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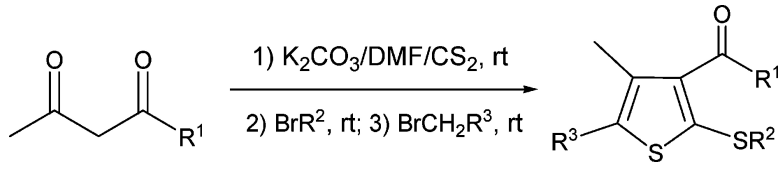

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Efficient One-Pot Synthesis of Highly Substituted Thiophene Library from 1,3-Dicarbonyl Compounds

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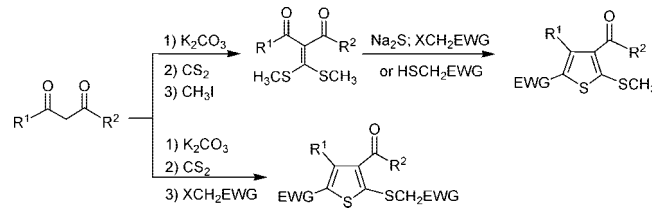
A facile and efficient one-pot synthesis of highly substituted thiophenes has been developed and employed for the preparation of a small focused library. Treatment of 1,3-dicarbonyl compounds **1** with CS_2 in the presence of K_2CO_3 in DMF at room temperature, followed by stepwise addition of alkyl bromides **2** and methylene active bromides **3**, provided via intramolecular cyclization 2,3,4,5-tetrasubstituted thiophenes **4** in yields of 77−94%. This protocol, combining construction and modification of the thiophene ring, increases the structural diversity of final products from readily available materials. A mechanism for the one-pot synthesis of thiophenes of type **4** has been proposed. A small focused library of thiophenes is prepared using the sequential addition of reagents to achieve unique substitution in the 2 and 5 position of the thiophene ring.

Introduction

Thiophene derivatives have emerged as a class of important heterocycles because of their presence in a broad spectrum of natural and synthetic organic molecules with diverse biological properties[1–4] and utility in organic synthesis as versatile intermediates. [5,6] Blair and co-workers have reviewed some cases for which the thiophene replacement of the annulated benzene ring in some biologically active compounds maintains the activity but modifies the selectivity of these bioisosteres.[7] The general synthetic approaches to such thia-heterocycles involve either the functionalization in the α- and *β*-position to the sulfur atom of the preconstructed thiophene nucleus,[8] or the construction of thiophene ring from appropriately substituted open chain precursors.[9] The latter becomes more attractive for its general applicability to achieve more flexible substitution patterns. Gewald and co-workers developed the synthesis of 2-aminothiophenes from the multicomponent condensation of ketones or aldehydes, cyanoacetate, and elemental sulfur.[10] Later, there were some papers reported on the variations and improvements on the originally published Gewald synthesis of polysubstituted thiophenes.[11] While each of these approaches represents an important advance toward the objective of a general method for the synthesis of thiophenes, each of them, however, suffers from significant limitations in terms of harsh conditions, long reaction time, low yields, expensive catalyst, or difficult purification. Thus, new and efficient methodologies for the construction of thiophene skeleton are still desirable.

On the other hand, the utility of α-oxo ketene-*S,S*-acetals as versatile intermediates in organic synthesis has been recognized over the last decades.[12] On the basis of the cyclization of α-oxo ketene-*S,S*-acetals, obtained from methylene active compounds, carbon disulfide, and alkyl halides, an alternative access to substituted thiophenes has been developed.[13] This protocol involves either two-step reaction procedure, namely the preparation of α-oxo ketene-*S,S*-acetals, the replacement reaction from a methylene active halide bearing an electron-withdrawing group (EWG) and subsequent intramolecular Aldol condensation reaction or one-pot synthesis directly from methylene active compounds, as shown in Scheme 1. For the two-step procedure, each step requires its own condition, reagents, solvent, and catalyst. After each reaction is completed, the solvent and the waste are removed and discarded, and the intermediate product is separated and purified. In the replacement reaction stage, the release of alkyl thiolate anions will be unavoidable, which may create safety and environmental problems. In addition, both the two-step procedure and the one-pot synthesis suffer from significant limitations in scope or substituted pattern, for example, the specific and accurate sulfanyl group on the thiophene ring. These obstacles limited these methods as attractive candidates for parallel synthesis or other high-throughput synthetic methods.

Scheme 1



During the course of our studies on the synthesis and application of α-oxo ketene-*S,S*-acetals,[14,15] we developed a facile and efficient one-pot synthesis of 2,3,4,5-tetrasubstituted thiophenes that involves (1) the deprotonation of 1,3-dicarbonyl compound, (2) the nucleophilic addition to carbon disulfide, (3) the *S*-alkylation with an alkyl bromide, (4) the *S*-alkylation with a methylene active bromide, and (5) the intramolecular cyclization reaction, affording highly substituted thiophenes with flexible substituted patterns, for example, sulfanyl groups. This protocol combining construction and modification of the

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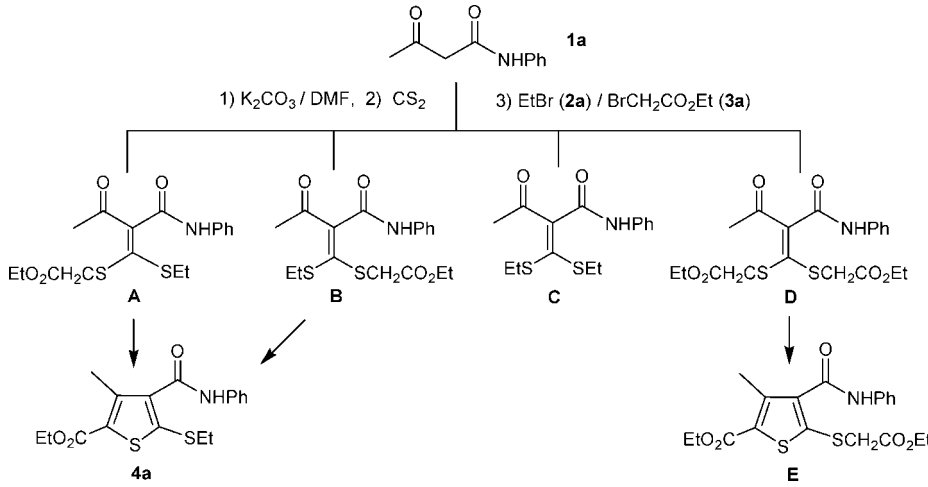
Scheme 2



