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Domino Synthesis of Tetrasubstituted Thiophenes from 1,3-Enynes with Mercaptoacetaldehyde

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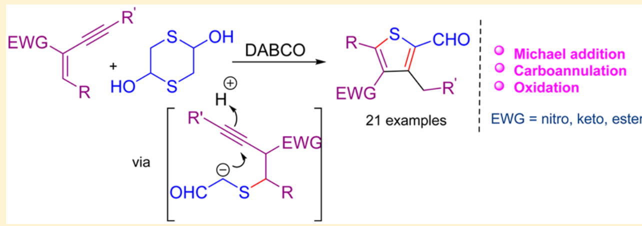
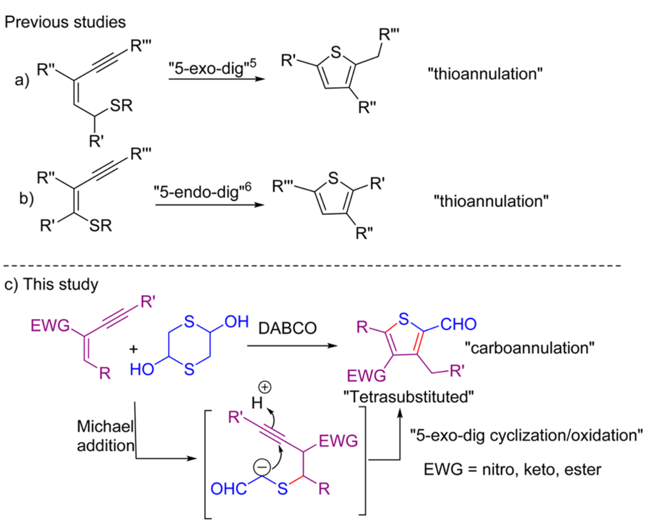
Supporting Information

ABSTRACT: Domino synthesis of tetrasubstituted thiophenes is described from 1,3-enynes and mercaptoacetaldehyde using DABCO at room temperature via a Michael addition, 5-exo-dig carboannulation, and oxidation sequence under air. The broad substrate scope and mild reaction conditions are significant practical features.

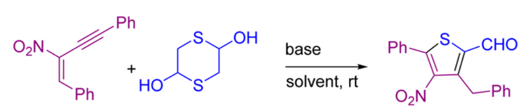


Functionalized thiophenes are key structural scaffolds in many bioactive natural products, pharmaceutically active agents, and drug candidates.[1] In addition, they find broad applications in material sciences as versatile building blocks: for example, in the assembly of organic semiconductor, field effect transistor, light emitting diode, photovoltaic material, etc.[2] Considerable efforts have thus been made on the development of effective methods for substituted thiophenes synthesis via either the α-metalation/β-halogenation of the thiophene ring or the thioannulation of the suitably substituted acylic precursors.[3,4] Among these, the annulation of the enynes is attractive, as they afford effective synthetic routes for the construction of thiophenes with a diverse substitution pattern.[5,6] The annulation of 2-en-4-yne-1-thiols has been accomplished via 5-exo-dig cyclization (Scheme 1a),[5] while the cyclization of thiobutenynes has been achieved via 5-endo-dig cyclization (Scheme 1b).[6] In continuation of our studies on heterocycles,[7]

Scheme 1. Enynes in Functionalized Thiophene Synthesis



we here report a conceptually new route for the construction of tetrasubstituted thiophenes via the domino Michael addition, 5-exo-dig carboannulation, and oxidation of 1,3-enynes with mercaptoacetaldehyde using DABCO at room temperature (Scheme 1). This new reaction affords advantages such as direct introduction of aldehyde and nitro/keto/ester functionalities in the thiophene ring with a broad substrate scope and metal-free mild reaction conditions.



