Ferrocene Sutdies. VIII. Pyridoferrocenes (1)

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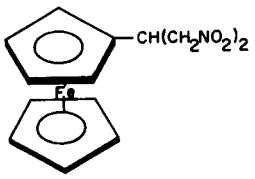
Although a relatively large number of ferrocenes have been prepared in which a heterocyclic system is a substituent on the ferrocene, relatively few ferrocenes exist with a heterocyclic ring fused to one of the rings of the ferrocene (2). In this paper we report on attempts to prepare pyridoferrocenes from ferrocenecarboxaldehyde using classical isoquinoline syntheses that might be applied to benzaldehydes.

The reaction of ferrocenecarboxaldehyde and nitromethane under anhydrous conditions has been reported to give β-nitrovinylferrocene (3,4). We find that the use of 50% sodium hydroxide for the condensation followed by neutralization with cold aqueous acetic acid is more convenient, although the dinitro compound **1** can be obtained if care is not taken to keep the temperature under control. Reduction of β-nitrovinylferrocene with lithium aluminum



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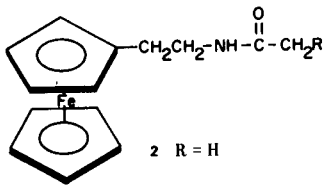
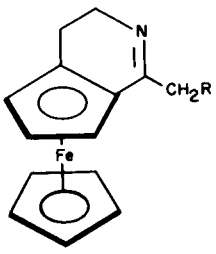


2 R = H

3 R = 3,4-$(CH_3O)_2C_6H_3$

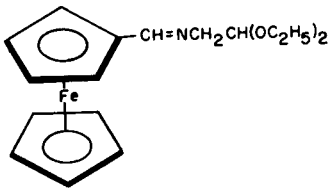
hydride gave β-ferrocenylethylamine which was converted to the *N*-acetyl (**2**) and *N*-(3,4-dimethoxyphenyl)acetyl (**3**) compounds.

Pauson and co-workers (5) have reported the use of phosphorus oxychloride to convert 2 to 5′,6′-dihydro-2′-methylpyrido[3′,4′]ferrocene (**4**). We find that since unreacted starting material can be recovered, polyphosphoric ester (PPE) is more convenient for the preparation of **4**.



4 R = H

5 R = 3,4-$(CH_3O)_2C_6H_3$



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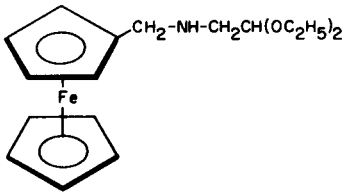
In a similar manner amide **3** was converted to the dihydropyridoferrocene **5**. All attempts to dehydrogenate the dihydro compound **4** failed.

Reaction of ferrocenecarboxaldehyde with aminoacetal gave the imine **6**. An attempt to convert **6** to pyrido[3′,4′]-ferrocene by the Pomeranz-Fritsch synthesis failed using PPA, phosphorus oxychloride, or PPE under a variety of conditions. Reduction of the imine **6** gave the saturated amine **7** which gave only decomposition products on treatment with PPE. Bobbitt (6) has introduced various modi-



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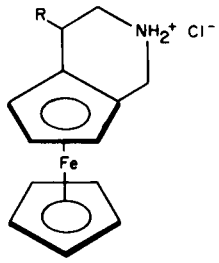

8 R = OH

9 R = H

fications to the Pomeranz-Fritsch reaction and application of methods based on Bobbitt's work to **7** gave tetrahydropyridoferrocenes. Treatment of the hydrochloride of **7** with hydrochloric acid caused cyclization to take place and gave 5′-hydroxy-1′,2′,5′,6′-tetrahydropyrido[3′,4′]ferrocene hydrochloride (**8**). Reductive cyclization of a hydrochloric acid solution of **7** over palladium on carbon gave the tetrahydropyridoferrocene **9**. The mass spectra of **8** and **9** are consistent with the structures indicated and are shown in the Experimental.

EXPERIMENTAL

All melting points were taken in capillaries and are corrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. and by Galbraith Laboratory, Knoxville, Tenn.

β-Nitrovinylferrocene.

