A Novel and Expeditious Approach to Thiophene-3-carboxylates

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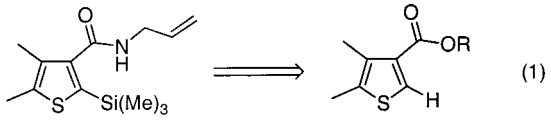
Introduction

Silthiofam **1** is the active ingredient in "Latitude", a novel fungistat being marketed by Monsanto for protection of wheat against Take-All disease.[1] Modification of the discovery chemistry route to **1** led to an efficient and scaleable synthesis starting from the ester **2a** (eq 1).



(1)

1, Silthiofam

2a, R = Et
2b, R = Me

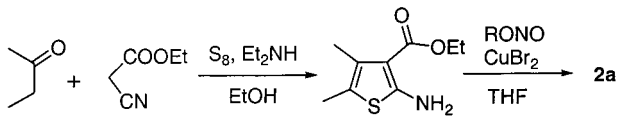
Ester **2a** was originally prepared by a Gewald[2] reaction/deamination sequence (Scheme 1). Although this constituted a short route to **2** from inexpensive raw materials, there were several serious concerns (low yield, regioisomer formation, hazardous reagents) about this chemistry that led us to seek alternate routes to the compound.

We describe herein a convenient, high-yield, and mechanistically interesting synthesis of **2b**, and application of the method to the synthesis of other thiophene-3-carboxylates, a relatively inaccessible class of compounds.

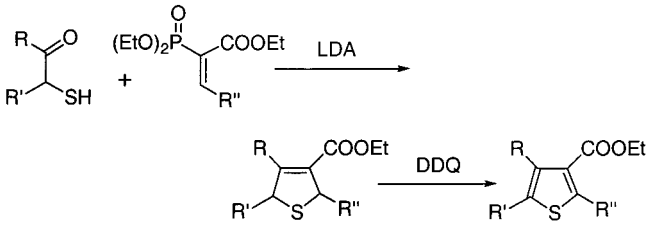
Results and Discussion

A review of the literature revealed only a few potentially general approaches to thiophene-3-carboxylate esters, each of these having certain disadvantages. The Gewald reaction, because of the formation of regioisomers from unsymmetrical ketones and the frequently inefficient deamination, typically gives modest yields, as was the case with **2a** (∼20%). In 1995, Damon[3] and coworkers reported a new procedure that alleviated these particular problems. The method involved a cycloaddition

Scheme 1

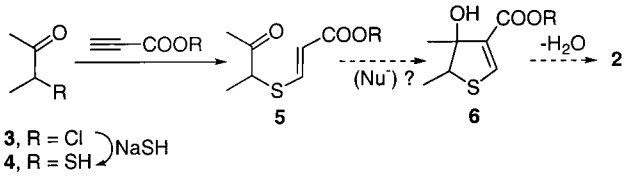


Scheme 2[a]



[a] Reference 3.

Scheme 3



reaction between α-mercaptoketones and 2-phosphonoacrylate esters as shown in Scheme 2.

The phosphorus substituent stabilizes the anion formed by the initial conjugate addition and facilitates ring closure through a Wittig-type reaction. The drawbacks of this method from our point of view were the added cost and waste arising from the need for a phosphorus substituent and the fact that the products still required oxidation to give the thiophenes.

In another approach,[4] thiophene-3-carboxylates have been formed directly by reaction of α-mercaptoketones with propiolate esters; however the conditions were harsh and the yields were low (7−58%). Still, we considered the route to have potential if milder conditions could be used, perhaps by performing the sequence in stepwise fashion, as shown in Scheme 3.

The known 3-mercapto-2-butanone **4**[5] was prepared from the inexpensive, readily available 3-chloro-2-butanone **3**. The mercaptan added to methyl or ethyl propiolate[6] to give **5** in good yield under mild conditions. A subsequent, internal Baylis−Hillman-type[7] reaction could be achieved upon prolonged heating of **5** with PPh_3, but the conversion to **6** was only about 30%. Other nucleophiles such as DABCO, iodide, or thiocyanate were ineffective.

