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Journal of Organometallic Chemistry 692 (2007) 791–800
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis, characterization and crystal structures of boron-containing intermediates in the reductive amination of ferrocenecarboxaldehyde to a bis(ferrocenylmethyl) amine

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Received 3 August 2006; received in revised form 8 October 2006; accepted 8 October 2006
Available online 14 October 2006

Abstract

Reaction of ferrocenecarboxaldehyde with aqueous methylamine leads to [(methylimino)methyl]ferrocene, which is reduced to *N*-(ferrocenylmethyl)-*N*-methylamine by $NaBH_4$. This amine reacts with ferrocenecarboxaldehyde and $NaCNBH_3$ to give the tertiary ammonium salt, di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride. Hydrolysis of the $NaCNBH_3$ reaction mixture produces the free amine, di(*N*-(ferrocenylmethyl))-*N*-methylamine. Thermolysis of di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride in refluxing tetrahydrofuran converts it to the cyanoborane adduct, di(*N*-ferrocenylmethyl)-*N*-methylamine–cyanoborane, with elimination of H_2. The new compounds are fully characterized by using spectroscopic and physical methods, including X-ray crystal structure determinations of di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride, di(*N*-(ferrocenylmethyl))-*N*-methylamine, and di(*N*-(ferrocenylmethyl))-*N*-methylamine–cyanoborane.

Keywords: Ferrocene; Reductive amination; Ammonium cyanoborohydride; Amine–cyanoborane adduct; X-ray crystal structure; NMR spectroscopy

1. Introduction

The stability, low cost and reversible redox activity of ferrocene have led to widespread applications of ferrocene monomers, oligomers, and polymers, e.g., as catalysts for organic synthesis [1–7], in conducting polymers [8,9], in photoinduced electron-transfer systems [10], as electron-transfer mediators [11] and as metal scavengers [12]. The stability of ferrocenes in aqueous, aerobic media has made them ideal for applications in biological systems, with ferrocene derivatives of amino acids, carbohydrates, DNA, and hormones being thoroughly investigated [13].

Biot and co-workers recently reported that the reductive amination of 1,2-ferrocenedicarboxaldehyde with aminoquinolines gives aza-[3]-1,2-ferrocenophanes [14] (Scheme 1). These results indicated that a five-membered ring containing a nitrogen atom can be closed under mild conditions ($NaCNBH_3$ at room temperature) on the 1,2-positions of a cyclopentadienyl ligand. We are interested in the formation of conducting polymers that incorporate cyclopentadienyl metal centers fused to polyheterocycle backbones, e.g., poly(ferroceno[*c*]pyrrole) (Scheme 2), in which the ferrocene could act as a redox ''switch'' to reversibly dope the polymer.

Polymers that incorporate ferrocene often show enhanced conductivities [15,16]. If unsubstituted at the 2,5-pyrrole positions, a ferroceno[*c*]pyrrole would be susceptible to electrochemical polymerization [17]. Thus, Biot's synthesis could lead to monomers amenable to oxidative polymerization after oxidation of the pyrrolidine to a pyrrole [18–22]. Our interest in organometallic heterocycles [23–28] has led us to study the scope of the reductive amination of ferrocenyl aldehydes.

Reductive amination of ferrocenecarboxaldehyde [29] has received surprisingly little study. Biot and co-workers

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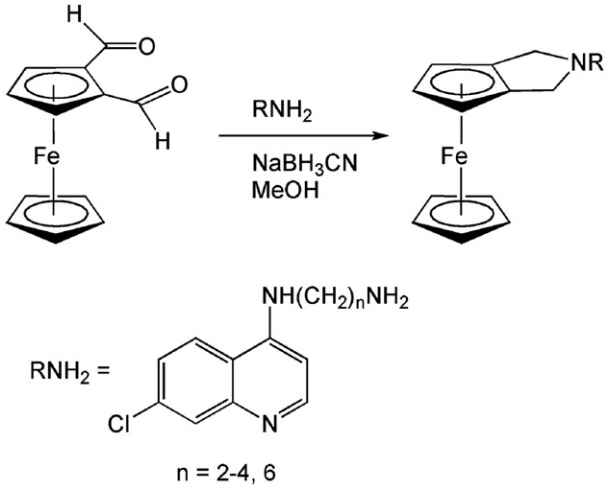
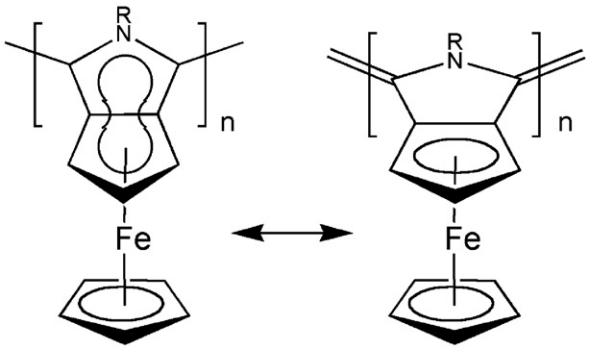
doi:10.1016/j.jorganchem.2006.10.015



Scheme 1. Synthesis of aza-[3]-ferrocenophanes from 1,2-ferrocenecarboxaldehyde [14].



Scheme 2. Target poly(ferroceno[*c*]pyrrole).

attributed low yield (32%) of their fused-ring product to a substantial amount of by-products due to the long reaction times needed for complete conversion to the fused-ring product [14]. We reasoned that a study of the individual steps in reductive amination, employing the simpler methylamine, could lead to a higher yield and better control over the reaction. We report here a study of a simple starting point, reductive amination of ferrocenecarboxaldehyde with methylamine, which leads to a surprisingly rich range of products.

