Synthesis of 2-substituted benzo[\textit{b}]thiophene via a Pd-catalyzed coupling of 2-iodothiophenol with phenylacetylene\(^\dagger\)

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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[\textit{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[\textit{b}]thiophene 1,1-dioxide and (4-methoxyphenyl)(2-(4-methoxyphenyl)benzo[\textit{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[\textit{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[\textit{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
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-iodo-
thiophenol 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). 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-halothiophenols and alkynes. As shown
in Scheme 2, different alkynes with either electron-withdrawing
groups (–F, –Br) or electron-donating groups (–Bu, –OCH3) can
generate the desired products in yields from 41 to 78% under
the standard conditions (3b–3e). Moreover, 2-halothiophenols
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 pharma-
ceutical 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.

| Entry | Catalyst | Ligand | Additive | T/°C | Yielda (%) |
|-------|----------|--------|----------|------|------------|
| 1     | CuI      | —      | —        | 100  | 14         |
| 2     | CuCl     | —      | —        | 100  | Trace      |
| 3     | NiCl2    | —      | —        | 100  | 4          |
| 4     | CoCl2. 6H2O | —   | —        | 100  | 8          |
| 5     | FeSO4    | —      | —        | 100  | 5          |
| 6     | Pd[PPh3]Cl2 | —    | —        | 100  | 28         |
| 7     | Pd[PPh3] | —      | —        | 100  | 21         |
| 8     | Pd(OAc)2 | —      | —        | 100  | 34         |
| 9     | —        | —      | —        | 100  | Trace      |
| 10    | Pd(OAc)2 | —      | AgOAc    | 100  | 68         |
| 11    | Pd(OAc)2 | —      | Ag2CO3   | 100  | 66         |
| 12    | Pd(OAc)2 | —      | AgTFA    | 100  | 71         |
| 13    | Pd(OAc)2 | PPh3   | AgTFA    | 100  | 75         |
| 14    | Pd(OAc)2 | —      | TMEDA    | 100  | 81         |
| 15    | Pd(OAc)2 | —      | L-Proline| 100  | 69         |
| 16    | Pd(OAc)2 | —      | Pyridine | 100  | 72         |
| 17    | Pd(OAc)2 | —      | TMEDA    | 100  | 82         |
| 18    | Pd(OAc)2 | —      | TMEDA    | 110  | 85         |
| 19    | Pd(OAc)2 | —      | TMEDA    | 115  | 84         |
| 20    | Pd(OAc)2 | —      | TMEDA    | 120  | 84         |
| 21a   | Pd(OAc)2 | —      | TMEDA    | 110  | 87         |
| 22a   | Pd(OAc)2 | —      | TMEDA    | 110  | 82         |
| 23a   | Pd(OAc)2 | —      | TMEDA    | 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.
Furthermore, 2-(4-(tert-butyl)phenyl)benzo[b]thiophene 1,1-dioxide 4 can be easily obtained by adding H$_2$O$_2$ 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).\textsuperscript{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 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.\textsuperscript{12}
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 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 benzothiophenes from 2-halothiophenols 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 benzothiophene 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 benzothiophenes. 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 of benzothiophene ring. Moreover, the application of this method was considered as an example by the synthesis of 2-(4-(tert-butyl)phenyl)benzothiophene 1,1-dioxide and (4-methoxyphenyl)(2-(4-methoxyphenyl)benzothiophene-3-yl)methanone, which exhibit a fluorescence quantum yield up to 1 and use as a cannabinoid receptor ligand, respectively.

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Notes and references

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