JOC The Journal of Organic Chemistry

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One-Pot Two-Component [3 + 2] Cycloaddition/Annulation Protocol for the Synthesis of Highly Functionalized Thiophene Derivatives

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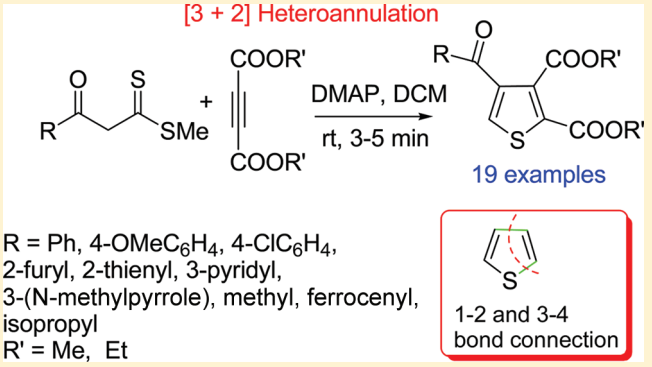
Supporting Information

ABSTRACT: An efficient and experimentally rapid protocol for the synthesis of hitherto unreported 2,3-dicarboalkoxy-4-aroyl/heteroaroyl/alkanoyl thiophenes has been developed via 1−2 (C−S) and 3−4 (C−C) bond connections promoted by 4-dimethylaminopyridine (DMAP). Optimally, the reaction takes only 3−5 min when β-oxodithioester and dialkyl acetylenedicarboxylate are stirred in DCM at room temperature in the presence of DMAP. This method allows a clean and general synthesis of previously inaccessible and synthetically demanding thiophenes containing the ferrocenyl group. The speed, experimental ease, and high yields of this process are improvements over existing methods to access this important substructure.



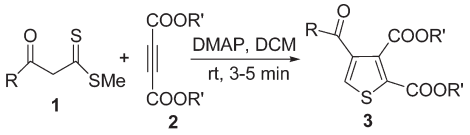
Thiophenes are widespread in nature and have emerged as a class of important heterocycles because of their presence in a broad spectrum of natural and synthetic organic molecules with diverse biological properties.[1,2] Over the years, thiophene derivatives have attracted considerable attention from both medicinal and synthetic chemists due to their utility as versatile intermediates[3] in organic synthesis. Additionally, anthelmintic and insecticidal activities have been ascribed to appropriately functionalized thiophene derivatives.[4] Moreover, thiophene derivatives have been identified as potent antiplatelet agent (Plavix)[5] a blockbuster drug used in the treatment of coronary artery disease. Articaine[6] is the most commonly used dental anesthetic in Europe, and PaTrin-2[7] is an inhibitor of the DNA repair enzyme O6-methylguanine-DNA methyl transferase with potential to increase the effectiveness of alkylating agents as cancer therapeutics. Recently, a number of thiophenes have been reported to show excellent and marked potent activity toward CB1 receptors with good CB1/CB2 selectivity.[8] Furthermore, thiophene derivatives also find broad applications as functional materials in electrically conducting organic materials,[9] semiconductors,[10] organic light-emitting diodes (OLEDs),[11] organic field effect transistors (OFETs),[12] organic solar cells,[13] lasers,[14] dyes, liquid crystals, and molecular wires.[15]

Numerous synthetic routes to thiophene derivatives have been reported[16] performing variations and improvements on the originally published Gewald and Paal−Knorr synthesis of polysubstituted thiophenes.[17] The general synthetic approaches to thiophene derivatives involve either modification of the preconstructed thiophene ring (usually α-metalation or β-halogenation)[18] or the construction of thiophene ring via the annulation reactions of suitably substituted open chain precursors.[19] The latter allows regioselective preparation of the thiophene derivatives and thus represents an attractive but less developed methodology. Alternatively, access to substituted thiophenes from α-oxoketene-*S*,*S*-acetals has been reported.[20] Recently, utilizing one-pot multicomponent strategy, numerous highly substituted thiophene derivatives have been synthesized.[21] Ashokan and co-workers[22] reported the synthesis of 2,3,4-trisubstituted thiophenes by the alkylation of β-ketodithioesters with α-haloketones. Further, regioselective synthesis of polysubstituted thiophenes from Baylis−Hillman adducts have been carried out by Kim and co-workers.[23] Albeit the reported approaches are useful tools and represent important advances toward the objective of a general method for the synthesis of thiophenes, most of them suffer from significant limitations in terms of harsh reaction conditions, long reaction time, low yields, expensive catalyst, and use of strong base or difficult purification. Therefore, more general, efficient, rapid, and viable routes are very much desirable in view of their broad array of applications in the areas of biology, material science, and chemistry and would be of great relevance to both synthetic and medicinal chemists.