1a 2 3a (1)

First, optimization of the reaction conditions was performed using (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne **1a** as a standard substrate with 1,4-dithiane-2,5-diol **2** in the presence of different bases and solvents under air (eq 1). Gratifyingly, the reaction occurred efficiently to furnish the target 3-benzyl-4-nitro-5-phenylthiophene-2-carbaldehyde **3a** in 4 h with >99% conversion and 100% selectivity when the substrates **1a** and **2** were stirred with 2.0 equiv of DABCO in $CHCl_3$ at room temperature in an open vessel (see Supporting Information Table S1). In a set of bases screened, DABCO exhibited superior results compared to DBU, Et_3N, and $^iPr_2NH$ (entries 1−4). In contrast, inorganic bases such as K_2CO_3, $NaHCO_3$, and Cs_2CO_3 failed to produce the target product (entries 5−7). $CHCl_3$ was found to be the solvent of choice, whereas CH_2Cl_2, dioxane, toluene, and DCE produced **3a** in 52−89% (entries 2 and 8−11). Decreasing the amount of DABCO (1.5 equiv) led to a drop in the yield to ≤77%. A control experiment confirmed that the target heterocycle **3a** was not formed without the base, and the starting materials were recovered intact.

With the optimal reaction conditions, the scope of the procedure was explored for the reaction of various substituted

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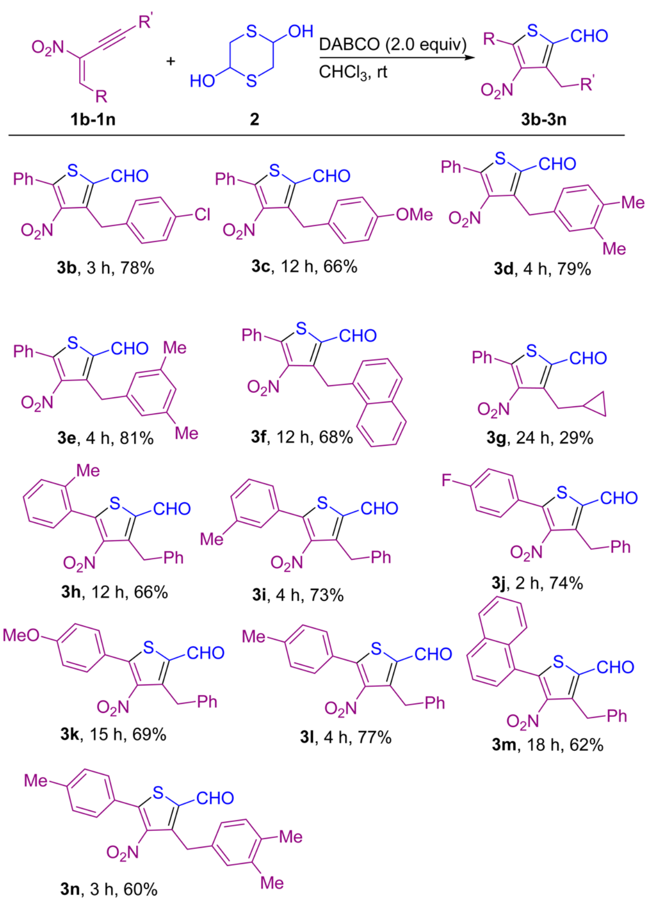
1,3-enynes **1b**−**1n** bearing nitro functionality (Scheme 2). The substrates bearing electron-withdrawing groups in the aryl rings exhibited greater reactivity compared to that containing electron-donating groups. For examples, the substrates **1b** and **1j** bearing chloro and fluoro substituents underwent reaction to furnish **3b** and **3j** in 78% and 74% yield, respectively, whereas **1c** and **1k** with a methoxy group in aryl rings required a slightly longer reaction time to produce thiophenes **3c** and **3k** in 66% and 69% yields, respectively. The reactions of mono-, di-, and trimethyl substituted enynes **1d**−**1e**, **1i**, **1l**, and **1n** furnished the corresponding substituted thiophenes **3d**−**3e**, **3i**, **3l**, and **3n** in 60−81% yields. In addition, the enynes bearing *ortho*-methyl and naphthyl groups **1f**, **1h**, and **1m** underwent reaction to give thiophenes **3f**, **3h**, and **3m** in 62−68% yields, while the reaction of aliphatic enyne **1g** produced thiophene **3g** in 29% yield. Recrystallization of **3b** gave single crystals whose structure was determined by X-ray analysis (see Supporting Information).

