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Regioselective and Stepwise [8 + 2] Cycloaddition Reaction between Alkynyl−Fischer Carbene Complexes and Tropothione

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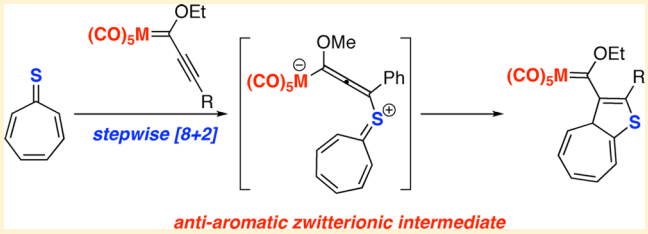
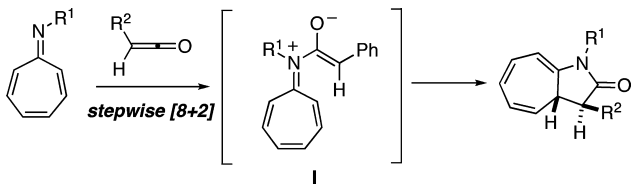
Supporting Information

ABSTRACT: The formal [8 + 2] cycloaddition reaction between alkynyl Fischer carbene complexes and tropothione leads to the regioselective formation of novel 3a*H*-cyclohepta[*b*]thiophene carbene complexes. Computational DFT calculations indicate that the process proceeds stepwise via antiaromatic zwitterionic intermediates



Fischer carbene complexes having an alkenyl or alkynyl group attached to the carbene carbon atom are useful reagents to undergo highly regioselective cycloaddition processes under mild reaction conditions.[1−7] This is mainly due to the strong activating effect exerted by the metal fragment which behaves in the cycloaddition reaction similarly to a Lewis acid directly attached to the carbonyl group of the corresponding isolobal organic esters.[8−12] Based on these and related transformations, the term "super-esters" has been coined for these organometallic compounds. Although the chemical literature contains an impressive number of work focused on [4 + 2][8−12] and [3 + 2][13−16] cycloaddition reactions involving α,β-unsaturated carbene complexes, high-order cycloaddition processes have attracted much less attention. In fact, only a single example of a [8 + 2] cycloaddition between alkynyl carbene complexes and 8-azaheptafulvenes has been reported so far by Barluenga and co-workers.[17] Moreover, nothing is known about the reaction mechanism of this transformation. Whereas a concerted reaction pathway through aromatic transition states has been computationally suggested by us for [4 + 2][18] and [3 + 2][19,20] cycloaddition reactions involving Fischer carbenes, a stepwise process is followed in the [8 + 2] reaction between 8-azaheptafulvenes and organic ketenes (Scheme 1).[21] The latter transformation involves the formation of a zwitterionic intermediate **I** which has been experimentally trapped and fully characterized. Therefore, a stepwise pathway is very likely to occur as well in the [8 + 2] reaction reported by Barluenga and co-workers.[17]

Scheme 1. Stepwise [8 + 2] Cycloaddition Reaction between 8-Azaheptafulvenes and Ketenes



Within the context of our ongoing work on the reaction mechanisms and synthetic applications of cycloaddition reactions involving organic and organometallic reagents,[22−27] we report herein the high-order [8 + 2] cycloaddition reaction[28,29] between alkynyl carbene complexes and tropothione, which occurs with total regioselectivity and through a stepwise reaction mechanism.

A tropothione solution, readily prepared from tropone and P_2S_5,[29] was added to a CH_2Cl_2 solution of the corresponding alkynyl carbene complex **1a−f** (1:1 equimolecular amounts), and the mixture was stirred at room temperature for 5−10 min (Scheme 2a). Removal of the solvent and purification of the residue by column chromatography allowed the isolation of the corresponding 3a*H*-cyclohepta[*b*]thiophene carbene complexes **3a−f**,[30] which maintain the carbene functionality susceptible to further modifications, in moderate to excellent yields. The process is compatible with different substitutions at the triple bond as well as with tungsten derived carbenes (no significant differences between the reaction yields, **3a** vs **3b**, in the reactions of chromium(0)− and tungsten(0)−carbene complexes and tropothione **2** were observed). The presence of additional metal centers (complex **1c**) is also compatible with this cycloaddition reaction. Furthermore, by using a bis-carbene complex (**1h**), bis-cycloadduct **3h** having a pentacyclic bimetallic array was obtained with a 67% reaction yield. Compound **3h** was formed as 1:1 racemic mixture of the two possible RR/SS and *meso*-RS diastereomers.

