

Synthesis of squaric acid ester-containing ferrocene derivatives

Angélica Aguilar-Aguilar,^a Eduardo Peña-Cabrera,^{*a} and Lanny S. Liebeskind^b

^a *Facultad de Química. Universidad de Guanajuato. Col. Noria Alta S/N. Guanajuato, GTO. Mexico 36050*

^b *Emory University, Department of Chemistry, 1515 Pierce Drive, Atlanta, Georgia 30322. USA*
E-mail: eduardop@quijote.ugto.mx

(received 12 May 04; accepted 11 Jun 04; published on the web 14 Jun 04)

Abstract

The synthesis of the first three members of the family of the squarylferrocenes is reported. Their preparation involved both the traditional squaric acid chemistry as well as the Liebeskind-Srögl cross-coupling.

Keywords: Ferrocene, squaric acid esters, cyclobutendione, Liebeskind-Srögl cross-coupling

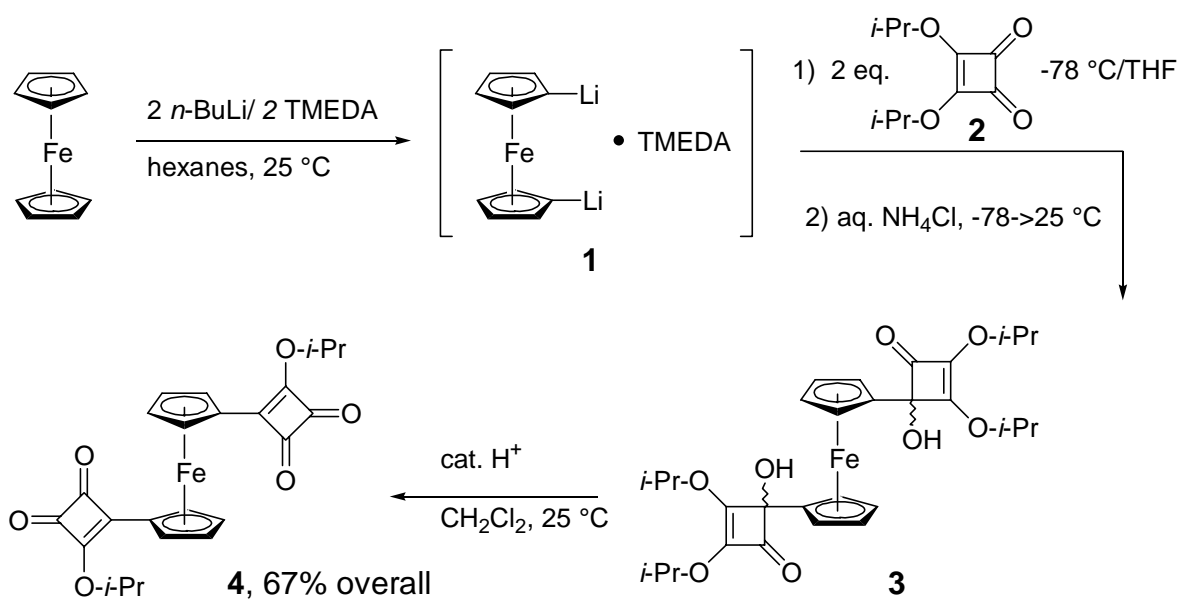
Introduction

Ever since its discovery fifty years ago, the chemistry of ferrocene has developed dramatically.¹ Its remarkable and versatile properties have allowed its use in a wide variety of applications such as homogeneous asymmetric catalysis, organic synthesis, chemical sensors, molecular electronics, and so on.²

As part of a program of developing novel ferrocene derivatives to be used as precursors of ligands in homogeneous catalysis, polymers, DNA intercalators, etc., we considered the preparation of ferrocene derivatives that contain a moiety capable of undergoing easy transformation into a variety of functionally useful systems. Squaric acid esters, and the cyclobutendiones prepared from them, have proven to be extremely useful for the synthesis of organometallic, aromatic, heteroaromatic, and non-aromatic polycyclic products.³ Thus, we envisioned that the cyclobutendione moiety, once attached to ferrocene, would be a suitable starting material for the synthesis of the aforementioned ferrocene derivatives. Our results were first disclosed in a preliminary format in 2001.⁴ Zora *et al.*,⁵ building on our initial disclosure, recently published chemistry very similar to ours. We therefore more formally describe herein our studies of the synthesis of “squarylferrocenes”.