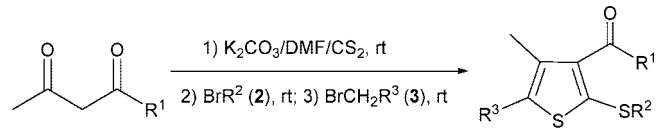
thiophene ring increases the structural diversity of the final products from readily available materials, which appeals to us for parallel synthesis. We herein report our results for the efficient one-pot synthesis of highly substituted thiophenes **4** from 1,3-dicarbonyl compounds **1**, the proposed mechanism involved, and its application in the parallel synthesis of a small focused library of thiophenes **4**.

Results and Discussion

There are extensive work reported on the synthesis of α-oxo ketene-*S,S*-acetals in the presence of varied of base/solvent systems.[12] According to our previous work[14] and other reports,[16] we choose 1,3-dicarbonyl compounds as substrate, K_2CO_3 as the base, and *N,N*-dimethylformamide (DMF) as the reaction medium for the investigations. The reaction of 3-oxo-*N*-phenylbutanamide **1a** with CS_2 (1.1 equiv), ethyl bromide **2a** (1.0 equiv), and ethyl bromoacetate **3a** (1.0 equiv) in the presence of K_2CO_3 (5.0 equiv) in DMF at room temperature was initially investigated. In theory, the use of two different halides might lead to a mixture of several products, which in some cases are barely separable (Scheme 2); this is the reason few reports of such systems have appeared in the literature.[17]

In our experiment, when **1a** was treated with K_2CO_3 in DMF at room temperature, followed by the addition of CS_2 and a mixture of **2a** and **3a**, two main products were obtained after workup and column chromatography of the resulting reaction mixture, and characterized as 2-[bis(ethylthio)methylene]-3-oxo-*N*-phenylbutanamide **C** (yield 45%) and ethyl 5-(2-ethoxy-2-oxoethylthio)-3-methyl-4-(phenylcarbamoyl) thiophene-2-carboxylate **E** (yield 48%), respectively, on the basis of their spectral and analytical data. The result indicates that the reactivity of **2a** and **3a** is different. Then we performed the reaction by the variation of the addition sequence of two alkyl bromides. When **3a** was loaded 30 min earlier than **2a**, similar results were obtained, in which both compounds **C** and **E** were isolated as main products but in slightly lower yields. The inverse addition sequence of **2a** and **3a**, namely, **2a** was loaded 3.0 h earlier than the addition of **3a**, led to the formation of one predominant product, which is different from **C** and **E** as indicated by TLC results. After workup and separation by column chromatography, the product was characterized as ethyl 5-(ethylthio)-3-methyl-4-(phenylcarbamoyl)thiophene-2-carboxylate **4a** (69% yield), a substituted thiophene. A series of experiments revealed that 4.0 equiv of K_2CO_3 was effective for the synthesis of **4a**, and the optimal results were obtained when the reaction of **1a** with carbon disulfide (1.1 equiv) and **2a** (1.0 equiv) was performed in the presence of K_2CO_3 (4.0 equiv) in DMF at room temperature for 6.0 h, followed by addition of **3a** (1.0 equiv), and stirred at room temperature for 0.5 h, whereby the yield of **4a** reached 88%. It should be noted that the use of different alkyl bromides allows us to increase the diversity of the substituents on the thiophene framework, in particular the sulfanyl group.

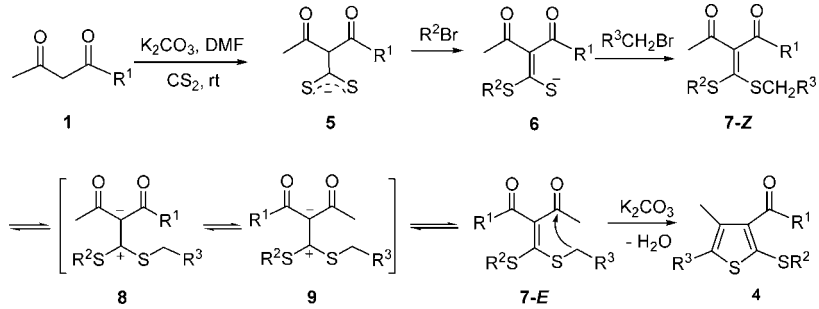
Table 1. One-Pot Parallel Synthesis of Tetrasubstituted Thiophenes **4** from 1,3-Dicarbonyl Compounds **1**



