JOC Article

Mechanism and Regioselectivity of the Cycloaddition of Thiones Derived from Meldrum's Acid, Malonates, or Other Dicarbonyls

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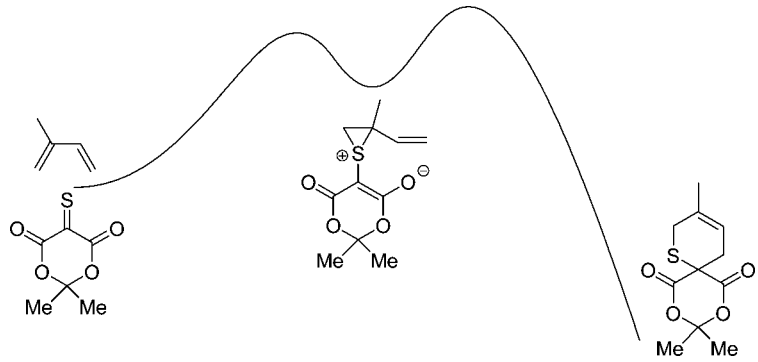

Several α,α-dioxothiones were generated in situ and reacted with 1,3-dienes of varying electronic and steric properties. It was found that thiones **10a** and **11a** reacted well with electron-rich or electron-poor dienes and are complementary in their regioselectivities when steric effects are at play. The calculated preferred mechanistic pathway implies a thiiranium zwitterion intermediate.

Introduction

Thiones and thioaldehydes have been known to participate efficiently as dienophiles in Diels−Alder reactions.[1] The breadth of reactions available to manipulate the carbon−sulfur bond (e.g., desulfurization, elimination, or Pummerer rearrangement) make cycloadditions of such dienophiles leading to dihydrothiapyrans a powerful method to form carbon−carbon bonds.[2] Yet, few examples of the use of thiocarbonyl dienophiles in total syntheses are documented.[3,4] The use of thiocarbonyl dienophiles in synthesis is limited perhaps because the level of regioselectivity observed with unsymmetrical 1,3-dienes is not always useful and often difficult to predict.[1,3] It is documented that the nature of the substituent on the thione or thioaldehyde greatly influences the regiochemical outcome of their Diels−Alder reactions.[1] Electron-deficient substituents render the sulfur electrophilic and thus enlarge sulfur's orbital coefficient in the lowest unoccupied molecular orbital (LUMO). The regiochemistry of addition from the reaction of **1** with Danishefsky's diene **2**, for example, was interpreted in such a way (Scheme 1).[5] Recently, we reported a synthetic approach to the picrasane framework of anticancer quassinoids in which we used a regio- and stereoselective hetero-Diels−Alder reaction of α,α-dioxothiones **10b,c** and **11a** (Scheme 1, bottom).[4] Diethyl thiomalonate (**10b**, Figure 1) reacted with 1,3-diene **5** to afford a 1:2 mixture of cycloadducts **6b** and **7b** (Scheme 1). We were able to reverse the regioselectivity by using a bulkier malonate **10c**. Interestingly, thione **11a**, derived from Meldrum's acid,[6] led to a much increased ratio of 15:1 for **8a**:**9a**.

Relatively little information exists concerning the mechanism and selectivity issues of the Diels−Alder reactions of thiones and thioaldehydes, other than results using electronically very

(1) (a) Boger, D. L.; Weinreb, S. M. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic Press Inc.: San Diego, 1987; Organic Chemistry, a Series Monograph, Vol. 47, pp 120−145. (b) Weinreb, S. M.; Staib, R. S. *Tetrahedron* **1982**, *38*, 3087–3128.

(2) For a review on the use of thiocarbonyl compounds in carbon-carbon forming reactions, see: Metzner, P. *Synthesis* **1992**, 1185–1199.

(3) Vedejs, E.; Galante, R. J.; Goekjan, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 3613–3622.

(4) Perreault, S.; Spino, C. *Org. Lett.* **2006**, *8*, 4385–4388.

(5) (a) Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1983**, *105*, 6999–7001. (b) Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556–1562. (c) Vedejs, E.; Eberlein, T. H.; Varie, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445–1447.

(6) For a review of the use of Meldrum acid derivative in the synthesis of natural products, see: Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789–811.

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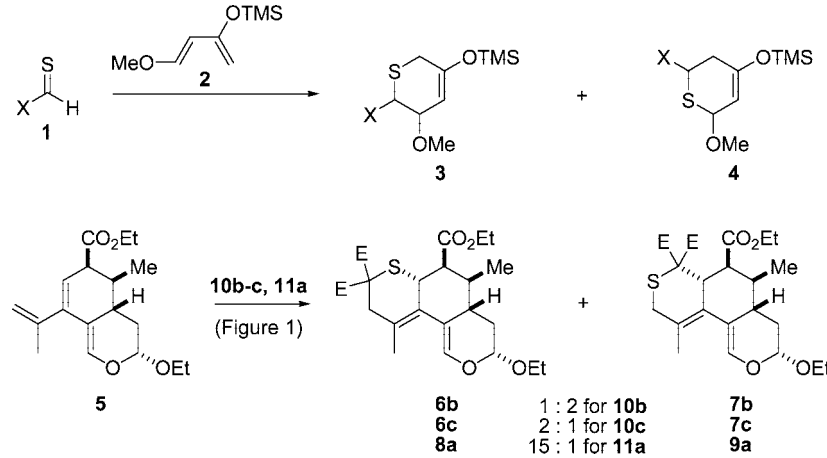
SCHEME 1. Diels−Alder Reactions of Thiones and Thioaldehydes



SCHEME 2. Cycloaddition Reactions of Thiones 10a or 11a−c with Isoprene 12

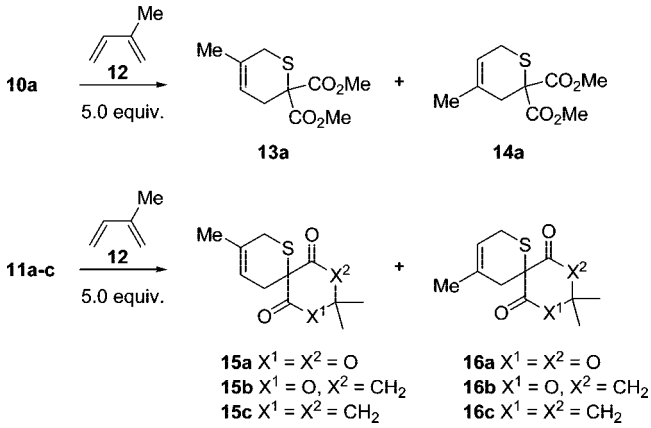


TABLE 1. Regioisomeric Ratios Obtained and Calculated in the Reaction of 12 with Thiones 10a and 11a−c

entry	thione	yield (%)[a]	exptl ratio of **13**:**14** or **15**:**16**[b]	calcd ratio[c]
1	**10a**	56	3:1	1.4:1
2	**11a**	53	15:1	6.1:1
3	**11b**	58	6:1	
4	**11c**	82	3:1	2.0:1

[a] Isolated yields of pure compounds. [b] Ratios measured by ^{1}H NMR. [c] Calculated from $\Delta G^{\ddagger}_{298}$ italic figures in Figures 2−7.

biased 1,3-dienes, such as Danishefsky's diene.[7] Malonate-derived thiones[8] **10a−c** and Meldrum's acid-derived thione **11a**[4] are highly reactive thiones that should give high regioselectivities in their Diels−Alder reactions. We herein disclose experimental results and detailed DFT calculations that demonstrate the exceptional characteristics of these thiones in formal [4 + 2]-cycloadditions. In addition, calculations suggest a new alternate, perhaps preferred, mechanism of reaction.

