A New [2+2+1] Heterocyclization for the Synthesis of 2,3,5-Trisubstituted Thiophenes under Microwave Irradiation

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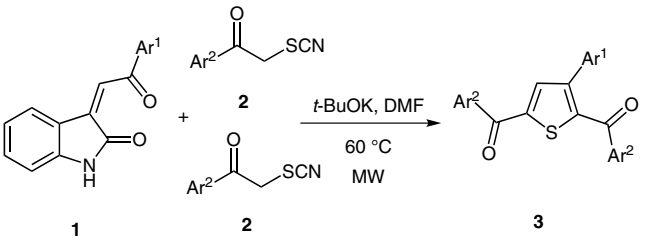
Abstract: A new three-component strategy for the efficient synthesis of 2,3,5-trisubstituted thiophene derivatives through a [2+2+1] heterocyclization between 3-(2-aryl-2-oxoethylidene)-2-oxindoles and α-thiocyanato ketones under microwave irradiation is described. The bond-forming efficiency, accessibility, and generality of this synthesis make it highly valuable to assemble thiophene scaffolds.

Key words: heterocyclization, substituted thiophene, three-component reactions, α-thiocyanato ketone, 3-(2-aryl-2-oxoethylidene)-2-oxindole

Thiophene derivatives are undoubtedly an important class of sulfur heterocycles, possessing a wide range of biological activities such as anticancer activity[1]and protein inhibition.[2] They are also used as conducting polymers[3] and photochromic molecular switches.[4] The incorporation of the thiophene moiety into organic semiconducting materials is a highly active topic.[5] Thiophenes and their derivatives are arguably the most important monomers for semiconducting polymers[6] and oligomers,[5a,7] which have widespread utility in the preparation of plastic solar cells,[6a,8] and organic field effect transistors.[5a,7a,c,9] Owing to their unique biological and chemical characteristics, some modern methodologies for the construction of polysubstituted thiophenes have been developed. Most of them involves the Gewald method,[10] the Hinsberg synthesis,[11] thio-Claisen rearrangement reaction,[12] cyclization of α-bromoacetophenone derivatives[12d,13] or 1-mercapto-3-yn-2-ols,[14] [3+2]-self annulation of bis(aroylmethyl) sulfide,[15] Fiesselmann thiophene synthesis,[16] and other methods.[17] Despite these methodologies, an exploration of a facile protocol for the direct formation of thiophenes, and their efficient multifunctionalization in particular, is highly desirable.

Multicomponent domino reactions (MDRs) have gained considerable popularity in the synthetic community. They provide efficient access to complex molecules from readily available starting materials.[18] They also form an ideal platform for the rapid generation of both complexity and diversity in a collection of compounds with predefined functionality, such as ligands for catalysis or bioactive compounds. Recently, we have engaged in the development of new multicomponent domino reactions that can provide easy access to new core structures of chemical and pharmaceutical interest.[19] As a result of our continued efforts on these domino processes, herein we disclose a new base-promoted [2+2+1] cyclization of 3-(2-aryl-2-oxoethylidene)-2-oxindoles **1** and α-thiocyanato ketones **2** under microwave irradiation (MW) yielding 2,3,5-trisubstituted thiophene derivatives **3** (Scheme 1). The notable feature of the present domino strategy is that, it demonstrates the formation of a thiophene skeleton with the concomitant achievement of polyfunctionalization residing at different sites of the thiophene unit. This is readily achieved in a domino fashion involving [3+2] cycloaddition, ring-opening of in situ generated thiophenes, S_N2 reaction, and Knoevenagel condensation sequence, forming up to three σ-bonds in a one-pot operation from common and preformed starting materials (Schemes 1 and 2). This strategy is very useful in synthetic organic chemistry.



Scheme 1 Synthesis of 2,3,5-trisubstituted thiophenes

α-Thiocyanato ketones have attracted great attention as interesting intermediates due to their easy transformation into highly valuable molecules that can be applied to both organosulfur and heterocyclic chemistry.[20] Our strategy for the synthesis of 2,3,5-trisubstituted thiophenes is through the reaction of 3-(2-aryl-2-oxoethylidene)-2-oxindoles **1** and α-thiocyanato ketones **2**. Our initial experiments focused on the three-component domino reaction of 3-[2-(4-fluorophenyl)-2-oxoethylidene]-1,3-dihydro-2*H*-indol-2-one (**1a**) and 1-(4-chlorophenyl)-2-thiocyanatoethanone (**2a**) in a ratio of 1:2 using a wide range of readily available base promoters (e.g., Et_3N, K_2CO_3, Cs_2CO_3, NaOH, and NaOEt) at 60 °C under microwave irradiation (Table 1). The reaction scarcely proceeded to provide the expected product **3a** in the presence of triethylamine at 60 °C (entry 1). Very poor yields (24% and 27%) of product **3a** were observed when potassium or cesium carbon-