The spectroscopical data (1D- and 2D-NMR experiments) suggest that the cycloaddition reaction occurs with total regioselectivity leading exclusively to the cycloadduct having the sulfur atom of the tropothione attached to the β-carbon atom of the triple bond of the initial alkynyl carbene complex.

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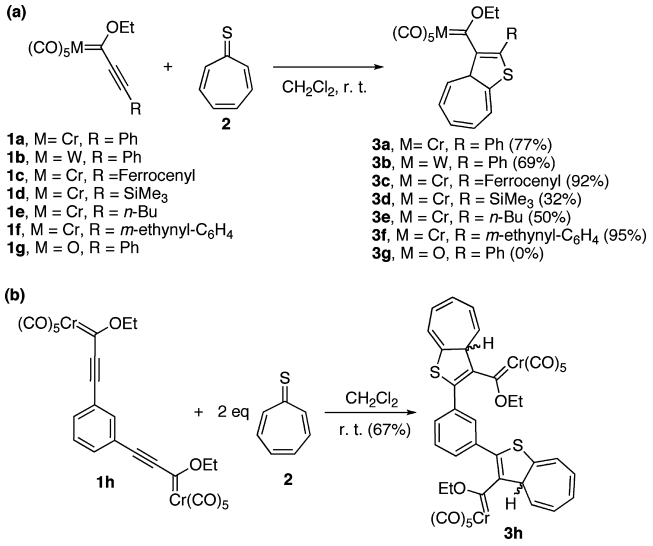
Scheme 2. [8 + 2] Cycloaddition Reaction between Alkenyl Fischer Carbene Complexes 1a–h and Tropothione 2



This result is in agreement with the high regioselectivity observed for related [3 + 2] cycloaddition processes[19,20] and for the [8 + 2] reaction described by Barluenga's group.[17] The origin of this complete regioselectivity is found in the much higher electrophilicity of the β-carbon atom compared to the α-carbon in the initial alkynyl carbene complex **1**.[20] The role of the metal in the cycloaddition reaction is decisive, since no reaction was observed when ethyl 3-phenylpropiolate (**1g**) (the organic counterpart of complexes **1a,b**) was mixed with 1 equiv of tropothione under the same reaction conditions which led to the complete transformation of complexes **1**. The use of higher temperatures (boiling CH_2Cl_2) or prolonged reaction times was of no avail. This finding clearly illustrates the activating "super-ester" effect of the metal moiety described above.

Single crystals of cycloadduct **3c** suitable for X-ray diffraction analysis were grown in hexanes/ethyl acetate solution at −20 °C. As seen in Figure 1, the sulfur atom of the tropothione is attached to the terminal carbon atom of the triple bond (C17),

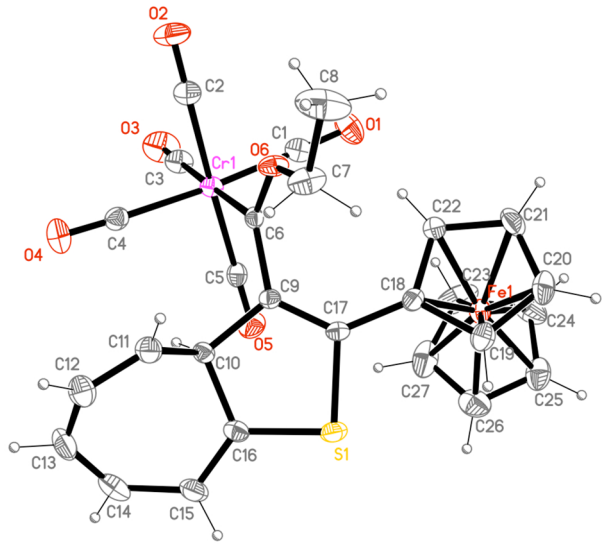


Figure 1. ORTEP diagram of compound **3c**.

thus confirming the regioselectivity of the process suggested by the spectroscopical study.

In order to gain a deeper insight into the reaction mechanism of the formal [8 + 2] cycloaddition reaction between carbene complexes **1** and tropothione, a DFT-computational study has been carried out.[31] The corresponding reaction profiles (PCM-M06/def2-SVP//B3LYP/def2-SVP level) of alkynylmethoxy-carbene complex **1M** and thione **2** are depicted in Figure 2, which gathers the computed free energies (at 298 K) in CH_2Cl_2 solution.