We chose isoprene **12** to initiate our study because it is a weakly electronically biased diene in Diels−Alder cycloadditions. In addition, steric effects are minimal in this diene and as such it was deemed ideal to study the difference in regioselectivity between various thiones. Thiones **10a−c** were formed by treatment of alkyl bromomalonates with elemental sulfur following Abelman's procedure,[8] while thiones **11a−c** were generated using the method of Capozzi[9] involving the phthalimide derivatives **19**. All thiones studied reacted at room temperature with isoprene to give regioisomer **13** or **15** as the major product, in line with what is expected if the C═S bond is polarized with the negative end at carbon and positive end at a sulfur (Scheme 2 and Table 1). The structure of the major regioisomer **15a** was unambiguously assigned from a single crystal X-ray diffraction analysis (see Supporting Information). The other structures could easily be inferred from comparison of ^{1}H NMR data. A look at Table 1 reveals a significant difference in regioselectivity between Meldrum's acid-derived thione **11a** and the other thiones (compare entry 2 with entries 1, 3, and 4). The lower levels of regioselectivity obtained with thiones **11b** and **11c** (entries 3 and 4) indicate that steric effects have little influence on the regiochemical outcome of these reactions. To gain better insight of the particularities of thione **11a**, we performed high-level calculations.

Computational Analysis. The B3LYP functional,[10] in conjunction with the 6-31+G(d) basis set, is known to give acceptable relative energies and geometries for a broad variety of pericyclic reactions. We then supplemented this original basis set with another d diffuse function and even a f diffuse function to all heavy atoms[11] to gain a better representation of the soft sulfur atom.[12] Therefore gas-phase transition structures (TSs) were optimized using the B3LYP functional and the 6-31+G(f2d) basis set. Harmonic vibrational frequencies (at the same level of theory) were employed to characterize optimized geometries as either first-order saddle structures (one imaginary frequency)

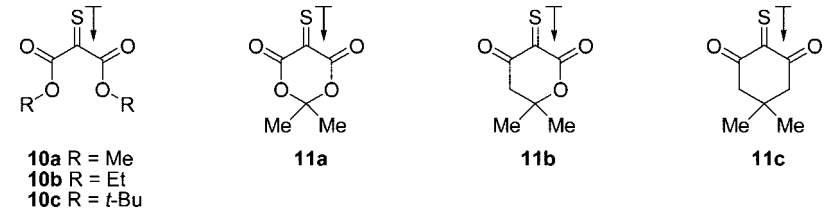


FIGURE 1. Structures of thiones **10** and **11**.

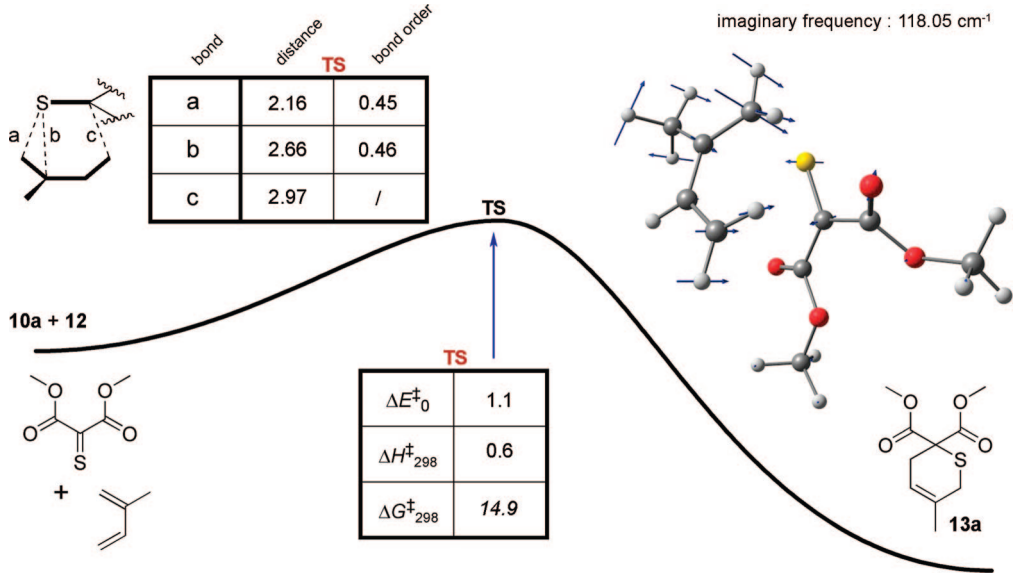


FIGURE 2. Calculated B3LYP/6-31+G(f2d) free energy profiles computed at 25 °C for the reaction of thione **10a** with isoprene **12** leading to major product **13a**. Bond distances (Å), bond orders, and relative energies (kcal/mol) are shown for the TS. The value of the only imaginary frequency of the TS is indicated together with a vectorial description of atomic motions.

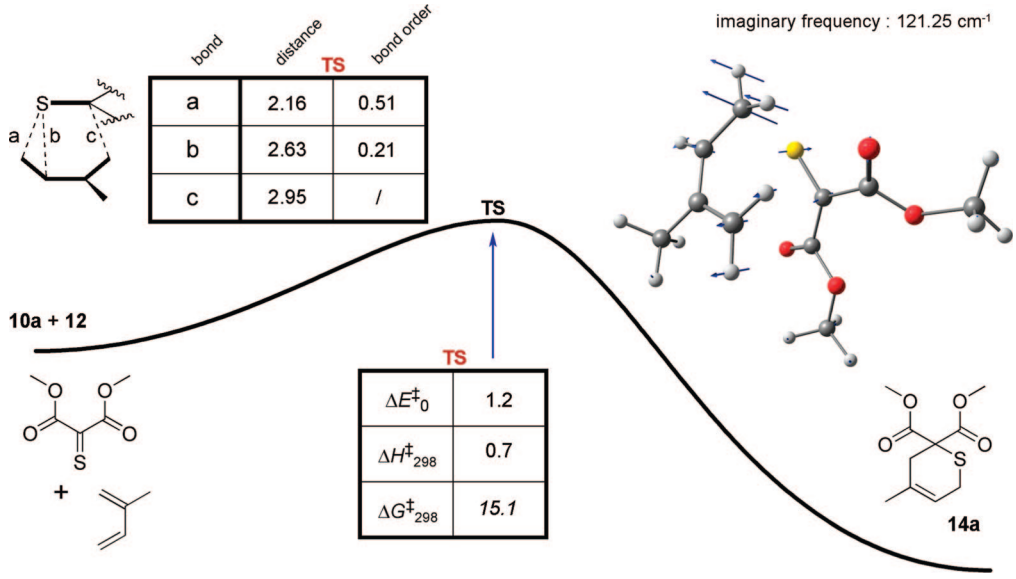


FIGURE 3. Calculated B3LYP/6-31+G(f2d) free energy profiles computed at 25 °C for the reaction of thione **10a** with isoprene **12** leading to minor product **14a**. Bond distances (Å), bond orders, and relative energies (kcal/mol) are shown for the TS. The value of the only imaginary frequency of the TS is indicated together with a vectorial description of atomic motions.

or minima (only real frequency) and to provide after scaling by 0.965[13] zero-point vibrational energies (ZPVEs) and enthalpies and free energies. ZPVE (0 K) corrected relative energies (ΔE_{rel}) were calculated using the electronic energies from optimized starting thiones **10a** and **11a,c** and isoprene **12** and TSs (i.e., $\Delta E_{relTS} = E_{TS} - E_{thione} - E_{12}$). All relative enthalpies ΔH_{rel} and free energies ΔG_{rel} were calculated at 25 °C. Salient TS ZPVE corrected relative energies and geometrical parameters are summarized in Figures 2−7. Adducts populations (**13a**−**14a**, **15a,c**−**16a,c**), calculated using the TS free energies, are presented in Table 1. The good agreement between synthetic and calculated regioselectivities for the reactions (Table 1) allows the experimental findings to be explained through interpretation of the TS geometries. IRC calculations[14] (B3LYP/6-31+(f2d)) confirmed that all isolated transition structures indeed belong to the reaction paths. The GAMESS (version 11, 2008) program was used throughout.[15] Optimized geometries (in Cartesian coordinate form) are provided as Supporting Information as well as IRC pathways as multistructures xyz files.

Examination of the theoretical calculations shows that dimethyl thiomalonate (**10a**) reacts with isoprene **12** in a one-step process to give regioisomeric adducts **13a** and **14a** through a Diels−Alder-like transition state (Figures 2 and 3). Despite being concerted, these reactions appear to be highly unsymmetrical as shown by the geometry of the transition states. While C−S distances a and b are relatively short (2.16 and 2.63−2.66 Å, respectively) the C−C distance c is very long (2.95−2.97 Å). Bond order[16] analysis of these transition states further reveals that both bonds a and b "contain" a fair share of electrons,

(7) For kinetic data on the Diels−Alder reactions of several diarylthiones, see: Rohr, U.; Schatz, J.; Sauer, J. *Eur. J. Org. Chem.* **1998**, 2875–2883.