These modest results led us to discontinue efforts on this particular route. However, the ready availability of mercaptan **4** and the ease with which it underwent

(1) Phillion, D.; Wong, S. C.; Shortt, B. U.S. Patent 5,486,621 A, 1996.

(2) For a review of the Gewald synthesis, see: Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocycl. Chem.* **1999**, *36*, 333. For a recent review of thiophene synthesis, see: Nakayama, J. *Comp. Heterocycl. Chem. II* **1996**, *2*, 607−677.

(3) (a) Coppola, G. M.; Damon, R. E.; Yu, H. *Synlett.* **1995**, 1143. (b) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, *56*, 226. (c) We could find only one report in the literature of the base-catalyzed addition of an α-mercaptoketone to a simple acrylate ester (ethyl acrylate). Only conjugate addition of the mercaptan, without cyclization, was observed; see: Rühlmann, K.; Heuchel, D.; Schräpler, U.; Gramer, D. *J. Prakt. Chem.* **1960**, *11*, 40.

(4) Bohlmann, F.; Bresinsky, E. *Chem. Ber.* **1964**, *97*, 2109.

(5) (a) Asinger, F.; Thiel, M.; Kalzendorf, I. *Liebigs Ann. Chem.* **1957**, *610*, 25. (b) Dubief, R.; Robbe, Y.; Fernandez, J.-P.; Subra, G.; Terol, A.; Chapat, J.-P.; Sentenac-Roumanou, H.; Fatome, M. *Eur. J. Med. Chem.* **1986**, *21*, 461.

(6) For a review, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(7) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001.

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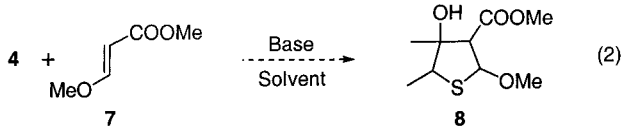
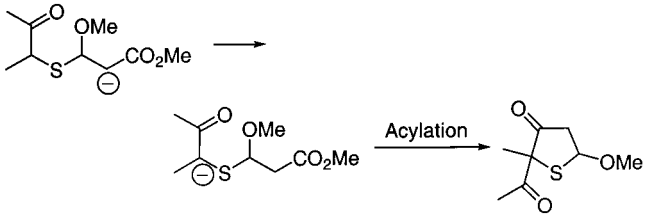
conjugate additions to unsaturated esters were appealing features of this approach. We therefore looked for a propiolate equivalent that would undergo a cycloaddition reaction similar to Damon's and yet also provide a product in the requisite oxidation state. Methyl 3-methoxyacrylate **7** met several of our criteria. This material is reasonably inexpensive, readily available, and known to react with some heteronucleophiles in the desired sense (by initial conjugate addition).[8] Thus, the cycloaddition reaction shown in eq 2 was conceived.



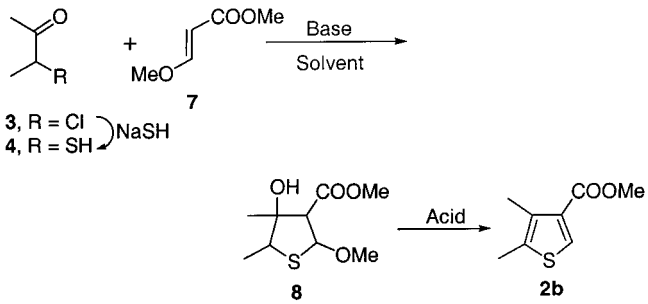
7 8 (2)

A review of the literature, however, did not encourage pursuit of this approach. First, the only reported reactions of thiols with 3-methoxyacrylates resulted in simple methoxide displacement by the thiol through an addition/elimination mechanism.[9a] Such a reaction in our case would produce acrylate **5** (Scheme 3), which we already knew to be a dead end product.[9b] Second, since Damon and co-workers went to the trouble to develop the phosphonoacrylate method and the only reported reaction of an α-mercaptoketone with an *unactivated* acrylate gave addition but no cyclization,[3c] the implication is that a phosphorus substituent on the acrylate is required for this type of cycloaddition. Finally, two earlier studies[10,11] strongly suggest that a proton transfer would take place in our proposed scheme to convert an unstabilized ester enolate into a sulfur-stabilized, ketone enolate (Scheme 4). The resulting enolate might then be acylated by the ester as shown or undergo any number of other side reactions.

