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# A Thioannulation Approach to Substituted Thiophenes from Morita–Baylis–Hillman Acetates of Acetylenic Aldehydes

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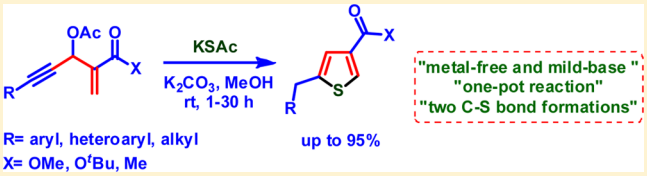
Supporting Information

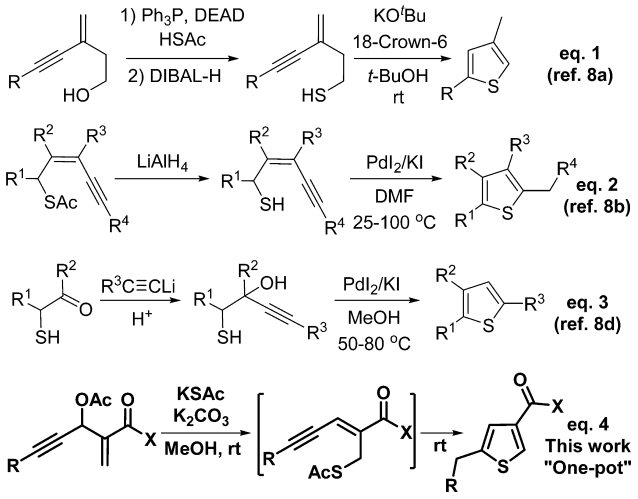
**ABSTRACT:** A new protocol has been developed for the synthesis of substituted thiophenes under mild and metal-free reaction conditions via the base-promoted thioannulation of Morita–Baylis–Hillman acetates of acetylenic aldehydes with potassium thioacetate involving a tandem allylic substitution/deacetylative 5-exo-*dig*-thiocycloisomerization. The obtained products provide an entry to 4*H*-thieno[3,2-*c*]chromene and thieno[3,2-*c*]dihydroquinoline.




## INTRODUCTION

Thiophenes are important motifs in several bioactive natural products as well as pharmaceuticals.[1] Moreover, thiophene derivatives also serve in organic material science due to their structural rigidity and distinct electronic properties.[2] Although over the years efforts have been made aimed at the synthesis of substituted thiophenes, they are limited numbers when compared to furans or pyrroles. The majority of the methods involve the substitution of thiophene ring via metalation or halogenations,[3] while thiophene syntheses from the corresponding acyclic precursors are limited.[4−8] Among these, Gewald reaction[4] and Paal–Knorr thiophene synthesis[5] are traditional methods in which the sulfur atom is introduced using elemental sulfur and $H_2S$ or Lawesson's reagent, respectively, besides others.[6,7] Alternatively, thioannulation of alkynyl thiol is an attractive method to access substituted thiophenes, and very few such methods are available (Scheme 1).[8] In 1993, Marshall and DuBay reported the cyclization of *β*- and *α*-alkynyl thiols under strongly basic conditions using KO$^t$Bu in $^t$BuOH in the presence of 18-crown-6 (eq 1).[8a] In 2000, Gabriele and co-workers described the palladium-catalyzed cycloisomerization of (*Z*)-2-en-4-yne-1-thiols (eq 2).[8b] Recently, they have also reported two more methods, an iodocyclization[8c] and palladium-catalyzed heterocyclodehydration of 1-mercapto-3-yn-2-ols (eq 3).[8d] Although these methods are efficient, they necessitate preconstruction of the desired alkynyl thiol. Further, the majority of these methods require the use of either a metal catalyst or higher temperature or strong base. In this Article, we report a novel thioannulation approach for the synthesis of substituted thiophenes under mild and metal-free conditions starting from easily accessible Morita–Baylis–Hillman (MBH) acetate of acetylenic aldehydes. During our recent studies,[9] we envisaged that an intermolecular allylic substitution of MBH acetate of acetylenic aldehyde with a suitable thio-reagent followed by deacetylative intramolecular 5-exo-*dig*-thiocycloisomerization in one pot (two C–S bond formations) would be a convenient process for the synthesis of substituted thiophenes (Scheme 1).

**Scheme 1. Access to Substituted Thiophenes from Alkynyl Thiols**




## RESULTS AND DISCUSSION

To find the suitable reaction conditions for the proposed thioannulation, MBH acetate **1a**, derived from the reaction of 3-phenylpropiolaldehyde with methyl acrylate, was employed as a model substrate. Initially, compound **1a** was treated with $Na_2S{\cdot}9H_2O$ (1 equiv) in $CH_2Cl_2$ at room temperature, wherein the formation of a (*Z*)-dialkyl thio-ether **3** was observed in 94% yield (entry 1, Table 1).[10,11] Next, few other thio-reagents were examined, and it was found that the reaction of **1a** with KSAc in the presence of $K_2CO_3$ produced the thiophene **2a** in 94% yield (entry 6, Table 1). In the absence of $K_2CO_3$, the reaction of **1a**

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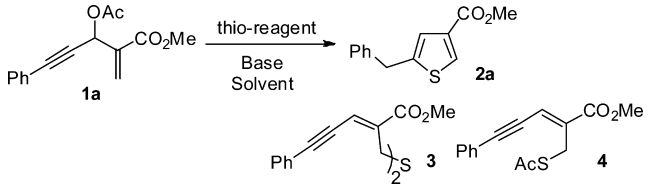
**Table 1. Optimization of Reaction Conditions**




| entry | thio-reagent | base | solvent | $T$ (°C) | time (h) | product | yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | $Na_2S{\cdot}9H_2O$ | | $CH_2Cl_2$ | rt | 9 | **3** | 94 |
| 2 | KSAc | | $CH_3CN$ | rt | 4 | **4** | 92 |
| 3 | Lawesson's reagent | | $CH_2Cl_2$ | rt | 24 | complex mixture | |
| 4 | NaHS | $K_2CO_3$ | MeOH | rt | 20 | **2a** | 49 |
| 5 | KSAc | $K_2CO_3$ | $CH_3CN$/MeOH | rt | 20 | **2a** | 35 |
| 6 | KSAc | $K_2CO_3$ | MeOH | rt | 18 | **2a** | 94 |
| 7 | KSAc | $K_2CO_3$ | DMF/MeOH | rt | 20 | **2a** | 41 |
| 8 | KSAc | $K_2CO_3$ | THF | rt | 20 | **2a** | |

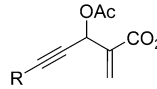
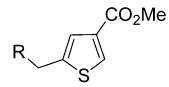
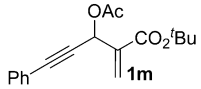
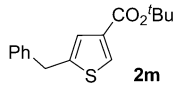
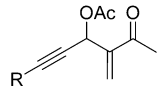
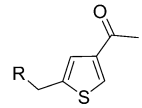
[a]Isolated yield.

with KSAc provided the (*Z*)-allylic thioacetate **4** (entry 2, Table 1).[11] While Lawesson's reagent did not promote the product formation (entry 3, Table 1), sodium hydrosulfide provided the thiophene **2a** in only 49% yield (entry 4, Table 1). In the series of examined solvents ($CH_3CN$/MeOH, MeOH, DMF/MeOH, THF), methanol proved to be the best solvent for this one-pot reaction (entries 5−8, Table 1).