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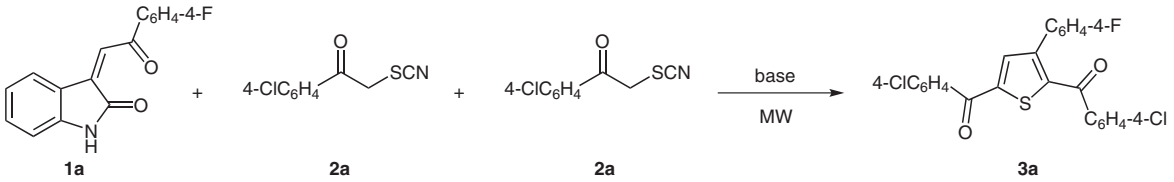
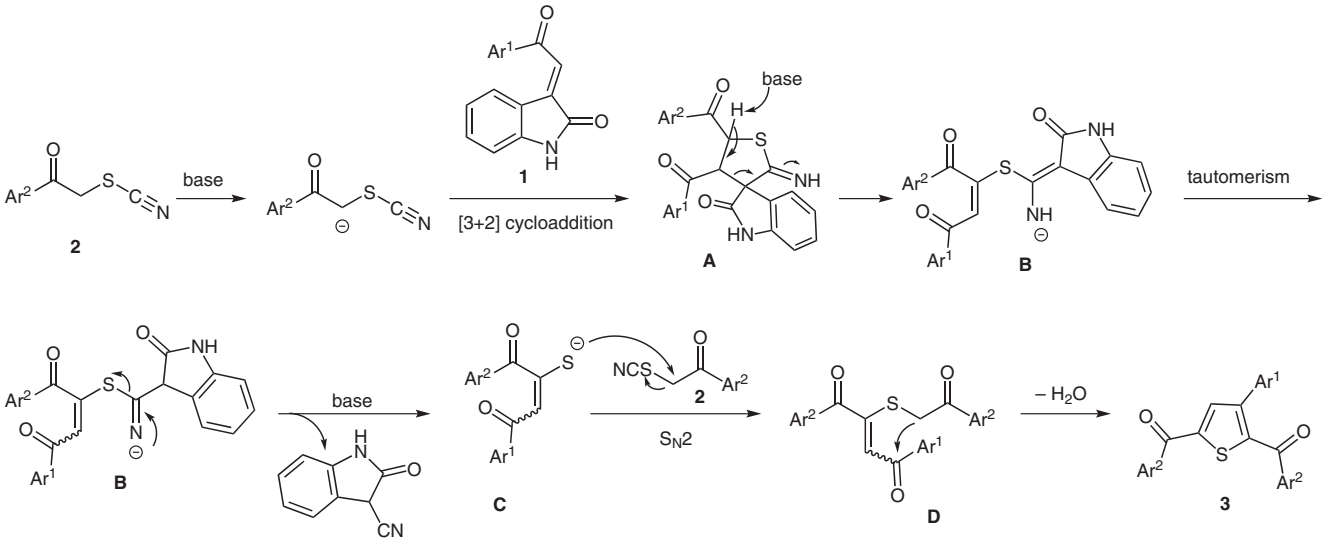
ate were used as base promoters (entries 2 and 3). The reaction promoted by sodium hydroxide or sodium ethoxide generated a slightly higher yield of **3a** (entries 4 and 5). Gratifyingly, the identical reaction performed in *N*,*N*-dimethylformamide using potassium *tert*-butoxide as a base promoter provided a higher yield (67%) of product **3a** (entry 6). Subsequently, different solvents were screened, and it was found that the reaction worked more efficiently in *N*,*N*-dimethylformamide than in acetonitrile or ethanol (entries 7 and 8). Further increases in the reaction temperature failed to improve the yield of the desired product **3a** (entries 9 and 10).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Base	Solvent	Temp (°C)	Time (min)	Yield[b] (%)
1	Et_3N	DMF	60	15	trace
2	K_2CO_3	DMF	60	15	17
3	Cs_2CO_3	DMF	60	15	24
4	NaOH	DMF	60	15	38
5	NaOEt	DMF	60	15	43
6	*t*-BuOK	DMF	60	15	67
7	*t*-BuOK	MeCN	60	15	trace
8	*t*-BuOK	EtOH	60	15	23
9	*t*-BuOK	DMF	80	15	60
10	*t*-BuOK	DMF	100	15	51

[a] Reaction conditions: molar ratio **1**/**2** (1:2), base (1.0 equiv).
[b] Isolated yield was based on substrate **1**.



