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Cite this: *RSC Adv.*, 2017, 7, 7753

Synthesis of 2-substituted benzo[*b*]thiophene via a Pd-catalyzed coupling of 2-iodothiophenol with phenylacetylene†

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A Pd(II)-catalyzed Sonogashira type cross-coupling reaction between 2-iodothiophenol and phenylacetylene has been developed. A series of 2-substituted benzo[*b*]thiophenes were obtained in moderate to good yield (up to 87%). The application of this method was demonstrated by the synthesis of 2-(4-(*tert*-butyl)phenyl)benzo[*b*]thiophene 1,1-dioxide and (4-methoxyphenyl)(2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone, which exhibit a fluorescence quantum yield of up to 1 and can be used as a cannabinoid receptor ligand, respectively.

Received 10th November 2016

Accepted 9th January 2017

DOI: 10.1039/c6ra26611h

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Introduction

As a crucial class of heterocyclic compounds, 2-substituted benzo[*b*]thiophenes have broad biological properties¹ and diversified applications in the field of materials science.² They are usually considered as important structural motifs in pharmaceuticals and biologically active molecules. For example, as shown in Fig. 1, Bi-BTBT, raloxifene, and *i*Pr-BTBT are examples of commercial drugs and organic semiconductors containing benzo[*b*]thiophene cores.³

The normal approaches to synthesize 2-substituted benzo[*b*]thiophenes are normally focused on a coupling cyclization

reaction of *o*-bromoalkynylbenzenes with various thiol surrogates upon lithium halogen exchange at $-78\text{ }^{\circ}\text{C}$ (Scheme 1a)⁴ or the annulation of alkynylbenzenes (Scheme 1b).⁵ While in the process of reporting this study, a similar study was reported by Fu and co-workers using the electrophilic cyclization of *o*-alkynyl thioanisole (Scheme 1c).⁶ However, the major obstacles of these methods are a result of the harsh reaction conditions or the limitation of the starting materials used.

On the other hand, the Sonogashira cross-coupling reaction⁷ between aryl or alkenyl halides with terminal alkynes in the presence of a transition-metal catalyst has become one of the most powerful methods to prepare alkyl-aryl and diaryl-substituted acetylenes.⁸ In a continuation of our study on catalytic Sonogashira cross-coupling reaction and synthesis of sulfur-containing heterocyclic compounds,⁹ herein we report

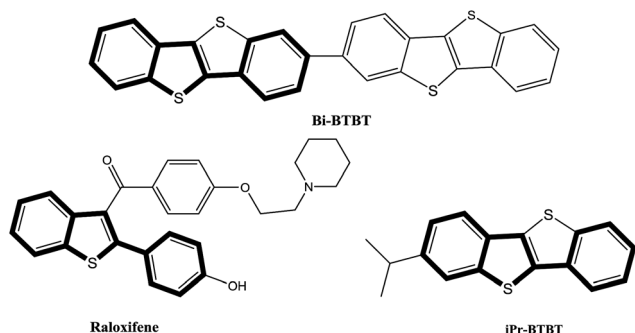
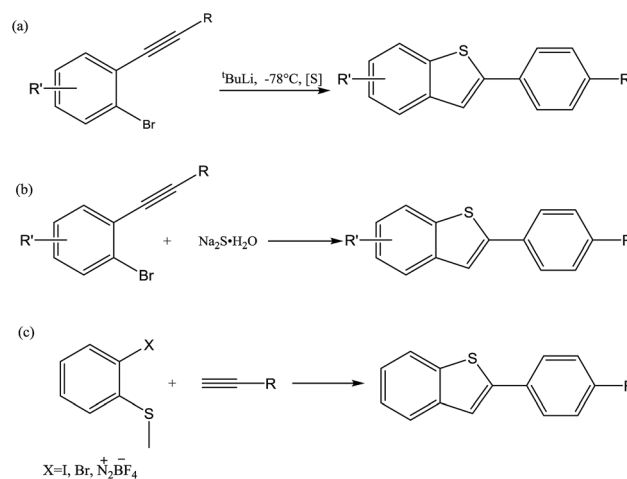


Fig. 1 Selected pharmaceutical and biologically active 2-substituted benzo[*b*]thiophenes.



