refluxed for 15 h. After addition of H_2O (2 mL), the solvent was removed in vacuo and the residue was extracted with $CHCl_3$ (2 × 15 mL). Evaporation of the $CHCl_3$ in vacuo gave a white solid, which was dissolved in THF (40 mL), and 80 mL of 9 N HCl was added. The mixture was stirred at room temperature for 5 h and evaporated in vacuo. The residue was treated with 50 mL of 5% aqueous LiOH and extracted with Et_2O (5 × 100 mL). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a crude product, which was chromatographed on alumina with $CHCl_3$ as eluent to afford 1.55 g (67%) of **11** as a colorless oil: IR (neat) 1113 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35–2.9 (m, 12 H), 3.15–3.4 (m, 23 H), 4.55 (s, 4 H), 6.85–7.5 (m, 3 H); mass spectrum, *m/e* 482.6 (M^+).

Anal. Calcd for $C_{25}H_{42}N_2O_7$: C, 62.22; H, 8.77. Found: C, 62.19; H, 8.59.

Cryptand Phenol 2. Cryptand **11** (1.38 g, 2.9 mmol) was dissolved in 6 mL of anhydrous pyridine and 1.5 g of anhydrous LiI was added. The mixture was heated at 100 °C for 15 h and the pyridine was evaporated in vacuo. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extracts were dried over $MgSO_4$ and evaporated in vacuo. Chromatography of the residue on alumina with $CHCl_3$ as eluent gave a semisolid product that was dissolved in $CHCl_3$ and washed with deionized H_2O (3 × 10 mL). Evaporation of the $CHCl_3$ and removal of H_2O by coevaporation with C_6H_6 in vacuo gave 0.91 g (67%) of **2** as a pale yellow viscous oil: IR (neat) 3304 (OH), 1132–1109 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.5–3.0 (m, 12 H), 3.3–3.9 (m, 20 H), 4.63 (s, 4 H), 6.6–7.4 (m, 3 H), 7.33 (s, 1 H); mass spectrum, *m/e* 468.6 (M^+).

Anal. Calcd for $C_{24}H_{40}N_2O_7$: C, 61.52; H, 8.60. Found: C, 61.47; H, 8.56.

Diol 12. Diester **6** (4.10 g, 12 mmol) was refluxed with $LiAlH_4$ (1.18 g, 31 mmol) in 30 mL of THF for 3 h. The reaction mixture was treated consecutively with a solution of H_2O (1.2 mL) and THF (6 mL), 15% aqueous NaOH (1.2 mL), and a mixture of H_2O (6 mL) and THF (6 mL). Solid material was filtered and washed with THF. The filtrate and washings were combined and evaporated in vacuo and the residue was chromatographed on alumina with EtOAc–MeOH (10:1) as eluent to afford 0.80 g (27%) of **12** as a colorless, viscous liquid: IR (neat) 3416 (OH), 1109, 1070 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87 (br s, 2 rH), 3.35–3.9 (s + m, 11 H), 4.58 (s, 4 H), 6.9–7.5 (m, 3 H).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.75; H, 7.81.

Dimesylate 13. A solution of diol **12** (2.34 g, 9.1 mmol) and Et_3N (2.95 g, 29 mmol) in CH_2Cl_2 (40 mL) was cooled to −10 °C and a solution of methanesulfonyl chloride (2.60 g, 22 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h, diluted with cold CH_2Cl_2 (50 mL), washed consecutively with 5% HCl, H_2O, 5% aqueous $NaHCO_3$, and H_2O, dried ($MgSO_4$), and evaporated in vacuo to give 3.52 g (94%) of **13** as a colorless oil: IR (neat) 1354, 1172 (S=O), 1107 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (s, 6 H), 3.80 (m, 7 H), 4.1–4.5 (m, 4 H), 4.60 (s, 4 H), 6.9–7.6 (m, 3 H).

Anal. Calcd for $C_{15}H_{24}O_9S_2$: C, 43.68; H, 5.87. C, 43.43; H, 5.93.

Cryptand 11 from Dimesylate 13. Under nitrogen, BuLi (0.49 g, 7.6 mmol) was added slowly to a stirred solution of 1,10-diaza-18-crown-6 (2.00 g, 7.6 mmol) in THF (40 mL) at room temperature. After 1 h, a solution of **13** (3.14 g, 7.6 mmol) in THF (25 mL) was added and the mixture was stirred at room temperature for 12 h and then refluxed for 4 days. The solvent was evaporated in vacuo and the residue was chromatographed on alumina with EtOAc as eluent to give 0.25 g (7%) of **11**.

