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Synthesis of Spirocyclic Oxindole Dihydrothiophenes by DBU-Catalyzed [3 + 2] Annulation of Morita–Baylis–Hillman Carbonates with Isothiocyanates

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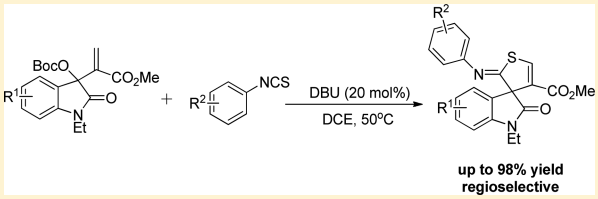
Supporting Information

ABSTRACT: A highly regioselective DBU-catalyzed [3 + 2] annulation of Morita–Baylis–Hillman carbonates with isothiocyanates was developed. This method allows rapid and efficient synthesis of spirocyclic oxindole dihydrothiophene products in moderate to high yields with excellent regioselectivities under simple conditions. A plausible reaction mechanism is also proposed.



Among the various classes of natural and non-natural organic sulfur compounds, dihydro- and especially tetrahydrothiophenes have played important roles in biological and medicinal chemistry.[1] Many methods have been developed for the construction of these special structures.[2] Furthermore, spirooxindole derivatives with the spirooxindole as the core structural motif usually possess important biological and pharmaceutical activities.[3] As a result, enormous efforts have been devoted to building heterocyclic oxindoles.[4] However, only a few routes to the spiro dihydro- or tetrahydrothiophenes oxindoles have been reported so far.[5] In 2012, Xiao and co-workers first described a formal [3 + 2] annulation between 1,4-dithiane-2,5-diol and 3-alkenyloxindoles to construct enantioenriched spirocyclic oxindole-fused-tetrahydrothiophenes, which was catalyzed by an organo-cinchona-based squaramide.[5a] Subsequently, Feng's group reported the same domino reaction to asymmetrically synthesize spiro tetrahydrothiophene oxindoles using a *N*,*N*′-doxide–nickel(II) complex system in good yields with excellent enantioselectivities.[5c]

The Morita–Baylis–Hillman (MBH) carbonates, which are derived from isatins and act as very useful synthons, have attracted a great deal of attention from organic chemists.[6] Mostly, MBH adducts, being very useful 1,3-dipole precursors, have been used to synthesize many heterocyclic architectures with a variety of electron-deficient olefins by nucleophilic tertiary phosphine[7] or tertiary amine[8] catalysis. Over the past decades, numerous protocols using MBH carbonates and electron-deficient olefins via allylic P intermediates[9] or N intermediates[10] have been reported with nucleophilic phosphine and nitrogen catalysis. We envisioned building the spiro dihydro- or tetrahydrothiophene oxindole scaffolds by [3 + 2] annulation with isatin-derived MBH carbonates and phenyl isothiocyanates via nucleophilic catalysis. Among these transformations, the [3 + 2] annulation between isatin-derived MBH carbonates and isothiocyanates[11] under nitrogen Lewis bases catalysis produced spiro heterocycle oxindoles with high regioselectivities.

In our initial attempts, we utilized Morita–Baylis–Hillman carbonate **1a** (1.0 equiv) derived from isatin and phenyl isothiocyanate **2a** (1.0 equiv) as substrates and 20 mol % PPh_3 as the catalyst. After 22 h, isothiocyanate **2a** was completely consumed, while some carbonate **1a** still remained in the reaction mixture and the reaction gave a low yield (43%). To our delight, it was found that the [3 + 2] annulation reaction gave the corresponding cyclic products **3a** and another compound **4** in 91% total yield with a ratio of **3a**/**4** of 3:1 (Table 1, entry 1) when 5.0 equiv of phenyl isothiocyanate **2a** was added. However, compound **4** could not be separated, and its structure was not identified. Several other phosphine catalysts were also screened for this reaction, but none of the results was satisfactory (Table 1, entries 2–4).

Due to the poor regioselectivity given by the phosphine catalysts, we explored the nitrogen Lewis bases as catalyst. It was found that neither NEt_3 nor DIPEA catalyzed the reaction (Table 1, entries 8 and 9). Low catalytic activity was observed when 1,4-diazabicyclic[2.2.2]octane (DABCO) was used as the catalyst (Table 1, entry 5). 4-*N*,*N*-dimethylpyridine (DMAP) gave better yield but no regioselectivity (Table 1, entry 6). However, DBU as the catalyst gave the highest yield and regioselectivity, and almost no **4** was produced. When DBU was used as the catalyst, several solvents were screened for best results. When dichloroethane (DCE) was used as the solvent, less reaction time was needed, and even higher yield was seen (Table 1, entry 10). Lower yields were observed when other solvents such as tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), chloroform, and ethyl

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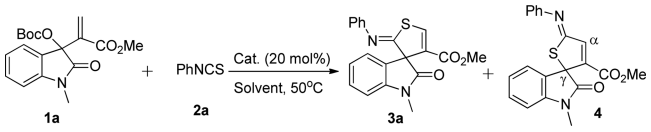
Table 1. Conditions Optimization



