An Aquatic Pseudo-Four-Component Reaction for the Synthesis of Highly Substituted Thiophenes

Hassan Zali-Boeini,* Maryam Ghani

Department of Chemistry, University of Isfahan, 81746-73441, Isfahan, Iran
Fax +98(311)6689732; E-mail: h.zali@chem.ui.ac.ir

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Abstract: A novel and simple procedure was developed for the construction of fully substituted thiophenes. A series of α-haloacetophenone derivatives were converted into fully substituted thiophenes by treatment with sodium sulfide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene and sodium iodide in aqueous ethanol under aerobic conditions. A mechanism for the reaction is proposed.

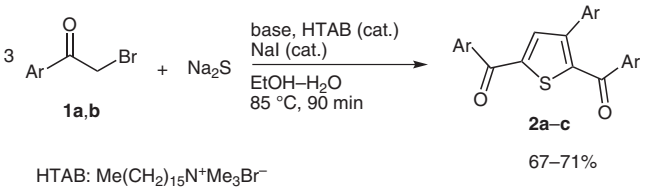
Key words: sulfur, heterocycles, alkyl halides, coupling, dehydrogenation, multicomponent reactions

Thiophenes are undoubtedly an important class of sulfur heterocycles, and their synthesis has attracted a great deal of research because of their presence in natural products,[1] conducting polymers,[2] and hole-transport materials for organic light-emitting diodes,[3] and their use in medicinal chemistry as isosteric replacements for the phenyl group.[4]

The most general method for the preparation of highly substituted thiophenes is the Gewald method, in which elemental sulfur reacts with a molar equivalent of an activated acetonitrile and a carbonyl compound in the presence of a suitable base.[5] Another route to fully substituted thiophenes, known as the Hinsberg method, relies on the condensation reaction between a diketone and a sulfide containing reactive methylene groups.[6] We and other research groups have previously shown that a one-pot thio-Claisen reaction and a ring closure of thioacetomorpholides with propargyl bromide leads to trisubstituted thiophenes via an α-allenyl thioacetomorpholide intermediate.[7] We have also reported an efficient method for the synthesis of fully substituted thiophenes that is based on the reaction between thioacetomorpholides and α-bromoacetophenone derivatives.[8]

In continuation of our research in this area, we report a new, one-pot, convenient route to fully substituted thiophenes through the reaction of α-haloacetophenone derivatives with sodium sulfide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in aqueous ethanol as the reaction medium.

We found that when we treated an α-bromoacetophenones **1** with sodium sulfide in aqueous ethanol as the solvent in the presence of a base, a phase-transfer catalyst (*N*,*N*,*N*-trimethylhexadecylammonium bromide; HTAB), and a catalytic amount of sodium iodide at 85 °C, we obtained the corresponding trisubstituted thiophene **2** in a good yield (67–71%) (Scheme 1).



Scheme 1 Synthesis of trisubstituted thiophenes

At the start of our study, we dissolved 2-bromo-1-(4-bromophenyl)ethanone (**1a**; 3 mmol) as a model compound in *N*,*N*-dimethylformamide and treated the solution with 5 M aqueous sodium sulfide (0.22 mL) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene as base and a catalytic amount of HTAB at 85 °C. The reaction proceeded sluggishly with the formation of various tarry and colored materials together with small amounts of the thiophene derivative **2a** (33%). To optimize our reaction conditions, we examined the effects of various solvents and bases on the reaction of dibromo ketone **1a** with 5 M sodium sulfide solution at various temperatures. The results of this study are summarized in Table 1.