Potentiometric Titrations. Determination of protonation constants for **1** and **2** and stability constants for their complexes were performed by potentiometric titrations at 25.0 ± 0.1 °C in a manner similar to that described earlier.[19,20] For determination of a protonation constant, 25.0 mL of a 1.0×10^{-3} M ligand solution was prepared and the ionic strength was adjusted to 0.10 with Me_4NCl. An excess of standard HCl solution was added to protonate all basic sites and then the solution was titrated with 0.10 M Me_4NOH solution. An equivalent amount of metal salt solution was added to the protonated ligand solution ([ligand]:[metal ion] = 1.0) while the total titrate volume was kept constant to determine a stability constant. The resulting solution was then titrated with the 0.10 M Me_4NOH solution. All calculations were performed with a Hewlett-Packard HP87 personal computer using the methods and programs described earlier.[24]

Acknowledgment. This research was supported by the Division of Basic Chemical Sciences, Office of Basic Energy Sciences, U.S. Department of Energy, through Grants DE-AS05-80ER10604 to R.A.B. and DE-FG05-84ER13292 to C.A.C.

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Utilization of α,β-Unsaturated Acids as Michael Acceptors for the Synthesis of Thieno[2,3-*b*]thiopyrans

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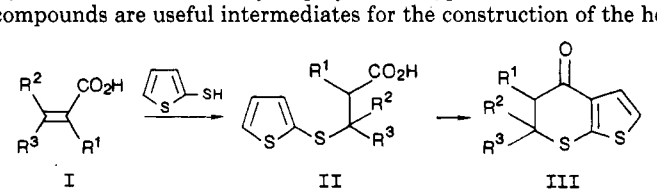
A general and versatile method that extends the synthetic utility of the Michael reaction is described for the preparation of substituted propionic acids of the type II. The addition of 2-mercaptothiophene to commercially available acrylic acids I, instead of the commonly employed esters, provides a facile and high-yielding synthesis of II. In turn, these compounds are useful intermediates for the construction of the heteroaryl thieno[2,3-*b*]thiopyrans III. An example of an anti-Michael addition, involving the use of 3-(4-pyridyl)propionic acid, is also presented.



I II III

The pharmacological properties of **1**[1] have stimulated interest in developing a general and versatile method for the construction of the thieno[2,3-*b*]thiopyran nucleus. The preparation of the parent heterocycle has been de-

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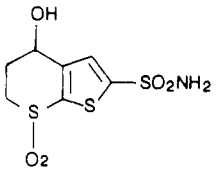
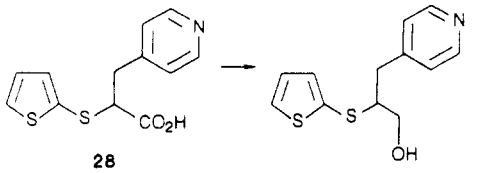


1

scribed previously[2,3] and involves alkylation of 2-mercaptothiophene (**2**) with 3-bromopropionic acid (**3**) to afford 3-(2-thienylthio)propionic acid (**4**). The intramolecular Friedel–Crafts cyclization of **4** gave the thieno-[2,3-*b*]thiopyran **5** (Scheme I). In principle, an acrylic acid derivative, acting as a Michael acceptor on reaction with 2-mercaptothiophene, could serve as the source for the propionic acid intermediate **7**. The commercial availability of a large variety of acrylic acid derivatives **6** suggested an attractive alternative for the synthesis of **7**. In this paper, we report on the utilization of α,β-unsaturated acids **6** (R = H)[4] in the Michael reaction, in contrast to the more commonly employed esters.[5] Although a few isolated examples of the reaction of thiols with α,β-unsaturated acids have been reported in the literature,[4] no one has explored the scope and limitations of this reaction.

The general utility of this approach is illustrated in Table I. The reaction is successful with a broad range of acrylic acid derivatives **6** containing alkyl, aryl, and heteroaryl moieties. Except for the use of acrylic acid **9** (entry 1), high yields of Michael adducts **7** were realized when the acids were utilized in this reaction. The reaction conditions involved refluxing 2-mercaptothiophene **2** and **6** in THF for 18–24 h with Et_3N. In the absence of Et_3N, no reaction occurred except, as might be expected, for the pyridine example **27**.