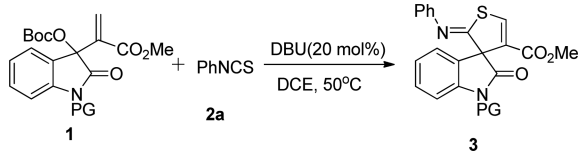
entry	catalyst	solvent	time (h)	yield[b] (%)	3a/4[c]
1	PPh_3	CH_3CN	12	91	3:1
2	DPPB	CH_3CN	12	66	10:1
3	Me_3P	CH_3CN	10	nd.	
4	$(Bu)_3P$	CH_3CN	10	nr.	
5	DABCO	CH_3CN	5	37	>20:1
6	DMAP	CH_3CN	5	48	1:1
7	DBU	CH_3CN	12	78	>20:1
8	NEt_3	CH_3CN	24	nd.	
9	DIPEA	CH_3CN	24	nr.	
10	DBU	DCE	1.5	87	>20:1
11	DBU	THF	2	33	>20:1
12	DBU	$CHCl_3$	2	60	>20:1
13	DBU	EA	1	80	>20:1
14	DBU	DMSO	1	21	>20:1

[a]The reactions were carried out with **1a** (0.1 mmol), **2a** (0.5 mmol), and 20 mol % of catalyst in 1.5 mL of solvent at 50 °C. [b]Isolated total yields. [c]The regioisomeric ratio of **3a**:**4** was determined by ^{1}H NMR; these regioisomers could not be separated by flash column chromatography.

acetate (EA) were used (Table 1, entries 11−13). Therefore, dichloroethane (DCE) was proved to be the optimal solvent for the cyclization reaction.

Based on the optimal catalyst and solvent, MBH carbonates derived from isatins with different N substituents were then examined. The results are shown in Table 2. All of the reactions

Table 2. Screening of N-Protecting Groups of Isatin Derivatives



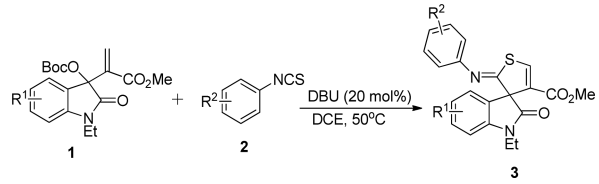
entry	PG	time (h)	yield[b] (%)
1	Me	1.5	87
2	Et	1.5	98
3	propyl	1.5	97
4	butyl	1.5	60
5	Bn	1.5	84
6	Ac	1.5	73
7	Ph	1.5	57
8	Boc	1.5	70

[a]The reactions were carried out with **1** (0.1 mmol), **2a** (0.5 mmol), and 20 mol % of DBU in 1.5 mL of solvent at 50 °C for 1.5 h. [b]Isolated total yields.

proceeded smoothly under the optimal conditions. Generally, lower yields were observed when the N-protecting groups were electron withdrawing (Table 2, entries 6−8), while higher yields were obtained when the N-protecting groups were electron donating (Table 2, entries 1−5). Among the electron-donating groups, ethyl (Et) was the most favorable protection group (Table 2, entry 2).

Based on the further optimized reaction conditions, we next examined the scope and limitations of the [3 + 2] annulation reaction catalyzed by DBU. Various MBH carbonates **1** and phenyl isothiocyanates **2a** with different substituents on the benzene ring were tested. The results were summarized in Table 3. MBH adducts were obtained in moderate to high yields (81−

Table 3. Substrate Scope of the Reaction



entry	R^1	R^2	time (h)	products	yield[b] (%)
1	**1b** (H)	H	1.5	**3b**	98
2	**1c** (4-Cl)	H	1.5	**3c**	89
3	**1d** (5-Cl)	H	1.5	**3d**	95
4	**1e** (6-Cl)	H	1.5	**3e**	98
5	**1f** (5-Br)	H	1.5	**3f**	94
6	**1g** (6-Br)	H	1.5	**3g**	86
7	**1h** (7-Br)	H	1.5	**3h**	81
8	**1i** (5-F)	H	1.5	**3i**	90
9	**1j** (7-F)	H	1.5	**3j**	96
10	**1k** (5-OMe)	H	1.5	**3k**	94
11	**1l** (5-NO_2)	H	1.5	**3l**	95
12	**1m** (5-Me)	H	1.5	**3m**	71
13	**1n** (7-Me)	H	1.5	**3n**	66
14	**1o** (5,7-di-Me)	H	2	**3o**	74
15	H	**2b** (4-Cl)	1.5	**3p**	98
16	H	**2c** (4-Br)	1.5	**3q**	95
17	H	**2d** (4-F)	1.5	**3r**	98
18	H	**2e** (4-OMe)	1.5	**3s**	77
19	H	**2f** (4-CF_3)	1.5	**3t**	60
20	H	**2g** (3,5-di-CF_3)	1.5	**3u**	62

[a]All reactions were carried out using **1** (0.1 mmol), **2** (0.5 mmol), and DBU (20 mol %) in 1.5 mL of DCE at 50 °C for 1.5 or 2 h. [b]Isolated yield.

