EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001001

Link to VoR: https://doi.org/10.1002/ejoc.202001001

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Synthesis of Spiro[benzofuran-2,2'-benzo[*b*]thiophene]-3,3'-diones via PIDA/CuBr-Mediated Spirocyclization

Xuemin Li,[a][d] Huiyuan Liang,[a][d] Yaxin O Yang,[a] Xi Wang,[a] Jingran Zhang,[a] Donghua Wang,[a] Fengxia Sun,[c] Yunfei Du*,[a][b]

Abstract: A phenyliodine(III) diacetate (PIDA)/CuBr-mediated construction of the novel 3*H*,3'*H*-spiro[benzofuran-2,2'-benzo[*b*]thiophene]-3,3'-dione skeleton was realized from the reaction of (*Z*)-3-hydroxy-1-(2-hydroxyphenyl)-3-(2-halogenphenyl)prop-2-en-1-ones with potassium ethylxanthate in the presence of 1,10-phen. The reaction sequence was postulated to encompass a PIDA-mediated oxidative C-O bond formation followed by a CuBr-mediated spirocyclization step.

Introduction

Spiroheterocycles are a class of special spirocyclic compounds containing heteroatoms such as nitrogen, sulfur, and/or oxygen in the spiro ring systems. Due to their particular structure, they have been found to possess the advantageous features of good stereoselectivity and versatile biological properties,[1] which enable them to find wide application in medicines,[2] pesticides,[3] dyes,[4] materials[5] and other fields. Although numerous spiroheterocyclic compounds have been documented so far, the majority of them possess N-atom and/or O-atom within the spiro-ring skeletons,[6] while the S-containing spiroheterocycles are relatively less explored.[7] However, this outcome does not devalue the importance of S-containing spiroheterocycles, as some of them have been found to display various biological activities.[8] For examples, spirothiosteroids (**A**, Figure 1) can be used as progesterone receptors to mimic some of the physiological effects of progesterone. [8a] 4, 8-Diaza-1-thia-spiro[4.5]decane-3-carbox-ylic acid derivatives (**B**, Figure 1), also a class of S-containing spiroheterocycle, can not only protect the liver, reduce inflammation, analgesia, sedation, reduce blood lipid, hypoglycemic, hypotensive, anti-arteriosclerosis, anti-convulsion, anti-epilepsy, vasodilation, but also inhibit platelet aggregation.[8b]

As the spiroheterocycles bearing S-atom in their spiro-ring system are an important class of compounds, much effort has been devoted to the assembly of this special type of heterocyclic skeleton.[7] Literature survey reveals that the predominant existing strategies adopted for the construction of this S-containing spiroheterocyclic compounds include the 1,3-dipolar cycloaddition reactions,[7a-b] radical cycloaddition reactions,[7c] cycloaddition reaction without catalyst,[7d-i] microwave irradiation[7j] and catalytic synthesis.[7k-n] For instances,

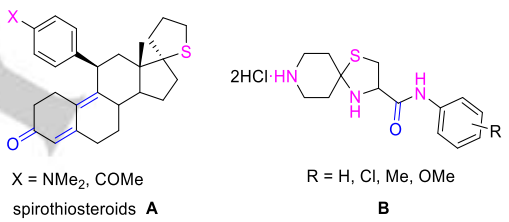

Figure 1. Representative sulfur-containing spiroheterocyclic compounds with application values.

Kochikyan[7f] disclosed an elegant synthesis of spiroheterocyclic compounds from ethyl 5-alkoxymethyl-2-oxotetrahydrofuran-3-carboxylates which reacted with bromine and substituted thioureas (Scheme 1a). In 2019, Behera et. al.[7h] reported that thiadiazolo[3,2-*c*] thiazolines were prepared from the reaction of hydrazine intermediates with thioglycolc acid methanol in DMF at high temperature (Scheme 1b). Kawada and co-workers[7i] synthesized spirobenzothiophene compounds by heating 2-(5-oxo-1,3-oxathiolan-4-yl) benzoic acid with acetic anhydride in triethylamine (Scheme 1c). Yus and co-workers[7k] realized synthesis of 1-thiaspiro[4.5]decane via a $Hg(OAc)_2$-mediated spirolization of hydroxythiol in CF_3CO_2H (Scheme 1d). Glorius, Neugebauer and co-workers[7l] converted benzothiophene derivatives to a class of scarcely explored S-containing spiroheterocycles through an enantioselective NHC-catalyzed intramolecular hydroacylation/dearomatization transformation (Scheme 1e). Although the above approaches have been reported, the overall number of these methods for construction of the S-containing spiroheterocyclic skeleton are relatively limited. Furthermore, all these existing methods utilize the Scontaining substrates, which are somewhat not readily accessible, as the starting materials. In these regards, the development of novel strategy for synthesis of S-containing spiroheterocycles, by introducing the S-atom from the readily

