JOCNote

Synthesis of 1,3-Dithiin Dithioortho Esters from the Reaction of Fischer Carbenes and 3*H*-1,2-Dithiole-3-thiones

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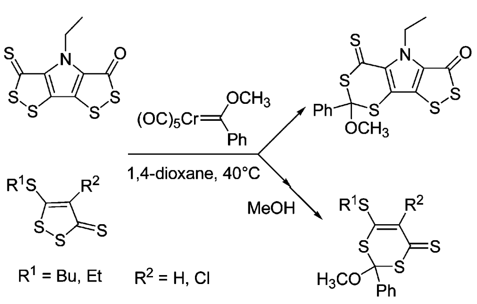


Tricyclic 4-ethyl-5-thioxo-3*H*,5*H*-bis[1,2]dithiolo[3,4-d][4,3-b]pyrrol-3-one and monocyclic 3*H*-1,2-dithiole-3-thione derivatives reacted with Fischer carbene complexes, giving 1,3-dithiin dithioortho esters through insertion of the carbenic carbon into the S−S bond next to the thiocarbonyl function of the substrate.

Fischer carbene complexes have been shown to be very efficient and versatile starting materials for carrying out a wide variety of organic transformations.[1]

In a previous article about the reactivity of a series of 5-alkylthio-3*H*-1,2-dithiole-3-thione derivatives with Fischer carbene complexes, we reported the insertion of the carbene ligand into the C3−C4 bond of 5-alkylthio-3*H*-1,2-dithiole-3-thione to give mainly the complexes 6-alkylthio[pentacarbonylchromium{or tungsten}(0)]- 4*H*-1,2-dithiin-3-thione.[2] Afterward, we worked on this reaction with the aim of establishing the role of the alkylthio and thiocarbonyl groups present in the 1,2-dithiole-3-thione derivatives, as well as the 4-substituent, in the insertion reaction, and the results are reported in this Note. In addition, the new results clearly show that the assignment of structures reported in previous work[2] was not correct.

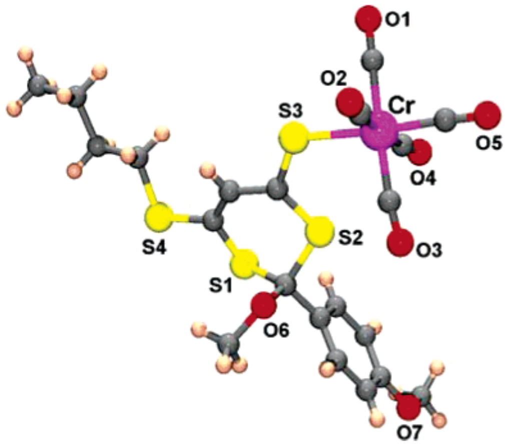
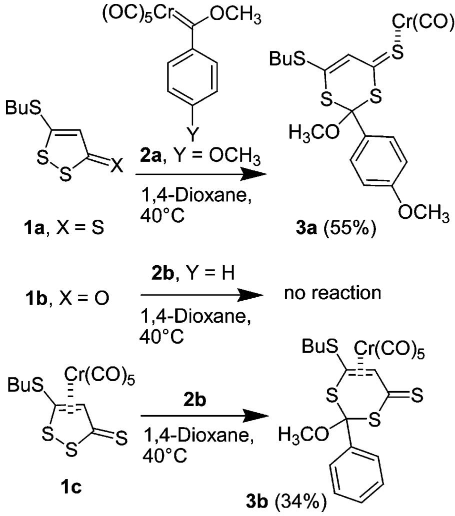


FIGURE 1. Single-crystal X-ray diffraction structure of **3a**.