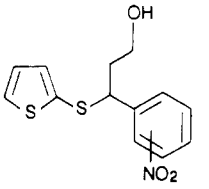
In contrast to the regiochemistry observed for the alkyl and arylacrylic acids in the Michael reaction with **2**, the substituted pyridine **27** gave anomalous results. While the Michael reaction of the silyl ester **25** provided the normal adduct **26**, the acid **27** gave the anti-Michael product **28**. Although the latter reaction is not without precedent, only a few scattered examples are found in the literature.[6] The structures of **26** and **28** were determined by ^{1}H NMR spectroscopy. Both compounds possessed nearly identical spectra except for the methine proton, which was observed as a triplet at δ 4.5 in the case of **26** and at δ 3.8 for the corresponding **28**. The upfield shift of the methine proton of **28** is presumably due to the anisotropic effect of the adjacent carbonyl group. Further support for the assigned structure was provided by the borane reduction[7] of **28** to yield the alcohol **35**. In the ^{1}H NMR spectra for **35**, the



28 35

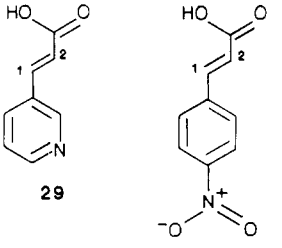
triplet observed for **28** is replaced by a multiplet in the range of δ 3.0. For the 3-pyridyl derivative **29**, the normal course of the Michael reaction is followed and **30** was obtained. In this example, the methine proton was observed at δ 4.5, as in compound **26**. It is noteworthy that the pyridine compound itself adequately served as base in this reaction.

Surprisingly, the powerful electron-withdrawing *p*-nitro- and *o*-nitrocinnamic acids **31** and **33** failed to give the corresponding anti-Michael adducts, yielding instead the normal addition products **32** and **34**, respectively. The structures **32** and **34** were confirmed by ^{1}H NMR spectroscopy and reduction to the corresponding alcohols **36** and **37**, respectively. In the spectra of **36** and **37** the triplet for the methine proton was retained, appearing at δ 4.35 and 4.85, respectively, to further substantiate their structural assignments.



36: *p*-NO_2
37: *o*-NO_2

A protonated intermediate such as **38** may be responsible for directing the addition to **27** in an anti-Michael fashion, since AM1 calculations (Table II) indicate that **27** has a higher proton affinity (212.7 kcal/mol) than either **29** or **31** (210.6 and 188.4 kcal/mol, respectively). It has



29 31

been previously suggested[8] that anti-Michael addition may be rationalized as preferred nucleophilic attack at the less negatively charged carbon, which may also have the larger LUMO coefficient. Examination of the charges and LUMO coefficients (Table III) for atoms 1 and 2 of **38** indicates a charge and LUMO coefficient reversal from the neutral **27**. Thus, nucleophilic attack would be predicted, and is observed, to lead to an anti-Michael product. Since this is also true for **39** and **40**, reaction presumably pro-

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(3) Cagniant, P.; Cagniant, D. *Bull. Soc. Chim. Fr.* **1966**, 2172.
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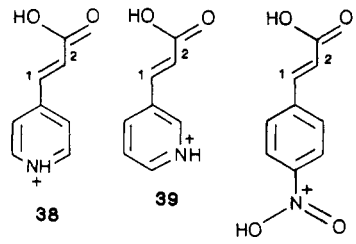
(7) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Storky, T. P. *J. Org. Chem.* **1973**, *38*, 2786.

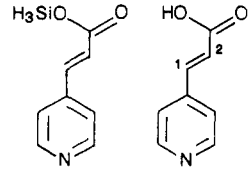
(8) See: Bumgardner, C. L.; Bunch, J. L.; Whangbo, M. H. *J. Org. Chem.* **1986**, *51*, 4083 for rationalization of the anti-Michael addition of PhO^- and PhS^- to benzoyl(trifluoromethyl)acetylene. Since the observed regiochemistry is correlated with properties of the substrates, this approach assumes that the transition state for the addition is reactant-like. This would be the case if nucleophilic addition to the double bond were rate-determining and exothermic, followed by or concerted with protonation. Indeed, AM1 calculations indicate that nucleophilic attack of CH_3O^- on **27**, **38**, **29**, and **31** is exothermic by 42.6, 160.5, 42.2, and 49.6 kcal/mol, respectively.



38 39 40

ceeds via the neutral species **29** and **31**, whose charge distributions are in accord with preferred Michael addition. For comparison, the charge distributions and LUMO coefficients of two simple α,β-unsaturated systems, **9** and methyl acrylate, are also listed in Table III; these are correctly predicted to give Michael products.