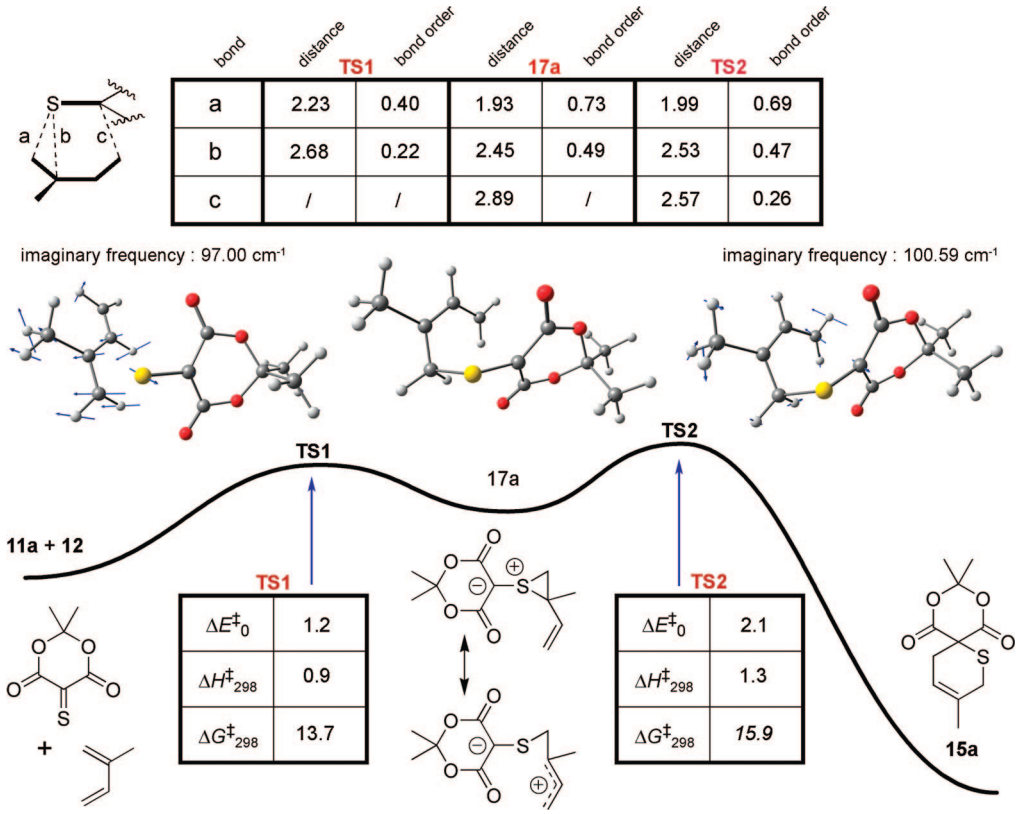


FIGURE 4. Calculated B3LYP/6-31+G(f2d) free energy profiles computed at 25 °C for the reaction of thione **11a** with isoprene **12** leading to major product **15a** via thiiranium zwitterion intermediate **17a**. Bond distances (Å), bond orders, and relative energies (kcal/mol) are shown for the TSs. The value of the only imaginary frequency of each TS is indicated together with a vectorial description of atomic motions.

whereas bond c is virtually "empty". This bonding pattern suggests that a transient thiiranium zwitterion species might appear along the pathway. Such three membered ring formed by the sulfur atom and one alkene of isoprene is more easily generated from the methyl substituted alkene (bond order for bond b of 0.46 and 0.21 in TSs leading to **13a** and **14a**, respectively, Figures 2 and 3). This difference of stability might be the dominant factor at work, resulting in preferred formation of adduct **13a**. The large asynchronicity of the transition state is confirmed by the motions of the atoms (imaginary frequency) of very large amplitude across bond a.

Equivalent concerted transition states were not located for reactions involving isoprene and thiones **11a,c**. Rather, multistage mechanisms were found. A first, least energetic step leads to thiiranium zwitterions intermediates **17a,c** and **18a,c** (Figures 4−7). The bond length and bond orders of these TS1s match closely with these of concerted TSs (Figures 2 and 3). It is noteworthy that all thiiranium zwitterions intermediates **17a,c** and **18a,c** are largely asymmetrical as reflected both in the bond lengths and bond orders for a and b. Canonical representations of these ions (Figures 4−7) are in excellent agreement with these theoretical observations. Bond a is consistently very short as in the final products **14a,c** and **15a,c**. Close examination of the most energetic determining step represented by TS2s indicates its true nature. This reaction consists in the transfer of the bond b electrons of the thiiranium zwitterions into bond c of the adducts. This is indeed strongly supported by TS2s bonds b and c of identical lengths (2.51−2.57 Å) and similar bond orders.

Results and Discussion

As discussed above, calculations indicate that the reactions of thiones **11a** and **11c** follow a [2 + 1]-cycloaddition pathway involving a transition state TS1 leading to the thiiranium zwitterion intermediates **17a** or **18c**, respectively. The intermediates then collapse to the cycloadducts **15a** and **15c**, respectively, via a second transition state TS2 (Figures 4 and 6). The reaction involving **10a** goes through a very asynchronous [4 + 2]-cycloaddition. Thiiranium ions are known and several theoretical treatments of them have been disclosed.[17] Toma and co-workers have also found, by calculation, a thiiranium

(8) (a) Abelman, M. M. *Tetrahedron Lett.* **1991**, *32*, 7389–7392. (b) Kirby, G. W.; McGregor, W. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3175–3181.
(9) Capozzi, G.; Menichetti, S.; Nativi, C.; Rosi, A.; Valle, G. *Tetrahedron* **1992**, *48*, 9023–9032.
(10) Hertwig, R. H.; Koch, W. *Chem. Phys. Lett.* **1997**, *268*, 345–351.
(11) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294–301.
(12) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265–3269.
(13) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502–16513.
(14) (a) Gonzales, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154–2161. (b) keywords used during calculations: $IRC PATH=GS2 STRIDE=0.25 $END.
(15) (a) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363. (b) Default OPTTOL=0.0001 value used during calculations.
(16) Mayer, I. *J. Comput. Chem.* **2007**, *28*, 204–221.
(17) (a) Chesnut, D. B. *Heteroat. Chem.* **2005**, *16*, 263–270. (b) Bravo, F.; Visto, A.; Alcázar, E.; Molas, P.; Bo, C.; Castillón, S. *J. Org. Chem.* **2003**, *68*, 686–691. (c) Taniguchi, N. *J. Org. Chem.* **2006**, *71*, 7874–7876. (d) Destro, R.; Lucchini, V.; Modena, G.; Pasquato, L. *J. Org. Chem.* **2000**, *65*, 3367–3370. (e) Fachini, M.; Lucchini, V.; Modena, G.; Pasi, M.; Pasquato, L. *J. Am. Chem. Soc.* **1999**, *121*, 3944–3950. (dd) Schmid, G. H.; Strukelj, M.; Dalipi, S.; Ryan, M. D. *J. Org. Chem.* **1987**, *52*, 2403–2407. (ee) Sromek, A. W.; Gevorgyan, V. *Top. Curr. Chem.* **2007**, *274*, 77–124. (f) Fox, D. J.; House, D.; Warren, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2462–2482.