Under the optimized conditions, the scope of this annulation reaction using a variety of MBH acetates of acetylenic aldehydes was evaluated (Table 2). The results revealed that the approach serves as a general and efficient method for the synthesis of diversely substituted thiophenes in good yields. In addition, the substitution and their electronic properties on alkyne were found to have a limited effect on this thioannulation. MBH acetates **1b** and **1c** containing *p*-tolyl and 1-naphthyl groups on alkyne provided the corresponding thiophenes **2b** and **2c**, respectively, in excellent yields (entries 2,3, Table 2). For the substrates bearing aryl substitution with either electron-donating or electron-withdrawing group on alkyne functionality, **1d−1g**, the reaction proceeded smoothly to give the desired thiophenes **2d−2g** in good yield (entries 4−7, table 2). The presence of halo groups on phenyl ring enhances the possibility of synthetic utility of the present method by structural modification. Heteroaryl-substituted MBH acetates, **1h** (3-indolyl) and **1i** (2-thiophenyl), were also effectively employed in the described reaction (entries 8 and 9, Table 2). The present annulation reaction was equally successful when applied to MBH acetates derived from acetylenic aldehydes containing aliphatic substitution on alkyne functionality, **1j−1l**, to give the corresponding thiophenes **2j−2l**, respectively (entries 10−12, Table 2). Additionally, we extended the scope of MBH acetates derived from different activated alkenes such as *tert*-butyl acrylate or methyl vinyl ketone. Gratifyingly, the annulation reaction of substrates **1m−1o** worked well to furnish thiophenes **2m−2o** in good yield (entries 13−15, Table 2). Treatment of substrate **1p**, which contains two MBH acetate groups tethered to phenyl ring, with KSAc in the presence of $K_2CO_3$ in MeOH resulted in a smooth reaction to deliver bis-thiophene **2p** in 68% yield (Scheme 2).

A possible reaction mechanism is shown in Scheme 3. In the first step, MBH acetate **1a** reacts with KSAc to provide allylic thioacetate **4**.[12] Next, $K_2CO_3$-mediated deacetylation of **4** provides the thiol **4a**,[13] which further undergoes 5-exo-*dig*-cyclization to yield the intermediate **4b** and subsequent isomerization furnishes the thiophene **2a**.[8b,14] The intermediate compounds **4** (entry 2, Table 1) and **4a** (at lower temperature) were isolated and fully characterized. Further, **4** and **4a** were also independently treated with $K_2CO_3$ in MeOH, and the successful formation of **2a** was observed in both cases.

**Table 2. Synthesis of 2,4-Disubstituted Thiophenes[a]**

| Entry | MBH-Acetate (**1**) | Time (h) | Thiophene (**2**)[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 |  | 18 |  | |
| | R = Ph, **1a** | | R = Ph, **2a** | 94 |
| 2 | R = 4-*Me*-$C_6H_4$, **1b** | 20 | R = 4-*Me*-$C_6H_4$, **2b** | 95 |
| 3 | R = 1-Naphthyl, **1c** | 22 | R =1-Naphthyl, **2c** | 84 |
| 4 | R = 4-*MeO*-$C_6H_4$, **1d** | 8 | R = 4-*MeO*-$C_6H_4$, **2d** | 82 |
| 5 | R = 4-*Cl*-$C_6H_4$, **1e** | 6 | R = 4-*Cl*-$C_6H_4$, **2e** | 73 |
| 6 | R = 2-*I*-$C_6H_4$, **1f** | 12 | R = 2-*I*-$C_6H_4$, **2f** | 82 |
| 7 | R = 3-$CF_3$-$C_6H_4$, **1g** | 8 | R = 3-$CF_3$-$C_6H_4$, **2g** | 76 |
| 8 | R = 3-*NBoc*-Indole, **1h** | 12 | R = 3-*NBoc*-Indole, **2h** | 69 |
| 9 | R = 2-Thiophenyl, **1i** | 8 | R = 2-Thiophenyl, **2i** | 90 |
| 10 | R = $nC_3H_7$, **1j** | 4 | R = $nC_3H_7$, **2j** | 68 |
| 11 | R = $nC_6H_{13}$, **1k** | 6 | R = $nC_6H_{13}$, **2k** | 70 |
| 12 | R = $nC_8H_{17}$, **1l** | 4 | R = $nC_8H_{17}$, **2l** | 62 |
| 13 |  | 6 |  | 88 |
| 14 |  | |  | |
| | R = Ph, **1n** | 15 | R = Ph, **2n** | 86 |
| 15 | R = 4-*MeO*-$C_6H_4$, **1o** | 30 | R = 4-*MeO*-$C_6H_4$, **2o** | 85 |

[a]Reaction conditions: MBH acetate **1** (1 mmol), KSAc (1.1 mmol), $K_2CO_3$ (2.2 mmol), MeOH (5 mL), rt. [b]All of the products were characterized by $^1H$, $^{13}C$ NMR, IR, and MS spectra. [c]Isolated yield.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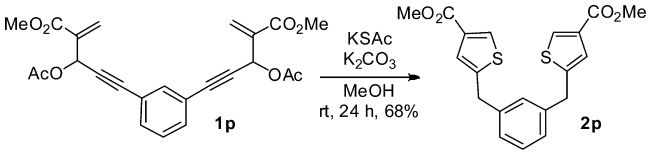
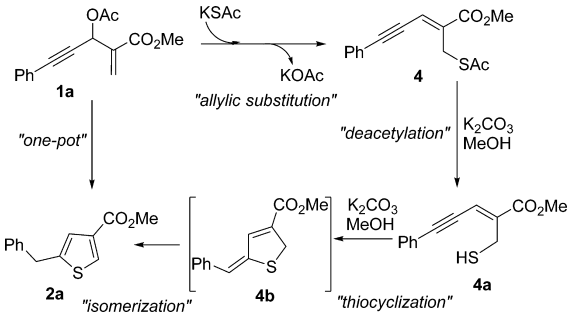
**Scheme 2. Synthesis of Bis-thiophene 2p**



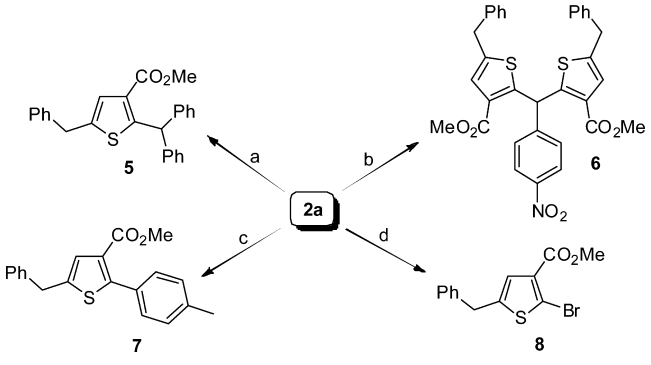

**Scheme 3. Proposed Mechanism for the Thioannulation**




Inspired by these results, we predicted that the present reaction could find potential applications in organic synthesis because the obtained thiophenes have two reactive sites: (i) C-5 position and (ii) C-4 ester group, as a handle for additional diversification. Indeed, this assumption was proved by further investigation using **2a** as a substrate. For example, a direct C5-substitution was successfully accomplished via an acid-catalyzed electrophilic substitution reaction of **2a** with diphenylmethanol in the presence of $BF_3{\cdot}Et_2O$ (5 mol %) to give **5** in 95% yield. The treatment of **2a** with 4-nitrobenzaldehyde in the presence of $BF_3{\cdot}Et_2O$ (20 mol %) provided the triaryl methane **6** in 79% yield. Palladium-catalyzed C−H activation of **2a** with 4-iodo toluene in the presence of $Pd(OAc)_2$ gave **7** in 65% yield. Alternatively, bromination of **2a** with NBS in acetonitrile provided the bromothiophene **6** in 81% yield, which can be further diversified through Pd-catalyzed coupling reaction (Scheme 4).