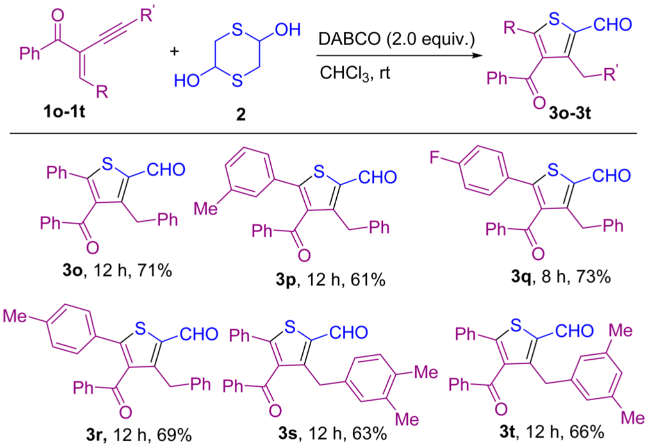
Scheme 2[a]



[a]Reaction conditions: **1b**−**1n** (0.5 mmol), **2** (0.35 mmol), DABCO (1 mmol), $CHCl_3$ (3.0 mL), rt, air.

Next, the utility of the protocol was screened for the reaction of 1,3-enynes **1o**−**1t** containing ketone functionality (Scheme 3). These substrates required a slightly longer time (8−12 h) compared to that of the nitro compounds. For example, the substrate **1o** with R and R′ = Ph underwent reaction to give thiophene **3o** in 71% yield. The reaction of the enyne **1q** with the electron-withdrawing 4-fluoro group in the aryl ring furnished **3q** in 73% yield. In addition, mono- and dimethyl substituted aryl groups in the enynes **1p** and **1r**−**1t** could be converted into the thiophene derivatives **3p** and **3r**−**3t** in 61−69% yields.

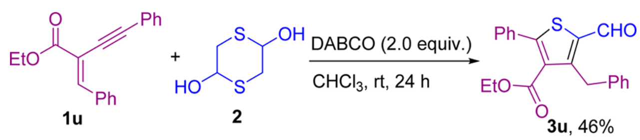
Scheme 3[a]



[a]Reaction conditions: **1o**−**1t** (0.5 mmol), **2** (0.35 mmol), DABCO (1 mmol), $CHCl_3$ (3.0 mL), rt, air.

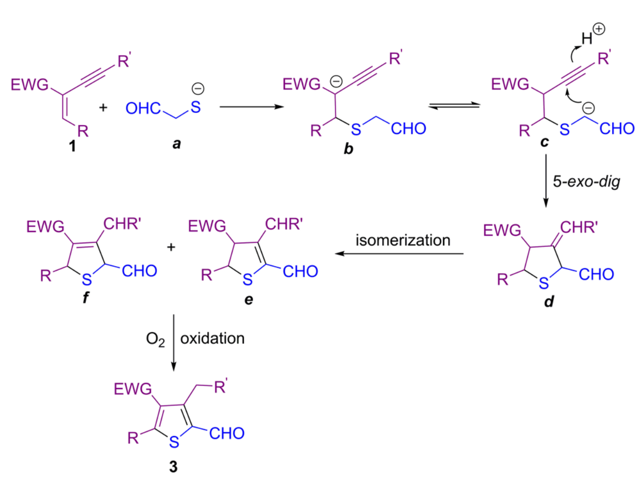
Finally, the compatibility of the protocol was investigated for the reaction of 1,3-enyne **1u** bearing ester functionality (Scheme 4). The substrate required a longer reaction time (24 h) compared to that of the enyne bearing nitro and keto functionalities. For example, the enyne **1u** bearing an ethyl ester underwent reaction to furnish thiophene derivative **3u** in 46% yield. These results suggest that a broad range of enynes can be coupled with mercaptoacetaldehyde to yield highly functionalized thiophene-2-carbaldehdyes under metal-free mild reaction conditions.

Scheme 4. Synthesis of 3u from 1,3-Enyne Bearing Ester



The proposed reaction pathway is shown in Scheme 5. 1,4-Dithiane-2,5-diol **2** with DABCO can produce ***a*** that may undergo Michael addition with 1,3-enyne **1** to furnish

Scheme 5. Plausible Mechanism



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carbanion ***b***. The latter may transform into ***c*** that can be stabilized by "CHO" as well as the vacant *d* orbital of "S". 5-Exo-dig carboannulation[8,9] of ***c*** may lead to the formation of ***d*** that may undergo isomerization to furnish ***e*** and ***f***, which may undergo oxidation[10] using air to yield the target product **3**. The proposed reaction pathway also explains the necessity of excess DABCO to produce the target products in good yields.

