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Regioselective Metal-Free One-Pot Synthesis of Functionalized 2-Aminothiophene Derivatives

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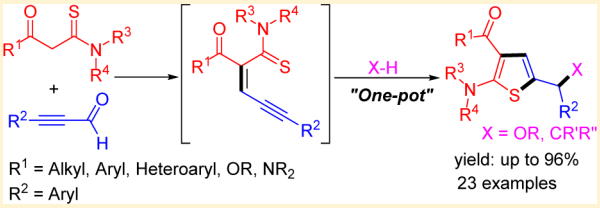
Supporting Information

ABSTRACT: A facile metal-free synthesis of 2-aminothiophene derivatives by the reaction of 2-ynals with thioamides in alcohols has been developed. This transformation allows the assembly of 2-aminothienyl ether derivatives via a well-designed aldol condensation/regioselective intramolecular cyclization/conjugate addition cascade reaction and provides a straightforward synthetic protocol for constructing 2,3,5-trisubstituted 2-aminothiophenes.



INTRODUCTION

Highly functionalized thiophenes are the key structural units in many bioactive pharmacophores,[1] natural products,[2] and functional materials[3] and are also employed as valuable building blocks in synthetic organic chemistry.[4] Therefore, many synthetic methods have been developed for the construction of substituted thiophenes.[5] Among these, annulation of suitable acyclic precursors has drawn great attention.[6,7] The representative example is the Gewald reaction, which utilizes elemental sulfur for the introduction of the thiophene sulfur atom.[8,9] In addition, thioannulation of alkynyl thiol has been emerging as an attractive approach to construct substituted thiophenes.[10] Most of these methods require the preconstruction of the desired alkynyl thiol and the use of a metal catalyst. For example, Gabriele and co-workers described the palladium-catalyzed cycloisomerization of (*Z*)-2-en-4-yne-1-thiols (Scheme 1, eq 1).[10c] Reddy and co-workers reported a thioannulation of in situ formed alkynyl thiols by treating acetates of Morita−Baylis−Hillman adducts derived from 2-ynals with potassium thioacetate (Scheme 1, eq 2).[10g] Moreover, thioamides as a class of practical and readily available compounds have been widely used for the synthesis of thiophenes.[11] We recently demonstrated two facile and efficient synthetic approaches to tetra-substituted 2-aminothiophenes via oxidative coupling of thioamides with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and copper-catalyzed coupling of thioamides with alkynoates, respectively.[12]

On the other hand, elegant studies were reported for the synthesis of functionalized furans through the catalyzed cyclization of ene−yne ketones (Scheme 1, eq 3).[13] For example, Clark and co-workers developed a tetrahydrothiophene-catalyzed furan-forming cascade reaction via a formation of the key active intermediate sulfonium ylide.[13a] Vicente and López described a novel zinc-catalyzed cyclization/C−O or C−N bond formation of ene−yne ketones, affording a series of functionalized furans.[13c] Wang and co-workers demonstrated a highly efficient Pd-catalyzed synthesis of 2-alkenyl-substituted furans by the reaction of conjugated ene−yne ketones and benzyl/aryl bromides via a carbene migratory insertion process.[13d] Jiang and co-workers described a convenient and regioselective Cu(I)-catalyzed cyclization of ene−yne ketones and subsequent oxidation of (2-furyl) carbene complexes, affording trisubstituted furan derivatives in good yields.[13e] In view of the stronger nucleophilic ability of the sulfur atom compared to that of the carbonyl oxygen, we envisaged that the reaction would proceed regioselectively to afford structurally and biologically important trisubstituted 2-aminothiophenes if thioamides are employed instead of normal 1,3-dicarbonyl compounds to react with 2-ynals, as shown in Scheme 1 (eq 4).

To the best of our knowledge, investigations on the formation of the 2-aminothienyl ether derivatives from 2-ynals and thioamides through a conjugated ene−yne thiocarbonyl cyclization reaction have not been reported, although Jørgensen reported an efficient organocatalyzed stereoselective one-pot synthesis of optically active 2-aminothiophenes via a cascade of enantioselective amino-catalyzed epoxidation or aziridination of α,β-unsaturated aldehydes, aldol condensation with thioamides, and subsequent ring annulation.[11d] We report herein a facile, regioselective, and metal-free synthesis of trisubstituted 2-aminothiophene via an one-pot aldol condensation/intramolecular cyclization/conjugate addition cascade reaction of 2-ynals and thioamides in excellent yields.

RESULTS AND DISCUSSION

Initially, the reaction of *N*,*N*-dimethyl-3-oxobutanethioamide (**1a**) and 3-phenylpropiolaldehyde (**2a**) was carried out in methanol at the temperature of 40 °C using AcOH and CuBr as the catalytic system according to Jiang's report,[13e] affording desired product **3aa** in 36% yield, accompanied by an unexpected byproduct **4aa** in 10% yield (Table 1, entry 1).