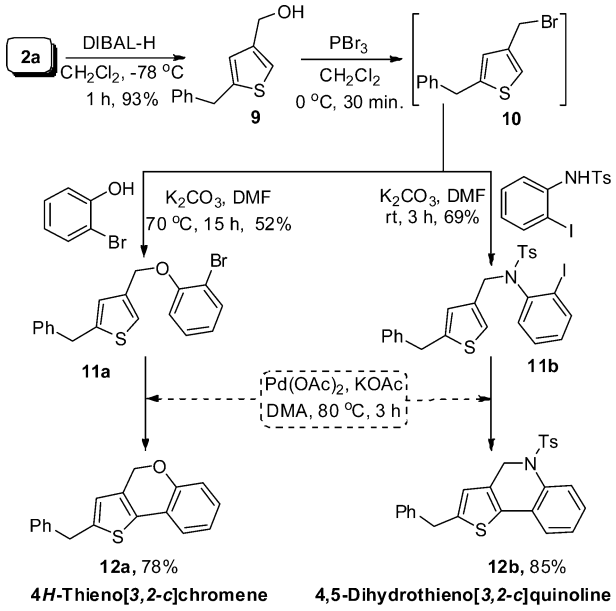
In addition, thiophene **2a** was conveniently utilized in the synthesis of 4*H*-thieno[3,2-*c*]chromene (**12a**) and thieno[3,2-*c*]dihydroquinoline (**12b**) as shown in Scheme 5. First, ester group of **2a** was reduced (DIBAL-H) to alcohol **9**, which upon treatment with $PBr_3$ in $CH_2Cl_2$ provided the corresponding

**Scheme 4. C5-Functionalization Reactions of 2a**[a]




[a]Reagents and conditions: (a) diphenyl methanol, $BF_3{\cdot}Et_2O$ (5 mol %), $CH_2Cl_2$, rt, 1 h, 95%; (b) 4-nitro benzaldehyde, $BF_3{\cdot}Et_2O$ (20 mol %), $CH_2Cl_2$, reflux, 24 h, 79%; (c) 4-iodo toluene, $Pd(OAc)_2$ (10 mol %), DMA, 80 °C, 12 h, 65%; (d) NBS, $CH_3CN$, 0 °C to rt, 24 h, 81%.

**Scheme 5. Synthesis of 4*H*-Thieno[3,2-*c*]chromene (12a) and Thieno[3,2-*c*]dihydroquinoline (12b)**




bromide **10**. The bromide **10** was used in *O*-alkylation of 2-bromophenol to get **11a**, and subsequent cyclization through an intramolecular Pd-catalyzed C−H activation offered the desired 4*H*-thieno[3,2-*c*]chromene (**12a**) in 78% yield.[15] Similarly, *N*-alkylation of 2-iodo *N*-tosylaniline with **10** to **11b** followed by cyclization gave thieno[3,2-*c*]dihydroquinoline (**12b**) in good yield (85%).

In conclusion, we have developed a new, versatile, and metal-free method for the synthesis of substituted thiophenes from MBH acetates of acetylenic aldehydes. A simple base ($K_2CO_3$) promotes the [4 + 1]-thioannulation of KSAc with MBH acetates through a tandem allylic substitution/deacetylative thiocycloisomerization (two C−S bond formations). This strategy complements previously described methods based on metal-catalyzed cyclization of alkynyl thiols. The utility of the obtained thiophenes as handy synthons in the construction of other thiophene-based heterocycles was also demonstrated. Further, the present method may find various applications toward novel thiophene-based heterocycles.

## EXPERIMENTAL SECTION

**General.** Reactions were monitored by thin-layer chromatography carried out on silica plates using UV-light and anisaldehyde or potassium permanganate or *β*-naphthol for visualization. Column chromatography was performed on silica gel (60−120 mesh) using *n*-hexane and ethyl acetate as eluent. Evaporation of solvents was conducted under reduced pressure at temperatures less than 45 °C. FTIR spectra were recorded on KBr thin film. $^1H$ NMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solvent on a 300, 500, and 600 MHz NMR spectrometer. Chemical shifts $\delta$ and coupling constants $J$ are given in ppm (parts per million) and Hz (hertz), respectively. Chemical shifts are reported relative to residual solvent as an internal standard for $^1H$ and $^{13}C$ ($CDCl_3$: $\delta$ 7.26 ppm for $^1H$ and 77.0 ppm for $^{13}C$). Mass spectra were obtained on VG 70-70H or LC/MSD trapSL spectrometer operating at 70 eV using direct inlet system.

Morita−Baylis−Hillman acetates **1a**−**1p** have been prepared using the literature procedure[9,16] and known compound data as compared to the reported data. Characterization data for new compounds (**1b**, **c**, **f**, **g**, **h**, **l**, **m**, and **1p**) are given below.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**Methyl 3-Acetoxy-2-methylene-5-(*p*-tolyl)pent-4-ynoate (1b).** 1.02 g, 86%; pale yellow solid; mp 60−62 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.35 (d, $J$ = 7.9 Hz, 2H), 7.12 (d, $J$ = 7.9 Hz, 2H), 6.52 (d, $J$ = 5.9 Hz, 2H), 6.34 (s, 1H), 3.81 (s, 3H), 2.35 (s, 3H) 2.12 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.2, 164.8, 139.0, 136.6, 131.7, 129.0, 128.9, 118.7, 87.3, 83.0, 62.1, 52.1, 21.4, 20.7. IR (KBr): $\nu_{max}$ = 2950, 2924, 2853, 2230, 1742, 1725, 1510, 1438, 1365, 1252, 1219, 1145, 1026, 975, 921, 815, 528 cm$^{-1}$. MS (ESI): $m/z$ 295 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{16}H_{16}O_4Na$ (M + Na)$^+$, 295.0940; found, 295.0940.

**Methyl 3-Acetoxy-2-methylene-5-(naphthalen-1-yl)pent-4-ynoate (1c).** 1.04 g, 90%; pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.27 (d, $J$ = 8.1 Hz, 1H), 7.85 (d, $J$ = 8.1 Hz, 2H), 7.70 (d, $J$ = 7.1 Hz, 1H), 7.62−7.49 (m, 2H), 7.45−7.38 (m, 1H), 6.68 (s, 1H), 6.58 (s, 1H), 6.43 (s, 1H), 3.85 (s, 3H), 2.17 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.2, 164.8, 136.5, 133.2, 132.9, 130.9, 129.3, 129.1, 128.1, 126.9, 125.7, 124.9, 119.3, 126.3, 88.4, 85.2, 62.2, 52.1, 20.8. IR (KBr): $\nu_{max}$ = 2951, 2229, 1726, 1639, 1437, 1368, 1262, 1222, 1147, 1018, 991, 801, 773 cm$^{-1}$. MS (ESI): $m/z$ 331 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{19}H_{16}O_4Na$ (M + Na)$^+$, 331.0940; found, 331.0940.