Table 1 Effects of Various Solvents, Bases, and Temperatures on the Synthesis of Thiophene **2a**

Entry	Solvent	Base	Yield (%)	
			At 85 °C	At 110 °C[a]
1	DMF	K_2CO_3	22	31
2	DMF	DBU	33	32
3	DMF	Et_3N	<5	11
4	MeCN	K_2CO_3	25	27
5	MeCN	DBU	42	35
6	EtOH–H_2O[b]	K_2CO_3	29	31
7	EtOH–H_2O[b]	DBU	71	66
8	H_2O[c]	DBU	38[c]	–

[a] Colored or tarry byproducts were also formed.
[b] In the presence of HTAB (5.5 mol%) and NaI (10 mol%).
[c] Reflux conditions.

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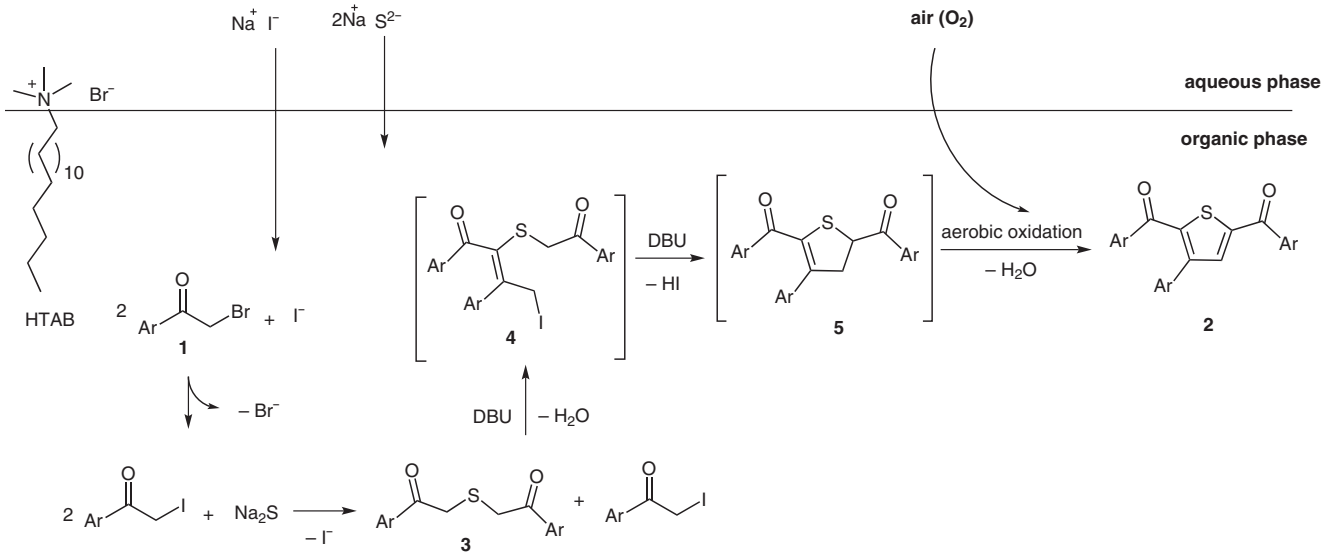


Scheme 2 Proposed mechanism for the formation of substituted thiophenes

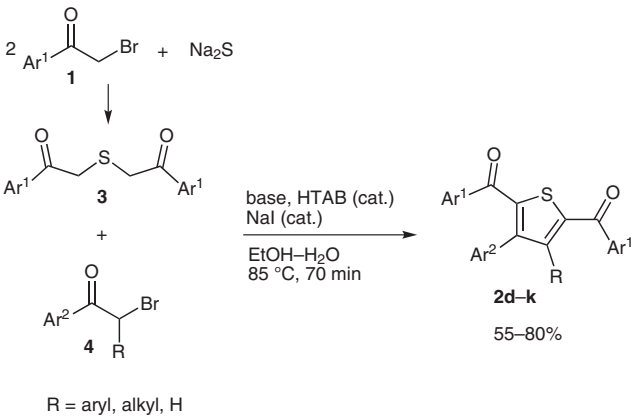
As is clear from Table 1, the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base in aqueous ethanol containing HTAB (5.5 mol%) and sodium iodide (10 mol%) as the catalyst system at 85 °C provided the best conditions for obtaining a good yields of the highly substituted thiophene **2a**. We also showed that the reaction proceeded better in the presences of catalytic amount of sodium iodide (10 mol%), because the reaction of **1a** with sodium sulfide under identical conditions in the absence of sodium iodide resulted in a marked decrease in the yield of product **2a** (57%).