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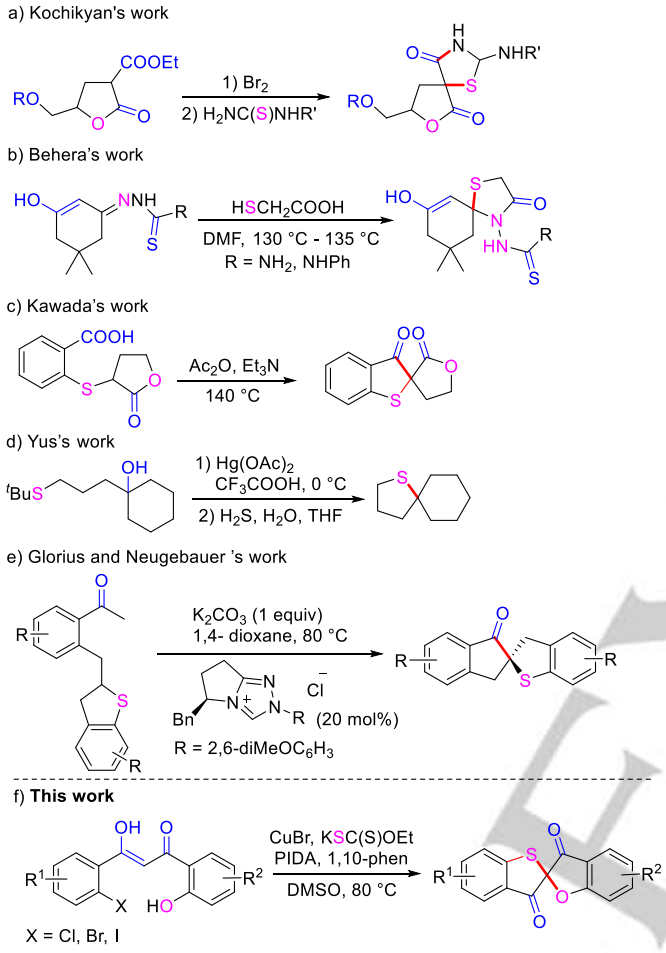
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ chem.201xxxxxx

available S-source, should be highly desirable. In this communication, we reported an alternative method for the construction of 3*H*,3'*H*-spiro[benzofuran-2,2'-benzo[*b*]thiophene]-3,3'-dione skeleton via PIDA/CuBr-mediated intramolecular spirolization of (*Z*)-3-hydroxy-1-(2-hydroxyphenyl)-3-(2-iodophenyl)prop-2-en-1-ones, using potassium ethyl xanthate[9] as S-source to introduce S-atom into the spiroheterocyclic product (Scheme 1f).

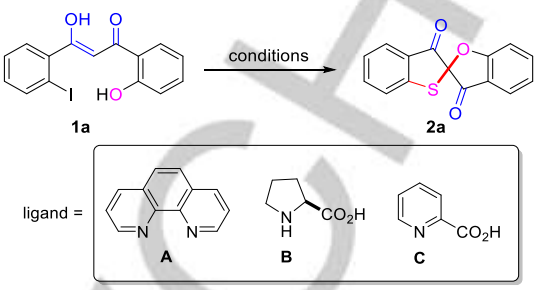


Scheme 1. General Methods for Synthesis of S-Containing Spiroheterocycles.

Results and discussion

Nowadays, transition metal-mediated coupling reaction between aryl halides and S-containing alkyl thiol has become a powerful approach for the construction of aryl C(sp^2)-S bond.[10] In our previous work, we have realized the construction of spiro-2,2'-benzo[*b*]furan-3,3'-one skeleton through a PIDA-mediated spirolization of benzyl protected 3-hydroxy-1,3-bis(2-hydroxyphenyl)prop-2-en-1-ones, during the process of which dual intramolecular C-O bond forming reaction occurs.[11] In continuation of our interest in the assemblage of spiroheterocyclic framework,[6e-g,12] we were motivated to investigate whether we could combine the strategy of transition-metal mediated aryl C(sp^2)-S bond formation with that of the PIDA-mediated C-O/C-S bond formation to produce the S-containing 3*H*,3'*H*-spiro[benzofuran-2,2'-benzo[*b*]thioph-ene]-3,3'-dione compound, an analogue of the previously reported spiro-2,2'-benzo[*b*]furan-3,3'-one compound.