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Scheme 1. Strategies for the Synthesis of Thiophenes

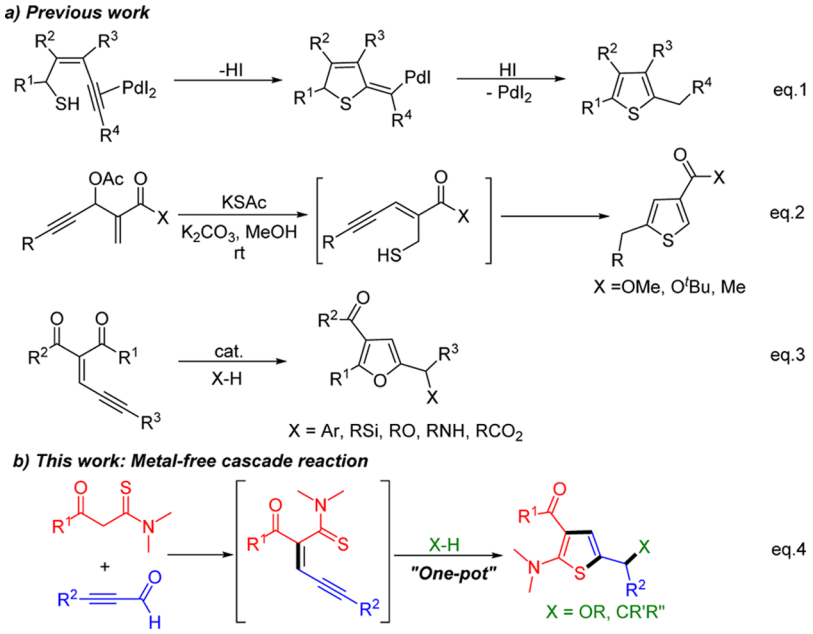
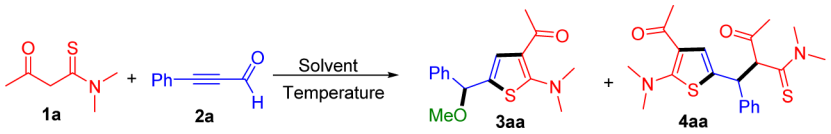


Table 1. Optimization of Reaction Conditions[a]



entry	ratio (**1a**/**2a**)	solvent	temp (°C)	yield of **3aa** (%)	yield of **4aa** (%)
1[b,c]	1.2:1	MeOH	40	36	10
2[b,c]	1.2:1	DCM	40	0	38
3[c]	1.2:1	DCM	40	0	58
4[c]	1.2:1	MeOH	40	40	26
5[c]	1.2:1	MeOH	reflux	71	23
6[c,d]	1.2:1	MeOH	reflux	74	21
7[d,e]	**1:2**	**MeOH**	**reflux**	**94**	**trace**
8[d,e]	1:3	MeOH	reflux	94	trace
9[d,e]	1:2	MeOH (1 mL)	reflux	90	trace
10[d,e]	1:2	MeOH (4 mL)	reflux	94	trace

[a]The reaction was carried out at 0.2 mmol scale in 2 mL of corresponding solvent under air atmosphere. [b]AcOH (10 mol %) was stirred for 0.5 h at 40 °C, then CuBr (10 mol %) was added for an additional 4 h. [c]Isolated yields were based on compound **2a**. [d]Under nitrogen. [e]Isolated yields were based on compound **1a**.

The yield of **4aa** can be further improved to 38% by using dichloromethane (DCM) as solvent instead of MeOH (Table 1, entry 2). Interestingly, the reaction occurred smoothly to give **4aa** in better yield (58%, entry 3) in the absence of AcOH and CuBr. We further investigated the reaction in methanol under a metal-free system and found that the reaction proceeded to give a slightly better result when compared with the yield of **3aa** from the first try (entry 4 vs 1). Encouraged by this result, we further optimized the metal-free reaction system. When the reaction temperature was increased from 40 °C to reflux, the yield of the desired product **3aa** was dramatically improved to 71% but was still accompanied by 23% of byproduct **4aa** (entry 5). Further optimization by adjusting the molar ratio of the substrates **2a** and **1a** showed that 2 equiv of **2a** was optimal to afford the desired product **3aa** in 94% yield (entries 6−8). When the reaction was carried out under nitrogen, the yield of **3aa** was slightly increased (entry 5 vs 6). When the amount of methanol was screened, we found that 2 mL of methanol as solvent was optimal (entries 7, 9, and 10). Therefore, the combination of substrate **1a** (0.2 mmol) and **2a** (0.4 mmol) for 2 mL of MeOH at refluxing temperature under nitrogen was found to be the optimal reaction conditions (entry 7).

Under the optimized conditions, the scope of this reaction was evaluated as shown in Scheme 2. Different thioamides **1** successfully reacted with 3-phenylpropiolaldehyde (**2a**) in methanol to afford the corresponding 2-aminothiophene ether derivatives in good to excellent yields. The results revealed that various R^1 groups, such as aliphatic, aromatic, and heterocyclic groups, linked to the carbonyl had a clear effect on the yield of corresponding **3**. Except for bulkier *tert*-butyl (**3ca**, 55%), aliphatic *β*-keto *N*,*N*-dimethylthioamides (**3aa**, **3ba**, 93%, 84%) were more active than the corresponding aromatic and heterocyclic *β*-ketothioamides (**3da**−**3ia**, 50−78%) under the

