Interesting Contrasts in Electrocyclic Reactions for Thieno[3,2-*b*]- and -[2,3-*b*]pyrans with Chromenes[1]

Ignatius J. Turchi,† Jeffery B. Press,*,§ James J. McNally,§ Mary Pat Bonner,*,§ and Kirk L. Sorgi‡

Medicinal Chemistry Department and Chemical Development Department, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477, and Chemical Development Department, The R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869

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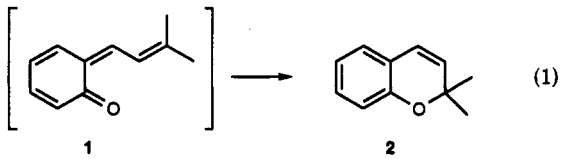
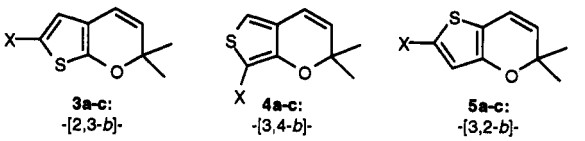
Thienopyrans **3**, **4**, and **5** were synthesized and found to have remarkable differences in stability. Systems **3** and **5** undergo electrocyclic ring-opening to **8** and **18**, respectively. In acid milieu at room temperature, system **5** exists in an equilibrium with ring-opened thienopyranone **18**. Ground state and activation parameters for the open and closed forms of thienopyrans **3** and **5** as well as the isosteric chromene **2** were calculated using the AM1 Hamiltonian. The Gibbs' free energy differences between the open and closed isomers in each system were found to be predictive of the observed equilibria. The mechanism for ring-opening in both thienopyran systems is proposed to be acid-catalyzed based on the calculated temperatures required for ring-opening as well as experimentally determined results.

Electrocyclization of *o*-quinomethides **1** is a well-known preparative route to a variety of benzopyrans **2** (eq 1).[2] In all reported cases, quinomethide intermediates are generated in situ but are never directly observed, presumably due to their facile cyclization to benzopyran products.[3] Ring-opening of chromenes may be accomplished by irradiation to give highly colored quinomethides, which cannot be isolated as a consequence of spontaneous reversion to the colorless benzopyrans.[4] However, quinomethides generated in the presence of methanol can be trapped as their methanol adducts; heating these adducts causes elimination of methanol, regenerating the quinomethides which spontaneously cyclize to the benzopyran.[5] All of these data indicate that the electrocyclization of quinomethides to benzopyrans is a thermodynamically favored reaction.



1 2 (1)

As a part of our ongoing research of thiophene isosteres of benzo-fused systems,[1] we attempted to synthesize **3**, **4**, and **5**, the thiophene isosteres of chromene. In principle, these derivatives may be prepared from the appropriately substituted derivatives of the previously reported thienopyranones[6] by borohydride reduction and subsequent acid-catalyzed dehydration.



a: X=H; b: X=Cl; c: X=Br

In fact, alcohol **7a** forms in high yield from **6a** by the action of sodium borohydride, but when **7a** is treated with *p*-toluenesulfonic acid in methylene chloride, even at 0 °C, complete decomposition occurs without formation of any detectable amounts of **3a** (Scheme I). In order to examine what effects substitution on the thiophene ring may have, derivatives such as **3b** and **3c** were required. Halogenation of thieno[2,3-*b*]pyranone **6a** with sulfuryl chloride or *N*-bromosuccinimide gives the expected halogenated derivatives **6b** and **6c**, respectively, and reduction to the corresponding alcohols **7b** and **7c** proceeds in high yield. However, when **7b** or **7c** is treated with *p*-toluenesulfonic acid, none of the expected pyran **3b** or **3c** is produced. Instead, ring-opened *Z*-derivatives **8b** and **8c** form exclusively and slowly isomerize upon standing (or more rapidly upon exposure to iodine) to *E*-derivatives **9b** and **9c**, respectively. These ring-opened products presumably arise from the desired pyrans **3b** and **3c** by an unanticipated and facile $6\pi[4n+2]$ electrocyclic ring-opening to isosteres of *o*-quinomethides or by ring-opening of a carboniun ion intermediate formed during dehydration or protonation. We were struck by the spontaneous ring-opening of **3b** and **3c** and by the facility with which the aromaticity of the thiophene ring is lost which is in contrast to *o*-quinomethides which spontaneously ring-close to the corresponding benzopyrans.

Further investigation shows that a similar ring-opening does not occur in the isomeric thieno[3,4-*b*]pyrans **4**. Alcohol **11a** (prepared by reduction of ketone **10**[6]) de-

† Chemical Development Department, Raritan, NJ.
‡ Chemical Development Department, Spring House, PA.
§ Medicinal Chemistry Department.

(1) This is the 16th paper in our series of studies of thiophene systems. For the previous paper, see: Sanfilippo, P. J.; McNally, J. J.; Press, J. B.; Falotico, R.; Giardino, E.; Katz, L. B. *Bio. Org. Med. Chem. Lett.* **1993**, *3*, 1385.