Scheme 1 Selected examples of the commonly used synthetic methods to prepare 2-substituted benzo[*b*]thiophenes.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra26611h



the palladium-catalyzed synthesis of 2-substituted benzo[*b*]thiophenes using 2-halothiophenols and phenylacetylenes as starting materials.

Results and discussion

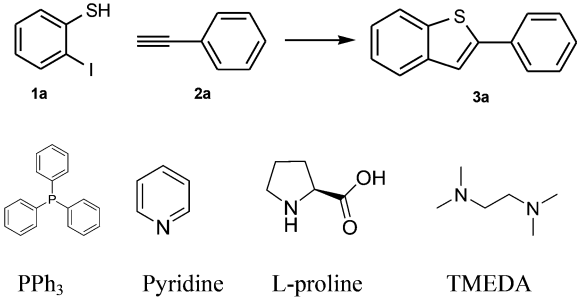
Our investigation started with the model substrates 2-iodothiophenol **1a** and phenylacetylene **2a**. As shown in Table 1, a variety of transition metal salts were tested and palladium acetate exhibited the best catalytic ability with a yield of 34% (Entries 1–8). Moreover, other metals including nickel, cobalt, and iron salts gave much less yields of 4%, 8%, and 5%, respectively (Entries 3, 4, and 5). In the case of copper salt, the coupling product between the alkyne was found to be the major product (Entries 1 and 2).¹⁰ The blank experiment further confirmed that no reaction occurred in the absence of a catalyst

and ligand (Entry 9). Furthermore, silver salts were found to be beneficial to the reaction. In addition, AgTFA was shown to be the best one with a yield of 71% (Entries 10–12). Moreover, the ligand was also proved to promote the catalysis by up to 81% yield in the case of TMEDA (Entries 13–16). Lastly, screening the reaction temperature and catalyst loading indicated that 110 °C and 15 mol% catalyst were optimal for the reaction with yields up to 87% (Entries 17–23). Hence, it was concluded that the best conditions were 15 mol% Pd(OAc)₂, 20 mol% TMEDA, and 1.1 equiv. AgTFA in DMF at 110 °C for 24 h.

With the optimal reaction conditions in hand, we then explored the scope of 2-iodothiophenols and alkynes. As shown in Scheme 2, different alkynes with either electron-withdrawing groups (–F, –Br) or electron-donating groups (–*t*Bu, –OCH₃) can generate the desired products in yields from 41 to 78% under the standard conditions (**3b–3e**). Moreover, 2-iodothiophenols with various functional groups (such as –F, –Cl, and –CF₃) can also be successfully applied in this method and novel compounds such as **3g**, **3h**, and **3i** were also obtained in around 50% yield, which have great potential, especially in pharmaceutical compounds and materials synthesis.

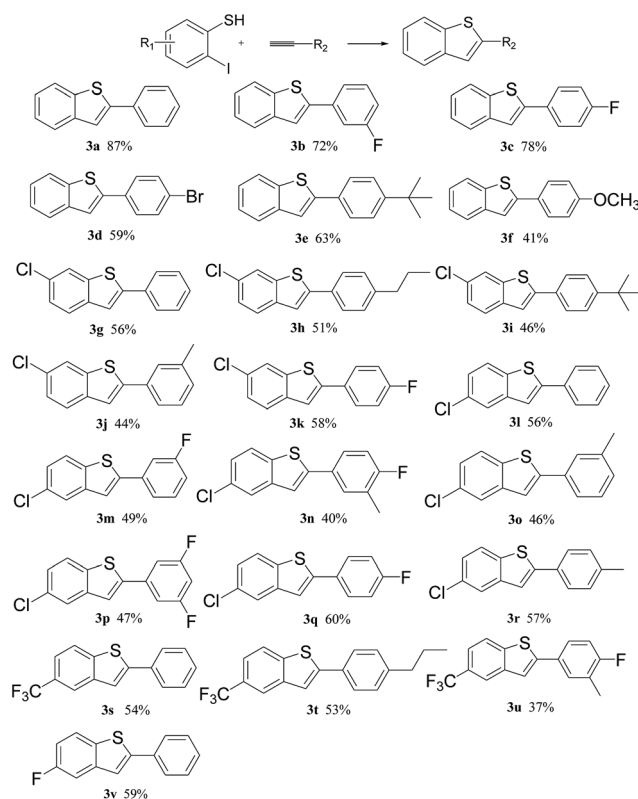
To further explore the potential application of this method, the reaction of **1a** and **2a** was scaled up to 10.0 mmol in a 50 mL one-necked flask and the same efficiency was maintained (Scheme 3). The desired product can be obtained in 75% yield, which confirms its suitability for large-scale reaction.