A mechanism for the reaction has been proposed and is shown in Scheme 2.

It seems likely that the α-bromoacetophenone **1** undergoes halogen exchange to form the corresponding iodo derivative, which reacts with sodium sulfide to form the sulfide **3**. Condensation of **3** with a second molecule of **1** gives intermediate **4**, which undergoes elimination of hydrogen iodide to form intermediate **5**. Aerobic oxidation of this intermediate leads to the corresponding thiophene **2**. Note that our attempts to isolate intermediates **4** and **5** were unsuccessful, whereas intermediate **3** could be isolated.

The proposed mechanism implies that the presence of air is necessary for the final step of the reaction to proceed. Interestingly, when a stream of air (or oxygen) was bubbled through the reaction mixture, the product yield was not significantly altered. The use of manganese dioxide as a mild oxidant for oxidative dehydrogenation produced only very slightly higher yields of the product than those obtained in the original form of the reaction. Unfortunately, we failed in our attempts to produce trisubstituted thiophenes under our optimized conditions by using α-chloroacetophenone derivatives as the α-halo ketones.

It initially appeared that only trisubstituted thiophenes bearing identical aryl groups could be prepared by this approach. Fortunately, however, we found that trisubstituted and fully substituted thiophenes bearing different aryl groups could prepared by the treatment under the optimized reaction conditions of an α-substituted α-bromoacetophenone **4** with a sulfide **3**, formed *in situ* by reaction of two equivalents of an α-bromoacetophenone **1** with sodium sulfide (Scheme 3).



Scheme 3 Two-step preparation of tri- and tetrasubstituted thiophenes bearing different aryl groups

We confirmed the generality of our method by the successful synthesis of eleven diverse thiophene derivatives in moderate-to-good yields (58–80%) under rather mild conditions (Table 2).

In conclusion, we have developed a novel, general, and efficient method for the construction of fully substituted thiophenes from α-bromoacetophenone derivatives as readily available starting materials. The reaction occurs under reasonably mild conditions in aqueous ethanol as a nonpolluting, safe, and green medium.