A 50% sodium hydroxide solution (14 ml.) was added dropwise to a cooled (0°), well stirred solution of 10 g. of ferrocenecarboxaldehyde and 20 g. of nitromethane in 30 ml. of methanol. After initiation (as evidenced by the formation of the yellow precipitate) an additional 10 ml. of methanol was added. The addi-

tion of base took place over 30 minutes and then the reaction mixture was stirred at 0° for an additional 30 minutes. At this time ice was added to the reaction solution, which was then slowly added to 50% aqueous acetic acid. An immediate neutralization of the excess base took place and also the dehydration of the product as evidenced by formation of a purple precipitate. This purple solid was filtered from the reaction solution within 10 minutes after the addition had been completed. The reaction mixture was stirred and cooled externally and internally throughout the neutralization. The precipitate was washed with distilled water several times and then taken up in benzene and dried over magnesium sulfate. After removal of the solvent, 9.5 g. of purple precipitate resulted. Dry column chromatography of this material on Fluorsil using 10% (by volume) benzene in carbon tetrachloride (increased to 30% benzene in carbon tetrachloride at the end of the elution) gave 6.25 g. (66%) of blue crystalline material, m.p. 138.5° (reported (3,4) m.p. 139-140°), after removal of solvent.

2-Ferrocenyl-1,3-dinitropropane (**1**).

To 20 g. of ferrocenecarboxaldehyde and 40 g. of nitromethane in 100 ml. of methanol was added, dropwise, 28 ml. of 50% sodium hydroxide solution. In this experiment two or three ml. of the sodium hydroxide solution was added at once, thus causing over, heating, and the reaction proceeded very exothermically from this point on. All of the yellow precipitate (sodium salt of the condensation product of the nitromethane and benzaldehyde) was seen to go into solution, with a brown solution being formed. The remaining sodium hydroxide solution was added and the mixture filtered into some glacial acetic acid. A brown precipitate resulted which was filtered and washed with water several times. The precipitate was taken up in benzene and dried over magnesium sulfate. The benzene solvent was removed giving a black tar, which was dissolved in methylene chloride, decolorized (Norite A and Cealite 535), and filtered. "Skellysolve B" was added to the hot solution until a point was reached where one drop more would have cause precipitation of the product. A total of 4.91 g. (17%) of flat golden yellow crystals, m.p. 102-5-104°, were obtained; ν (potassium bromide): 1550, 1445, 1380, 1112, 1010, 850, 825 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}FeN_2O_4$: C, 49.08; H, 4.43; N, 8.80; Fe, 17.55. Found: C, 49.17; H, 4.49; N, 8.77; Fe, 17.49.

β-Ferrocenylethylamine.

Crude β-nitrovinylferrocene (23.22 g.) in a 50% THF-ether solution was added dropwise to 8.0 g. of lithium aluminum hydride in 100 ml. of ether. After the addition was complete the solution was refluxed for 2 hours and then stirred overnight at room temperature. The excess lithium aluminum hydride was destroyed by the consecutive addition of 50 ml. of moist ether, 25 ml. of water, 50 ml. of a 20% sodium hydroxide solution, and 25 ml. of water, until the precipitate agglomerated. The yellow ether solution was then decanted and the agglomerated precipitate washed with several small portions of ether. The organics were then dried over magnesium sulfate and the solvents removed to give a yellow oil which was vacuum distilled at 120-125°/0.5 mm, giving 9.59 g. (50%) of pure amine. ν (neat): 3920, 3375, 3380, 3110, 2930, 2850, 1600 (wide), 1475, 1435, 1415, 1225, 1110, 1045, 1030, 1005, 835 (wide) cm^{-1}.

A picrate was formed having m.p. = 185° dec. (Reported (5) m.p. = 185°).

A hydrochloride, m.p. 233-234°, was formed.

Anal. Calcd. for $C_{12}H_{16}ClFeN$: Cl, 13.35. Found: Cl, 13.31.

5′,6′-Dihydro-2′-methylpyrido[3′,4′]ferrocene (**4**).

β-Ferrocenylethylamine was treated with acetic anhydride in benzene to give a 74% yield of **2**, m.p. 119-120.5° (reported (5) m.p. 117-118°). ν (potassium bromide); 3290, 3090, 2930, 2890, 2850, 1675, 1640, 1560, 1475, 1445, 1375, 1305, 1285, 1230, 1220, 1200, 1115, 1075, 1050, 1025, 1005, 825 cm^{-1}.