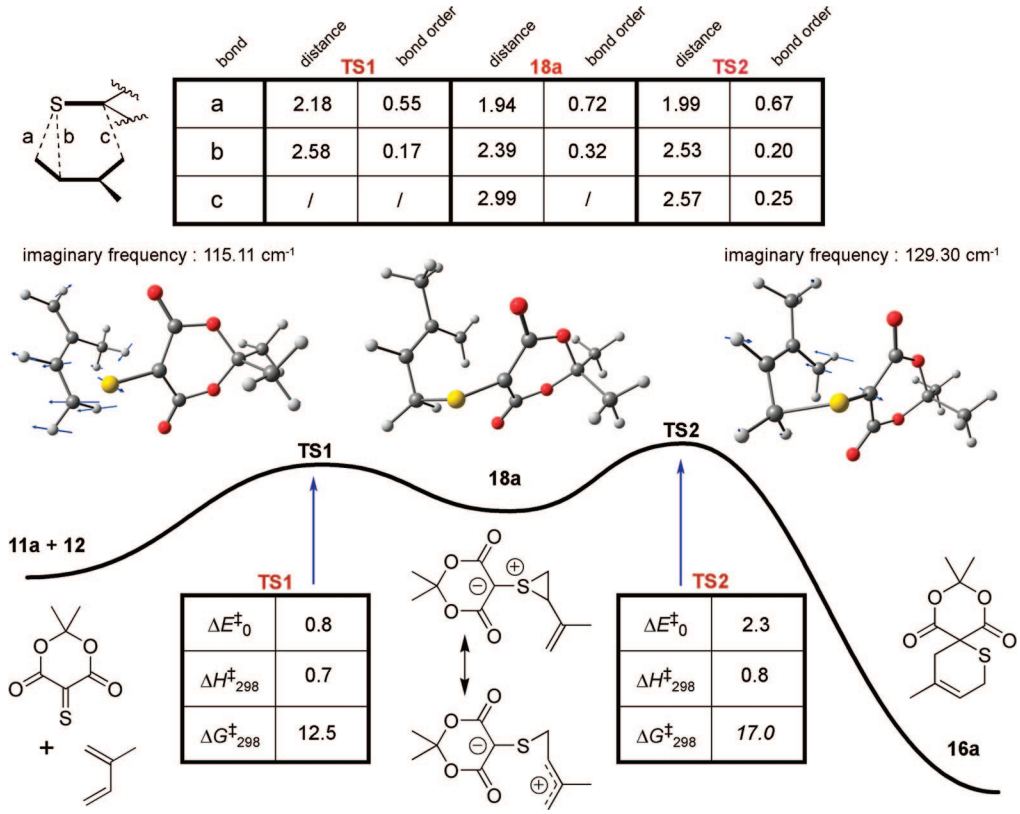


FIGURE 5. Calculated B3LYP/6-31+G(f2d) free energy profiles computed at 25 °C for the reaction of thione **11a** with isoprene **12** leading to minor product **16a** via thiiranium zwitterion intermediate **18a**. Bond distances (Å), bond orders and relative energies (kcal/mol) are shown for the TSs. The value of the only imaginary frequency of each TS is indicated together with a vectorial description of atomic motions.

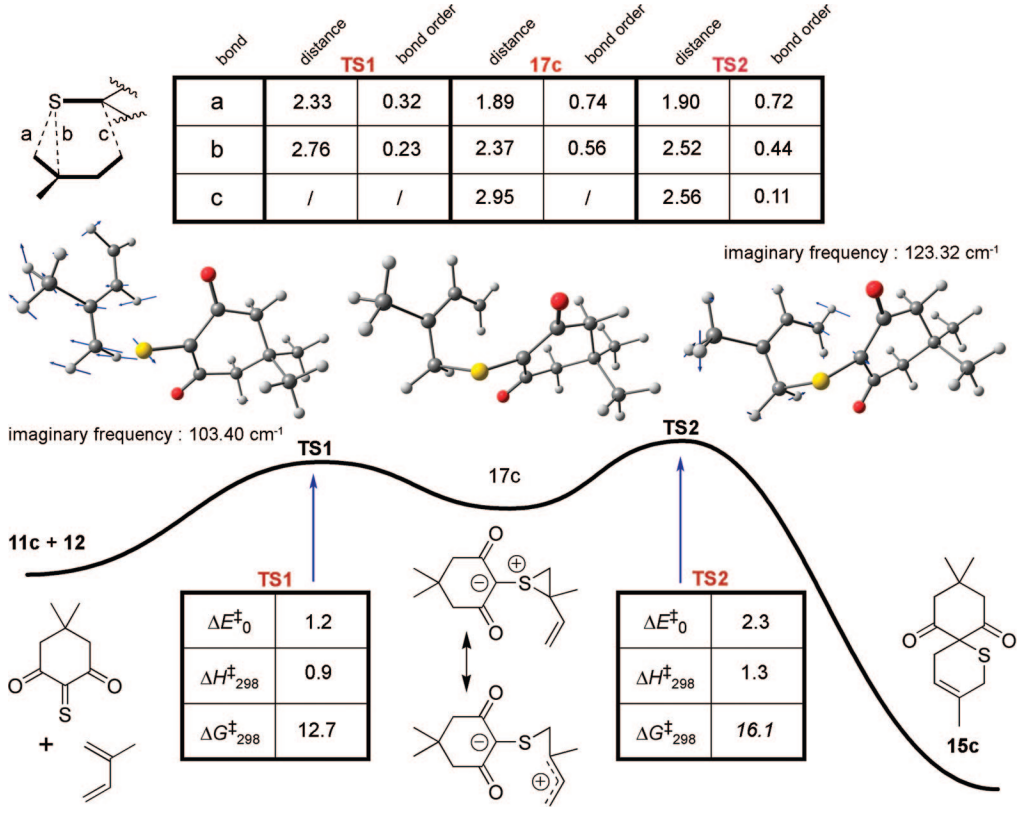


FIGURE 6. Calculated B3LYP/6-31+G(f2d) free energy profiles computed at 25 °C for the reaction of thione **11c** with isoprene **12** leading to major product **15c** via thiiranium zwitterion intermediate **17c**. Bond distances (Å), bond orders, and relative energies (kcal/mol) are shown for the TSs. The value of the only imaginary frequency of each TS is indicated together with a vectorial description of atomic motions.

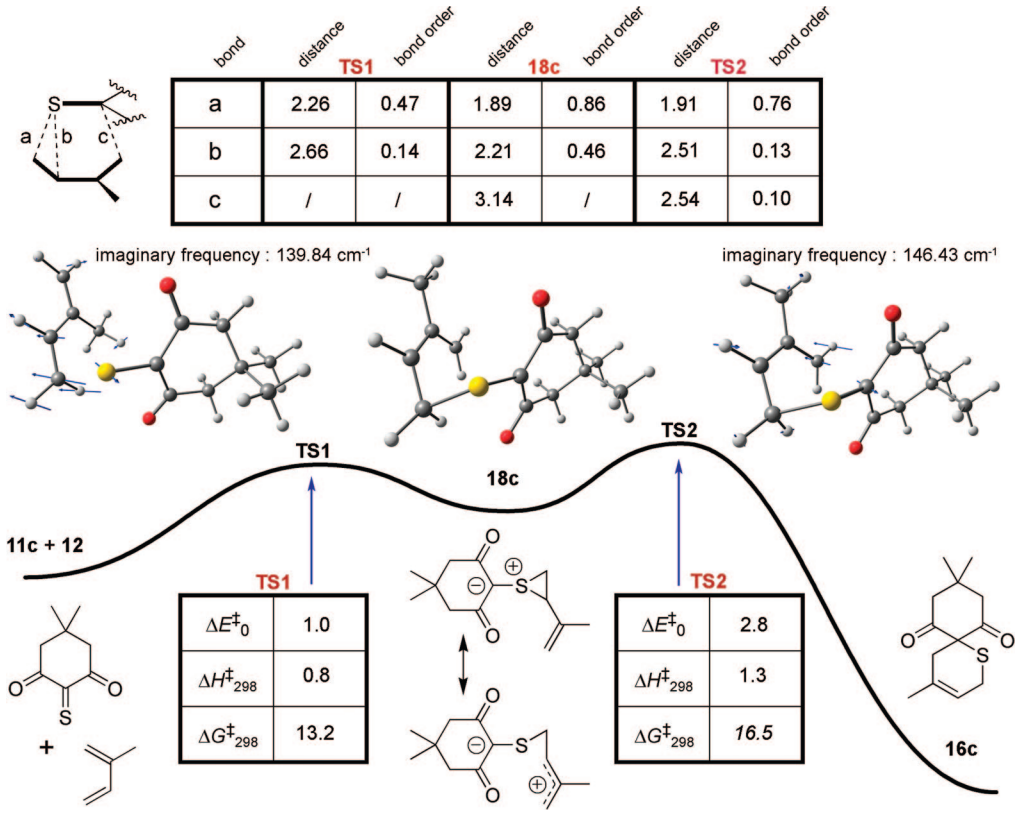
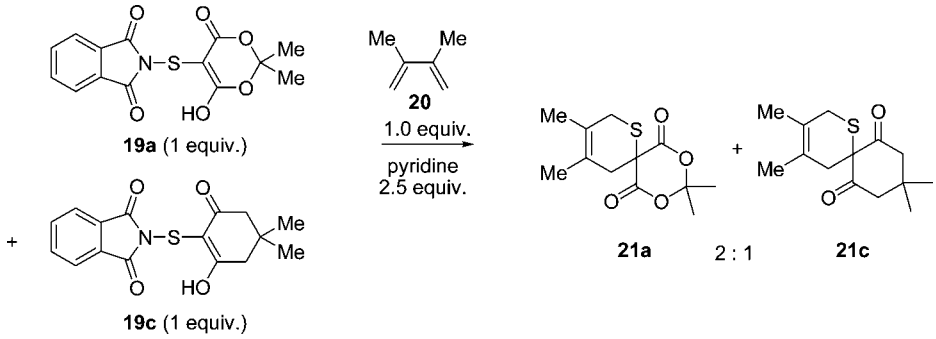