It seems likely that the ester **25** is also protonated, but not at the pyridyl nitrogen; model MNDO calculations on the silyl ester **41** predict a 3.6 kcal/mol higher proton affinity at the carbonyl oxygen. Protonation at this site serves to reinforce the Michael addition preference of **41** over **27** by increasing the polarization of the 1–2 bond (atomic charges of 0.21 and −0.23 and LUMO coefficients of 0.55 and −0.19 at atoms 1 and 2, respectively).



41 27

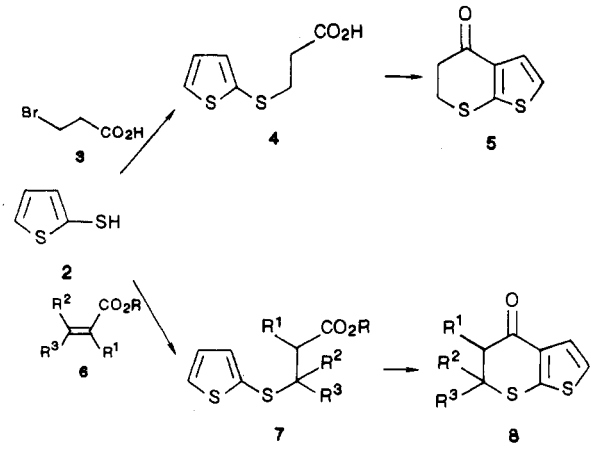
When the Michael adduct **26** was treated under the conditions utilized to prepare the anti-Michael product **28**, compound **26** was recovered unchanged. This result clearly rules out rearrangement of **26** through a retro-Michael reaction followed by recombination of **2** and **27** to yield the thermodynamically more stable product **28**. Thus, this observation supports the reaction pathway discussed vide supra for the formation of **26** and **28**, respectively, via separate mechanisms.

The use of esters (entries 2 and 9) in this reaction is encumbered by several distinct disadvantages. In addition to adding two steps in the overall sequence, subsequent hydrolysis of the esters **11** and **21** gave the desired acids **13** and **23**, respectively, but in very low yield. The isolation of *p*-methoxycinnamic acid (**24**) in quantitative yield from the hydrolysis of **21** in EtOH with 2 equiv of KOH at room temperature confirms that the retro-Michael reaction competes favorably with the hydrolysis of esters in these reactions. This problem could be circumvented by the use of the *tert*-butyldimethylsilyl (TBDMS) esters[9] (**12**, **15**, **22**, and **25**), which were readily hydrolyzed by dilute acid treatment (2 N HCl) to the desired acids (**13**, **16**, **23**, and **26**, respectively) in good yields. However, the high cost of TBDMS chloride precluded the routine usage of TBDMS esters for the synthesis of **7**. Interestingly, this method was necessary for the synthesis of the 3-(4-pyridyl)propionic acid (**26**) since the free acid **27** yielded the reverse Michael adduct **28** (entries 11 and 12).

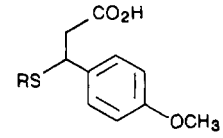
In addition to 2-mercaptothiophene (**2**), other sulfur nucleophiles, thiophenol **42** and benzyl mercaptan **43**, were investigated to further extend the scope of this reaction. Although **42** reacted with **24** to afford **44** in 81% yield, the reaction required heating at reflux for 3 days.[10] Under

(9) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817 and references cited therein.

Scheme I



the same conditions, **43** failed to yield the propionic acid derivative **45**. However, the use of the stronger base, tetrabutylammonium fluoride (TBAF),[11] afforded **45** after heating at reflux for 5 days.[10] In contrast, the carbon nucleophile diethyl malonate failed to yield a Michael adduct when TBAF was employed as catayst.



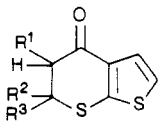
44: R=C_6H_5
45: R=$C_6H_5CH_2$

In this study, the rate of reaction appears markedly dependent on the pK_a value for the nucleophile (Table IV). The trend in calculated MNDO deprotonation enthalpies (DPEs) for the thiols are in agreement with this observation (see Table IV), but the low MNDO DPE for diethyl malonate belies its observed higher pK_a and its lack of reaction. However, the observed DPE for diethyl malonate is 348.3 kcal/mol,[12a] approximately 10 kcal/mol higher than the calculated value. In addition, it seems likely that the absolute values of the MNDO DPEs for **2**, **42**, and **43** may be too high by as much as 5–10 kcal/mol based on previously reported MNDO[12b] and AM1[12c] DPEs for alcohols.