As initially envisaged, two different reaction pathways, i.e., concerted versus stepwise, are possible. From the data in Figure 2, it becomes obvious that a concerted pathway is not competitive in view of the high activation barrier of the process ($\Delta G^{\ddagger}_{298}$ = 58.6 kcal/mol) via the saddle point **TS1**. This computed value makes the transformation unfeasible under the reaction conditions used in the experiment (i.e., room temperature). Instead, the stepwise pathway, which starts with the nucleophilic addition of the sulfur atom of the thione to the β-carbon atom of the carbene complex **1M**, is much more likely to occur in view of the much lower activation barrier of this process ($\Delta G^{\ddagger}_{298}$ = 16.6 kcal/mol, via **TS2**). This addition leads to the formation of zwitterionic intermediate **INT1** which easily evolves to the final cycloadduct **3M** via **TS3** (computed barrier energy of $\Delta G^{\ddagger}_{298}$ = 7.2 kcal/mol), a saddle point associated with the corresponding carbon–carbon bond formation/ring-closure reaction. Therefore, the computed low activation barriers and the exergonicity of the overall cycloaddition (ΔG_R = −18.6 kcal/mol), which are compatible with a reaction at room temperature, make the stepwise pathway the preferred reaction profile for this [8 + 2] transformation.[32]

Very likely, the stepwise nature of the cycloaddition finds its origin in the high stabilization of the zwitterionic intermediate **INT1**. Thus, the negative charge is highly delocalized in the electron-withdrawing pentacarbonylmetal moiety (computed NBO-charge on chromium atom of −2.45e). Similarly, the positive charge is mainly located at the sulfur atom (+0.40e) but also delocalized within the seven-membered ring.[33] As a result, it can be proposed that the resonance form **INT1-B** (Figure 3a), which resembles the tropylium cation, has a significant contribution in the description of the sulfur-substituted zwitterion **INT1**. Consequently, some degree of aromaticity should be expected in this species. In fact, the seven-membered ring of **INT1** exhibits high planarity (C1(S)–C2–C3–C4 dihedral angle of 0.6°) and bond-length equalization (C–C bond distances in the range of 1.377–1.429 Å, intermediate between single and double bonds) thus satisfying the so-called geometric criterion for aromaticity. In contrast, the data computed for the analogous nitrogen-substituted zwitterionic intermediate **I**, formed in the analogous stepwise [8 + 2] cycloaddition reaction between 8-azafulvenes and ketenes (Scheme 1),[21] showed that this compound is not planar and exhibits a higher bond length alternation. Moreover, the computed positive nuclear independent chemical shifts (NICS)[34] values confirmed the antiaromatic nature of the latter species.[21]

To check the aromaticity of **INT1**, the corresponding NICS values were also computed. Both the NICS(0) computed at the [3,+1] ring critical point of the electron density[35–40] (NICS(0) = +5.8 ppm) and the corresponding out-of-plane component computed 1 Å above this point ($NICS(1)_{zz}$ = +2.8 ppm) indicate that the sulfur-substituted zwitterion **INT1** is not aromatic either.[41] This result has been also confirmed by