Scheme 4

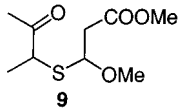


Scheme 5



Because of the potential advantages of the approach, we proceeded despite these misgivings and were pleased to find that the reaction of mercaptan **4** with acrylate **7** in fact can be made to proceed very well to provide hydroxy ester **8** in good yield (Scheme 5). Moreover, tetrahydrothiophene **8** was readily converted into **2b** by treatment with acid,[10,12] thereby confirming the viability of the whole sequence.

A brief survey of solvents and bases for the key cyclization showed that nonpolar, aprotic solvents[13] (notably toluene) were preferred and that NaOMe was the weakest base that efficiently promoted the reaction. The use of protic solvents (MeOH), no solvent, or amine bases led to the formation of variable amounts of the acyclic sulfide **9**, with a consequent reduction in the overall yield of **2b**.



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Optimization of the cycloaddition step included an investigation of the interesting mechanistic features of the reaction. The cyclization reaction is an equilibrium process, as formulated in Scheme 6. The mercaptide anion derived from **4** adds to acrylate **7** in conjugate fashion to give the enolate shown, along with the cyclized alkoxide. Protonation of these species by MeOH (derived from NaOMe) or the mercaptan produces the corresponding products **9** and **8**, respectively. Even at the earliest time points after the acrylate addition, cyclic alcohol **8** is favored over acyclic ketone **9** by at least a 4:1 ratio, and this ratio then increases slowly over time. It is typical to obtain ratios of about 8:1 after a few hours and 15−20:1 after stirring for ca. 16 h at room temperature. Submission of a purified sample of the acyclic ketone **9** to the reaction conditions produced **8** cleanly, with about 50% conversion in 4 h. Thus, it seems likely that a substantial portion of alcohol **8** forms through direct cyclization of the intermediate ester enolate, without the intervention of (protonated) **9** but that most of the **9** that does form also slowly cyclizes to **8**. Treatment of pure cyclic alcohol **8** with NaOMe in toluene produces mainly the aromatized product **2b** along with a small amount of ring-opened **9**, but the conversion (to **2b**) seems to be stoichiometric rather than catalytic in NaOMe. Recall that the aromatization produces water, which would

(8) (a) Ataka, K.; Oku, M.; Hirotsu, K. Jpn. Kokai Tokkyo Koho, patent number JP 04134055, 1992. (b) Maywald, V.; Steinmetz, A.; Rack, M.; Gotz, N.; Gotz, R.; Henkelmann, J.; Becker, H.; Aiscar, B.; Juan, J. PCT Int. Appl. WO0031042A2, 2000.

(9) (a) Two of our academic consultants, in fact, expected this to happen; see: Croxall, W. J.; Friemiller, L. R.; Shropshire, E. Y. *J. Am. Chem. Soc.* **1950**, *72*, 4275. Lozac'H, N.; LeGrand, L.; Bignebat, N. *Bull. Chim. Soc. Fr.* **1964**, 3247. (b) A referee has pointed out the possibility that methoxide could, in principle, add to **5** to give intermediate **9** (see Scheme 6 and accompanying discussion) and ultimately cyclic product **8**. We agree, though this was never tried.