SCHEME 1



Selected starting materials **1a**−**c**, **4**, and **6a**,**b** were subjected to reaction with pentacarbonyl[(methoxy)(aryl)vinylidenechromium(0)] **2a**,**b** in dioxane at 40 °C. The reaction of **1a** with **2a** gave, after column chromatography, the insertion product **3a** (55%) as blue crystals (Scheme 1). Surprisingly, single-crystal X-ray diffraction afforded the unexpected structure 6-butylthio-2-methoxy-2-(4-methoxyphenyl)-*S*-[pentacarbonylchromium(0)]-[1,3]dithiin-4-thione **3a** coming from the insertion of the carbene moiety into the S−S bond (Figure 1).[3]

Under similar conditions, **1b** was completely unreactive with **2b**, and therefore the presence of the thiocarbonyl group is necessary to get a reaction product (Scheme 1). We then subjected compound **1c**,[4] having an additional chromium complex, to reaction with **2b**, and after column chromatography we only separated the product **3b** (34%), which showed exactly

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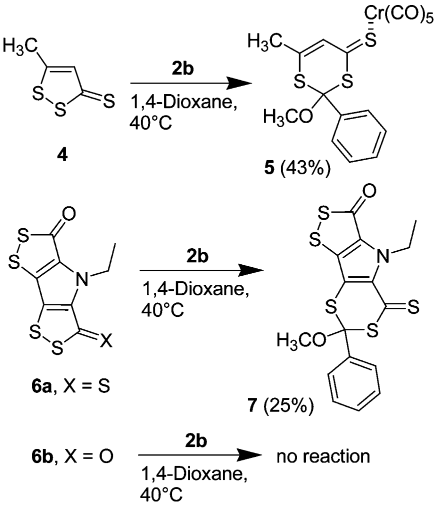
(1) (a) Dötz, K. H. *Metal Carbenes in Organic Synthesis*; Springer: New York, 2004. (b) Barluenga, J.; Santamaria, J.; Tomas, M. *Chem. Rev.* **2004**, *104*, 2259.

(2) Granados, A. M.; Kreiker, J.; de Rossi, R. H. *Tetrahedron Lett.* **2002**, *43*, 8037.

(3) X-ray measurements were made using a Bruker SMART CCD area-detector diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å). Crystal data for **3a**: $C_{21}H_{20}CrO_7S_4$, $M = 564.61$, monoclinic, $P2(1)/n$, $a = 11.3847(13)$ Å, $b = 12.0263(13)$ Å, $c = 19.227(2)$ Å, $\alpha = 90°$, $\beta = 97.452(2)°$, $\gamma = 90°$; $V = 2610.2(5)$ Å^3, $Z = 4$, $D_{calcd} = 1.437$ g cm^{-1}, μ(Mo Kα) = 0.795 mm^{-1}. Brown prism, (0.20 × 0.20 × 0.20) mm^3. 24 994 measured reflections, 4588 independent ($R_{int} = 0.0449$), 3617 observed ($I > 2\sigma(I)$). $R_1 = 0.0566$, w$R_2 = 0.1322$ (all data). CCDC 290963.

10.1021/jo052168e CCC: $33.50

SCHEME 2



the same spectral and physical data of the product that we previously described from the reaction of **1a** with **2b**,[2] although this time it was obtained in slightly lower yield. Therefore, complexation of the starting material has little influence on the reaction pathway.

Under the light of structure **3a** and, after careful comparison of all spectral data, we assigned the 1,3-dithiin-4-thione structure **3b** to the product of the reaction of **1c** with **2b** (Scheme 1). The coordination site of the pentacarbonylchromium[0] moiety in **3b** will be discussed later in this Note.

We then performed the reaction of a simpler starting material **4** with **2b** under similar conditions, from which we obtained the crystalline brown product **5** (43%) (Scheme 2), which was characterized spectroscopically. The crystals were not good enough to get a refined structure by single-crystal X-ray diffraction. However, it was clear from the crystallographic data that the $Cr(CO)_5$ moiety was close to the thiocarbonyl group.[5] Therefore, it is also evident that the presence of an alkylthio group in the starting material is not necessary for the reaction. On the other side, the reaction of the tricyclic bisdithiolopyrrole **6a** with **2b** gave the orange crystalline [1,2]dithiolo [1,3]-dithiinopyrrole **7** (25%), a new heterocyclic system, which was fully characterized by spectroscopy (Scheme 2).