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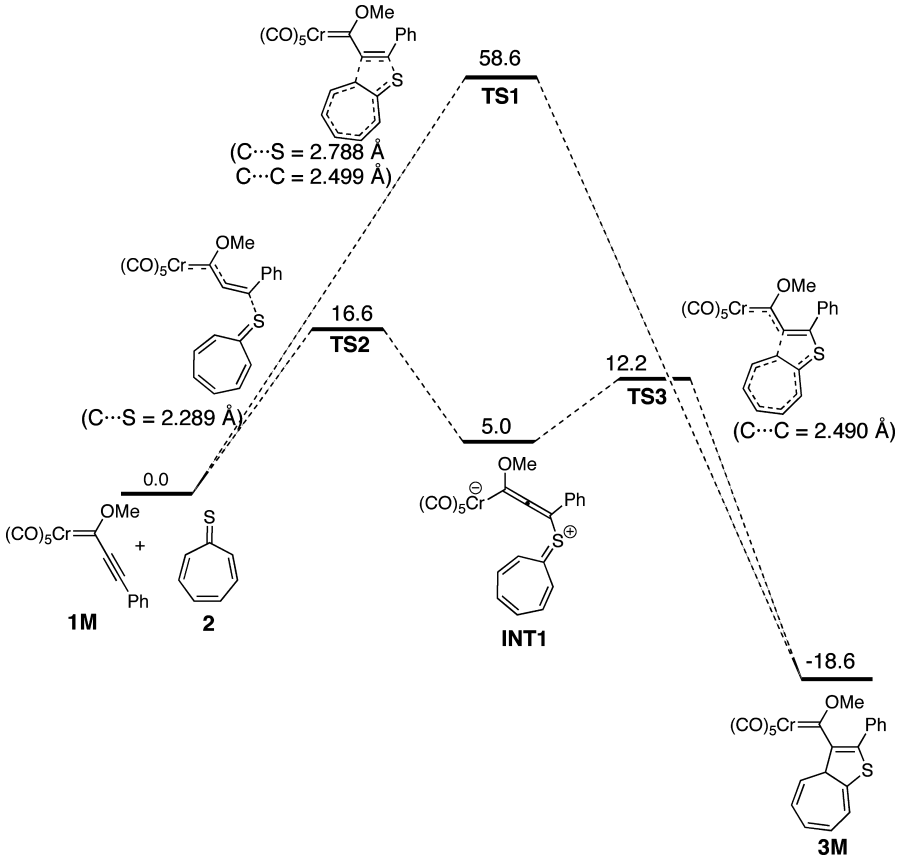

Figure 2. Computed reaction profile (PCM-M06/def2-SVP//B3LYP/def2-SVP level) for the [8 + 2] cycloaddition reaction between carbene complex **1M** and tropothione **2**. Relative free energies (ΔG_{298}) are given in kcal/mol.

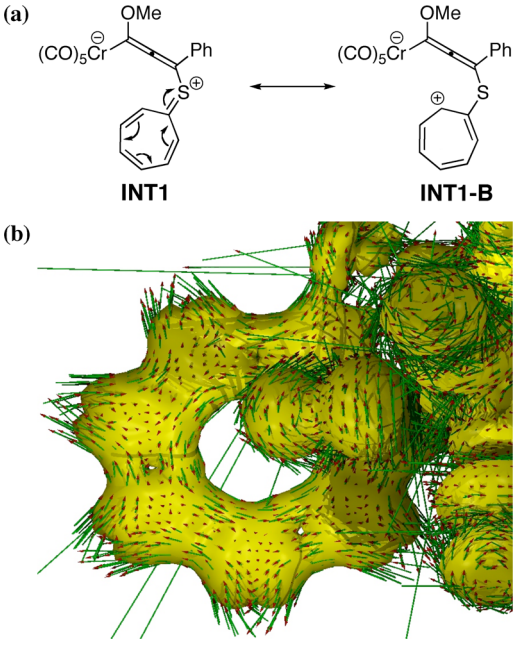

Figure 3. (a) Resonance forms of zwitterion **INT1**. (b) AICD plot of **INT1** (isosurface value of 0.035).

applying the anisotropy of the induced current density (AICD) method, developed by Herges and co-workers,[42,43] on **INT1** to visualize the delocalization of electrons within the ring. As readily seen in Figure 3b, a clear paratropic current (anticlockwise vectors) is observed, thus confirming the antiaromatic nature of this species despite the planarity and bond equalization of the ring.[44−48] Therefore, it can be concluded that the contribution of the resonance form **INT1-B** cannot be that significant. Moreover, this finding also shows that the exocyclic heteroatom plays a major role in the aromatic nature of these cationic heptafulvenes[49] and, consequently, in the stability of the intermediate zwitterions.

In summary, a formal [8 + 2] cycloaddition reaction between alkynyl Fischer carbene complexes and tropothione has been described. The process leads to the regioselective formation of 3a*H*-cyclohepta[*b*]thiophene carbene complexes, which maintain the pentacarbonyl−metal carbene functionality. By means of computational-DFT methods, it was found that this transformation proceeds stepwise through an antiaromatic zwitterionic intermediate.

■ EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under argon atmosphere. All solvents used in this work were purified immediately before use. Flame-dried glassware was used for moisture-sensitive reactions. Identification of products was made by thin-layer chromatography (Kiesegel 60F-254). UV light (λ= 254 nm) and potassium permanganate (aqueous solution) were used to develop the plates. Unless otherwise noted, NMR spectra were recorded at 25 °C in $CDCl_3$ on a 300 MHz (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). ^{1}H NMR splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. IR spectra were taken on a MIR (8000−400 cm^{-1}) spectrometer as solid films by slow evaporation of the solvent using the ATR (atenuated total reflectance) technique. MS spectra (HRMS)

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were acquired on a Fourier transform ion cyclone resonance mass spectrometer (4.7 T). Alkynyl Fischer carbene complexes **1a–g**[50] and tropothione **2**[28,30] were prepared following the described procedures.

General Procedure for Cycloaddition Reactions. To a solution of the corresponding alkynyl carbene **1a–g** (0.5 mmol) in CH_2Cl_2 (5 mL) at room temperature was added a solution of tropothione **2** (0.5 mmol) in CH_2Cl_2 dropwise. The mixture was stirred at room temperature for 5–10 min. The solvent was then removed in vacuo and the crude mixture purified by flash column chromatography to give pure carbene complexes **3a–g**. Compound **3h** was prepared from biscarbene **1h** following the same procedure for monocarbenes but using 2 equiv of the tropothione **2**.

3a: red oil (182 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3H), 7.26–7.20 (m, 2H), 6.63 (dd, J = 11.0, 6.1 Hz, 1H), 6.52 (dd, J = 11.0, 5.6 Hz, 1H), 6.24 (dd, J = 6.2, 2.2 Hz, 1H), 6.16 (dd, J = 9.3, 5.7 Hz, 1H), 4.94 (dd, J = 9.3, 4.7 Hz, 1H), 4.82–4.71 (m, 2H), 4.60–4.58 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 340.9, 222.5, 214.9, 147.5, 134.9, 134.3, 133.9, 130.6, 129.2, 129.1, 128.8, 128.5, 125.8, 116.1, 115.0, 77.1, 59.7, 12.9; IR (ATR) ν 2058, 1938 cm^{-1}; HRMS (FTMS) m/z calcd for $C_{23}H_{16}CrO_6S$ [M + H] = 473.0151, found 473.0156.

3b: dark red oil (208 mg, 69%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.34 (m, 5H), 6.63 (dd, J = 10.9, 6.0 Hz, 1H), 6.53 (dd, J = 10.9, 5.6 Hz, 1H), 6.24 (dd, J = 6.1, 2.2 Hz, 1H), 6.18 (dd, J = 9.4, 5.6 Hz, 1H), 5.01 (dd, J = 9.3, 4.7 Hz, 1H), 4.80–4.69 (m, 1H), 4.59–4.49 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 310.5, 201.9, 196.4, 149.9, 137.7, 134.2, 130.5, 129.2, 129.0, 128.8, 128.4, 125.8, 116.1, 115.4, 79.0, 58.5, 13.9; IR (ATR) ν 2066, 1917 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{16}WO_6S$ [M − H] = 603.0104, found 603.0105.

3c: dark red oil (267 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (dd, J = 11.1, 6.3 Hz, 1H), 6.46 (dd, J = 11.1, 5.7 Hz, 1H), 6.22 (dd, J = 6.2, 2.1 Hz, 1H), 6.11 (dd, J = 9.3, 6.1, Hz, 1H), 4.79–4.74 (m, 2H), 4.61 (s, 2H), 4.37 − 4.20 (m, 9H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 343.0, 223.0, 215.5, 134.6, 131.8, 130.3, 128.2, 125.6, 115.1, 114.7, 76.2, 70.4, 70.0, 69.7, 67.2, 60.7, 14.8; IR (ATR) ν 2057, 1931 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{20}CrFeO_6S$ [M − H] = 578.9652, found 578.9652.

3d: red solid (75 mg, 32%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (dd, J = 11.0, 6.2 Hz, 1H), 6.46 (dd, J = 11.0, 5.8 Hz, 1H), 6.19 (dd, J = 6.2, 2.2 Hz, 1H), 6.11 (dd, J = 9.0, 5.8 Hz, 1H), 5.44–5.33 (m, 1H), 5.11–5.01 (m, 1H), 4.77–4.69 (m, 2H), 1.73 (t, J = 7.1 Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 340.4, 223.4, 216.1, 160.0, 139.4, 136.6, 130.4, 128.3, 125.2, 114.8, 113.4, 77.4, 61.0, 15.3, 0.1; IR (ATR) ν 2058, 1931 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{20}CrO_6SSi$ [M + H] = 469.0239, found 469.0239.