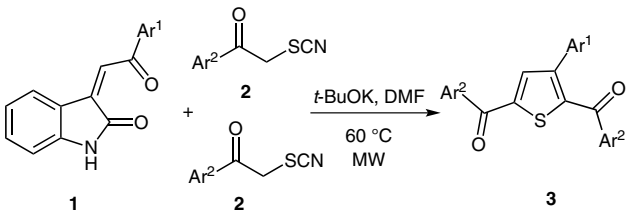
Scheme 2 Proposed mechanism for the formation of products **3**

With the above optimized conditions in hand, we then proceeded to explore the substrate diversity of this potassium *tert*-butoxide promoted domino reaction of 3-(2-aryl-2-oxoethylidene)-2-oxindoles **1** and α-thiocyanato ketones **2**. All the reactions proceeded efficiently and afforded the desired products in moderate to good yields. The results are presented in Table 2. The substituents on the phenyl ring of α-thiocyanato ketones did not hamper the reaction process. Reactions of chloro-, bromo-, methoxy-, or nitro-substituted α-thiocyanato ketones **2** with **1** worked well to provide the desired products in good yields (Table 2). It was found that there was a little difference between the substitution effect of an electron-donating group and that of an electron-withdrawing group, although it seemed as if electron-donating substituents favored this reaction more than strong electron-withdrawing substituents such as the nitro group. Subsequently, the scope of this interesting transformation with different 3-(2-aryl-2-oxoethylidene)-2-oxindoles was investigated (Table 2). Several different substituents on the aryl ring were compared and substituents bearing electron-withdrawing (4-fluoro, **1a**; 4-chloro, **1b**), or electron-donating (4-methyl, **1d**; 4-methoxy, **1e**; 3,4-dimethoxy, **1f**) groups were found to be suitable for this domino reaction. Moreover, naphthalen-2-yl substituted 2-oxindoles **1g** were also converted into the corresponding naphthalen-2-yl-substituted thiophenes **3r** and **3t** in 67% and 69% yields, respectively. The tolerance of functionalities such as chloro and bromo in this protocol provides the opportunity for various further chemical manipulations in the products. It is worth mentioning that this protocol provides a straightforward pathway to synthesize polysubstituted thiophenes with concomitant achievement of C2, C5 bis-aroylations, and C3-arylation in a one-pot operation. Moreover, it also gives a new example for the construction of polysubstituted thiophene motif in an economical fashion, providing a valuable strategy to discover new bioactive compounds.

In all cases, the products can be precipitated out after the reaction mixture was poured into cold water and was neutralized by diluted acidic solution. The structural elucidation of the products was determined from its IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra. The structure of compound **3i** was unambiguously confirmed by X-ray analysis (Figure 1).

On the basis of experimental results, a plausible reaction mechanism for this domino reaction is postulated in Scheme 2. α-Thiocyanato ketones **2** deprotonated by potassium *tert*-butoxide undergo [3+2] cycloaddition of 3-(2-aryl-2-oxoethylidene)-2-oxindoles **1** to convert them into intermediate **A**, followed by base-promoted ring opening of in situ generated thiophenes **A** to yield intermediate **B**. The subsequent tautomerism and elimination reaction affords intermediate **C**; 2-oxo-2,3-dihydro-1*H*-indole-3-carbonitrile was detected by gas chromatography–mass spectrometry (GC-MS) analysis. Then, an S_N2-type reaction between intermediate **C** and α-thiocyanato ketone **2** occurs, affording intermediate **D**, which is trans-

Table 2 Domino Synthesis of Substituted Thiophenes **3**[a]