Table 1. Optimization of the Reaction Conditions. [a]



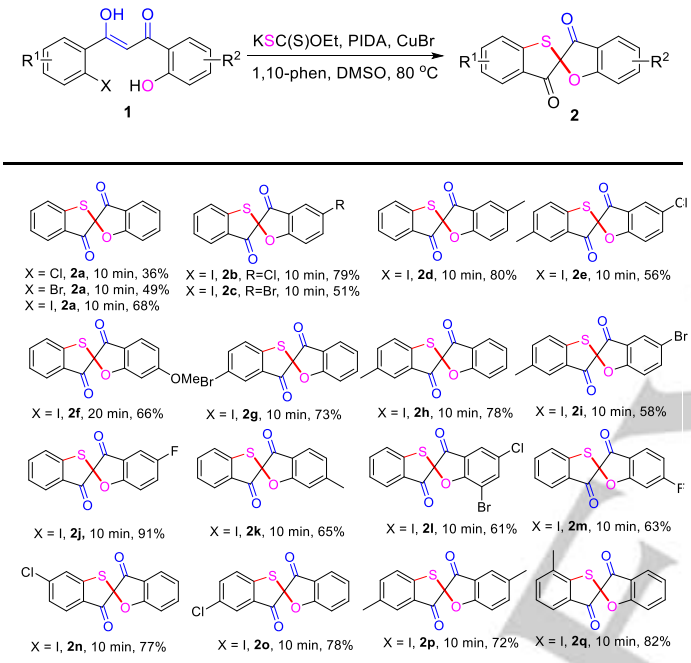
Entry	Oxidant	Catalyst	S Reagent	Ligand	Temp (°C)	Yield (%)[b]
1	$Cu(OTf)_2$	none	KSC(S)OEt	none	80	NR
2	PIDA	$Cu(OTf)_2$	KSC(S)OEt	none	80	31
3	PIDA	CuI	KSC(S)OEt	none	80	32
4	PIDA	CuSCN	KSC(S)OEt	none	80	38
5	PIDA	CuBr	KSC(S)OEt	none	80	43
6	PIFA	CuBr	KSC(S)OEt	none	80	NR
7	TBHP	CuBr	KSC(S)OEt	none	80	37
8	PhIO	CuBr	KSC(S)OEt	none	80	24
9	PIDA	CuBr	KSCN	none	80	NR
10	PIDA	CuBr	S_8	none	80	NR
11	PIDA	CuBr	K_2S	none	80	NR
12	PIDA	CuBr	KSC(S)OEt	none	100	63
13	PIDA	CuBr	KSC(S)OEt	none	60	40
14	PIDA	CuBr	KSC(S)OEt	none	40	27
15	PIDA	CuBr	KSC(S)OEt	none	rt	NR
16	**PIDA**	**CuBr**	**KSC(S)OEt**	**A**	**80**	**68**
17	PIDA	CuBr	KSC(S)OEt	**B**	80	43
18	PIDA	CuBr	KSC(S)OEt	**C**	80	43

[a] Reaction conditions: **1a** (1.0 mmol), oxidant (3 mmol), catalyst (0.2 mmol), 1,10-phen (0.2 mmol) and S reagent (2 mmol) in DMSO (4 mL). [b] Isolated yield. NR = no reaction occurred.

We set out to investigate the viability of the postulated cascade oxidative C-O bond and C-S bond formations toward synthesis of spiroheterocycle **2a** by using (*Z*)-3-hydroxy-1-(2-hydroxyphenyl)-3-(2-iodophenyl)prop-2-en-1-one **1a** as substrate, potassium ethylxanthate as sulfur source, $Cu(OTf)_2$ as copper oxidant and DMSO as solvent. However, to our disappointment, no reaction occurred when the reaction mixture was conducted at 80 °C for 24 h (Table 1, entry 1). To our delight, when PIDA was employed as an oxidant and $Cu(OTf)_2$ as a catalyst, the desired 3*H*,3'*H*-spiro[benzofuran-2,2'-benzo[*b*]thiophene]-3,3'-dione **2a** was formed in 31% yield (Table 1, entry 2). The structure of **2a** was undoubtedly confirmed by X-ray diffraction analysis.[13] The copper catalysts including CuI, CuSCN and CuBr were further tested,[10l,14] and the results showed that CuBr gave the best result (Table 1, entries 3-5). With CuBr as the catalyst, several oxidants including phenyliodine(III) bis(trifluoroacetate) (PIFA), tert-butyl hydroperoxide (TBHP) and iodosobenzene (PhIO) were also screened. However, none of these reagents outcompeted PIDA