In conclusion, the DABCO-mediated domino reaction of 1,3-enynes with mercaptoacetaldehyde is described to assemble tetrasubstituted thiophenes at room temperature via a Michael addition, carboannulation, and oxidation sequence. The use of a mild organic base, broad substrate scope, and metal-free conditions are the significant practical advantages. In addition, the aldehyde and nitro functionalities can be further converted into useful derivatives which may be of immense interest in biological and material sciences.

EXPERIMENTAL SECTION

General Information. $Pd(PPh_3)_2Cl_2$ (98%), CuI (98%), DABCO (98%), and 1,4-dithiane-2,5-diol (97%) were purchased from commercial sources. 1,3-Enynes **1a**−**1u** were synthesized according to a reported procedure.[11,12] The progress of the reaction was monitored by analytical TLC on silica gel G/GF 254 plates. The column chromatography was performed with silica gel 60−120 mesh. NMR (^{1}H and ^{13}C) spectra were recorded on DRX-400 and 600 MHz instruments using $CDCl_3$ as a solvent and Me_4Si as an internal standard. Chemical shifts (δ) were reported in ppm, and spin−spin coupling constants (J) were given in hertz. The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet. Melting points were determined by melting point apparatus and are uncorrected. FT-IR spectra were recorded using an IR spectrometer. High-resolution mass spectra were recorded on a QTof ESI-MS instrument. For single crystal X-ray analysis, the intensity data were collected using a CCD diffractometer using Mo Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structures were solved by direct methods using SHELXL-97 (Göttingen, Germany).

General Procedure for the Synthesis of Substituted Thiophenes 3a−3u. To a stirred solution of 1,4-dithiane-2,5-diol **2** (0.35 mmol) and enyne **1** (0.5 mmol) in $CHCl_3$ (2 mL), DABCO (1.0 mmol) in $CHCl_3$ (1.0 mL) was added under air. The stirring was continued until completion of the reaction. The progress of the reaction was monitored using TLC with hexane and ethyl acetate as eluent. The solvent was then evaporated in a rotary evaporator, and the residue was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford analytically pure products.

3-Benzyl-4-nitro-5-phenylthiophene-2-carbaldehyde ***3a***. Yellow liquid; yield 82% (132 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.49−7.43 (m, 5H), 7.32−7.29 (m, 2H), 7.25−7.23 (m, 1H), 7.18 (d, J = 7.2 Hz, 2H), 4.49 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 181.8, 149.7, 142.7, 137.2, 137.0, 130.8, 129.6, 129.3, 129.1, 128.6, 128.4, 127.3, 32.1; FT-IR (neat) 3417, 3029, 2923, 2853, 1665, 1602, 1558, 1546, 1518, 1494, 1453, 1443, 1384, 1349, 1216, 1056, 1028, 794, 744, 695, 663 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{14}NO_3S$ 324.0689, found 324.0696.

3-(4-Chlorobenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde ***3b***. Colorless solid; yield 78% (139 mg); mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.04−7.97 (m, 5H), 7.83−7.80 (m, 2H), 7.67 (d, J = 8.4 Hz, 2H), 5.00 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 181.6, 150.0, 144.1, 142.0, 137.0, 135.6, 133.3, 131.0, 129.8, 129.5, 129.4, 129.3, 128.6, 31.5; FT-IR (KBr) 3452, 2936, 2853, 1666, 1546, 1517, 1491, 1408, 1384, 1347, 1263, 1216, 1093, 1057, 1029, 1014, 807, 748, 694, 668 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{13}ClNO_3S$ 358.0299, found 358.0299.

