Displacement of the Hydroxy-group from Ferrocenylmethanol by Amines

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The reaction of ferrocenylmethanol with piperidine, t-butylamine, cyclohexylamine, or benzylamine to afford the appropriately substituted ferrocenylmethylamine proceeds efficiently in dilute aqueous acetic acid. The reaction with piperidine in aqueous solution is very slow outside the pH range 4—7. Aniline, p-nitroaniline, p-anisidine, and urea effect nucleophilic substitution of ferrocenylmethanol in the absence of acetic acid. The mechanism is discussed and evidence is presented that in this reaction aniline is a more effective nucleophile than piperidine.

In connection with an investigation into the free-radical chemistry of ferrocene we required samples of N-t-butylferrocenylmethylamine (5) and related amines. In principle, the most direct route to such compounds is by nucleophilic substitution of a derivative of ferrocenylmethane containing a suitable leaving group. The quaternary salt (1) has been frequently used as a substrate for nucleophilic displacement reactions,[1] including attack by primary and secondary amines.[2] However, in our hands treatment of the salt (1) in aqueous solution with t-butylamine gave only a low yield (22%) of the required product (5).

In view of its ready availability,[3] ferrocenylmethanol (2) is an attractive starting material for the preparation of derivatives of ferrocenylmethane. It undergoes nucleophilic displacement of the hydroxy-group by substituted malonic esters,[4] by NNN'N'-tetramethyl-methanediamine,[5] and by aniline.[6] However, it has been reported[6] to be inert towards attack by benzylamine and by piperidine. Addition of aluminium chloride to the reaction mixture facilitates the attack of primary and secondary aliphatic amines on α-substituted ferrocenylmethanols,[7] but the method gives poor yields when ferrocenylmethanol itself is employed as starting material. Very recently it has been reported[8] that although substitution of ferrocenylmethanol fails when the nucleophile is readily protonated, derivatives of ferrocenylmethylamine can be prepared by nucleophilic

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displacements on α-ferrocenylmethylium tetrafluoroborate.

In the light of the previous work we concluded that direct conversion of ferrocenylmethanol into *N*-alkyl derivatives of ferrocenylmethylamine should be possible if nucleophilic displacements were conducted in slightly acidic media. In the event the amine (5) was obtained in excellent yield when ferrocenylmethanol was heated with t-butylamine in dilute aqueous acetic acid (see Table 1). Similar experiments involving cyclohexylamine, benzylamine, and piperidine were equally

urea in aqueous solution. When the reaction of ferrocenylmethanol with aniline was conducted in aqueous methanol containing acetic acid the yield of the amine (10) was lower and the methyl ether (3) was also formed. No substitution occurred when the ether (3) was heated with aniline in water, or when the amine (8) was refluxed in methanolic acetic acid.

In an attempt to elucidate its mechanism the reaction of ferrocenylmethanol with piperidine was conducted in buffer solutions over a wide range of values of pH (see Table 2). In media of pH >7 the reaction proceeded

TABLE 1

Products from the reaction [a] of amines with ferrocenylmethanol and related compounds

Reactants	Solvent	pH [b]	Products [c]	Yields (%)
(2) + Bu^{t}NH$_2$	H$_2$O	ca. 11		
(2) + Bu^{t}NH$_2$	H$_2$O–HOAc	5.2	(5)	Quant.
(2) + piperidine	H$_2$O–HOAc	5.1	(8)	97
(2) + cyclohexylamine	H$_2$O–HOAc	5.0	(6)	89
(2) + PhCH$_2$·NH$_2$	H$_2$O–HOAc	4.9	(7)	92
(2) + PhNH$_2$	H$_2$O–MeOH	8.8	(10)	95
(2) + PhNH$_2$	H$_2$O–MeOH–HOAc	4.3	{ (10) (3)	50 15
(2) + p-O$_2$N·C$_6$H$_4$·NH$_2$	H$_2$O–MeOH	7.9	(11)	84
(2) + p-MeO·C$_6$H$_4$·NH$_2$	H$_2$O–MeOH	9.7	(12)	70
(2) + NH$_2$·CO·NH$_2$	H$_2$O	7.2	(9)	33
(2) + Bu^{t}NH$_2$ + PhNH$_2$	H$_2$O	ca. 11	(10)	15
(2) + cyclohexylamine + PhNH$_2$	H$_2$O	ca. 11	(10)	15
(8)	H$_2$O–MeOH–HOAc	5.0		
(3) + PhNH$_2$	H$_2$O	8.1		

[a] Each reaction mixture was boiled under reflux for 12 h. [b] The pH of the reaction mixture was determined at the beginning of the experiment. [c] Starting material was recovered from those experiments which afforded no amine product or low yields of products.

successful. It thus appears that this procedure should be generally useful for the preparation of a wide range of amines directly from ferrocenylmethanol.