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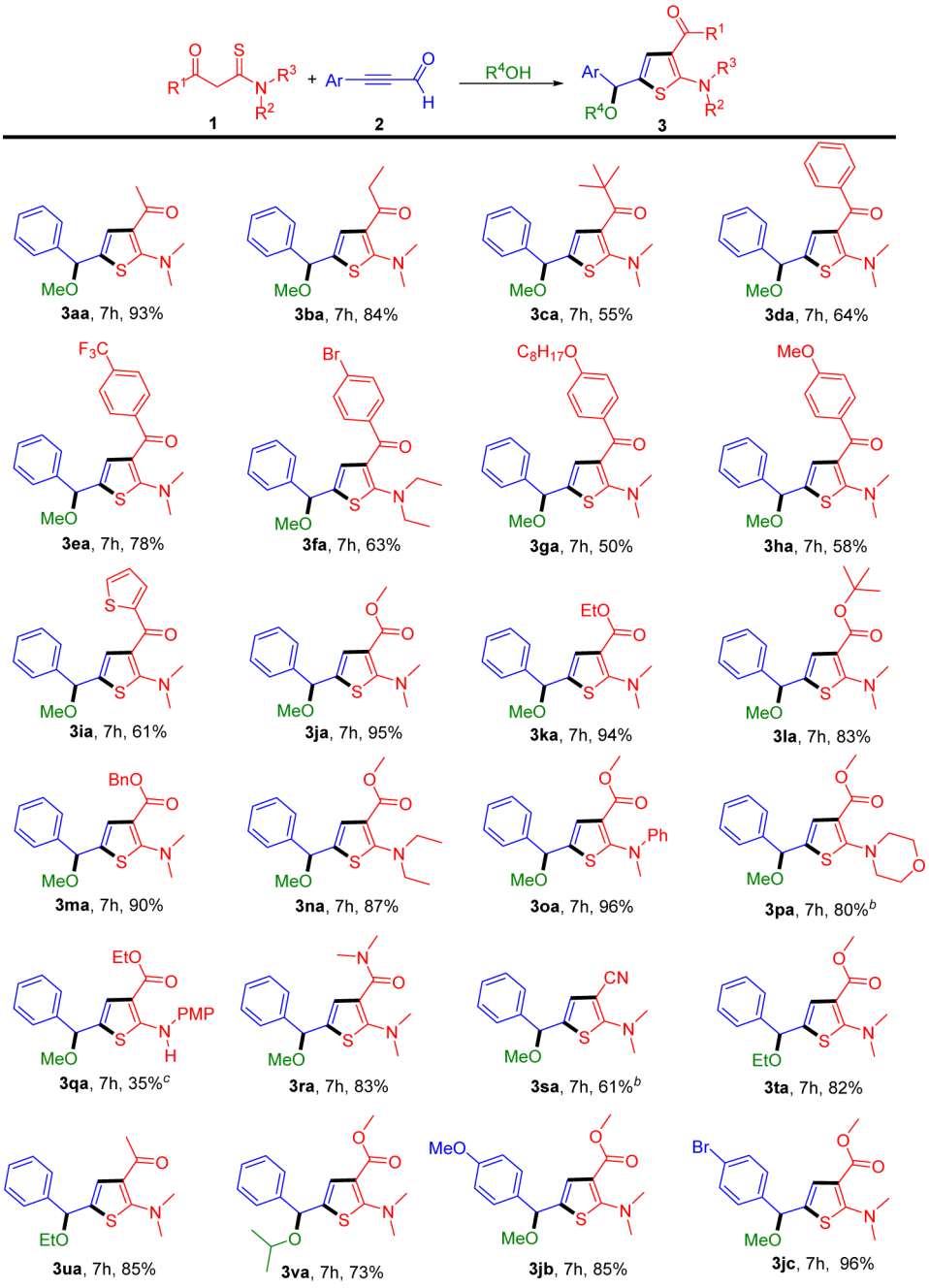
Scheme 2. Synthesis of Substituted Thiophene Ether Derivatives[a]



[a]Reaction conditions: **1** (0.2 mmol) and **2** (0.4 mmol) in 2 mL of alcohol at refluxing temperature under nitrogen were stirred until the reaction was completed as judged by thin-layer chromatography. Yields are of the isolated products. [b]10 mol % of KOAc was used. [c]10 mol % of KOAc was used at 90 °C for 10 h.

optimized reaction conditions. The thioamides with an electron-withdrawing group on the phenyl ring (**3ea**, 78%) was found to be more active than the one with an electron-donating group (**3ga** and **3ha**, 50 and 58%, respectively). Furthermore, malonate-derived thioamides **1j**−**m** all reacted smoothly with 3-phenylpropiolaldehyde (**2a**), affording **3ja**−**3ma** in excellent yields (83−95%).

The reaction can tolerate the change of the *N*,*N*-dimethyl motif of thioamides, and substrates **1n**−**o** with *N*,*N*-diethyl and methylphenyl groups reacted with **2a** to generate the desired products in good to excellent yields (**3na**, **3oa**, 87%, 96%). Unexpectedly, methyl 3-morpholino-3-thioxopropanoate (**1p**) was inactive under the optimized reaction conditions; however, the reaction proceeded well, affording the desired product when KOAc was added (**3pa**, 80%). The N-monosubstituted *β*-ketothioamide **1q** can also be transformed to the corresponding product **3qa** in lower yield when KOAc was added. Moreover, thioamide **1r** was also compatible with the optimized reaction system (**3ra**, 83%). Various simple primary and secondary alcohols instead of methanol were also probed and found to be suitable for this transformation, leading to the corresponding 2-aminothiophene ether derivatives **3ta**−**3va** in good yields. We also tried different alkyne aldehyde substrates bearing an electron-donating (**2b**) or electron-withdrawing (**2c**) group on

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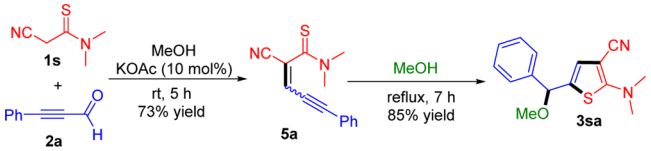
the phenyl ring and affording the corresponding 2-aminothiophene ether derivatives in 85 and 96% yields, respectively. Unfortunately, when an aliphatic 2-ynal (oct-2-ynal) was subjected to this reaction system, no desired product was observed, presumably due to its lower reactivity.