(2) For reviews of synthesis of chromenes see: (a) Hepworth, J. D. Pyrans and Fused Pyrans: (iii) Synthesis and Applications. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 3, pp 737–874. (b) Schweizer, E. E.; Meeder-Nycz, D. 2*H*- and 4*H*-Benzopyrans. *Chromenes, Chromanones and Chromones*; Ellis, G. P., Ed.; John Wiley & Sons: New York, 1977; Vol. 31, pp 11–140.

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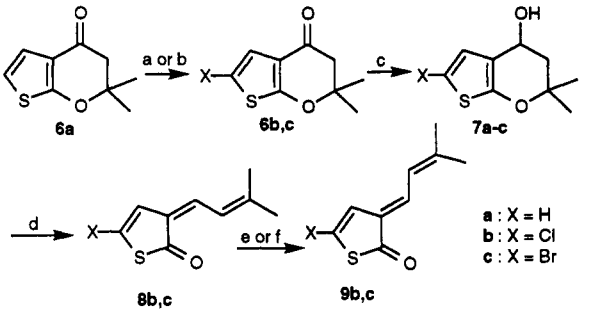
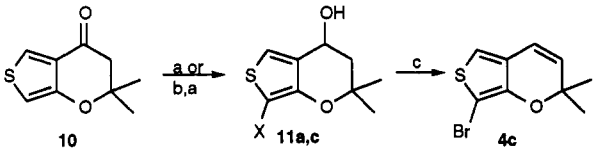
Scheme I[a]



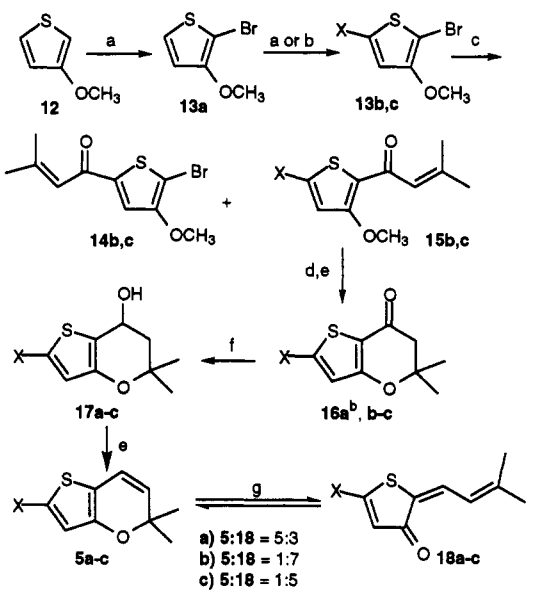
[a] (a) SO_2Cl_2; (b) NBS; (c) $NaBH_4$; (d) *p*-TSA; (e) rt, weeks (f) I_2.

Scheme II[a]



[a] (a) $NaBH_4$; (b) NBS; (c) *p*-TSA, Δ.

Scheme III[a]



[a] (a) NBS; (b) NCS; (c) *n*-BuLi, $(Me)_2CH{=}CHCONMe(OMe)$; (d) BCl_3; (e) *p*-TSA, (f) $NaBH_4$; (g) $CHCl_3$.[b] See ref 6.

composes upon heating in the presence of *p*-toluenesulfonic acid with no detectable formation of dehydration or ring opened products. Alcohol **11c** (derived by bromination of **10** prior to borohydride reduction) dehydrates to form thienopyran **4c** only after heating and there is no evidence or ring-opening during the reaction (Scheme II).

We recently reported the synthesis and chemical elaboration of thieno[3,2-*b*]pyran **5a**[7] as a part of a program to synthesize thiophene isosteres of the potassium channel opener cromakalim.[8] In contrast to the -[2,3-*b*]-(**3a**) and -[3,4-*b*]-(**4a**) derivatives, **5a** could be isolated and stored for several hours. However, prolonged storage, even at 0 °C, resulted in the formation of multiple products. In order to make direct comparisons between this system and the substituted -[2,3-*b*]-(**3b,c**) and [3,4-*b*]-(**4c**) derivatives (*vide supra*), halogenated derivatives **5b** and **5c** were required. Attempts to halogenate **5a** or alcohol **17a** directly (Scheme III) gave intractable mixtures of decomposition products, while the precursor thienopyranone **16a** reacted to give substitution α to the ketone. Thus, an alternate synthesis of derivatives **5b** and **5c** was developed (Scheme III).

Reaction of 3-methoxythiophene (**12**) with 1 equiv of bromine leads to selective formation of 2-bromo-3-methoxythiophene (**13a**). Subsequent reaction with chlorine or a second equivalent of bromine provides the dihalo adducts **13b** and **13c**, respectively. Transmetalation of **13b** with *n*-butyllithium and reaction with *N*-methoxy-*N*,3,3-trimethylacrylamide gives the 2-acylated-5-chloro derivative **15b** exclusively. On the other hand, transmetalation of **13c** can and does occur at either the 2- or the 5-position. Despite a possible *ortho*-directing influence of the methoxy substituent, transmetalation at the 5-position predominates. Reaction of the mixture of anions with *N*-methoxy-*N*,3,3-trimethylacrylamide gives a mixture of 2- and 5-acyl products (**14c**/**15c** = 3:1) which are separable by chromatography. Demethylation using boron trichloride and subsequent treatment with a catalytic amount of protic acid results in ring closure to the desired thienopyranones **16b** and **16c**. Reduction of thienopyranones **16a–c** with sodium borohydride affords the desired alcohols **17a–c** in good yields.