In agreement with previous work [6] we found that the amine (10) was formed in good yield when aniline and ferrocenylmethanol were heated in aqueous methanol

(1) R = $\overset{+}{N}$Me$_3$I$^-$ (5) R^1 = H, R^2= Bu^t (10) R = H
(2) R = OH   (6) R^1=H, R^2=cyclohexyl   (11) R = NO$_2$
(3) R = OMe   (7) R^1= H, R^2= CH$_2$Ph   (12) R = OMe
(4) R = $\overset{+}{O}$H$_2$ (8) R^{1}R^2 =[CH$_2$]$_5$
                     (9) R^1 = H, R^2= CO·NH$_2$

in the absence of added acid. These conditions were also suitable for the preparation of compounds (11) and (12) containing *p*-nitro- and *p*-methoxy-substituents, respectively. *N*-Ferrocenylmethylurea (9) was obtained in modest yield by heating ferrocenylmethanol with

very slowly, whilst at low pH tars and ferrocenium salts were formed. One reaction conducted at pH 0.6 at
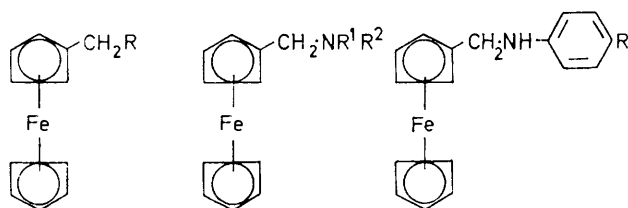
TABLE 2

pH Dependence of the reaction of ferrocenylmethanol with piperidine

pH	Solvent	Time (h)	Temp.[a]	Products [b]	Yields (%)
7.9	H$_2$O	12	B	(8)	Trace
6.5	H$_2$O	12	B	(8)	60
7.8	H$_2$O–MeOH	12	A		
7.8	H$_2$O–MeOH	12	B	(3)	Trace
8.1	H$_2$O–MeOH	72	B	{ (8) (3)	22 5
5.1	H$_2$O	12	B	(8)	97
3.8	H$_2$O–MeOH	12	B	{ (8) (3)	23 62
1.3	H$_2$O	12	B	Tars	
0.6	H$_2$O–MeOH	6	A	(FcCH$_2$)$_2$O	67

[a] A, stirred at ambient temperature; B, boiled under reflux. [b] Ferrocenylmethanol was recovered from reactions conducted at pH >6.

room temperature afforded bisferrocenylmethyl ether. When the solvent contained methanol both the amine (8) and the methyl ether (3) were produced; the latter compound (3) was the major product from the reaction conducted at pH 3.8.
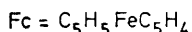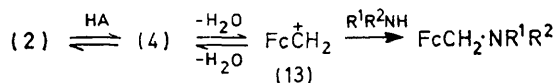
The data presented in Table 2 indicate that the rate of reaction of ferrocenylmethanol with piperidine, and

presumably with other aliphatic amines, is dependent on the acidity of the medium. A mechanism consistent with this observation involves initial formation of the conjugate acid (4) of the alcohol in an equilibrium step. The subsequent nucleophilic displacement proceeds by direct attack of amine on the conjugate acid (4) or more probably as indicated through the cation (13), the remarkable stability of which [9,10] facilitates its formation from ferrocenylmethanol in acidic solution.[10,11] In terms of this mechanism the reaction, when conducted in media of low pH, fails to yield the desired product because of the high degree of protonation of the amine

$$(2) \underset{HA}{\rightleftharpoons} (4) \underset{-H_2O}{\overset{-H_2O}{\rightleftharpoons}} Fc\overset{+}{C}H_2 \xrightarrow{R^1R^2NH} FcCH_2{\cdot}NR^1R^2$$
$$(13)$$

$$Fc = C_5H_5FeC_5H_4$$

nucleophile. However, under such conditions the intermediate cation (13) will react with methanol, if present, to afford the ether (3). Under conditions of high pH the reaction is very slow because of the unfavourable position of the equilibrium (2) $\rightleftharpoons$ (4).

