followed by hydrochloric-acid-catalysed removal of the pyran group.

1-Carboxy-2-hydroxyferrocene underwent facile conversion into the ferrocenylacetate IV on treatment with acetic anhydride in pyridine. The acetate IV is the ferrocene analogue of aspirin, and it was tested for anti-inflammatory activity *. The acetate IV (ferrocenylaspirin) was compared with acetylsalicyclic acid (aspirin) in one of the standard anti-inflammatory animal models, the carrageenan paw oedema test in the rat [15]. Ferrocenylaspirin and aspirin were administered orally or intraperitoneally at 50 and 200 mg kg^{-1}, and one hour after adminstration the rats received a subplantar injection of carrageenan. The volumes of the injected rat paws were assessed at hourly intervals for five hours with a mercury plethysmograph [16]. Intraperitonal administration of a large dose of ferrocenyl aspirin IV (200 mg kg^{-1}) killed all the rats tested. Administration of 50 mg kg^{-1} resulted in 20% mortality with the rest of the rats in this group showing severe signs of toxicity which rendered assessment of any anti-inflammatory activity meaningless. Oral administration of ferrocenylaspirin IV (200 mg kg^{-1}) produced much less toxicity in the rats, but no anti-inflammatory activity was observed at this high dosage or at the lower dosage (50 mg kg^{-1}) (Table 1). The lack of biological

* These tests were carried out by the N.R.D.C.

TABLE 2

INFRARED CARBONYL AND HYDROXYL STRETCHING FREQUENCIES (cm^{-1}) FOR SOME 1,2-DISUBSTITUTED FERROCENES

Compound	R	Carbonyl	Hydroxyl
II	CO_2H	1660	—
V	CO_2H	1650	3380
II	CO_2Me	1710	—
V	CO_2Me	1682	3460
II	CHO	1680	—
V	CHO	1630	3400
II	$CH{=}CHCO_2H$	1670	—
V	$CH{=}CHCO_2H$	1660	3400

activity in the present tests is in marked contrast to our previous findings with the ferrocene analogues of commercial β-lactam antibiotics [5].

Condensation of the lithiopyran II (R = Li) with paraformaldehyde and dimethylformamide gave the ferrocenylalcohol II ($R = CH_2OH$) and the aldehyde II (R = CHO) respectively. The alcohol underwent facile conversion to the aldehyde on treatment with "active" manganese dioxide in chloroform [17,18]. The aldehyde II (R = CHO) readily formed an oxime and this was dehydrated with dicyclohexylcarbodiimide to give the cyanide II (R = CN). Treatment of the aldehyde with malonic acid in pyridine gave the substituted acrylic acid II ($R = CH{=}CHCO_2H$).

Most of the 2-substituted ferrocenyloxypyrans prepared were treated with acid to liberate the corresponding 2-substituted hydroxyferrocenes. Several of these hydroxyferrocenes (V, $R = CO_2H$, CO_2Me, CHO, $CH{=}CHCO_2H$) were air stable, that is they could be handled in air and recrystallized without special precautions. The unusual stability of these 2-substituted hydroxyferrocenes relative to hydroxyferrocene was probably due to the presence of an electron-withdrawing group next to the hydroxy group and to intramolecular hydrogen bonding. The presence of intramolecular hydrogen bonding in these molecules was supported by their infrared spectra.

In the 2-substituted ferrocenyloxypyrans (II, $R = CO_2H$, CO_2Me, CHO and $CH{=}CHCO_2H$) removal of the pyran group reduced the carbonyl stretching frequencies with the appearance of a hydroxyl frequency in the region 3380—3460 cm^{-1} (characteristic of H-bonded phenolic OH) (Table 2).

Experimental

Ferroceneboronic acid

Boron tribromide (300 g, 1.2 mol) and ferrocene (186 g, 1.0 mol) were added to carbon disulphide (1500 cm^3) and heated under reflux for 24 h. After cooling, the reaction mixture was filtered into 2 *M* sodium hydroxide (2000 cm^3). The alkaline solution was extracted three times with ether, filtered and cooled to 0°C. The aqueous solution was acidified with 2 *M* hydrochloric acid and a yellow precipitate was deposited. The precipitate was collected by filtration, washed with water and dried under vacuum to give ferroceneboronic acid (126 g, 55%), which crystallised from ether as orange plates, m.p. 143—148°C (lit. [19] m.p. 143—148°C).

Tetrahydropyran-2-yloxyferrocene

Ethyl acetate (1.1 cm^3) saturated with hydrogen chloride and 2,3-dihydropyran (8 cm^3, 0.095 mol) were added to hydroxyferrocene (7.26 g, 0.036 mol) in ethyl acetate (80 cm^3). The mixture was stirred for 1.5 h and poured into 2% sodium hydroxide. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and evaporated to leave an orange oil which was chromatographed on alumina. Light petroleum (b.p. 40—60°C) eluted tetrahydropyran-2-yloxyferrocene I (8.50 g, 83%) which crystallised from light petroleum as an orange solid, m.p. 58°C (Found: C, 63.29; H, 6.32; M^+, 286. $C_{15}H_{18}FeO_2$ calcd.: C, 62.97; H, 6.29%; *M*. 286). PMR (60 MHz) (δ, CCl_4) 1.70 (7H, s(br), pyran), 3.75 and 4.10 (10 H, t and s, ferrocene and pyran), 5.15 ppm (1 H, s, pyran).