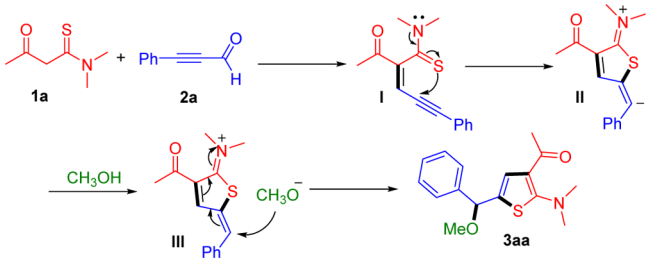
It is worth mentioning that when the reaction of 2-cyano-*N*,*N*-dimethylethanethioamide (**1s**) with 3-phenylpropiolaldehyde (**2a**) was carried out at room temperature under nitrogen for 5 h, an aldol condensation product **5a** was isolated in 73% yield, which can be further converted to 2-aminothienyl ether **3sa** in 85% yield under the optimized reaction conditions (Scheme 3). Therefore, compound **5a** would be considered as the key intermediate for this facile 2-aminothiophene formation protocol.

Scheme 3. Reaction of Substrates 1s and 2a



Based on these findings and previous results,[10b,13a] a proposed mechanism of this transformation is illustrated in Scheme 4. Aldol condensation of **1a** with **2a** generates the key

Scheme 4. Proposed Reaction Pathway



intermediate **I**, which is subjected to a spontaneous intramolecular cyclization and subsequent protonation to yield intermediate **III**. Finally, a conjugate addition of alcohol to the intermediate **III** affords the 2-aminothienyl ether **3aa**.

CONCLUSION

In conclusion, we have developed a facile metal-free synthetic method for constructing 2-aminothiophene ethers by treating 2-ynals with thioamides in various alcohols (methanol, ethanol, and isopropyl alcohol). The reaction is applicable to a variety of thioamides, such as ketothioamides, malonate-derived thioamides, and 2-cyanoethanethioamide, affording corresponding 2-aminothiophene ethers **3** in good to excellent yields (up to 96%). In addition, with a simple solvent change to DCM, the reaction can yield an unexpected 2-aminothiophene **4aa** via a double addition of thioamide. Finally, a metal-free reaction pathway was proposed to account for the regioselective and straightforward synthesis of 2-aminothiophene ethers via a tandem aldol condensation/intramolecular cyclization/conjugate addition. It should be pointed out that this transformation presents a novel metal-free synthetic protocol, which is complementary and superior to previous synthetic methods for the formation of 2,3,5-trisubstituted 2-aminothiophene derivatives.

EXPERIMENTAL SECTION

General Information. Melting points were obtained in open capillary tubes using a micro melting point apparatus and were uncorrected. Mass spectra were recorded on TOF mass spectrometer. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded using $CDCl_3$ (δ_H = 7.26 ppm) and DMSO-d_6 (δ = 2.50 ppm) as solvent at ambient temperatures on a 400 MHz spectrometer. Data are presented as follows: chemical shift (in ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (*J*/Hz), and interpretation. ^{13}C NMR spectra were recorded by broadband spin decoupling for $CDCl_3$ (δ_C = 77.2 ppm) and DMSO-d_6 (δ = 39.5 ppm) at ambient temperatures on a 100 MHz spectrometer. Chemical shift values are reported in parts per million on the scale. TLC (thin-layer chromatography) was performed using commercially prepared 100−400 mesh silica gel plates, and visualization was effected at 254 or 365 nm. Unless otherwise noted, all reagents and solvents were used as purchased. Alcohols were dried and distilled from magnesium sulfate under nitrogen.

General Procedure for the Preparation of Polysubstituted Thiophenes 3. 2-ynal **2**[14] (0.4 mmol) was added to a solution of thioamide compound **1**[12b] (0.2 mmol) in dried alcohol (2 mL) under nitrogen. Then the resulting mixture was stirred at refluxing temperature until the reaction was completed, as judged by TLC. After the solvent was evaporated in vacuo, the residue was purified by column chromatography on 100−200 mesh silica gel to afford pure polysubstituted thiophenes **3**.

*1-{2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophen-3-yl}ethan-1-one (**3aa**):* A light yellow oil (93% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.33 (m, 4H), 7.32−7.25 (m, 1H), 7.14 (s, 1H), 5.42 (s, 1H), 3.27 (s, 3H), 2.85 (s, 6H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.9, 166.3, 141.2, 129.3, 128.4, 127.6, 127.2, 126.2, 119.4, 80.3, 56.0, 45.4, 29.3; HRMS (EI-TOF) calcd for $C_{16}H_{19}NO_2S$ $[M]^+$ 289.1136, found 289.1138; IR (KBr, cm^{-1}) 3027, 2935, 2824, 1649, 1513, 1453, 1406, 1326, 1138, 1088, 1058, 701.