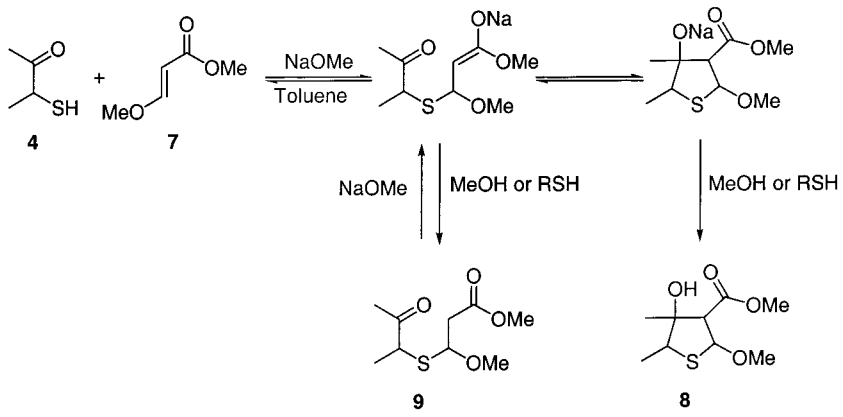
(10) Kaneko, H.; Yamato, Y.; Kurokawa, M. *Chem. Pharm. Bull.* **1968**, *16*, 1200. This paper describes a conceptually related approach to thiophene-2-carboxylates, in which α-mercaptoesters react with 3-methoxy-2-enones to give tetrahydrothiophenes. These are subsequently aromatized by acid treatment. However, the cycloaddition follows a different pathway from our proposed reaction; the initial ketone enolates formed by conjugate addition undergo proton transfer to afford sulfur-stabilized ester enolates, which then add to the ketones to furnish the tetrahydrothiophenes.

(11) Just such a proton transfer (with subsequent enolate acylation) was observed by Hendrickson in the reaction of mercaptoacetone with diethyl acetylenedicarboxylate, and the enolate stability argument was given. See: Hendrickson, J. B.; Rees, R.; Templeton, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 107.

(12) Fevig, T. L.; Lau, P. H.; Phillips, W. G. PCT Int. WO9919321A1, 1999. U.S. Patent 6,037,478, 2000.

(13) Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983**, *48*, 4330. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1990.

Scheme 6



react with the catalyst.[14] In both experiments, small amounts of mercaptobutanone **4** and methoxyacrylate **7** are also formed. At no time in these experiments did any other impurities appear at levels greater than about 2−3%. Thus, the potential competing reaction pathways mentioned above either do not occur or are reversible and highly disfavored. In particular, elimination of methoxide to give acrylate **5** (Scheme 3) is not observed.[9b] Methoxide elimination after cyclization also does not seem to occur significantly; the small amount of aromatized product that is often seen in the cyclization mixture probably arises by dehydration followed by very rapid methoxide elimination (no intermediates are observed). Also, the proton transfer that would give the ketone enolate of **9** (see Scheme 4) either does not occur, is reversible, or simply leads to protonated product **9** as the predominant pathway.

Finally, we note that the cyclization to give **8** is highly stereoselective. Only three (of eight possible) diastereoisomers of **8** have been detected, with the major one accounting for more than 95% of the total. We have not been able to make a definitive assignment of the stereochemistry, but the major isomer is believed to have the C-3 and C-5 ring hydrogens *cis* to one another, with the hydroxy group *cis* to the ester (see Supporting Information for NOESY data and a brief discussion).

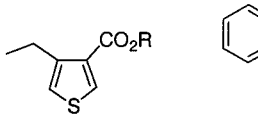
Having chosen NaOMe/toluene as the conditions for the cyclization step, we optimized the other steps in order to obtain a convenient, operationally simple route to **2b**. In particular, we considered isolation of the two intermediates, mercaptan **4** and tetrahydrothiophene **8**, to be undesirable. Low molecular weight α-mercaptoketones such as **4** are foul-smelling,[15] volatile, and not very stable thermally, tending to undergo a dehydrative dimerization. Since the cyclization reaction is run in toluene, we considered forming **4** in a two-phase mixture of water and toluene and carrying the toluene solution of **4** forward. In practice, this works very well in the case of mercaptoketone **4** because α-chloroketone **3** has good solubility in water, whereas product **4** has low solubility in the resulting salt solution and is efficiently extracted into the toluene. No phase transfer catalyst (PTC) is required.

The toluene solution of **4** so obtained can be used in the next step, provided there is a minimal amount of water present. The cyclization step can tolerate the small amount of water that is *dissolved* in the solution of **4**, but a careful phase separation must be made since the presence of additional, undissolved water will result in a lower yield and possible difficulty in initiating the cyclization reaction. Good results are ensured if the solution of **4** is dried with $CaCl_2$ or other drying agents prior to use.