**Methyl 3-Acetoxy-5-(2-iodophenyl)-2-methylenepent-4-ynoate (1f).** 0.90 g, 80%; white solid; mp 40−41 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.83 (d, $J$ = 7.9 Hz, 1H), 7.47 (dd, $J$ = 7.7, 1.7 Hz, 1H), 7.31 (dd, $J$ = 7.5, 1.1 Hz, 1H), 7.03 (dd, $J$ = 7.5, 1.7 Hz, 1H), 6.59−6.56 (m, 2H), 6.51 (s, 1H), 3.82 (s, 3H), 2.14 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.1, 164.7, 138.6, 136.0, 133.0, 129.9, 129.7, 128.3, 127.6, 100.5, 88.7, 87.3, 61.9, 52.1, 20.7. IR (KBr): $\nu_{max}$ = 2950, 1725, 1634, 1434, 1365, 1258, 1219, 1147, 763 cm$^{-1}$. MS (ESI): $m/z$ 385 (M + H)$^+$. HRMS (ESI): $m/z$ calcd for $C_{15}H_{14}O_4I$ (M + H)$^+$, 384.9931; found, 384.9924.

**Methyl 3-Acetoxy-2-methylene-5-(3-(trifluoromethyl) phenyl)pent-4-ynoate (1g).** 0.94 g, 82%; pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.72 (s, 1H), 7.67−7.56 (m, 2H), 7.49−7.41 (m, 1H), 6.54 (d, $J$ = 4.7 Hz, 2H), 6.32 (s, 1H), 3.83 (s, 3H), 2.14 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.2, 164.7, 136.2, 134.9, 129.1, 128.8, 128.7, 128.6, 125.4, 125.5, 122.7, 85.4 (2), 61.8, 52.2, 20.7. IR (KBr): $\nu_{max}$ = 2956, 2851, 1749, 1730, 1437, 1369, 1334, 1271, 1224, 1168, 1130, 1034, 805, 696, 605 cm$^{-1}$. MS (ESI): $m/z$ 349 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{16}H_{13}F_3O_4Na$ (M + Na)$^+$, 349.0658; found, 349.0663.

***tert*-Butyl 3-(3-Acetoxy-4-(methoxycarbonyl)pent-4-en-1-yn-1-yl)-1*H*-indole-1-carboxylate (1h).** 0.89 g, 80%; yellow solid; mp 92−93 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.14 (d, $J$ = 8.3 Hz, 1H), 7.80 (s, 1H), 7.63 (d, $J$ = 6.7 Hz, 1H), 7.40−7.29 (m, 2H), 6.59 (s, 1H), 6.56 (s, 1H), 6.40 (s, 1H), 3.83 (s, 3H), 2.15 (s, 3H), 1.67 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.3, 164.9, 148.8, 136.6, 134.5, 130.2, 129.7, 129.1, 125.2, 123.2, 119.9, 115.2, 101.9, 87.2, 84.4, 79.4, 62.3, 52.2, 28.0, 20.8. IR (KBr): $\nu_{max}$ = 2978, 2230, 1738, 1633, 1451, 1369, 1262, 1227, 1156, 1098, 1045, 1023, 915, 748, 609 cm$^{-1}$. MS (ESI): $m/z$ 420 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{22}H_{23}NO_6Na$ (M + Na)$^+$, 420.1418; found, 420.1420.

**Methyl 3-Acetoxy-2-methylenetridec-4-ynoate (1l).** 0.99 g, 85%; yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.45 (s, 1H), 6.29 (s, 1H), 6.24 (s, 1H), 3.79 (s, 3H), 2.23 (dt, $J$ = 6.7, 1.5 Hz, 2H), 2.09 (s, 3H), 1.54−1.48 (m, 2H), 1.40−1.33 (m, 2H), 1.32−1.21 (m, 8H), 0.88 (t, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.2, 165.0, 137.0, 128.7, 88.6, 74.8, 62.0, 52.0, 31.7, 29.1, 28.9, 28.7, 28.2, 22.5, 20.8, 18.6, 14.0. IR (KBr): $\nu_{max}$ = 2928, 2856, 2236, 1748, 1731, 1269, 1225, 989 cm$^{-1}$. MS (ESI): $m/z$ 317 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{17}H_{26}O_4Na$ (M+Na)$^+$, 317.1723; found, 317.1731.

***tert*-Butyl 3-Acetoxy-2-methylene-5-phenylpent-4-ynoate (1m).** 1.09 g, 94%; pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.49−7.43 (m, 2H), 7.37−7.29 (m, 3H), 6.51 (s, 1H), 6.43 (s, 1H), 6.23 (s, 1H), 2.13 (s, 3H), 1.51 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.3, 163.6, 138.1, 131.9, 128.8, 128.3, 128.0, 121.9, 87.0, 83.9, 81.7, 62.2, 28.0, 20.9. IR (KBr): $\nu_{max}$ = 2972, 2923, 2853, 2230, 1747, 1718, 1367, 1253, 1220, 1145, 1016, 983, 919, 846, 770, 757, 690 cm$^{-1}$. MS (ESI): $m/z$ 323 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{18}H_{20}O_4Na$ (M + Na)$^+$, 323.1253; found, 323 0.1253.

**Dimethyl 5,5′-(1,3-Phenylene)bis(3-acetoxy-2-methylenepent-4-ynoate) (1p).** 0.93 g, 75%; pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.56 (s, 1H), 7.42 (d, $J$ = 7.8 Hz, 2H), 7.27 (t, $J$ = 7.8 Hz, 1H), 6.51 (d, $J$ = 5.8 Hz, 4H), 6.30 (s, 2H), 3.82 (s, 6H), 2.13 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.2, 164.8, 136.4, 135.3, 132.2, 129.2, 128.4, 122.2, 85.9, 84.6, 61.9, 52.2, 20.8. IR (KBr): $\nu_{max}$ = 2924, 2853, 1746, 1727, 1440, 1366, 1261, 1223, 1147, 1019, 974, 809, 686 cm$^{-1}$. MS (ESI): $m/z$ 461 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{24}H_{22}O_8Na$ (M + Na)$^+$, 461.1206; found, 461.1196.

**General Procedure for the Preparation of Substituted Thiophenes (2a−2p).** To a solution of MBH acetate (1.0 mmol) and potassium thioacetate (1.1 mmol) in 5 mL of MeOH was added potassium carbonate (2.2 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 4−30 h (Table 2). After the completion of the reaction (monitered by TLC), the mixture was evaporated in vacuo. Residue was purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding substituted thiophene.

**Methyl 5-Benzylthiophene-3-carboxylate (2a).** 218 mg, 94%; pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.90 (s, 1H), 7.32−7.27 (m, 2H), 7.25−7.18 (m, 4H), 4.10 (s, 2H), 3.81 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.1, 144.9, 139.4, 132.9, 131.5, 128.5, 128.4, 126.6, 125.4, 51.9, 35.9. IR (KBr): $\nu_{max}$ = 3109, 3025, 2946, 1716, 1458, 1393, 1244, 1084, 740 cm$^{-1}$. MS (ESI): $m/z$ 233 (M + H)$^+$. HRMS (ESI): $m/z$ calcd for $C_{13}H_{13}O_2S$ (M + H)$^+$, 233.0631; found, 233.0613.