Cyclization of several of these propionic acid derivatives **7** yielded the corresponding thieno[2,3-*b*]thiopyran **8** in a high-yielding, one-step process. In the case of **4**, the compound was converted to the intermediate acid chloride with oxalyl chloride followed by cyclization with $SnCl_4$ to provide **5** in 96% yield. Similarly, compounds **13**, **16**, and **23** were cyclized to their corresponding thieno[2,3-*b*]thiopyran **46**, **47**, and **48**, respectively, in high yield. A similar procedure for the preparation of **5** utilizing thionyl chloride–$SnCl_4$ has previously been reported by Cagniant and Cagniant;[3] however, in our hands, the thieno[2,3-*b*]thiopyran **5** was only obtained in 30–40% yield with their conditions.

In summary, the ease of reaction and the ready availability of starting materials offers an attractive one-step

(10) The reactions were monitored by observing the appearance and disappearance of the methine and olefinic protons of the product and starting materials, respectively, in the ^{1}H NMR spectra.
(11) Kuwajima, I.; Murofushi, T.; Nakamura, E. *Synthesis* **1976**, *602*.
(12) (a) Bartmess, J. E.; McIver, R. T., Jr. In *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic: New York, 1979; Vol. 2, Chapter 11. (b) Olivella, S.; Urpi, F.; Vilarrasa, J. *J. Comput. Chem.* **1984**, *5*, 230. (c) Dewar, M. J. S.; Dieter, K. M. *J. Am. Chem. Soc.* **1986**, *108*, 8075.



46: $R^1 = CH_3$; $R^2 = R^3 = H$
47: $R^1 = H$; $R^2 = R^3 = CH_3$
48: $R^1 = R^2 = H$; $R^3 = p\text{-}CH_3OC_6H_4$

synthesis of substituted propionic acids of the type **7** via the Michael reaction. Since the use of α,β-unsaturated acids as Michael acceptors has been limited, this study further extends the utility of the Michael reaction in organic synthesis. In addition, the regiochemistry demonstrated by the pyridine example **27** may also possess useful synthetic applications for controlling the selectivity for the direction of the Michael reaction. Furthermore, this methodology provides a practical and convenient source of substituted propionic acids **7** for the construction of thieno[2,3-*b*]thiopyrans of the type **8**.

Experimental Section

^{1}H NMR spectra were determined in the indicated solvent on Varian T-60, XL300, or GE-NMR NT 360 spectrometers with tetramethylsilane as an internal standard for proton spectra. Mass spectra were taken on a high-resolution mass spectrometer at an ionizing voltage of 70 eV. The data were processed by a DS50 data acquisition system. Melting points were determined on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Liquids were distilled by short-path distillation, and boiling points are uncorrected. Silica gel 60 (230–400 mesh) (E. Merck, Darmstadt) was used for column chromatography. Solutions were dried over Na_2SO_4 and concentrated to dryness with a Buchi rotary evaporator under water aspirator pressure (20 mm).

The general procedure for the preparation of substituted propionic acid derivatives is demonstrated by the synthesis of **3-(2-Mercaptothiopheneyl)-3-phenylpropionic Acid (19)**. A mixture of **18** (4.2 g, 0.028 mol), THF (40 mL), Et_3N (1.45 g, 0.014 mol), and **3-(2-Thienylthio)-3-phenylpropionic** (3.6 g, 0.03 mol) was heated at reflux under N_2. After 21 h, the solution was poured into dilute aqueous HCl and extracted with EtOAc (3×). The organic extracts were dried, filtered, and concentrated to dryness. The residue was triturated with petroleum ether, and the solid was filtered to yield 7.15 g (95%) of **19**: mp 61–63 °C; ^{1}H NMR ($CDCl_3$) δ 2.95 (d, 2 H, J = 7), 4.45 (t, 3 H, J = 7), 6.9 (m, 2 H), 7.2 (s, 5 H, and m, 1 H), 10.3 (br s, 1 exch). Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.06; H, 4.58. Found: C, 59.33; H, 4.83.

The physical data for the remaining compounds are found in Table I and the spectral data can be obtained from supplementary material.

***tert*-Butyldimethylsilyl *p*-Methoxycinnamate (22).** To a solution of **24** (62 g, 0.35 mol) in DMF (500 mL) was added *tert*-butyldimethylsilyl chloride (52 g, 0.35 mol) followed by imidazole (25.3 g, 0.37 mol). The solution was heated at 50 °C for 5 h and then concentrated nearly to dryness under high vacuum (1 mm). Water was added, and the mixture was extracted with EtOAc (2×), the organic extracts were back washed with saturated $NaHCO_3$ and H_2O, dried, filtered, and concentrated to dryness to yield 97 g (95%) of **22**: ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 6 H), 0.95 (s, 9 H), 4.85 (s, 3 H), 6.3 (d, 1 H, J = 14), 6.85 (d, 2 H, J = 9), 7.45 (d, 2 H, J = 9), 7.6 (d, 1 H, J = 14). Anal. Calcd for $C_{16}H_{24}O_3S$: C, 65.71; H, 8.27. Found C, 65.87; H, 8.41.