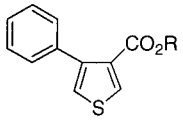
To avoid isolation of tetrahydrothiophene **8**, an in situ aromatization procedure was developed. Thus, addition of a strong mineral acid like HCl, H_2SO_4, or H_3PO_4 (at high concentration) directly to the vigorously stirred reaction mixture containing **8** effectively catalyzes elimination of water and MeOH from **8** to provide **2b**. HCl is the preferred acid because of its toluene solubility and volatility.

Isolation of **2b** involves a simple aqueous workup, evaporation of most of the toluene under reduced pressure, and distillation of the product through an efficient fractionating column. In this way, **2b** is obtained in 70−75% isolated yield (from **3**) and >97% purity. The process can be run safely on large scale and requires no expensive reagents or extreme reaction conditions. A multi-kilogram scale procedure is given in the Experimental Section.

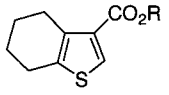
We believe that, if general, the present method would compare very favorably with the previously mentioned approaches with respect to yield, brevity, convenience, and cost. We therefore selected the four thiophene targets shown below to test the tolerance of the chemistry with respect to the α-haloketone starting material. The ethyl compound **10b** was needed anyway for a reference standard, and the other three were chosen to see whether aromatic and cyclic ketones could be used. In each case,



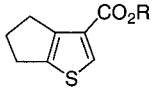
10a R = Me (19%)
10b R = H (14%)



11a R = Me (60%)
11b R = H (50%)



12a R = Me (0%)



13a R = Me (52%)

(14) The implication is that NaOH is a poor catalyst for the reaction. By using a larger amount of NaOMe, the equilibrium can be driven all the way to the aromatized product **2b** (obviating the need for HCl treatment), but the overall yield is significantly lower for reasons that are not fully understood.

(15) Hofmann, T.; Schieberle, P. *J. Agric. Food Chem.* **1995**, *43*, 2187.

the procedure described in the Experimental Section for **2b** was followed, starting from, respectively, 1-bromo-2-butanone,[16] 2-chloroacetophenone, or the 2-chlorocycloalkanones. For convenience, some of the products were isolated and characterized as the carboxylic acids (b series) after hydrolysis with NaOH, with the unoptimized, overall yields from the haloketones shown in parentheses.

In general, the cyclization and aromatization phases of the process ran similarly for all of the α-mercaptoketones obtained, so that the overall yields largely reflect the highly variable results obtained in the first step, formation of the mercaptoketones. For example, reaction of 1-bromo-2-butanone with NaSH as described above gave a symmetrical sulfide as the major product, limiting the yield of the required mercaptan to about 30%. This product distribution is attributed to the use of a more reactive α-haloketone (relative to **3**). For reasons that are unclear, the 2-chlorocyclohexanone was an even poorer substrate under these conditions, affording only a trace of mercaptan in one run. The reaction produced a white solid, the spectral data and physical properties of which did not match those reported in the literature for the known mercaptan.[17] On the other hand, chlorocyclopentanone and chloroacetophenone were converted cleanly into the desired mercaptans, though in a much slower reaction in the latter case compared with **3**, presumably as a result of the lower water solubility of chloroacetophenone.[18] Clearly, the conditions developed for conversion of **3** into mercaptobutanone **4** are highly specific for this compound and may need modification when applied to other substrates. Alternatively, the general method reported by Damon[3] could be used. By starting from aldehydes instead of α-haloketones, Damon's method also greatly increases the range of accessible α-mercaptoketones.

In summary, this limited study suggests that the key step in the sequence, the reaction of α-mercaptoketones with methoxyacrylate **7** to give compounds analogous to **8**, may have some generality. It is expected that the aromatization step will be very general, with the proviso that any acid-labile groups elsewhere in the molecule will be vulnerable. The procedure for α-mercaptoketone formation presented here does not seem to have wide applicability, however. Modification of this procedure or selection of an alternate route may be required in some cases.