Ether/light petroleum (b.p. 40—60°C) eluted a product containing two pyran moieties (0.9 g, 6%) which crystallised from light petroleum as a yellow solid, m.p. 131—133°C (Found: C, 64.96; H, 7.08; M^+, 370. $C_{20}H_{26}O_3Fe$ calcd.: C, 64.71; H, 7.01%, *M*, 370).

Reaction of tetrahydropyran-2-yloxyferrocene with hydrochloric acid

Tetrahydropyran-2-yloxyferrocene (1.0 g, 0.0035 mol) was dissolved in ethanol and 2 *M* hydrochloric acid (2 cm^3) was added. The reaction mixture was stirred at room temperature for 0.5 h, diluted with water (50 cm^3), made alkaline with 2 *M* sodium hydroxide and extracted with ether. The aqueous solution was neutralised with 2 *M* hydrochloric acid and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to give hydroxyferrocene (0.66 g, 94%) (m.p. and infrared spectrum identical to those of an authentic sample).

Lithiation of tetrahydropyran-2-yloxyferrocene

n-Butyllithium (0.0077 mol) was added to a solution of tetrahydropyran-2-yloxyferrocene (2.0 g, 0.007 mol) in ether (50 cm^3). The mixture was stirred at room temperature for 2 h to give a solution of the lithiopyran (II, R = Li).

2-(Tetrahydropyran-2-yloxy)ferrocenecarboxylic acid

A solution of the lithiopyran (II, R = Li) was prepared from tetrahydropyran-2-yloxyferrocene (4.0 g, 0.014 mol) and n-butyllithium (0.0154 mol) as described previously. The lithiopyran (II, R = Li) was poured slowly onto solid carbon dioxide (10 g) in ether (50 cm^3). After the solid carbon dioxide had evaporated the reaction mixture was poured into aqueous 10% potassium hydroxide (100 cm^3). The aqueous layer was washed with ether, made just acid with 2 *M* hydrochloric acid and extracted with ether. The combined ether extracts were dried ($MgSO_4$), filtered and evaporated to give 2-(tetrahydropyran-2-yloxy)-ferrocenecarboxylic acid (II, R = CO_2H) (3.84 g, 88%) which crystallised from cold ether/light petroleum as red crystals, m.p. 124°C (Found: C, 58.09; H, 5.52; M^+, 330. $C_{16}H_{17}O_4Fe$ calcd.: C, 58.21; H, 5.46%; *M*, 330).

2-Hydroxyferrocenecarboxylic acid

2-(Tetrahydropyran-2-yloxy)ferrocenecarboxylic acid (3.0 g, 0.009 mol) was dissolved in ethanol (200 cm^3) and 2 *M* hydrochloric acid (20 cm^3) was added. The mixture was stirred for 1 h, diluted with water (100 cm^3) and neutralised with 2 *M* sodium hydroxide. The ethanol was evaporated and the residual aque-

ous solution was extracted with ether. The combined ether extracts were dried ($MgSO_4$), filtered and evaporated to give 2-hydroxyferrocenecarboxylic acid (V, R = CO_2H) (1.7 g, 78%) which crystallised from cold ether/light petroleum (b.p. 40—60°C) to give dark red crystals, m.p. 160°C (decomp.). (Found: C, 53.58; H, 3.98; M^+, 246. $C_{11}H_{10}FeO_3$ calcd.: C, 53.70; H, 4.06%; *M*, 246).

Methyl 2-hydroxyferrocenecarboxylate

Diazomethane (0.03 mol) in ether (20 cm^3) was added to a solution of 2-hydroxyferrocenecarboxylic acid (2.0 g, 0.00813 mol) in ether (100 cm^3) and the mixture was stirred for 4 h. The ether was evaporated and the resulting oil was dissolved in 10% potassium hydroxide. The alkaline solution was washed with ether, acidified and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to give methyl 2-hydroxyferrocenecarboxylate (1.23 g, 59%) which crystallised from ether/light petroleum (b.p. 40—60°C) as orange crystals, m.p. 46°C (Found: C, 55.45; H, 4.66; M^+, 260. $C_{12}H_{12}O_3Fe$ calcd.: C, 55.41; H, 4.62%; *M*, 260).