^{13}C NMR showed a downfield shift of 4.3 ppm in the *N*-CH_2 signal of **7** with respect to **6a**, probably due to shielding of the CH_2 by the nonplanar thiocarbonyl group and a downfield shift of 2.2 ppm of the C=S signal of **7** with respect to **6a**, in agreement with the insertion of the carbene in the cycle. The structure **7** was confirmed by single-crystal X-ray diffraction (Figure 2).[6] It is interesting to note that **7** was not complexed with $Cr(CO)_5$ and that the insertion of the carbene occurred only into the S−S bond near the thiocarbonyl group. Additionally, the reaction of the diketone **6b** with **2b** gave no product, showing that the presence of the dithiolethione moiety is necessary to get reaction products with Fischer carbene complexes.

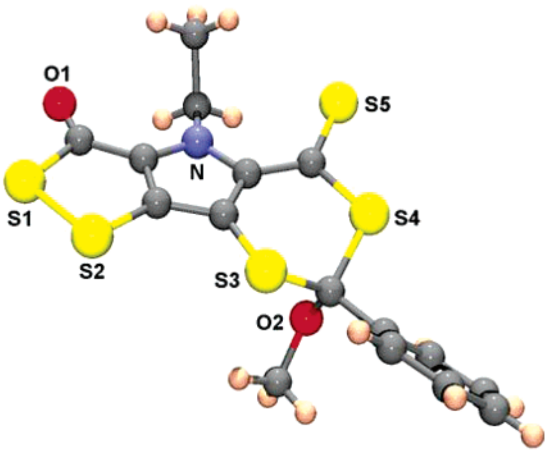
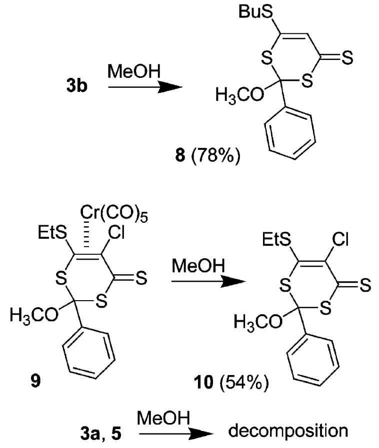


FIGURE 2. Single-crystal X-ray diffraction structure of **7**.

SCHEME 3



To confirm the structures and get the free heterocycle in the cases where the products were obtained as metal complexes such as **3a**,**b**, **5**, and **9**,[7] the compounds were exposed to ligand exchange using MeOH as competitor ligand. Under these conditions complexes **3b** and **9** were demetalated quite easily, giving **8** (78%) and **10** (54%), respectively.[8] On the other hand, complexes **3a** and **5** gave only decomposition products (Scheme 3).

The dissimilar reactivity of these complexes suggested the existence of structural differences that could be evidenced by a careful examination of the IR spectra of **3a**,**b** and **9** compared with those of **8** and **10**. The IR spectrum of **8** and **10** showed the absence of bands corresponding to the chromium pentacarbonyl moiety in the region between 1900 and 2100 cm^{-1} (observed in the IR spectrum of **3a**,**b** and **9**) and the presence of signals at 1600−1750 cm^{-1}, corresponding to the vibration of the C=C double bond in the heterocyclic ring. It is noteworthy that these signals are absent in the spectra of **3b** and **9**, but there is a signal at 1604 cm^{-1} in the spectrum of **3a**.

These data indicate that the C=C double bond is involved in the coordination with the metal in compounds **3b** and **9** but not

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[4] This compound was obtained as follows: In a quartz tube, we added 5-butylthio-3*H*-1,2-dithiole-3-thione (222 mg, 1 mmol), $Cr(CO)_6$ (264 mg, 1.2 mmol), and benzene (15 mL). The mixture was irradiated at 254 nm with a UV lamp as N_2 was bubbled through the solution.

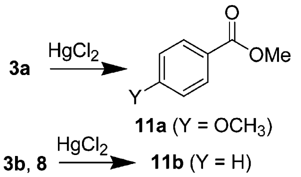
[5] We thank Prof. Ricardo Baggio, Dpto. de Física, Comisión Nacional de Energía Atómica, Buenos Aires, Argentina, for this study.