Results and Discussion

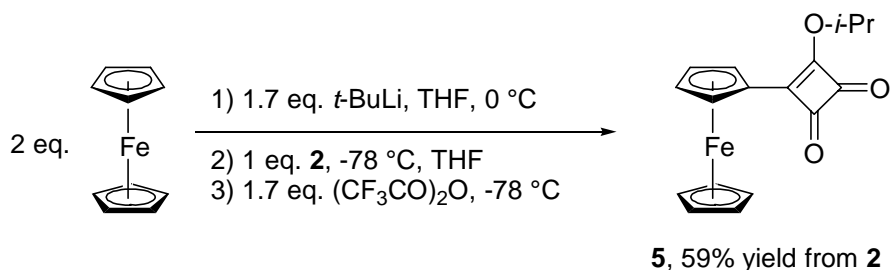
The 1,1'-bis-substituted derivative **4** was prepared as illustrated in **Scheme 1** based on the well-know chemistry of the squaric esters.



Scheme 1. Synthesis of bis-squarylferrocene **4**.

Addition of 1,1'-bis-lithioferrocene **1**,⁶ to two equivalents of di-*i*-propyl squaric acid ester **2**, gave a mixture of diastereomeric adducts **3**. Acid-catalyzed rearrangement of the crude reaction mixture in dichloromethane gave **4** as a deep red solid in 67% overall yield.

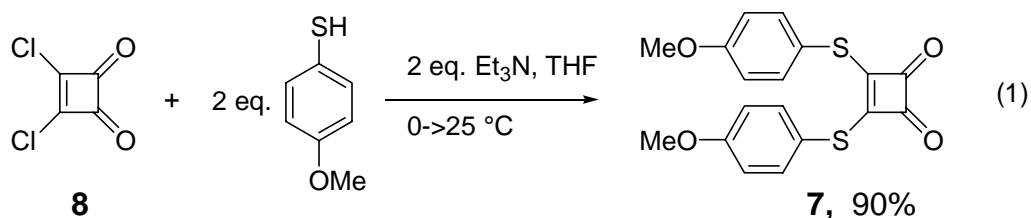
In a similar fashion, the monosubstituted analogue **5**, was synthesized in 59% yield according to **Scheme 2** using the conditions reported by Kagan⁷ to selectively generate mono-lithioferrocene from ferrocene. In this case, the best results were obtained after a trifluoroacetic anhydride quench.⁸



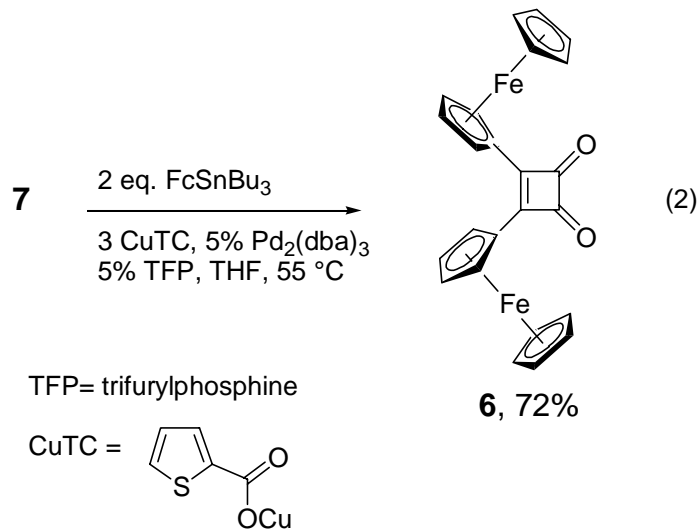
Scheme 2. Synthesis of squarylferrocene **2**.

Having been able to place one and two squaric ester units onto the ferrocene molecule, our next goal was to connect two ferrocene units to a single cyclobutendione moiety. It was envisioned that the Pd-catalyzed, Cu(I)thiocarboxylate-mediated cross-coupling of either organoboranes or organostannanes with thioethers, i.e., the Liebeskind-Srögl cross-coupling,⁹ would be suitable to achieve the synthesis of 3,4-bisferrocenyl-3-cyclobutene-1,2-dione **6**.