Entry	Product	Ar^1	Ar^2	Yield[b] (%)
1	**3a**	4-FC_6H_4 (**1a**)	4-ClC_6H_4 (**2a**)	67
2	**3b**	4-FC_6H_4 (**1a**)	4-BrC_6H_4 (**2b**)	75
3	**3c**	4-ClC_6H_4 (**1b**)	4-ClC_6H_4 (**2a**)	77
4	**3d**	4-ClC_6H_4 (**1b**)	4-BrC_6H_4 (**2b**)	79
5	**3e**	4-ClC_6H_4 (**1b**)	Ph (**2c**)	69
6	**3f**	4-ClC_6H_4 (**1b**)	4-$MeOC_6H_4$ (**2d**)	72
7	**3g**	Ph (**1c**)	4-ClC_6H_4 (**2a**)	62
8	**3h**	Ph (**1c**)	4-BrC_6H_4 (**2b**)	73
9	**3i**	4-MeC_6H_4 (**1d**)	4-ClC_6H_4 (**2a**)	67
10	**3j**	4-MeC_6H_4 (**1d**)	3-ClC_6H_4 (**2e**)	55
11	**3k**	4-MeC_6H_4 (**1d**)	4-BrC_6H_4 (**2b**)	78
12	**3l**	4-MeC_6H_4 (**1d**)	4-$MeOC_6H_4$ (**2d**)	70
13	**3m**	4-MeC_6H_4 (**1d**)	4-$O_2NC_6H_4$ (**2f**)	51
14	**3n**	4-$MeOC_6H_4$ (**1e**)	4-ClC_6H_4 (**2a**)	68
15	**3o**	4-$MeOC_6H_4$ (**1e**)	3-ClC_6H_4 (**2e**)	66
16	**3p**	4-$MeOC_6H_4$ (**1e**)	4-BrC_6H_4 (**2b**)	74
17	**3q**	3,4-$(MeO)_2C_6H_3$ (**1f**)	3-ClC_6H_4 (**2e**)	55
18	**3r**	naphthalen-2-yl (**1g**)	4-ClC_6H_4 (**2a**)	67
19	**3s**	naphthalen-2-yl (**1g**)	4-BrC_6H_4 (**2b**)	69

[a] Reaction conditions: molar ratio **1**/**2** (1:2), *t*-BuOK (1.0 equiv), DMF (1.5 mL), 60 °C.
[b] Isolated yield was based on the substrates **1**.

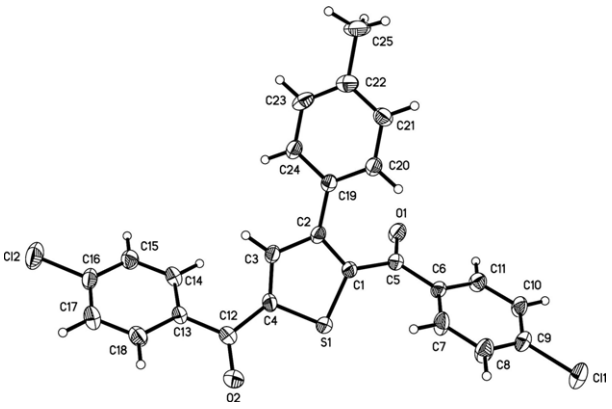


Figure 1 ORTEP drawing of **3i**[21]

formed into final product **3** through a Knoevenagel condensation reaction.

In conclusion, we have developed a new [2+2+1] heterocyclization between 3-(2-aryl-2-oxoethylidene)-2-oxindoles and α-thiocyanato ketones as an alternative method for the efficient synthesis of 2,3,5-trisubstituted thiophenes. This domino strategy allows us to build blocks of thiophene derivatives with a wide variety of substituents. The relatively mild reaction conditions, selective modification of thiophene skeleton, and high bond-forming efficiency (BFE) make this domino strategy highly viable for future applications. A detailed investigation of the mechanism and the applications of this reaction are currently in progress.

Microwave irradiation was carried out with initiator from Biotage Company, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on an FT-IR-Tensor 27 spectrophotometer in KBr pellets. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-Q II, HRMS/MS instrument (Bruker). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

[3-(4-Fluorophenyl)thiophene-2,5-diyl]bis[(4-chlorophenyl)methanone] (3a); Typical Procedure

3-[2-(4-Fluorophenyl)-2-oxoethylidene]-1,3-dihydro-2*H*-indol-2-one (**1a**, 1 mmol, 0.267 g, 1.0 equiv) was introduced into a 10-mL Initiator^{TM} reaction vial, 1-(4-chlorophenyl)-2-thiocyanatoethanone (**2a**, 2.0 mmol, 0.422 g, 2.0 equiv), *t*-BuOK (1.0 mmol, 0.112 g, 1.0 equiv), and DMF (1.5 mL) were then successively added. Subsequently, the reaction vial was closed and then pre-stirred for 20 s. The mixture was irradiated (time: 15 min, temp: 60 °C; absorption level: high; fixed hold time) until TLC (petroleum ether–EtOAc, 3:1) revealed that conversion of the starting material **1a** was complete. The mixture was then cooled to r.t. and diluted with cold H_2O (20 mL). The solid product was collected by Büchner filtration and it was purified by recrystallization (95% EtOH) to afford pure **3a** as a white solid; yield: 0.305 g (67%); mp 152–153 °C.