Dehydration of alcohols **17a–c** with *p*-toluenesulfonic acid at 0 °C forms **5a–c** as desired. These derivatives are sufficiently stable for isolation, characterization, and storage in *neutral* solvents for several days. However, if chloroform solutions of **5a** are allowed to stand at room temperature, equilibrium takes place over 2–12 h to give mixtures of the ring-opened **18a** and unreacted **5a** in a ratio of 3:5. When compound **18a** was isolated and resubjected to the reaction conditions, a 3:5 ratio of **18a** to **5a** was reestablished, confirming that equilibration was occurring in chloroform. Although the equilibrium ratios differ, derivatives **5b** and **5c** exhibit similar phenomena. Such an equilibrium is not established for ring closed derivatives **5a–c** or for ring-opened derivatives **18a–c** in neutral solvents such as benzene or base-washed pentane, which suggests that ring-opening is most likely catalyzed by trace amounts of acid in chloroform.

It is interesting that aromatic thiophene systems **3** and **5** rearrange to the nonaromatic open-chain isomeric forms, and furthermore, that each system behaves differently under identical reaction conditions. In light of the differences observed for the isomers **3–5**, as well as the contrast to the literature reports for the isosteric chromenes,[3] we undertook a series of molecular orbital calculations for isomeric pairs **1** and **2**, **3** and **8**, and **5** and **18** employing the AM1 Hamiltonian. The heats (Δ*H*) and entropies (Δ*S*) of formation were calculated to give the free energies of formation (Δ*G*).

In the case of *o*-quinomethide **1** and the benzopyran **2**, the free energy of reaction (ΔΔ*G* = 10.55 kcal/mol) was determined from the difference in the free energies (Δ*G*) of the products and the reactants (Table I). The magnitude and sign of the free energy of reaction predicts that

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Table I. Ground State Parameters (AM1) for Benzopyrans[a]

2 ⇌ 1

ΔH	-2.21	11.69
ΔS	100.98	112.16
$\Delta\Delta G$		10.55

[a] ΔH and ΔG in kcal/mol, ΔS in eu (cal/mol deg); ΔS and ΔG at 300 K. ΔH is the heat of formation, ΔS is entropy, and $\Delta\Delta G$ is the difference in the heats of formation between the reactant and product.

Table II. Ground State and Activation Parameters (AM1) for Thieno[2,3-*b*]pyrans[a]

3a-c ⇌ 8a-c

a: X = H		
ΔH	7.25	5.23
ΔS	100.70	108.71
$\Delta\Delta G$		-4.43
$\Delta H^{\ddagger}$	27.67	
$\Delta S^{\ddagger}$	0.21	
$\Delta G^{\ddagger}$	27.61	
b: X = Cl		
ΔH	1.04	-0.75
ΔS	107.68	115.82
$\Delta\Delta G$		-4.24
c: X = Br		
ΔH	9.49	8.70
ΔS	110.49	118.69
$\Delta\Delta$G		-3.25

[a] ΔH and ΔG in kcal/mol, ΔS in eu (cal/mol deg); ΔS and ΔG at 300 °K. ΔH is the heat of formation, ΔS is entropy, and $\Delta\Delta G$ is the difference in the heats of formation between the reactant and product.

any potential equilibrium would lie exclusively on the side of the ring-closed aromatic isomer **2** consistent with the experimental fact.

The AM1 results for the thieno[2,3-*b*]pyran system (**3**, Table II) are in stark contrast to those determined for the benzopyran system. The differences in Gibbs' free energies between opened and closed forms show dramatically that any potential equilibrium should lie to the side of the ring-opened thienones **8a–c** ($\Delta\Delta G$ = -4.43, -4.24, and -3.25, respectively). Since these values are equivalent to equilibrium constants on the order of 10^6, essentially 100% ring-opened isomers are predicted which is also consistent with experimentally observed results.

In the thieno[3,2-*b*]pyran systems **5a–c** wherein an equilibrium between closed and opened forms **18a–c** is experimentally observed, the calculated ground state parameters (Table III) reflect the experimental equilibrium constants as measured by ^{1}H NMR. In the -[3,2-*b*]-systems, there are much smaller overall changes in Gibbs' free energies between open and closed forms ($\Delta\Delta G$ = -1.78, -1.35, and -0.58 for X = H, Cl, and Br, respectively) as compared to those calculated for the -[2,3-*b*]-system (**3**), which suggests an equilibrium could exist. In one case (**5b**; X = Cl), the AM1 calculations were in agreement with the experimental NMR results: the equilibrium constant of 7.0 (as derived from the ^{1}H NMR ratio) correlates with an experimental Gibbs free energy of -1.34. These values are essentially identical with the calculated results.