2. Experimental

2.1. General procedures

Reactions were carried out by using standard Schlenk techniques under nitrogen. Ferrocenecarboxaldehyde (**1**) was prepared according to Rosenblum et al. [29]. Aqueous methylamine (Aldrich), $NaBH_4$ (Merck), $NaCNBH_3$ (Aldrich), ethanol (Aaper), and deuterated solvents (Cambridge Isotopes) were used without further purification. Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl and distilled under nitrogen. Proton and carbon NMR spectra were obtained on Varian Gemini 200 or Varian VXR-400 NMR spectrometers. Infrared spectra were obtained on a Mattson Galaxy Series FTIR 5000. Melting points are uncorrected. Elemental analyses were performed at the University of Illinois, Urbana. Mass spectra were collected at the University of Kentucky Mass Spectrometry Center.

Data were collected at 90 K on a Nonius KappaCCD diffractometer. The crystals on which data were collected were typical of the others in the batch, which had been grown by slow evaporation from solvent at room temperature. Crystals were mounted on glass fibers with Paratone N oil. The main programs used were DENZO-SMN to obtain cell parameters and for data reduction, SCALEPACK for absorption correction [30], SHELXS-97 for structure solution and SHELXL-97 for refinement. Hydrogen atoms were placed in geometrically calculated positions. Two independent molecules in the asymmetric unit of **4** refined satisfactorily with essentially identical geometries. The structure of **5** has disordered cyclopentadienyl rings that refined satisfactorily in two orientations: C7–C11 with occupancies 0.471(15) and 0.529(15), and C18–C22 with occupancies 0.534(15) and 0.466(15). No complications were encountered in the solution or refinement of **6**.

2.2. Synthesis of [(methylimino)methyl]ferrocene (2)

In a 25-mL round-bottom flask, ferrocenecarboxaldehyde (522 mg, 2.43 mmol) was added to a stirred solution of 40% aqueous methylamine (10 mL) at 0 °C. The solution was allowed to warm to room temperature and stir for 2 h. The reaction mixture was washed with ethyl ether (4×20 mL) and the combined ether extracts were dried over $MgSO_4$. The volatiles were removed in vacuo to give **2** (460 mg, 83.2%) as a deep red, crystalline solid. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 3.32 (d, 3H, $^4J = 1.2$ Hz, Me), 4.16 (s, 5H, Cp), 4.33 (t, 2H, $^3J = 2.0$ Hz, C_4H_5), 4.59 (t, 2H, $^3J = 2.0$ Hz, C_4H_5), 8.10 (br s, 1H, CH).

2.3. Synthesis of N-(ferrocenylmethyl)-N-methylamine (3)

In a 50-mL Schlenk flask, **2** (480 mg, 2.11 mmol) was added to a suspension of $NaBH_4$ (200 mg, 5.29 mmol) in 25 mL of ethanol. The solution immediately turned yellow-orange and was allowed to stir for 2 h at room temperature. The volatiles were removed in vacuo and the product was extracted with ethyl ether (3×30 mL). The combined ether extracts were washed with water and dried over $MgSO_4$. The volatiles were removed in vacuo to give **3** (390 mg, 80.5%) as a yellow-orange oil. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 0.85 (br s, 1H, NH), 2.43 (s, 3H, CH_3), 3.46 (s, 2H, CH_2), 4.08 (m, 2H, C_4H_5), 4.10 (s, 5H, Cp), 4.16 (m, 2H, C_4H_5).

2.4. Synthesis of di(N-(ferrocenylmethyl))-N-methylammonium cyanoborohydride (4)

In a 125-mL Schlenk flask, **3** (370 mg, 1.61 mmol) and $NaCNBH_3$ (152 mg, 2.43 mmol) were added to a stirred solution of ferrocenecarboxaldehyde (**1**, 517 mg, 2.38 mmol) in 40 mL of ethanol. The dark red solution was allowed to stir at room temperature for 2 h. The volatiles were removed in vacuo and the product was isolated by chromatography with a thin pad of silica and ethyl ether. The product was eluted with acetone and the volatiles were removed in vacuo to give **4** (290 mg, 39.6%) as a yellow-orange solid. Slow recrystallization from ethyl ether at room temperature in air gave orange, single crystals. M.p.: 158–159 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 1.55 (br s, 1H, NH), 2.30 (s, 3H, Me), 3.82 (s, 4H, CH_2), 4.16 (s, 10H, Cp), 4.29–4.31 (m, 8H, C_4H_5). ^{13}C NMR (50 MHz, CD_2Cl_2, ppm): δ 37.7 (Me), 55.6 (CH_2), 69.5 (CN), 69.8 (Cp), 70.8 (C_4H_5), 71.8 (C_4H_5), 74.0 (C_4H_5). IR (KBr, cm^{-1}): 3442 (NH), 2335 (BH_2), 2175 (CN). MS (MALDI-TOF): *m/z* 453 (M^+-Me), 427 (M^+-BH_3CN). Anal. Calc. for $C_{24}H_{29}N_2BFe_2$: C, 61.59; H, 6.25; N, 5.99. Found: C, 60.94; H, 6.15; N, 6.00%.

2.5. Synthesis of di(N-(ferrocenylmethyl))-N-methylamine (5)

Di(*N*-(ferrocenylmethyl))-*N*-methylamine was synthesized by the same procedure as **4** (employing 349 mg of **3**) only with a slight modification in the workup. The reaction solution was washed with water (3×30 mL) and the volatiles were removed in vacuo. The product was isolated by chromatography with a thick pad of silica with 50/50 hexanes/ethyl ether. The product was eluted with ethyl ether and the volatiles were removed in vacuo to give **5** (90 mg, 13.8%) as an orange solid. Slow recrystallization from hexanes at room temperature in air gave orange, single crystals. M.p.: 68–69 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.05 (s, 3H, Me), 3.33 (s, 4H, CH_2), 4.08 (10H, s, Cp), 4.09 (m, 4H, C_4H_5), 4.15 (m, 4H, C_4H_5). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, ppm): δ 41.2 (Me), 56.4 (CH_2), 68.1 (C_4H_5), 68.7 (Cp), 70.4 (C_4H_5), 83.5 (C_4H_5). IR (KBr, cm^{-1}): 1631, 1611 (Cp). MS (EI): *m/z* 427 (M^+). Anal. Calc. for $C_{23}H_{25}NFe_2$: C, 64.67; H, 5.90; N, 3.28. Found: C, 64.44; H, 5.87, N, 3.36%.