[6] Crystal data for **7**: $C_{16}H_{13}NO_2S_5$, $M = 411.57$, triclinic, $P\bar{1}$, $a = 10.1366(7)$ Å, $b = 13.4877(9)$ Å, $c = 13.6520(10)$ Å, $\alpha = 104.6560(10)°$, $\beta = 90.4560(10)°$, $\gamma = 102.9130(10)°$; $V = 1756.0(2)$ Å^3, $Z = 4$, $D_{\text{calcd}} = 1.557$ g cm^{-1}, μ(Mo Kα) = 0.669 mm^{-1}. Red plate, (0.40 × 0.30 × 0.05) mm^3. 19 207 measured reflections, 7188 independent ($R_{\text{int}} = 0.0292$), 5948 observed ($I > 2\sigma(I)$). $R_1 = 0.0531$, w$R_2 = 0.1271$ (all data). CCDC 290964.

[7] Complex **9** was obtained as described in ref 2.

[8] See Supporting Information for details of experimental procedures.

SCHEME 4



in **3a**. On the other hand, the signal corresponding to the thiocarbonyl group at 1045 cm^{-1} in the spectra of **3b** and **9** shows only small changes compared with that of **8** and **10**. Additionally, a noticeable increase in the intensity and complexity of the thiocarbonyl absorption band of **3a** in comparison with the corresponding one for **3b** was also observed.[9] We conclude that the C═C double bond in the heterocyclic ring of **3b** and **9** is involved in the coordination with the metal while the coordination site involves the C═S bond in compounds **3a** and **5**. This difference in structure is responsible for their behavior in the demetalation reactions mentioned above. Aumann and co-workers previously reported the impossibility of displacing the metal from a complex between pentacarbonyltungsten(0) and a cyclic thioketone.[10]

To confirm the structure of the products, we studied the hydrolysis of **3a**,**b** and **8** with HgCl$_2$. This method was selected by considering the similarity between the structure of the obtained 1,3-dithiins and the 1,3-dithianes, very well-known as protecting groups for carbonyl compounds.[11] Therefore, reaction of either 1,3-dithiin complexes or free heterocycles with mercuric chloride should give methyl benzoates that could not be formed from 1,2-dithiins such as the ones proposed in previous work.[2] We effectively obtained methyl *p*-methoxybenzoate **11a** as the hydrolysis product from **3a** and methyl benzoate **11b** from **3b** and **8** that were identified in all cases by GC−MS from the crude reaction mixture (Scheme 4). The same procedure was applied to the compounds reported in ref 2 and in all the cases methyl benzoate was formed.

In conclusion, we have shown that Fischer carbene complexes reacted with 3*H*-1,2-dithiole-3-thione derivatives to give 1,3-dithiin derivatives that result from the insertion of the carbenic carbon into the S−S bond. This reaction did not take place when the thiocarbonyl group was replaced by a carbonyl group, which may indicate that the reaction begins with the attack of the nucleophilic thiocarbonyl group to the electrophilic carbenic carbon of the Fischer carbene complex. In addition, the fact that with all the compounds reported previously[2] methyl benzoate was obtained under the hydrolysis conditions (Scheme 4) allowed us to rectify our previosly published structure for the products of related reactions.[2] The products obtained in the reactions reported here belong to a novel type of 1,3-dithiin dithioortho esters that fill a large gap in the synthetic methodology for the preparation of the scarcely known 1,3-dithiin derivatives[12] or the extremely rare compounds having a dithioortho ester group.[13] The in vitro cytotoxicity toward cancer cell lines of 2-vinyl-4*H*-1,3-dithiin from extracts of *Allium victorialis* has been reported.[14] Therefore, the synthesis of 1,3-dithiin derivatives can be considered as an important tool in the search of new therapeutic agents.