	substrates							
entry	**1**	R^1	**2**	R^2	**3**	R^3	product **4**	yield[a] (%)
1	**1a**	C_6H_5NH	**2a**	Et	**3a**	CO_2Et	**4a**	88
2	**1b**	2-MeC_6H_4NH	**2a**	Et	**3a**	CO_2Et	**4b**	85
3	**1c**	4-ClC_6H_4NH	**2a**	Et	**3a**	CO_2Et	**4c**	94
4	**1d**	2-$MeOC_6H_4NH$	**2a**	Et	**3a**	CO_2Et	**4d**	92
5	**1e**	NHMe	**2a**	Et	**3a**	CO_2Et	**4e**	82
6	**1f**	NH_2	**2a**	Et	**3a**	CO_2Et	**4f**	83
7	**1g**	OEt	**2a**	Et	**3a**	CO_2Et	**4g**	79
8	**1h**	Me	**2a**	Et	**3a**	CO_2Et	**4h**	86
9	**1a**	C_6H_5NH	**2b**	Bn	**3a**	CO_2Et	**4i**	93
10	**1b**	2-MeC_6H_4NH	**2b**	Bn	**3a**	CO_2Et	**4j**	90
11	**1c**	4-ClC_6H_4NH	**2b**	Bn	**3a**	CO_2Et	**4k**	87
12	**1d**	2-$MeOC_6H_4NH$	**2b**	Bn	**3a**	CO_2Et	**4l**	85
13	**1e**	NHMe	**2b**	Bn	**3a**	CO_2Et	**4m**	82
14	**1f**	NH_2	**2b**	Bn	**3a**	CO_2Et	**4n**	79
15	**1g**	OEt	**2b**	Bn	**3a**	CO_2Et	**4o**	84
16	**1h**	Me	**2b**	Bn	**3a**	CO_2Et	**4p**	88
17	**1a**	C_6H_5NH	**2a**	Et	**3b**	C_6H_5CO	**4q**	77
18	**1a**	C_6H_5NH	**2b**	Bn	**3b**	C_6H_5CO	**4r**	85
19	**1c**	4-ClC_6H_4NH	**2a**	Et	**3b**	C_6H_5CO	**4s**	89
20	**1c**	4-ClC_6H_4NH	**2b**	Bn	**3b**	C_6H_5CO	**4t**	86
21	**1g**	OEt	**2a**	Et	**3b**	C_6H_5CO	**4u**	91
22	**1g**	OEt	**2b**	Bn	**3b**	C_6H_5CO	**4v**	90
23	**1h**	Me	**2a**	Et	**3b**	C_6H_5CO	**4w**	89
24	**1h**	Me	**2b**	Bn	**3b**	C_6H_5CO	**4x**	87

[a] Isolated yields.

Scheme 3



With the establishment of the novel cyclization to thiophenes, we applied this protocol in the parallel synthesis of a small focused 24-membered library of substituted thiophenes **4**. The library contained six different β-oxo amides **1a**−**1f**, one β-oxo ester **1g**, and one acetylacetone **1h**, which were deprotonated with K_2CO_3 and then reacted, in sequence, with carbon disulfide, two different alkyl bromides **2a** and **2b**, and two different methylene active bromides **3a** and **3b**. All the reactions proceeded smoothly to afford the corresponding substituted thiophenes **4a**−**4x** in good to high yields, respectively. As noted in Table 1, the yields were in the range of 77−94%. These results demonstrated the efficiency and versatility of the one-pot synthesis of thiophenes of type **4** from 1,3-dicarbonyl compounds **1**. Therefore, we provided a facile and efficient one-pot parallel synthesis of highly substituted thiophenes **4** bearing variable R^1, R^2, and R^3 substituted groups.

On the basis of the results, together with our previous reports,[14] a mechanism for the reaction of 1,3-dicarbonyl compound **1** with CS_2 and alkyl bromides is proposed as depicted in Scheme 3. In the presence of K_2CO_3, the reaction starts from the deprotonation of compound **1** to afford enolate, which undergoes a nucleophilic attack on carbon disulfide to form thiolate salt **5**. Treated with alkyl bromide **2**, the *S*-alkylation of **5** occurs to give thiolate salt **6**. Further *S*-alkylation with active methylene bromide **3** leads to the formation of α-oxo ketene-*S,S*-acetals, as a mixture of the isomers **7**-*Z* and **7**-*E*. Through the resonance of the C=C double bond, there exists an equilibrium between the two isomers.[18] Clearly, the configuration of isomer **7**-*E* facilitates the intramolecular cyclization reaction under basic conditions and gives rise to the final product, substituted thiophene **4**.

Conclusions

In summary, a facile and efficient one-pot synthesis of highly substituted thiophenes has been developed and employed for the preparation of a small focused library. By using the sequential addition of reagents, we synthesized a series of thiophenes with amenable substitution in the 2- and 5-position of the thiophene ring in good to high yields. This protocol, combining construction and modification of the thiophene ring, increases the structural diversity of final products from readily available materials. In addition, the sulfanyl and carbonyl substituents in the 2- and 3-position to the thiophene ring are quite reactive; this makes these compounds good candidates as precursors for further synthetic transformations. The simplicity of execution, mild conditions, high yields, ready availability of substrates, flexible substituted patterns, and broad range of potential utility of the products, make the protocol attractive for academic research and practical applications.

Experimental Section

General Procedure for the Synthesis of Substituted Thiophenes 4. To a solution of 1,3-dicarbonyl compound **1** (2.0 mmol) and K_2CO_3 (8.0 mmol) in DMF (5 mL) was added CS_2 (2.2 mmol) and alkyl bromide **2** (2.0 mmol). The reaction was vigorously shaken at room temperature for 6.0 h, followed by addition of a methylene active bromide **3** (2.0 mmol). The mixture was shaken at room temperature for an additional 0.5 h, after which 10 mL of water was added to quench the reaction. The resulting mixture was transferred into a 100 mL Erlenmeyer flask and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated in vacuo. The residue was purified by flash silica gel chromatography (petroleum ether/Et_2O, 4:1) to give product **4**.

Ethyl 5-(Ethylthio)-3-methyl-4-(phenylcarbamoyl)thiophene-2-carboxylate (4a): white solid; mp 81−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3H), 1.38 (t, J = 7.5 Hz, 3H), 2.65 (s, 3H), 2.99 (q, J = 7.5 Hz, 2H), 4.33 (q, J = 7.5 Hz, 2H), 7.17 (m, 1H), 7.38 (m, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 15.1, 31.7, 61.4, 120.2, 125.0, 127.9, 129.4, 137.9, 139.2, 142.2, 146.3, 162.0, 162.2; IR (KBr, cm^{-1}) 750, 1106, 1128, 1318, 1398, 1528, 1597, 1703, 1740; Anal. Calcd for $C_{17}H_{19}NO_3S_2$ C 58.43, H 5.48, N, 4.01; found C 58.51, H 5.40, N 3.92; MS calcd *m*/*z* 349.1, Found 350.1 $[M + 1]^+$.