N-acetyl-β-ferrocenylethylamine (**2**) (3.0 g.) and 18.0 g. of PPE were combined in 150 ml. of chloroform and heated to reflux temperature for 8 hours. At that time the mixture had developed a deep purple color and the chloroform was removed under vacuum. The purple residue was poured over ice, and after the decomposition of the PPE complex, the aqueous solution was extracted three times with small portions of benzene. The benzene solution was washed with water, dried over sodium sulfate, and the solvent removed giving slightly more than 2 g. of the starting material. The purple aqueous layer was neutralized with a 20% sodium hydroxide solution and extracted with benzene. The organic layer was washed with water and dried over sodium sulfate giving a yellow oil (0.60 g., 25%) which was entirely converted to its picrate (0.240 g. 15.8% yield), m.p. 216° (reported (5) m.p. = 214°); ν (potassium bromide): 3260, 3190, 3100, 3000, 2925, 1625, 1560, 1490, 1435, 1365, 1330, 1320, 1275, 1170, 1115, 1080, 1005 cm^{-1}.

N-(3,4-Dimethoxyphenylacetyl)-β-ferrocenylethylamine (**3**).

To a stirred solution of 6.87 g. (0.03 mole) of the β-ferrocenylethylamine in benzene (100 ml.) was added dropwise 3.22 g. (0.015 mole) of (3,4-dimethoxyphenyl)acetyl chloride. After the addition was complete, the reaction mixture was stirred for 30 minutes and then washed with several small portions of water, and then with a small amount of dilute sodium hydroxide, and dried over magnesium sulfate. The benzene extract yielded 6.27 g. (quantitative) of crude product which was recrystallized from benzene-heptane giving m.p. = 112-113.5°; ν (potassium bromide): 3410, 3100, 3080, 2950, 2910, 2860, 1640, 1610, 1590, 1550, 1520, 1465, 1440, 1425, 1350, 1320, 1265, 1240, 1190, 1160, 1140, 1110, 1050, 1040, 1025, 1005, 960, 880, 825, 810, 790, 770 cm^{-1}.

Anal. Calcd. for $C_{22}H_{25}NO_3Fe$: C, 64.87; H, 6.18. Found: C, 65.00; H, 6.23.

5′,6′-Dihydro-2′-(3,4-dimethoxybenzyl)pyrido[3′,4′]ferrocene (**5**).

One g. of the amide **4** was placed in 10.0 g. of PPE and heated on a steam bath for one hour. The purple solution was poured into ice water and after complete decomposition of the complex, the purple solution was neutralized with a 20% sodium hydroxide solution. The resultant yellow solution was extracted with benzene which was then washed with water, dried with magnesium sulfate, filtered and the solvent removed to give a reddish oil. The oil was then chromatographed on alumina with chloroform; ν (neat): 3090, 2975, 2960, 2920, 2600, 1655, 1590, 1515, 1465, 1420, 1345, 1305, 1270, 1240, 1220, 1170, 1140, 1110, 1075, 1030 (wide), 975, 925, 800-750 (wide) cm^{-1}.

The oil gave a green picrate, m.p. dec. slowly from 145°; ν (potassium bromide): 3400, 3075, 1670, 1630, 1610, 1570, 1555, 1520, 1425, 1370, 1320, 1275, 1225, 1170, 1150, 1115, 1080, 1025, 1005 (shoulder) cm^{-1}.

Anal. Calcd. for $C_{28}H_{26}N_4FeO_9$: N, 9.06. Found: N, 8.85.

N-(Ferrocenylidene)β,β-(diethoxy)ethylamine (**6**).

A mixture of ferrocencarboxaldehyde (25.0 g., 0.128 mole) with aminoacetaldehyde diethylacetal (19.5 g., 0.147 mole) in 1200 ml. of benzene to which 0.05 g. of *p*-toluene sulfonic acid had been added was refluxed for 24 hours during which time water was removed as its azetrope. The solution was then cooled to room temperature, filtered and the benzene removed under vacuum to give 40.9 g. of a crude orange solid. The product was recrystallized from Skellysolve B to give 37.0 g. (96%), m.p. 72.5-

74°; ν (potassium bromide): 2975, 2870, 1650 (C=N), 1140, 1110, 1070, 1010 cm^{-1}.

Anal. Calcd. for $C_{17}H_{23}NO_2Fe$: C, 62.02; H, 7.04; N, 4.25; Fe, 16.97. Found: C, 62.02; H, 6.94; N, 4.31; Fe, 16.89.

N-Ethyl(β,β-diethoxy)aminomethylferrocene Hydrochloride (**7**).