Experimental Section

Representative Insertion Reaction. Synthesis of Compound 3a. 5-Butylthio-3*H*-1,2-dithiole-3-thione **1a** (250 mg, 1.12 mmol) and pentacarbonyl[(methoxy)(*p*-methoxyphenyl)vinylidenechromium(0)] **2a** (600 mg, 1.75 mmol) were added to 40 mL of dry dioxane contained in a Schlenk tube under a nitrogen atmosphere, and the mixture was warmed to 45 °C with continuous stirring. After 3 h, no substrate was observed by TLC. Then the solvent was removed at reduced pressure at a temperature below 40 °C. The crude material was purified by column chromatography using a mixture of petroleum ether/diethyl ether 80/20 v/v as eluent. Yield of **3a**: 355 mg (54.5%), blue crystals mp 71.4−71.9 °C. ^{1}H NMR (CDCl$_3$, 200 MHz): δ 0.97 (t, 3H); 1.53 (m, 2H); 1.73 (m, 2H); 3.11 (m, 2H); 3.27 (s, 3H); 3.86 (s, 3H); 7.00 (d, 2H); 7.59(d, 2H); 7.67 (s, 1H). ^{13}C NMR (CDCl$_3$, 50 MHz): δ 13.48; 21.83; 30.66; 33.68; 54.06; 55.48; 96.85; 114.60; 127.56; 128.67; 131.02; 149.11; 161.24; 206.33; 215.06; 223.96. HRMS calculated for $C_{21}H_{20}CrO_7S_4$: 563.94969; found 563.94978.

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Supporting Information Available: Detailed experimental data for the synthesis of new compounds, physical data, and HRMS, IR, ^{1}H, and ^{13}C NMR spectra of all new compounds and crystallographic data for compounds **3a** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] See the compared IR spectra in the Supporting Information

[10] Wu, P.; Aumann, R.; Fröhlich, R.; Wegelius, E.; Saavenketo, P. *Organometallics* **2000**, *19*, 2373.

[11] The protection of carbonyl groups is routinely achieved by the formation of dithio acetals and ketals. Due to the resistance of these groups to conventional acid-catalyzed hydrolytic cleavage, various available methods for deprotection, by using transition metal-induced hydrolysis, are widely used. See, for example: Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

[12] See, for example: (a) Degl'Innocenti, A.; Capperucci, A.; Nocentini, T.; Biondi, S.; Fratini, V.; Castagnoli, G.; Malesci, I. *Synlett* **2004**, 2159−2162. (b) Nizovtseva, T. V.; Komarova, T. N.; Nakhmanovich, A. S.; Larina, L. I.; Lopyrev, V. A. *Arkivoc* **2003** (xiii), 191. (c) Li, G. M.; Niu, S.; Segi, M.; Tanaka, K.; Nakajima, T.; Zingaro, R. A.; Reibenspies, J. H.; Hall, M. B. *J. Org. Chem.* **2000**, *65*, 6601. (d) Fujii, T.; Kusanagi, H.; Takahashi, O.; Horn, E.; Furukawa, N. *Tetrahedron* **1999**, *55*, 5027. (e) Bianchini, C.; Frediani, P.; Herrera, V.; Jiménez, M. V.; Meli, A.; Rincón, L.; Sánchez-Delgado, R.; Vizzala, F. *J. Am. Chem. Soc.* **1995**, *117*, 4333. (f) For a review, see: Freeman, F. *Heterocycles* **1990**, *31*, 701.

[13] See, for example: (a) Kwang-Fu Shen, C.; Duong, H. M.; Sonmez, G.; Wudl, F. *J. Am. Chem. Soc.* **2003**, *125*, 16206. (b) Blagoev, M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2000**, *83*, 3163. (c) Herrmann, E.; Gais, H. J.; Rosenstock, B.; Raabe, G.; Lindner, H. J. *Eur. J. Org. Chem.* **1998**, 275. (d) Becher, J.; Simonsen, O.; Saether, H.; Hansen, T. K.; Jorgensen, T.; Bowadt, S. *Heterocycles* **1993**, *35*, 445. (e) Herdewijn, P. A. M.; Van Aerschot, A.; Jie, L.; Esmans, E.; Feneau-Dupont, J.; Declercq, J. P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1729.

[14] Lee, K. T.; Choi, J. H.; Kim, D. H.; Son, K. H.; Kim, W. B.; Kwon, S. H.; Park, H. J. *Arch. Pharm. Res.* **2001**, *24*, 44.