β-Ketodithioesters, which were not commercially sourced, were prepared according to reported procedures.[24] The utility of β-ketodithioesters as versatile intermediates in organic synthesis has been well recognized.[25] In continuation of our ongoing research interest for the synthesis of heterocycles via one-pot reaction from β-ketodithioesters,[26] and with the aim to devise a more general synthetic route for heterocycles, we explored the highly substituted thiophenes via heteroaromatic annulation of β-ketodithioesters with dialkyl acetylenedicarboxylates. Thus,

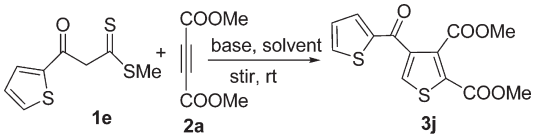
Received: April 5, 2011
Published: August 18, 2011

Scheme 1. Synthesis of 2,3,4-Trisubstituted Thiophenes



1a, R=C_6H_5; **1b**, R=4-$OMeC_6H_4$; **1c**, R=4-ClC_6H_4; **1d**, R=2-furyl; **1e**, R=2-thienyl; **1f**, R=3-(N-methylpyrrole); **1g**, R=3-pyridyl; **1h**, R=*i*-Pr; **1i**, R=Me; **1j**, R=ferrocenyl; **2a**, R' = Me; **2b**, R' = Et

Table 1. Base and Solvent Screen for Thiophene Synthesis



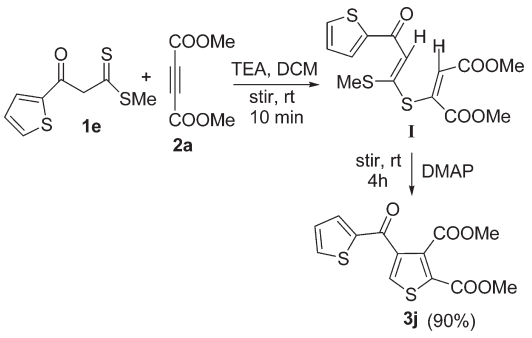
entry	base (equiv)	solvent	time	yield[a] (%)
1	none	DCM	24 h	NR[b]
2	TEA (1)	DCM	10 min	AP[c]
3	DABCO (1)	DCM	4 h	82
4	DBU (1)	DCM	5 min	78
5	DMAP (1)	DCM	3 min	90
6	DMAP (0.5)	DCM	30 min	40
7	DMAP (1.2)	DCM	3 min	88
8	DMAP (1)	EtOH	10 min	72
9	DMAP (1)	CH_3CN	7 min	82
10	DMAP (1)	water	24 h	NR[b]

[a] Isolated pure yields. [b] No reaction. [c] No thiophene; only addition product (AP) α-oxoketene dithioacetal **I** was obtained in 88% yield.

when β-ketodithioesters **1** were treated with dialkyl acetylenedicarboxylates **2** in dichloromethane in the presence of base 4-dimethylaminopyridine at room temperature, the corresponding 2,3,4-trisubstituted thiophenes **3** were obtained within 3−5 min in good yields (Scheme 1). The Lewis base DMAP is the prototypical synthetic nucleophilic catalyst, which has become not only a useful tool in synthesis but also a contextual testing ground for applying new design principles to asymmetric catalysis.[27]