Table 1 Optimization of the reaction conditions^a



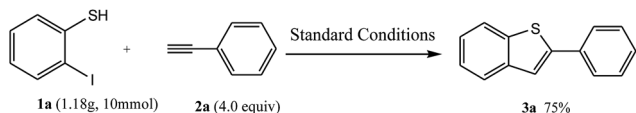
Entry	Catalyst	Ligand	Additive	T/°C	Yield ^b (%)
1	CuI	—	—	100	14
2	CuCl	—	—	100	Trace
3	NiCl ₂	—	—	100	4
4	CoCl ₂ ·6H ₂ O	—	—	100	8
5	FeSO ₄	—	—	100	5
6	Pd(PPh ₃)Cl ₂	—	—	100	28
7	Pd(PPh ₃) ₄	—	—	100	21
8	Pd(OAc) ₂	—	—	100	34
9	—	—	—	100	Trace
10	Pd(OAc) ₂	—	AgOAc	100	68
11	Pd(OAc) ₂	—	Ag ₂ CO ₃	100	66
12	Pd(OAc) ₂	—	AgTFA	100	71
13	Pd(OAc) ₂	PPh ₃	AgTFA	100	75
14	Pd(OAc) ₂	TMEDA	AgTFA	100	81
15	Pd(OAc) ₂	L-Proline	AgTFA	100	69
16	Pd(OAc) ₂	Pyridine	AgTFA	100	72
17	Pd(OAc) ₂	TMEDA	AgTFA	105	82
18	Pd(OAc) ₂	TMEDA	AgTFA	110	85
19	Pd(OAc) ₂	TMEDA	AgTFA	115	84
20	Pd(OAc) ₂	TMEDA	AgTFA	120	84
21 ^c	Pd(OAc) ₂	TMEDA	AgTFA	110	87
22 ^d	Pd(OAc) ₂	TMEDA	AgTFA	110	87
23 ^e	Pd(OAc) ₂	TMEDA	AgTFA	110	86

^a Reaction conditions: 2-iodothiophenol **1a** (0.5 mmol), phenylacetylene **2a** (4 equiv.), catalyst (10 mol%), ligand (20 mol%), and additive (1.1 equiv.) in DMF (2 mL) under N₂ for 24 h. ^b Isolated yields. ^c Pd(OAc)₂ (15 mol%). ^d Pd(OAc)₂ (20 mol%). ^e Pd(OAc)₂ (25 mol%).