2.6. Synthesis of di(N-(ferrocenylmethyl))-N-methylamine–cyanoborane (6)

In a 125-mL Schlenk flask, **4** (80.0 mg, 0.171 mmol) was added to 40 mL of THF. The solution was allowed to reflux overnight. The reaction was allowed to cool to room temperature and the volatiles were removed in vacuo. The product was isolated by chromatography with a thin pad of silica and ethyl ether as eluent. The ether layer was collected and the volatiles were removed in vacuo to give **6** (38.6 mg, 48.5%) as a yellow-orange powder. Slow recrystallization from ethyl ether at room temperature in air gave yellow, single crystals. M.p.: 163–164 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.26 (s, 3H, Me), 3.78 (s, 4H, CH_2), 4.17 (10H, s, Cp), 4.29–4.42 (m, 8H, C_4H_5). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, ppm): δ 45.5 (Me), 60.8 (CH_2), 66.9 (CN), 69.8 (Cp), 70.8 (C_4H_5), 73.4 (C_4H_5), 76.1 (C_4H_5). IR (KBr, cm^{-1}): 2424 (CN), 2384, 2330 (BH), 1633 (Cp). MS (EI): *m/z* 466 (M^+), 427 (M^+-BH_2CN). Anal. Calc. for $C_{24}H_{27}N_2BFe_2$: C, 61.86; H, 5.84; N, 6.01. Found: C, 62.26; H, 5.99; N, 5.39%.

3. Results

3.1. Synthesis of bis(ferrocenylmethyl)amines

Reaction of ferrocenecarboxaldehyde (**1**) [29] with 40% aqueous methylamine, starting at 0 °C followed by warming to room temperature, led to [(methylimino)methyl]ferrocene (**2**) in 82.3% yield (Scheme 3). The imine **2** was reduced with excess $NaBH_4$ in ethanol (2 h, room temperature) to give *N*-(ferrocenylmethyl)-*N*-methylamine (**3**) in 80.5% yield. Methylamine **3** reacted with 1.5 equivalents of ferrocenecarboxaldehyde in a suspension of $NaCNBH_3$ in ethanol under mild conditions to give the tertiary ammonium salt, di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride (**4**), in moderate yield (39.6%). Adding a water wash to the workup led to the free amine, di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**), in 13.8% yield. Conversion of the salt **4** to the cyanoborane adduct, di(*N*-ferrocenylmethyl)-*N*-methylamine–cyanoborane (**6**) with elimination of H_2 was accomplished in 48.5% yield by refluxing the salt **4** in THF for 18 h. The reactions are summarized in Scheme 3.

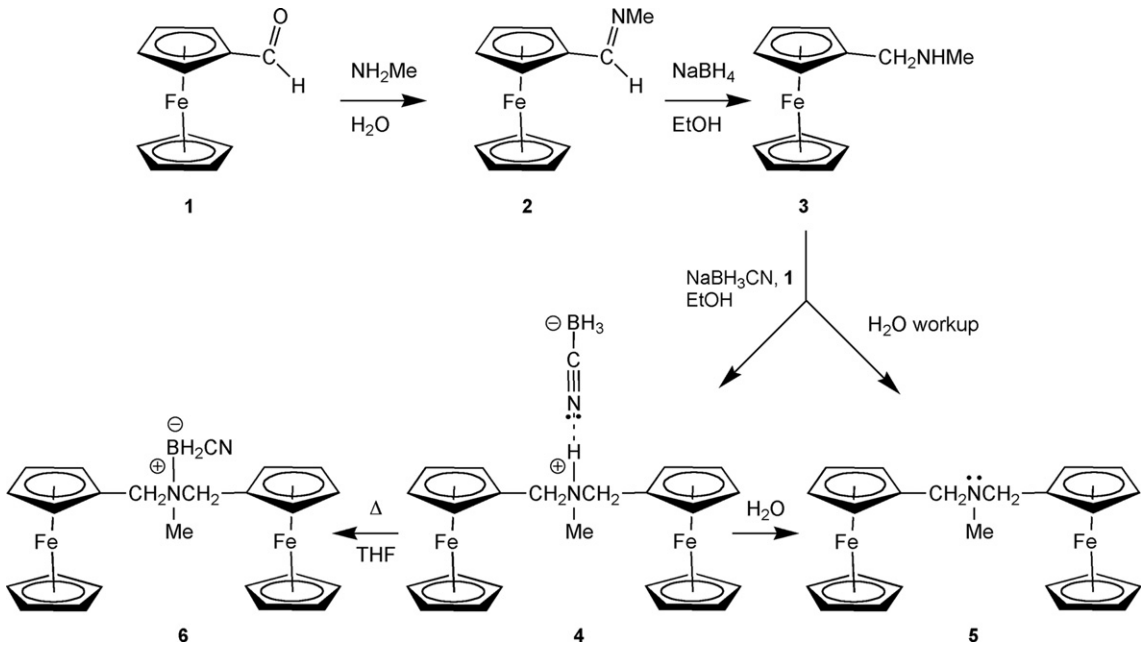
3.2. Spectroscopic and crystallographic characterization

New compounds, di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride (**4**), di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**), and di(*N*-(ferrocenylmethyl))-*N*-methylamine–cyanoborane (**6**), were fully characterized by using spectroscopic and physical methods, including ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry and elemental analysis. The structures of **4**–**6** were determined by X-ray crystallographic methods (Figs. 1–3 and Tables 1 and 2) [31]. Significant features are discussed below.