**Methyl 5-(4-Methylbenzyl)thiophene-3-carboxylate (2b).** 234 mg, 95%; pale yellow solid, mp 52−54 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.91 (d, $J$ = 1.5 Hz, 1H), 7.21 (d, $J$ = 1.5 Hz, 1H), 7.13 (s, 4H), 4.08 (s, 2H), 3.83 (s, 3H), 2.33 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 163.2, 145.4, 136.4, 136.2, 132.9, 131.4, 129.3, 128.4, 125.2, 51.6, 35.6, 20.9. IR (KBr): $\nu_{max}$ = 2950, 2920, 1717, 1460, 1242, 1220, 1082, 989, 772 cm$^{-1}$. MS (ESI): $m/z$ 247 (M + H)$^+$. HRMS (ESI): $m/z$ calcd for $C_{14}H_{15}O_2S$ (M + H)$^+$, 247.0787; found, 247.0775.

**Methyl 5-(Naphthalen-1-ylmethyl)thiophene-3-carboxylate (2c).** 237 mg, 84%; pale yellow solid, mp 60−62 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.02−7.96 (m, 1H), 7.90−7.85 (m, 2H), 7.79 (d, $J$ = 7.9 Hz, 1H), 7.52−7.36 (m, 4H), 7.20 (d, $J$ = 2.2 Hz, 1H), 4.57 (s, 2H), 3.80 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.2, 144.9, 135.2, 133.9, 133.0, 131.5, 131.3, 128.7, 127.8, 126.9, 126.2, 125.7, 125.5, 123.7, 125.4, 51.6, 33.5. IR (KBr): $\nu_{max}$ = 2924, 1720, 1539, 1463, 1389, 1241, 1082, 982, 849, 773 cm$^{-1}$. MS (ESI): $m/z$ 283 (M + H)$^+$. HRMS (ESI): $m/z$ calcd for $C_{17}H_{15}O_2S$ (M + H)$^+$, 283.0787; found, 283.0755.

**Methyl 5-(4-Methoxybenzyl)thiophene-3-carboxylate (2d).** 215 mg, 82%; pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.91 (s, 1H), 7.19 (s, 1H), 7.15 (d, $J$ = 8.5 Hz, 2H), 6.85 (d, $J$ = 8.5 Hz, 2H), 4.06 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.1, 158.3, 145.7, 132.9, 131.5, 131.3, 129.5, 125.1, 113.9, 55.1, 51.5, 35.1. IR (KBr): $\nu_{max}$ = 2951, 2921, 1717, 1611, 1512, 1462, 1248, 1034, 740 cm$^{-1}$. MS (ESI): $m/z$ 263 (M + H)$^+$. HRMS (ESI): $m/z$ calcd for $C_{14}H_{15}O_3S$ (M + H)$^+$, 263.0736; found, 263.0710.

**Methyl 5-(4-Chlorobenzyl)thiophene-3-carboxylate (2e).** 195 mg, 73%; pale yellow solid; mp 52−53 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.92 (d, $J$ = 1.4 Hz, 1H), 7.28 (d, $J$ = 7.9 Hz, 2H), 7.20 (s, 1H), 7.16 (d, $J$ = 7.9 Hz, 2H), 4.09 (s, 2H), 3.84 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 163.0, 144.3, 137.9, 133.1, 132.5, 131.6, 129.9, 128.7, 125.6, 51.7, 35.3. IR (KBr): $\nu_{max}$ = 3109, 2950, 2917, 1716, 1546, 1462, 1246, 1087, 741 cm$^{-1}$. MS (ESI): $m/z$ 267 (M + H)$^+$. HRMS (ESI): $m/z$ calcd for $C_{13}H_{12}O_2ClS$ (M + H)$^+$, 267.0241; found, 267.0246.

**Methyl 5-(2-Iodobenzyl)thiophene-3-carboxylate (2f).** 293 mg, 82%; pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.93 (d, $J$ = 1.3 Hz, 1H), 7.85 (dd, $J$ = 7.9, 1.5 Hz, 1H), 7.34−7.28 (m, 1H), 7.27−7.20 (m, 2H), 6.95 (td, $J$ = 7.7, 1.7 Hz, 1H), 4.24 (s, 2H), 3.83 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.1, 143.2, 142.1, 139.6, 132.9, 131.6, 129.8, 128.5, 128.5, 125.9, 100.3, 51.6, 41.0. IR (KBr): $\nu_{max}$ = 2947, 1714, 1634, 1460, 1241, 1082, 1011, 770, 741 cm$^{-1}$. MS (ESI):


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$m/z$ 359 $(M + H)^+$. HRMS (ESI): $m/z$ calcd for $C_{13}H_{12}O_2IS$ $(M + H)^+$, 358.9597; found, 358.9608.

**Methyl 5-(3-(Trifluoromethyl)benzyl)thiophene-3-carboxylate (2g).** 228 mg, 76%; pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.95 (d, $J$ = 1.4 Hz, 1H), 7.54−7.41 (m, 4H), 7.23 (d, $J$ = 1.4 Hz, 1H), 4.18 (s, 2H), 3.84 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 163.0, 143.5, 140.3, 133.2,131.9, 131.8, 129.1, 125.9, 125.2, 125.2, 123.7, 123.6, 51.7, 35.7. IR (KBr): $\nu_{max}$ = 2953, 1718, 1463, 1332, 1251, 1164, 1124, 1074, 989, 854, 769, 742, 703 $cm^{-1}$. MS (ESI): $m/z$ 301 $(M + H)^+$. HRMS (ESI): $m/z$ calcd for $C_{14}H_{12}F_3O_2S$ $(M + H)^+$, 301.0505; found, 301.0511.

***tert*-Butyl 3-((4-(Methoxycarbonyl)thiophen-2-yl)methyl)-1*H*-indole-1-carboxylate (2h).** 256 mg, 69%; pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.12 (d, $J$ = 7.9 Hz, 1H), 7.91 (s, 1H), 7.56−7.41 (m, 2H), 7.39−7.27 (m, 2H), 7.29−7.04 (m, 1H), 4.21 (s, 2H), 3.83 (s, 3H) 1.67 (s, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 163.2, 143.8, 132.9, 131.4, 129.7, 125.4, 124.5, 124.4, 123.9, 123.6, 122.5, 119.0, 118.6, 115.3, 83.7, 51.7, 29.6, 28.1. IR (KBr): $\nu_{max}$ = 2924, 2852, 1724, 1455, 1369, 1303, 1251, 1157, 1079, 1015, 856, 743 $cm^{-1}$. MS (ESI): $m/z$ 394 $(M + Na)^+$. HRMS (ESI): $m/z$ calcd for $C_{20}H_{25}N_2O_4S$ $(M + NH_4)^+$, 389.1535; found, 389.1562.

**Methyl 5-(Thiophen-2-ylmethyl)thiophene-3-carboxylate (2i).** 215 mg, 90%; pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.94 (s, 1H), 7.29 (dd, $J$ = 2.7, 1.5 Hz, 1H), 7.20−7.17 (m, 1H), 6.94 (dd, $J$ = 5,3, 2.7 Hz, 1H), 6.90−6.87 (m, 1H), 4.32 (s, 2H), 3.84 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 162.9, 144.0, 141.8, 132.9, 131.5, 126.7, 125.5, 125.4, 124.3, 51.5, 30.0. IR (KBr): $\nu_{max}$ = 3108, 2950, 2846, 1715, 1544, 1462, 1260, 1234, 770 $cm^{-1}$. MS (ESI): $m/z$ 239 $(M + H)^+$. HRMS (ESI): $m/z$ calcd for $C_{11}H_{11}O_2S_2$ $(M + H)^+$, 239.0195; found, 239.0194.