The present data do not allow the mechanism of the reaction of ferrocenylmethanol with aromatic amines to be defined. The results of experiments conducted in the absence of added acid indicate that the reaction of ferrocenylmethanol with aniline proceeds much more rapidly than that with aliphatic amines. This was confirmed by heating the alcohol (2) in water with a mixture of aniline and t-butylamine (or cyclohexylamine); only the substituted aniline (10) was formed. The fact that the yields of amine (10) obtained from these experiments conducted at high pH (ca. 11) were very much less than that afforded by the experiment conducted at pH 8.8 suggests that the reaction of ferrocenylmethanol with aniline also proceeds via the cation (13). However it is clear that, whatever the nature of the intermediate, under conditions of high pH it is much more reactive towards attack by aniline than by aliphatic amines. Quantitative evaluation of this unusual order of relative nucleophilicity, and elucidation of the phenomena underlying it, will require a detailed kinetic investigation.

Since the reaction of aromatic amines sometimes proceeds by substitution at the *para*-position (for example, treatment of triphenylmethanol with aniline in acetic acid affords *p*-triphenylmethylaniline [12]) it appeared desirable to prepare the ferrocene derivative (15) by an unambiguous method. This was readily achieved by reduction of *p*-nitrobenzoylferrocene (14). The properties of the product (15) were different from

those of the compound (10) obtained from the reaction of aniline with ferrocenylmethanol.

$$FcCO\text{—}\langle\text{—}\rangle\text{—}NO_2 \xrightarrow{i,ii} FcCH_2\text{—}\langle\text{—}\rangle\text{—}NH_2$$
$$(14) \qquad\qquad (15)$$
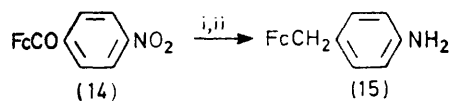
Reagents: i, LiAlH$_4$ – AlCl$_3$, ii, Pt – NH$_2{\cdot}$NH$_2$

The mass spectra of the compounds prepared in this work were determined. Most of the amines behaved like monoalkylferrocenes and derivatives of ferrocenylmethane;[13] the ion current was carried principally by metal-containing species, and prominent ions at m/e 199, 121, and 56, together with appropriate metastables, indicated the occurrence of the consecutive fragmentations $FcCH_2NR^1R^{2+} \longrightarrow C_5H_5FeC_6H_6{}^+ \longrightarrow C_5H_5Fe^+ \longrightarrow Fe^+$. In some cases hydrogen transfer occurred simultaneously with expulsion of all or part of the side chain to give ions with m/e 186 (FcH$^+$) and 200 (FcCH$_3{}^+$). The benzylamine derivative (7) gave strong peaks at m/e 238 and 212 attributed respectively to the loss from the molecular ion of C_5H_7 and C_7H_9. The *p*-nitro-compound (11) gave an intense peak at m/e 199 ($C_5H_5FeC_6H_6{}^+$) but was otherwise unusual in that the base peak at m/e 138 and other important peaks at m/e 108 and 92 clearly arise from the *p*-nitroaniline unit and do not contain Fe. The base peak at m/e 215 in the spectrum of the urea (9) is attributed to $M^+ -$ HNCO. The formation of an ion with m/e 137 ($C_5H_5FeNH_2{}^+$) suggests that the urea (9) undergoes a rearrangement similar to that shown by ferrocenylmethanols,[14] whereby expulsion of the fragment C_6H_6NCO is accompanied by migration of the aminogroup onto the metal atom. The *para*-substituted aniline (15) behaved differently from its *N*-substituted isomer (10) in giving an extremely stable molecular ion which showed little tendency to fragment to give $C_5H_5FeC_6H_6{}^+$.

EXPERIMENTAL

Mass spectra were recorded on a Hitachi–Perkin-Elmer RMU-6D double-focussing spectrometer operating at 70 eV. ^{1}H N.m.r. spectra were determined at 60 MHz for solutions in carbon tetrachloride with tetramethylsilane as internal standard. pH Measurements were made with a Pye pH meter using a single glass–calomel electrode standardized against freshly prepared buffer solutions. Analytical t.l.c. was performed on plates coated with Merck silica gel HF$_{254}$, with mixtures of ether and light petroleum as solvents. Plates for preparative t.l.c. were coated with a 1 : 1 mixture of Merck Kieselgel HF$_{254}$ and Kieselgel G.

