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Unusual Condensation of 3-Thia[5](1,1′)ferrocenophane-1,5-dione with Glyoxal. Formation of [1.1](2,3)Thiopheno(1,1′)ferrocenophane-1,7-dione

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Received October 29, 2007

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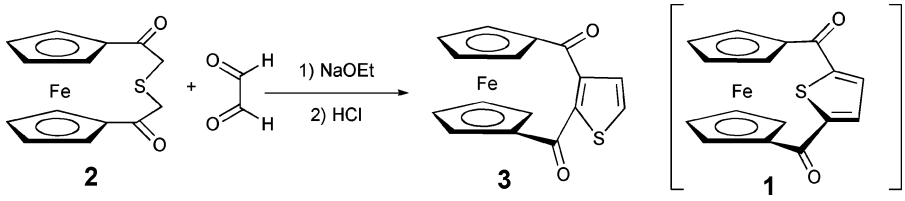


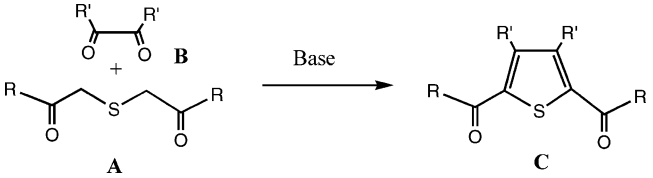
When 3-thia [5](1,1′)ferrocenophane-1,5-dione **2** was condensed with glyoxal in the presence of sodium ethoxide, a thiophene-2,3-diyl derivative **3** was obtained as a sole product, instead of the expected 2,5-substituted compound **1**.

Introduction

The Hinsberg thiophene synthesis in Scheme 1 is well-known for the preparation of thiophene-2,5-dicarboxylic acid derivatives **C** (R = OAlkyl, R′ = H, alkyl, aryl) by condensation of thiadiacetate ester **A** (R = OAlkyl) with 1,2-dicarbonyl compounds **B** (R′ = H, alkyl, aryl).[1] Instead of a simple aldol-type mechanism, a Stobbe-type mechanism has been proposed to account for isolation of the half ester as the product and confirmed by ^{18}O labeling experiments.[2]

Replacement of the ester groups to keto groups, i.e., the use of a diketosulfide **A** (R = alkyl, aryl), is an apparent extension expected to provide thiophene-2,5-dicarbonyl compounds **C** (R = alkyl, aryl),which was actually mentioned by Hinsberg.[1] Since activation by a ketonic carbonyl group is stronger than that by an ester carbonyl, this extension appeared to be easy, but the reaction had long been unreported before we examined the reaction closely.[3] What we found was that the direct condensation failed with 1,2-diketones **B** (R, R′= aryl, alkyl) leading to complex self-condensations, because the initial addition reaction was reversible.[4] However, when glyoxal was used instead, the reaction was very fast and efficient to provide 2,5-diacylthiophenes for many substituents R under mildly basic conditions.[5]

SCHEME 1. Base-Catalyzed Formation of 2,5-Disubstituted Thiophenes



This condensation reaction could be extended to the diketosulfide moiety incorporated in macrocyclic systems affording a variety of thiophenophanediones.[5−7] For the cyclic systems, however, it was crucial to add a dilute sodium alkoxide solution very slowly to a mixture of cyclic diketosulfide and glyoxal even for unstrained cyclic systems. Otherwise, possibly for conformational reasons, the condensation of the diketosulfide with glyoxal was much slower than that of the open chain compounds and glyoxal was preferentially consumed by the Cannizzaro reaction and the self-condensations of the diketosulfide occurred to give tarry products. As was expected, when the ring size of the cyclic diketosulfide was decreased, the yield of the resulting thiophenophanediones tended to be reduced, but considerable strain could be tolerated,[6−8] even though this condensation reaction apparently involves many intermediate steps as the double aldol-type condensations.

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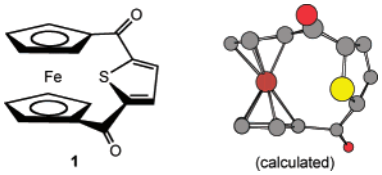
‡ University of Hyogo.