Ethyl 5-(Ethylthio)-3-methyl-4-(*o*-tolylcarbamoyl)thiophene-2-carboxylate (4b): white solid; mp 104−106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24−1.39 (m, 6H), 2.35 (s, 3H), 2.66 (s, 3H), 3.00 (q, J = 7.0 Hz, 2H), 4.33 (q, J = 7.0 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 7.22−7.25 (m, 2H), 7.71 (s, 1H), 7.98 (d, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.28, 13.3, 13.8, 17.2, 30.5, 60.0, 121.8, 124.4, 125.8, 126.6, 128.2, 129.7, 134.4, 138.1, 140.7, 145.1, 160.6, 161.0; IR (KBr, cm^{-1}) 752, 1106, 1280, 1368, 1455, 1583, 1631, 1679, 1706; Anal. Calcd for $C_{18}H_{21}NO_3S_2$ C 59.48, H 5.82, N 3.85; Found C 59.62, H 5.73, N 3.78.

Ethyl 4-(4-Chlorophenylcarbamoyl)-5-(ethylthio)-3-methylthiophene-2-carboxylate (4c): white solid; mp 108−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J =

7.5 Hz, 3H), 1.38 (t, J = 7.5 Hz, 3H), 2.65 (s, 3H), 3.00 (q, J = 7.5 Hz, 2H), 4.33 (q, J = 7.5 Hz, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.5 Hz, 2H), 7.93 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 14.6, 15.1, 31.8, 61.4, 121.4, 128.0, 129.4, 130.0, 136.4, 138.7, 142.4, 146.4, 161.9, 162.2; IR (KBr, cm^{-1}) 821, 1160, 1262, 1305, 1454, 1518, 1593, 1704; Anal. Calcd for $C_{17}H_{18}ClNO_3S_2$ C 53.18, H 4.73, N 3.65; Found C 53.31, H 4.81, N, 3.60.

Ethyl 5-(Ethylthio)-4-(2-methoxyphenylcarbamoyl)-3-methylthiophene-2-carboxylate (4d): white solid; mp 99−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.0 Hz, 3H), 1.37 (t, J = 7.0 Hz, 3H), 2.66 (s, 3H), 3.00 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 4.33 (q, J = 7.0 Hz, 2H), 6.92 (d, J = 7.5 Hz, 1H), 6.99−7.02 (m, 1H), 7.08−7.10 (m, 1H), 8.35 (s, 1H), 8.52 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 14.6, 15.2, 31.5, 56.0, 61.3, 110.4, 120.2, 121.4, 124.4, 127.5, 127.7, 139.4, 143.4, 145.8, 148.4, 161.9, 162.1; IR (KBr, cm^{-1}) 756, 1059, 1104, 1295, 1530, 1649, 1709; Anal. Calcd for $C_{18}H_{21}NO_4S_2$ C 56.97, H 5.58, N 3.69; Found C 56.85, H 5.49, N 3.75.

Ethyl 5-(Ethylthio)-3-methyl-4-(methylcarbamoyl)-thiophene-2-carboxylate (4e): white solid; mp 136−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.0 Hz, 3H), 2.57 (s, 3H), 2.97 (q, J = 7.0 Hz, 2H), 3.00 (d, J = 5.0 Hz, 3H), 4.31 (q, J = 7.0 Hz, 2H), 6.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 13.27, 13.29, 13.8, 25.5, 30.1, 59.9, 126.2, 138.1, 140.6, 144.6, 160.7, 163.8; IR (KBr, cm^{-1}) 793, 1092, 1248, 1408, 1541, 1627, 1704; Anal. Calcd for $C_{12}H_{17}NO_3S_2$ C 50.15, H 5.96, N 4.87; Found C 50.24, H 5.84, N 4.81.

Ethyl 4-Carbamoyl-5-(ethylthio)-3-methylthiophene-2-carboxylate (4f): white solid; mp 83−85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3H), 1.38 (t, J = 7.0 Hz, 3H), 2.64 (s, 3H), 3.02 (q, J = 7.5 Hz, 2H), 4.34 (q, J = 7.5 Hz, 2H), 5.83 (s, 1H), 6.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 14.6, 15.2, 31.4, 61.3, 127.4, 137.3, 143.7, 146.2, 161.9, 165.5; IR (KBr, cm^{-1}) 760, 1137, 1291, 1450, 1530, 1614, 1644, 1708, 1747; Anal. Calcd for $C_{11}H_{15}NO_3S_2$ C 48.33, H 5.53, N 5.12; Found C 48.46, H 5.49, N 5.18.

Diethyl 5-(Ethylthio)-3-methylthiophene-2,4-dicarboxylate (4g): white solid; mp 68−69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.0 Hz, 3H), 1.40 (t, J = 6.5 Hz, 3H), 1.45 (t, J = 7.0 Hz, 3H), 2.73 (s, 3H), 3.05 (q, J = 7.0 Hz, 2H), 4.31 (q, J = 7.5 Hz, 2H), 4.36 (q, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 14.28, 14.32, 15.5, 29.0, 60.8, 60.9, 123.8, 127.7, 148.1, 156.0, 161.8, 163.7; IR (KBr, cm^{-1}) 781, 1110, 1417, 1525, 1682, 1706; Anal. Calcd for $C_{13}H_{18}O_4S_2$ C 51.63, H 6.00; Found C 51.52; H 6.06; MS calcd m/z 302.1, found 325.1 $[M + 23]^+$.