FIGURE 7. Calculated B3LYP/6-31+G(f2d) free energy profiles computed at 25 °C for the reaction of thione **11c** with isoprene **12** leading to minor product **16c** via thiiranium zwitterion intermediate **18c**. Bond distances (Å), bond orders, and relative energies (kcal/mol) are shown for the TSs. The value of the only imaginary frequency of each TS is indicated together with a vectorial description of atomic motions.

SCHEME 3. Competition between Thiones 11a and 11c for 2,3-Butadiene 20



zwitterion intermediate in the hetero-Diels−Alder reaction between methylvinyl ether (dienophile) and a thione analogous to **11b** (the diene).[18,19]

We ran a competition experiment opposing thiones **11a** and **11c** (1.0 equiv each) for their cycloaddition with 2,3-dimethylbutadiene **20** (1.0 equiv). We chose these two thiones for the competition experiment because of their small difference in terms of steric volume and also because they are generated under identical reaction conditions. We mixed the two thione precursors **19a** and **19c** in the presence of **20** and added the base (Scheme 3). Twice as much cycloadduct **21a** was formed than cycloadduct **21c**. So, thione **11a** is either more reactive than thione **11c** or it is formed faster. Either way, we believe this is a result of the higher polarization of the C═S bond in **11c**.

The higher polarization of thione **11a** in comparison to **10a**, **11b**, and **11c** may appear unexpected at first glance. However, we believe that the reasons behind this increased polarization parallel those behind the accrued acidity of Meldrum's acid **22**

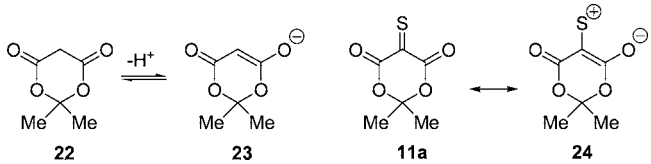
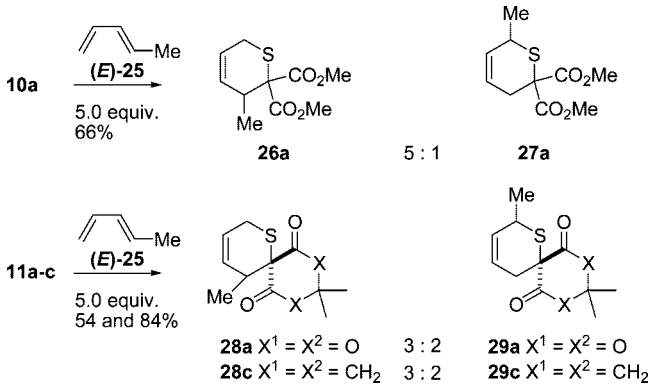


FIGURE 8. Parallel between the accrued acidity of Meldrum's acid and the higher polarization of thione **11a**.

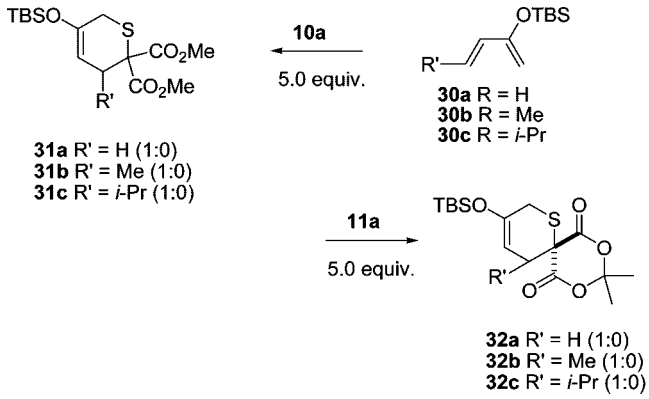
(18) (a) Legnani, L.; Lunghi, C.; Albini, F. M.; Nativi, C.; Richichi, B.; Toma, L. *Eur. J. Org. Chem.* **2007**, 3547–3554. For leading articles concerning the use of thiones as dienes, see: (b) Boccardo, G; Capozzi, G; Giuntini, M; Menichetti, S.; Nativi, C. *Tetrahedron* **1997**, *53*, 17383–17394. (c) Capozzi, G.; Franck, R. W.; Mattioli, M.; Menichetti, S.; Nativi, C.; Valle, G. *J. Org. Chem.* **1995**, *60*, 6416–6426. (d) Capozzi, G.; Menichetti, S.; Nativi, C.; Rosi, A.; Franck, R. W. *Tetrahedron Lett.* **1993**, *34*, 4253–4256.

(19) For a discussion on the cycloaddition of singlet oxygen and the possible involvement of a related perepoxide zwitterions, see: (a) Adam, W.; Prein, M. *Acc. Chem. Res.* **1996**, *29*, 275–283. (b) Leach, A.; Houk, K. N. *Chem. Commun.* **2002**, 1243–1255. (c) Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151–9179.

SCHEME 4. Regioselectivity of the Cycloadditions of Thiones 10a, 11a, and 11c with Diene 25



SCHEME 5. Perfectly Regioselective Reactions of Thiones 10a and 11a with Dienes 30a−c

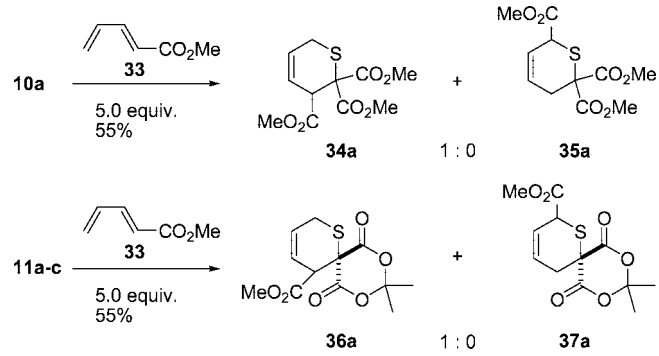


compared to the acids corresponding to **10a**, **11b**, and **11c** (CH_2 instead of C=S).[20] Indeed, the acidities of the β-dicarbonyl compounds corresponding to **11b** and **11c** were also found to be lower than that of Meldrum's acid itself.[20] Dipolar repulsion and electronic induction of the inner-ring oxygens have been invoked, among other reasons, as possible causes of this phenomenon.[20] In the same way the acidity of Meldrum's acid **22** is a reflection of the relative stability of the resulting enolate **23**, the higher reactivity and regioselectivity displayed by thione **11a** may be a reflection of the relative importance of its polarization, i.e. of its resonance structure **24** (Figure 8).

We probed the regioselectivity of the cycloadditions of thiones **10a**, **10b**, **11a**, and **11c** with several dienes (Schemes 4–7). We were surprised by the observed regioselectivities of additions for thiones **10a**, **11a**, and **11c** with diene *E*-**25** to give **26a**, and **28a,c** (Scheme 4). Normally, one would expect a C1-substituent in a diene (as in *E*-**25**) to better direct the regiochemical outcome of a cycloaddition than the same substituent at C2 (as in **12**). While this seems to be the case for thione **10a** (5:1 with *E*-**25** vs 3:1 with **12**), thiones **11a** and **11c** led to a lower ratio of regioisomers in their reaction with diene *E*-**25** than with isoprene. In each case, however, the major isomer was the one predicted on the basis of FMO theory. The fact that thiones **11a** and **11c** give the same ratio suggests that steric effects could be responsible for the lower-than-expected regioselectivity.