The crystalline bisarylthiocyclobutendione partner **7** was prepared in a straightforward manner in 90% yield, as shown in eq. 1, starting from 3,4-dichloro-3-cyclobutene-1,2-dione **8**.¹⁰



Then, **7** was coupled with ferrocenyltributylstannane¹¹ according to eq. 2 to produce **6** in 72% yield¹² under mild reaction conditions.



In conclusion, we have developed a simple and efficient method to prepare derivatives **4**, **5** and **6** using readily available starting materials. The Pd-catalyzed, Cu(I) mediated cross-coupling of thioethers and ferrocenyltributylstannane complemented conveniently the traditional squaric acid chemistry for the synthesis of the first three members of the family of “squarylferrocenes”. The scope and limitations of the Liebeskind-Srögl cross-coupling reaction for the preparation of more elaborate analogues of this series is underway, as well as the applications of the “squarylferrocenes” in the synthesis of polymeric materials, ion sensors and new dinuclear organometallic compounds and will be published in due course.

Experimental Section

General Procedures. ^1H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer in deuteriochloroform (CDCl_3) with either tetramethylsilane (TMS) (0.0 ppm) or chloroform (7.26 ppm) as internal reference unless otherwise indicated. Data are reported in the following order: chemical shift in ppm, multiplicities (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), m (multiplet), exch (exchangeable), app (apparent)), coupling constants, J (Hz), and integration. Infrared spectra were recorded on a Perkin-Elmer FTIR 1600 series spectrophotometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium 40-67%), and w (weak 20-40%).

Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV-light. THF was dried over activated 4Å molecular sieves. TMEDA was distilled from sodium and stored over activated 4Å molecular sieves. All reactions were performed under a dry N_2 atmosphere in oven- and or flame-dried glassware.

Experimental procedures

1,1'-Bis{3-(4-isopropoxy-3-cyclobutene-1,2-dioxo)} ferrocene (4). To a mixture of *n*-BuLi (hexane solution, 6.78 mmol) and TMEDA (1.0 mL, 6.78 mmol) was added a hexane (20 mL) solution of ferrocene (0.5 g, 2.7 mmol) *via* cannula under nitrogen at 25 °C. The mixture was stirred for 12 h, after which a bright yellow precipitate of 1,1'-bislithioferrocene¹ was formed. The suspension was left to sediment and then washed with dry hexane (3 x 20 mL). The resulting yellow solid was suspended in dry hexane (20 mL). To a cold (-78 °C, dry ice-acetone) THF (20 mL) solution of 3,4-diisopropoxy-3-cyclobutene-1,2-dione (1.07 g, 5.4 mmol) was added drop-wise the hexane suspension of 1,1'-bislithioferrocene *via* cannula under nitrogen. The mixture was stirred for 30 min and then quenched with a saturated NH_4Cl (15 mL) aqueous solution at -78 °C. The mixture was allowed to reach 25 °C and was then extracted with ether (3 x 20 mL); the combined organic fractions were dried with anhyd. MgSO_4 , filtered and concentrated in vacuo. The resulting material was dissolved in CH_2Cl_2 (40 mL) and a drop of conc. HCl was added. After TLC analysis indicated rearrangement of the adduct (ca. 1.5 h) (R_f = 0.23, 20% EtOAc/hexane, UV-light), the solvent was evaporated. The product was purified by MPLC (EtOAc/hexane gradient) to obtain a purple-red solid (0.84 g, 67%); mp 210 °C (dec.); IR (KBr): 3108 (m), 2929 (m), 1788 (s), 1596 (s), 1470 (s), 1385 (s), 1090 (s), 762 (m). ^1H RMN (200 MHz, CDCl_3): δ 5.4 (m, J = 6.2 Hz, 2H), 4.95 (app. t, J = 1.8 Hz, 4H), 4.6 (app. t, J = 1.8 Hz, 4H), 1.5 (d, J = 6.2 Hz, 12H). ^{13}C RMN (50 MHz, CDCl_3): 192.7, 191.9, 191.3, 175.7, 80.1, 73.8, 70.7, 70.0, 22.8. Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{FeO}_6$: C, 62.36; H, 4.80. Found: C, 62.22; H, 4.92.