(Table 1, entries 6-8). Further study on the other sulfur reagents revealed that when potassium ethylxanthate was replaced by KSCN, S_8 and K_2S, no product formation was observed (Table 1, entries 9-11). Temperature optimization studies identified the ideal temperature to be 80 °C (Table 1, entries 12-15). To our delight, the yield of **2a** increased when 1,10-phen[15] was employed as an additive (Table 1, entry 16). We also studied the other ligands including *L*-proline or picolinic acid, however, only 1, 10-phen gave the best result. (Table 1, entries 17-18). Based on all the screening results, the optimal reaction conditions were concluded to be 1 mmol of substrate **1a**, 3 equiv of PIDA, 0.2 equiv of CuBr, 0.2 equiv of 1,10-phen, 2 equiv of KSC(S)OEt with DMSO as solvent at 80 °C.

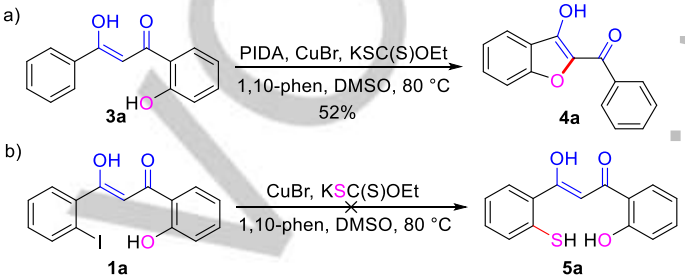
Table 2. Study of Substrate Scope. [a,b]



[a] Reaction conditions: **1** (1 mmol), PIDA (3 mmol), CuBr (0.2 mmol), 1,10-phen (0.2 mmol) and KSC(S)OEt (2 mmol) in DMSO (4 mL) at 80 °C. [b] Isolated yield.

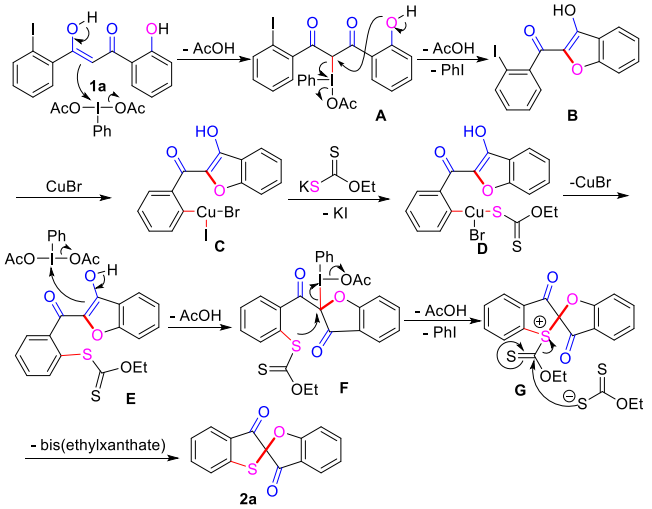
With the optimal conditions in hand, we came to explore the generality and scope of this newly established spirolization method. As indicated by the results in Scheme 2, substrates bearing less reactive C-X bonds, such as C-Br, C-Cl, could afford the desired product **2a** in relatively lower yield. Further study revealed that the substrates bearing either electron-donating groups or electron-withdrawing groups could be converted to the corresponding S-containing spiroheterocycles in satisfactory to good yield. The method worked equally well for the substrates bearing various R^1 and R^2 substituent on the two phenyl rings. To be more specific, for substrates bearing R^2 substituent (Me, OMe, F, Cl, Br), the reaction all delivered the corresponding products in good yields (Table 2, **2b-d**, **2f**, **2j-m**). While R^1 substituent, being either the electron-donating (Me) or the electron-withdrawing (Cl, Br) groups, could be well tolerated, with the corresponding products in most cases obtained in good yields (Table 2, **2g-h**, **2n-o, 2q**).[16] The method was also applicable to the substrates bearing both R^1 and R^2 substituents concurrently, with the corresponding product achieved in relatively lower yields (Table 2, **2e**, **2i**, **2p**).