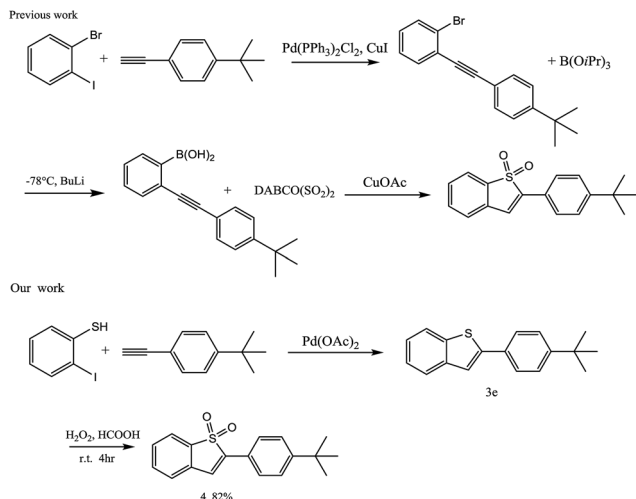


Scheme 2 The synthesis of different benzo[*b*]thiophenes.^{a,b} ^a Reaction conditions: 2-iodothiophenol (0.5 mmol), alkyne (4 equiv.), Pd(OAc)₂ (15 mol%), TMEDA (20 mol%), and AgTFA (1.1 equiv.) in DMF (2 mL) under N₂ at 110 °C for 24 h. ^b Isolated yield.





Scheme 3 The gram scale reaction performed under the standard conditions.



Scheme 4 A comparison of the synthesized compounds **4** and **5**.

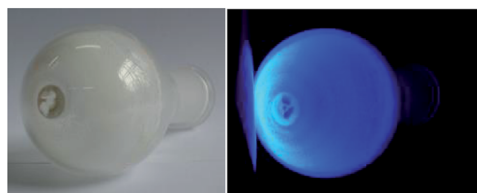


Fig. 2 Images of compound **4** in MeCN (1.0×10^{-5} mol L⁻¹) and the solid state under sunlight (left) and under 360 nm UV light (right).

Furthermore, 2-(4-(*tert*-butyl)phenyl)benzo[*b*]thiophene 1,1-dioxide **4** can be easily obtained after adding H₂O₂ into **3e** at room temperature, which could shorten one step and uses milder reaction conditions when compared with those reported in the literature (Scheme 4).¹¹ Furthermore, Fig. 2 shows images of the compound **4** in MeCN and the solid state under sunlight (left) and under 360 nm UV light (right). Fig. 3 displays the absorption and emission spectra of compound **4** in MeCN (1.0×10^{-5} mol L⁻¹). Note that compound **4** in MeCN exhibited an

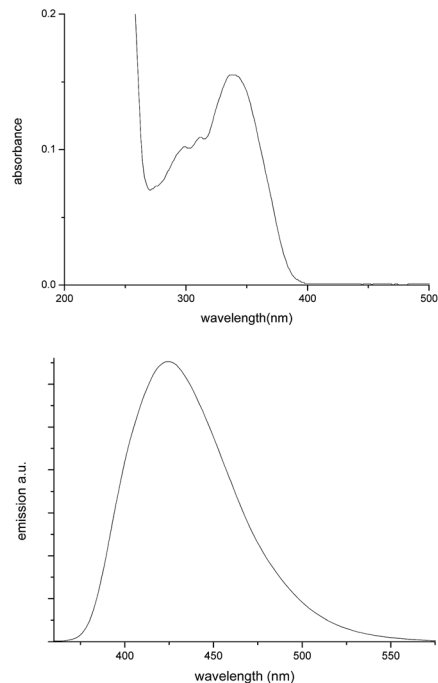
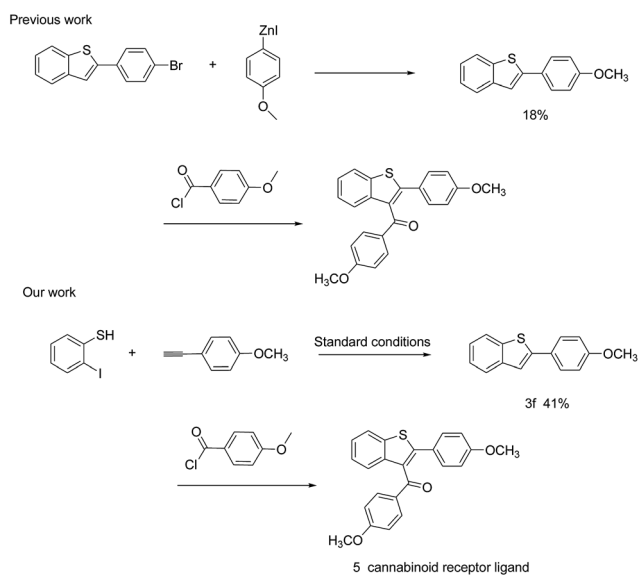
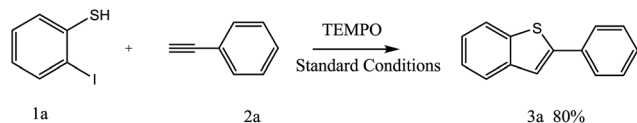