4. Discussion

4.1. Synthesis

Our interest in generalizing the preparation of aza-[3]-1,2-ferrocenophanes via the double reductive amination of 1,2-ferrocenedicarboxaldehyde (Scheme 1) led us to reexamine the reductive amination of the more readily available ferrocenecarboxaldehyde (**1**) to *N*-(ferrocenylmethyl)-*N*-methylamine (**3**). Subsequent reductive amination



Scheme 3. Synthesis of di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride (**4**), di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**) and di(*N*-(ferrocenylmethyl))-*N*-methylamine–cyanoborane (**6**).

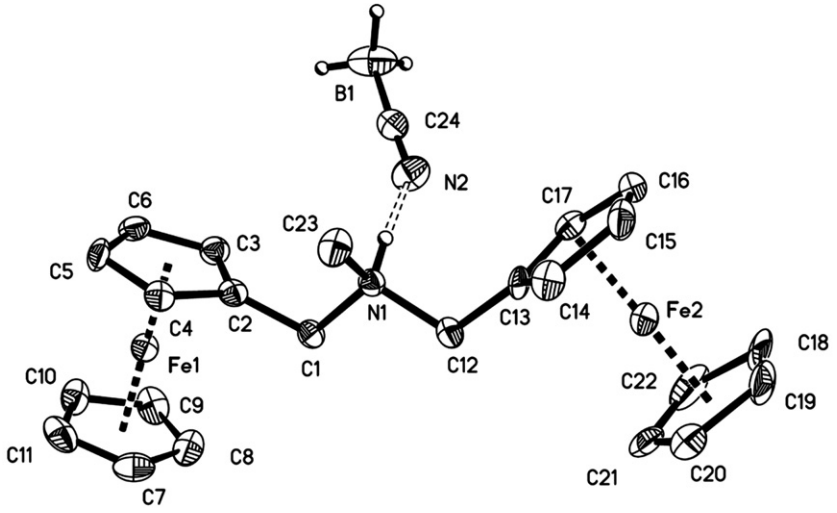


Fig. 1. Molecular structure of di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride (**4**) plotted with 50% probability ellipsoids.

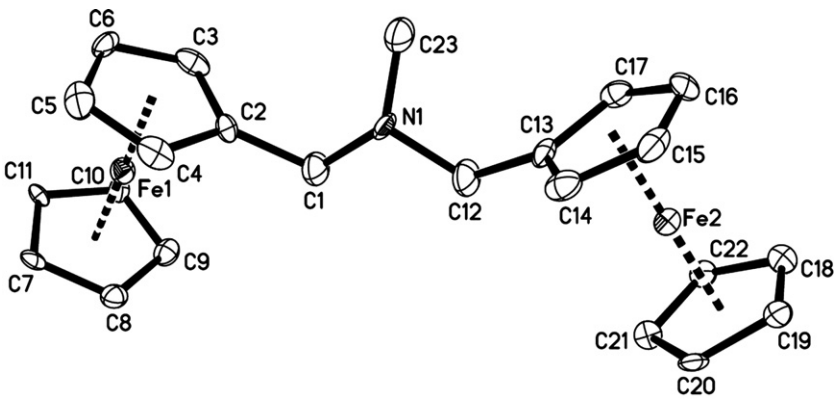


Fig. 2. Molecular structure of di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**) plotted with 50% probability ellipsoids.

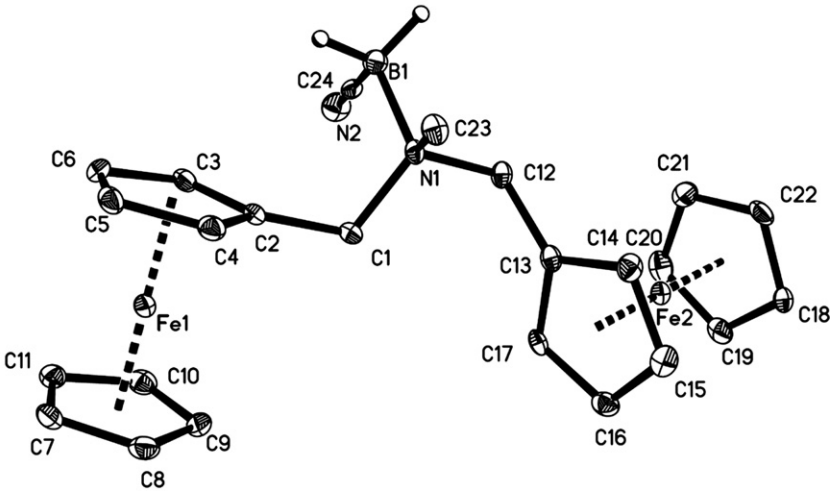


Fig. 3. Molecular structure of di(*N*-(ferrocenylmethyl))-*N*-methylamine–cyanoborane (**6**) plotted with 50% probability ellipsoids.