A control experiment was carried out to gain some insights on the reaction mechanism. When compound **3a**, in which there is no iodo group substituted on the left pheny ring, was applied to the standard conditions, benzofuran **4a** was formed in 52% yield (Scheme 2). Furthermore, when substrate **2a** was subjected to the standard conditions with the exclusion of PIDA, no thiolated product **5a** was found. These results might indicate that the PIDA-mediated oxidative C-O bond formation occurred first during the reaction process.



Scheme 2. Control Experiments for Mechanistic Studies.

Based on the above results as well as the previous literature reports,[17] we postulated a mechanistic pathway for this novel cascade process for synthesizing 3*H*,3'*H*-spiro[benzofuran-2,2'-benzo[*b*]thiophene]-3,3'-dione products (Scheme 3). First, the enolic carbon in **1a** nucleophilically attacked the iodine center of PIDA to give the C-I intermediate **A**.[18] Next, an intramolecular C-O bond formation occurred in **A** to give benzofuran **B**, with the release of one molecule of PhI and acetate. It is worth noting that all of our attempts to isolate and characterize intermediate **B** proved to be infertile. In the presence of copper(I) bromide, Cu was then inserted into the C(sp^2)-I bond, leading to the formation



Scheme 3. Plausible Mechanism.

of a benzofuran-copper(III) complex **C**. Followed by its reaction with potassium ethylxanthate, copper(III) intermediate **D** was formed. Next, reductive elimination of CuBr from **D** afforded intermediate **E**, which reacted with the second molecule of PIDA to give the C-I intermediate **F**. After that, an intramolecular S-C bond formation occurred in **F** to give the sulfonium **G**, with the release of PhI and acetate. Finally, the reaction of intermediate **G** with another molecule of ethylxanthate gave rise to the title product, with the formation of bis(ethoxythiocarbony)sulfide[19] as a byproduct.

Conclusion

In conclusion, we have presented a PIDA/CuBr-mediated spirocyclization reaction involving an intramolecular oxidative C-O bond formation step followed by C-S bond formation process, enabling a convenient synthesis of 3*H*,3'*H*-spiro[benzofuran-2,2'-benzo[*b*]thiophene]-3,3'-dione in satisfactory to good yield. This could represent an alternative strategy for the assemblage of S-containing spiroheterocycles, which features a cascade process introducing S-atom from the readily available potassium ethylxanthate at late stage, rather than utilizing the S-containing substrate. Further studies on the reaction mechanism are still in progress in our lab.

Experimental Section

General Procedure for the synthesis of compound 2: To a suspension of substrate **1** (1.5 mmol), xanthate (3 mmol), CuBr (0.3 mmol), 1, 10-phen (0.3 mmol) in DMSO (5 mL) was added PIDA (4.5 mmol) portionwise at 80 ºC. The resulting mixture was kept at the same temperature until TLC indicated the total consumption of substrate **1**. Then H_2O (30 mL) was added and the reaction mixture was extracted with DCM (3 x 30 mL). The organic phase was washed with sat. NaCl, dried with anhy. Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography on silica gel to afford the desired compound **2**.

3*H*,3'*H*-Spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2a): Following the general procedure for preparation of **2**, **2a** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 274 mg, 68%, an orange solid, mp. 145 - 146 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.67 – 7.62 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.21 (t, *J* = 7.4 Hz, 1H). 13C NMR (150 MHz, $CDCl_3$) δ 160.1, 154.7, 148.3, 142.9, 142.6, 138.4, 129.6, 128.8, 127.7, 127.6, 127.1, 126.8, 123.5, 122.5, 113.7, 112.0, 91.6. HRMS (ESI) m/z calcd for $C_{15}H_8NaO_3S^+$ [M + Na^+] 291.0086, found 291.0089.

5-Methyl-3*H*,3'*H*-2,2'-spiro[*b*][benzofuran]-3,3'-dione (2b): Following the general procedure for preparation of **2**, **2b** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 479 mg, 79%, an orange solid, Decomposition > 300 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 192.8, 170.8, 150.3, 138.8, 137.5, 129.1, 128.3, 126.9, 126.3, 124.8, 124.6, 120.7, 115.2, 95.9. HRMS (ESI) m/z calcd for $C_{15}H_7{}^{35}ClNaO_3S^+$ [M + Na^+] 324.9697, found 324.9700.