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Analyses were carried out by the Australian Microanalytical Service, Melbourne.

Preparation of Amines from Ferrocenylmethanol.—The following general method was employed. Ferrocenylmethanol [3] (0.2—0.5 g) was mixed with 4 mol. equiv. of amine in water (20 ml), or a mixture of water (15 ml) and methanol (5 ml). If required, sufficient glacial acetic acid was added dropwise with stirring to give the required pH value. The mixture was then heated under reflux for 12 h, cooled, poured into aqueous 5% acetic acid (200 ml), and extracted with light petroleum (2 × 50 ml). In some experiments ferrocenylmethanol was recovered from the organic layer. The aqueous layer was made alkaline with sodium carbonate, and was then extracted with light petroleum (2 × 100 ml). Evaporation of the petroleum solution afforded the crude product, which was purified as necessary (after assay by t.l.c.) by crystallization, preparative t.l.c., or column chromatography on silica gel. Further details of solvents and yields are given in Table 1. Amines prepared by the general procedure were (a) N-*t*-*butylferrocenylmethylamine*, which crystallized from hexane as orange plates, m.p. 60—62° (Found: C, 66.1; H, 7.9; N, 5.05. $C_{15}H_{21}FeN$ requires C, 66.4; H, 7.8; N, 5.2%), δ 1.1 (9 H, s, Bu^t), 3.3 (2 H, s, FcCH_2), 3.9br (1 H, s, NH), and 3.9—4.2 (9 H, m, Fc); *m/e* 271 (M^+, 69%), 214 (27), 200 (18), 199 (100), 186 (23), 178 (14), 149 (16), 128 (18), 122 (11), and 121 (44); (b) N-*ferrocenylmethylpiperidine*, as yellow plates, m.p. 86—87° (lit.,[15] 84—85.5°), δ 2.2 and 1.4 (10 H, 2m, piperidine H), 3.2 (2 H, s, FcCH_2), and 4.0 (9 H, s, Fc); *m/e* 283 (M^+, 87%), 282 (17), 204 (13), 200 (100), 199 (97), 186 (19), 134 (15), 122 (18), 121 (57), and 56 (18); (c) N-*cyclohexylferrocenylmethylamine*, which crystallized from hexane in orange plates, m.p. 35—37° (Found: C, 68.6; H, 8.0; N, 4.7. $C_{17}H_{23}FeN$ requires C, 68.6; H, 7.7; N, 4.7%), δ 1.2 and 1.7 (11 H, 2m, cyclohexyl), 2.4br (1 H, m, NH), 3.5 (2 H, s, FcCH_2), and 4.1 (9 H, m, Fc); *m/e* 297 (M^+, 74%), 296 (13), 295 (11), 200 (46), 199 (100), 186 (15), 149 (12), 127 (24), 122 (10), 121 (42), 99 (20), 57 (11), 56 (98), and 55 (11); (d) N-*benzylferrocenylmethylamine*, as a yellow oil (Found: C, 71.0; H, 6.4; N, 4.6. $C_{18}H_{19}FeN$ requires C, 70.8; H, 6.3; N, 4.6%), δ 1.3br (1 H, s, NH), 3.8 (2 H, s, FcCH_2), 3.9 (2 H, s, PhCH_2), 3.9—4.2 (9 H, m, Fc), and 7.1 (5 H, s, Ph); *m/e* 305 (M^+, 100%), 200 (53), 199 (46), 186 (14), 152 (10), 148 (18), 147 (10), 121 (45), 106 (22), 91 (27), and 56 (18); (e) N-*phenylferrocenylmethylamine*, as yellow plates, m.p. 84—85° (lit.,[16] 85—86°), δ 3.5br (1 H, s, NH), 3.9 (2 H, s, FcCH_2), 4.0—4.3 (9 H, m, Fc), and 6.4—7.2 (5 H, m, Ph); *m/e* 291 (M^+, 49%), 200 (18), 199 (100), 121 (43), and 56 (14); (f) N-*p*-*nitrophenylferrocenylmethylamine*, m.p. 148—150° (lit.,[17] 143.5—145.5°) (Found: C, 60.5; H, 4.8; N, 8.2. Calc. for $C_{17}H_{16}FeN_2O_2$: C, 60.7; H, 4.8; N, 8.3%), δ 4.0—4.3 (9 H, m, Fc), 4.2 (2 H, s, FcCH_2), 4.6br (1 H, s, NH), 6.16 and 8.16 (4 H, 2d, *J* 9 Hz, C_6H_4); *m/e*