IR (KBr): 1650, 1586, 1504, 1365, 1287, 1266, 1219, 1173, 1088 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.93 (s, 1 H, CH), 7.69–7.63 (m, 4 H, H_{Ar}), 7.42–7.32 (m, 4 H, H_{Ar}), 7.10–7.06 (m, 2 H, H_{Ar}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.8, 186.7, 162.4 (J_{CF}^1 = 244.7 Hz), 145.3, 144.9, 142.1, 138.7, 138.6, 137.1, 135.5, 135.3, 131.8 (J_{CF}^2 = 8.8 Hz), 131.7, 131.4, 130.9 (J_{CF}^3 = 3.2 Hz), 129.5, 129.0, 115.7 (J_{CF}^4 = 21.6 Hz).

HRMS (EI): m/z [M]$^+$ calcd for $C_{24}H_{13}Cl_2FO_2S$: 453.9997; found: 454.0023.

[3-(4-Fluorophenyl)thiophene-2,5-diyl]bis[(4-bromophenyl)methanone] (3b)

White solid; yield: 0.406 g (75%); mp 150–151 °C.

IR (KBr): 1649, 1583, 1542, 1508, 1397, 1281, 1265, 1175, 1096 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.96–7.92 (m, 3 H, H_{Ar}), 7.82 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.57 (d, J = 9.0 Hz, 4 H, H_{Ar}), 7.44 (d, J = 8.4 Hz, 1 H, CH), 7.40–7.36 (m, 1 H, H_{Ar}), 7.29 (d, J = 8.54 Hz, 1 H, H_{Ar}), 7.10–7.06 (m, 1 H, H_{Ar}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.4, 186.3, 161.9 (J_{CF}^1 = 244.9 Hz), 144.8, 144.3, 141.5, 136.5, 135.3, 135.1, 131.9, 131.3 (J_{CF}^2 = 6.2 Hz), 131.3, 131.2, 130.3 (J_{CF}^3 = 3.1 Hz), 130.2, 127.4, 127.2, 115.1 (J_{CF}^4 = 21.6 Hz).

HRMS (EI): m/z [M]$^+$ calcd for $C_{24}H_{13}Br_2FO_2S$: 541.8987; found: 541.8965.

[3-(4-Chlorophenyl)thiophene-2,5-diyl]bis[(4-chlorophenyl)methanone] (3c)

White solid; yield: 0.363 g (77%); mp 182–183 °C (Lit.[12d] 178.2 °C).

IR (KBr): 1649, 1586, 1484, 1400, 1365, 1286, 1266, 1173, 1088 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.94 (s, 1 H, CH), 7.69–7.65 (m, 4 H, H_{Ar}), 7.43 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.36 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.31 (d, J = 8.4 Hz, 2 H, H_{Ar}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.7, 186.7, 145.1, 145.0, 142.2, 138.9, 138.7, 137.0, 135.5, 135.4, 133.6, 133.3, 131.8, 131.7, 131.4, 129.5, 129.0, 128.7.

HRMS (EI): m/z [M]$^+$ calcd for $C_{24}H_{13}Cl_3O_2S$: 469.9702; found: 469.9733.

[3-(4-Chlorophenyl)thiophene-2,5-diyl]bis[(4-bromophenyl)methanone] (3d)

White solid; yield: 0.441 g (79%); mp 172–174 °C (Lit.[12d] 179 °C).

IR (KBr): 1638, 1588, 1458, 1303, 1286, 1217, 1121, 1011 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.93 (d, J = 8.8 Hz, 3 H, H_{Ar}, CH), 7.82 (d, J = 8.0 Hz, 2 H, H_{Ar}), 7.58 (s, 4 H, H_{Ar}), 7.36 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.31 (d, J = 8.0 Hz, 2 H, H_{Ar}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.3, 186.3, 144.5, 144.4, 141.7, 136.4, 135.3, 135.2, 133.1, 132.7, 131.9, 131.4, 131.3, 131.2, 130.8, 128.2, 127.5, 127.2.

HRMS (EI): m/z [M]$^+$ calcd for $C_{24}H_{13}Br_2ClO_2S$: 557.8692; found: 557.8699.

[3-(4-Chlorophenyl)thiophene-2,5-diyl]bis(phenylmethanone) (3e)

White solid; yield: 0.277 g (69%); mp 191–192 °C.