(1) Hinsberg, O. *Ber*. **1910**, *43*, 901−906.
(2) Wynberg, H.; Kooreman, H. J. *J. Am. Chem. Soc*. **1965**, *87*, 1739.
(3) We learned that the reaction had been examined to some extent in a dissertation, which eluded description in the literature: (a) Gronowitz, S. In *Thiophene and its Derivatives*; John Wiley & Sons, Inc.: New York, 1985; Part One, pp 1−213. (b) Rose, E. Über Synthesen von Thiophenverbindungen, dissertation, Friedrich Alexander Universität, Erlangen-Nürnberg, 1961.
(4) Miyahara, Y.; Inazu, T.; Yoshino, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1187.
(5) Miyahara, Y. *J. Heterocycl. Chem.* **1979**, *16*, 1147.
(6) Miyahara, Y.; Inazu, T.; Yoshino, T. *Chem. Lett.* **1978**, 563. Miyahara, Y.; Inazu, T.; Yoshino, T. *J. Org. Chem.* **1984**, *49*, 1177.
(7) Miyahara, Y.; Inazu, T.; Yoshino, T. *Chem. Lett.* **1980**, 397. Miyahara, Y.; Inazu, T.; Yoshino, T. *Tetrahedron Lett.* **1984**, *25*, 415−418.

10.1021/jo702335w CCC: $40.75
Published on Web 02/07/2008

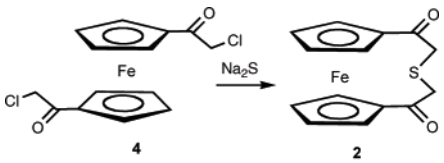
In examining the applicability of this reaction, we thought the mildness of the reaction conditions would allow the synthesis of ferrocenothiophenophanes, of which redox properties will have interesting practical applications in material chemistry. We selected [1.1](2,5)thiopheno(1,1′)ferrocenophane-1,7-dione (**1**) as the first target molecule, not just because the starting material was readily available, but because we were interested in how much strain could be brought into the thiophenophane systems. Although the DFT calculations[9] of **1** revealed severe deformation

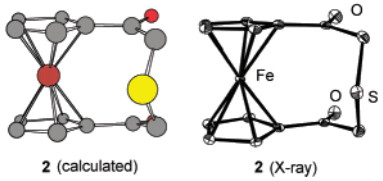


of its thiophene-2,5-dicarbonyl moiety out of planarity together with considerable opening up of the ferrocene rings, we thought the synthesis would be feasible in view of our previous successes in obtaining considerably strained systems with deformed thiophene-2,5-dicarbonyl moieties.[6,7]

Results and Discussion

The precursor of **1**, 3-thia[5](1,1′)ferrocenophane-1,5-dione (**2**), is strain-free as predicted by DFT calculations [the interplanar angle between the two cyclopentadienyl (CP) rings is 1.1°]. Nonetheless, it was surprising to find that a yield as high as 73% was readily achieved by the reaction of 1,1′-bis-(chloroacetyl)ferrocene (**4**) with sodium sulfide by simply adding their solutions in tetrahydrofuran (THF) and 75% ethanol, respectively, to acetone at room temperature over 3 h. (In refluxing ethanol under high dilution conditions over 8 h, the yield dropped to only 24.5%.) Actually, apart from formation of black powder due to the instability of the ferrocene compounds, no other product was detected by thin layer chromatography. Therefore, once one of the chloro groups was replaced by an NaS group, the intramolecular cyclization to form **2** is much more favored over intermolecular reactions, even though the chloroacetyl groups in **3** are expected to be far apart for steric and dipolar reasons.

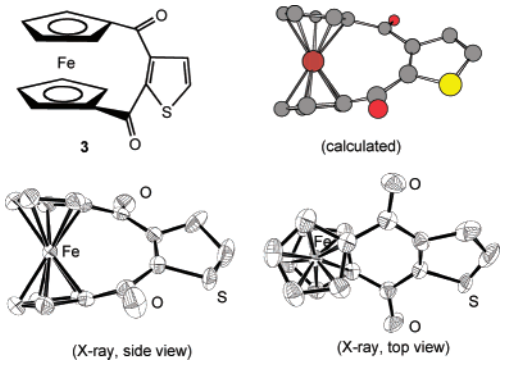




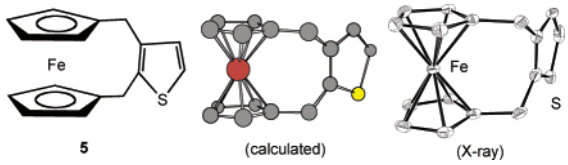
The X-ray crystallographic analysis established the structure of **2** as shown. The interplanar angle between the CP rings was 2.7°, demonstrating the usefulness of the DFT calculations for predicting the structure of the ferrocenophane.