98%) and excellent regioselectivity (up to >20:1) with MBH carbonates bearing electron-withdrawing substituents on the different positions of the benzene ring (Table 3, entries 1−11). However, MBH adducts were produced in lower yields with MBH carbonates bearing electron-donating substituents (Table 3, entries 12−14), probably because the electron-withdrawing substituents could stabilize allylic nitrogen−ylide intermediates. We have also explored the effect of substituent groups at different positions on the aromatic ring of phenyl isothiocyanates on the reaction. The phenyl isothiocyanates with electron-withdrawing groups gave high yields (Table 3, entries 15−17), but lower yields were observed when the substituents were electron-donating groups (Table 3, entries 18−20). Clearly, substrates with various substituents on both of the phenyl rings were well tolerated in the reaction. The structure and the configuration of the product **3g** was determined by X-ray crystallographic analysis.[12]

Additionally, we have also tested some aliphatic isothiocyanates under the same reaction conditions, but no reactions were observed.

In the case of the DBU-catalyzed reaction, there were only a few examples in which the DBU was used as a nucleophilic

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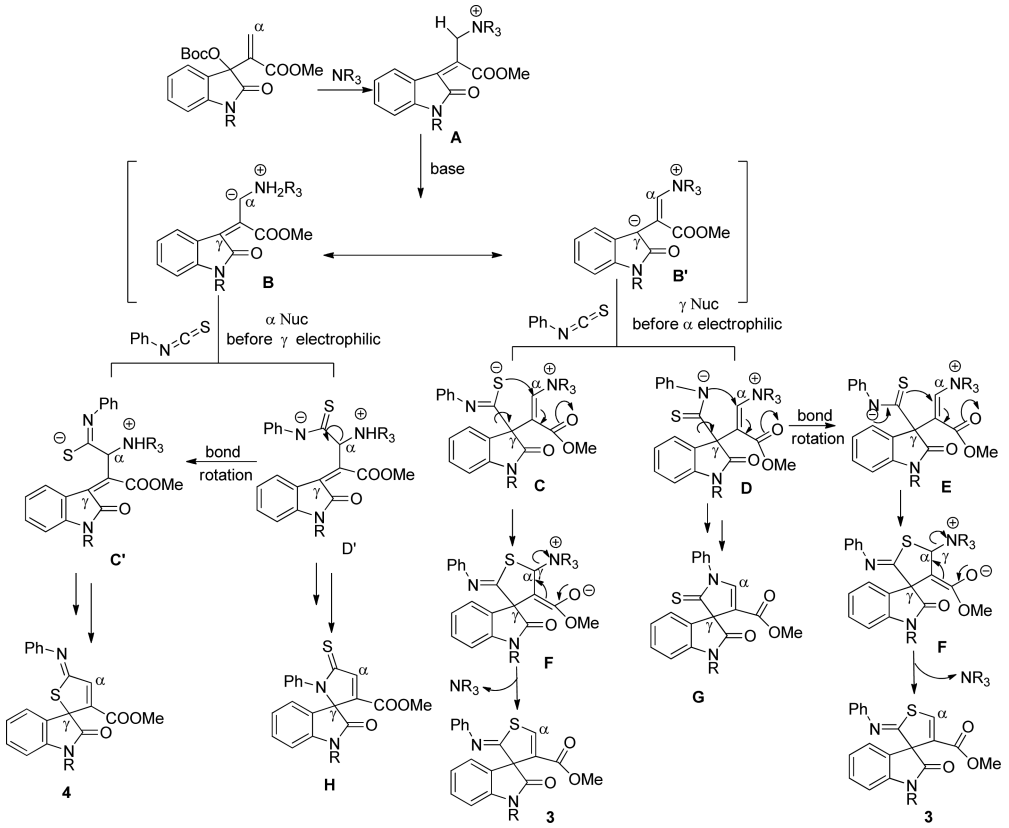
Scheme 1. Proposed Reaction Mechanism



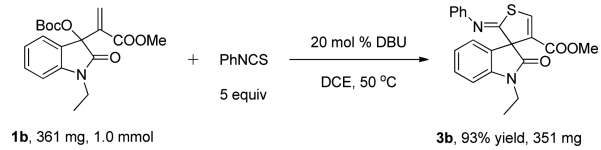
catalyst.[13] In 1993, Bertrand and co-workers proposed that DBU could act as a strong nucleophile.[14] Recently, Sun's group has also reported a highly efficient synthesis of spiro-skeletons in the presence of DBU under mild conditions.[15]

On the basis of the results described above and literature reported,[16] a plausible reaction mechanism is proposed in Scheme 1. First, Lewis base DBU acts as a nucleophilic trigger[17] and attacks the α-position of MBH carbonates to release carbon dioxide and *tert*-butoxide anion to afford intermediates **A**. Then the in situ generated *tert*-butoxide anion deprotonates the intermediates **A** to yield the allylic nitrogen ylides **B** or **B′**. Subsequently, the electron-deficient isothiocyanate reacts with ylides **B** or **B′** to generate either zwitterionic intermediates **C, C′** or **D, D′**. Finally, these intermediates undergo intramolecular thia-Michael addition to provide annulation product **3** and products **4**. We succeed in separating these two compounds by employing semipreparative HPLC. According to our proposed mechanism, isomer **4** is produced as a product after attack from the α-position by sulfur as nucleophile. Under normal circumstances, the 3-position of the oxindole has stronger nucleophilicity; therefore, compound **3** is the main product after attack from the β-position by sulfur as nucleophile.[18] Furthermore, intermediates **D** can be converted to **E** by bond rotation, which is then transformed into product **3** after a multiple-step conversion.