**Methyl 5-Butylthiophene-3-carboxylate (2j).** 135 mg, 68%; pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.12 (s, 1H), 5.78 (t, $J$ = 7.5 Hz, 1H), 4.13−4.10 (m, 2H), 3.78 (s, 3H), 2.06 (q, $J$ = 7.3 Hz, 2H), 1.55−1.42 (m, 2H), 0.94 (t, $J$ = 6.8 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 163.3, 146.5, 130.4, 123.7, 124.3, 51.6, 33.4, 29.5, 22.0, 13.7. IR (KBr): $\nu_{max}$ = 3447, 2962, 1719, 1632, 1461, 1240, 749 $cm^{-1}$. MS (ESI): $m/z$ 237 $(M + K)^+$. HRMS (ESI): $m/z$ calcd for $C_{10}H_{13}O_2S$ $(M - H)^+$, 197.0630; found, 197.0638.

**Methyl 5-Heptylthiophene-3-carboxylate (2k).** 168 mg, 70%; pale yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.10 (s, 1H), 5.77 (t, $J$ = 7.5 Hz, 1H), 4.11 (s, 2H), 3.77 (s, 3H), 2.07 (q, $J$ = 8.4 Hz, 2H), 1.48−1.41 (m, 2H), 1.36−1.24 (m, 6H), 0.88 (t, $J$ = 6.5 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 163.4, 146.6, 130.5, 124.4, 123.7, 51.6, 31.7, 31.4, 29.8, 29.0, 28.9, 22.6, 14.0. IR (KBr): $\nu_{max}$ = 2926, 2856, 1718, 1460, 1386, 1235, 1086, 767 $cm^{-1}$. MS (ESI): $m/z$ 241 $(M + H)^+$. Anal. Calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39; S, 13.34. Found: C, 64.88; H, 8.52; S, 13.19.

**Methyl 5-Nonylthiophene-3-carboxylate (2l).** 166 mg, 62%; pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.88 (s, 1H), 7.18 (s, 1H), 3.84 (s, 3H), 2.78 (t, $J$ = 7.5 Hz, 2H), 1.70−1.63 (m, 2H), 1.39−1.22 (m, 12H), 0.90−0.86 (m, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 163.3, 146.5, 132.8, 130.4, 124.3, 51.6, 39.1, 31.8, 31.3, 29.8, 29.4, 29.2, 28.9, 22.6, 14.0. IR (KBr): $\nu_{max}$ = 2926, 2854, 1720, 1543, 1461, 1380, 1240, 1087, 990, 859, 744 $cm^{-1}$. MS (ESI): $m/z$ 307 $(M + K)^+$. HRMS (ESI): $m/z$ calcd for $C_{15}H_{23}O_2S$ $(M - H)^+$, 267.1413; found, 267.1419.

***tert*-Butyl 5-Benzylthiophene-3-carboxylate (2m).** 141 mg, 88%; pale yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.82 (d, $J$ = 2.0 Hz, 1H), 7.33−7.29 (m, 2H), 7.25−7.22 (m, 3H), 7.17 (s, 1H), 4.11 (s, 2H), 1.55 (s, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 162.1, 144.5, 139.6, 135.1, 130.8, 128.6, 128.5, 126.6, 125.6, 80.7, 36.1, 28.1. IR (KBr): $\nu_{max}$ = 3028, 2975, 2927, 1709, 1544, 1456, 1367, 1251, 1163, 1081, 851, 739, 699 $cm^{-1}$. MS (ESI): $m/z$ 297 $(M + Na)^+$. HRMS (ESI): $m/z$ calcd for $C_{16}H_{18}O_2NaS$ $(M + Na)^+$, 297.0919; found, 297.0920.

**1-(5-Benzylthiophen-3-yl)ethanone (2n).** 186 mg, 86%; pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.85 (d, $J$ = 1.3 Hz, 1H), 7.36−7.29 (m, 2H), 7.28−7.21 (m, 4H), 4.12 (s, 2H), 2.47 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 192.2, 145.4, 142.3, 139.3, 131.3, 128.6, 128.5, 126.7, 124.4, 36.0, 27.0. IR (KBr): $\nu_{max}$ = 2916, 1672, 1453, 1396, 1242, 757, 700 $cm^{-1}$. MS (ESI): $m/z$ 217 $(M + H)^+$. HRMS (ESI): $m/z$ calcd for $C_{13}H_{13}OS$ $(M + H)^+$, 217.0682; found, 217.0672.

**((Methoxybenzyl)thiophen-3-yl)ethanone (2o).** 209 mg, 85%; yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.83 (s, 1H), 7.21 (s, 1H), 7.15 (d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 4.06 (s, 2H), 3.79 (s, 3H), 2.46 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 192.3, 158.3, 146.2, 142.3, 131.5, 131.3, 129.5, 124.2, 114.0, 55.2, 35.2, 29.6. IR (KBr): $\nu_{max}$ = 2925, 2851, 1672, 1610, 1510, 1454, 1246, 1177, 1032, 761 $cm^{-1}$. MS (ESI): $m/z$ 247 $(M + H)^+$. HRMS (ESI): $m/z$ calcd for $C_{14}H_{15}O_2S$ $(M + H)^+$, 247.0787; found, 247.0804.

**Dimethyl 5,5′-(1,3-Phenylenebis(methylene))bis(thiophene-3-carboxylate) (2p).** 263 mg, 68%; pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.92 (d, $J$ = 1.3 Hz, 2H), 7.29−7.10 (m, 6H), 4.10 (s, 4H), 3.84 (s, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 163.2, 144.8, 139.9, 133.0, 131.5, 129.0, 128.8, 127.0, 125.5, 51.6, 35.9. IR (KBr): $\nu_{max}$ = 3418, 3108, 2949, 1715, 1460, 1247, 1084, 989, 855, 742 $cm^{-1}$. MS (ESI): $m/z$ 387 $(M + H)^+$. HRMS (ESI): $m/z$ calcd for $C_{20}H_{19}O_4S_2$ $(M + H)^+$, 387.0719; found, 387.0734.

**(2*Z*,2′*Z*)-Dimethyl 2,2′-(Thiobis(methylene))bis(5-phenylpent-2-en-4-ynoate) (3).** To a solution of MBH acetate (1.0 mmol) in 5 mL of dichloromethane was added $Na_2S{\cdot}9H_2O$ (1.1 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 9 h. After the completion of the reaction (monitered by TLC), the mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexanes) to afford compound **3** as a pale yellow oil (404 mg, 94%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.53−7.44 (m, 4H), 7.40−7.28 (m, 6H), 6.90 (s, 2H), 3.87 (s, 4H), 3.78 (s, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 166.3, 160.4, 137.7, 133.5, 121.3, 114.4, 114.1, 103.4, 84.7, 55.2, 31.1. IR (KBr): $\nu_{max}$ = 2947, 2443, 1935, 1732, 1593, 1517, 1343, 1037, 851 $cm^{-1}$. MS (ESI): $m/z$ 431 $(M + H)^+$. HRMS (ESI): $m/z$ calcd for $C_{26}H_{23}O_4S$ $(M + H)^+$, 431.1312; found, 431.1318.