IR (KBr): 1626, 1587, 1509, 1491, 1360, 1220, 1168, 1025 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.14 (d, J = 7.2 Hz, 2 H, H_{Ar}), 8.04 (d, J = 7.2 Hz, 4 H, H_{Ar}), 7.72 (d, J = 7.2 Hz, 1 H, CH), 7.66–7.59 (m, 4 H, H_{Ar}), 7.52–7.48 (m, 4 H, H_{Ar}).

HRMS (EI): m/z [M]$^+$ calcd for $C_{24}H_{15}ClO_2S$: 402.0481; found: 402.0509.

[3-(4-Chlorophenyl)thiophene-2,5-diyl]bis[(4-methoxyphenyl)methanone] (3f)

White solid; yield: 0.333 g (72%); mp 138–139 °C.

IR (KBr): 1622, 1589, 1570, 1509, 1295, 1266, 1168, 1123 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 (d, J = 8.4 Hz, 2 H, H_{Ar}), 7.90 (s, 1 H, CH), 7.71 (d, J = 8.8 Hz, 2 H, H_{Ar}), 7.40–7.33 (m, 4 H, H_{Ar}), 7.14 (d, J = 8.8 Hz, 2 H, H_{Ar}), 6.93 (d, J = 8.8 Hz, 2 H, H_{Ar}), 3.89 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.2, 186.0, 164.1, 163.8, 144.8, 143.6, 142.1, 135.7, 133.6, 133.3, 132.7, 132.4, 131.1, 129.4, 129.3, 128.9, 114.7, 114.4, 56.1, 56.1.

HRMS (EI): m/z [M]$^+$ calcd for $C_{26}H_{19}ClO_4S$: 462.0693; found: 462.0666.

(3-Phenylthiophene-2,5-diyl)bis[(4-chlorophenyl)methanone] (3g)

Pale yellow solid; yield: 0.270 g (62%); mp 175–177 °C.

IR (KBr): 1642, 1586, 1534, 1399, 1287, 1259, 1213, 1087 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (d, J = 7.6 Hz, 2 H, H_{Ar}), 7.93 (s, 1 H, CH), 7.69–7.63 (m, 4 H, H_{Ar}), 7.41–7.30 (m, 4 H, H_{Ar}), 7.24 (s, 3 H, H_{Ar}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.0, 186.8, 146.3, 144.8, 142.1, 138.7, 138.6, 137.0, 135.6, 135.3, 134.4, 131.75, 131.70, 129.6, 129.5, 128.9, 128.8, 128.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{24}H_{14}Cl_2O_2S$: 436.0092; found: 436.0087.

(3-Phenylthiophene-2,5-diyl)bis[(4-bromophenyl)methanone] (3h)
White solid; yield: 0.382 g (73%); mp 163–164 °C.

IR (KBr): 1639, 1583, 1475, 1396, 1257, 1211, 1171, 1066 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.94–7.92 (m, 3 H, H_{Ar}, CH), 7.82 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.58–7.50 (m, 4 H, H_{Ar}), 7.34–7.29 (m, 2 H, H_{Ar}), 7.24–7.23 (m, 3 H, H_{Ar}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.2, 186.9, 146.3, 144.8, 142.0, 137.0, 135.9, 135.6, 134.4, 132.4, 131.9, 131.8, 130.3, 129.6, 128.8, 128.5, 128.0, 127.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{24}H_{14}Br_2O_2S$: 523.9081; found: 523.9083.

[3-(*p*-Tolyl)thiophene-2,5-diyl]bis[(4-chlorophenyl)methanone] (3i)
White solid; yield: 0.302 g (67%); mp 208–209 °C.

IR (KBr): 1643, 1585, 1541, 1400, 1259, 1210, 1173, 1086 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.90 (s, 1 H, CH), 7.69–7.64 (m, 4 H, H_{Ar}), 7.40 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.21 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.05 (d, *J* = 7.8 Hz, 2 H, H_{Ar}), 2.22 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.1, 186.8, 146.2, 144.6, 141.5, 138.8, 138.6, 138.3, 136.9, 135.6, 135.3, 131.8, 131.7, 131.5, 129.5, 129.4, 129.4, 129.0, 21.1.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{25}H_{16}Cl_2O_2S$: 450.0248; found: 450.0253.

[3-(*p*-Tolyl)thiophene-2,5-diyl]bis[(3-chlorophenyl)methanone] (3j)
Pale yellow solid; yield: 0.247 g (55%); mp 132–133 °C.