Using 3-oxo-3-thiophen-2-yldithiopropionic acid methyl ester **1e** and the dimethyl acetylenedicarboxylate **2a** as test substrates for the synthesis of 2,3,4-trisubstituted thiophenes, optimization of the reaction conditions was investigated through screening of various bases using different solvents at room temperature. Initially, a test reaction using the above model reaction was performed without any base in DCM at room temperature to establish the real effectiveness of the base. It was found that no trace amount of the desired product was obtained even after 24 h of stirring (Table 1, entry 1), and the starting materials were totally unreacted (monitored by TLC). With this failure, we next performed the reaction of **1e** and **2a** in the presence of different bases like TEA, DABCO, DBU, and DMAP separately, at room temperature. Thus, when above model reaction was carried out in the presence of TEA, to our surprise the reaction ended to give adduct of **1e** and **2a** within 10 min (Scheme 2, Table 1, entry 2), the reaction was further stirred but no change was observed even after 24 h. The adduct was isolated in 88% yield and identified as

Scheme 2. Thiophene Formation via α-Oxoketene Dithioacetal I



α-oxoketene dithioacetal **I** with the help of analytical and spectral studies. However, when α-oxoketene dithioacetal **I** was further stirred with DMAP (1 equiv) at room temperature for 4 h gave the desired thiophene **3j** in 94% yield. Interestingly, in case of DABCO also first the adduct α-oxoketene dithioacetal **I** was formed, which upon further stirring for 4 h converted to the desired thiophene in 82% yield (Table 1, entry 3). Notably, DBU (1 equiv) facilitated the formation of desired thiophene in 78% yield in 5 min at room temperature (Table 1, entry 4). To our delight, the desired thiophene **3j** was formed exclusively in 90% yield within 3 min, when **1e** was treated with **2a** in the presence of DMAP (1 equiv) at room temperature (Table 1, entry 5). The higher reactivity of the base DMAP may be attributed to the presence of electron-donating dimethylamino group at para-position of the pyridine ring.

With DMAP base as good promoter in hand, next we intended to optimize its loading, and it was found that the use of 1 equiv of DMAP provided the best result. Reducing the equivalents of DMAP in the reaction increased the reaction time and lowered the yield drastically (Table 1, entry 6). However, no better yield was obtained when the DMAP was increased to 1.2 equiv (Table 1, entry 7). We immediately undertook a study to examine the effects of different solvents on this transformation. The results demonstrated that DCM appeared to be the best choice for this transformation (Table 1). Thus, the best yield, cleanest reaction, and most facile workup were achieved employing 1 equiv of DMAP in DCM at room temperature.

On the basis of above optimized reaction conditions, we commenced exploration of our substrate scope. To assess the generality and applicability of this methodology, attempts to expand the scope of the reaction proved successful and a wide range of R groups (aromatic, heteroaromatic, and aliphatic) were incorporated, which provided a functional handle for further manipulation. Results are summarized in Table 2. Even extremely electron-rich aromatic β-ketodithioesters such as **1d** and **1e** proceeded smoothly (Table 2, entries 7−10). In addition to incorporation of aryl, heteroaryl, and aliphatic substituents at the 4-position, ferrocenyl group is also viable for this protocol (Table 2, entry 19). However, when some unsymmetric electron-deficient alkynes such as 3-phenylpropiolate and acetyl phenylacetylene were used under the optimized reaction conditions, the starting materials were completely consumed after 6 h of stirring, but it led to a mixture of very close spots on the TLC plate that could not be isolated, thus limiting the scope of this reaction to some extent. To overcome the above problem, the model reaction was performed under various varying conditions,