Yet, steric effects were not at all important in the cycloadditions between thiones **10a** or **11a** and electron-rich dienes **30a−c** (Scheme 5). Both thiones led to a single regioisomer with all three dienes **30a−c**.[21] Perhaps the strong influence exerted by the ether oxygen on the regiochemistry overrode steric effects in these cases.

SCHEME 6. Regioselectivity of the Cycloadditions of Thiones 10a and 11a with Diene 33



Thiones **10b** and **11a** reacted just as well with electron-poor dienes. Reaction with 1-carbomethoxy-1,3-butadiene (**33**) afforded in each case a single regioisomer **34a** or **36a** (Scheme 6). Compound **36a** is crystalline and amenable to X-ray diffraction analysis (see Supporting Information). If one considers the thione's sulfur atom as electrophilic, the regiochemical outcome of the reaction of thione **10a** and **11a** with **33** may seem counter-intuitive. However, one arrives at the correct prediction for the regiochemistry from FMO considerations ($HOMO_{diene}-LUMO_{thione}$). We wanted to see the effect a C2-ester would have but we could not use 2-carbomethoxy-1,3-butadiene because it dimerizes too fast.[22] We used instead 2-carbomethoxy-1-ethyl-1,3-butadiene (**38**). Again, thione **11a** led to a lower regioselectivity than expected in its reaction with **38** while thione **10a** reacted to give **34a** as the major product in a 11: 1 ratio (Scheme 7). These results, taken together with the ones shown in Scheme 1 for diene **5**, indicate that thiones **10a** (or **10b**) and **11a** are quite complementary. Thiones **10a,b** give reasonable ratios of regioisomers despite detrimental steric effects (dienes **25** or **38**), while thione **11a** gives very high regioselectivities when steric effects are minimal (isoprene **12**) or beneficial (diene **5**).

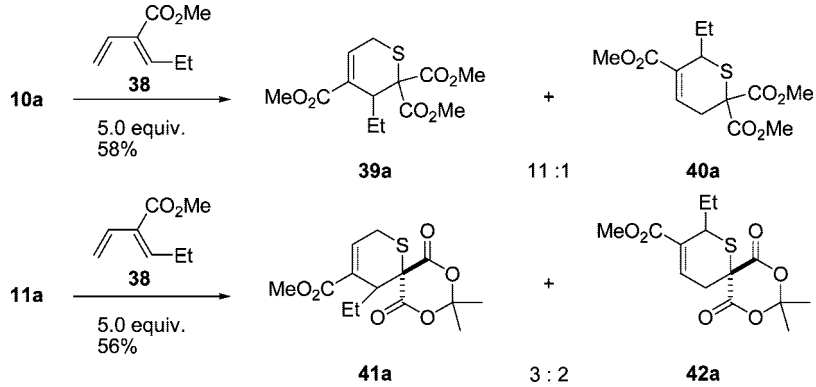
It is beyond the scope of this article to survey the methods to transform dihydrothiapyrans into useful products. It is worth mentioning, however, that we have found very mild conditions to cleave open the dioxanedione moiety of cycloadducts derived from thione **11a**. After several failed hydrolysis attempts using aqueous acidic media or Lewis acids, we found that catalytic $Ni(acac)_2$ in refluxing methanol hydrolyzed the dioxanedione fragment in **8a** without causing decomposition of this quite sensitive molecule (Scheme 8). Concomitant decarboxylation of the monocarboxylic acid afforded ester **44** in 95% yield. Alternatively, the β-hydroxy acid **43** was prepared in quantitative yield and as a single diastereomer by treating **8a** with sodium borohydride in THF. We could not ascertain the stereochemistry at the new chiral center in **43**.

(20) (a) Arnett, E. M.; Harrelson, J. A., Jr *J. Am. Chem. Soc.* **1987**, *109*, 809–812. (b) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1870–1872. (c) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872–1874. (d) Byun, K.; Mo, Y.; Gao, J. *J. Am. Chem. Soc.* **2001**, *123*, 3974–3979. (e) Nakamura, S.; Hirao, H.; Ohwada, T. *J. Org. Chem.* **2004**, *69*, 4309–4316. (f) Lee, I.; Han, I. S.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2003**, *24*, 1141–1149.

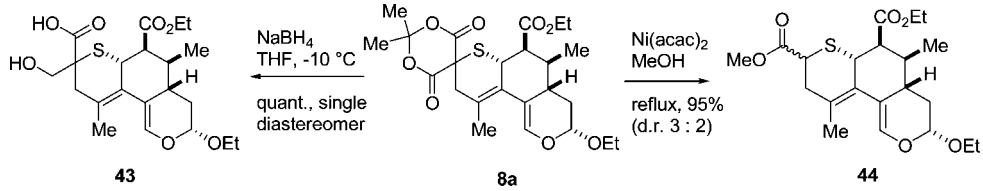
(21) The instability of the final products in these cases prevented their purification. However, the proton NMR spectra of the crude cycloadducts leave no doubt that only one isomer was formed in each case (see Supporting Information).

(22) (a) Sydnes, L. K.; Skattebøl, L.; Chapleo, C. B.; Leppard, D. G.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chim. Acta* **1975**, *58*, 2061–2073. (b) Spino, C.; Crawford, J. *Can. J. Chem.* **1993**, *71*, 1094–1097, and references therein.

SCHEME 7. Regioselectivity of the Cycloadditions of Thiones 10a and 11a with Diene 33



SCHEME 8. Mild Conditions for the Cleavage of the Dioxanedione Moiety



In conclusion, we have shown by experiments that thiones **10a** and **11a** are useful thiones in cycloadditions with electron-rich or electron-poor dienes. Calculations show a stepwise mechanism involving a thiiranium zwitterionic intermediate. Thiones **10a** and **11a** are complementary in that they can give different levels of regioselectivity depending on the electronics and sterics of the substrate. Lastly, it is possible to cleave open the dioxanedione moiety in cycloadducts derived from **11a** using very mild conditions. Cycloadducts from such reactions can be useful synthetic intermediates, and we are currently using this methodology in the synthesis of complex terpenes of the quassinoids family.

Experimental Section

General Procedure A for the Cycloaddition Reactions of Dienes 12, 20, 30, 33, and 38 with Thiones 11a−c. Diene (1.2−5.0 equiv) was added to a solution (or suspension) of thione precursor (1.0 equiv) in dichloromethane (0.2 M) at room temperature. Pyridine (1.1 equiv) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl. The phases were separated, and the aqueous phase was extracted three times with dichloromethane. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product was purified by flash chromatography on a silica gel column.

General Procedure B for the Cycloaddition Reactions of Dienes 12, 20, 30, 33, and 38 with Thiones 10a,b. A solution of dimethylbromomalonate (90%, available from Aldrich, 1.0 equiv) or diethylbromomalonate (available from Aldrich, 1.0 equiv) in dichloromethane (0.2 M) was added over a period of 3 h with a syringe pump to a mixture of diene (1.2 to 5.0 equiv), triethylamine (1.5 equiv), and sulfur powder (2.0 equiv) in dichloromethane (0.2 M) at room temperature. The reaction mixture was stirred overnight at room temperature, filtered on Celite, and evaporated under reduced pressure. The crude product was purified by flash chromatography on a silica gel column.

Dihydrothiopyrans 13a and 14a. Reaction of isoprene **12** (425 μL, 4.25 mmol) with dimethylbromomalonate (200 mg, 0.85 mmol) according to general procedure B. The crude product (3:1 mixture of **13a** and **14a**) was purified by flash chromatography on a silica gel column eluting with 10% ethyl acetate in hexanes to give **13a** and **14a** (110 mg, 56% of 3:1 mixture) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.61−5.57 (m, 1H of **13a**), 5.56−5.51 (m, 1H of **14a**), 3.78 (s, 6H), 3.21−3.17 (m, 2H of **14a**), 3.09 (s, 2H of **13a**), 2.80−2.76 (m, 2H of 220), 2.67 (s, 2H of 221), 1.75 (s, 3H). IR ($CHCl_3$, cm^{-1}): 3045, 2996, 2954, 2920, 1737, 1267. LRMS (*m*/*z*, relative intensity): 230 (M^+, 70), 155 (45), 139 (40), 111 (100). HRMS calcd for $C_{10}H_{14}O_4S$ 230.0613, found 230.0615.