Table 1
Crystal data and structure refinement for compounds **4**, **5**, and **6**

Compound	**4**	**5**	**6**
Formula	$C_{24}H_{29}BFe_2N_2$	$C_{23}H_{25}Fe_2N$	$C_{24}H_{27}BFe_2N_2$
Formula weight (amu)	468.00	427.14	465.99
T (K)	90(2)	90(2)	90(2)
Crystal system	Triclinic	Orthorhombic	Triclinic
Space group	$P\bar{1}$	$P2_12_12_1$	$P\bar{1}$
Z	4	4	2
a (Å)	8.8296(2)	5.73420(10)	10.3376(2)
b (Å)	13.9010(4)	11.4496(3)	10.7913(2)
c (Å)	18.5772(5)	28.5815(9)	11.5755(2)
α (°)	92.3961(11)	90	106.2742(8)
β (°)	91.0359(11)	90	107.8493(8)
γ (°)	103.2296(11)	90	110.9530(8)
V (Å^3)	2216.82(10)	1876.50(8)	1031.60(3)
D_{calc} (Mg/m^3)	1.402	1.512	1.500
F(000)	976	888	484
Crystal size (mm^3)	$0.28 \times 0.22 \times 0.15$	$0.20 \times 0.15 \times 0.15$	$0.10 \times 0.10 \times 0.08$
Radiation	Mo Kα ($\lambda = 0.7107$ Å)	Mo Kα ($\lambda = 0.7107$ Å)	Mo Kα ($\lambda = 0.7107$ Å)
Monochromator	Graphite	Graphite	Graphite
Absorption coefficient μ (mm^{-1})	1.321	1.55	1.419
Diffractometer	NONIUS KappaCCD	NONIUS KappaCCD	NONIUS KappaCCD
2θ Range (°)	1.10–25.00	1.42–27.45	2.06–27.47
Limiting indices	$-10 \leqslant h \leqslant 10$, $-16 \leqslant k \leqslant 16$, $-22 \leqslant l \leqslant 22$	$-7 \leqslant h \leqslant 7$, $-14 \leqslant k \leqslant 14$, $-36 \leqslant l \leqslant 36$	$-13 \leqslant h \leqslant 13$, $-13 \leqslant k \leqslant 13$, $-15 \leqslant l \leqslant 15$
Reflections collected	15013	4271	23773
Independent reflections (R_{int})	7829 (0.0424)	4271 (0.0000)	4717 (0.0528)
Absorption correction	Semi-empirical from equivalents	None	Semi-empirical from equivalents
Refinement program	SHELX-97	SHELX-97	SHELX-97
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	7829/0/527	4271/160/328	4717/0/263
Goodness-of-fit on F^2	1.154	0.969	1.036
Absolute structure (Flack) parameter	–	−0.007(30)	–
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0621$, $wR_2 = 0.1396$	$R_1 = 0.0534$, $wR_2 = 0.0727$	$R_1 = 0.0351$, $wR_2 = 0.0735$
R indices (all data)	$R_1 = 0.0878$, $wR_2 = 0.1480$	$R_1 = 0.1296$, $wR_2 = 0.0899$	$R_1 = 0.0566$, $wR_2 = 0.0815$
Largest difference in peak and hole (e Å^{-3})	1.004 and −0.603	0.550 and −0.539	0.707 and −0.398

of a second equivalent of **1** with the amine **3** to give di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**) is similar to the ring closure that results in an aza-[3]-1,2-ferrocenophane. Close examination of the reductive amination of **1** led to the isolation of several interesting boron-containing intermediates.

Table 2
Selected bond distances (Å) and angles (°) for **4**–**6**

	4	**5**	**6**
Fe–C (av)	2.040(9)	2.05(2)	2.046(8)
N1–C1	1.521(7), 1.514(7)	1.466(5)	1.523(3)
N1–C12	1.502(8), 1.505(7)	1.471(5)	1.521(3)
N1–C23	1.489(7), 1.497(7)	1.472(6)	1.491(3)
N2–C24	1.159(8), 1.146(8)	–	1.146(3)
B1–N1	–	–	1.619(3)
B1–C24	1.549(11), 1.575 (10)	–	1.599(3)
C1–C2	1.487(8), 1.484(8)	1.499(6)	1.492(3)
C12–C13	1.478(8), 1.487(8)	1.489(6)	1.496(3)
C–C(Cp, av)	1.42(1)	1.42(1)	1.424(5)
C23–N1–C12	112.5(5), 111.8(4)	109.0(4)	109.35(17)
C23–N1–C1	112.5(5), 112.5(4)	111.6(4)	109.78(17)
C12–N1–C1	109.0(4), 109.5(4)	107.9(3)	108.82(16)
C1–N1–B1	–	–	113.45(17)
C23–N1–B1	–	–	107.62(17)
C24–N1–B1	–	–	107.88(18)
C12–N1–B1	–	–	107.73(16)
C2–C1–N1	113.4(5), 112.9(5)	113.2(4)	112.81(17)
C4–C2–C1	125.6(6), 126.3(5)	127.0(5)	127.5(2)
C3–C2–C1	126.8(6), 126.3(5)	126.8(5)	125.3(2)
C13–C12–N1	112.0(5), 113.1(5)	113.8(4)	116.76(17)
C14–C13–C12	127.3(5), 126.2(5)	126.6(5)	127.1(2)
C17–C13–C12	126.1(6), 125.6(6)	127.3(5)	125.2(2)
N2–C24–B1	177.8(8), 178.5(6)	–	179.7(3)
Cp–Fe1–Cp′	177.9(3), 177.8(3)	177.6(5), 175.8(5)	178.5(1)
Cp–Fe2–Cp′[a]	178.7(3), 179.2(3)	179.7(5), 177.7(5)	179.0(1)
C–C–C (Cp, av)[a]	108.0(6)	108.0(10)	108.0(4)

[a] Cp and Cp′ are cyclopentadienyl ring centroids.