Table 2 Efficient Preparation of Various Highly Substituted Thiophenes

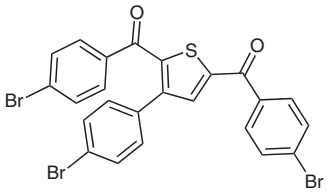
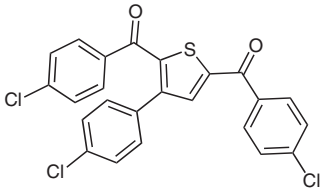
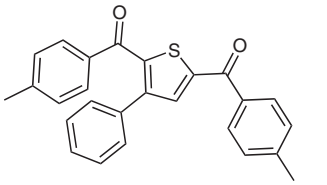
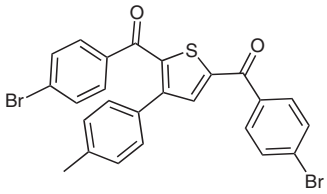
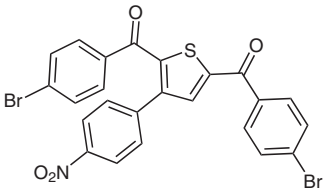
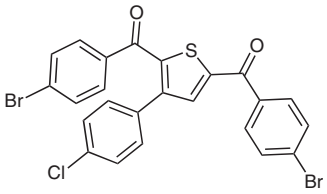
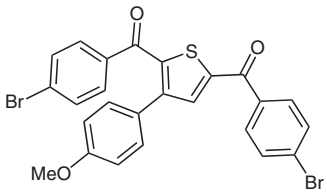
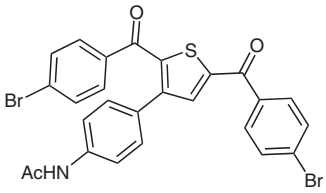
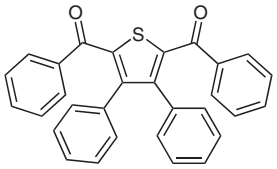
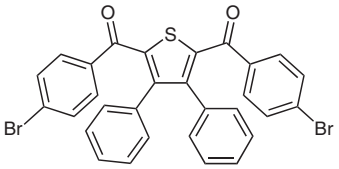
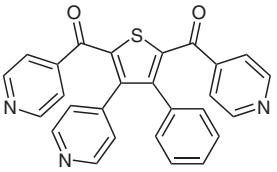
Entry	Ar^1	Ar^2	Ar^3	R	Product[a]	Yield (%)[b]
1	4-BrC_6H_4	4-BrC_6H_4	4-BrC_6H_4	H	 **2a**	71
2	4-ClC_6H_4	4-ClC_6H_4	4-ClC_6H_4	H	 **2b**	67
3	4-Tol	4-Tol	Ph	H	 **2c**[9]	63
4	4-BrC_6H_4	4-BrC_6H_4	4-Tol	H	 **2d**	69
5	4-BrC_6H_4	4-BrC_6H_4	4-$O_2NC_6H_4$	H	 **2e**	77
6	4-BrC_6H_4	4-BrC_6H_4	4-ClC_6H_4	H	 **2f**	80
7	4-BrC_6H_4	4-BrC_6H_4	4-$MeOC_6H_4$	H	 **2g**	66

Table 2 Efficient Preparation of Various Highly Substituted Thiophenes (continued)

Entry	Ar^1	Ar^2	Ar^3	R	Product[a]	Yield (%)[b]
8	4-BrC_6H_4	4-BrC_6H_4	4-$AcNHC_6H_4$	H	 **2h**	58
9	Ph	Ph	Ph	Ph	 **2i**[9]	65
10	4-BrC_6H_4	4-BrC_6H_4	Ph	Ph	 **2j**	67
11	4-pyridyl	4-pyridyl	4-pyridyl	H	 **2k**[9]	61

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and IR spectroscopy.
[b] Isolated yields.

All reagents, unless otherwise stated, were used as received from commercial suppliers. TLC was performed on aluminum plates coated with UV-active silica gel (silica gel 60 F_{254}). Flash chromatography was performed on silica gel (60 Å, 230–400 mesh) with elution by reagent-grade solvents. NMR spectra were recorded at 400 MHz (^{1}H NMR) or 100 MHz (^{13}C NMR) on a Bruker Avance 400 spectrometer and are referenced to residual solvent. High-resolution mass spectra were obtained with a ZAB high-resolution mass spectrometer (Vacuum Generators). IR spectra were recorded on a PerkinElmer Spectrum 1000 spectrophotometer.

Trisubstituted Thiophenes 2; General Procedure (Method A)
5 M aq Na_2S (0.22 ml, 1.1 mmol) was added slowly to a stirred warm (50 °C) soln of α-bromoacetophenone **1** (3 mmol) in EtOH (10 mL) containing NaI (15 mg, 0.1 mmol) and HTAB (20 mg, 0.055 mmol). The mixture was stirred for 20 min before DBU (2 mmol, 0.30 mL) was added. The mixture was then heated to 85 °C with vigorous stirring for a further 70 min, cooled to r.t., and poured into cold H_2O (10 mL). The precipitated gummy product was extracted with EtOAc (15 mL). The EtOAc soln was concentrated under vacuum, and the residue was purified by flash column chromatography [silica gel, EtOAc–hexane (1:5)].