Fig. 3 The absorption and emission spectra of compound **4** in MeCN (1.0×10^{-5} mol L⁻¹).

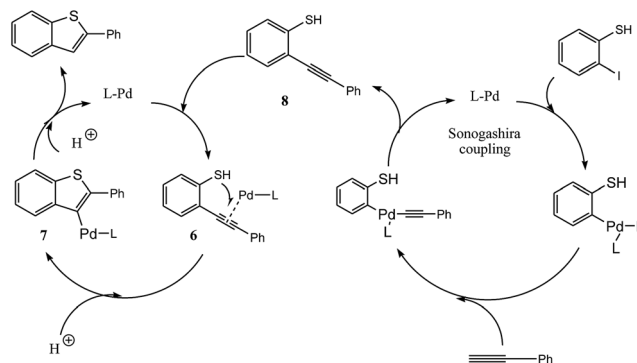
unexpectedly high fluorescence quantum yield of up to 1 that was measured using quinine sulfate as a standard (quinine in 5.0×10^{-5} mol L⁻¹ sulfuric acid), which would show broad prospects for use in organic light-emitting diodes (OLEDs).

Besides this, we also tried to synthesize the benzothiophene derivative (4-methoxyphenyl)(2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone **5** using product **3f** as the starting material in a higher yield than that reported in the literature. Compound **5** has been reported as a new cannabinoid receptor ligand and an intermediate of thrombin inhibitor.¹²





Scheme 5 The radical/electron trapping experiment.



Scheme 6 The proposed reaction pathway.

To explore the reaction pathway, a radical trapping experiment was carried out by the addition of a typical radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl). Almost the same yield (80%) indicated that the reaction did not involve a radical intermediate (Scheme 5). Furthermore, the intermediate 2-(phenylethynyl)benzenethiol **8** was observed by GC/MS in the reaction between 2-iodothiophenol and phenylacetylene after 3 hours.

Based on the experimental and literature data, we proposed a reaction pathway for the palladium-catalyzed synthesis of 2-substituted benzo[*b*]thiophenes from 2-halophenols and alkynes, which consists of two steps: the Sonogashira coupling of 2-halothiophenol with the alkyne and the subsequent cyclization of 2-alkynylthiophenol (Scheme 6). First, the Pd-catalyzed Sonogashira coupling of 2-halothiophenol with the alkyne affords intermediate **8**. Then, coordination of Pd with intermediate **8** may provide complex **6**, whose subsequent addition to the C–C triple bond gave intermediate **7**. Protonation of intermediate **7** results in the formation of benzo[*b*]thiophene and the regenerated Pd-catalyst.

Conclusions

In summary, we developed an efficient catalytic system using 2-iodothiophenols as the starting material for the synthesis of a variety of 2-substituted benzo[*b*]thiophenes. This protocol involves the following advantages: easily available starting materials and simple operations with moderate to good yields, and will contribute a new optional route for the construction the benzo[*b*]thiophene ring. Moreover, the application of this method was considered as an example by the synthesis of 2-(4-(*tert*-butyl)phenyl)benzo[*b*]thiophene 1,1-dioxide and (4-methoxyphenyl)(2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl) methanone, which exhibit a fluorescence quantum yield up to 1 and use as a cannabinoid receptor ligand, respectively.

Acknowledgements

We are grateful to the Natural Science Foundation of China (grant no. 21372169, 21472128, J1310008). We also acknowledge the comprehensive training platform of the specialized laboratory, College of Chemistry, Sichuan University for HRMS analysis.

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