Methyl 2-methoxyferrocenecarboxylate

Methyl 2-hydroxyferrocenecarboxylate (1.0 g, 0.004 mol) was dissolved in ether (100 cm^3) and diazomethane (0.012 mol) in ether (20 cm^3) was added. The mixture was stirred for 6 h. The ether was evaporated to leave an orange oil which was chromatographed on alumina. Light petroleum eluted methyl 2-methoxyferrocenecarboxylate (0.23 g, 21%) which crystallised from light petroleum (b.p. 40—60°C) as orange crystals, m.p. 39°C (Found: C, 56.57, H, 5.35; M^+, 274. $C_{13}H_{14}O_3Fe$ calcd.: C, 56.93; H, 5.11%, *M*, 274). PMR (60 MHz) (δ, CCl_4) 3.65 (3H, 3, Me); 3.75 (3H, s, Me), 3.90 (2H, m, ferrocene), 4.10 (5H, s, ferrocene), 4.40 ppm (1H, m, ferrocene).

Methyl 2-(tetrahydropyran-2-yloxy)ferrocenecarboxylate

2-(Tetrahydropyran-2-yloxy)ferrocenecarboxylic acid (0.5 g, 0.0015 mol) was dissolved in ether (50 cm^3) and diazomethane (0.006 mol) in ether (20 cm^3) was added. The mixture was stirred for 5 h and worked up as previously described to give an orange oil which was chromatographed on alumina. Light petroleum (b.p. 40—60°C) eluted methyl 2-(tetrahydropyran-2-yloxy)ferrocenecarboxylate (0.45 g, 87%) which crystallised from light petroleum (b.p. 40—60°C) as orange crystals, m.p. 91.5°C (Found: C, 59.50; H, 5.88; M^+, 344. $C_{17}H_{20}O_4Fe$ calcd.: C, 59.33; H, 5.82%; *M*, 344).

Hydrolysis of methyl 2-(tetrahydropyran-2-yloxy)ferrocenecarboxylate

The ester (II, R = CO_2Me) (0.4 g, 0.0012 mol) was dissolved in ethanol (50 cm^3) and 2 *M* hydrochloric acid (20 cm^3) was added. The mixture was stirred for 30 min and worked up as previously described to give methyl 2-hydroxyferrocenecarboxylate (0.24 g, 75%) which crystallised from ether/light petroleum (b.p. 40—60°C) as orange crystals (infrared spectrum and m.p. identical to those of an authentic sample).

2-Acetoxyferrocenecarboxylic acid

2-Hydroxyferrocenecarboxylic acid (5.0 g, 0.0203 mol) was dissolved in pyri-

dine (15 cm^3) and acetic anhydride (4.0 cm^3, 0.039 mol) was added. The stirred solution was heated at 60—70°C for 10 min and then stirred at room temperature for 30 min. The solution was hydrolysed with water (20 cm^3) and ether (100 cm^3) was added. The ether layer was washed with 0.05 *M* hydrochloric acid until the ether was neutral. The ether layer was extracted twice with aqueous sodium bicarbonate. The combined aqueous extracts were acidified and extracted with ether. The ether extracts were washed with water, dried ($MgSO_4$) and evaporated to give 2-acetoxyferrocenecarboxylic acid (3.9 g, 64%) which crystallised from light petroleum (b.p. 40—60°C) as orange needles m.p. 136°C (Found: C, 54.33; H, 4.22; O, 22.44; Fe, 19.29; M^+, 288. $C_{13}H_{12}O_4Fe$ calcd.: C, 54.19; H, 4.17; O, 22.23; Fe, 19.40%; *M*, 288). PMR (60 MHz) (δ, CCl_4) 2.22 (3H, s, Me) 4.30 and 4.60 (8H, s and m, ferrocene), 11.48 ppm (1H, s, OH; this signal disappeared on the addition of D_2O).

2-Tetrahydropyran-2-yloxy)ferrocenemethanol

A solution of the lithiopyran (II, R = Li) was prepared from tetrahydropyran-2-yloxyferrocene (5.0 g, 0.017 mol) and n-butyllithium (0.0187 mol) and a suspension of paraformaldehyde (0.62 g, 0.20 mol) in ether (25 cm^3) was added dropwise. The reaction mixture was stirred for 2 h, hydrolysed with water and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and evaporated to leave a red oil which was chromatographed on alumina. Elution with light petroleum (b.p. 40—60°C) gave tetrahydropyran-2-yloxyferrocene (1.95 g, 39%). Ether eluted 2-(tetrahydropyran-2-yloxy)ferrocenemethanol (2.95 g, 61%) which crystallised from ether/light petroleum (b.p. 40—60°C) as an orange solid, m.p. 59—60°C (Found: C, 60.51; H, 6.37; M^+, 316. $C_{16}H_{20}O_3Fe$ calcd.: C, 60.80; H, 6.30%; *M*, 316). PMR (60 MHz) (δ, CCl_4) 1.65 (7H, s, pyran), 2.53 (1H, s, OH; this signal disappeared on the addition of D_2O), 3.65 (2H, t, CH_2), 3.80 (2H, m, ferrocene and pyran), 4.00 (5 H, s, ferrocene), 4.30 (2H, d, ferrocene), 5.10 ppm (1H, s, pyran).

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