3-(4-Methoxybenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde ***3c***. Yellow liquid; yield 66% (116 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.48−7.44 (m, 5H), 7.09 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.41 (s, 2H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 181.9, 158.8,149.6, 144.3, 143.4, 136.9, 130.9, 129.7, 129.6, 129.3, 129.2, 128.6, 114.6, 55.4, 31.3; FT-IR (neat) 3443, 2929, 2837, 1665, 1609, 1584, 1558, 1526, 1511, 1458, 1442, 1384, 1350, 1303, 1249, 1217, 1177, 1031, 818, 757, 740, 694, 667 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{16}NO_4S$ 354.0795, found 354.0786.

3-(3,4-Dimethylbenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde ***3d***. Yellow liquid; yield 79% (138 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.49−7.44 (m, 5H), 7.06 (d, J = 7.8 Hz, 1H), 6.93 (s, 1H), 6.89 (d, J = 7.8 Hz, 1H), 4.41 (s, 2H), 2.22 (s, 3H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 182.0, 149.5, 144.3, 143.3, 137.4, 137.0, 135.7, 134.6, 130.8, 130.3, 129.6, 129.3, 128.6, 125.8, 31.7, 20.0, 19.5; FT-IR (neat) 3442, 2921, 2850, 1665, 1546, 1519, 1443, 1384, 1349, 1216, 1057, 1028, 1001, 814, 774, 757, 694, 663 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{18}NO_3S$ 352.1002, found 352.1002.

3-(3,5-Dimethylbenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde ***3e***. Yellow liquid; yield 81% (142 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.50−7.45 (m, 5H), 6.87 (s, 1H), 6.76 (s, 2H), 4.39 (s, 2H), 2.27 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 182.1, 149.5, 144.3, 143.1, 138.8, 137.1, 137.0, 130.8, 129.7, 129.3, 129.0, 128.6, 126.2, 32.0, 21.5; FT-IR (neat) 3408, 2919, 2854, 1665, 1601, 1547, 1520, 1489, 1443, 1384, 1349, 1281, 1216, 1163, 1053, 1029, 1000, 843, 796, 750, 694 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{18}NO_3S$ 352.1002, found 352.1000.

3-(Naphthalen-1-ylmethyl)-4-nitro-5-phenylthiophene-2-carbaldehyde ***3f***. Yellow liquid; yield 68% (127 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.61−7.48 (m, 7H), 7.37 (t, J = 7.8 Hz, 1H), 7.02 (d, J = 6.6 Hz, 1H), 4.92 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 181.9, 149.5, 144.6, 142.1, 137.7, 133.9, 133.7, 131.5, 130.9, 129.6, 129.4, 129.2, 128.7, 128.2, 126.9, 126.4, 125.7, 125.5, 122.9, 29.5; FT-IR (neat) 3451, 3058, 2922, 2852, 1664, 1598, 1547, 1516, 1443, 1398, 1384, 1347, 1221, 1028, 797, 771, 754, 737, 694, 667 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{22}H_{16}NO_3S$ 374.0845, found 374.0848.

3-(Cyclopropylmethyl)-4-nitro-5-phenylthiophene-2-carbaldehyde ***3g***. Yellow liquid; yield 29% (42 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.48−7.45 (m, 5H), 3.02 (d, J = 6.6 Hz, 2H), 1.06 (t, J = 6.0 Hz, 1H), 0.58 (d, J = 7.2 Hz, 2H), 0.28 (d, J = 4.8 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 181.7, 149.1, 145.0, 136.6, 130.8, 129.8, 129.4, 128.6, 126.8, 30.8, 12.6, 5.5; FT-IR (neat) 3442, 3003, 2962, 2854, 1665, 1546, 1519, 1443, 1384, 1349, 1260, 1237, 1210, 1079, 1054, 1020, 792, 762, 746, 694, 663 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{14}NO_3S$ 288.0689, found 288.0686.

3-Benzyl-4-nitro-5-(o-tolyl)thiophene-2-carbaldehyde ***3h***. Yellow liquid; yield 66% (111 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.40−7.37 (m, 1H), 7.33−7.29 (m, 3H), 7.28−7.23 (m, 3H), 7.19 (d, J = 7.2 Hz, 2H), 4.60 (s, 2H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 182.0, 151.1, 145.2, 142.6, 137.7, 137.5, 137.2, 130.6, 130.5, 129.7, 129.3, 129.1, 128.4, 127.3, 126.1, 32.3, 20.0; FT-IR (neat) 3440, 3062, 3028, 2924, 2853, 1667, 1602, 1548, 1515, 1495, 1453, 1383, 1347, 1288, 1233, 1216, 1160, 1076, 1056, 1030, 983, 908, 804, 749, 718, 700, 660 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{16}NO_3S$ 338.0845, found 338.0854.