5'-Bromo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2c): Following the general procedure for preparation of **2**, **2c** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 266 mg, 51%, an orange solid, mp. 225 - 227 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.9 Hz, 1H), 8.15 (d, *J* = 2.7 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.75 – 7.68 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.8, 192.6, 171.3, 150.4, 141.4, 137.6, 128.4, 128.0, 126.8, 126.2, 124.6, 121.3, 116.1, 115.6, 100.1. HRMS (ESI) m/z calcd for $C_{15}H_7{}^{79}BrNaO_3S^+$ [M + Na^+] 368.9191, found 368.9198.

5'-Methyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2d): Following the general procedure for preparation of **2**, **2d** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 339 mg, 80%, an orange solid, mp. 210 - 212 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.66 (td, *J* = 8.1, 1.3 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.9, 193.6, 171.0, 150.6, 140.2, 137.2, 133.3, 128.2, 127.2, 126.0, 124.9, 124.6, 119.5, 113.4, 95.5, 77.3, 77.0, 76.8, 20.7. HRMS (ESI) m/z calcd for $C_{16}H_{10}NaO_3S^+$ [M + Na^+] 305.0243, found 305.0246.

6-Fluoro-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2e): Following the general procedure for preparation of **2**, **2e** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 390 mg, 82%, an orange solid, mp. 207 - 208 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 2.0 Hz, 1H), 7.65 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.47 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 2.38 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 192.9, 170.8, 147.2, 138.7, 138.7, 136.5, 129.0, 128.3, 127.0, 124.8, 124.3, 120.8, 115.1, 96.3, 20.7. HRMS (ESI) m/z calcd for $C_{16}H_9ClNaO_3S^+$ [M + Na^+] 338.9853 found 338.9855.

6'-Methoxy-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2f): Following the general procedure for preparation of **2**, **2f** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 295 mg, 66%, an orange solid, Decomposition > 300 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 1H), 7.64 (dd, *J* = 10.0, 4.9 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 6.74 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 191.1, 175.1, 169.1, 150.6, 137.2, 128.1, 127.2, 126.6, 126.0, 124.6, 113.1, 112.5, 96.8, 96.1, 56.2. HRMS (ESI) m/z calcd for $C_{16}H_{10}NaO_4S^+$ [M + Na^+] 321.0192, found 321.0195.

5-Bromo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2g): Following the general procedure for preparation of **2**, **2g** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 380 mg, 73%, an orange solid, mp. 147 - 149 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 2.0 Hz, 1H), 7.77 – 7.72 (m, 3H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 1H), 7.22 (dd, *J* = 11.4, 4.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.2, 192.3, 172.4, 149.3, 139.8, 139.1, 130.6, 128.8, 125.8, 125.7, 123.6, 119.8, 119.3, 113.9, 95.4, 77.2, 77.0, 76.8. HRMS (ESI) m/z calcd for $C_{15}H_7{}^{79}BrNaO_3S^+$ [M + Na^+] 368.9191, found 368.9193.

5-Methyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2h): Following the general procedure for preparation of **2**, **2h** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 330 mg, 78%, an orange solid, mp. 168 - 170 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 1H), 7.59 (s, 0H), 7.47 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 0H), 7.25 (s, 0H), 7.20 (t, *J* = 7.5 Hz, 1H), 2.38 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.0, 193.5, 172.5, 147.4, 138.9, 138.6, 136.3, 128.2, 127.3, 125.6, 124.3, 123.4, 119.6, 113.9, 95.6, 77.3, 77.1, 76.9, 20.7. HRMS (ESI) m/z calcd for $C_{16}H_{10}NaO_3S^+$ [M + Na^+] 305.0243, found 305.0248.

5'-Bromo-5-methyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2i): Following the general procedure for preparation of **2**, **2i** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 314 mg, 58%, an orange solid, mp. 185 - 186 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 2.1 Hz, 1H), 7.79 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.59 (s, 1H), 7.52 – 7.46 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.8,

192.7, 171.2, 147.2, 141.4, 138.7, 136.5, 128.3, 127.9, 127.0, 124.3, 121.3, 116.0, 115.5, 96.1, 20.7. HRMS (ESI) m/z calcd for $C_{16}H_9{}^{79}BrNaO_3S^+$ [M + Na$^+$] 382.9348, found 382.9348.