**(*Z*)-Methyl 2-((Acetylthio)methyl)-5-phenylpent-2-en-4-ynoate (4).** To a solution of MBH acetate (1.0 mmol) in 5 mL of acetonitrile was added potassium thioacetate (1.1 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 4 h. After the completion of the reaction, the mixture was evaporated in vacuo. Residue was purified by column chromatography on silica gel (EtOAc:hexanes) to afford the compound **4** as a pale yellow oil (252 mg, 92%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.59−7.54 (m, 2H), 7.40−7.34 (m, 3H), 6.94 (s, 1H), 4.18 (s, 2H), 3.81 (s, 3H), 2.34 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 194.2, 165.9, 137.3, 132.0, 129.4, 128.4, 122.4, 122.1, 104.5, 85.1, 52.2, 30.1, 27.2. IR (KBr): $\nu_{max}$ = 2951, 2195, 1714, 1609, 1437, 1356, 1255, 1095, 758 $cm^{-1}$. MS (ESI): $m/z$ 297 $(M + Na)^+$. HRMS (ESI): $m/z$ calcd for $C_{15}H_{14}O_3NaS$ $(M + Na)^+$, 297.0556; found, 295.0559.

**(*Z*)-Methyl 2-(Mercaptomethyl)-5-phenylpent-2-en-4-ynoate (4a).** To a solution of MBH acetate (1.0 mmol) and potassium thioacetate (1.1 mmol) in 5 mL of MeOH was added potassium carbonate (2.2 mmol) at −5 °C. The reaction mixture was stirred at −5 to 0 °C for 30 min. After the completion of the reaction (monitered by TLC), the reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexanes) to afford compound **4a** as a pale yellow solid (150 mg, 65%); mp 122−124 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.53−7.46 (m, 2H), 7.43−7.31 (m, 3H), 6.76 (s, 1H), 4.30 (s, 2H), 3.82 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 164.4, 144.8, 134.5, 128.5, 128.2, 127.1, 123.4, 97.2. 84.1, 52.0, 40.1. IR (KBr): $\nu_{max}$ = 2924, 2854, 1695, 1597, 1440, 1343, 1232, 1079, 915, 744, 687 $cm^{-1}$. MS (ESI): $m/z$ 231 $(M - H)^+$. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21; S, 13.80. Found: C, 67.28; H, 5.25; S, 13.75.

**Methyl 2-Benzhydryl-5-benzylthiophene-3-carboxylate (5).** To a solution of substituted thiophene **2a** (1.0 mmol) and


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diphenylmethanol (1.2 mmol) in dichloromethane (5 mL) was added $BF_3{\cdot}Et_2O$ (5 mol %) at 0 °C, and the mixture was stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexanes) to afford compound **5** as a white solid (378 mg, 95%); mp 122−123 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.31−7.24 (m, 7H), 7.23−7.18 (m, 5H), 7.17−7.14 (m, 3H), 7.11 (s, 1H), 6.57 (s, 1H), 4.00 (s, 2H), 3.68 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.3, 156.2, 143.4, 141.5, 139.3, 128.8, 128.5 (2), 128.2, 127.7, 126.9, 126.6 (2), 51.3, 50.4, 35.9. IR (KBr): $\nu_{max}$ = 2950, 2920, 1952, 1717, 1546, 1479, 1292, 1225, 1190, 1147, 1005, 777, 696 cm$^{-1}$. MS (ESI): $m/z$ 399 (M + H)$^+$. HRMS (ESI): $m/z$ calcd for $C_{26}H_{23}O_2S$ (M + H)$^+$, 399.1413; found, 399.1417.

**Dimethyl 2,2′-((4-Nitrophenyl)methylene)bis(5-benzylthiophene-3-carboxylate) (6).** To a solution of substituted thiophene **2a** (1.0 mmol) and 4-nitrobenzaldehyde (1.2 mmol) in dichloromethane (5 mL) was added $BF_3{\cdot}Et_2O$ (20 mol %) at room temperature, and the mixture was stirred at reflux for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexanes) to afford compound **6** as a brown solid (472 mg, 79%); mp 112−114 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.12 (d, $J$ = 8.5 Hz, 2H), 7.58 (s, 1H), 7.38 (d, $J$ = 8.5 Hz, 2H), 7.33−7.28 (m, 5H), 7.20−7.17 (m, 5H), 7.13 (s, 2H), 4.02 (s, 4H), 3.71 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 162.9, 152.8, 150.2, 146.8, 142.1, 139.0, 129.3, 128.7, 128.6, 128.5, 127.1, 126.7, 123.6, 51.5, 44.8, 35.9. IR (KBr): $\nu_{max}$ = 2924, 2851, 1711, 1520, 1484, 1346, 1250, 1201, 1015, 758, 700 cm$^{-1}$. MS (ESI): $m/z$ 598 (M + H)$^+$. HRMS (ESI): $m/z$ calcd for $C_{33}H_{28}NO_6S_2$ (M + H)$^+$, 598.1352; found, 598.1354.

**Methyl 5-Benzyl-2-(*p*-tolyl)thiophene-3-carboxylate (7).** To a stirred solution of thiophene **2a** (100 mg, 0.43 mmol) in dimethylacetamide (4 mL) waere added 4-iodotoluene (92 mg, 0.43 mmol), KOAc (84 mg, 0.86 mmol) ,and $Pd(OAc)_2$ (9.6 mg, 0.043 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. The mixture was then diluted by the addition of ice cold water (15 mL), and the aqueous phase was extracted with ethylacetate (2 × 10 mL). The combined organic layer was washed with brine (25 mL), dried over $Na_2SO_4$, and the organic solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 95:05) to give **7** as a pale yellow oil (90 mg, 65%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.39−7.24 (m, 7H), 7.19 (d, $J$ = 3.0 Hz, 2H), 7.15 (s, 1H), 4.10 (s, 2H), 3.70 (s, 3H), 2.37 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 163.7, 150.1, 142.4, 139.5, 138.3, 130.4, 129.4, 128.7, 128.6, 128.6, 127.4, 126.8, 126.7, 51.4, 36.0, 21.2. IR (KBr): $\nu_{max}$ = 2921, 2853, 1717, 1633, 1461, 1375, 1257, 1188, 1081, 1014, 811, 763, 703 cm$^{-1}$. MS (ESI): $m/z$ 345 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{20}H_{18}O_2NaS$ (M + H)$^+$, 345.0919; found, 345.0918.

**Methyl 5-Benzyl-2-bromothiophene-3-carboxylate (8).** To a stirred solution of thiophene **2a** (100 mg, 0.43 mmol) in $CH_3CN$ (8 mL) was added NBS (90 mg, 0.51 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted by the addition of ice cold water (15 mL), and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (25 mL), dried over $Na_2SO_4$, and evaporated the organic solvent under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 95:05) to give **8** as a pale yellow oil (109 mg, 81%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.36−7.27 (m, 3H), 7.25−7.19 (m, 2H), 7.07 (d, $J$ = 1.5 Hz, 1H), 4.04 (s, 2H), 3.84 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 162.3, 144.6, 138.6, 130.4, 128.7, 128.5, 126.9, 126.5, 117.9, 51.7, 36.1. IR (KBr): $\nu_{max}$ = 3450, 3026, 2948, 1716, 1458, 1242, 1022, 988, 769, 698 cm$^{-1}$. MS (ESI): $m/z$ 313 (M + H)$^+$. Anal. Calcd for $C_{13}H_{11}BrO_2S$: C, 50.17; H, 3.56; S, 10.30. Found: C, 50.23; H, 3.8; S, 10.42.