These calculated ground state parameters strongly support the observed fact that the benzopyran equilibrium lies to the side of the ring closed forms (Table I, $\Delta\Delta G$ = +10.55) while the equilibria for the thieno[3,2-*b*]pyran and the thieno[2,3-*b*]pyran systems shift toward the ring-opened thienones (Tables II and III, $\Delta\Delta G$ = -0.58 to -4.43 kcal/mol). Consideration of the calculated activation parameters for the unsubstituted thienopyrans, however, indicates that these processes should not occur at room temperature as is observed experimentally. For example, the $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ values for the thieno[2,3-*b*]pyran **3a** (Table II) and for the thieno[3,2-*b*]pyran **5a** (Table III) are quite high (27–30 kcal/mol).

Table III. Ground State and Activation Parameters (AM1) for Thieno[3,2-*b*]pyran[a]

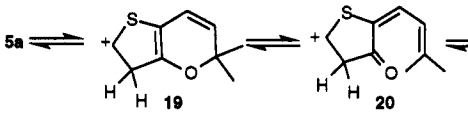
5a-c ⇌ 18a-c

a: X = H		
ΔH	4.89	5.86
ΔS	99.58	108.74
$\Delta\Delta G$		-1.78
$\Delta H^{\ddagger}$	30.27	
$\Delta S^{\ddagger}$	0.51	
$\Delta G^{\ddagger}$	30.12	
b: X = Cl		
ΔH	-1.08	0.21
ΔS	107.14	115.92
$\Delta\Delta G$		-1.35
c: X = Br		
ΔH	7.87	10.05
ΔS	109.58	118.78
$\Delta\Delta G$		-0.58

[a] ΔH and ΔG in kcal/mol, ΔS in eu (cal/mol deg); ΔS and ΔG at 300 °K. ΔH is the heat of formation, ΔS is entropy, and $\Delta\Delta G$ is the difference in the heats of formation between the reactant and product.

Using these values and assuming $t_{1/2}$ of 24 h, the temperature required for ring-opening of **5a** was calculated to be 93 °C.[9] Similarly, a temperature of 63 °C would be required for ring opening of **3a**. Thus, electrocyclic ring-opening at room temperature is probably not the operative mechanism for ring-opening of thienopyrans. In addition, since base-washed pentane solutions of thieno[3,2-*b*]-pyrans were stable for longer than 2 days, it is likely that acid catalysis effects these unusual electrocyclic ring openings for the derivatives **5a–c**.

With this information in hand as well as a preliminary analysis of the reaction coordinate of each of these reactions, which is beyond the scope of this paper,[10] a possible mechanism for the acid-catalyzed ring-opening of **5a** is shown (eq 2). Kinetic protonation may occur at



(2)

the 3-position of thiophene to produce **19**. Rapid ring-opening to a high-energy species **20** with immediate deprotonation leads directly to **18a**. Our calculations of the free energy of activation ($\Delta G^{\ddagger}$ = 10.48) support this as a possible room temperature reaction process. While protonation of other positions of the thienopyran (for example on oxygen or α to sulfur) is also possible, the corresponding mechanisms do not have calculated free energies of activation low enough for room temperature processes. These studies of reaction coordinates of both the -[2,3-*b*]- and -[3,2-*b*]- series are ongoing and will be reported in future communications.

(9) The calculated activation entropy and energy parameters were used to solve for the individual activation energies (E_a) and half-lives (assuming first-order kinetics) and the temperatures were subsequently determined using the Arrhenius equation and the appropriate rate constants.

(10) Calculations are subject of further reports in this laboratory.

In conclusion, experimentally-determined electrocyclic ring-openings of thieno[2,3-*b*]- (3) and thieno[3,2-*b*]pyrans (5) and chromones (2) have surprisingly disparate outcomes. While the -[2,3-*b*]pyrans completely ring-open, the -[3,2-*b*]pyrans exist as mixtures of ring-opened and ring-closed isomers. These findings are supported by ground state theoretical predictions using AM1 molecular orbital methodology. Especially noteworthy are the ground state calculations for the thieno[3,2-*b*]pyrans, which predict the experimentally observed room temperature equilibrium between opened and closed forms, an unusual phenonmenon for 6π electron ring-opening reactions. Comparative calculations for the benzopyran system (2) predict that this equilibrium lies exclusively to the ring-closed side in agreement with reported experimental findings. Theoretical calculations and experimental observations indicate that the mechanism for ring opening is an acid-catalyzed process.

We believe that these results demonstrate the utility of the AM1 molecular model as a predictive tool for thermal electrocyclic reactions. Furthermore, the corroborations of experimental and theoretical findings for sulfur-containing heterocyclic systems are, to our knowledge, unprecedented. Additional calculations for these processes are ongoing in our laboratories.

Experimental Section

Melting point determinations were done on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds had spectra (IR, ^{1}H NMR, MS) consistent with their assigned structures and were homogeneous by thin-layer chromatography. ^{1}H NMR were determined on a Brucker WP-100 FT or a GE QE-300 spectrometer. MS were determined on a Finnigan Mat 8230 using desorption chemical ionization techniques. Silica gel 60, 230–400 mesh, was used for both flash chromatography and medium pressure chromatography.