A solution of 80 ml. of absolute ethanol containing 13.17 g. (0.04 mole) of the imine **6** was added to 0.4 g. of platinum oxide which had been prereduced under 40 ml. of the same solvent. The mixture was reduced at room temperature and approximately 7 pounds pressure, until the uptake of hydrogen ceased (6-8 hours). The catalyst was removed by filtration and washed with several small portions of absolute ethanol. The ethanol was removed from the filtrate and washings *in vacuo* to give 12.3 g. of a yellow oil. A hydrochloride was made by passing dry hydrochloric acid through an anhydrous ether solution of the amine giving 14.32 g. (97%) of the hydrochloride, m.p. 159-160°, from *n*-butanol; ν (potassium bromide): 3400 (NH), 3100, 2975, 2940, 2770 to 2490 (series of strong peaks), 1585, 1480, 1450, 1425, 1400, 1380, 1375, 1320, 1250, 1200.

Anal. Calcd. for $C_{17}H_{26}NClO_2Fe$: C, 55.53; H, 7.13; N, 3.81. Found: C, 55.44; H, 7.17; N, 3.72.

5'-Hydroxy-1',2',5',6'-tetrahydropyrido[3',4']ferrocene Hydrochloride (**8**).

Five g. of *N*-ethyl(β,β-diethoxy)aminomethylferrocene hydrochloride (7·HCl) were dissolved in enough of a 50:50 (vol.) mixture of 6*N* hydrochloric acid and dioxane mixture to accomplish solution. After 12 hours at room temperature, the solution was cooled and a greenish yellow solid filtered. Recrystallization from methanol-water gave a solid which did not melt, but darkened slowly to 300°; ν (potassium bromide): 3300, 3050, 1615, 1455, 1445, 1420, 1395, 1330, 1290, 1280, 1248, 1109, 1090, 1053, 1027, 1005, 998, 975, 935, 900, 860, 840, 820 cm^{-1}. Mass spectrum: 257 (100%), 255 (10); 240 (10), 239 (18), 238 (10), 229 (12), 228 (62), 227 (10), 200 (40), 199 (20), 174 (10), 173 (20), 134 (34), 133 (16), 122 (12), 121 (58), 119 (16), 118 (76), 117 (50), 91 (24), 90 (12), 89 (14), 77 (20), 66 (78), 65 (46), 63 (12), 56 (52), 54 (4), 36 (42).

Anal. Calcd. for $C_{13}H_{16}NClOFe$: C, 53.18; H, 5.49; N, 4.77; Cl, 12.08. Found: C, 53.09; H, 5.47; N, 4.48; Cl, 12.02.

1',2',5',6'-Tetrahydropyrido[3',4']ferrocene Hydrochloride (**9**).

Five g. of the amine **7** was dissolved in 100 ml. of 6*N* hydrochloric acid, washed with 50 ml. of ether, and allowed to stand for about 15 hours. Two of 5% Pd/C were added and the solution was reduced at room temperature and 7 pounds pressure until hydrogenation ceased (about 4-6 hours). The catalyst was removed by filtration and the solution brought to a basic *p*H by the slow addition of 20% sodium hydroxide solution. The yellow oily free amine was extracted with benzene. The benzene solution was washed with several small portions of water and dried over magnesium sulfate. The solvent was removed giving a yellow oil which was placed in ether and dry hydrogen chloride gas added. The resultant hydrochloride precipitate was filtered from the solution, washed with several small portions of ether and recrystallized from *n*-butanol, and dried, giving m.p. 204-206°, with darkening from 160° ; ν (potassium bromide): 3400, 3060, 2940, 2730, 2615, 2500, 2440, 1580, 1480, 1460, 1450, 1430, 1410, 1380, 1370, 1310, 1295, 1110, 1060, 1035, 1001, 879, 860, 801, 675 cm^{-1}; 241 (100%), 240 (19), 239 (13), 214 (5), 213 (27), 212 (69), 175 (12), 173 (26), 148 (8), 121 (51), 120 (21), 119 (9), 118 (39), 117 (44), 91 (31), 65 (13), 56 (37), 54 (2), 36 (26).

Anal. Calcd. for $C_{13}H_{16}NClFe$: C, 56.25; H, 5.81; N, 5.05. Found: C, 56.21; H, 5.91; N, 4.96.

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(2) See F. D. Popp and E. B. Moynahan, *Adv. Heterocyclic Chem.*, 13, 1 (1971) for comprehensive review of both types of heterocyclic ferrocenes.

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(6) See J. M. Bobbitt, *Adv. Heterocyclic Chem.*, 15, 99 (1973) for leading references.