dx.doi.org/10.1021/jo200685e |*J. Org. Chem.* 2011, 76, 8009–8014

Table 2. Substrate Scope for the Synthesis of Thiophenes

entry	R	R′	product	time (min)	yield[a] (%)
1	C_6H_5	Et	**3a**	3	92
2	C_6H_5	Me	**3b**	3	94
3	4-$OMeC_6H_4$	Et	**3c**	3	93
4	4-$OMeC_6H_4$	Me	**3d**	3	94
5	4-ClC_6H_4	Et	**3e**	4	92
6	4-ClC_6H_4	Me	**3f**	5	92
7	2-furyl	Et	**3g**	4	94
8	2-furyl	Me	**3h**	4	95
9	2-thienyl	Et	**3i**	5	88
10	2-thienyl	Me	**3j**	5	90
11	3-(*N*-methylpyrrole)	Et	**3k**	5	85
12	3-(*N*-methylpyrrole)	Me	**3l**	5	88
13	3-pyridyl	Et	**3m**	5	83
14	3-pyridyl	Me	**3n**	5	85
15	isopropyl	Et	**3o**	3	80
16	isopropyl	Me	**3p**	3	84
17	methyl	Et	**3q**	3	84
18	methyl	Me	**3r**	3	87
19	ferrocenyl	Me	**3s**	5	76

[a] Isolated pure yields.

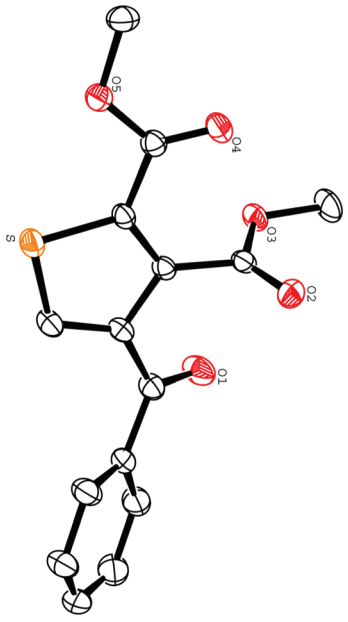


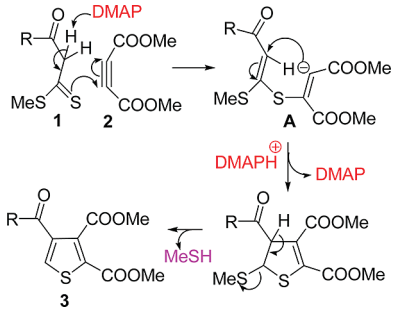
Figure 1. ORTEP diagram of **3b**.

but unfortunately our all efforts were found to be ineffective. The low electron-withdrawing ability of phenyl group may be responsible for this outcome.

The structures of all the thiophene derivatives **3a**−**s** were deduced from their satisfactory elemental and spectral (IR, ^{1}H, ^{13}C NMR, and mass) studies and unequivocally established by the X-ray single crystal diffraction analysis (see the Supporting Information) of one representative compound 4-benzoyl-2,3-dicarbomethoxythiophene **3b** (Figure 1).[28]

On the basis of the above experimental results together with the related reports, a plausible reaction scenario for this one-pot two-component heteroannulation is outlined in Scheme 3. The

Scheme 3. Plausible Mechanism for the Synthesis of Thiophene



first step in the mechanism is believed to be the abstractions of acidic proton of β-ketodithioester **1** by DMAP followed by nucleophilic attack on the sp-hybridized carbon of the 2,3-dimethyl acetylenedicarboxylate **2** to generate open-chain adduct α-oxoketene dithioacetal **A**. The intermediate **A**, which is the key rate-determining step, undergoes intramolecular cyclization with the extrusion of MeSH to give the thiophene derivative **3**. The intermediacy of α-oxoketene dithioacetal **A** has been confirmed by its isolation and characterization when TEA was utilized as base. This operationally simple and two-component domino process concomitantly created two new C−S and C−C bond leading to thiophene ring.

CONCLUSION

In summary, a rapid and experimentally convenient synthesis of 2,3-dicarboalkoxy-4-aroyl/heteroaroyl/alkanoyl thiophenes has been developed for the first time via [3 + 2] heteroannulation of β-ketodithioesters and dialkyl acetylenedicarboxylates by 1−2 (C−S) and 3−4 (C−C) bond formation. In addition, the carboalkoxy and aroyl substituents in the 2-, 3-, and 4-positions to the thiophene ring are quite reactive; this makes these compounds good candidates as precursors for further synthetic transformations to meet the need for various useful purposes. The simplicity of execution, mild conditions, high yields, flexible substituted patterns, broad range of potential utility of the products, and more importantly the metal-catalyst-free procedure make the protocol attractive for academic research and practical applications.