3-Isopropoxy-4-ferrocenyl-3-cyclobutene-1,2-dione (5). To a cold solution (0 °C, ice-bath) of ferrocene (1.4 g, 7.56 mmol) in THF (10 mL) under N_2 was added *t*-BuLi (6.43 mmol) *via* syringe. The mixture was stirred at 0 °C for 20 min, and then added to a cold solution (-78 °C, dry ice-acetone) of 3,4-diisopropoxy-3-cyclobutene-1,2-dione (0.75 g, 3.78 mmol) in THF

(10 mL) *via* cannula. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, after which the starting dione was consumed and the 1,2-adduct was formed ($R_f = 0.34$, 20% EtOAc/hexane). Then, the temperature was gradually increased to $25\text{ }^{\circ}\text{C}$ and the mixture was stirred for 1 h. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and trifluoroacetic anhydride (1.35 g, 6.43 mmol) was added. The reaction mixture was stirred overnight at $25\text{ }^{\circ}\text{C}$ and quenched with satd. aqueous NH_4Cl (15 mL) at $-78\text{ }^{\circ}\text{C}$. Once the crude reaction mixture reached $25\text{ }^{\circ}\text{C}$, it was extracted with ether (3 x 20 mL) and the organic fractions were combined, dried with anhyd. MgSO_4 , filtered and concentrated *in vacuo*. The product was purified by gravity column chromatography (EtOAc/hexane gradient) followed by crystallization (hexane/ CH_2Cl_2) to give a purple-red solid (0.73 g, 59%); $R_f = 0.47$ (20% EtOAc/hexane); mp = $119\text{--}121\text{ }^{\circ}\text{C}$; IR (KBr): 3110 (m), 2978 (m), 2928 (m), 1787 (s), 1728 (s), 1595 (s), 1470 (s), 1383 (s), 1096 (s), 818 (m). ^1H RMN (200 MHz, CDCl_3): δ 5.27 (m, $J = 6.2$ Hz, 1H), 4.96 (app. t, $J = 1.8$ Hz, 2H), 4.64 (app. t, $J = 1.8$ Hz, 2H), 4.17 (s, 5H), 1.52 (d, $J = 6.2$ Hz, 6H). ^{13}C RMN (50 MHz, CDCl_3): 191.9, 191.1, 190.5, 179.9, 78.2, 72.2, 69.8, 68.1, 66.9, 22.3 (s). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{FeO}_3$: C, 62.99; H, 4.98. Found: C, 62.75; H, 4.84.

3,4-Bis-(*p*-methoxythiophenoxy)-3-cyclobuten-1,2-dione (7). To a cool ($0\text{ }^{\circ}\text{C}$) THF (10 mL) solution of dichlorodione **8** (250 mg, 1.6 mmol) was added *p*-methoxythiophenol (0.4 mL, 3.3 mmol) dropwise *via* syringe under N_2 , followed by the addition of triethylamine (0.43 mL, 3.3 mmol). The reaction mixture gradually reached $25\text{ }^{\circ}\text{C}$ and after 6 h was quenched with an equivalent volume of aq. NH_4Cl . Then, it was extracted with CH_2Cl_2 (3 x 30 mL), dried (anhyd. MgSO_4), and filtered. The solvent was removed *in vacuo* to give a yellow solid. The remaining solid was triturated in hexane and used directly in the following reactions (510 mg, 89%). For characterization purposes, the product was crystallized from hexane/EtOAc ($R_f = 0.3$, silica gel, 20% EtOAc/hexane); mp $133\text{ }^{\circ}\text{C}$; IR (KBr): 2939 (m), 2840 (m), 2366 (m), 1787 (s), 1807 (m), 1761 (s), 1740 (m), 1590 (s), 1571 (s). ^1H RMN (200 MHz, CDCl_3): δ 7.50 (d, $J = 8.94$ Hz, 2H), 6.90 (d, $J = 8.89$ Hz, 2H), 3.80 (s, $J = 1.8$ Hz, 3H). ^{13}C RMN (50 MHz, CDCl_3): 188.2, 186.7, 161.7, 136.4, 115.0, 66.1, 55.7. Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{O}_4\text{S}_2$: C, 60.32; H, 3.94; S, 17.89. Found: C, 59.99; H, 3.92; S, 17.58.