3-Benzyl-4-nitro-5-(m-tolyl)thiophene-2-carbaldehyde ***3i***. Yellow liquid; yield 73% (123 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.30−7.24 (m, 7H), 7.17−7.15 (d, J = 7.6 Hz, 2H), 4.47 (s, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 181.8, 150.0, 142.7, 139.3, 137.3, 136.9, 131.7, 129.5, 129.3, 129.2, 128.4, 127.3, 125.7, 32.1, 21.5; FT-IR (neat) 3443, 3029, 2922, 2854, 1665, 1602, 1546, 1519, 1494, 1453, 1384, 1349, 1220, 1030, 780, 698, 662 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{16}NO_3S$ 338.0845, found 338.0858.

3-Benzyl-5-(4-fluorophenyl)-4-nitrothiophene-2-carbaldehyde ***3j***. Yellow liquid; yield 74% (126 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.45−7.43 (m, 2H), 7.32−7.30 (m, 2H), 7.24 (d, J = 7.8 Hz, 1H), 7.17−7.13 (m, 4H), 4.49 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 179.2, 162.5 (d, J_{C-F} = 251.2 Hz), 160.9, 146.0, 141.8, 140.3, 134.6, 128.4 (d, J_{C-F} = 8.7 Hz), 128.3, 126.7, 125.9, 124.9, 123.1, 114.2 (d, J_{C-F} = 88.2 Hz), 114.0, 29.6; FT-IR (neat) 3440, 2922, 2852, 1665, 1602, 1549, 1519, 1495, 1453, 1412, 1384, 1347, 1223, 1161, 1054,

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1015, 837, 814, 786, 744, 700, 672, 668 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{13}FNO_3S$ 342.0595, found 342.0590.

*3-Benzyl-5-(4-methoxyphenyl)-4-nitrothiophene-2-carbaldehyde **3k**.* Yellow liquid; yield 69% (122 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.40−7.38 (m, 2H), 7.31−7.29 (m, 2H), 7.25−7.22 (m, 1H), 7.17 (d, J = 7.2 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 4.46 (s, 2H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 181.8, 161.8, 149.9, 143.8, 142.9, 137.3, 136.2, 130.2, 129.1, 128.5, 127.3, 121.8, 114.8, 55.6, 32.1; FT-IR (neat) 3449, 2921, 2850, 1663, 1604, 1558, 1545, 1518, 1494, 1454, 1438, 1384, 1346, 1299, 1259, 1217, 1179, 1028, 803, 832, 779, 745, 700, 667 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{16}NO_4S$ 354.0795, found 354.0791.

*3-Benzyl-4-nitro-5-(p-tolyl)thiophene-2-carbaldehyde **3l**.* Yellow liquid; yield 77% (130 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.34−7.29 (m, 4H), 7.25−7.22 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H), 4.47 (s, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 181.8, 150.0, 144.1, 142.8, 141.4, 137.3, 136.7, 130.1, 129.1, 128.5, 128.5, 127.3, 126.7, 32.1, 21.6; FT-IR (neat) 3441, 3029, 2923, 2856, 1722, 1665, 1603, 1547, 1520, 1495, 1453, 1410, 1384, 1349, 1280, 1219, 1187, 1123, 1075, 1029, 1019, 816, 800, 778, 745, 700, 663 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{16}NO_3S$ 338.0845, found 338.0850.

*3-Benzyl-5-(naphthalen-1-yl)-4-nitrothiophene-2-carbaldehyde **3m**.* Yellow liquid; yield 62% (116 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.97 (d, J = 6.6 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.55−7.47 (m, 5H), 7.33−7..31 (m, 2H), 7.24−7.20 (m, 3H), 4.63 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 182.0, 149.6, 145.9, 142.6, 138.1, 137.5, 133.5, 131.2, 131.1, 129.2, 128.9, 128.5, 128.4, 127.8, 127.4, 127.3, 126.9, 125.1, 124.2, 32.4; FT-IR (neat) 3406, 3058, 2924, 2854, 1665, 1602, 1546, 1515, 1494, 1472, 1453, 1439, 1391, 1346, 1265, 1218, 1109, 1029, 908, 800, 776, 738, 700 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{22}H_{16}NO_3S$ 374.0845, found 374.0850.