EXPERIMENTAL SECTION

General. The starting materials were commercially available and used as received without further purification. β-Oxodithioesters **1a**−**j** were prepared following the known procedure.[24] Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates. Infrared (IR) spectra are measured in KBr, and wavelengths (ν) are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on NMR spectrometer operating at 300 and 75.5 MHz, respectively. Chemical shifts (δ) are given in parts per million (ppm) using the residue solvent peaks as reference relative to TMS. *J* values are given in hertz. Mass spectra were recorded using electrospray ionization (ESI) mass spectrometry. The C, H, and N analyses were performed from microanalytical laboratory. The melting points are uncorrected.

*General Procedure for the Synthesis of the Trisubstituted Thiophenes (**3a**−**s**).* To a mixture of β-ketodithioester (1.0 mmol) and dialkyl acetylenedicarboxylate (1.0 mmol) in dichloromethane (3 mL) was added 4-dimethylaminopyridine (1.0 mmol), and the reaction

dx.doi.org/10.1021/jo200685e |*J. Org. Chem.* 2011, 76, 8009–8014

mixture was stirred for the stipulated period of time at room temperature. After completion of the reaction (monitored by TLC), water (20 mL) was added to the reaction mixture followed by extraction with dichloromethane (2 × 10 mL). The combined organic layer was dried over anhyd Na_2SO_4 and then evaporated in vacuo. The crude residue was purified by column chromatography over silica gel using ethyl acetate/hexane (1:10) as eluent to afford pure thiophenes.

Characterization Data of the Isolated Compounds. *4-Benzoyl-2,3-dicarboethoxythiophene (**3a**).* White solid; mp 53−54 °C. IR (KBr, cm^{-1}): 3031, 1729, 1632, 1220. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.81 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 4.43−4.34 (m, 4H), 1.40−1.35 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.5, 164.6, 160.3, 139.9, 137.2, 132.9, 132.7, 129.6, 129.1, 128.8, 128.3, 62.2, 62.1, 14.3, 13.6. MS: m/z = 332 (M^+). Anal. Calcd for $C_{17}H_{16}O_5S$: C, 61.43; H, 4.85. Found: C, 61.69; H, 4.62.

*4-Benzoyl-2,3-dicarbomethoxythiophene (**3b**).* White solid; mp 92−93 °C. IR (KBr, cm^{-1}): 3025, 1721, 1609, 1212. ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.81 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.4, 165.0, 160.6, 139.8, 137.7, 137.0, 133.0, 129.3, 128.5, 128.2, 127.6, 53.0, 52.8. MS: m/z = 304 (M^+). Anal. Calcd for $C_{15}H_{12}O_5S$: C, 59.20; H, 3.97. Found: C, 59.46; H, 4.25.

*2,3-Dicarboethoxy-4-(4-methoxybenzoyl)thiophene (**3c**).* White solid; mp 75−76 °C. IR (KBr, cm^{-1}): 3020, 1721, 1600, 1526, 1215. ^1H NMR (300 MHz, $CDCl_3$): δ 7.84−7.81 (m, 3H), 6.95 (d, J = 8.7 Hz, 2H), 4.40−4.34 (m, 4H), 3.88 (s, 3H), 1.39−1.33 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.2, 164.6, 163.6, 160.3, 140.5, 139.7, 136.2, 132.9, 131.9, 129.9, 113.8, 62.1, 62.0, 55.5, 14.1, 13.9. MS: m/z = 362 (M^+). Anal. Calcd for $C_{18}H_{18}O_6S$: C, 59.66; H, 5.01. Found: C, 59.82; H, 4.91.