336 (M^+, 38%), 200 (13), 199 (76), 139 (10), 138 (100), 121 (12), 108 (29), 92 (42), 80 (12), and 65 (54); (g) N-*p*-methoxyphenylferrocenylmethylamine, m.p. 54—55° (lit.,[17] 53—54°) (Found: C, 67.0; H, 5.9; N, 4.4. Calc. for $C_{18}H_{19}FeNO$: C, 67.3; H, 6.0; N, 4.4%), δ 3.4 (1 H, s, NH), 3.7 (3 H, s, OMe), 3.9 (2 H, s, FcCH_2), 4.0—4.2 (9 H, m, Fc), and 6.4—6.9 (4 H, m, C_6H_4); *m/e* 321 (M^+, 18%), 200 (18), 199 (100), and 121 (33); (h) *ferrocenylmethylurea*, as yellow plates, m.p. 163—164° (Found: C, 55.8; H, 5.4; N, 10.6. $C_{12}H_{14}FeN_2O$ requires C, 55.8; H, 5.5; N, 10.8%), δ 1.6br (2 H, s, NH_2), 2.2br (1 H, s, NH), 4.0—4.4 (9 H, m, Fc), and 4.1 (2 H, s, FcCH_2); *m/e* 258 (M^+, 8%), 241 (30), 216 (17), 215 (100), 214 (15), 213 (13), 199 (17), 186 (15), 163 (33), 150 (10), 149 (30), 137 (52), 129 (10), 122 (20), 121 (38), 97 (18), 95 (16), 93 (14), 85 (13), 83 (20), 81 (35), 78 (18), 73 (17), 71 (16), 69 (69), 57 (30), 56 (25), and 55 (28).

Reactions of Ferrocenylmethanol with Mixtures of Amines.—A mixture of ferrocenylmethanol (0.10 g), aniline (2 g), t-butylamine (2 g), and water (10 ml) was boiled under reflux for 12 h, and the mixture was then worked up by the usual procedure. The only component of the basic fraction was N-phenylferrocenylmethylamine (0.02 g). Ferrocenylmethanol (0.07 g) was recovered from the neutral fraction.

A similar result was obtained when ferrocenylmethanol (0.10 g) was treated in the same way with a mixture of cyclohexylamine and aniline. The only product isolated was N-phenylferrocenylmethylamine.

Reaction of Ferrocenylmethanol with Piperidine in Buffer Solutions.—Piperidine (0.2 g) and ferrocenylmethanol (0.10 g) were added to an appropriate buffer solution (10 ml), and the mixture was stirred at ambient temperature, or boiled under reflux. The maximum variation in the values of pH, which were determined at the commencement and the end of the reaction, was 0.4. The conditions under which each experiment was conducted, and the yields of products isolated by the usual work-up procedure, are summarized in Table 2.

p-(*Ferrocenylmethyl*)*aniline.*—A mixture of p-nitrobenzoylferrocene (0.10 g), lithium aluminium hydride (0.08 g), aluminium trichloride (0.27 g), and ether (10 ml) was stirred overnight at ambient temperature. Ethyl acetate (5 ml) was then added, followed by water (30 ml), and the organic layer was separated. After being washed with water and with aqueous sodium carbonate, the organic layer was evaporated, and the residue, dissolved in ethanol (5 ml) was added to a mixture of hydrazine (0.2 g), platinum oxide (50 mg), and ethanol (10 ml). The mixture was stirred for 12 h, then filtered, and evaporated. Chromatography of the residue on alumina afforded p-(ferrocenylmethyl)aniline, m.p. 112—113° (lit.,[18] 116—117°), δ 3.3br (2 H, s, NH_2), 3.5 (2 H, s, CH_2), 3.9 (9 H, m, Fc), and 6.3—7.0 (4 H, 2d, *J* 9 Hz, C_6H_4); *m/e* 291 (M^+, 100%), 290 (14), 169 (13), 168 (14), 167 (15), 121 (10), and 115 (10).

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