The condensation of **2** with glyoxal was conducted under our standard conditions, i.e., by adding dilute NaOEt to the mixture of **2** and glyoxal trimer dihydrate in ethanol−methylene chloride with a syringe pump over 18 h. After evaporation of the solvents, the residue was partitioned between methylene chloride and dilute HCl. The brown organic layer was separated, washed with water, and dried. When the solution was passed through a column of silica gel, reddish brown prisms (mp 230−232 °C), which we initially thought was the desired **1**, were obtained in 3.8% yield as the sole crystalline product. It should be noted here that the acidification in the aqueous workup was critical. In sharp contrast to all the other cases of thiophenophane synthesis, extraction of the product to the organic layer occurred only after acidification.

The product gave the correct molecular ion peak at *m*/*z* 322 in the EI mass spectrum. However, the thiophene protons did not appear as a singlet in the ^{1}H NMR spectrum expected from the symmetrical structure of **1**, but as an A_2B_2 quartet. The unsymmetrical structure was also evident from the ^{13}C NMR spectrum. Thus, we subjected this compound to the X-ray crystallographic analysis and found that, though the structure was disordered with two orientations of the thiophene ring in 61:39 ratio, the thiophene ring is clearly 2,3-substituted. The CP rings in this compound **3** are not opened up by the thiophene-2,5-dicabonyl group as predicted for **1**, but rather pinched (the interplanar angle of 9.1°) by the thiophene-2,3-dicarbonyl group, of which the thiophene ring is slanted with the angle of 46.1° and 46.8° with respect to each of the CP rings, respectively.



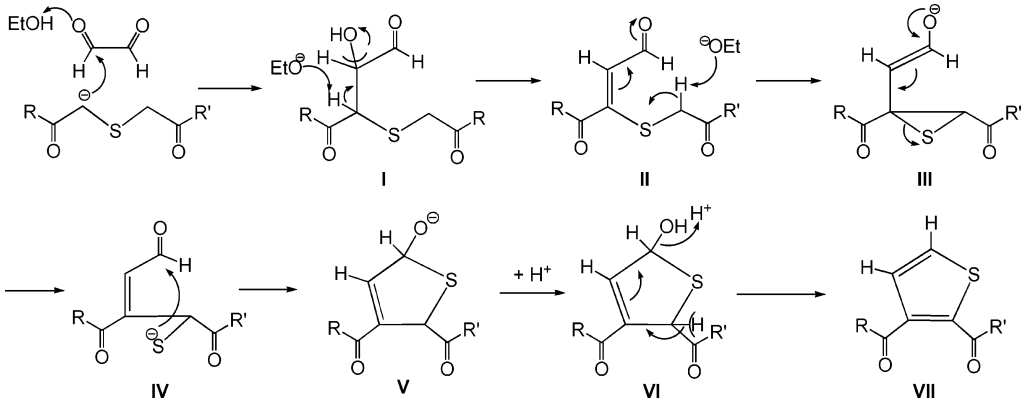
To further verify the structure, the carbonyl groups were converted to methylene groups by the Wolff−Kishner reduction. The resultant **5** obtained as orange-yellow plates (mp 177−179 °C) has clearly showed the 2,3-substitution pattern in the ^{1}H and ^{13}C NMR spectra. The X-ray crystal structure of **5**, though the direction of the thiophene ring is disordered in 1:1 ratio, clearly established its 2,3-substituted structure, which is strain-free as indicated by the interplanar angle of the CP rings of 3.5°.



Even though the expected strain would be excessive if **1** were to be formed, the formation of the 2,3-substituted thiophene ring is surprising. Particularly, in view of the mild basic reaction conditions and the brief acidic workup, rearrangement from 2,5-

(8) Miyahara, Y. *J. Org. Chem.* **2006**, *71*, 6516.
(9) All the DFT calculations were performed by using Gaussian 03 at the B3LYP/6-31G(d) level.