*2,3-Dicarbomethoxy-4-(4-methoxybenzoyl)thiophene (**3d**).* White solid; mp 128−129 °C. IR (KBr, cm^{-1}): 3028, 1723, 1598, 1258. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.82 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.1, 165.1, 163.6, 160.7, 140.4, 139.8, 136.4, 131.9, 129.7, 113.8, 55.5, 53.0, 52.9. MS: m/z = 334 (M^+). Anal. Calcd for $C_{16}H_{14}O_6S$: C, 57.48; H, 4.22. Found: C, 57.32; H, 4.35.

*4-(4-Chlorobenzoyl)-2,3-dicarboethoxythiophene (**3e**).* White solid; mp 73−74 °C. IR (KBr, cm^{-1}): 3091, 2954, 1734, 1653, 1256. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 4.43−4.34 (m, 4H), 1.40−1.34 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.2, 164.4, 160.1, 139.5, 139.5, 137.3, 135.4, 133.2, 130.7, 128.9, 62.2, 62.1, 14.0, 13.8. MS: m/z = 366 (M^+). Anal. Calcd for $C_{17}H_{15}ClO_5S$: C, 55.66; H, 4.12. Found: C, 55.45; H, 4.35.

*4-(4-Chlorobenzoyl)-2,3-dicarbomethoxythiophene (**3f**).* White solid; mp 123−124 °C. IR (KBr, cm^{-1}): 3098, 2958, 1733, 1653, 1261. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.2, 164.9, 160.5, 139.6, 137.4, 135.3, 130.8, 128.9, 53.1, 52.9. MS: m/z = 338 (M^+). Anal. Calcd for $C_{15}H_{11}ClO_5S$: C, 53.18; H, 3.27. Found: C, 52.85; H, 3.46.

*2,3-Dicarboethoxy-4-(2-furoyl)thiophene (**3g**).* White solid; mp 72−73 °C. IR (KBr, cm^{-1}): 3085, 2959, 1723, 1635, 1463, 1270. ^1H NMR (300 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.67 (s, 1H), 7.35 (d, J = 3.6 Hz, 1H), 6.61 (s, 1H), 4.46 (q, J = 6.9 Hz, 2H), 4.36 (q, J = 6.9 Hz, 2H), 1.43−1.34 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 164.8, 160.2, 152.2, 146.8, 140.0, 138.3, 137.6, 132.0, 119.9, 112.6, 62.1, 62.0, 14.0, 13.9. MS: m/z = 322 (M^+). Anal. Calcd for $C_{15}H_{14}O_6S$: C, 55.89; H, 4.38. Found: C, 55.61; H 4.52.

*2,3-Dicarbomethoxy-4-(2-furoyl)thiophene (**3h**).* White solid; mp 110−111 °C. IR (KBr, cm^{-1}): 3071, 2954, 1720, 1633, 1279. ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.68 (s, 1H), 7.37 (d, J = 3.3 Hz, 1H), 6.61 (d, J = 1.8 Hz, 1H), 4.00 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 165.3, 160.6, 152.3, 146.8, 140.1, 138.3, 137.8, 131.5, 119.9, 112.7, 53.1, 52.8. MS: m/z = 294 (M^+). Anal. Calcd for $C_{13}H_{10}O_6S$: C, 53.06; H, 3.43. Found: C, 53.33; H, 3.22.

*4-(2-Thienoyl)-2,3-dicarboethoxythiophene (**3i**).* White solid; mp 65−67 °C. IR (KBr, cm^{-1}): 3091, 2984, 1737, 1712, 1619, 1258. ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.73 (d, J = 4.2 Hz, 2H), 7.18 (t, J = 4.5 Hz, 1H), 4.45−4.33 (m, 4H), 1.40−1.35 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.8, 164.4, 160.2, 142.8, 139.9, 139.5, 135.7, 134.6, 134.1, 133.1, 128.1, 62.2, 62.1, 14.1, 13.9. MS: m/z = 338 (M^+). Anal. Calcd for $C_{15}H_{14}O_5S_2$: C, 53.24; H, 4.17. Found: C, 53.36; H, 4.07.