2-Chloro-5,6-dihydro-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyran-4-one (6b). SO_2Cl_2 (1.0 M in CH_2Cl_2, 19 mL, 19 mmol) was added to a solution of **6a**[6] (3.42 g, 18.7 mmol) in CH_2Cl_2 (150 mL) at 0 °C and stirred for 1 h. The resulting solution was washed several times with H_2O and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (15% Et_2O in pentanes) and recrystallized from hexanes to give **6b** as a pale yellow solid, 3.62 g (89%): mp 31–37 °C; IR (KBr) 1677, 1529, 1497 cm^{-1}; MS *m/z* 217 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 6H), 2.62 (s, 2H), 6.88 (s, 1H). Anal. Calcd for $C_9H_9ClO_2S$: C, 49.89; H, 4.19. Found: C, 49.65; H, 4.30.

(*Z*)-5-Chloro-3-(3-methyl-2-butenylidene)-2-oxo-3*H*-thiophene (8b). Sodium borohydride (0.30 g, 7.4 mmol) was added to a solution of **6b** (0.72 g, 3.3 mmol) in EtOH (15 mL) and stirred at room temperature for 16 h. The resulting solution was poured into H_2O (50 mL), and the intermediate alcohol **7b** was extracted into CH_2Cl_2 (25 mL), washed several times with H_2O, and dried over $MgSO_4$. The resulting solution was treated with a catalytic amount of *p*-TSA at 0 °C for 1.5 h to give **8b**, 0.53 g (80%), as an orange solid: mp 113–115 °C (recrystallized from hexane); IR (KBr) 1679, 1606, 1568 cm^{-1}; MS *m/z* 201 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3H), 1.95 (s, 3H), 6.30 (s, 1H), 6.98 (d, *J* = 12.4 Hz, 1H), 7.33 (m, 1H). Anal. Calcd for C_9H_9ClOS: C, 53.86; H, 4.52. Found: C, 54.13; H, 4.81.

(*E*)-5-Chloro-3-(3-methyl-2-butenylidene)-2-oxo-3*H*-thiophene (9b). A solution of **8b** (0.17 g, 0.85 mmol) and catalytic amount of iodine in methylene chloride (30 mL) was stirred at rt for 3 h. The resulting solution was washed with 5% aqueous sodium thiosulfate and filtered through a plug of silica gel. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (2% Et_2O in pentanes) to give **9b**, 0.11 g (65%), as a yellow solid: mp 102–106 °C; IR (KBr) 1684, 1611, 1567 cm^{-1}; MS *m/z* 201 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 6H), 6.24 (m, 1H), 6.64 (d, *J* = 1.1 Hz, 1H) and 7.28 (d, *J* = 11.0 Hz, 1H). Anal. Calcd for C_9H_9ClOS: C, 53.86; H, 4.52. Found: C, 54.13; H, 4.81.

2-Bromo-5,6-dihydro-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyran-4-one (6c). NBS (6.0 g, 33.9 mmol) was added to a solution of **6a**[6] (6.0 g, 33.3 mmol) in CH_2Cl_2 (100 mL). The resulting solution was stirred at rt for 2 h, washed several times with water, and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (15% Et_2O in pentanes) and recrystallized from hexanes to give **6c** as a pale yellow solid, 7.29 g (84%): mp 52–53 °C; IR (KBr) 2983, 1677, 1524, 1490 cm^{-1}; MS *m/z* 261 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 6H), 2.61 (s, 2H), 7.06 (s, 1H). Anal. Calcd for $C_9H_9BrO_2S$: C, 41.40; H, 3.47. Found: C, 41.45; H, 3.43.

(*Z*)-5-Bromo-3-(3-methyl-2-butenylidene)-2-oxo-3*H*-thiophene (8c) was prepared from **6c** (2.87 g, 10.9 mmol) to give **8c**, 1.9 g (71%), as an orange solid: mp 112–115 °C (recrystallized from hexane); IR (KBr) 2925, 1665, 1605, 1540 cm^{-1}; MS *m/z* 245 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H), 1.99 (s, 3H), 6.50 (s, 1H), 7.02 (d, *J* = 12.4 Hz, 1H), and 7.32 (m, 1H). Anal. Calcd for C_9H_9BrOS: C, 44.10; H, 3.71. Found: C, 44.21; H, 3.71.

(*E*)-5-Bromo-3-(3-methyl-2-butenylidene)-2-oxo-3*H*-thiophene (9c) was prepared from **8c** (1.0 g, 6.02 mmol) to give **9c**, 0.865 g (87%), as a yellow solid: mp 115–116 °C; IR (KBr) 1687, 1608, 1564 cm^{-1}; MS *m/z* 245 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 1.99 (d, *J* = 1.2 H, 6H), 6.26 (m, 1H), 6.86 (d, *J* = 0.9 Hz, 1H), 7.27 (d, *J* = 12.5 Hz, 1H). Anal. Calcd for C_9H_9BrOS: C, 44.10; H, 3.71. Found: C, 44.10; H, 3.34.