Silyl esters **12** and **15** were prepared by the same procedure. Silyl ester **25** was obtained with Et_3N instead of imidazole as base in the above reaction. These materials were used directly in the next step without purification.

***tert*-Butyldimethylsilyl 2-methylacrylate (12)**: obtained in 83% yield; bp 58–70 °C (10 mm); ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 6 H), 0.85 (s, 9 H), 1.8 (d, 3 H, J = 2), 5.5 (m, 1 H), 6.05 (m, 1 H).

***tert*-Butyldimethylsilyl 3,3-dimethylacrylate (15)**: obtained in 66% yield, bp 85–97 °C (11 mm); ^{1}H NMR ($CDCl_3$) δ 0.36 (s, 6 H), 0.95 (s, 9 H), 1.9 (s, 3 H), 2.1 (s, 3 H), 5.65 (m, 1 H).

***tert*-Butyldimethylsilyl 3-(4-pyridyl)acrylate (25)**: obtained in 52% yield; ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 6 H), 1.0 (s, 9 H), 6.5 (d, 1 H, J = 14), 7.4 (m, 2 H), 7.5 (d, 1 H, J = 14), 8.7 (d, 2 H, J = 6).

2-(2-Thienylthio)-3-(4-pyridyl)propanol (35). To a suspension of **28** (662 mg, 2.5 mmol) in THF (10 mL) was added dropwise under N_2 at room temperature a solution of 1.0 M BH_3 in THF (10 mL, 10 mmol). After 20 h, NaOH (2 pellets) and saturated K_2CO_3 were added successively, and the layers were separated. The aqueous layer was further extracted with EtOAc (2×). The organic layers were dried, filtered, and concentrated to dryness. The residue was chromatographed on a Still column (40 mm) with silica gel, and the product was eluted with $CHCl_3$ to yield 0.45 g (72%) of **35** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.20 (br s, 1 exch), 3.05 (d, 2 H, J = 3), 3.1 (m, 1 H), 3.65 (d, 2 H, J = 5), 7.0 (m, 2 H), 7.3 (d, 2 H, J = 7, m, 1 H), 8.4 (d, 2 H, J = 5). The measured mass was 251.042358 (calcd for $C_{12}H_{13}NOS_2$ theoretical mass 251.043858).

Compounds **36** and **37** were prepared in an analogous manner except only 2 equiv of BH_3 was used per equivalent of acid.

3-(2-Thienylthio)-3-(*p*-nitrophenyl)propanol (36): obtained as an oil in 100% yield; ^{1}H NMR ($CDCl_3$) δ 2.3 (m, 2 H, 1 exch), 4.35 (t, 1 H, J = 7), 6.9 (m, 2 H), 7.35 (m, 2 H), 8.1 (d, 2 H, J = 9). The measured mass was 295.032944 (calcd for $C_{13}H_{13}NO_3S_2$ theoretical mass 295.03364).

3-(2-Thienylthio)-3-(*o*-nitrophenyl)propanol (37): obtained as an oil in 100% yield; ^{1}H NMR ($CDCl_3$) δ 2.3 (m, 2 H + 1 exch), 3.8 (t, 2 H, J = 5), 4.85 (t, 1 H, J = 7), 6.8 (m, 2 H), 7.5 (m, 5 H). The measured mass was 295.032974 (calcd for $C_{13}H_{13}NO_3S_2$ theoretical mass 295.03364).

3-(Phenylthio)-3-(*p*-methoxyphenyl)propionic acid (44): obtained in 81% yield; mp 99–102 °C (trituration in hexane); ^{1}H NMR (Me_2SO-d_6) δ 2.8 (d, 2 H, J = 7), 3.70 (s, 3 H), 4.65 (t, 1 H, J = 7), 6.8 (d, 2 H, J = 9), 7.25 (d, 2 H, J = 9), 7.3 (s, 5 H). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59. Found: C, 66.67, H, 5.22.