*1-{2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophen-3-yl}propan-1-one (**3ba**):* A light yellow oil (84% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ7.41−7.33 (m, 4H), 7.32−7.25 (m, 1H), 7.16 (s, 1H), 5.42 (s, 1H), 3.27 (s, 3H), 2.84 (s, 6H), 2.73 (q, *J* = 7.3 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.2, 166.1, 141.3, 129.4, 128.3, 127.6, 126.7, 126.2, 118.9, 80.3, 56.0, 45.3, 33.8, 8.8; HRMS (EI-TOF) calcd for $C_{17}H_{21}NO_2S$ $[M]^+$ 303.1293, found 303.1291; IR (KBr, cm^{-1}) 3028, 2935, 2822, 1655, 1603, 1514, 1453, 1407, 1315, 1191, 1135, 1090, 1040, 701.

*1-{2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophen-3-yl}-2,2-dimethylpropan-1-one (**3ca**):* A light yellow oil (55% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.33 (m, 4H), 7.29−7.28 (m, 1H), 7.09 (s, 1H), 5.46 (s, 1H), 3.27 (s, 3H), 2.75 (s, 6H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 202.5, 164.2, 141.5, 128.3, 128.3, 127.5, 126.1, 125.7, 116.7, 80.2, 55.9, 45.0, 43.6, 27.9; HRMS (EI-TOF) calcd for $C_{19}H_{25}NO_2S$ $[M]^+$ 331.1606, found 331.1605; IR (KBr, cm^{-1}) 3028, 2929, 2822, 1645, 1603, 1519, 1453, 1405, 1322, 1184, 1124, 1088, 1058, 703.

*{2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophen-3-yl}-(phenyl)methanone (**3da**):* A yellow oil (64% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.37−7.31 (m, 4H), 7.29−7.22 (m, 1H), 6.75 (s, 1H), 5.38 (s, 1H), 3.25 (s, 3H), 2.88 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.7, 166.2, 141.3, 140.0, 131.6, 128.8, 128.4, 128.3, 128.3, 127.5, 127.0, 126.2, 115.1, 80.0, 55.9, 44.8; HRMS (EI-TOF) calcd for $C_{21}H_{21}NO_2S$ $[M]^+$ 351.1293, found 351.1296; IR (KBr, cm^{-1}) 3027, 2933, 2820, 1639, 1596, 1575, 1525, 1406, 1328, 1127, 1085, 699.

*{2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophen-3-yl}[4-(trifluoromethyl)phenyl]methanone (**3ea**):* A yellow oil (78% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90−7.84 (m, 4H), 7.36−7.30 (m, 4H), 7.29−7.23 (m, 1H), 6.78 (s, 1H), 5.38 (s, 1H), 3.25 (s, 3H), 2.93 (s,

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6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 185.9, 167.2, 143.8, 141.3, 131.1(q, J_{C-F} = 30 Hz), 129.4, 128.3, 128.2, 127.5, 127.2, 126.1, 125.3 (q, J_{C-F} = 4.0 Hz), 114.6, 80.0, 55.9, 54.8, 44.9; HRMS (EI-TOF) calcd for $C_{22}H_{20}F_3NO_2S$ $[M]^+$ 419.1167, found 419.1168; IR (KBr, cm^{-1}) 3027, 2962, 1628, 1524, 1452, 1410, 1324, 1261, 1104, 1092, 1066, 801, 701.

*(4-Bromophenyl){2-(diethylamino)-5-[methoxy(phenyl)methyl]-thiophen-3-yl}methanone (**3fa**):* A yellow oil (63% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.39−7.31 (m, 4H), 7.30−7.24 (m, 1H), 6.71 (s, 1H), 5.38 (s, 1H), 3.24 (s, 3H), 3.20 (q, J = 7.1 Hz, 4H), 0.96 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.5, 163.6, 141.0, 138.4, 131.3, 130.9, 128.7, 128.3, 127.6, 127.5, 126.3, 125.6, 117.2, 80.2, 56.0, 49.2, 11.7; HRMS (EI-TOF) calcd for $C_{23}H_{24}{}^{79}BrNO_2S$ $[M]^+$ 457.0711. found 457.0714; IR (KBr, cm^{-1}) 3028, 2932, 2820, 1630, 1603, 1583, 1506, 1400, 1330, 1287, 1118, 1070, 843, 701.

*{2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophen-3-yl}[4-(octyloxy)phenyl]methanone (**3ga**):* A yellow oil (50% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, J = 8.8 Hz, 2H), 7.39−7.31 (m, 4H), 7.30−7.23 (m, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.76 (s, 1H), 5.37 (s, 1H), 4.02 (t, J = 6.5 Hz, 2H), 3.25 (s, 3H), 2.83 (s, 6H), 1.77−1.66 (m, 2H), 1.44−1.36 (m, 2H), 1.35−1.20 (m, 8H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.1, 164.9, 161.6, 141.3, 132.0, 131.1, 128.4, 128.3, 127.5, 127.0, 115.5, 114.0, 80.1, 67.7, 55.9, 44.6, 31.2, 28.7, 28.6, 28.5, 25.4, 22.1, 13.9; HRMS (EI-TOF) calcd for $C_{29}H_{37}NO_3S$ $[M]^+$ 479.2494, found 479.2499; IR (KBr, cm^{-1}) 3030, 2928, 2822, 1629, 1599, 1526, 1452, 1418, 1306, 1251, 1168, 1119, 1088, 846, 706.