Ethyl 4-Acetyl-5-(ethylthio)-3-methylthiophene-2-carboxylate (4h): white solid; mp 59−61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.0 Hz, 3H), 2.53 (s, 3H), 2.63 (s, 3H), 2.98 (q, J = 7.0 Hz, 2H), 4.29 (q, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.5, 15.8, 30.5, 31.7, 61.3, 125.7, 140.3, 145.7, 151.8, 161.9, 196.2; IR (KBr, cm^{-1}) 655, 798, 1060, 1237, 1450, 1673, 1702; Anal. Calcd for $C_{12}H_{16}O_3S_2$ C 52.91, H 5.92; Found: C 52.80; H 5.84.

Ethyl 5-(Benzylthio)-3-methyl-4-(phenylcarbamoyl)-thiophene-2-carboxylate (4i): white solid; mp 143−144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3H), 2.61 (s, 3H), 4.13 (s, 2H), 4.35 (q, J = 7.0 Hz, 2H), 7.14−7.18 (m, 1H), 7.19−7.20 (m, 2H), 7.26−7.27 (m, 3H), 7.28−7.36 (m, 2H), 7.50 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 15.1, 42.8, 61.4, 120.4, 125.0, 128.2, 129.07, 129.10, 129.3, 136.3, 137.7, 140.0, 141.3, 146.0, 161.9, 162.5; IR (KBr, cm^{-1}) 756, 1117, 1303, 1373, 1447, 1534, 1603, 1660, 1707; Anal. Calcd for $C_{22}H_{21}NO_3S_2$ C 64.21, H 5.14, N 3.40; Found C 64.39, H 5.03, N 3.46. MS calcd m/z 411.1, found 412.1 $[M + 1]^+$.

Ethyl 5-(Benzylthio)-3-methyl-4-(o-tolylcarbamoyl)-thiophene-2-carboxylate (4j): white solid; mp 138−140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3H), 2.28 (s, 2H), 2.63 (s, 3H), 4.16 (s, 2H), 4.35 (q, J = 7.0 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 7.21−7.24 (m, 7H), 7.35 (m, 1H), 7.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 15.1, 18.4, 42.7, 61.4, 125.5, 126.0, 128.1, 128.2, 129.0, 129.1, 129.4, 130.3, 130.7, 130.8, 135.5, 136.2, 140.1, 141.3, 145.8, 161.9, 162.4; IR (KBr, cm^{-1}) 763, 1127, 1252, 1303, 1371, 1459, 1518, 1657, 1706; Anal. Calcd for $C_{23}H_{23}NO_3S_2$ C 64.91, H 5.45, N 3.29; Found C 64.82, H 5.38, N 3.22.

Ethyl 5-(Benzylthio)-4-(4-chlorophenylcarbamoyl)-3-methylthiophene-2-carboxylate (4k): white solid; mp 136−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3H), 2.60 (s, 3H), 4.12 (s, 2H), 4.35 (q, J = 7.0 Hz, 2H), 7.17−7.18 (m, 2H), 7.27−7.31 (m, 5H), 7.43 (d, J = 7.5 Hz, 2H), 7.49 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 15.1, 42.8, 61.5, 121.6, 128.3, 129.0, 129.1, 129.2, 130.0, 136.28, 136.31, 140.4, 140.8, 145.8, 161.9, 162.1; IR (KBr, cm^{-1}) 827, 1106, 1169, 1302, 1373, 1425, 1530, 1601, 1659, 1707, 1741; Anal. Calcd for $C_{22}H_{20}ClNO_3S_2$ C 59.25, H 4.52, N 3.14; Found C 59.34, H 4.68, N 3.07.

Ethyl 5-(Benzylthio)-4-(2-methoxyphenylcarbamoyl)-3-methylthiophene-2-carboxylate (4l): white solid; mp 98−99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 2.66 (s, 3H), 3.85 (s, 3H), 4.17 (s, 2H), 4.33 (q, J = 7.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.99−7.03 (m, 1H), 7.08−7.11 (m, 1H), 7.24−7.25 (m, 5H), 8.33 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 15.2, 42.1, 56.0, 61.3, 110.4, 120.4, 121.4, 124.5, 127.6, 128.0, 128.1, 128.9, 129.3, 135.9, 140.1, 142.2, 145.6, 148.5, 161.9; IR (KBr, cm^{-1}) 756, 1118, 1251, 1334, 1485, 1520, 1601, 1660, 1710; Anal. Calcd for $C_{23}H_{23}NO_4S_2$ C 62.56, H 5.25, N 3.17; Found C 62.45, H 5.17, N 3.23.

Ethyl 5-(Benzylthio)-3-methyl-4-(methylcarbamoyl)-thiophene-2-carboxylate (4m): white solid; mp 144−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 2.50 (s, 3H), 2.77 (d, J = 5.0 Hz, 3H), 4.08 (s, 2H), 4.32 (q, J = 7.0 Hz, 2H), 5.12 (s, 1H), 7.17 (d, J = 5.5 Hz, 2H), 7.31−7.33 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.8, 10.2, 22.0, 38.2, 56.6, 123.4, 124.28, 124.31, 124.7, 132.3, 134.0, 138.1, 140.5, 157.2, 160.2; IR (KBr, cm^{-1}) 670, 1257, 1361, 1558, 1635, 1701; Anal. Calcd for $C_{17}H_{19}NO_3S_2$ C 58.43, H 5.48, N 4.01; Found C 58.31, H 5.39, N 4.08.

Ethyl 5-(Benzylthio)-4-carbamoyl-3-methylthiophene-2-carboxylate (4n): white solid; mp 100−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 2.58 (s, 3H),

4.14 (s, 2H), 4.32 (q, J = 7.0 Hz, 2H), 5.55 (s, 2H), 7.21−7.23 (m, 2H), 7.28−7.32 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 15.1, 42.6, 61.4, 128.2, 128.9, 129.1, 129.2, 136.3, 139.9, 141.0, 145.6, 161.9, 166.0; IR (KBr, cm^{-1}) 764, 1276, 1376, 1450, 1529, 1691, 1743; Anal. Calcd for $C_{16}H_{17}NO_3S_2$ C 57.29, H 5.11, N 4.18; Found C 57.14, H 5.03, N 4.11.