To demonstrate the potential value of this protocol, a large-scale reaction was performed for the synthesis of **3b**. The reaction of **1b** on a 1.0 mmol scale using 20 mol % of DBU provided spirocyclic product **3b** in a high yield of 93% (Scheme 2).

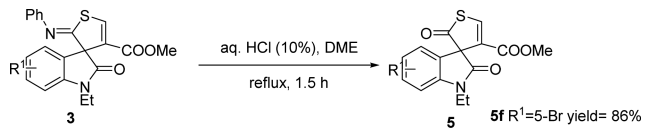
More importantly, these spirocyclic oxindole dihydrothiophene compounds could be easily hydrolyzed and then converted into the corresponding dihydrothiophenone derivatives.[19] The hydrolysis reaction proceeded smoothly and

Scheme 2. Large-Scale Study



produced the desired product **5** in 86% yield in the presence of 10% hydrochloric acid and 1,2-dimethoxyethane (DME) (1:3, v/v) at reflux temperature for 1.5 h (Scheme 3).

Scheme 3. Hydrolysis Reaction



In conclusion, we have reported a new method for the synthesis of spirocyclic oxindole dihydrothiophenes by DBU-catalyzed [3 + 2] annulation between MBH carbonates of isatins and isothiocyanates. The reaction produced the corresponding products in moderate to high yields with excellent regioselectivities. As a nucleophilic base, DBU was found to be very efficient for catalyzing [3 + 2] annulation reaction.

EXPERIMENTAL SECTION

General Information. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Analytical thin-layer chromatography (TLC) was performed on silicycle silica gel plates, and the compounds were visualized by irradiation with UV light. ^{1}H NMR and ^{13}C NMR spectra were

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recorded using TMS as an internal standard and $CDCl_3$ as the solvent. Chemical shifts are given in δ relative to TMS. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), integration, coupling constant (Hz), and assignment. The spectra were recorded in $CDCl_3$ as the solvent at room temperature, TMS served as the internal standard (δ = 0 ppm) for ^1H NMR, and $CDCl_3$ was used as the internal standard (δ = 77.00 ppm) for ^{13}C NMR. Some of the compound NMR may have solvent EtOAc and H_2O peaks. ^1H NMR (EtOAc): δ 1.26, 2.05, 4.12. ^{13}C NMR (EtOAc): δ 14.19, 21.04, 60.49, 171.36. ^1H NMR (H_2O): δ 1.56. IR spectra were recorded with a FT-IR instrument and are reported in wavenumbers (cm^{-1}). HRMS were recorded using ESI (FT-ICR).

General Procedure for the Synthesis of Products 3. To a suspension of MBH carbonates **1** (0.1 mmol) in DCE (1.5 mL) were sequentially added catalyst DBU (0.02 mmol) and phenyl isothiocyanates **2** (0.5 mmol), and the mixture was then stirred and heated with an oil bath at 50 °C for 1.5 or 2 h. The mixture was directly subjected to flash column chromatography on silica gel (200−300 mesh, petroleum ether/ethyl acetate 3:1) to yield the corresponding products.

*(Z)-Methyl ethyl-2-oxo-2′-(phenylimino)-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3b**):* white solid; 97% yield (37 mg); mp 162−165 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.35−7.26 (m, 3H), 7.14−7.11 (m, 2H), 7.06−6.95 (m, 1H), 6.93−6.85 (m, 1H), 6.84 (d, J = 7.6 Hz, 2H), 4.02−3.93 (m, 1H), 3.82−3.73 (m, 1H), 3.59 (s, 3H), 1.337 (t, J = 7.2 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$) δ = 172.3, 167.9, 160.5, 150.4, 143.5, 141.7, 130.3, 129.4, 129.2, 128.4, 125.6, 122.7,122.5, 119.5, 109.2, 67.8, 51.8, 35.4, 12.2 ppm; IR (KBr) ν 3416, 3058, 2954, 2923, 2851, 2367, 1717, 1643, 1607, 1487, 1466, 1361, 1307, 1124, 1096, 1078, 1044, 1023, 915, 833, 739, 696 cm^{-1}; HRMS (ESI) for $C_{21}H_{18}N_2O_3S$ $[M + H]^+$ calcd 379.1111, found 379.1116.

*(Z)-Methyl 4-chloro-1-ethyl-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene]-4′-carboxylate (**3c**):* white solid; 89% yield (37 mg); mp 140−143 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.34−7.25 (m, 3H), 7.13 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.88−6.82 (m, 3H), 3.99−3.90 (m, 1H), 3.78−3.69 (m, 1H), 3.61 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 167.2, 160.4, 150.6, 145.4, 142.8, 130.3, 130.1, 129.1, 128.1, 125.4, 125.3, 123.1, 119.2, 107.1, 67.6, 51.7, 35.6, 11.9 ppm; IR (KBr) 3404, 3058, 2955, 2924, 2853, 2373, 1718, 1646, 1607, 1459, 1378, 1262, 1231, 1208, 1154, 1126, 1083, 1047, 1009, 913, 835, 775, 740, 697 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}ClN_2O_3S$ $[M + H]^+$ calcd 413.0721, found 413.0725.

