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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.

Introduction

As a crucial class of heterocyclic compounds, 2-substituted benzo[*b*]thiophenes have broad biological properties[1] 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 iPr-BTBT are examples of commercial drugs and organic semiconductors containing benzothiophene 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 °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 reaction[7] 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 diarylsubstituted 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

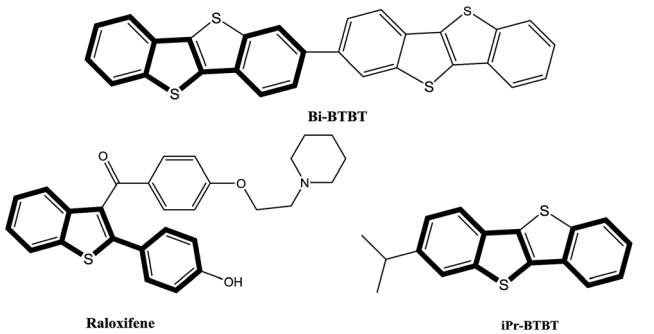
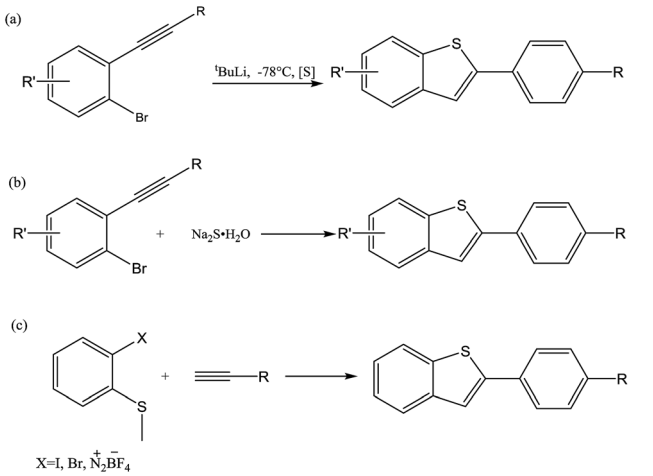


Fig. 1 Selected pharmaceutical and biologically active 2-substituted benzo[*b*]thiophenes.



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

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

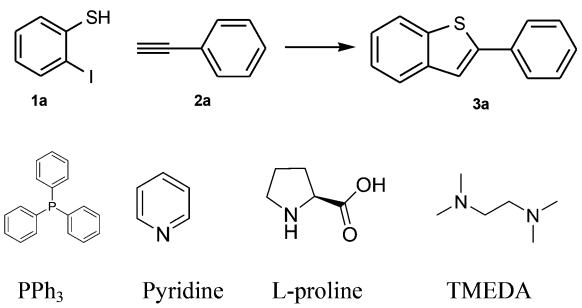
Results and discussion

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, $-OCH_3$) 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 $-CF_3$) 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.

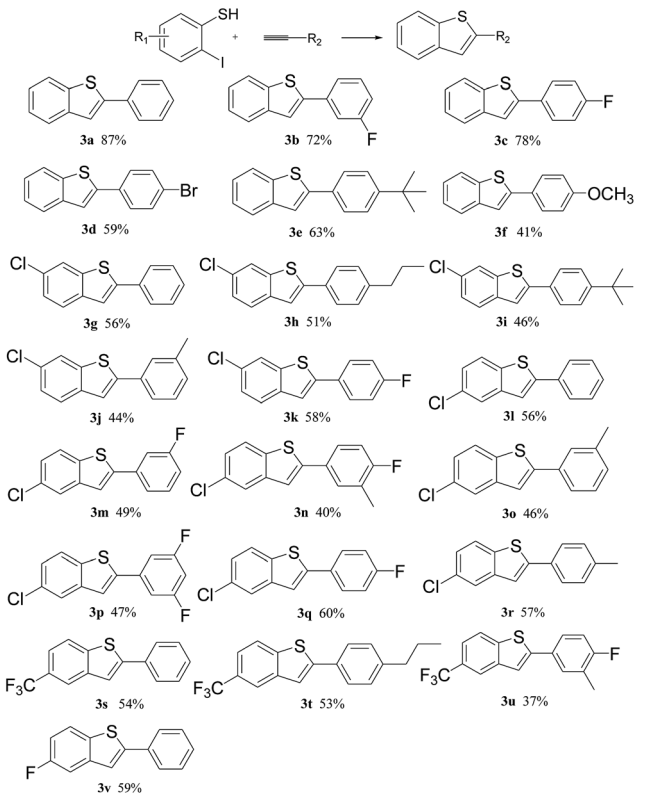
To further explore the potential application of this method, the reaction of **1a** and **2a** was scaled up to 10.0 mmol in a 50 mL one-necked flask and the same efficiency was maintained (Scheme 3). The desired product can be obtained in 75% yield, which confirms its suitability for large-scale reaction.