Diethyl 5-(Benzylthio)-3-methylthiophene-2,4-dicarboxylate (4o): white solid; mp 74−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (t, J = 5.0 Hz, 3H), 1.43 (t, J = 5.5 Hz, 3H), 2.78 (s, 3H), 4.29 (s, 2H), 4.36 (q, J = 6.0 Hz, 2H), 7.35−7.40 (m, 3H), 7.45 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.29, 14.3, 15.4, 39.7, 60.9, 124.1, 127.9, 128.6, 128.7, 129.2, 134.9, 147.9, 155.1, 161.7, 163.6; IR (KBr, cm^{-1}) 698, 769, 1058, 1224, 1406, 1530, 1717; Anal. Calcd for $C_{18}H_{20}O_4S_2$ C 59.32, H 5.53; Found C 59.46, H 5.39.

Ethyl 4-Acetyl-5-(benzylthio)-3-methylthiophene-2-carboxylate (4p): white solid; mp 62−64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3H), 2.49 (s, 3H), 2.66 (s, 3H), 4.19 (s, 2H), 4.33 (q, J = 7.0 Hz, 2H), 7.32−7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 15.7, 31.6, 41.4, 61.3, 128.0, 128.1, 129.0, 129.4, 135.5, 141.0, 145.4, 161.9, 162.7, 196.2; IR (KBr, cm^{-1}) 766, 1107, 1258, 1383, 1514, 1640, 1706; Anal. Calcd for $C_{17}H_{18}O_3S_2$ C 61.05, H 5.42; Found C 61.27, H 5.58; MS calcd m/z 334.1, found 335.0 $[M + 1]^+$.

5-Benzoyl-2-ethylsulfanyl-4-methyl-thiophene-3-carboxylic Acid Phenylamide (4q): white solid; mp 165−166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3H), 2.48 (s, 3H), 3.01 (q, J = 7.5 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.65 (t, J = 7.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.8, 11.6, 27.1, 115.5, 120.4, 124.0, 124.63, 124.67, 128.2, 131.8, 133.0, 134.4, 134.7, 138.5, 140.5, 157.4, 184.3; IR (KBr, cm^{-1}) 720, 753, 1247, 1366, 1614, 1658; Anal. Calcd for $C_{21}H_{19}NO_2S_2$ C 66.11, H 5.02; Found C 66.05, H 4.96.

5-Benzoyl-2-(benzylthio)-4-methyl-*N*-phenylthiophene-3-carboxamide (4r): white solid; mp 132−134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.13 (s, 2H), 7.17−7.20 (m, 1H), 7.21 (m, 2H), 7.28 (m, 3H), 7.35−7.38 (m, 2H), 7.46−7.48 (m, 2H), 7.60−7.61 (m, 1H), 7.68 (s, 1H), 7.76−7.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1, 42.8, 120.4, 125.1, 128.2, 128.7, 129.1, 129.2, 129.3, 129.5, 133.0, 136.2, 137.7, 139.3, 141.5, 144.7, 162.1, 189.0; IR (KBr, cm^{-1}) 673, 868, 1136, 1222, 1290, 1356, 1379, 1453, 1513, 1615, 1694, 1740; Anal. Calcd for $C_{26}H_{21}NO_2S_2$ C 70.40, H 4.77, N 3.16; Found C 70.51, H 4.91, N 3.21.

5-Benzoyl-*N*-(4-chlorophenyl)-2-(ethylthio)-4-methylthiophene-3-carboxamide (4s): white solid; mp 173−174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J = 6.5 Hz, 3H), 2.45 (s, 3H), 3.01 (q, J = 7.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.61 (m, 3H), 7.79 (d, J = 7.5 Hz, 2H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 16.1, 31.8, 104.4, 121.2, 128.5, 129.1, 129.2, 129.9, 132.7, 136.2, 136.6, 138.7, 139.2, 144.9, 161.9, 188.7; Anal. Calcd for $C_{21}H_{18}ClNO_2S_2$ C 60.64, H 4.36; Found C 60.59, H 4.31.

5-Benzoyl-2-(benzylthio)-*N*-(4-chlorophenyl)-4-methylthiophene-3-carboxamide (4t): white solid; mp 198−199 °C; ^{1}H NMR (300 MHz, CDCl3) δ 2.41 (s, 3H), 4.11 (s, 2H), 7.19 (s, 2H), 7.27−7.32 (m, 5H), 7.44−7.59 (m, 6H), 7.74 (d, J = 7.5 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 42.7, 121.4, 128.0, 128.5, 128.6, 128.8, 129.2, 129.8, 132.8, 135.9, 136.1, 137.5, 139.0, 140.3, 141.0, 144.3, 161.8, 188.7; Anal. Calcd for $C_{26}H_{20}ClNO_2S_2$ C 65.33, H 4.22; Found C 65.29, H 4.27.

Ethyl 5-Benzoyl-2-(ethylthio)-4-methylthiophene-3-carboxylate (4u): white solid; mp 66−68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (t, J = 7.5 Hz, 3H), 1.48 (t, J = 7.0 Hz, 3H), 2.53 (s, 3H), 3.08 (q, J = 7.0 Hz, 2H), 4.42 (q, J = 7.0 Hz, 2H), 7.52 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 13.3, 16.1, 28.2, 59.9, 126.9, 127.4, 128.0, 131.4, 132.4, 138.6, 145.6, 156.2, 162.7, 187.9; IR (KBr, cm^{-1}) 781, 938, 1239, 1409, 1575, 1632, 1692; Anal. Calcd for $C_{17}H_{18}O_3S_2$ C 61.05, H 5.42; Found C 61.21, H 5.28; MS calcd m/z 334.1, found 335.1 $[M + 23]^+$.