*(Z)-Methyl 5-chloro-1-ethyl-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene]-4′-carboxylate (**3d**):* white solid; 95% yield (39 mg); mp 164−167 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.34−7.25 (m, 3H), 7.16−7.10 (m, 2H), 6.87−6.85 (m, 3H), 3.99−3.89 (m, 1H), 3.80−3.78 (m, 1H), 3.62 (s, 3H), 1.317 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 167.2, 160.4, 150.1, 142.3, 142.2, 131.8, 129.4, 129.3, 127.94, 127.90, 125.8, 123.1, 119.6, 110.1, 67.7, 52.0, 35.6, 12.1 ppm; IR (KBr) ν 3429, 3058, 2955, 2926, 2853, 2372, 1719, 1645, 1607, 1592, 1486, 1461, 1438, 1377, 1340, 1264, 1230, 1143, 1117, 1041, 920, 835, 764, 741, 698 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}ClN_2O_3S$ $[M + H]^+$ calcd 413.0721, found 413.0727.

*(Z)-Methyl 6-chloro-1-ethyl-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene]-4′-carboxylate (**3e**):* white solid; 98% yield (40 mg); mp 182−184 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.31 (t, J = 8.0 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 7.05−7.00 (m, 2H), 6.93 (s, 1H), 6.83 (d, J = 7.2 Hz, 2H), 3.98−3.89 (m, 1H), 3.79−3.72 (m, 1H), 3.61 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 167.3, 160.5, 150.1, 144.9, 142.0, 135.2, 129.2, 128.7, 127.9, 125.7, 123.5, 122.6, 119.5, 109.9, 67.3, 51.9, 35.6, 12.0 ppm; IR (KBr) ν 3418, 3058, 2956, 2923, 2853, 2373, 1720, 1639, 1606, 1545, 1460, 1317, 1343, 1264, 1121, 1072, 1042, 916, 838, 789, 742 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}ClN_2O_3S$ $[M + H]^+$ calcd 413.0721, found 413.0728.

*(Z)-Methyl 5-bromo-1-ethyl-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene-4′-carboxylate (**3f**):* white solid; 94% yield (43 mg); mp 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.47−7.45 (m, 1H), 7.41 (d, J = 6.4 Hz, 2H), 7.32 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 2 Hz, 1H), 7.17−7.13 (m, 3H), 3.99−3.90 (m, 1H), 3.80−3.70 (m, 1H), 3.63 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 167.0, 160.4, 150.1, 142.7, 142.2, 132.2, 132.1, 129.5, 129.2, 128.9, 127.9, 127.0, 125.8, 125.7, 125.2, 119.5, 115.0, 110.5, 67.5, 51.9, 35.5, 12.0 ppm; IR (KBr) ν 3421, 2956, 2923, 2854, 2369, 1879, 1719, 1639, 1604, 1460, 1377, 1335, 1263, 1117, 1041, 919, 742, 703 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}BrN_2O_3S$ $[M + H]^+$ calcd 459.0196, found 459.0198.

*(Z)-Methyl 6-bromo-1-ethyl-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene]-4′-carboxylate (**3g**):* white solid; 86% yield (40 mg); mp 198−200 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.19−7.12 (m, 2H), 7.08 (d, J = 6.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 7.2 Hz, 2H), 3.98−3.89 (m, 1H), 3.79−3.70 (m, 1H), 3.62 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 167.2, 160.5, 150.2, 145.0, 142.1, 129.3, 127.9, 125.8, 125.6, 123.8, 123.1, 119.5, 112.6, 67.4, 51.9, 35.6, 12.1 ppm; IR (KBr) ν 3415, 3059, 2955, 2927, 2854, 2370, 1722, 1641, 1591, 1488, 1378, 1265, 1243, 1219, 1127, 1082, 1043, 914, 885, 742, 707 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}BrN_2O_3S$ $[M + H]^+$ calcd 459.0196, found 459.0202.

*(Z)-Methyl 7-bromo-1-ethyl-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene]-4′-carboxylate (**3h**):* white solid; 81% yield (37 mg); mp 198−200 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.91−6.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 167.3, 160.4, 150.1, 142.0, 141.3, 135.3, 133.1, 129.2, 128.3, 125.8, 123.9, 121.5, 119.5, 67.3, 51.9, 37.1, 14.3 ppm; IR (KBr) ν 3427, 3058, 2955, 2926, 2853, 2375, 1721, 1646, 1579, 1486, 1464, 1343, 1265, 1225, 1186, 1109, 1084, 1039, 1011, 917, 836, 769, 741, 697 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}BrN_2O_3S$ $[M + H]^+$ calcd 459.0196, found 459.0198.

*(Z)-Methyl 1-ethyl-5-fluoro-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene]-4′-carboxylate (**3i**):* white solid; 90% yield (36 mg); mp 166−168 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.07−7.01 (m, 1H), 6.90−6.84 (m, 4H), 3.99−3.91 (m, 1H), 3.80−3.71 (m, 1H), 3.62 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 167.3, 160.4, 159.0 (d, J_{C-F} = 240.0 Hz), 150.2, 142.2, 139.6 (d, J_{C-F} = 2.0 Hz), 131.6 (d, J_{C-F} = 8.1 Hz), 129.2, 127.9, 125.7, 119.5, 115.6 (d, J_{C-F} = 23.3 Hz), 110.9 (d, J_{C-F} = 25.2 Hz), 109.6 (d, J_{C-F} = 8.0 Hz), 67.9, 51.9, 35.5, 12.1 ppm; IR (KBr) ν 3397, 3051, 2956, 2924, 2854, 2374, 1860, 1719, 1639, 1587, 1492, 1459, 1378, 1343, 1311, 1264, 1208, 1160, 1113, 1072, 1038, 912, 767, 701 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}FN_2O_3S$ $[M + H]^+$ calcd 397.1017, found 397.1023.