IR (KBr): 1649, 1578, 1525, 1435, 1350, 1259, 1126, 1020 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.65 (s, 1 H, H_{Ar}), 8.54 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 8.42 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 8.28 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 8.20 (s, 1 H, CH), 8.04 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 8.00 (s, 1 H, H_{Ar}), 7.91 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.61 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.17 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 6.95 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 2.15 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.7, 185.8, 147.9, 147.0, 146.9, 144.7, 141.5, 138.0, 137.5, 137.3, 137.2, 135.3, 135.2, 130.9, 130.7, 130.2, 129.3, 128.7, 127.3, 127.0, 124.1, 123.9, 20.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{25}H_{16}Cl_2O_2S$: 450.0248; found: 450.0230.

[3-(*p*-Tolyl)thiophene-2,5-diyl]bis[(4-bromophenyl)methanone] (3k)
White solid; yield: 0.421 g (78%); mp 168–169 °C (Lit.[12d] 162.4 °C).

IR (KBr): 1643, 1582, 1539, 1396, 1259, 1209, 1173, 1067 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95–7.89 (m, 3 H, H_{Ar}, CH), 7.82 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.59–7.53 (m, 4 H, H_{Ar}), 7.20 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.05 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 2.23 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.8, 186.4, 145.7, 144.1, 140.9, 137.7, 136.4, 135.3, 135.1, 131.9, 131.4, 131.2, 131.2, 130.9, 128.85, 128.81, 127.4, 127.1, 20.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{25}H_{16}Br_2O_2S$: 537.9238; found: 537.9260.

[3-(*p*-Tolyl)thiophene-2,5-diyl]bis[(4-methoxyphenyl)methanone] (3l)
Pale yellow solid; yield: 0.309 g (70%); mp 138–139 °C.

IR (KBr): 1633, 1598, 1507, 1421, 1285, 1261, 1168, 1034 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.86 (s, 1 H, CH), 7.71 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.25 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.15–7.08 (m, 4 H, H_{Ar}), 6.91 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 3.89 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 2.23 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.0, 185.5, 163.5, 163.2, 144.1, 143.8, 140.9, 137.4, 135.1, 132.1, 131.7, 131.3, 129.0, 128.9, 128.8, 128.5, 114.1, 113.8, 55.5, 20.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{27}H_{22}O_4S$: 442.1239; found: 442.1231.

[3-(*p*-Tolyl)thiophene-2,5-diyl]bis[(4-nitrophenyl)methanone] (3m)
Yellow solid; yield: 0.241 g (51%); mp 197–198 °C.

IR (KBr): 1650, 1600, 1520, 1406, 1347, 1268, 1228, 1105 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.42 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 8.21 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 8.10 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.93 (s, 1 H, CH), 7.82 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.20 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.00 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 2.17 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.5, 186.4, 149.8, 149.4, 147.0, 144.6, 141.5, 141.4, 141.4, 138.1, 137.5, 137.3, 130.6, 129.8, 129.2, 128.8, 123.9, 123.3, 20.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{25}H_{16}N_2O_6S$: 472.0729; found: 472.0722.

[3-(4-Methoxyphenyl)thiophene-2,5-diyl]bis[(4-chlorophenyl)methanone] (3n)
Pale yellow solid; yield: 0.317 g (68%); mp 129–131 °C.

IR (KBr): 1646, 1586, 1509, 1398, 1257, 1212, 1173, 1086 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.89 (s, 1 H, CH), 7.69–7.63 (m, 4 H, H_{Ar}), 7.40 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.25 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 6.78 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 3.69 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.7, 186.3, 159.3, 145.6, 144.1, 140.6, 138.2, 138.1, 136.5, 135.1, 134.9, 131.2, 131.2, 130.5, 129.0, 128.5, 126.3, 113.8, 55.2.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{25}H_{16}Cl_2O_3S$: 466.0197; found: 466.0216.

[3-(4-Methoxyphenyl)thiophene-2,5-diyl]bis[(3-chlorophenyl)methanone] (3o)
Yellow solid; yield: 0.307 g (66%); mp 121–122 °C.

IR (KBr): 1644, 1578, 1526, 1436, 1351, 1256, 1135, 1029 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.66 (s, 1 H, H_{Ar}), 8.56 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 8.42 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 8.28 (d, *J* = 8.0 Hz, 1 H, CH), 8.21 (s, 1 H, H_{Ar}), 8.05–7.98 (m, 2 H, H_{Ar}), 7.93–7.89 (m, 1 H, H_{Ar}), 7.62–7.58 (m, 1 H, H_{Ar}), 7.22 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 6.69 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 3.63 (s, 3 H, OCH_3).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{25}H_{16}Cl_2O_3S$: 466.0197; found: 466.0222.