Ethyl 5-Benzoyl-2-(benzylthio)-4-methylthiophene-3-carboxylate (4v): white solid; mp 80−81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (t, J = 7.0 Hz, 3H), 2.55 (s, 3H), 4.29 (s, 2H), 4.41 (q, J = 6.5 Hz, 2H), 7.31−7.39 (m, 3H), 7.44 (d, J = 7.0 Hz, 2H), 7.52 (t, J = 7.0 Hz, 2H), 7.62 (t, J = 7.0 Hz, 1H), 7.79 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 17.0, 39.8, 61.0, 127.7, 127.9, 128.4, 128.7, 129.1, 129.3, 132.4, 133.6, 134.9, 139.5, 146.4, 163.7, 188.8; IR (KBr, cm^{-1}) 698, 1071, 1244, 1406, 1513, 1616, 1687; Anal. Calcd for $C_{22}H_{20}O_3S_2$ C 66.64, H 5.08; Found C 66.48, H 5.17.

1-[5-Benzoyl-2-(ethylthio)-4-methylthiophen-3-yl]ethanone (4w): white solid; mp 84−85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (t, J = 7.0 Hz, 3H), 2.48 (s, 3H), 2.60 (s, 3H), 3.01 (q, J = 7.0 Hz, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7,78 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 17.0, 30.4, 31.6, 128.4, 129.0, 132.5, 134.4, 139.5, 140.1, 144.2, 152.6, 188.8, 196.2; IR (KBr, cm^{-1}) 643, 786, 1289, 1354, 1511, 1638; Anal. Calcd for $C_{16}H_{16}O_2S_2$ C 63.13, H 5.30; Found C 63.29, H 5.24; MS calcd m/z 304.1, found 305.1 $[M + 1]^+$.

1-[5-Benzoyl-2-(benzylthio)-4-methylthiophen-3-yl]-ethanone (4x): white solid; mp 74−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.53 (s, 3H), 4.16 (s, 2H), 7.28−7.31 (m, 5H), 7.48 (m, 2H), 7.58−7.59 (m, 1H), 7.75 (d, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 31.7, 41.7, 128.1, 128.7, 128.8, 129.0, 129.40, 129.42, 132.8, 135.5, 139.6, 144.0, 189.0, 196.9; IR (KBr, cm^{-1}) 772, 986, 1268, 1313, 1386, 1478, 1653, 1693; Anal. Calcd for $C_{21}H_{18}O_2S_2$ C 68.82, H 4.95; Found C 68.98, H 4.84. MS calcd m/z 366.1, found 367.1 $[M + 1]^+$.

2-(Bis-ethylsulfanyl-methylene)-3-oxo-*N*-phenyl-butyramide (C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.31 (t, J = 7.0 Hz, 6H), 2.50 (s, 3H), 2.95 (q, J = 7.5 Hz, 4H), 7.14 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.58 (d, J = 7.0 Hz, 2H), 8.32−8.36 (m, 1H) (known compound, see ref 15e).

Ethyl 5-(2-ethoxy-2-oxoethylthio)-3-methyl-4-(phenylcarbamoyl)thiophene-2-carboxylate (E): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.0 Hz, 3H), 2.63 (s, 3H), 3.83 (s, 2H), 4.22 (q, J = 7.0 Hz, 2H), 4.33 (q, J = 7.0 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.76 (d, J = 7.5 Hz, 2H), 9.62 (s, 1H) (known compound, see ref 14c).

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra copies of compounds **4a**−**4x**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocyclic*; Wiley-VCH; New York, 2003;: Chapter 5, Section 5.6. (b) Gronowitz, S. *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Gronowitz, S., Ed.; Wiley, New York, 1991; Vol. 44, Part 3, Chapter 2. (c) Russell, R. K.; Press, J. B. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. W. F., Padwa, A., Eds.; Pergamon; New York, 1996; Vol. 2, pp 679−729.

(2) (a) Modica, M.; Santagati, M.; Guccione, S.; Russo, F.; Cagnotto, A.; Goegan, M.; Mennini, T. *Eur. J. Med. Chem.* **2000**, *35*, 1065–1079. (b) Wu, C.; Decker, E. R.; Blok, N.; Bui, H.; You, T. J.; Wang, J.; Bourgoyne, A. R.; Knowles, V.; Berens, K. L.; Holland, G. W.; Brock, T. A.; Dixon, R. A. F. *J. Med. Chem.* **2004**, *47*, 1969–1986. (c) World Drug Index, Derwent Information 2000, www.derwent.co.uk.

(3) (a) Lisowski, V.; Enguehard, C.; Lancelot, J.-C.; Caignard, D.-H.; Lambel, S.; Leonce, S.; Pierre, A.; Atassi, G.; Renard, P.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2205–2208. (b) Doré, K.; Dubus, S.; Ho, H. A.; Lévesque, I.; Brunette, M.; Corbeil, G.; Boissinot, M.; Boivin, G.; Bergeron, M. G.; Boudreau, D.; Leclerc, M. *J. Am. Chem. Soc.* **2004**, *126*, 4240–4244.

(4) (a) Campos, P. J.; Anon, E.; Cermen Malo, M.; Rodriguez, M. A. *Tetrahedron* **1999**, *55*, 14079–14088. (b) Ramos, A. C.; Pelaez, R.; Lopez, J. L.; Caballero, E.; Medarde, M.; San Feliciano, A. *Tetrahedron* **2001**, *57*, 3963–3977. (c) Goeb, S.; Nicola, A. D.; Ziessel, R. *Synthesis* **2005**, 1169–1177. (d) Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929–1958. (e) Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197–198.

(5) For reviews, see: (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109–118.

(6) For papers, see: (a) Vriezema, D. M.; Hoogboom, J.; Velonia, K.; Takazawa, K.; Christianen, P. C. M.; Maan, J. C.; Rowan, A. E.; Nolte, R. J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 772–776. (b) Yu, H.; Pullen, A. E.; Büschel, M. G.; Swager, T. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3700–3703. (c) Rodrı´guez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2003**, *44*, 7411–7415. (d) Apsel, B.; Bender, J. A.; Escobar, M.; Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1075–1077. (e) Krishna, U. M.; Srikanth, G. S. C.; Trivedi, G. K.; Deodhar, K. D. *Synlett* **2003**, 2383–2385.