*(Z)-Methyl 1-ethyl-7-fluoro-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene]-4′-carboxylate (**3j**):* white solid; 96% yield (38 mg); mp 138−140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.16−7.05 (m, 2H), 7.02−6.97 (m, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 7.6 Hz, 2H), 4.12−4.05 (m, 1H), 4.00−3.91 (m, 1H), 3.62 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 171.9, 167.4, 160.5, 150.1, 147.4 (d, J_{C-F} = 243.0 Hz), 141.9, 132.8 (d, J_{C-F} = 3.6 Hz), 130.5, 130.4, 129.2, 128.1, 125.7, 123.4 (d, J_{C-F} = 6.6 Hz), 119.5, 118.4 (d, J_{C-F} = 3.1 Hz), 117.7, 67.9, 51.9, 37.6, 13.6 ppm; IR (KBr) ν 3427, 3055, 2955, 2926, 2854, 2369, 1723, 1627, 1585, 1461, 1377, 1345, 1264, 1225, 1125, 1022, 863, 830, 705 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}FN_2O_3S$ $[M + H]^+$ calcd 397.1017, found 397.1014.

*(Z)-Methyl 1-ethyl-5-methoxy-2-oxo-2′-(phenylimino)-2′H-spiro-[indoline-3,3′-thiophene]-4′-carboxylate (**3k**):* white solid; 94% yield (38 mg); mp 148−150 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.32−7.26 (m, 2H), 7.15−7.11 (m, 1H), 6.85 (d, J = 5.6 Hz, 4H), 6.74 (s, 1H), 3.99−3.89 (m, 1H), 3.78−3.71 (m, 4H), 3.60 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 167.9, 160.5, 155.9, 150.4, 141.7, 136.9, 131.5, 129.2, 128.4, 125.6, 119.6, 113.3, 110.3, 109.4, 68.1, 55.8, 51.8, 35.4, 12.1 ppm; IR (KBr) ν 3429, 3055, 2955, 2928, 2853, 2373, 1717, 1642, 1603, 1496, 1459, 1437, 1342, 1305, 1265, 1213, 1167, 1120, 1078, 1029, 924, 838, 792, 768, 739, 702 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}N_2O_4S$ $[M + H]^+$ calcd 409.1217, found409.1221.

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*(Z)-Methyl 1-ethyl-5-nitro-2-oxo-2′-(phenylimino)-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3l**):* white solid; 95% yield (40 mg); mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34−8.32 (m, 1H), 8.02 (d, J = 1.6 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 7.03(d, J = 8.4 Hz, 1H), 6.86 (t, J = 7.6 Hz, 2H), 4.05−3.96 (m, 1H), 3.89−3.80 (m, 1H), 3.64 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 166.3, 160.3, 149.7, 149.6, 143.4, 143.0, 131.1, 129.4, 127.3, 126.7, 126.1, 119.5, 118.7, 108.6, 67.3, 52.1, 36.0, 12.1 ppm; IR (KBr) ν 3434, 2955, 2926, 2854, 2372, 1735, 1712, 1647, 1607, 1521, 1490, 1461, 1379, 1338, 1265, 1228, 1143, 1116, 1088, 1039, 925, 853, 832, 795, 742, 704 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}N_3O_5S$ $[M + H]^+$ calcd 424.0962, found 424.0967.

*(Z)-Methyl 1-ethyl-5-methyl-2-oxo-2′-(phenylimino)-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3m**):* white solid; 71% yield (28 mg); mp 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.32−7.28 (m, 2H), 7,14−7.11 (m, 2H), 6.93 (s, 1H), 6.86−6.81 (m, 3H), 3.99−3.90 (m 1H), 3.79−3.71 (m, 1H), 3.59 (s, 3H), 2.31 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 172.3, 168.0, 160.6, 150.4, 141.5, 141.1, 132.2, 130.3, 129.7, 129.1, 128.6, 125.5, 123.3, 119.6, 108.9, 67.8, 51.8, 35.4, 21.0, 12.1 ppm; IR (KBr) ν 3398, 3089, 2954, 2923, 2854, 2369, 1706, 1649, 1621, 1591, 1526, 1460, 1377, 1361,1284, 1211, 1166, 1121, 1076,1040, 1009, 923, 872, 838, 769, 743,689 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}N_2O_3S$ $[M + H]^+$ calcd 393.1267, found 393.1272.