3-Bromo-5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,4-*b*]pyran-7-one was prepared from **10**[6] (15.0 g, 82.6 mmol) to give the product as a dark grey solid, 15.1 g (70%): mp 63–72 °C; IR (neat) 1694, 1558, 1438 cm^{-1}; MS *m/z* 261 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6H), 2.63 (s, 2H), 7.99 (s, 1H). Anal. Calcd for $C_9H_9BrO_2S$: C, 41.40; H, 3.47. Found: C, 41.30; H, 3.46.

3-Bromo-5,6-dihydro-7-hydroxy-5,5-dimethyl-7*H*-thieno-[3,4-*b*]pyran (11c). Sodium borohydride (2.61 g, 69.0 mmol) was added to a solution of 3-bromo-5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,4-*b*]pyran-7-one (12.63 g, 48.4 mmol) in ethanol (200 mL) at room temperature. The mixture was stirred at rt for 3 h, poured into H_2O (600 mL), extracted with CH_2Cl_2, washed with H_2O, and dried over $MgSO_4$. The solvent was evaporated in vacuo to give **11c** as an amber oil, 12.06 g (95%): ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.50 (s, 3H), 1.60–2.20 (m, 3H), 4.81 (m, 1H) and 7.26 (s, 1H).

3-Bromo-5,5-dimethyl-5*H*-thieno[3,4-*b*]pyran (4c). A solution of **11c** (12.06 g, 45.8 mmol) and *p*-toluenesulfonic acid (0.26 g, 1.37 mmol) in benzene (300 mL) was heated to reflux for 3 h in an apparatus fitted with a Dean–Stark trap to remove H_2O. The resulting solution was cooled to room temperature and filtered through a pad of silica gel and eluted with CH_2Cl_2. The solvent was evaporated in vacuo to give **4c** as a brown oil, 10.23 g (91%): ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6H), 5.65 (d, *J* = 14 Hz, 1H), 6.37 (d, *J* = 14 Hz, 1H), 6.87 (s, 1H).

5,6-Dihydro-7-hydroxy-5,5-dimethyl-7*H*-thieno[3,2-*b*]pyran (17a) was prepared from **16a**[6] (3.1 g, 17.0 mmol) to give **17a**, 2.96 g (95%), as a brown oil: IR (neat) 3373, 2976, 1561, 1400 cm^{-1}; MS *m/z* 185 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.45 (s, 3H), 1.87 (m, 1H), 1.94 (d, *J* = 7.0 Hz, 1H, exchanges with D_2O), 2.16 (m, 1H), 4.88 (m, 1H), 6.57 (d, *J* = 5.4 Hz, 1H), 7.13 (d, *J* = 5.4 Hz, 1H).

5,5-Dimethyl-5*H*-thieno[3,2-*b*]pyran (5a). A mixture of **17a** (1.3g, 7.06 mmol), *p*-toluenesulfonic acid monohydrate (0.11 g, 0.58 mmol), and ground molecular sieves (1.3 g) was stirred at −5 °C for 1.5 h. The solids were removed by filtration and the resulting solution was washed with 1.0 N aqueous sodium hydroxide and dried over magnesium sulfate. The solvent was evaporated *in vacuo* to give **5a**, 1.17 g (99%), as a red oil: IR (neat) 2976, 1504, 1531 cm^{-1}; MS *m/z* 167 (MH$^+$); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 6H), 5.27 (d, *J* = 9.8 Hz, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 6.60 (d, *J* = 5.3 Hz, 1H), 6.99 (d, *J* = 5.3 Hz, 1H). This oil was used without further purification.

5,5-Dimethyl-5*H*-thieno[3,2-*b*]pyran (5a) was prepared from **16a**[6] (12.1 g, 66.4 mmol) to give **5a**, 11.0 g (99%).

(*Z*)-2-(3-Methyl-2-butenylidene)-3-oxo-2*H*-thiophene (18a). A solution of **5a** (3.2 g, 19.2 mmol) in chloroform (60 mL) was stirred at rt for 20 h. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (15% Et_2O in

pentanes) to give **18a**, 0.875 g (27%) as a yellow solid: mp 110–114 °C; IR (KBr) 3065, 1647, 1611, 1568 cm^{-1}; MS *m/z* 167 (MH^+); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.01 (s, 3H), 6.10 (d of q, *J* = 1.3 and 12.0 Hz, 1H), 6.34 (d, *J* = 6.1 Hz, 1H), 7.68 (d, *J* = 12.0 Hz, 1H), 8.01 (d of d, *J* = 1.3 and 6.1 Hz, 1H). Anal. Calcd for $C_9H_{10}O_2S$: C, 65.03; H, 6.06 Found: C, 64.88; H, 5.86.