Tri- and Tetrasubstituted Thiophenes 2; General Procedure (Method B)
Diketo sulfide **3** was prepared in situ by treatment of a first α-bromoacetophenone derivative **1** (2 mmol) with 5 M aq Na_2S, (0.22 mL, 1.1 mmol) in EtOH (15 mL) at 85 °C. To the resulting soln were added NaI (15 mg, 0.1 mmol), HTAB (20 mg, 0.055 mmol), and a second α-bromoacetophenone **4** (1.1 mmol). DBU (2 mmol, 0.3 ml) was then added and the mixture was vigorously stirred at 85 °C for 70 min. The thiophene product was isolated and purified as described in Method A.

[3-(4-Bromophenyl)thiene-2,5-diyl]bis[(4-bromophenyl)methanone] (2a)
White solid; yield: 430 mg (71%); mp 178.2 °C.

IR (KBr): 3122, 2847, 1642, 1508, 1131, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.0 Hz, 2 H), 7.72–7.67 (m, 3 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.20–7.31 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.5, 186.5, 144.8, 144.6, 142.4, 136.0, 135.4, 135.3, 133.2, 132.1, 131.8, 131.7, 131.2, 130.8, 130.4, 128.9, 128.3, 122.9.

HRMS (EI): *m/z* calcd for $C_{24}H_{13}Br_3O_2S$: 605.1358; found: 605.1349.

[3-(4-Chlorophenyl)thiene-2,5-diyl]bis[(4-chlorophenyl)methanone](2b)
White solid; yield: 316 mg (67%); mp 178.2 °C.

IR (KBr): 3122, 2847, 1642, 1508, 1131, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.38 (s, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.4, 186.9, 144.8, 144.6, 142.6, 135.9, 135.4, 135.3, 133.2, 132.1, 131.8, 131.7, 131.2, 130.8, 130.4, 128.9, 128.3, 122.9.

HRMS (EI): *m/z* calcd for $C_{24}H_{13}Cl_3O_2S$: 471.7828; found: 471.7823.

(3-Phenylthiene-2,5-diyl)bis[(4-tolyl)methanone] (2c)
White solid; yield: 250 mg (63%); mp 181 °C.

IR (KBr): 3110, 2925, 1648, 1502, 1120, 831 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.8 Hz, 2 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.42–7.40 (m, 3 H), 7.15 (s, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 2.23 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.4, 186.4, 144.8, 144.5, 142.4, 140.1, 139.7, 135.5, 135.4, 134.9, 134.7, 132.8, 131.2, 130.7, 130.1, 129.1, 128.8, 128.7, 32.1, 31.8.

HRMS (EI): *m/z* calcd for $C_{26}H_{20}O_2S$: 396.5008; found: 396.5015.

[3-(4-Tolyl)thiene-2,5-diyl]bis[(4-bromophenyl)methanone] (2d)
White solid; yield: 373 mg (69%); mp 162.4 °C.

IR (KBr): 3120, 2845, 1640, 1507, 1123, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.71 (s, 1 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 2.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.5, 186.6, 144.8, 144.6, 142.3, 135.8, 135.4, 135.3, 133.2, 132.1, 131.9, 131.7, 131.2, 130.8, 130.4, 128.9, 128.3, 122.9, 30.9.

HRMS (EI): *m/z* calcd for $C_{25}H_{16}Br_2O_2S$: 540.2663; found: 540.2655.

[3-(4-Nitrophenyl)thiene-2,5-diyl]bis[(4-bromophenyl)methanone] (2e)
Light-yellow solid; yield: 440 mg (77%); mp 188 °C.

IR (KBr): 3100, 2915, 1645, 1500, 1123, 830 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 7.61 (s, 1 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.05 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR(100 MHz, $CDCl_3$): δ = 191.5, 189.6, 144.8, 144.6, 142.3, 135.8, 135.4, 135.3, 133.2, 132.1, 131.8, 131.7, 131.2, 130.8, 130.4, 128.9, 128.3, 122.9.