Experimental Section

General. Microanalyses were performed by Galbraith Laboratories. The actual charges of substrates and reagents are given below. The molar amounts are calculated on the basis of the assays of the materials. Similarly, yields are calculated on the basis of assay corrected moles of substrates and products. ***Caution!*** *NaSH will react with acid to generate the highly toxic H_2S. Excess NaSH should be oxidized with bleach or hydrogen peroxide prior to disposal. The oxidation is highly exothermic.* The 3-mercapto-2-butanone is foul smelling, with a very low detection limit. The material should be kept in the fume hood. The α-haloketones are potent irritants and lachrymators and should be handled with due care.

Methyl 4,5-Dimethylthiophene-3-carboxylate (2b). A 35-L jacketed reactor equipped with an overhead stirrer, a bottom drain valve, a dropping funnel, a thermocouple, and a nitrogen inlet was charged with toluene (6.5 kg), NaSH[19] (43% aqueous solution, 3.43 kg, 26.34 mol), and water (2.72 kg). The mixture was stirred vigorously, and cooling was applied by means of the glycol/water mixture circulating through the jacket to bring the reaction mixture to 10 °C. The 3-chloro-2-butanone **3** (2.50 kg, 22.91 mol) was charged through the addition funnel over about 2 h, the reaction temperature being maintained at 15−20 °C by adjusting the feed rate and jacket temperature. After the addition was complete, the mixture was stirred vigorously for 1 h while the jacket temperature was raised to 25 °C. Stirring was then stopped, the phases were allowed to separate and settle for 10 min, and then the lower, aqueous phase was drained out of the bottom of the reactor. The agitator was pulsed a few times to knock water off the reactor walls and complete the phase separation. *Note: the aqueous phase can be deodorized prior to disposal by treatment with bleach (**caution!** exothermic reaction).* After drainage of the aqueous phase, the drain stem was washed with water and acetone, and dried under a stream of nitrogen. The homogeneous, light yellow organic phase containing 3-mercapto-2-butanone **4** was then drained into a tightly sealed polypropylene container, and the reactor was cleaned out with water and acetone and dried under a strong stream of nitrogen.

The solution of **4** (8.75 kg) was then returned to the clean, dry reactor along with a toluene rinse (280 g). A portion of the methyl 3-methoxyacrylate (**7**, 250 g, 2.29 mol) was added to the solution through the dropping funnel, and the mixture was stirred vigorously with the jacket temperature at 15 °C. Solid NaOMe (128 g, 2.29 mol) was added all at once, causing an immediate temperature rise of ca. 3 °C followed by slow cooling of the mixture. After about 30 min, the reaction temperature started rising against the cooling jacket, signaling the initiation of the cyclization. The remaining acrylate (2.28 kg, 19.13 mol) was then added in over 2 h to maintain the reaction temperature below 30 °C. After the addition was completed, the mixture was stirred overnight at room temperature.

The mixture was cooled to 10 °C with good stirring, and concentrated HCl (1.67 kg, 16.93 mol) was added in over about 30 min, producing an exotherm (to 28 °C) and a precipitate of NaCl. The mixture was stirred at room temperature for 1.5 h,

(16) 1-Chloro-2-butanone was not readily available.

(17) Anderson, M. B.; Ranasinghe, M. G.; Palmer, J. T.; Fuchs, P. L. *J. Org. Chem*. **1988**, *53*, 3125. In particular, the compound melted higher and over a very broad range, 144−164 °C, compared with the reported melting point of 131−133 °C. Also, the ^{13}C NMR spectrum of the material showed a major component having six distinct carbons, none of which was a ketone carbonyl. Submission of a small portion of the substance to the cyclization reaction conditions afforded no product corresponding to **8**. The material has not been further characterized or identified, but the ^{13}C NMR spectrum and lack of reactivity suggest that it is a dehydrated dimer. An analogous compound forms from 3-mercapto-2-butanone, but only upon exposure of the compound to heat or traces of acid. It is unclear why mercaptocyclohexanone alone should dimerize and dehydrate so readily under our conditions, but a referee has indicated that mercaptocyclohexanone is indeed especially prone to dimerize and dehydrate and that α-mercaptoketones, once they dimerize, only revert to the monomer in polar solvents. In support of this, the monomeric mercaptan has been prepared by reaction of 2-chlorocyclohexanone with NaSH hydrate in EtOH at −5 °C (Asinger, F.; Schmitz, M. K. *Monatsh. Chem*. **1982**, *113*, 1191) or by reduction of a disulfide in aqueous MeOH (see paper by Fuchs et al. cited above). Thus, it seems likely that the mercaptans successfully prepared in this study are formed as monomers (in the aqueous phase) under our conditions and remain monomeric in the toluene solution. We thank the reviewer for bringing this information to our attention.