2-Bromo-5-chloro-3-methoxythiophene (13b). NBS (7.79 g, 43.8 mmol) was added in portions to a solution of 3-methoxythiophene in CH_2Cl_2 (200 mL) at 0 °C and stirred at 0 °C for 0.5 h. NCS (5.84 g, 43.8 mmol) was added in portions to the resulting solution and stirred an additional 1.5 h at 0 °C. The solution was washed several times with H_2O and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give **13b** as a brown oil 8.44 g (85%): ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H), 6.65 (s, 1H).

5-Chloro-3-methoxy-2-(3-methyl-1-oxo-2-buten-1-yl)-thiophene (15b) was prepared from **13b** (8.44 g, 37.1 mmol) to give **15b** (4.79 g, 56%) as a colorless solid, mp 91–92 °C (recrystallized from hexane): IR (KBr) 3095, 1646, 1594, 1541, 1426 cm^{-1}; MS *m/z* 231 (MH^+); ^1H NMR ($CDCl_3$) δ 1.98 (d, *J* = 1.2 Hz, 3H), 2.21 (d, *J* = 1.1 Hz, 3H), 3.94 (s, 3H), 6.74 (s, 1H), 6.81 (m, 1H). Anal. Calcd for $C_{10}H_{11}ClO_2S$: C, 52.06; H, 4.81. Found: C, 52.06; H, 4.77.

5-Chloro-3-hydroxy-2-(3-methyl-1-oxo-2-buten-1-yl)-thiophene was prepared from **15b** (3.5 g, 15.2 mmol) to give the product, 2.84 g (86%), as an orange solid: mp 65–66 °C (recrystallized from hexane); IR (KBr) 3091, 1639, 1576, 1550, 1448, 1407 cm^{-1}; MS *m/z* 217 (MH^+); ^1H NMR ($CDCl_3$) δ 2.00 (d, *J* = 1.2 Hz, 3H), 2.29 (d, *J* = 1.2 Hz, 3H), 6.05 (m, 1H), 6.66 (s, 1H) and 12.41 (br s, 1H, exchanges with D_2O). Anal. Calcd for $C_9H_9ClO_2S$: C, 49.89; H, 4.17. Found: C, 49.76; H, 4.09.

2-Chloro-5,6-dihydro-5,5-dimethylthieno[3,2-*b*]pyran-7-one (16b) was prepared from **15b** (2.46 g, 11.4 mmol) to give **16b**, 2.27 g (92%), as a beige solid: mp 68–69 °C (recrystallized from hexane); IR (KBr) 1675, 1540, 1440 cm^{-1}; MS *m/z* 217 (MH^+); ^1H NMR ($CDCl_3$) δ 1.50 (s, 6H), 2.65 (s, 2H), 6.57 (s, 1H). Anal. Calcd for $C_9H_9ClO_2S$: C, 49.89; H, 4.17. Found: C, 49.85; H, 4.14.

2-Chloro-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (5b) was prepared from **16b** (1.45 g, 6.69 mmol) give **5b**, 0.727 g (54%) as an oil: MS *m/z* 245 (MH^+); ^1H NMR ($CDCl_3$) δ 1.44 (s, 6H), 5.26 (d, *J* = 9.8 Hz, 1H), 6.16 (d, *J* = 9.8 Hz, 1H), 6.49 (s, 1H).

(*Z*)-5-Chloro-2-(3-methyl-2-butenylidene)-3-oxo-2*H*-thiophene (18b) was prepared from **5b** (0.65 g, 3.24 mmol) to give **18b**, 0.348 g (47%), as a yellow solid: mp 74–80 °C (recrystallized from hexane); IR (KBr) 1654, 1612, 1577, 1522 cm^{-1}; MS *m/z* 201 (MH^+); ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.00 (s, 3H), 5.96 (m, 1H), 6.34 (s, 1H), 7.63 (d, *J* = 12.1 Hz, 1H). Anal. Calcd for C_9H_9ClOS: C, 53.86; H, 4.52. Found: C, 53.83; H, 4.44.

2,5-Dibromo-3-methoxythiophene (13c). NBS (15.6 g, 0.103 mol) was added in portions to a solution of 3-methoxythiophene (5.0 g, 43.7 mmol) in methylene chloride (200 mL) at 0 to 5 °C and stirred for 1 h at 0 °C. The resulting solution was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give **13c** as a yellow oil, 11.2 g (94%), which decomposes within hours upon standing at rt. ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.78 (s, 1H).