Dihydrothiopyrans 15a and 16a. Reaction of isoprene **12** (156 μL, 1.55 mmol) with 2,2-dimethyl-5-(phtalimide-*N*-sulfenyl)-[1,3]dioxane-4,6-dione (**19b**) (100 mg, 0.31 mmol) according to general procedure A. The crude product (15:1 mixture of **15a** and **16a**) was purified by flash chromatography on a silica gel column eluting with 10% ethyl acetate in hexanes to give **15a** and **16a** (41 mg, 55% of 15:1 mixture) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.76 (br s, 1H of **16a**), 5.64 (br s, 1H of **15a**), 3.36−3.32 (m, 1H of **16a**), 3.20 (s, 1H of **15a**), 2.89−2.84 (m, 1H of **15a**), 2.72 (s, 1H of 215), 2.01 (s, 3H of **16a**), 2.00 (s, 3H of 214), 1.85 (s, 3H of **15a**) 1.82 (s, 3H of **16a**), 1.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 164.9 (s), 129.0 (s), 119.8 (d), 106.2 (s), 44.3 (s), 30.7 (t), 29.5 (q), 29.4 (t), 27.4 (q), 23.9 (q). IR ($CHCl_3$, cm^{-1}): 2993, 2936, 2912, 1732. LRMS (*m*/*z*, relative intensity): 242 (M^+, 3), 184 (20), 156 (85), 140 (40), 111 (100). HRMS calcd for $C_{11}H_{14}O_4S$ 242.0613, found 242.0616. Mp: 83−85 °C.

2,2-Dimethyl-5-(phtalimide-*N*-sulfenyl)-[1,3]dioxane-4,6-dione (19a). *N*-(Chlorosulfenyl)phtalimide[23] (1.72 g, 8.1 mmol) was dissolved in THF (10.0 mL) and the solution was cooled to −10 °C. A solution of 2,2-dimethyl-[1,3]dioxane-4,6-dione (Meldrum's acid) (700 mg, 4.9 mmol) in THF (5.0 mL) was then added over a 15 min period. The mixture was stirred 1 h at −10 °C. The solid obtained was filtered, washed with cold THF and dried under vacuum to give **19a** (1.44 g, 92%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95−7.92 (m, 2H), 7.85−7.80 (m, 2H), 1.86 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.4 (s), 161.0 (s), 135.2 (d), 134.3 (s), 131.6 (s), 124.5 (d), 124.3 (s), 123.6 (s), 107.7 (s), 58.5 (s), 28.3 (q). IR (neat, cm^{-1}): 3202, 3061, 1744, 1714. LRMS (*m*/*z*, relative intensity): 356 ($C_{16}H_8N_2O_4S_2$, 10), 324 ($C_{16}H_8N_2O_4S$, 10), 147 ($C_8H_5NO_2$, 100). Mp: 189 °C (degradation).

Dihydrothiopyrans 26a and Its Regioisomer 27a. Reaction of *trans*-1,3-pentadiene (*E*)-**25** (425 μL, 4.26 mmol) with dimethylbromomalonate (200 mg, 0.85 mmol) according to general procedure B. The crude product (5:1 mixture of **26a** and **27a**) was purified by flash chromatography on a silica gel column eluting with 3%

ethyl acetate in hexanes to give **26a** (87 mg, 44%) and a 1:1 mixture of **26a/27a** (43 mg, 22%) as colorless oils.

26a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.84−5.70 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.17 (dq, 1H, J = 17.6 and 2.2 Hz), 3.07−2.97 (m, 1H), 2.97 (dd, 1H, J = 17.6 and 5.0 Hz), 1.07 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 168.8 (s), 168.5 (s), 132.4 (d), 120.7 (d), 60.8 (s), 53.2 (q), 33.3 (d), 25.6 (t), 17.1 (q). IR ($CHCl_3$, cm^{-1}): 3035, 3008, 2962, 1734, 1253. LRMS (*m*/*z*, relative intensity): 230 (M^+, 40), 155 (85), 111 (100). HRMS calcd for $C_{10}H_{14}O_4S$ 230.0613, found 230.0617.

27a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.85−5.73 (m, 1H), 5.70 (dq, 1H, J = 11.0 and 2.2 Hz), 3.80 (s, 3H), 3.78 (s, 3H), 3.64−3.53 (m, 1H), 2.86 (dm, 1H, J = 17.6 Hz), 2.69 (dm, 1H, J = 17.6 Hz), 1.32 (d, 3H, J = 7.1 Hz). IR ($CHCl_3$, cm^{-1}): 3034, 3007, 2962, 1733, 1252. LRMS (*m*/*z*, relative intensity): 230 (M^+, 30), 198 (50), 155 (75), 111 (100). HRMS calcd for $C_{10}H_{14}O_4S$ 230.0613, found 230.0608.

Dihydrothiopyrans 28a and Its Regioisomer 29a. Reaction of *trans*-1,3-pentadiene (*E*)-**25** (155 μL, 1.55 mmol) with 2,2-dimethyl-5-(phtalimide-*N*-sulfenyl)-[1,3]dioxane-4,6-dione (**19a**) (100 mg, 0.31 mmol) according to general procedure A. The crude product (3:2 mixture of **28a** and **29a**) was purified by flash chromatography on a silica gel column eluting with 5% ethyl acetate in hexanes to give **28a** (134 mg, 35%) and **29a** (70 mg, 19%) as white solids.

28a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.98−5.91 (m, 1H), 5.68 (dq, 1H, J = 10.7 and 2.2 Hz), 3.54 (dq, 1H, J = 17.3 and 2.2 Hz), 3.46−3.39 (m, 1H), 3.17 (ddt, 1H, J = 17.3, 5.7 and 1.6 Hz), 1.97 (s, 3H), 1.74 (s, 3H), 1.07 (d, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.2 (s), 161.8 (s), 131.3 (d), 121.5 (d), 105.9 (s), 48.9 (s), 35.8 (d), 28.9 (q), 27.8 (q), 26.2 (t), 16.5 (q). IR ($CHCl_3$, cm^{-1}): 3034, 3000, 2973, 1771, 1592, 1290. LRMS (*m*/*z*, relative intensity): 242 (M^+, 1), 184 (60), 156 (100), 111 (100), 97 (90). HRMS calcd for $C_{11}H_{14}O_4S$ 242.0613, found 242.0607. Mp: 74−76 °C.

29a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.93 (dm, 1H, J = 10.5 Hz), 5.84 (dm, 1H, J = 10.5 Hz), 3.75−3.66 (m, 1H), 3.14 (dq, 1H, J = 18.0 and 2.7 Hz), 2.56 (dm, 1H, J = 18.0 Hz), 2.02 (s, 3H), 1.75 (s, 3H), 1.37 (d, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 165.7 (s), 164.3 (s), 129.0 (d), 125.1 (d), 106.4 (s), 49.9 (s), 34.5 (d), 29.6 (t), 29.4 (q), 27.5 (q), 18.6 (q). IR ($CHCl_3$, cm^{-1}): 3034, 3000, 2977, 1737, 1592, 1294. LRMS (*m*/*z*, relative intensity): 242 (M^+, 2), 156 (95), 140 (85), 111 (85), 97 (100). HRMS calcd for $C_{11}H_{14}O_4S$ 242.0613, found 242.0609. Mp: 69−70 °C.

Dihydrothiopyrans 28c and Its Regioisomer 29c. Reaction of *trans*-1,3-pentadiene (*E*)-**25** (155 μL, 1.55 mmol) with 5,5-dimethyl-2-(phtalimide-*N*-sulfenyl)cyclohexane-1,3-dione (**16d**) (99 mg, 0.31 mmol) according to general procedure A. The crude product (3: 2 mixture of **28c** and **29c**) was purified by flash chromatography on a silica gel column eluting with 10% ethyl acetate in hexanes to give **28c** (40 mg, 53%) and **29c** (24 mg, 31%) as white solids.