*4-(2-Thienoyl)-2,3-dicarbomethoxythiophene (**3j**).* White solid; mp 110−112 °C. IR (KBr, cm^{-1}): 3087, 2976, 1737, 1723, 1260. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.75−7.73 (m, 2H), 7.17 (t, J = 4.2 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 164.9, 160.5, 142.5, 139.8, 139.5, 135.9, 134.7, 134.1, 132.4, 128.1, 53.1, 52.9. MS: m/z = 310 (M^+). Anal. Calcd for $C_{13}H_{10}O_5S_2$: C, 50.31; H, 3.25. Found: C, 50.52; H, 3.13.

*2,3-Dicarboethoxy-4-[3-(N-methylpyrroloyl)]thiophene (**3k**).* White solid; mp 112−113 °C. IR (KBr, cm^{-1}): 3095, 2956, 1725, 1630, 1284. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.22 (s, 1H), 6.63 (s, 2H), 4.44−4.32 (m, 4H), 3.71 (s, 3H), 1.38 (t, J = 3.6 Hz, 3H), 1.35 (t, J = 3.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9, 164.9, 160.5, 141.9, 139.6, 134.5, 132.3, 128.3, 124.3, 123.6, 110.6, 62.0, 61.9, 36.6, 14.0, 13.9. MS: m/z = 335 (M^+). Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18. Found: C, 57.46; H, 5.36; N, 4.02.

*2,3-Dicarbomethoxy-4-[3-(N-methylpyrroloyl)]thiophene (**3l**).* White solid; mp 109−110 °C. IR (KBr, cm^{-1}): 3087, 2935, 1733, 1624, 1285. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.23 (s, 1H), 6.62 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.7, 165.4, 160.7, 141.8, 139.6, 134.7, 131.6, 128.3, 124.1, 123.6, 110.5, 52.9, 52.7, 36.6. MS: m/z = 307 (M^+). Anal. Calcd for $C_{14}H_{13}NO_5S$: C, 54.71; H, 4.26; N, 4.56. Found: C, 54.53; H, 4.38; N, 4.64.

*2,3-Dicarboethoxy-4-(3-pyridoyl)thiophene (**3m**).* White solid; mp 72−73 °C. IR (KBr, cm^{-1}): 3075, 2967, 1737, 1714, 1632, 1278. ^1H NMR (300 MHz, $CDCl_3$): δ 9.03 (s, 1H), 8.82 (s, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.92 (s, 1H), 7.46 (q, J = 5.1 Hz, 1H), 4.46−4.35 (m, 4H), 1.41−1.36 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.6, 164.4, 160.0, 153.3, 150.1, 139.5, 139.1, 138.0, 136.7, 133.4, 132.9, 123.6, 62.3, 62.2, 14.0, 13.8. MS: m/z = 333 (M^+). Anal. Calcd for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20. Found: C, 57.89; H, 4.35; N, 4.46.

*2,3-Dicarbomethoxy-4-(3-pyridoyl)thiophene (**3n**).* White solid; mp 94−95 °C. IR (KBr, cm^{-1}): 3081, 2957, 1731, 1727, 1622, 1276. ^1H NMR (300 MHz, $CDCl_3$): δ 9.03 (s, 1H), 8.83 (s, 1H), 8.12 (d, J = 6.6 Hz, 1H), 7.95 (s, 1H), 7.47 (t, J = 5.1 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.6, 164.8, 160.4, 153.4, 150.1, 139.5, 139.1, 138.1, 136.7, 132.9, 132.8, 123.6, 53.2, 53.0. MS: m/z = 305 (M^+). Anal. Calcd for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.63; N, 4.59. Found: C, 55.25; H, 3.48; N, 4.78.

*2,3-Dicarboethoxy-4-isobutanoylthiophene (**3o**).* White solid; mp 71−72 °C. IR (KBr, cm^{-1}): 3085, 2986, 1732, 1712, 1693, 1259. ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 4.46 (q, J = 7.2 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.31−3.26 (m, 1H), 1.43−1.36 (m, 6H), 1.22 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.0, 160.8, 157.3, 129.2, 129.1, 128.5, 127.6, 55.3, 54.3, 34.5, 21.0, 15.0, 14.8. MS: m/z = 298 (M^+). Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.52; H, 5.95.