**(5-Benzylthiophen-3-yl)methanol (9).** To a stirred solution of thiophene **2a** (1 g, 4.31 mmol) in $CH_2Cl_2$ (50 mL) was added DIBAL-H (25% w/v in toluene, 9.2 mL, 12.93 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. The mixture was warmed to 0 °C, quenched with aqueous saturated sodium potassium tartarate (20 mL), and the mixture was stirred for 3 h. The aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (25 mL), dried over $Na_2SO_4$, and evaporated the organic solvent under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 90:10) to give **9** (817 mg, 93%) as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.36−7.28 (m, 2H), 7.27−7.20 (m, 3H), 7.01 (d, $J$ = 1.5 Hz, 1H), 6.77 (s, 1H), 4.58 (s, 2H), 4.11 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 145.5, 142.3, 140.4, 129.0, 128.9, 126.8, 125.2, 120.8, 61.0, 36.5. IR (KBr): $\nu_{max}$ = 3028, 2900, 2873, 1602, 1493, 1453, 1019, 770, 698 cm$^{-1}$. MS (ESI): $m/z$ 205 (M + H)$^+$. Anal. Calcd for $C_{12}H_{12}OS$: C, 70.55; H, 5.92; S, 15.70. Found: C, 70.23; H, 5.99; S, 15.64.

**2-Benzyl-4-((2-bromophenoxy)methyl)thiophene (11a).** To a stirred solution of alcohol **9** (400 mg, 1.96 mmol) in $CH_2Cl_2$ (15 mL) was added $PBr_3$ (0.40 mL, 1.96 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was then quenched by the dropwise addition of saturated $NaHCO_3$ (20 mL), and the aqueous phase was extracted with dichloromethane (2 × 15 mL). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (2 × 25 mL) and brine (25 mL) and dried over $Na_2SO_4$, and the volatiles were evaporated under reduced pressure to get the bromide **10**.

To a stirred solution of bromide **10** (160 mg, 0.60 mmol) in dry DMF (3 mL) were added 2-bromophenol (102 mg, 0.60 mmol) and $K_2CO_3$ (166 mg, 1.20 mmol) at room temperature, and the mixture was stirred at 70 °C for 15 h. The reaction mixture was then diluted by the addition of ice cold water (15 mL), and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (25 mL), dried over $Na_2SO_4$, and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 97:3) to give **11a** as a pale yellow oil (112 mg, 52%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.54 (d, $J$ = 7.9 Hz, 1H), 7.35−7.18 (m, 6H), 7.16 (s, 1H), 6.92 (d, $J$ = 8.3 Hz, 1H), 6.88−6.80 (m, 2H), 5.05 (s, 2H), 4.13 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 154.9, 145.1, 140.0, 137.1, 133.3, 128.6, 128.5, 128.3, 126.5, 124.7, 122.1, 121.3, 113.9, 112.5, 67.1, 36.2. IR (KBr): $\nu_{max}$ = 2921, 1636, 1476, 1277, 1221, 1027, 754, 699 cm$^{-1}$. MS (ESI): $m/z$ 383 (M + Na)$^+$. Anal. Calcd for $C_{18}H_{15}BrOS$: C, 60.17; H, 4.21; S, 8.92. Found: C, 60.33; H, 4.12; S, 9.02.

***N*-((5-Benzylthiophen-3-yl)methyl)-*N*-(2-iodophenyl)-4-methylbenzenesulfonamide (11b).** To a stirred solution of bromide **10** (200 mg, 0.75 mmol) in dry DMF (4 mL) were added 2-iodo (*N*Ts) aniline (276 mg, 0.75 mmol) and $K_2CO_3$ (260 mg, 1.87 mmol) at room temperature, and the mixture was stirred at the same temperature for 3 h. Next, the mixture was diluted by the addition of ice cold water (15 mL), and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (25 mL), dried over $Na_2SO_4$, and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 93:07) to give **11b** as a pale yellow oil (289 mg, 69%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.81 (dd, $J$ = 1.3 Hz, 1H), 7.63 (d, $J$ = 8.3 Hz, 2H), 7.35−7.10 (m, 8H), 6.95 (dt, $J$ = 7.7, 1.5 Hz, 1H), 6.79 (dd, $J$ = 1.5 Hz, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 4.63 (s, 2H), 4.01 (s, 2H), 2.44 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 143.5, 144.2, 140.9, 140.2, 140.1, 136.6, 135.5, 131.3, 129.7, 129.4, 128.4, 128.1, 126.9, 126.4, 123.6, 124.4, 119.0, 102.5, 50.0, 36.0, 21.5. IR (KBr): $\nu_{max}$ = 2921, 2851, 1464, 1348, 1219, 1160, 1089, 809, 772, 713, 568 cm$^{-1}$. MS (ESI): $m/z$ 582 (M + Na)$^+$. HRMS (ESI): $m/z$ calcd for $C_{25}H_{23}INO_2S_2$ (M + H)$^+$, 560.0209; found, 560.0229.

**General Procedure for the Preparation of Compounds 12a and 12b.** To a stirred solution of compound **11a** or **11b** (0.17 mmol)


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in dimethyleacetamide (4 mL) were added KOAc (0.34 mmol) and $Pd(OAc)_2$ (0.017 mmol) at room temperature, and the mixture was stirred at 80 °C for 3 h. The mixture then was cooled to room temperature, diluted by the addition of ice cold water (15 mL), and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (25 mL), dried over $Na_2SO_4$, and evaporated under reduced pressure. Residue was purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding product **12a** or **12b**.

**2-Benzyl-4*H*-thieno[3,2-*c*]chromene (12a).** 37 mg, 78%; pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.40−7.22 (m, 5H), 7.20−7.14 (m, 1H), 7.13−7.03 (m, 1H), 6.94−6.83 (m, 2H), 6.51 (s, 1H), 5.19 (s, 2H), 4.13 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 151.7, 143.9, 139.8, 131.2, 128.7, 128.6, 128.5, 128.2, 126.6, 125.2, 122.5, 122.4, 121.7, 116.3, 66.3, 36.3. IR (KBr): $\nu_{max}$ = 2922, 2851, 1633, 1475, 1217, 1031, 756, 697 cm$^{-1}$. MS (ESI): *m*/*z* 277 $(M - H)^+$. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{13}OS$ $(M - H)^+$, 277.0681; found, 277.0689.

**2-Benzyl-5-tosyl-4,5-dihydrothieno[3,2-*c*]quinoline (12b).** 62 mg, 85%; white solid; mp 131−132 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.77−7.73 (m, 1H), 7.41−7.27 (m, 4H), 7.25−7.16 (m, 3H), 7.09−7.03 (m, 1H), 6.97−6.93 (m, 2H), 6.71−6.64 (m, 2H), 6.52 (s, 1H), 4.81 (s, 2H), 4.01 (s, 2H), 2.13 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 144.6, 142.8, 139.9, 134.4, 133.1, 132.6, 131.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.5, 126.9, 126.8, 126.7, 123.3, 122.8, 46.4, 36.4, 21.3. IR (KBr): $\nu_{max}$ = 2924, 2854, 1685, 1637, 1599, 1488, 1450, 1342, 1161, 1090, 1057, 854, 764, 743, 699, 665, 565 cm$^{-1}$. MS (ESI): *m*/*z* 454 $(M + Na)^+$. HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}NO_2S_2$ $(M + H)^+$, 432.1086; found, 432.1093.

## ■ ASSOCIATED CONTENT

### Supporting Information

Copies of $^1$H and $^{13}$C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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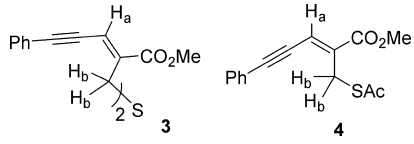


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