(7) Blair, J. B.; Marona-Lewicka, D.; Kanthasamy, A.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1999**, *42*, 1106–1111.

(8) For books, see: (a) Blicke, F. F. In *The Chemistry of Heterocyclic Compounds: Thiophenes and its Derivatives*; Hartough, H. D., Ed.; Interscience Publishers: New York, 1952; Chapter 2. (b) Gronowitz, S. *The Chemistry of Heterocyclic Compounds: Thiophene and its Derivatives*; Gronowitz, S. J.,Ed.; Wiley and Sons, New York, 1991, Vol. 44, Part 3, Chapter 2. (c) For a representative paper, see: Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286–5287.

(9) (a) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351–352. (b) Fazio, A.; Gabriele, B.; Salerno, G.; Destri, S. *Tetrahedron* **1999**, *55*, 485–502. (c) Ong, C. W.; Chen, C. M.; Wang, L. F.; Shieh, P. C. *Tetrahedron Lett.* **1998**, *39*, 9191–9192. (d) Stephensen, H.; Zaragoza, F. *J. Org. Chem.* **1997**, *62*, 6096–6097. (e) Marshall, J. A.; DuBay, W. J. *Synlett* **1993**, 209–210. (f) Wang, M.; Ai, L.; Zhang, J.; Liu, Q.; Gao, L. *Chin. J. Chem.* **2002**, *20*, 1591–1597.

(10) Gewald, K. *Angew. Chem.* **1961**, *73*, 114.

(11) (a) Mckibben, B. P.; Cartwright, C. H.; Castelhano, A. L. *Tetrahedron Lett.* **1999**, *40*, 5471–5474. (b) Dalgaard, L.; Jansen, L.; Lawesson, S.-O. *Tetrahedron* **1974**, *30*, 93–104. (c) Castanedo, G. M.; Sutherlin, D. P. *Tetrahedron Lett.* **2001**, *42*, 7181–7184. (d) Zhang, H.; Yang, G.; Chen, J.; Chen, Z. *Synthesis* **2004**, 3055–3059. (e) Hoener, A. P. F.; Henkel, B.; Gauvin, J.-C. *Synlett* **2003**, 63–66. (f) Gompper, R.; Kutter, E. *Angew. Chem.* **1962**, *74*, 251.

(12) For reviews on the synthesis and applications of α-oxo ketene-*S*,*S*-acetals, see: (a) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029–3096. (b) Tominaga, Y. *J. Heterocycl. Chem.* **1989**, *26*, 1167–1204. (c) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423–5506. (d) Kolb, M. *Synthesis* **1990**, 171–190. (e) Ila, H.; Junjappa, H.; Mohanta, P. K. *Progress in Heterocyclic Chemistry*, Gribble, G. H., Gilchrist, L. T. Eds.; Pergamon Press: Oxford, U.K, 2001; Vol. 13, Chapter 1, pp 1−24.

(13) (a) Sommen, G.; Comel, A.; Kirsch, G. *Synlett* **2001**, 1731–1734. (b) Msahraqui, S. H.; Hariharasubrahmanian, H.; Kumar, S. *Synthesis* **1999**, 2030–2032. (c) Sommen, G.; Comel, A.; Kirsch, G. *Tetrahedron Lett.* **2002**, *43*, 257–259. (d) Sommen, G.; Comel, A.; Kirsch, G. *Tetrahedron* **2003**, *59*, 1557–1564. (e) Sommen, G.; Comel, A.; Kirsch, G. *Synthesis* **2003**, 735–741. (f) Sommen, G.; Comel, A.; Kirsch, G. *Synlett* **2003**, 855–857. (g) Sommen, G.; Comel, A.; Kirsch, G. *Synthesis* **2004**, 451–455. (h) Datta, A.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 556–557. (i) Thomae, D.; Kirsch, G.; Seck, P. *Synthesis* **2007**, 1027–1032.

(14) (a) Ouyang, Y.; Dong, D.; Yu, H.; Liang, Y.; Liu, Q. *Adv. Synth. Catal.* **2006**, *348*, 206–210. (b) Dong, D.; Liu, Y.; Zhao, Y.; Qi, Y.; Wang, Z.; Liu, Q. *Synthesis* **2005**, 85–91. (c) Wang, Y.; Dong, D.; Yang, Y.; Huang, J.; Ouyang, Y.; Liu, Q. *Tetrahedron* **2007**, *63*, 2724–2728.

(15) (a) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579. (b) Dong, D.; Ouyang, Y.; Yu, H.; Liu, Q.; Liu, J.; Wang, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4535–4537. (c) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, *28*, 3580–3582. (d) Bi, X.; Dong, D.; Li, Y.; Liu, Q.; Zhang, Q. *J. Org. Chem.* **2005**, *70*, 10886–10889. (e) Huang, J.; Lu, Y.; Qiu, B.; Liang, Y.; Li, N.; Dong, D. *Synthesis* **2007**, 2791–2796.

(16) (a) Choi, E. B.; Youn, I. K.; Pak, C. S. *Synthesis* **1988**, 792–794. (b) Pak, C. S.; Choi, E. B. *Synthesis* **1992**, 1291–1294.

(17) Augustin, M.; Rudorf, W.-D.; Schmidt, U. *Tetrahedron* **1976**, *32*, 3055–3061.

(18) Shi, Y.; Zhang, J.; Grazier, N.; Stein, P. D.; Atwal, K. S.; Traeger, S. C.; Callahan, S. P.; Malley, M. F.; Galella, M. A.; Gougoutas, J. Z. *J. Org. Chem.* **2004**, *69*, 188–191.

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