5-Bromo-3-methoxy-2-(3-methyl-1-oxo-2-buten-1-yl)-thiophene (15c) and 2-Bromo-3-methoxy-5-(3-methyl-1-oxo-2-buten-1-yl)thiophene (14c). *n*-Butyllithium (2.5 M in hexane, 22.7 mL, 56.8 mmol) was syringed into a solution of **13c** (15.42 g, 56.7 mmol) in Et_2O (250 mL) at −78 to −70 °C and stirred for 0.5 h. *N*-Methoxy-*N*,3,3-trimethylacrylamide (8.9 g, 62.2 mmol) was syringed into the resulting solution at −78 to −70 °C. The solution was allowed to warm to rt over 1 h and then ice was added. The solution was washed with H_2O and saturated aqueous NaCl. After drying over $MgSO_4$ the solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (CH_2Cl_2/pentanes: 1/1) to give **15c**, 3.48 g (22%), as a yellow solid: mp 81–85 °C (recrystallized from hexane); IR (KBr) 3092, 1646, 1592, 1538, 1422 cm^{-1}; MS *m/z* 275 (MH^+); ^1H NMR ($CDCl_3$) δ 1.97 (d, *J* = 1.2 Hz, 3H), 2.21 (d, *J* = 1.3 Hz, 3H), 3.94 (s, 3H), 6.80 (m, 1H), 6.87 (s, 1H). Anal. Calcd for $C_{10}H_{11}BrO_2S$: C, 43.65; H, 4.03. Found: C, 43.77; H, 4.05. The major product was **14c** which was recovered from the column and crystallized from hexane to give 5.82 g (37%): mp 69.5–70.5 °C; MS *m/z* 275 (MH^+); ^1H NMR ($CDCl_3$) δ 2.01 (d, *J* = 0.8 Hz, 1H), 2.25 (d, *J* = 0.8 Hz, 1H), 3.93 (s, 3H), 6.51 (br s, 1H) and 7.33 (s, 1H). Anal. Calcd for $C_{10}H_{11}BrO_2S$: C, 43.65; H, 4.03. Found: C, 43.67; H, 3.94.

5-Bromo-3-hydroxy-2-(3-methyl-1-oxo-2-buten-1-yl)-thiophene. A solution of **15c** (1.5 g, 5.45 mmol) in CH_2Cl_2 (50 mL) was treated with BCl_3 (1.0 M in CH_2Cl_2, 17.4 mL, 17.4 mmol) at −15 to −5 °C for 1 h. Water was added to the solution, and the organic layer was separated, washed with H_2O, and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (5% Et_2O in pentanes) to give **15c** as a yellow solid, 1.08 g (76%), mp 67–68 °C: IR (KBr) 3088, 1639, 1575, 1559, 1444, 1400 cm^{-1}; MS *m/z* 261 (MH^+); ^1H NMR ($CDCl_3$) δ 1.99 (d, *J* = 1.2 Hz, 3H), 2.29 (d, *J* = 1.1 Hz, 3H), 6.06 (d of d, *J* = 1.1, 1.2 Hz, 1H), 6.80 (s, 1H) and 12.34 (br s, 1H). Anal. Calcd for $C_9H_9BrO_2S$: C, 41.40; H, 3.47. Found: C, 41.47; H, 3.51.

2-Bromo-5,6-dihydro-5,5-dimethylthieno[3,2-*b*]pyran-7-one (16c). A solution of 5-bromo-3-hydroxy-2-(3-methyl-1-oxo-2-buten-1-yl)thiophene (1.0 g, 3.83 mmol) and *p*-TSA (0.08 g) in toluene (25 mL) was heated to reflux for 20 h. The resulting solution was cooled to room temperature and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (10% Et_2O in pentanes) to give **16c** as an orange solid, 0.98 g (98%), mp 80–81 °C (recrystallized from hexane): IR (KBr) 1674, 1537, 1438 cm^{-1}; MS *m/z* 261 (MH^+); ^1H NMR ($CDCl_3$) δ 1.50 (s, 6H), 2.64 (s, 2H), 6.71 (s, 1H). Anal. Calcd for $C_9H_9BrO_2S$: C, 41.40; H, 3.47. Found: C, 41.58; H, 3.41.

2-Bromo-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (5c) was prepared from **16c** (1.55 g, 5.93 mmol) to give **5c** as a yellow oil, 1.22 g (84%): MS *m/z* 245 (MH^+); ^1H NMR ($CDCl_3$) δ 1.44 (s, 6H), 5.25 (d, *J* = 9.8 Hz, 1H), 6.18 (d, *J* = 9.8 Hz, 1H), 6.61 (s, 1H). Anal. Calcd for C_9H_9BrOS: C, 44.10; H, 3.71. Found: C, 44.31; H, 3.78.

(*Z*)-5-Bromo-2-(3-methyl-2-butenylidene)-3-oxo-2*H*-thiophene (18c) was prepared from **5c** (1.1 g, 4.49 mmol) to give **18c**, 0.75 g (68%) as a yellow solid, mp 80–84 °C (recrystallized from hexane): IR (KBr) 3068, 1648, 1608, 1573 cm^{-1}; MS *m/z* 245 (MH^+); ^1H NMR ($CDCl_3$) δ 1.99 (s, 6H), 5.97 (d of q, *J* = 1.2, 12.1 Hz, 1H), 6.53 (s, 1H), 7.60 (d, *J* = 12.1 Hz, 1H). Anal. Calcd for C_9H_9BrOS: C, 44.10; H, 3.71. Found: C, 44.31; H, 3.60.

Computational Procedure. The calculations were carried out using the AM1 Hamiltonian[11] as implemented in the MOPAC 5.0 and 6.0 programs.[12] Sulfur parameters[13] were read in from an external file. All geometries were fully optimized and transition states were located either by the reaction coordinate[14] or saddle[15] method. They were refined by minimizing the gradient norm[16] and characterized by calculating force constants.[16]

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