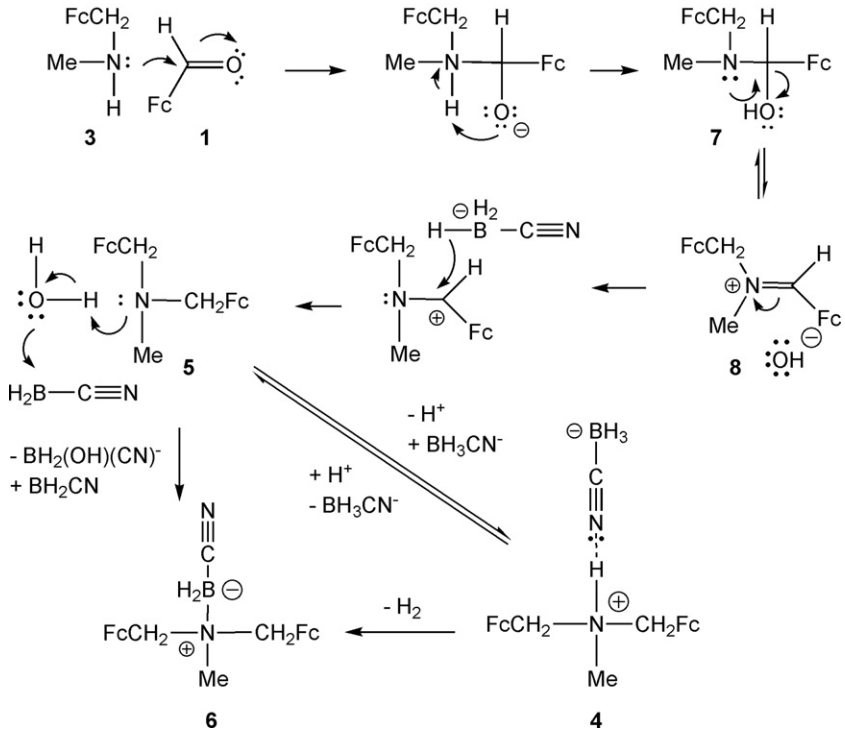
Myer and Allen reported the synthesis of *N*-(ferrocenylmethyl)-*N*-methylamine (**3**) in 56% yield via the in situ formation of [(methylimino)methyl]ferrocene (**2**) from ferrocenecarboxaldehyde (**1**) and methylamine hydrochloride, followed by reduction with $NaCNBH_3$ [32]. Cully and Watts reported the similar formation of $[Fe\{C_5H_4(CH_2NH_2Me)\}(Cp)][PF_6]$ from $MeNH_2$–$AlCl_3$ and aq. NH_4PF_6, followed by deprotonation with diethylamine to give the imine **2** [33]. Al-Najjar and co-workers prepared **2** by reacting **1** in refluxing benzene with methylamine liberated from aqueous methylamine hydrochloride by KOH [34]. Although we were unable to reproduce this last result, we found that **1** is most simply converted to **2** in 83.2% yield by stirring it in 40% aqueous methylamine (Scheme 3). The crude methylimine **2** varied from a crystalline solid to a thick oil, but attempted purification of the oil via silica chromatography led to hydrolysis back to **1**. Regardless of its physical state, **2** so obtained is pure enough for further reactions.

Methylimine **2** is reduced to the corresponding amine **3** in 80.5% yield by $NaBH_4$ in ethanol at room temperature (Scheme 3). The overall 69.8% conversion of the aldehyde **1** to the methylamine **3** improves on the one-step method of Myer and Allen. The amine is not stable to chromatography on silica, but is pure by ^1H NMR.

Reductive amination of a second equivalent of ferrocenecarboxaldehyde (**1**) with *N*-(ferrocenylmethyl)-*N*-methylamine (**3**) is analogous to the closure step in formation of an aza-[3]-1,2-ferrocenophane. The primary product of reductive amination of **1** with **3** and $NaCNBH_3$ is the unexpected salt, di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride (**4**), isolated in 39.6% yield (Scheme 3). The nature of the cyanoborohydride salt **4** was indicated by its low solubility in ethyl ether as well as the presence of BH and CN stretches (2335 and 2175 cm^{-1}, respectively) in its IR spectrum. Further characterization including MS, EA, and X-ray crystallographic analysis confirmed the identity of **4**.

Di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**) was obtained in low yield (13.8%) from the same reaction that gave **4** by including a water wash in the workup (Scheme 3). The salt **4** also converts to the amine **5** upon prolonged exposure to silica gel/dichloromethane. The amine **5**, unlike **4**, is very soluble in hexanes; it was fully characterized spectroscopically and by using X-ray crystallography.

Along with the cyanoborohydride salt **4**, we obtained a second product in very low yield from the attempted one-pot reductive amination of **1** with aqueous methylamine and $NaCNBH_3$ in ethanol at room temperature. X-ray crystallography revealed its structure as the amine–borane adduct, di(*N*-(ferrocenylmethyl))-*N*-methylamine–cyanoborane (**6**). We believe that compound **6** forms from a secondary reaction of the salt **4**. Initial attempts to form the cyanoborane **6** by thermolysis of solid **4** at 80 °C and



Scheme 4. Mechanism for the formation of **4**–**6**.

1 atm failed, giving an intractable mixture that included **4** and **5**. Heating the salt **4** in refluxing tetrahydrofuran for 18 h, similar to conditions used by Spielvogel et al. to prepare amine–BH_2CN from amine hydrochlorides and $NaCNBH_3$ [35] gave cyanoborane **6** in 45.8% yield (Scheme 3). Loss of H_2 was confirmed by mass spectrometry ($M^+ = 466$) as well as X-ray crystallographic analysis. Similar amine-borane adducts have pharmaceutical applications, displaying anti-cancer, anti-inflammatory, and anti-osteoporotic properties [36–39].

Scheme 4 depicts a mechanism for the formation of **4**–**6**, based in part on the work of Boga et al. [40] and Biot and co-workers [14]. Addition of methylamine **3** to aldehyde **1** gives an aminol (**7**). Equilibrium loss of hydroxide generates an iminium ion (**8**), which adds hydride from BH_3CN^- to give the amine **5**. Association of the liberated BH_2CN with water may provide the proton that forms the ammonium ion of **5**, which associates with BH_3CN^- to give the salt **4**. Deprotonation of **4** during the aqueous workup leads to the isolation of the free amine **5**. During the thermolysis of **4**, attack of BH_3CN^- on ammonium proton releases H_2, followed by association of **5** with the evolved cyanoborane to give the amine–borane adduct **6**.