(18) MacDowell, D. W. H.; Jeffries, A. T. *J. Org. Chem*. **1970**, *35*, 871. By way of comparison, the only previous synthesis of 4-phenylthiophene-3-carboxylic acid **11b** employed a very expensive starting material, 3,4-dibromothiophene and required two halogen−metal exchanges at −70 °C, a high vacuum distillation (0.2 mmHg), and a purification by column chromatography. The four-step synthesis did give a good overall yield (52%) of the product, however. The successful formation of **11a** is especially interesting mechanistically. In this case, the proton transfer/enolate acylation pathway (Scheme 4) would seem particularly favorable, since the process could be driven forward by aromatization of the acylation product (by methoxide elimination and tautomerization) to a hydroxythiophene. Although we made no attempt to isolate or identify the byproducts, the 60% isolated yield of desired product indicates that this is a minor pathway at best.

(19) NaSH can be obtained from bulk suppliers as aqueous solutions of various concentrations. We prefer 30−40% solutions because all of the NaSH remains in solution even below room temperature. Also, aqueous solutions have uniformly been of higher quality than solid NaSH from any source.

and then water (1.39 kg) was added to dissolve the salt. After stirring for 15 min, the phases were allowed to separate and settle for 15 min. The lower, aqueous phase was drained out, and the organic phase containing **2b** was washed similarly with 1.98 kg of 5% aqueous $NaHCO_3$. The aqueous phase was drained, and the organic phase was weighed into a small drum. The material weighed 10.59 kg and assayed as 29.8% **2b**, indicating a chemical yield of 3.16 kg of **2b**, or 81% yield from **3**.

The crude reaction mixture was placed in a 22-L flask equipped with a mechanical stirrer, a vacuum inlet, and a distillation head atop a two-tray, Oldershaw-type, vacuum-jacketed distillation column. Most of the toluene was distilled through the column at ca. 75 mmHg. The residue (6.04 kg) was then transferred to a 6-L flask, similarly equipped, but with a five-tray Oldershaw column. Two early fractions were collected, the first containing mostly toluene and the second consisting of toluene, acrylate **7**, methyl 3,3-dimethoxypropionate, and **2b**. The main fraction of **2b** came over at about 109 °C at 11.5 mmHg as a yellow liquid, affording 2.90 kg of material with >99% purity. The isolated yield was therefore 74% from chlorobutanone **3**. The main loss during distillation was in the fraction immediately preceding the main cut. An analytical sample was obtained by washing the distilled material with bleach (to destroy aliphatic sulfur compounds[20]) and redistilling it through a Vigreux column under vacuum. The compound was obtained as a nearly colorless liquid, bp 85 °C (3 mmHg): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (s, 1H), 3.80 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0, 134.3, 134.1, 132.4, 130.1, 51.5, 13.5, 13.4; MS (GC−MS) *m*/*z* 170 (M^+, 54%), 155 (17), 139 (100). Anal. Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92; S, 18.83. Found: C, 56.37; H, 5.98; S, 18.61.