3-(Benzylthio)-3-(*p*-methoxyphenyl)propionic Acid (45). A solution of **24** (5.3 g, 0.03 mol), **43** (4.1 g, 0.033 mol), and 1.0 M *tert*-butylammonium fluoride in THF (40 mL, 0.04 mol) was heated at reflux for 5 days. The reaction mixture was then poured into dilute acid, and the aqueous mixture was extracted with EtOAc (3×). The organic extracts were dried, filtered, and concentrated to dryness. Trituration of the residue with hexane gave 8.1 g (89%) of **45**: mp 58–61 °C (trituration with hexane); ^{1}H NMR (Me_2SO-d_6) δ 2.8 (d, 2 H, J = 7), 3.55 (s, 2 H), 3.7 (s, 3 H), 4.1 (t, 1 H, J = 7), 6.8 (d, 2 H, J = 9), 7.3 (s, 5 H). Anal. Calcd for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00. Found: C, 67.92; H, 6.17.

The general procedure for the preparation of thieno[2,3-*b*]-thiopyrans **8** is demonstrated by the following example: **5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-one (5).** Under N_2 in a three-neck flask was placed **4** (122.7 g, 0.65 mol), DMF (2.4 mL), and CH_2Cl_2 (600 mL). To the stirred solution was added dropwise at ambient temperature oxalyl chloride (91.4 g, 0.72 mol). After 1 h, the solution was cooled to −10 °C, and a solution of $SnCl_4$ (83.4 g, 0.32 mol) in CH_2Cl_2 (120 mL) was added dropwise. The mixture was then stirred at 0 °C, and after 0.5 h, H_2O (325 mL) was added. The mixture was separated, and the organic extract was washed with saturated Na_2CO_3, H_2O, and brine, dried, filtered, and concentrated to dryness. The residue was triturated with hexane to yield 102.9 g (93%) of **5**: ^{1}H NMR ($CDCl_3$) δ 2.82 (m, 2 H), 3.4 (m, 2 H), 7.0 (d, 2 H, J = 5), 7.45 (d, 2 H, J = 5).

5,6-Dihydro-4*H*-5-methylthieno[2,3-*b*]thiopyran-4-one (46): 90%; bp 102–108 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ 1.3 (d, 3 H, J = 7), 2.85 (m, 1 H), 3.25 (d, 2 H, J = 8), 6.9 (d, 1 H, J = 5), 7.4 (d, 1 H, J = 5). Anal. Calcd for $C_8H_8OS_2$: C, 52.14; H, 4.38. Found: C, 51.99; H, 4.44.

5,6-Dihydro-4*H*-5,6-dimethylthieno[2,3-*b*]thiopyran-4-one (47): 97%; mp 74–75 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 6 H); 2.75 (s, 2 H), 6.9 (d, 1 H, J = 5), 7.35 (d, 1 H, J = 5). Anal. Calcd for $C_9H_{10}OS_2$: C, 54.51; H, 5.08. Found: C, 54.64; H, 5.10.

5,6-Dihydro-4*H*-6-(*p*-methoxyphenyl)thieno[2,3-*b*]thiopyran-4-one (48): 75%; mp 82–83 °C (CH_2Cl_2–ligroin); ^{1}H NMR ($CDCl_3$) δ 3.05 (br s, 1 H), 3.15 (d, 1 H, J = 7), 3.75 (s, 3 H), 4.8 (dd, 1 H, J = 12, 5), 6.85 (d, 2 H, J = 9), 7.0 (d, 1 H, J = 5), 7.35 (d, 2 H, J = 9), 7.45 (d, 1 H, J = 5). Anal. Calcd for $C_{14}H_{12}O_2S_2$: C, 60.84; H, 4.38. Found: C, 60.94; H, 4.39.

All molecular geometries were created and initially optimized with the Merck molecular modeling system.[13] Molecular orbital

Table I. Reaction of 2 with Acrylic Acid Derivatives 6 via the Michael Reaction To Generate Propionic Acid Derivatives 7