The low yield of di(ferrocenylmethyl)methylamine (**5**) compared to Biot's 34% yield of 2-aza-[3]-1,2-ferrocenophane from 1,2-ferrocenedicarboxaldehyde is initially surprising, but is consistent with transition state theory [41]. Biot's substrate with aldehyde and amine held in local proximity has limited translation and rotation degrees of freedom. Our intermolecular amination, as opposed to Biot's intramolecular version, is not subject to these same restraints. Therefore, the greater decrease in entropy for the transition state of the intermolecular reaction compared to the intramolecular reaction predicts more rapid formation of aza-[3]-1,2-ferrocenophane than of di(ferrocenylmethyl)methylamine **5**.

A further complication in the formation of **4** and **5** is the competing reduction of ferrocenecarboxaldehyde (**1**) to ferrocenylmethanol, which was observed by ^1H NMR in the crude reaction mixture. Delaying the addition of reducing agent to the reaction mixture to allow for formation of the aminol intermediate **7** failed to produce higher yields of the salt **4**. The greatest yield of **4** was obtained by using an excess (1.5 equivalents) of **1**. As Boga suggested, the aminol **7** and iminium ion **8** exist in equilibrium (Scheme 4), and a hydride source must be present to convert the iminium ion **8** to the amine **5**. The low yield of the amine **5** may be due to decomposition during workup.

4.2. Spectroscopic characterization

All new compounds were fully characterized by spectroscopic methods. Table 3 lists selected ^1H and ^{13}C NMR data for compounds **2**–**6**.

Notable features of the ^1H NMR spectrum of methylimine **2** are resonances from methyl (δ 3.32, d, $^4J = 1.2$ Hz), imine (δ 8.10) broadened by the ^{14}N quadrupole, and substituted cyclopentadienyl (AA′BB′ at δ 4.59 and 4.33) groups [33]. For the methylamine **3**, the methyl (δ 2.43) and substituted cyclopentadienyl hydrogens (δ 4.08 and 4.10) shift to high field, and resonances for methylene (δ 3.46) and amine (δ 0.85, broad) appear [32].

Table 3
Selected ^{1}H and ^{13}C NMR Data (in $CDCl_3$) for **2–6**

Compound	δ_H (ppm)					δ_C (ppm)				
	Me	CH_2	C_5H_4	Cp	Other	Me	CH_2	C_5H_4	Cp	CN
2	3.32	–	4.33, 4.59	4.16	8.10 (CH)	–	–	–	–	–
3	2.43	3.46	4.08, 4.16	4.10	0.85 (NH)	–	–	–	–	–
4[a]	2.30	3.82	4.31–4.29	4.16	1.55 (NH)	37.7	55.6	70.8, 71.8, 74.0	69.8	69.5
5	2.05	3.33	4.09, 4.15	4.08	–	41.2	56.4	68.1, 70.4, 83.5	68.7	–
6	2.26	3.78	4.29–4.42	4.17	–	45.5	60.8	70.8, 73.4, 76.1	69.8	66.9

[a] ^{13}C NMR of **4** in CD_2Cl_2 due to low solubility.

For the cyanoborohydride salt **4**, ^{1}H resonances of the substituted cyclopentadienyl ring collapse to a multiplet (δ 4.30), with a slight downfield shift of methyl (δ 2.43) and methylene (δ 3.82) hydrogens compared to **3**, and a broad NH resonance (δ 1.55). The BH resonances are too broad to observe. ^{13}C NMR shows methyl (δ_C 37.7), methylene (δ_C 55.6), substituted cyclopentadienyl (δ_C 70.8, 71.8, 74.0), unsubstituted cyclopentadienyl (δ_C 69.8) and cyano (δ_C 69.5) resonances. The IR spectrum of **4** displays absorbances from BH (2335 cm^{-1}), CN (2175 cm^{-1}), and NH (3442 cm^{-1}) stretches.

The ^{1}H NMR spectrum of di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**) shows a general upfield shift from **4**, including methyl (δ 2.05), methylene (δ 3.33), substituted cyclopentadienyl (δ 4.09 and 4.15) and unsubstituted cyclopentadienyl (δ 4.09) resonances, attributed to higher electron density in the neutral amine than its ammonium salt. The ^{13}C NMR spectrum shows a similar upfield shift of substituted cyclopentadienyl (δ_C 68.1, 70.4, 83.5 ppm) and unsubstituted cyclopentadienyl (68.7 ppm) resonances, but methyl (δ_C 41.2 ppm) and methylene (δ_C 56.4 ppm) resonances are shifted slightly downfield. Its IR spectrum shows no NH, BH or CN stretches.

The ^{1}H NMR spectrum of di(*N*-(ferrocenylmethyl))-*N*-methylamine–cyanoborane (**6**) almost exactly matches that of the ammonium salt **4** rather than the amine **5**, attributed to positive charge on the ammonium-like nitrogen of the borane adduct. BH resonances are again too broad to observe. The ^{13}C NMR spectrum is very similar to that of the salt **4**, except that methyl (δ_C 45.5) and methylene (60.8) resonances are shifted to slightly lower field than in either **4** or **5** and the cyano group (δ_C 66.5) resonance is slightly upfield of that in **4**. The IR spectrum of **6** shows a complex series of absorbances between 2424 and 2330 cm^{-1}, attributed to overlapping BH and CN stretches. We assign the moderate intensity absorbance at 2424 cm^{-1} to the CN stretch and the shoulder from 2384 to 2330 cm^{-1} to the BH stretches. Typical amine–cyanoborane adducts show ν(CN) in the 2390 to 2430 cm^{-1} range with weaker ν(BH) shoulders ranging from 2350 to 2180 cm^{-1} [35,42].