5'-Fluoro-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2j): Following the general procedure for preparation of **2**, **2j** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 391 mg, 91%, an orange solid, mp. 201 - 203 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.45 (dt, *J* = 8.7, 3.1 Hz, 2H), 7.38 (dd, *J* = 6.5, 2.7 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.24 (dd, *J* = 9.0, 3.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.4, 193.4, 193.0, 168.7, 159.3, 157.7, 150.3, 137.4, 128.3, 127.0, 126.7, 126.5, 126.2, 124.6, 120.2, 120.2, 115.1, 115.0, 110.7, 110.5, 96.1. HRMS (ESI) m/z calcd for $C_{15}H_7FNaO_3S^+$ [M + Na$^+$] 308.9992, found 308.9996.

6'-Methyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2k): Following the general procedure for preparation of **2**, **2k** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 287 mg, 65%, an orange solid, mp. 163 - 164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.42 (td, *J* = 8.0, 1.3 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.10 – 7.05 (m, 1H), 6.97 – 6.92 (m, 1H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 193.6, 171.0, 150.6, 140.2, 137.2, 133.3, 128.1, 127.2, 126.0, 124.9, 124.6, 119.5, 113.4, 95.5, 20.7. HRMS (ESI) m/z calcd for $C_{16}H_{10}NaO_3\ S^+$ [M + Na$^+$] 305.0243, found 305.0247.

7'-Bromo-5'-chloro-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2l): Following the general procedure for preparation of **2**, **2l** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 349 mg, 61%, an orange solid, mp. 212 - 214 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.4, 192.2, 167.8, 150.2, 140.8, 137.7, 129.6, 128.5, 126.6, 126.4, 124.6, 123.7, 121.8, 107.6, 96.3, 77.3, 77.1, 76.8. HRMS (ESI) m/z calcd for $C_{15}H_6{}^{81}Br^{35}ClNaO_3S^+$ [M + Na$^+$] 402.8802, found 402.8809.

6'-Fluoro-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2m): Following the general procedure for preparation of **2**, **2m** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 271 mg, 63%, an orange solid, mp. 156 - 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 1H), 7.74 (ddd, *J* = 8.1, 5.7, 0.7 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.27 (m, 1H), 6.93 (dd, *J* = 13.6, 5.4 Hz, 2H).^{13}C NMR (150 MHz, $CDCl_3$) δ 193.4, 193.4, 193.0, 168.7, 159.3, 157.7, 150.3, 137.4, 128.3, 127.0, 126.7, 126.5, 126.2, 124.6, 120.2, 120.2, 115.1, 115.0, 110.7, 110.5, 96.1. HRMS (ESI) m/z calcd for $C_{15}H_7FNaO_3S^+$ [M + Na$^+$] 308.9992, found 308.9996.

6-Chloro-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2n): Following the general procedure for preparation of **2**, **2n** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 350 mg, 77%, an orange solid, mp. 234 - 236 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.29 (d, *J* = 8.6 Hz, 1H), 8.11 (dd, *J* = 11.7, 4.8 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.66 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 155.1, 149.1, 139.5, 137.2, 130.7, 127.8, 125.8, 124.4, 123.8, 120.5, 118.4, 117.8, 113.5. HRMS (ESI) m/z calcd for $C_{15}H_7{}^{35}ClNaO_3S^+$ [M + Na$^+$] 324.9697, found 324.9698.

5-Chloro-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2o): Following the general procedure for preparation of **2**, **2o** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 354 mg, 78%, an orange solid, mp. 246 - 248 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 – 7.72 (m, 3H), 7.62 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.26 – 7.20 (m, 1H).^{13}C NMR (150 MHz, $CDCl_3$) δ 193.3, 192.4, 172.4, 148.7, 139.2, 137.1, 133.7, 132.5, 128.5, 127.6, 125.7, 125.6, 123.6, 119.3, 113.9. HRMS (ESI) m/z calcd for $C_{15}H_7{}^{35}ClNaO_3S^+$ [M + Na$^+$] 324.9697, found 324.9698.

5,5'-Dimethyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-benzofuran]-3,3'-dione (2p): Following the general procedure for preparation of **2**, **2p** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 320 mg, 72%, an orange solid, mp. 235 - 237 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.45 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 2.38 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.0, 193.6, 171.0, 147.4, 140.1, 138.5, 136.2, 133.2, 128.2, 127.3, 124.9, 124.2, 119.5, 113.4, 95.9, 77.3, 77.0, 76.8, 20.7, 20.6. HRMS (ESI) m/z calcd for $C_{17}H_{12}NaO_3S^+$ [M + Na$^+$] 319.0399, found 319.0403.