28c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.76−5.66 (m, 2H), 3.45 (d, 1H, J = 14.8 Hz), 3.30−3.22 (m, 1H), 3.22−3.02 (m, 2H), 3.01 (d, 1H, J = 14.8 Hz), 2.44 (dd, 1H, J = 14.8 and 2.7 Hz), 2.26 (dd, 1H, J = 14.8 and 2.7 Hz), 1.12 (s, 3H), 1.05 (d, 3H, J = 7.1 Hz), 0.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 203.2 (s), 200.7 (s), 133.9 (d), 119.2 (d), 64.0 (s), 50.9 (t), 49.4 (t), 31.1 (d), 30.5 (s), 30.2 (q), 26.1 (t), 26.1 (q), 16.7 (q). IR ($CHCl_3$, cm^{-1}): 2961, 2885, 1725, 1695. LRMS (*m*/*z*, relative intensity): 238 (M^+, 70), 223 (30), 83 (100). HRMS calcd for $C_{13}H_{18}O_2S$ 238.1027, found 238.1030. Mp: 43−44 °C.

29c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.96−5.89 (dm, 1H, J = 10.4 Hz), 5.59 (dm, 1H, J = 10.4 Hz), 3.66 (d, 1H, J = 14.3 Hz), 3.44−3.34 (m, 1H), 3.23 (d, 1H, J = 13.8 Hz), 2.84 (dq, 1H, J = 18.4 and 2.7 Hz), 2.36 (dd, 1H, J = 13.8 and 2.7 Hz), 2.32 (dq, 1H, J = 18.4 and 2.7 Hz), 2.25 (dd, 1H, J = 14.3 and 2.7 Hz), 1.29 (d, 3H, J = 7.1 Hz), 1.18 (s, 3H), 0.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 202.8 (s), 127.2 (d), 63.7 (s), 50.9 (t), 49.0 (t), 34.6 (d), 31.0 (s), 30.4 (q), 26.1 (q), 24.0 (t), 19.5 (q). IR ($CHCl_3$, cm^{-1}): 2958, 2927, 2874, 1729, 1695. LRMS (*m*/*z*, relative intensity): 238 (M^+, 100), 223 (65), 83 (100). HRMS calcd for $C_{13}H_{18}O_2S$ 238.1027, found 238.1030. Mp: 91−92 °C.

Dihydrothiopyrans 34a and Its Regioisomer 35a. Reaction of diene **33** (60 mg, 0.43 mmol) with dimethylbromomalonate (41 mg, 0.28 mmol) according to general procedure B. The crude product (11: 1 mixture of **34a** and **35a**) was purified by flash chromatography on a silica gel column eluting with 10% to 20% ethyl acetate in hexanes to give **34a** (42 mg, 50%), **35a** (2 mg, 2%) and a mixture of **34a /35a** (5 mg, 6%) as colorless oils.

34a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.97 (dd, 1H, J = 5.0 and 3.3 Hz), 3.82 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 3.63 (t, 1H, J = 6.3 Hz), 3.39 (ddd, 1H, J = 19.2, 3.3 and 1.7 Hz), 3.26 (dd, 1H, J = 19.2 and 5.0 Hz), 1.61−1.51 (m, 2H), 0.88 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 168.6 (s), 168.2 (s), 167.3 (s), 134.5 (s), 132.0 (d), 61.8 (s), 53.4 (q), 52.1 (q), 38.4 (d), 26.5 (t), 26.0 (t), 11.8 (q). IR ($CHCl_3$, cm^{-1}): 3035, 3000, 2953, 2878, 2842, 1738, 1728, 1710, 1265. LRMS (*m*/*z*, relative intensity): 302 (M^+, 1), 270 (100), 213 (40), 183 (40). HRMS calcd for $C_{13}H_{18}O_6S$ 302.0824, found 302.0828.

35a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.11 (t, 1H, J = 4.4 Hz), 3.82−3.73 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.10 (ddd, 1H, J = 18.5, 4.4 and 1.7 Hz), 2.87 (ddd, 1H, J = 18.5, 4.4 and 1.8 Hz), 1.91−1.77 (m, 1H), 1.47−1.36 (m, 1H), 1.02 (t, 3H, J = 7.1 Hz). LRMS (*m*/*z*, relative intensity): 302 (M^+, 1), 270 (60), 241 (60), 213 (100). HRMS calcd for $C_{13}H_{18}O_6S$ 302.0824, found 302.0828.

Dihydrothiopyrans 36a and Its Regioisomer 37a. Reaction of diene **33** (65 mg, 0.46 mmol) with 2,2-dimethyl-5-(phtalimide-*N*-sulfenyl)-[1,3]dioxane-4,6-dione (**19a**) (100 mg, 0.31 mmol) according to general procedure A. The crude product (3: 2 mixture of **36a** and **37a**) was purified by flash chromatography on a silica gel column eluting with 10% to 25% ethyl acetate in hexanes to give **36a** and **37a** (55 mg, 56% of 3:2 mixture) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (t, 1H of **37a**, J = 5.0 Hz), 7.11 (td, 1H of **36a**, J = 4.6 and 1.5 Hz), 3.95−3.90 (m, 1H of **37a**), 3.79 (s, 3H of **37a**), 3.77 (s, 3H of **36a**), 3.68−3.64 (m, 1H of **36a**), 3.52 (dd, 2H of **36a**, J = 4.6 and 1.5 Hz), 3.10 (dd, 2H of **37a**, J = 5.0 and 1.1 Hz), 2.07 (s, 3H of **37a**), 1.91 (s, 3H of **36a**), 1.88−1.77 (m, 2H of **36a**), 1.82 (s, 3H of **36a**), 1.75 (s, 3H of **37a**), 1.69−1.52 (m, 2H of **37a**), 1.01 (t, 3H of **37a**, J = 7.1 Hz), 0.93 (t, 3H of **37a**, J = 7.7 Hz). IR ($CHCl_3$, cm^{-1}): 2953, 2878, 1776, 1738, 1729, 1710, 1291. LRMS (*m*/*z*, relative intensity): 283 ($(M - OMe)^+$, 1), 282 ($(M - MeOH)^+$, 2), 228 (20), 212 (50), 199 (100), 155 (70). HRMS calcd for $C_{13}H_{15}O_5S$ (M − OMe) 283.0640, found 283.0631. Mp: 118−119 °C.

1-Ethyl-2-carbomethoxy-l,3-butadiene 38. To a stirred solution of 2,5-dihydro-1,1-dioxyde-3-(methylcarboxylate)thiophene (available from Aldrich, 840 mg, 4.76 mmol) in THF (50 mL) at −78 °C was added a 1.60 M solution of *n*-BuLi in hexanes (6.20 mL, 9.92 mmol). The solution was stirred for 30 min at −78 °C and iodoethane (0.55 mL, 6.86 mmol) was added. The mixture was stirred 45 min at −78 °C and quenched with 1 N HCI. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed once with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a yellowish oil. A solution of this oil in toluene (10 mL) was stirred at 110 °C for 3 h. The solution was evaporated under reduced pressure and the crude product was purified by flash chromatography on a silica gel column eluting with 5% ethyl acetate in hexanes to give **38** (240 mg, 36% for 2 steps, *Z*/*E* = 6:1) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.73 (t, 1H of *E*, J = 7.7 Hz), 6.46 (dd, 1H of *E*, J = 17.6 and 11.5 Hz), 6.33 (dd, 1H of *Z*, J = 17.6 and 10.5 Hz), 5.95 (t, 1H of *Z*, J = 7.7 Hz), 5.55 (dd, 1H of *E*, J = 17.6 and 1.7 Hz), 5.37 (d, 1H of *E*, J = 11.5 Hz), 5.25 (d, 1H of *Z*, J = 17.6 Hz), 5.09 (d, 1H of *Z*, J = 10.5 Hz), 3.81 (s, 3H of *Z*), 3.76 (s, 3H of *E*), 2.36−2.25 (m, 2H), 1.04 (t, 3H of *Z*, J = 7.1 Hz), 0.90 (t, 3H of *E*, J = 7.1 Hz). IR ($CHCl_3$,

cm^{-1}): 3019, 2399, 1520, 1423, 1221, 1210. LRMS (*m*/*z*, relative intensity): 140 (M^+). HRMS calcd for $C_8H_{12}O_2$ 140.0837, found 140.0840.

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Supporting Information Available: Characterization data for all new compounds not included in the experimental section and ^1H NMR spectra for all new compounds; X-ray crystallographic data for compounds **15a** and **36a** in CIF format; video clips of cycloaddition reactions with isoprene. This material is available free of charge via the Internet at http://pubs.acs.org.

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