*3-(3,4-Dimethylbenzyl)-4-nitro-5-(p-tolyl)thiophene-2-carbaldehyde **3n**.* Yellow liquid; yield 60% (110 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 7.8 Hz, 1H), 694 (s, 1H), 6.90 (d, J = 7.8 Hz, 1H), 4.40 (s, 2H), 2.41 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 182.0, 149.8, 144.1, 143.3, 141.3, 137.4, 136.5, 135.6, 134.6, 130.3, 130.0, 129.7, 128.4, 126.8, 125.8, 31.7, 21.6, 20.0, 19.5; FT-IR (neat) 3449, 2920, 2856, 1664, 1609, 1546, 1521, 1447, 1411, 1383, 1349, 1219, 1187, 1125, 1054, 1020, 815, 766, 737, 667 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{20}NO_3S$ 366.1158, found 366.1157.

*4-Benzoyl-3-benzyl-5-phenylthiophene-2-carbaldehyde **3o**.* Yellow liquid; yield 71% (136 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.34−7.31 (m, 3H), 7.20−7.18 (m, 3H), 7.15 (t, J = 7.8 Hz, 2H), 7.10−7.07 (m, 2H), 7.03−7.02 (m, 3H), 4.33 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.4, 182.7, 182.6, 152.7, 149.9, 139.2, 138.6, 138.3, 136.7, 133.7, 132.3, 129.7, 129.6, 129.0, 128.8, 128.7, 128.3, 126.7, 32.9; FT-IR (neat) 3441, 3060, 3028, 2849, 1659, 1596, 1579, 1529, 1494, 1453, 1432, 1383, 1312, 1279, 1216, 1173, 1067, 1029, 1001, 981, 841, 759, 737, 692, 643 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{19}O_2S$ 383.1100, found 383.1105.

*4-Benzoyl-3-benzyl-5-(m-tolyl)thiophene-2-carbaldehyde **3p**.* Yellow liquid; yield 61% (121 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.34−7.31 (m, 1H), 7.16−7.12 (m, 3H), 7.10−7.06 (m, 4H), 7.04−6.99 (m, 4H), 4.33 (s, 2H), 2.19 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.5, 182.6, 153.09, 149.9, 139.0, 138.7, 138.4, 136.9, 133.5, 132.2, 130.4, 129.6, 129.5, 128.8, 128.8, 128.7, 128.3, 126.7, 125.9, 32.8, 21.3; FT-IR (neat) 3449, 3060, 3028, 2922, 2851, 1958, 1659, 1596, 1579, 1528, 1494, 1449, 1383, 1313, 1287, 1218, 1173, 1070, 1029, 1019, 1001, 983, 926, 850, 781, 734, 692, 670 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{26}H_{21}O_2S$ 397.1257, found 397.1256.

*4-Benzoyl-3-benzyl-5-(4-fluorophenyl)thiophene-2-carbaldehyde **3q**.* Yellow liquid; yield 73% (146 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.47 (d, J = 7.8 Hz, 2H), 7.37−7.34 (m, 1H), 7.31−7.29 (m, 3H), 7.16 (t, J = 7.8 Hz, 2H), 7.09−7.07 (m, 2H), 7.03−7.01 (m, 2H), 6.89−6.86 (m, 2H), 4.31 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.3, 182.5, 164.2 (d, J_{C-F} = 249.7 Hz), 162.6, 151.2, 149.8, 139.3, 138.6, 138.2, 136.6, 133.8, 130.7 (d, J_{C-F} = 8.7 Hz), 130.6, 129.6, 128.8, 128.7, 128.4, 126.8, 116.2 (d, J_{C-F} = 21.7 Hz), 116.1, 32.9; FT-IR (neat) 3463, 3062, 2850, 1659, 1600, 1579, 1558, 1530, 1508, 1494, 1453, 1407, 1383, 1313, 1279, 1216, 1160, 1101, 1066, 1029, 1014, 1001, 982, 834, 808, 790, 735, 692, 667 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{18}FO_2S$ 401.1006, found 401.1006.