*(Z)-Methyl 1-ethyl-7-methyl-2-oxo-2′-(phenylimino)-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3n**):* white solid; 66% yield (26 mg); mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.32−7.26 (m, 2H), 7.12 (t, J = 7.2 Hz, 1H), 7.07−7.05 (m, 1H), 6.94 (d, J = 6.8 Hz, 2H), 6.83 (d, J = 7.6 Hz, 2H), 4.21−4.11 (m, 1H), 4.06−3.97 (m, 1H), 3.61 (s, 3H), 2.57 (s, 3H), 1.35 (t, J = 6.8 Hz, 3H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 173.4, 168.3, 160.6, 150.5, 141.4, 133.5, 130.8, 129.2, 125.5, 122.7, 120.4, 120.0, 119.5, 67.4, 51.8, 37.3, 18.9, 14.2 ppm; IR (KBr) ν 3406, 3056, 2955, 2925, 2853, 2372, 1718, 1639, 1594, 1526, 1460, 1377, 1342, 1263,1220, 1120, 1084, 1023, 925, 828, 795, 743,702 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}N_2O_3S$ $[M + H]^+$ calcd 393.1267, found 393.1273.

*(Z)-Methyl 1-ethyl-5,7-dimethyl-2-oxo-2′-(phenylimino)-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3o**):* white solid; 74% yield (30 mg); mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.32−7.26 (m, 2H), 7.15−7.10 (m, 1H), 6.85 (d, J = 8.0 Hz, 3H), 6.75 (s, 1H), 4.19−4.09 (m, 1H), 4.03−3.94 (m, 1H), 3.61 (s, 3H), 2.52 (s, 3H), 2.26 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 168.4, 160.6, 150.5, 141.3, 138.9, 133.9, 132.1, 130.9, 129.1, 128.9, 125.5, 121.1, 119.6, 119.5, 67.5, 51.8, 37.2, 20.7, 18.8, 14.1 ppm; IR (KBr) ν 3415, 3056, 2955, 2854, 2373, 1718, 1647, 1592, 1544, 1483, 1466, 1439, 1368, 1339, 1265, 1222, 1170, 1089, 1031, 925, 858, 832, 768, 739, 698 cm^{-1}; HRMS (ESI) for $C_{23}H_{22}N_2O_3S$ $[M + H]^+$ calcd 407.1424, found 407.1428.

*(Z)-Methyl 2′-((4-chlorophenyl)imino)-1-ethyl-2-oxo-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3p**):* white solid; 98% yield (40 mg); mp 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.36−7.32 (m, 1H), 7.28−7.26 (m, 2H), 7.12−7.09 (m, 1H), 7.04 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.4 Hz, 2H), 4.01−3.92 (m, 1H), 3.81−3.73 (m, 1H), 3.59 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 166.3, 160.2, 149.6, 149.5, 143.3, 142.9, 130.9, 129.3, 127.2, 126.6, 126.1, 119.5, 118.6, 108.6, 67.2, 52.1, 35.9, 12.1 ppm; IR (KBr) ν 3408, 3054, 2958, 2925, 2854, 2372, 1719, 1639, 1609, 1587, 1466, 1377, 1351, 1311, 1265, 1235, 1201, 1113, 1076, 1040, 1011, 927, 893, 835, 741, 706 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}ClN_2O_3S$ $[M + H]^+$ calcd 413.0721, found 413.0726.

*(Z)-Methyl 2′-((4-bromophenyl)imino)-1-ethyl-2-oxo-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3q**):* white solid; 95% yield (44 mg); mp 162−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.36−7.32 (m, 1H), 7.11 (d, J = 6.8 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 4.01−3.92 (m, 1H), 3.81−3.72 (m, 1H), 3.59 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 169.1, 160.4, 149.3, 143.5, 141.2, 132.3, 130.1, 129.5, 128.7, 122.8, 122.6, 121.4, 118.8, 109.2, 67.9, 51.9, 35.4, 12.1 ppm; IR (KBr) ν 3408, 3084, 2959, 2927, 2869, 2370, 1718, 1701, 1638, 1609, 1582, 1491, 1465, 1436, 1377, 1352, 1311, 1265, 1236, 1158, 1112, 1040, 1008, 893, 836, 741, 709 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}BrN_2O_3S$ $[M + H]^+$ calcd 459.0196, found 459.0200.

*(Z)-Methyl 1-ethyl-2′-((4-fluorophenyl)imino)-2-oxo-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3r**):* white solid; 98% yield (39 mg); mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.35−7.31 (m, 1H), 7.12−7.10 (m, 1H), 7.06−6.93 (m, 4H), 6.84−6.80 (m, 2H), 4.01−3.92 (m, 1H), 3.82−3.73 (m, 1H), 3.59 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 168.4, 160.5 (d, J_{C-F} = 243.0 Hz), 159.3, 146.4 (d, J_{C-F} = 2.8 Hz), 143.5, 141.3, 130.2, 129.5, 128.6, 122.8, 122.5, 121.3 (d, J_{C-F} = 8.4 Hz), 116.1, 109.2, 67.9, 51.9, 35.4, 12.2 ppm; IR (KBr) ν 3427, 3056, 2924, 2855, 2371, 1879, 1719, 1647, 1610, 1489, 1466, 1377, 1349, 1265, 1232, 1152, 1079, 1044, 894, 841, 740, 705 cm^{-1}; HRMS (ESI) for $C_{21}H_{17}FN_2O_3S$ $[M + H]^+$ calcd 397.1017, found 397.1022.