*{2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophen-3-yl}(4-methoxyphenyl)methanone (**3ha**):* A yellow oil (58% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, J = 8.7 Hz, 2H), 7.38−7.32 (m, 4H), 7.30−7.23 (m, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.77 (s, 1H), 5.39 (s, 1H), 3.83 (s, 3H), 3.26 (s, 3H), 2.84 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 165.5, 162.7, 141.9, 132.7, 131.6, 128.9, 128.8, 128.0, 127.5, 126.7, 115.9, 114.1, 80.6, 56.4, 55.9, 45.2; HRMS (EI-TOF) calcd for $C_{22}H_{23}NO_3S$ $[M]^+$ 381.1399, found 381.1398.

*{2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophen-3-yl}-(thiophen-2-yl)methanone (**3ia**):* A yellow oil (61% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 4.9 Hz, 1H), 7.63 (d, J = 3.6 Hz, 1H), 7.40−7.32 (m, 4H),7.30−7.24 (m, 1H), 7.21 (t, J = 4.7 Hz, 1H), 7.06 (s, 1H), 5.43 (s, 1H), 3.27 (s, 3H), 2.88 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.5, 165.2, 145.7, 141.3, 133.2, 132.6, 128.3, 128.2, 128.1, 127.5, 127.1, 126.1, 114.4, 80.1, 55.9, 44.6; HRMS (EI-TOF) calcd for $C_{19}H_{19}NO_2S_2$ $[M]^+$ 357.0857, found 357.0855; IR (KBr, cm^{-1}) 3066, 2932, 2820, 1610, 1516, 1451, 1415, 1326, 1117, 1085, 1054, 705.

*Methyl 2-(Dimethylamino)-5-[methoxy(phenyl)methyl]-thiophene-3-carboxylate (**3ja**):* A light yellow oil (95% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.33 (m, 4H), 7.32−7.26 (m, 1H), 6.95 (s, 1H), 5.40 (s, 1H), 3.67 (s, 3H), 3.25 (s, 3H), 2.89 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 162.2, 141.1, 129.3, 128.4, 127.6, 126.9, 126.2, 108.2, 80.1, 56.0, 50.8, 45.0; HRMS (EI-TOF) calcd for $C_{16}H_{19}NO_3S$ $[M]^+$ 305.1086, found 305.1087; IR (KBr, cm^{-1}) 3027, 2947, 2821, 1701, 1602, 1524, 1451, 1436, 1326, 1217, 1137, 1108, 706.

*Ethyl 2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophene-3-carboxylate (**3ka**):* A light yellow oil (94% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (d, J = 4.4 Hz, 4H), 7.31−7.26 (m, 1H), 6.99 (s, 1H), 5.41 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.25 (s, 3H), 2.88 (s, 6H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 161.9, 141.2, 129.2, 128.3, 127.6, 126.9, 126.2, 108.7, 80.1, 59.3, 56.0, 45.0, 14.3; HRMS (EI-TOF) calcd for $C_{17}H_{21}NO_3S$ $[M]^+$ 319.1242, found 319.1243; IR (KBr, cm^{-1}) 3028, 2935, 2821, 1698, 1602, 1520, 1451, 1422, 1325, 1216, 1136, 1106, 705.

*tert-Butyl 2-(Dimethylamino)-5-[methoxy(phenyl)methyl]-thiophene-3-carboxylate (**3la**):* A light yellow oil (83% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.33 (m, 4H), 7.32−7.25 (m, 1H), 6.94 (s, 1H), 5.40 (s, 1H), 3.25 (s, 3H), 2.85 (s, 6H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.0, 161.6, 141.3, 129.2, 128.3, 127.6, 127.3, 126.2, 110.9, 80.1, 79.2, 56.0, 45.1, 28.0; HRMS (EI-TOF) calcd for $C_{19}H_{25}NO_3S$ $[M]^+$ 347.1555, found 347.1552; IR (KBr, cm^{-1}) 3026, 2928, 2821, 1691, 1602, 1522, 1451, 1421, 1389, 1329, 1240, 1134, 1109, 1090, 701.

*Benzyl 2-(Dimethylamino)-5-[methoxy(phenyl)methyl]-thiophene-3-carboxylate (**3ma**):* A light yellow oil (90% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41−7.25 (m, 10H), 7.05 (s, 1H), 5.42 (s, 1H), 5.19 (s, 2H), 3.25 (s, 3H), 2.88 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 161.6, 141.2, 136.7, 129.3, 128.4, 128.3, 127.8, 127.6, 126.9, 126.2, 108.1. 80.1, 64.9, 56.0, 45.1; HRMS (EI-TOF) calcd for $C_{22}H_{23}NO_3S$ $[M]^+$ 381.1399, found 381.1400; IR (KBr, cm^{-1}) 3030, 2945, 2821, 1698, 1602, 1525, 1452, 1422, 1326, 1214, 1134, 1105, 700.

*Methyl 2-(Diethylamino)-5-[methoxy(phenyl)methyl]thiophene-3-carboxylate (**3na**):* A colorless oil (87% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.34 (m, 4H), 7.32−7.27 (m, 1H), 6.89 (s, 1H), 5.40 (s, 1H), 3.65 (s, 3H), 3.28−3.24 (m, 7H), 1.05 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 162.3, 140.9, 130.3, 128.4, 127.7, 126.4, 110.4, 80.2, 56.0, 50.9, 48.9, 12.2; HRMS (EI-TOF) calcd for $C_{18}H_{23}NO_3S$ $[M]^+$ 333.1399, found 333.1401; IR (KBr, cm^{-1}) 3026, 2934, 2821, 1704, 1602, 1509, 1438, 1378, 1259, 1203, 1134, 1107, 703.