Table 1 Optimization of the reaction conditions[a]

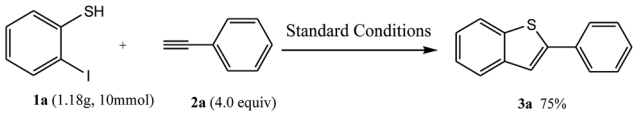


Entry	Catalyst	Ligand	Additive	*T*/°C	Yield[b] (%)
1	CuI	—	—	100	14
2	CuCl	—	—	100	Trace
3	$NiCl_2$	—	—	100	4
4	$CoCl_2 \cdot 6H_2O$	—	—	100	8
5	$FeSO_4$	—	—	100	5
6	$Pd(PPh_3)Cl_2$	—	—	100	28
7	$Pd(PPh_3)_4$	—	—	100	21
8	$Pd(OAc)_2$	—	—	100	34
9	—	—	—	100	Trace
10	$Pd(OAc)_2$	—	AgOAc	100	68
11	$Pd(OAc)_2$	—	Ag_2CO_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

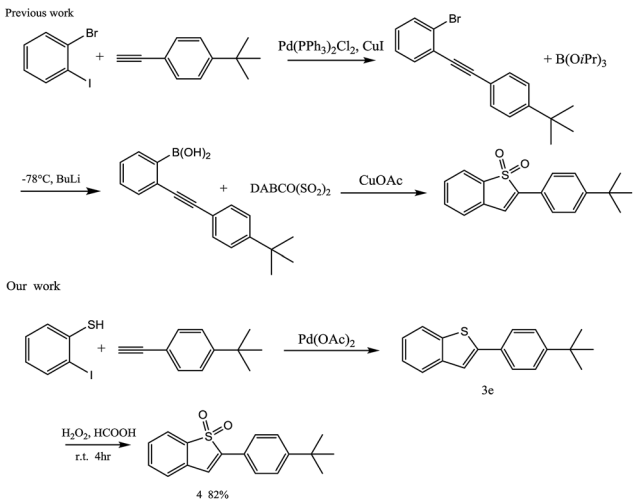
[a] Reaction conditions: 2-iodothiophenol **1a** (0.5 mmol), phenylacetylene **2a** (4 equiv.), catalyst (10 mol%), ligand (20 mol%), and additive (1.1 equiv.) in DMF (2 mL) under N_2 for 24 h. [b] Isolated yields. [c] $Pd(OAc)_2$ (15 mol%). [d] $Pd(OAc)_2$ (20 mol%). [e] $Pd(OAc)_2$ (25 mol%).



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 N_2 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 H_2O_2 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

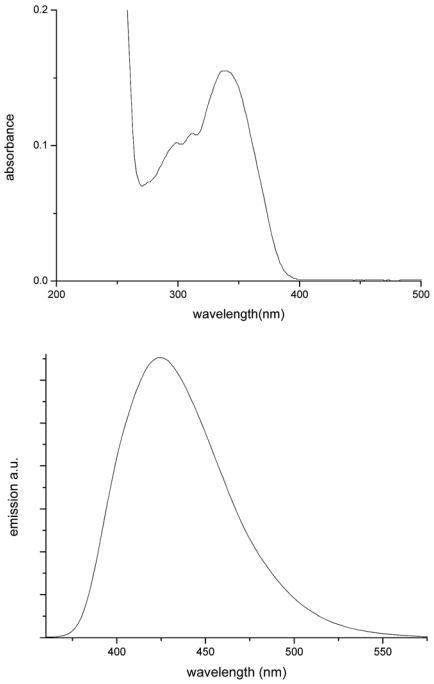
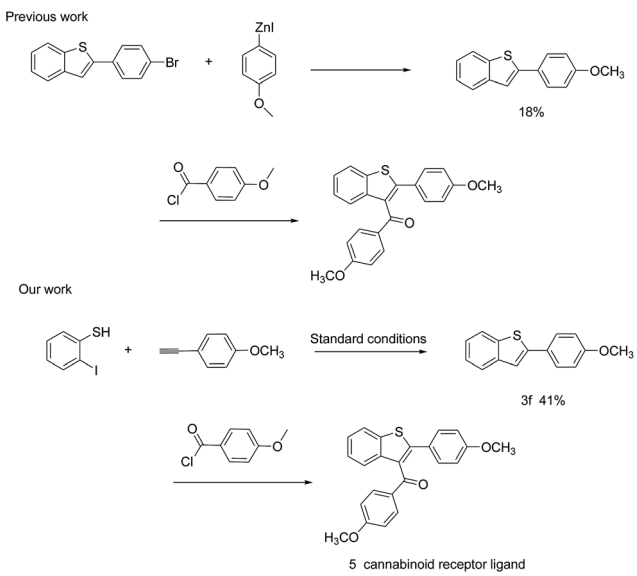
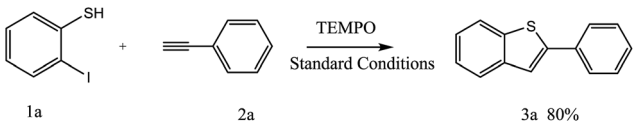


Fig. 3 The absorption and emission spectra of compound **4** in MeCN (1.0×10^{-5} mol L^{-1}).

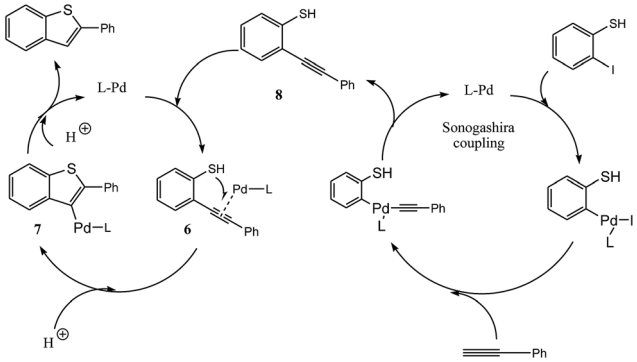
unexpectedly high fluorescence quantum yield of up to 1 that was measured using quinine sulfate as a standard (quinine in 5.0×10^{-5} mol L^{-1} sulfuric acid), which would shows broad prospects for use in organic light-emitting diodes (OLEDS).

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

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