entry	R	R^1	R^2	R^3	acrylic acid derivative 6	propionic acid derivative 7	% yield	mp, °C (RX solvent) or bp, °C (mmHg)
1	H	H	H	H	**9**	**4**	61	ref 2
2	CH_3	CH_3	H	H	**10**	**11**	92	no analysis[c]
3	TBDMS	CH_3	H	H	**12**	**13** (R = H)	80	130–138 (0.5)[a]
4	H	CH_3	H	H	**14**	**13**	95	
5	TBDMS	H	CH_3	CH_3	**15**	**16** (R = H)	40	125–131 (0.4)[a]
6	H	H	CH_3	CH_3	**17**	**16**	98	
7	H	H	C_6H_5	H	**18**	**19**	100	61–63 (pet. ether)[a,b]
8	CH_2CH_3	H	4-CH_3O-C_6H_4	H	**20**	**21**	89	no analysis[c]
9	TBDMS	H	4-CH_3O-C_6H_4	H	**22**	**23** (R = H)	97	112–114 (CH_3CN)[a]
10	H	H	4-CH_3O-C_6H_4	H	**24**	**23**	95	
11	TBDMS	H	4-C_5H_4N	H	**25**	**26** (R = H)	71	164–165 (CH_3CN)[a]
12	H	H	4-C_5-H_4N	H	**27**	**28**	88	148–150 (CH_3CN)[a]
13	H	H	3-C_5H_4N	H	**29**	**30**	96	98–100 (pet. ether)[a,b]
14	H	H	4-NO_2-C_6H_4	H	**31**	**32**	90	152–154 (CH_3CN)[a]
15	H	H	2-NO_2-C_6H_4	H	**33**	**34**	95	81–83 (hexane)[a,b]

[a] Good elemental analysis obtained. [b] Trituration. [c] Characterization by ^1H NMR spectroscopy.

Table II. Calculated AM1 Proton Affinities[a] (kcal/mol) of 27, 29, and 31

	27	29	31
$\Delta H_f(B)$	-43.35	-44.30	-49.34
$\Delta H_f(BH^+)$	111.19	112.26	129.49
PA	212.66	210.64	188.37
ΔPA[b]	0.00	-2.02	-24.29

[a] The proton affinity (PA) of a species B is defined as minus the heat of reaction for combination with a proton: $B + H^+ \rightarrow BH^+$; $PA(B) = \Delta H_f(B) + \Delta H_f(H^+) - \Delta H_f(BH^+)$. Since AM1 is known to give a very poor estimate of the heat of formation of H^+ (calcd 314.9, obsd 367.2), the experimental value[18] was used in calculating PAs. [b] PA relative to that for **27**.

Table III. Calculated AM1 LUMO Coefficients and Atomic Charges for Atoms 1 and 2 of 9, Methyl Acrylate, 27, 38, 29, 39, 31, and 40

	LUMO coefficients		atomic charges	
	1	2	1	2
9	-0.66	0.48	-0.12	-0.19
methyl acrylate	-0.65	0.48	-0.13	-0.19
27	-0.46	0.45	-0.04	-0.18
38	-0.11	0.35	-0.14	-0.06
29	-0.43	0.43	-0.02	-0.20
39	-0.06	0.16	-0.12	-0.09
31	-0.30	0.37	-0.05	-0.17
40	-0.01	0.19	-0.13	-0.07

calculations were carried out with either the MNDO[14] or AM1[15] semiempirical molecular orbital methods as implemented in the AMPAC package of programs.[16] The MNDO method was employed for species containing sulfur[17] or silicon, since AM1 is not currently parametrized for these elements. All MNDO and AM1 calculations were performed by using the RHF closed-shell method. Since both MNDO and AM1 give a very poor estimate (326.7 and 314.9 kcal/mol) of the heat of formation of H^+, the experimental value (367.2 kcal/mol)[18] was used in calculating proton affinities and deprotonation enthalpies.

Table IV. Calculated MNDO Deprotonation Enthalpies[a] (kcal/mol) and Observed pK_a's of Various Nucleophiles

	2	42	43	diethyl malonate
$\Delta H_f(BH)$	26.57	23.45	19.97	-180.49
$\Delta H_f(BH^-)$	-2.47	0.45	9.35	-209.43
DPE	338.16	344.20	356.58	338.26
ΔDPE[b]	0.00	6.04	18.42	0.20
pK_a	4.7[c]	6.5[d]	9.43[d]	13.0[d]

[a] The deprotonation enthalpy (DPE) of a species BH is defined as the heat of reaction for loss of a proton to form the conjugate base: $BH \rightarrow B^- + H^+$; $DPE(BH) = \Delta H_f(B^-) + \Delta H_f(H^+) - \Delta H_f(BH)$. The DPE of a compound is thus equal to the proton affinity of its conjugate base. Since MNDO is known to give a very poor estimate of the heat of formation of H^+ (calcd 326.7, obsd 367.2), the experimental value[18] was used in calculating DPEs. [b] DPE relative to that for **2**. [c] Value obtained at MSDRL. [d] Albert, A.; Serjeant, E. P. *Ionization Constants of Acids and Bases*; Wiley: New York, 1962; Chapter 8, p 13.

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Supplementary Material Available: Table of physical and spectral data for substituted propionic acid derivatives of **7** (1 page). Ordering information is given on any current masthead page.

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