*4-Benzoyl-3-benzyl-5-(p-tolyl)thiophene-2-carbaldehyde **3r**.* Yellow liquid; yield 69% (137 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.50 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.16 (t, J = 7.8 Hz, 2H), 7.09−7.06 (m, 2H),7.02−6.98 (m, 5H), 4.30 (s, 2H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.8, 182.6, 152.9, 149.8, 140.0, 138.8, 138.3, 138.2, 136.7, 129.8, 129.7, 129.6, 129.4, 128.8, 128.6, 128.4, 128.4, 126.7, 32.9, 21.4; FT-IR (neat) 3448, 3060, 3027, 2921, 2851, 1657, 1596, 1579, 1532, 1507, 1494, 1453, 1381, 1312, 1283, 1217, 1173, 1114, 1066, 1019, 1001, 980, 912, 843, 815, 791, 734, 690, 667 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{26}H_{21}O_2S$ 397.1257, found 397.1257.

*4-Benzoyl-3-(3,4-dimethylbenzyl)-5-phenylthiophene-2-carbaldehyde **3s**.* Yellow liquid; yield 63% (129 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.34−7.32 (m, 3H), 7.20−7.13 (m, 5H), 6.83 (d, J = 7.8 Hz, 1H), 6.75−6.72 (m, 2H), 4.25 (s, 2H), 2.03 (s, 3H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.5, 182.8, 152.2, 150.6, 139.2, 138.4, 136.8, 136.7, 135.6, 134.8, 133.4, 132.3, 130.3, 129.9, 129.7, 129.6, 128.9, 128.7, 128.2, 126.3, 32.4, 19.7, 19.3; FT-IR (neat) 3442, 3059, 2921, 2853, 2729, 1660, 1596, 1579, 1529, 1503, 1448, 1433, 1381, 1312, 1280, 1174, 1068, 1024, 1000, 981, 909, 841, 758, 728, 713, 691, 643 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{23}O_2S$ 411.1413, found 411.1414.

*4-Benzoyl-3-(3,5-dimethylbenzyl)-5-phenylthiophene-2-carbaldehyde **3t**.* Yellow liquid; yield 66% (135 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.34−7.31 (m, 3H), 7.19−7.18 (m, 3H), 7.15 (t, J = 7.8 Hz, 2H), 6.59 (d, J = 4.2 Hz, 3H), 4.25 (s, 2H), 2.06 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.5, 182.8, 152.3, 150.5, 139.2, 138.5, 138.2, 138.0, 136.7, 132.3, 129.7, 129.6, 128.9, 128.8, 128.7, 128.2, 126.8, 126.6, 32.7, 21.2, 21.1; FT-IR (neat) 3450, 3059, 2919, 2851, 1659, 1597, 1579, 1529, 1448, 1433, 1383, 1312, 1280, 1215, 1172, 1069, 1026, 1000, 987, 911, 844, 759, 728, 689, 672, 643 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{23}O_2S$ 411.1413, found 411.1410.

*Ethyl 4-Benzyl-5-formyl-2-phenylthiophene-3-carboxylate **3u**.* Colorless liquid; yield 46% (81 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.44−7.40 (m, 5H), 7.29−7.26 (m, 2H), 7.20−7.15 (m, 3H), 4.53 (s, 2H), 4.01 (q, J = 6.6 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 182.6, 164.4, 155.7, 149.6, 139.0, 138.6, 133.0, 132.0, 129.7, 128.9, 128.8, 128.7, 128.6, 126.8, 61.4, 32.8, 13.7; FT-IR (neat) 3441, 2958, 2852, 1716, 1662, 1601, 1533, 1496, 1453, 1403, 1384, 1285, 1207, 1077, 1016, 965, 754, 696, 661 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{19}O_3S$ 351.1049, found 351.1048.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00231.

Crystallographic data for **3b** (CIF)

Optimization studies, crystal structure of **3b**, and NMR spectra (^{1}H and ^{13}C) for products **3a−3u** (PDF)

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Notes

The authors declare no competing financial interest.

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