*Methyl 5-[Methoxy(phenyl)methyl]-2-[methyl(phenyl)amino]-thiophene-3-carboxylate (**3oa**):* A light yellow oil (96% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44−7.36 (m, 4H), 7.35−7.29 (m, 1H), 7.19 (t, J = 7.9 Hz, 2H), 7.04 (s, 1H), 6.82 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 8.2 Hz, 2H), 5.53 (s, 1H), 3.56 (s, 3H), 3.29 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 158.5, 148.5, 140.5, 139.6, 128.8, 128.6, 128.0, 126.5, 124.9, 122.6, 119.7, 115.3, 80.2, 56.3, 51.3, 41.4; HRMS (EI-TOF) calcd for $C_{21}H_{21}NO_3S$ $[M]^+$ 367.1242, found 367.1244; IR (KBr, cm^{-1}) 3028, 2947, 2821, 1712, 1599, 1495, 1452, 1438, 1389, 1329, 1253, 1215, 1158, 1110, 1088, 697.

*Methyl 5-[Methoxy(phenyl)methyl]-2-morpholinothiophene-3-carboxylate (**3pa**):* A colorless oil (80% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42−7.34 (m, 4H), 7.33−7.27 (m, 1H), 7.02 (s, 1H), 5.45 (s, 1H), 3.70 (t, J = 4.4 Hz, 4H), 3.68 (s, 3H), 3.26 (s, 3H), 3.09 (t, J = 4.6 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 162.4, 141.4, 132.9, 128.9, 128.3, 126.8, 126.8, 112.6, 80.5, 66.1, 56.6, 53.4, 51.6; HRMS (EI-TOF) calcd for $C_{18}H_{21}NO_4S$ $[M]^+$ 347.1191, found 347.1196; IR (KBr, cm^{-1}) 3027, 2950, 2822, 1705, 1602, 1500, 1440, 1374, 1324, 1246, 1188, 1116, 1087, 701.

*Methyl 5-[Methoxy(phenyl)methyl]-2-[(4-methoxyphenyl)-amino]thiophene-3-carboxylate (**3qa**):* A light yellow oil (35% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 7.38−7.31 (m, 4H), 7.31−7.27 (m, 1H), 7.25 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 6.86 (s, 1H), 5.42 (s, 1H), 4.22 (q, J = 7.0 Hz, 2H), 3.74 (s, 3H), 3.24 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 161.7, 156.7, 141.5, 134.4, 128.9, 128.2, 126.7, 124.2, 123.1, 115.2, 104.8, 80.3, 60.0, 56.5, 55.8, 14.9; HRMS (EI-TOF) calcd for $C_{22}H_{23}NO_4S$ $[M]^+$ 397.1348, found 397.1351. IR (KBr, cm^{-1}) 3238, 2930, 2827, 1663, 1595, 1554, 1509, 1432, 1235, 1177, 1112, 1065, 1032, 820, 696.

*2-(Dimethylamino)-5-[methoxy(phenyl)methyl]-N,N-dimethylthiophene-3-carboxamide (**3ra**).* A light yellow oil (83% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.33 (m, 4H), 7.32−7.25 (m, 1H), 6.57 (s, 1H), 5.38 (s, 1H), 3.25 (s, 3H), 2.89 (s, 6H), 2.73 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 156.7, 141.4, 130.2, 128.3, 127.5, 126.2, 126.1, 114.1, 80.2, 55.9, 43.8; HRMS (EI-TOF) calcd for

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J. Org. Chem. 2015, 80, 4611−4617

$C_{17}H_{22}N_2O_2S$ $[M]^+$ 318.1402, found 318.1401; IR (KBr, cm^{-1}) 3027, 2931, 2820, 1624, 1600, 1497, 1451, 1397, 1311, 1273, 1188, 1137, 1091, 702.

*2-(Dimethylamino)-5-[methoxy(phenyl)methyl]thiophene-3-carbonitrile (**3sa**):* A black oil (61% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.32 (m, 4H), 7.31−7.26 (m, 1H), 6.79 (s, 1H), 5.38 (s, 1H), 3.26 (s, 3H), 3.10 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 141.4, 128.9, 128.8, 128.2, 127.0, 126.6, 118.3, 80.7, 80.1, 56.5, 43.3; HRMS (EI-TOF) calcd for $C_{15}H_{16}N_2OS$ $[M]^+$ 272.0983, found 272.0984; IR (KBr, cm^{-1}) 3028, 2930, 2821, 2201, 1543, 1452, 1426, 1380, 1321, 1273, 1186, 1122, 1087, 709.

*Methyl 2-(Dimethylamino)-5-[ethoxy(phenyl)methyl]thiophene-3-carboxylate (**3ta**):* A light yellow oil (82% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.32 (m, 4H), 7.31−7.25 (m, 1H), 6.93 (s, 1H), 5.51 (s, 1H), 3.66 (s, 3H), 3.51−3.37 (m,2H), 2.88 (s, 6H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 162.2, 141.5, 129.9, 128.3, 127.6, 126.5, 126.2, 108.3, 78.3, 63.5, 50.8, 45.0, 15.1; HRMS (EI-TOF) calcd for $C_{17}H_{21}NO_3S$ $[M]^+$ 319.1242, found 319.1245; IR (KBr, cm^{-1}) 3061, 3027, 2949, 1699, 1602, 1520, 1451, 1436, 1326, 1217, 1137, 1108, 1070, 701.