4.3. X-ray crystal structure determinations of 4, 5 and 6

The crystal structure of di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride (**4**) has two unique, but essentially identical, molecules in the asymmetric unit. The cation has a nearly planar "W" arrangement of the di(*N*-(ferrocenylmethyl)) chain, with torsion angles [C12–N1–C1–C2] = 177.2(5)°/−176.7(5)° and [C1–N1–C12–C13] of 175.9(5)°/−173.7(5)° (molecules A/B). The two ferrocenes of **4** are *syn* with respect to the C1–N1–C12 plane, with a [Fe1–Cp1(centroid)–Cp2(centroid)–Fe2] torsion angle of 6.5°/−6.8°. In the anion, the cyanide displays a typical triple bond with a length of 1.159(8)/1.146(8) Å and a N2–C24–B1 angle of 177.8(8)°/178.5(6)°. The cyano nitrogen atom (N2) is pointed toward the ammonium nitrogen atom (N1), with hydrogen bonding evident between them: H–N2 = 0.93/0.93 Å (calculated); H···N1 = 1.86/1.91 Å; N1–N2 = 2.773(8)/2.801(7) Å; and N1–H···N2 angles = 166.4°/159.2°. Although κ-N coordination of cyanoborohydride to Lewis acidic metal centers is common [43–45], relatively few structures with hydrogen bonds to BH_3CN^- have been reported. In [Na{*N*,*N*′,*N*″,*N*‴-tetrakis(2-hydroxyethyl)cyclen}]$^+$[BH_3CN]$^-$, the nitrogen atom of cyanoborohydride is hydrogen-bonded to the hydroxy proton of a sodium-coordinated alcohol in a geometry similar to that of **4** [44]. In contrast, the cyano nitrogen atom of [Na(triethanolamine)]$^+$[BH_3CN]$^-$ coordinates to a sodium ion while its hydrides form dihydrogen bonds with the hydroxy protons of sodium-coordinated alcohols, yet in *N*-[2-(6-aminopyridyl)acetamidine]$^+$[BH_3CN]$^-$ all three B–H bonds form dihydrogen bonds with N–H bonds without any involvement of the cyano nitrogen [43].

The crystal structure of di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**) shows disorder in the unsubstituted cyclopentadienyl rings, but is otherwise well determined. Like **4**, **5** has a nearly planar "W" arrangement of the di(*N*-(ferrocenylmethyl)) unit, with [C2–C1–N1–C12] and [C1–N1–C12–C13] torsion angles of 174.8(4) and −168.8(5)° and a *syn* arrangement of the ferrocenes, with a [Fe1–Cp1 centroid–Cp2 centroid–Fe2] torsion angle of −2.6°. The N–C bonds of **5** (average 1.469(6) Å) are significantly shorter than those of **4** (1.51(1) Å), a typical difference between a tertiary amine and its ammonium salt [46]. For all three structures, the nitrogen to ferrocenylmethyl carbon bond is slightly shorter than the nitrogen to methyl carbon bonds.

The overall geometry of di(*N*-(ferrocenylmethyl))-*N*-methylamine–cyanoborane (**6**) differs from **4** and **5**. The C2–C1–N1–C12–C13 chain is twisted from planarity, with

the Fe1 side still nearly planar ([C12–N1–C1–C2] torsion angle of −173.19(17)°) but the Fe2 side nonplanar ([C1–N1–C12–C13] torsion angle of −55.6(2)°). The ferrocenes are in a *gauche* orientation, with a [Fe1–Cp1 centroid–Cp2 centroid–Fe2] torsion angle of 113.2°. The boron–nitrogen bond length of 1.619(3) Å and very acute C24–B1–N1 angle of 107.88(18)° are similar to those in other amine-cyanoboranes (e.g., 1.567(10), 1.629(9) Å and 110.1(6)°, 109.3(5)° in 1,4-diaminobutyl-*N*,*N*′-bis(cyanoborane) [39]; 1.597(4) Å and 109.4(3)° in *N*-methyl-N′-methyl(diisopropylphosphonate)amine–cyanoborane [38]; 1.606(5) Å and 109.6(3)° in 5-methyl-2-(1-methyl-1,2,5,6-tetrahydropyridine-3-yl)benzoxazole-cyanoborane) [37]. The cyano group shows a C24–N2 triple-bond length of 1.146(3) Å and a B1–C24–N2 angle of 179.7(3)°. The carbon–nitrogen single-bond lengths (average 1.51(1) Å) are similar to those of **4** but longer than those of **5**, reflecting the ammonium-like character of the nitrogen in **6**.

5. Summary and continuing research

Conversion of ferrocenecarboxaldehyde (**1**) to [(methylimino)methyl]ferrocene (**2**) and reduction to *N*-(ferrocenylmethyl)-*N*-methylamine (**3**) proceed conveniently and in high yield. Reductive amination of **1** with amine **3** and $NaCNBH_3$ is surprisingly complicated, giving di(*N*-(ferrocenylmethyl))-*N*-methylammonium cyanoborohydride (**4**) or di(*N*-(ferrocenylmethyl))-*N*-methylamine (**5**) in moderate yield, depending on workup conditions. Thermolysis of the salt **4** to an unusual amine-borane adduct, di(*N*-(ferrocenylmethyl))-*N*-methylamine–cyanoborane (**6**), proceeds smoothly in refluxing THF. The details of this intermolecular reductive amination suggest that the intramolecular reaction, converting 1,2-ferrocenedicarboxaldehyde to aza-[3]-1,2-ferrocenophanes, should be an efficient, general approach to metallocene-fused pyrrolidines and pyrroles.

Acknowledgments

We thank the Research Corporation and the University of Kentucky Research Challenge Trust Fund for support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2006.10.015.

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