SCHEME 2. Proposed Mechanism for the Formation of 2



to 2,3-substitution is highly unlikely. However, since the DFT calculation predicts that **3** is in fact much more stable than **1** (50.6 kcal/mol), instead of the normal double aldol condensation path leading to excessively strained **1**, **2** managed to find a suitable path to some stable compound in the reaction with glyoxal and found a course to **3**. Although we have experienced low yields in the synthesis of strained thiophenophane,[6] this low yield should be attributed to the unusual reaction course along with the instability of the intermediate ferrocene compounds in air. We tried a variety of alterations in the reaction conditions including solvents and bases, resulting in rather adverse effects. For example, the yield dropped seriously when the reaction temperature was lowered (at 0 °C, 0% yield), while at higher temperatures **2** tended to be recovered, due possibly to preferential consumption of glyoxal by the Cannizzaro reaction. However, we could improve the yield somewhat (11.9%) by simultaneous addition of both of the glyoxal and NaOEt solutions to the solution of **2** kept at 40 °C. Although a highly polar red material, presumably a diol formed by addition of **2** to glyoxal, was eluted in a small quantity in the chromatographic separation in some cases, its purification or dehydration ($SOCl_2$/pyridine)[2] failed due to extensive decomposition. Therefore, the diol does not appear to be an intermediate in this condensation.

This remarkable reaction may be reasonably explained by a mechanism involving an episulfide **III** as the key intermediate shown in Scheme 2. This mechanism is compatible with the fact that the immediate product of the base-catalyzed condensation is the salt **V**, which needs to be subjected to acidic workup for acid-catalyzed dehydration to form the thiophene ring.

We are currently studying whether this reaction is specific to ferrocene compound **2** or will occur as well in the other systems if the necessary steric requirements are satisfied.

Experimental Section

1,1′-Bis(chloroacetyl)ferroecene (4). To an ice-cold solution of ferrocene-1,1′-dicarbonyl chloride[10] (10.56 g, 0.034 mol) dissolved in 100 mL of CH_2Cl_2 was added an ethereal solution of diazomethane prepared from 44 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide[11] over 10 min with shaking occasionally. After standing for 2 h at room temperature the precipitated red bis(diazoketone) was decomposed by slowly adding 50 mL of concd HCl with shaking with cooling in an ice bath. After addition of CH_2Cl_2, the phases were separated and the organic phase was washed with water and dried over $MgSO_4$. After evaporation of the solvents, the residue was dissolved in CH_2Cl_2 and filtered through a short column of silica gel. The eluate was concentrated on an evaporator until crystals started to separate and then cyclohexane was added. The product was obtained as an orange powder (9.81 g, 85.2%), mp 127.5−128.5 °C. Anal. Calcd for $C_{14}H_{12}O_2Cl_2Fe$: C, 49.60; H, 3.57. Found: C, 49.71; H, 3.59. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (t, J = 2.0, 4H), 4.62 (t, J = 2.0, 4H), 4.35 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 74.4, 71.3, 46.0. IR (KBr) $\nu_{C=O}$ 1683 cm^{-1}.

3-Thia[5](1,1′)ferrocenophane-1,5-dione (2). A solution of **4** (6.78 g, 0.020 mol) in tetrahydrofuran (freshly distilled from benzophenone ketyl, 200 mL) and a solution of $Na_2S\cdot 9H_2O$ (4.80 g, 0.020 mol) in water (50 mL) and EtOH (150 mL) were added simultaneously to stirred acetone (400 mL) at room temperature over 3 h under nitrogen. After evaporation, the residue was mixed with water and extracted three times with dichloromethane. After washing with water (2×) and brine, the deep brown solution was dried over Na_2SO_4. The solution was chromatographed on silica gel eluting with 10:1 dichloromethane−EtOAc to give 4.38 g (73.0%) of crystalline powder: brick red granules from 4:1 chloroform−EtOAc, mp 217−218 °C dec. Anal. Calcd. for $C_{14}H_{12}O_2SFe$: C, 56.02, H, 4.02. Found: C, 55.90; H, 4.05. MS (EI) m/z 300 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94 (t, J = 2.0, 4H), 4.58 (t, J = 2.0, 4H), 3.47 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 74.0, 71.3, 39.4. IR (KBr) $\nu_{C=O}$ 1670, 1647 cm^{-1}.