7'-Methyl-3*H*,3'*H*-spiro[benzofuran-2,2'-benzo[b]thiophene]-3,3'-dione （**2q**）: Following the general procedure for preparation of **2**, **2q** was purified by silica gel chromatography (5% EtOAc/PE). Yield: 347 mg, 82%, an orange solid, mp. 194-196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (ddd, *J* = 8.6, 7.3, 3.7 Hz, 2H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.25 – 7.18 (m, 2H), 2.36 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 193.8, 172.6, 150.2, 138.9, 137.6, 133.9, 127.0, 126.3, 125.60, 125.57, 123.4, 119.6, 113.9, 18.7. HRMS (ESI) m/z calcd for $C_{16}H_{10}NaO_3S^+$ [M + Na$^+$] 305.0243, found 305.0245.

General Procedure for the synthesis of compound 4a: To a suspension of substrate **3a** (1.5 mmol), xanthate (3 mmol), CuBr (0.3 mmol), 1, 10-phen (0.3 mmol) in DMSO (5 mL) was added PIDA (4.5 mmol) portionwise at 80 °C. The resulting mixture was kept at the same temperature until TLC indicated the total consumption of substrate **3a**. Then H_2O (30 mL) was added and the reaction mixture was extracted with DCM (3 x 30 mL). The organic phase was washed with sat. NaCl, dried with anhy. Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography on silica gel to afford the desired compound **4a**.

2-Benzoylbenzofuran-3(2*H*)-one (11): Following the general procedure for preparation of **4**, **11** was purified by silica gel chromatography (10% EtOAc/PE). Yield: 203 mg, 71%, a yellow solid, mp. 105 - 106 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.7, 4.8 Hz, 3H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.15 (td, *J* = 7.7, 1.6 Hz, 1H), 6.57 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.7, 177.5, 162.5, 135.8, 133.7, 132.4, 128.8, 128.5, 126.8, 119.1, 119.0, 118.8, 92.3. HRMS (ESI) m/z calcd for $C_{15}H_{10}NaO_3^+$ [M + Na$^+$] 261.0522, found 261.0527.

Acknowledgments

We acknowledge the National Natural Science Foundation of China (#21472136) for financial support. We thank the instrument analytical center of School of Pharmaceutical Science and Technology at Tianjin University for providing the analysis and Yan Gao and Dr Xiangyang Zhang for the helpful discussion.

Keywords: PIDA • CuBr • potassium ethylxanthate • heterocycle • spirocyclization

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[13] CCDC-1976474 (compound **2a**) contains the supplementary crystallographic data for this work. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[16] We also tried to study the reaction of (*Z*)-3-hydroxy-1-(2-hydroxyphenyl)-3-(2-iodo-6-methylpheny-l)-prop-2-en-1-one, but failed to obtain successful results, due to the fact that its preparation could not be realized by the similar methods.

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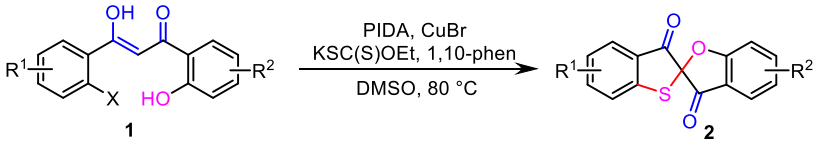

1

X = Cl, Br, I

R^1 = F, Cl, Br, Me

R^2 = F, Cl, Br, Me, OMe

2

19 examples

up to 91% yield

A phenyliodine(III) diacetate (PIDA)/CuBr-mediated construction of the novel 3*H*,3'*H*-spiro[benzofuran-2,2'-benzo[*b*]thiophene]-3,3'-dione skeleton was realized from the reaction of (*Z*)-3-hydroxy-1-(2-hydroxyphenyl)-3-(2-halogenphenyl)prop-2-en-1-ones with potassium ethylxanthate in the presence of 1,10-phen. The reaction sequence was postulated to encompass a PIDA-mediated oxidative C-O bond formation followed by a CuBr-mediated spirocyclization step.

*Heterocycle; Spirocyclization

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Page No. – Page No.

Synthesis of Spiro[benzofuran-2,2'-benzo[*b*]thiophene]-3,3'-diones via PIDA/CuBr-Mediated Spirocyclization