*1-{2-(Dimethylamino)-5-[ethoxy(phenyl)methyl]thiophen-3-yl}-ethan-1-one (**3ua**):* A light yellow oil (85% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41−7.33 (m, 4H), 7.30−7.24 (m, 1H), 7.12 (s, 1H), 5.53 (s, 1H), 3.54−3.38 (m, 2H), 2.85 (s, 6H), 2.34 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.9, 166.3, 141.6, 130.0, 128.3, 127.5, 126.8, 126.1, 119.5, 78.4, 63.5, 45.4, 29.2, 15.1; HRMS (EI-TOF) calcd for $C_{17}H_{21}NO_2S$ $[M]^+$ 303.1293, found 303.1292; IR (KBr, cm^{-1}) 3060, 3028, 2972, 1648, 1603, 1515, 1451, 1405, 1326, 1137, 1090, 701.

*Methyl 2-(Dimethylamino)-5-[isopropoxy(phenyl)methyl]-thiophene-3-carboxylate (**3va**):* A light yellow oil (73% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41−7.33 (m, 4H), 7.30−7.25 (m, 1H), 6.90 (s, 1H), 5.64 (s, 1H), 3.66 (s, 3H), 3.63−3.57 (m, 1H), 2.88 (s, 6H), 1.15 (d, J = 6.1 Hz, 3H), 1.10 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 162.2, 142.0, 130.7, 128.3, 127.5, 126.3, 126.1, 108.3, 75.5, 68.5, 50.8, 45.0, 22.1, 22.0; HRMS (EI-TOF) calcd for $C_{18}H_{23}NO_3S$ $[M]^+$ 333.1399, found 333.1400; IR (KBr, cm^{-1}) 3061, 3026, 2969, 1702, 1602, 1524, 1452, 1436, 1377, 1326, 1216, 1134, 1108, 701.

*Methyl 2-(Dimethylamino)-5-[methoxy(4-methoxyphenyl)-methyl]thiophene-3-carboxylate (**3jb**):* A colorless oil (85% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, J = 7.5 Hz, 2H), 6.92 (d, J = 7.6 Hz, 2H), 6.88 (s, 1H), 5.33 (s, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 3.22 (s, 3H), 2.89 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 162.2, 158.7, 132.9, 129.8, 127.7, 126.5, 113.7, 108.3, 79.8, 55.8, 55.0, 50.8, 45.0; HRMS (EI-TOF) calcd for $C_{17}H_{21}NO_4S$ $[M]^+$ 335.1191, found 335.1193; IR (KBr, cm^{-1}) 3066, 2948, 2836, 1701, 1610, 1512, 1459, 1437, 1248, 1136, 1108, 837.

*Methyl 5-[(4-Bromophenyl)(methoxy)methyl]-2-(dimethylamino)thiophene-3-carboxylate (**3jc**):* A yellow oil (96% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 6.99 (s, 1H), 5.43 (s, 1H), 3.67 (s, 3H), 3.25 (s, 3H), 2.89 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 162.7, 141.1, 131.8, 129.0, 128.9, 127.7, 121.2, 108.6, 79.8, 56.5, 51.4, 45.5; HRMS (EI-TOF) calcd for $C_{16}H_{18}{}^{79}BrNO_3S$ $[M]^+$ 383.0191, found 383.0193; IR (KBr, cm^{-1}) 3062, 2947, 2822, 1699, 1589, 1519, 1436, 1328, 1217, 1137, 1108, 1089, 823.

*2-{[4-Acetyl-5-(dimethylamino)thiophen-2-yl](phenyl)methyl}-N,N-dimethyl-3-oxobutanethioamide (**4aa**):* A light yellow solid, R_f = 0.20 (petroleum ether/ethyl acetate = 1:1); mp 65−67 °C; ^{1}H NMR analysis of the crude mixture showed a dr of 10:7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.25 (m, 2H), 7.24−7.08 (m, 3H), 6.82 (s, 1H), 5.28 (d, J = 11.4 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.81 (s, 6H), 2.29 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 195.0, 190.1, 165.3, 139.9, 128.7, 128.1, 127.0, 126.5, 125.5, 119.6, 52.5, 48.5, 44.9, 44.4, 28.5, 26.8; HRMS (EI-TOF) calcd for $C_{21}H_{26}N_2O_2S_2$ $[M]^+$ 402.1436, found 402.1435; IR (KBr, cm^{-1}) 3027, 2926, 1727, 1647, 1601, 1516, 1452, 1408, 1326, 1110, 702.

*2-Cyano-N,N-dimethyl-5-phenylpent-2-en-4-ynethioamide (**5a**):* A red oil (73% yield), R_f = 0.20 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.55 (m, 2H), 7.45−7.36 (m, 3H), 6.99 (s, 1H), 3.49 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 132.5, 130.4, 130.2, 128.6, 123.9, 121.3, 114.3, 106.4, 85.1, 44.1; HRMS (EI-TOF) calcd for $C_{14}H_{12}N_2S$ $[M]^+$ 240.0721, found 240.0723; IR (KBr, cm^{-1}) 3058, 2922, 2191, 1727, 1646, 1570, 1451, 1261, 1095, 1022, 800, 692.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra data for all 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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