[3-(4-Methoxyphenyl)thiophene-2,5-diyl]bis[(4-bromophenyl)methanone] (3p)
Pale yellow solid; yield: 0.410 g (74%); mp 152–153 °C (Lit.[12d] 167.5 °C).

IR (KBr): 1646, 1583, 1395, 1367, 1257, 1211, 1174, 1066 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95–7.88 (m, 3 H, H_{Ar}, CH), 7.82 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.55 (s, 4 H, H_{Ar}), 7.25 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 6.78 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 3.69 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.3, 187.0, 159.8, 146.1, 144.6, 141.1, 137.0, 135.9, 135.9, 132.4, 131.9, 131.8, 131.8, 131.0, 127.9, 127.7, 126.8, 114.3, 55.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{25}H_{16}Br_2O_3S$: 553.9187; found: 553.9163.

[3-(3,4-Dimethoxyphenyl)thiophene-2,5-diyl]bis[(3-chlorophenyl)methanone] (3q)
White solid; yield: 0.273 g (55%); mp 132–133 °C.

IR (KBr): 1637, 1578, 1528, 1435, 1349, 1244, 1124, 1022 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 1 H, CH), 8.52 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 8.35–8.28 (m, 2 H, H_{Ar}), 8.22 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 8.06 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.80–7.76 (m, 2 H, H_{Ar}), 7.51–7.47 (m, 1 H, H_{Ar}), 6.79 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 6.64 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 3.77 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.2, 186.3, 149.4, 148.6, 148.3, 147.6, 147.3, 145.2, 141.9, 138.0, 137.8, 135.8, 135.5, 131.2, 130.6, 127.8, 127.3, 126.9, 124.5, 124.4, 122.7, 113.5, 111.9, 56.0, 55.8.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{26}H_{18}Cl_2O_4S$: 496.0303; found: 496.0286.

[3-(Naphthalen-2-yl)thiophene-2,5-diyl]bis[(4-chlorophenyl)methanone] (3r)
White solid; yield: 0.326 g (67%); mp 152–153 °C.

IR (KBr): 1642, 1585, 1537, 1399, 1263, 1207, 1119, 1012 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10–8.02 (m, 3 H, H_{Ar}, CH), 7.92 (s, 1 H, H_{Ar}), 7.83 (s, 2 H, H_{Ar}), 7.77 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.72–7.66 (m, 4 H, H_{Ar}), 7.52–7.43 (m, 3 H, H_{Ar}), 7.30 (d, *J* = 8.0 Hz, 2 H, H_{Ar}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.6, 186.4, 145.8, 144.4, 141.7, 138.2, 136.7, 135.1, 135.0, 132.4, 132.1, 131.3, 131.2, 131.1, 129.0, 128.5, 128.4, 128.0, 127.8, 127.4, 126.7 (2), 126.6 (6), 126.5.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{28}H_{16}Cl_2O_2S$: 486.0248; found: 486.0218.

[3-(Naphthalen-2-yl)thiophene-2,5-diyl]bis[(4-bromophenyl)methanone] (3s)
White solid; yield: 0.396 g (69%); mp 149–150 °C.

IR (KBr): 1648, 1588, 1526, 1462, 1366, 1260, 1174, 1041 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 (s, 1 H, CH), 7.96 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.92 (s, 1 H, H_{Ar}), 7.83 (d, *J* = 8.4 Hz, 4 H, H_{Ar}), 7.77 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.60 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.51–7.49 (m, 2 H, H_{Ar}), 7.44 (d, *J* = 8.4 Hz, 3 H, H_{Ar}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.2, 187.0, 146.3, 144.9, 142.1, 137.2, 135.9, 135.8, 132.9, 132.6, 132.5, 131.9, 131.8, 131.8, 131.7, 129.0, 128.5, 128.3, 127.9, 127.8, 127.2, 127.1, 127.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{28}H_{16}Br_2O_2S$: 573.9238; found: 573.9266.

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(21) Single-crystal growth was carried out in co-solvent of EtOH and DMF at r.t. *Crystal data for* ***3i***: $C_{25}H_{16}Cl_2O_2S$, crystal dimension 0.30 × 0.26 × 0.12 mm, Triclinic, space group $P\bar{1}$, a = 8.4815(7) Å, b = 11.1246(11) Å, c = 11.7946(9) Å, α = 105.568(2)°, β = 92.2080(10)°, γ = 101.557(2)°, V = 1045.26(16) Å^3, Mr = 451.34, Z = 2, λ = 0.71073 Å, μ (MoKα) = 0.431 mm^{-1}, $F(000)$ = 464, R_1 = 0.0544, wR_2 = 0.1256.