3e: dark orange oil (113 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, J = 11.2, 6.4 Hz, 1H), 6.46 (dd, J = 10.9, 5.7 Hz, 1H), 6.18 (dd, J = 6.2, 2.2 Hz, 1H), 6.09 (dd, J = 8.9, 5.9 Hz, 1H), 5.15 − 5.04 (m, 2H), 4.81 (dd, J = 9.3, 4.6 Hz, 1H), 4.52 (s, 1H), 2.43–2.15 (m, 2H), 1.72 (t, J = 7.1 Hz, 3H), 1.50 − 1.38 (m, 2H), 1.38 − 1.27 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 342.4, 223.3, 213.9, 147.4, 137.0, 134.1, 130.5, 128.6, 125.3, 116.0, 115.3, 77.2, 59.4, 31.6, 29.6, 22.5, 15.5, 13.9; IR (ATR) ν 2058, 1931 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{20}CrO_6S$ [M − H] = 451.0313, found 451.0313.

3f: red oil (236 mg, 95%); ^{1}H NMR (700 MHz, acetone-d_6) δ 7.56 (d, J = 7.7 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J = 7.7 Hz, 1H), 6.68 (dd, J = 11.1, 6.3 Hz, 1H), 6.57 (dd, J = 11.1, 5.7 Hz, 1H), 6.37 (dd, J = 6.2, 1.8 Hz, 1H), 6.22 (dd, J = 8.9, 6.0 Hz, 1H), 5.04 (dd, J = 9.2, 4.7 Hz, 2H), 5.01–4.97 (m, 1H), 4.59 (s, 1H), 3.78 (s, 1H), 1.38 (t, J = 7.0 Hz, 3H); ^{13}C NMR (176 MHz, acetone-d_6) δ 343.3, 225.3, 217.4, 135.5, 134.8, 134.2, 134.0, 133.1, 132.0, 131.0, 130.7, 130.3, 127.4, 124.8, 117.9, 116.3, 83.9, 81.4, 79.8, 61.5, 15.6; IR (ATR) ν 2059, 1934 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{16}CrO_6S$ [M + H] = 497.0156, found 497.0156.

3h: dark orange oil (1:1 mixture of isomers, 290 mg, 67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.13 (m, 4H), 6.65 (dd, J = 11.0, 6.5 Hz, 2H), 6.54 (dd, J = 11.0, 5.4 Hz, 2H), 6.25–6.24 (m, 2H), 6.20–6.16 (m, 2H), 4.97–4.77 (m, 6H), 4.55 (s, 2H), 1.34 (t, J = 6.94 Hz, 3H), 1.29 (t, J = 6.94 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 342.9, 342.5, 223.6, 216.0, 216.0, 148.6, 148.4, 134.8, 134.4, 133.8, 133.7, 133.6, 133.3, 130.7,129.4, 129.2, 129.0, 128.6, 128.4, 126.0, 125.9, 116.4, 116.3, 115.1, 115.0, 77.7, 77.5, 77.4, 66.1, 60.0, 15.1, 145.0; IR (ATR) ν 2095, 1931 cm^{-1}; HRMS (ESI) m/z calcd for $C_{40}H_{26}Cr_2O_{12}S_2$ [M + H] = 866.9760, found 866.9762.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of isolated compounds, crystallographic data for compound **3c**, computational details, Cartesian coordinates (in Å), and free energies of all the stationary points discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(30) The cyclohepta[*b*]thiophene ring is present in numerous biologically active natural products and drugs such as pizitofen.
(31) See the computational details in the Supporting Information.
(32) We also computed the corresponding reaction profile for the reaction of tropotione and methyl 3-phenylpropiolate. As expected, only the concerted pathway was located on the potential energy surface. The computed high activation barrier ($\Delta G^{\ddagger}_{298}$ = 28.6 kcal/mol) of this process justifies why the reaction of **1g** and **2** does not occur at room temperature. In view of this barrier energy, the process might be feasible at higher temperatures. However, tropothione **2** is reported to be thermally unstable. See: Machiguchi, T. *Tetrahedron* **1995**, *51*, 1133.
(33) Computed NBO charges (with summed hydrogen atoms): C1 = −0.14e, C2 = +0.09e, C3 = +0.07e, C4 = 0.07e, C5 = +0.09e, C6 = +0.10e, C7 = + 0.11e.
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