3,4-Bisferrocenyl-3-cyclobuten-1,2-dione (6). To a deoxygenated (N_2 purge) THF (3 mL) solution of ferrocenyltributylstannane (0.394 g, 0.83 mmol) and bisthiodione **7** (0.100 g, 0.28 mmol) was added $\text{Pd}_2(\text{dba})_3$ (13 mg, 0.014 mmol), trifurylphosphine (3 mg, 0.014 mmol), and CuTC (160 mg, 0.84 mmol). The mixture was stirred under N_2 at $55\text{ }^{\circ}\text{C}$ for 2 h, then the solvent was removed under vacuum. The product was purified by gravity column chromatography (EtOAc/hexane gradient) to give a deep red solid (91 mg, 72%). $R_f = 0.6$ (20% EtOAc/hexane, silica gel); mp $189\text{ }^{\circ}\text{C}$. IR (KBr) 3436 (s), 2851 (m), 2360 (m), 1771 (s), 1575 (s), 1489 (s), 1284 (s). ^1H NMR (200 MHz, CDCl_3): δ 5.1 (m, 4H), 4.7 (m, 4H), 4.26 (s, 10H). ^{13}C RMN (50 MHz, CDCl_3): 196.4, 187.3, 73.4, 70.8, 69.9, 69.4. Anal. Calcd for $\text{C}_{24}\text{H}_{18}\text{Fe}_2\text{O}_2$: C, 64.04; H, 4.03. Found: C, 64.03; H, 4.04.

Acknowledgements

Financial support from CONACyT (Mexico) Grant No. 27600- E, CONCyTEG (Mexico) Grant No. GTO-2003-C02-11921 is gratefully acknowledged as well as graduate scholarship for A. A.-A. The synthesis of the ferrocenylcyclobutenediones **4** and **5** was carried out by author E. P-C during a stay at Emory University funded by NIH grant #CA40157.

References

1. For recent advances on ferrocene chemistry see the special issue of the *Journal of Organometallic Chemistry* on the 50th Anniversary of the Discovery of Ferrocene *J. Organomet. Chem.* **2001**, 637.
2. Togni, A.; Hayashi, T., Eds; *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Material Science*; VCH: New York, 1995.
3. (a) Moore, H. W. ; Yerxa, B. R. In *Synthetic Utility of Cyclobutenediones*; Halton, B., Ed.; JAI Press: Greenwich, CT, 1995; Vol. 4, pp 81. (b) Liebeskind, L. S. *Tetrahedron Symp. Print* **1989**, 45, 3053. (c) Koo, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1995**, 117, 3389. (d) Sun, L.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, 118, 12473. (e) Paquette, L. A.; Doussot, P. *Res. Chem. Intermed.* **1996**, 22, 767. (f) Ohno, M.; Yamamoto, Y.; Eguchi, *Synlett* **1998**, 1167.
4. Peña-Cabrera, E.; Villanueva-Rendón, A. D.; Robles-García, J.; Mendoza-Díaz, G.; Liebeskind, L. S. the 11th IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis. Abstract Book P050 Taipei, Taiwan, July 2001.
5. Zora, M.; Yucel, B.; Acikalin, S. *Tetrahedron Lett.* **2003**, 44, 2237.
6. (a) McCulloch, B.; Brubaker Jr.; C. H. *Organometallics* **1984**, 3, 1707, (b) McCulloch, B.; Ward, D. L.; Woolins, J. D.; Brubaker Jr.; C. H. *Organometallics* **1985**, 4, 1425.
7. Guillaneux, D.; Kagan, H. *J. Org. Chem.* **1995**, 60, 2502.
8. Onofrey, T. J.; Gomez, D.; Winters, M.; Moore, H. W. *J. Org. Chem.* **1997**, 62, 5658.
9. (a) Liebeskind, L. S.; Srogl, J. S. *Org. Lett.* **2002**, 4, 979. (b) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, 5, 801. (c) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, 5, 803. (d) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, 3, 91. (e) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, 3, 2149. (f) Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, 4, 979. (g) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, 4, 983. (h) Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C. *Pure Appl. Chem.* **2002**, 74, 115. (i) Egi, M. ; Wittenberg, R.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2003**, 5, 3033.
10. Yamamoto, Y.; Shirasaki, Y.; Eguchi, S. *J. Chem. Soc.* **1993**, 263.
11. Liu, C.; Lou, S.; Liang, Y. *Synth. Comm.* **1998**, 28, 2271, also see ref. 7.

12. For preliminary results, see: Peña-Cabrera, E.; Aguilar-Aguilar, A.; Hernández-Barba, A.; Rodríguez-Cendejas, C.; Liebeskind, L. S. *Abstracts of Papers 20th Int. Conf. Organomet. Chem.*, Corfu, Greece, 7-12 July, 2002; p 194.