HRMS (EI): *m/z* calcd for $C_{24}H_{13}Br_2NO_4S$: 571.2373; found: 571.2365.

[3-(4-Chlorophenyl)thiene-2,5-diyl]bis[(4-bromophenyl)methanone] (2f)
White solid; yield: 448 mg (80%); mp 179 °C.

IR (KBr): 3092, 2905, 1655, 1510, 1113, 825 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.8 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.71 (s, 1 H), 7.59 (d, *J* = 8.8 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.5, 186.6, 144.8, 144.6, 142.3, 135.8, 135.4, 135.3, 133.2, 132.1, 131.8, 131.7, 131.2, 130.8, 130.4, 128.9, 128.3, 122.9.

HRMS (EI): *m/z* calcd for $C_{24}H_{13}Br_2ClO_2S$: 560.6848; found: 560.6843.

[3-(4-Methoxyphenyl)thiene-2,5-diyl]bis[(4-bromophenyl)methanone] (2g)
White solid; yield: 367 mg (66%); mp 167.5 °C.

IR (KBr): 3090, 2901, 1657, 1500, 1106, 829 cm^{-1}.

^{1}H NMR(400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 7.61 (s, 1 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5, 184.6, 144.8, 144.6, 142.3, 135.8, 135.4, 135.3, 133.2, 132.1, 131.8, 131.7, 131.2, 130.8, 130.4, 128.9, 128.3, 123.0, 47.7.

HRMS (EI): *m/z* calcd for $C_{25}H_{16}Br_2O_3S$: 556.2657; found: 556.2650.

***N*-{4-[2,5-Bis(4-bromobenzoyl)-3-thienyl]phenyl}acetamide (2h)**
Off-white solid; yield: 338 mg (58%); mp 164.5 °C.

IR (KBr): 3093, 2898, 1649, 1503, 1125, 830 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 1 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.15 (s, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.5, 186.6, 169.9, 144.8, 144.6, 142.3, 135.8, 135.4, 135.3, 133.2, 132.1, 131.8, 131.7, 131.2, 130.8, 130.4, 128.9, 128.3, 122.9, 35.9.

HRMS (EI): *m/z* calcd for $C_{26}H_{17}Br_2NO_3S$: 583.2911; found: 583.2906.

(3,4-Diphenylthiene-2,5-diyl)bis[(4-bromophenyl)methanone] (2j)
White solid; yield: 403 mg (67%); mp 176 °C.

IR (KBr): 3098, 2905, 1651, 1507, 1126, 829 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–2.92 (m, 9 H), 7.38–7.51 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.8, 138.7, 135.3, 134.0, 132.7, 129.1, 129.0, 128.9, 128.8, 128.5, 127.2.

HRMS (EI): *m/z* calcd for $C_{30}H_{18}Br_2O_2S$: 602.3357; found: 602.3349.

(3-Pyridin-4-ylthiene-2,5-diyl)bis(pyridin-4-ylmethanone) (2k)
Light-yellow solid; yield: 227 mg (61%); mp 169 °C.

IR (KBr): 3100, 2911, 1657, 1509, 1131, 834 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (d, *J* = 8.8 Hz, 2 H), 8.71 (s, 1 H), 8.67 (d, *J* = 8.8 Hz, 2 H), 8.54 (d, *J* = 8.8 Hz, 2 H), 8.30 (d, *J* = 8.8 Hz, 2 H), 8.20–8.26 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.5, 189.6, 154.8, 152.3, 145.8, 145.4, 143.2, 142.1, 141.8, 141.5, 140.8, 140.4, 139.3, 138.9, 138.8.

HRMS (EI): *m/z* calcd for $C_{21}H_{13}N_3O_2S$: 371.4118; found: 371.4125.

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