[1.1](2,3)Thiopheno(1,1′)ferrocenophane-1,7-dione (3). Method A: To a solution of **2** (868 mg, 2.89 mmol) and glyoxal (0.504 g of glyoxal trihydrate dissolved in 15 mL of EtOH) in CH_2Cl_2 (250 mL) and EtOH (100 mL) was added a solution of NaOEt (0.55 g of Na dissolved in 100 mL of EtOH, 15 mL) over 18 h. After evaporation, water was added to the residue and the mixture was acidified (HCl) and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and chromatographed (silica gel, CH_2Cl_2) to give deep red prisms (35.5 mg, 3.8%). Further elution gave a deep red powder (90.2 mg), of which dehydration by $SOCl_2$−pyridine resulted in decomposition.

Method B: To a solution of **2** (600 mg, 2.00 mmol) and 1 mL of a glyoxal stock solution (16.8 g of glyoxal trihydrate dissolved in 500 mL of MeOH) in CH_2Cl_2 (150 mL) and EtOH (50 mL) kept at 40 °C was injected the glyoxal solution (20 mL) and a solution of NaOEt (0.55 g of Na dissolved in 100 mL of EtOH, 20 mL) by means of a syringe pump over 10 h. Stirring was continued for an additional 5 h at 40 °C and the solvents were evaporated. The residue was, after addition of water, acidified with concd HCl and extracted twice with chloroform. The combined extracts were washed with water, dried over $MgSO_4$, and passed through a column of silica gel (chloroform). The orange solution of the diketone was eluted slowly to give red crystals (76.9 mg, 11.9%). Dark-red prisms (PhH), mp 230−232 °C, sublimable at 170−180 °C/0.1 mmHg. Anal. Calcd for $C_{16}H_{10}O_2SFe$: C, 59.65; H, 3.13. Found: C, 59.69;

(10) Knobloch, E. W.; Rauscher, W. H. *J. Pol. Sci.* **1961**, *54*, 651−656.
(11) de Boer, Th. J.; Backer, H. J. *Organic Syntheses*; John Wiley & Sons: New York, 1963; Collect. Vol. IV, pp 250-253.

H, 3.15. MS (EI) *m*/*z* 322 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 4.9, 1H), 7.55 (d, J = 4.9, 1H), 4.69 (t, J = 2.0, 2H), 4.67 (t, J = 2.0, 2H), 4.66 (t, J = 2.0, 2H), 4.60 (t, J = 2.0, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 187.5, 146.2, 142.4, 131.3, 130.7, 79.2, 78.8, 76.3, 75.8, 75.4, 75.3. IR (KBr) $\nu_{C=O}$1621 cm^{-1}.

[1.1](2,3)Thiopheno(1,1′)ferrocenophane (5). A solution of **3** (74.1 mg, 0.23 mmol) in dioxane (2 mL) was added to a refluxing mixture of hydrazine hydrate (100%, 3 mL) and ethylene glycol (5 mL) over 5 min and heated under reflux for 30 min and, after addition of KOH (1.0 g), for 30 min. Then volatiles were removed by a Dean−Stark trap and the bath temperature was raised to 220 °C for 30 min. When cooled, the reaction mixture was diluted with water and extracted with hexane. The extract was washed with dilute HCl and then water, and dried over $MgSO_4$. Filtration through a column of silica gel (PhH) afforded orange-yellow plates (33.2 mg, 49.1%), mp 177−179 °C dec. Anal. Calcd for $C_{16}H_{14}SFe$: C, 65.32, H, 4.80. Found: C, 65.57; H, 4.85. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 5.0 Hz, 1H), 6.95 (d, J = 5.0 Hz, 1H), 4.00 (m, 4H), 3.93 (m, 2H), 3.86 (m, 2H), 3.61 (s, 2H), 3.47 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 136.4, 130.6, 120.2, 89.2, 87.9, 68.4, 67.7 (superimposed), 68.5 68.1, 26.5, 25.7.

Acknowledgment. We thank Prof. Teruo Shinmyozu for the use of the instrument to measure the X-ray data.

Supporting Information Available: The details of the X-ray structural analyses of **2**, **3**, and **5** are deposited as a combined CIF file, along with the DFT optimized coordinates for **1**, **2**, **3**, and **5** in Gaussian job file format (gjf), and the ^{1}H and ^{13}C spectra of **2**, **3**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702335W