*2,3-Dicarbomethoxy-4-isobutanoylthiophene (**3p**).* White solid; mp 108−110 °C. IR (KBr, cm^{-1}): 3094, 2981, 1735, 1720, 1690, 1262. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H), 4.00 (s, 3H), 3.89 (s, 3H), 3.31−3.26 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3, 165.7, 160.6, 139.4, 136.1, 131.7, 129.2, 53.1, 52.8, 36.9, 18.9. MS: m/z = 270 (M^+). Anal. Calcd for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22. Found: C, 53.46; H, 5.03.

*4-Acetyl-2,3-dicarboethoxythiophene (**3q**).* White solid. mp 63−65 °C IR (KBr, cm^{-1}): 3064, 2979, 1725, 1720, 1682, 1270. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 4.45 (q, J = 6.9 Hz, 2H), 4.34

(q, J = 6.9 Hz, 2H), 2.51 (s, 3H), 1.44−1.33 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5, 165.1, 160.2, 140.5, 138.7, 136.9, 132.3, 62.2, 62.0, 27.0, 14.0, 13.8. MS: m/z = 270 (M^+). Anal. Calcd for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22. Found: C, 53.18; H, 5.47.

*4-Acetyl-2,3-dicarbomethoxythiophene (**3r**).* White solid; mp 99−100 °C. IR (KBr, cm^{-1}): 3056, 2977, 1729, 1714, 1687, 1265. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 4.00 (s, 3H), 3.89 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5, 165.6, 160.6, 140.6, 138.7, 136.9, 131.9, 53.1, 52.9, 27.0. MS: m/z = 242 (M^+). Anal. Calcd for $C_{10}H_{10}O_5S$: C, 49.58; H, 4.16. Found: C, 49.76; H, 4.07.

*2,3-Dicarbomethoxy-4-η^5-ferrocenylthiophene (**3s**).* Reddish solid; mp 135−137 °C. IR (KBr, cm^{-1}): 3103, 2926, 1727, 1630, 1262. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 4.91 (s, 2H), 4.62 (s, 2H), 4.27 (s, 5H), 4.00 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5, 165.4, 160.8, 141.4, 139.6, 134.1, 131.7, 72.9, 70.9, 70.3, 70.0, 53.0, 52.8. MS: m/z = 412 (M^+). Anal. Calcd for $C_{19}H_{16}FeO_5S$: C, 55.36; H, 3.91. Found: C, 55.27; H, 4.03.

*2-(1-Methylsulfanyl-3-(2-thienoyl)propenylsulfanyl)but-2-enedioic Acid Dimethyl Ester (**I**).* Colorless sticky liquid. IR (KBr, cm^{-1}): 2931, 1723, 1626, 1243. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63−7.59 (m, 2H), 7.11 (t, J = 4.2 Hz, 1H), 7.00 (s, 1H), 6.80 (s, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 164.8, 158.5, 145.5, 144.7, 133.3, 130.7, 128.2, 128.1, 125.7, 121.1, 53.6, 52.4, 17.3. MS: m/z = 358 (M^+). Anal. Calcd for $C_{14}H_{14}O_5S_3$: C, 46.91; H, 3.94. Found: C, 47.12; H, 3.76.

■ ASSOCIATED CONTENT

Supporting Information. Full experimental details, analytical and spectroscopic data (copies of ^{1}H and ^{13}C NMR for compounds **3** and **I**). X-ray structures and crystallographic information files (CIF) for compound **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We gratefully acknowledge the generous financial support from Council of Scientific and Industrial Research (Grant 01(2260)/08/EMR-II) and Department of Science and Technology (Grant SR/S1/OC-66/2009), New Delhi. The authors (G.C.N. and S.S) thank CSIR, New Delhi, for a senior research fellowship.

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(28) The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC 818986 (**3b**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.