*(Z)-Methyl 1-ethyl-2′-((4-methoxyphenyl)imino)-2-oxo-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3s**):* white solid; 77% yield (32 mg); mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.33−7.29 (m, 1H), 7.10 (d, J = 6.4 Hz, 1H), 7.02 (t, J = 7.2 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.82 (s, 4H), 3.99−3.92 (m, 1H), 3.79−3.74 (m, 4H), 3.58 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 166.3, 160.6, 157.5, 143.5, 143.4, 141.8, 130.4, 129.3, 128.3, 122.6, 122.5, 121.2, 114.3, 109.1, 67.8, 55.3, 51.8, 35.3, 12.1 ppm; IR (KBr) ν 3411, 3075, 2924, 2851, 2372, 1897, 1719, 1608, 1504, 1464, 1378, 1347, 1265, 1128, 1079, 1021, 906, 831, 742, 706 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}N_2O_4S$ $[M + H]^+$ calcd 409.1217, found 409.1224.

*(Z)-Methyl 1-ethyl-2-oxo-2′-((4-(trifluoromethyl)phenyl)imino)-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3t**):* white solid; 60% yield (27 mg); mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.61−7.55 (m, 2H), 7.37−7.33 (m, 1H), 7.13 (d, J = 6.8 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.97−6.89 (m, 3H), 4.01−3.92 (m, 1H), 3.83−3.74 (m, 1H), 3.59 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.1, 160.4, 153.1, 143.4, 140.9, 129.8, 129.3 (d, J_{C-F} = 107.5 Hz), 127.6, 127.2, 126.5 (q, J_{C-F} = 3.7 Hz), 125.3, 123.8, 122.7 (d, J_{C-F} = 37.5 Hz), 119.7, 109.3, 68.0, 51.9, 35.4, 12.1 ppm; IR (KBr) ν 3414, 3057, 2952, 2928, 2854, 1720, 1643, 1608, 1488, 1466, 1411, 1377, 1324, 1265, 1226, 1163, 1125, 1065, 1044, 1014, 929, 909, 850 cm^{-1}; HRMS (ESI) for $C_{22}H_{17}F_3N_2O_3S$ $[M + H]^+$ calcd 447.0985, found 447.0990.

*(Z)-Methyl 2′-((3,5-bis(trifluoromethyl)phenyl)imino)-1-ethyl-2-oxo-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**3u**):* white solid; 62% yield (32 mg); mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.64 (s, 1H), 7.40−7.36 (m, 1H), 7.27 (d, J = 6.4 Hz, 2H), 7.16−7.07 (m, 2H), 6.97 (d, J = 7.6 Hz, 1H), 4.02−3.93 (m, 1H), 3.84−3.75 (m, 1H), 3.62 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 171.8, 160.2, 151.3, 143.6, 140.0, 132.8 (q, J_{C-F} = 33.4 Hz), 129.8, 129.6 (d, J_{C-F} = 15.2 Hz), 124.3, 123.0, 122.7, 121.6, 120.1, 119.1, 109.4, 68.6, 52.0, 35.5, 12.2 ppm; IR (KBr) ν 3427, 3060, 2955, 2927, 2854, 2373, 1720, 1647, 1609, 1489, 1467, 1439, 1374, 1349, 1278, 1227, 1178, 1136, 1079, 1046, 1010, 938, 917, 892, 847, 739 cm^{-1}; HRMS (ESI) for $C_{23}H_{16}F_6N_2O_3S$ $[M + H]^+$ calcd 515.0859, found 515.0866.

*(Z)-Methyl 1-methyl-2-oxo-5′-(phenylimino)-5′H-spiro[indoline-3,2′-thiophene]-3′-carboxylate (**4**):* ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.34 (ddd, J = 8.9, 8.0, 4.4 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.18−7.12 (m, 1H), 7.06 (dt, J = 7.6, 3.8 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 3.68 (s, 1H), 3.29 (s, 1H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 172.96, 166.39, 161.83, 150.34, 146.22, 143.68, 143.62, 130.09, 129.24, 127.08, 125.98, 124.04, 123.33, 120.25, 108.80, 52.67, 29.70, 27.19; ESI HRMS calcd for $C_{20}H_{16}N_2O_3S$ + H 365.0954, found 365.0953.

*Methyl 5-bromo-1-ethyl-2,2′-dioxo-2′H-spiro[indoline-3,3′-thiophene]-4′-carboxylate (**5f**):* white solid; 86% yield (33 mg); mp 121−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.49−7.47 (m, 1H), 7.14−7.13 (m, 1H), 6.82 (d, J = 8.36 Hz, 1H) 3.91−3.83 (m, 1H), 3.77−3.68(m, 1H), 3.65 (s, 3H), 1.29 (t, J = 7.24 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 196.9, 168.7, 159.8, 143.1, 141.3, 132.9, 128.1, 127.4, 125.9, 115.3, 110.7, 70.4, 52.2, 35.7, 12.0 ppm; IR (KBr) ν 3419, 2953, 1712, 1604, 1483, 1338, 1263, 1228, 1105, 1025, 906, 810, 733 cm^{-1}; HRMS (ESI) for $C_{15}H_{12}BrNO_4S$ $[M + H]^+$ calcd 381.9743, found 381.9745.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01315.

Crystal data for compound **3g** and ^{1}H and ^{13}C spectra (PDF)

X-ray data for compound **3g** (CIF)

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Notes

The authors declare no competing financial interest.

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