4-Ethylthiophene-3-carboxylic Acid (10b). The ester **10a** was prepared by using the procedure described above for **2b**, starting from 1-bromo-2-butanone (48.1 g, 0.287 mol). The crude toluene solution of the product was washed with bleach to oxidize aliphatic sulfide impurities. After evaporation of the toluene, the residue was purified by silica gel chromatography (hexane/EtOAc, 6:1) to give an oil. The purest fractions (8.0 g, 19% yield from 1-bromo-2-butanone) were combined and hydrolyzed to carboxylic acid **10b** by refluxing for 4 h with a slight excess of NaOH in water. The product (6.5 g, 14% yield from 1-bromo-2-butanone) was obtained as a white solid, mp 77−79 °C, after a standard acid/base workup. The total chemical yields are somewhat higher than the values given above, because impure chromatography fractions containing **10a** were not used: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (v br s, 1H), 8.23 (d, J = 3.2 Hz, 1H), 6.96 (s, 1H), 2.92 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 146.2, 136.8, 130.7, 121.7, 23.4, 14.4; MS (GC−MS) *m*/*z* 156 (M^+, 54%), 155 (17), 139 (100). Anal. Calcd for $C_7H_8O_2S$: C, 53.82; H, 5.16; S, 20.53. Found: C, 53.83; H, 5.27; S, 20.79.

4-Phenylthiophene-3-carboxylic Acid (11b). The ester **11a** was prepared starting from 2-chloroacetophenone (50 g, 0.317 mol) by using the procedure described above for **2b**, except that the solid chloroketone was added to the NaSH as a solution in toluene, with the result that this reaction was substantially more dilute. The mercaptan was formed cleanly but much more slowly (20 h) than mercaptobutanone **4**. The mercaptan solution was dried over $CaCl_2$ prior to the cyclization step. After evaporation of most of the toluene, the crude ester **11a** was obtained as a yellow oil (74.4 g). A 10 g portion of this oil was purified by chromatography over silica gel (hexane/EtOAc, 5:1) to give the product as a pale yellow oil (5.54 g). The total yield was therefore 41.22 g (60% from 2-chloroacetophenone). The ester **11a** (5.10 g, 23.4 mmol) was hydrolyzed by treatment with NaOH (2.25 g of 50% solution, 28.1 mmol) in 30 mL of water at reflux for 4 h. The mixture was cooled and extracted with diethyl ether, and the phases were separated. The aqueous phase was acidified with concentrated HCl. The precipitated product was collected by vacuum filtration, washed with water, and dried overnight in a vacuum oven at 50 °C to afford 4.77 g (100% crude yield) of a pale tan solid. Recrystallization from toluene (25 mL/g **11b**, 84% recovery) gave an analytical sample as white crystals, mp 207−208 °C (lit.[18] mp 206−208 °C). The spectral data for this compound agree well with those reported. Anal. Calcd for $C_{11}H_8O_2S$: C, 64.69; H, 3.95; S, 15.70. Found: C, 64.66; H, 3.98; S, 15.95.

Methyl 4,5-Cyclopentathiophene-3-carboxylate (13a). The ester **13a** was prepared by using the procedure described above for **2b**, starting from 2-chlorocyclopentanone (75.8 g, 0.627 mol). The mercaptan solution was dried over $CaCl_2$ prior to the cyclization step. The crude product solution containing **13a** was washed with bleach (exothermic), most of the toluene was evaporated, and the dark residue was distilled through a Vigreux column under vacuum. The main fraction came over at 110−112 °C at ca. 5 mmHg. The product was obtained as a light yellow liquid (60.1 g, >98% purity, 52% yield from 2-chlorocyclopentanone), which crystallized upon standing. An analytical sample was obtained by recrystallization from EtOH (1 mL/g **13a**) to afford white crystals, mp 38−40 °C: MS (GC−MS) *m*/*z* 182 (M^+, 73%), 167 (66), 151 (49), 123 (100); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (s, 1H), 3.80 (s, 3H), 2.90 (t, J = 7.3 Hz, 2H), 2.84 (t, J = 7.3 Hz, 2H), 2.45 (pentet, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 147.0, 143.4, 135.5, 127.9, 51.7, 29.6, 29.2, 29.1. Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53; S, 17.60. Found: C, 59.01; H, 5.52; S, 17.77.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **8** and **9**, and NOESY data for **8** along with a brief discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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