Divergent synthesis of 3-substituted thieno[3,4-b]thiophene derivatives via hydroxy-based transformations†

Yue Zhou, Jie Hao and Dongbing ZhaoID*

Herein, we have developed the first Pd-catalytic method for the preparation of 3-hydroxythieno[3,4-b]thiophene-2-carboxylate, which can be widely utilized as the chemical building block for modular assembly of structurally diverse 3-substituted thieno[3,4-b]thiophene derivatives via hydroxy-based transformation. Furthermore, we have evaluated the effect on their photophysical properties of the introduction of different substitutions at the C3-position and prepared conjugated polymers bearing 3-substituted thieno[3,4-b]thiophene units. We demonstrated that the photoluminescence (PL) properties of thieno[3,4-b]thiophene-2-carboxylate can be efficiently modulated by introducing different functional groups at the C3-position.

As is well recognized, thiophene-based conjugated molecules have played an indispensable role in the development of organic optoelectronics. Among various thiophene building blocks, the thieno-[3,4-b]thiophene (TT) unit with functional groups has recently emerged as an extremely attractive electron-withdrawing building block in organic electronics. In particular, thieno[3,4-b]thiophenes (TbTs) bearing a carboxyl group have been widely used in the development of donor and acceptor materials in organic solar cells (OSCs) represented by the PTB series family polymers and IDT-derived non-fullerene small molecules acceptors with state-of-the-art power conversion efficiencies (PCEs) (Scheme 1). Thieno[3,4-b]thiophene (TbT) is an asymmetric fused bithiophene containing four functionalization positions, in which the proaromatic thiophene can effectively stabilize the quinoidal resonance of the aromatic thiophene, narrow the energy gap, and modulate the electronic structures of the resulting molecules.

Historically, synthesis of thieno[3,4-b]thiophenes (TbTs) bearing a carboxyl group involved: (1) Cu-mediated coupling between 4-bromothiophene-3-carbaldehyde and 2-mercaptoacetate (Scheme 2a). However, this method is suitable only for the preparation of 3-unsubstituted thieno[3,4-b]thiophenes; (2) the non-catalytic multi-step cyclization reaction from 3-substituted thiophene-2-carboxylate (Scheme 2b). Even though this method has the capacity to access 3-substituted thieno[3,4-b]thiophenes, it still suffers from disadvantages such as linear multi-step synthesis (more than 5 steps needs for each product), low yields, harsh reaction conditions, and limited substrate scopes. Thus, development of a methodology to access thieno[3,4-b]thiophenes with various substitution patterns at the 3-position in a rapid and modular manner from readily available precursors is highly appealing. Herein, we have developed the first Pd-catalytic method for the preparation of 3-hydroxythieno[3,4-b]thiophene-2-carboxylate.

State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, 94 Weijin Road, Tianjin 300071, China.
E-mail: dongbing.chem@nankai.edu.cn
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9qm00128j

Received 26th February 2019, Accepted 30th April 2019
DOI: 10.1039/c9qm00128j
rsc.li/frontiers-materials

RESEARCH ARTICLE
Table 1 Optimization of directed hydroarylation of unactivated alkene 1a with ethyl 2-mercaptoacetate 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$</td>
<td>CuO</td>
<td>—</td>
<td>DMSO</td>
<td>60</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$</td>
<td>CuO</td>
<td>—</td>
<td>DMSO</td>
<td>140</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>CuO</td>
<td>Phen</td>
<td>DMSO</td>
<td>140</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>DIPEA</td>
<td>Pd$_2$dba$_3$</td>
<td>Xantphos</td>
<td>Toluene</td>
<td>120</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>K$_2$CO$_3$</td>
<td>Pd$_2$dba$_3$</td>
<td>Xantphos</td>
<td>Toluene</td>
<td>120</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>KO'Bu</td>
<td>Pd$_2$dba$_3$</td>
<td>Xantphos</td>
<td>Toluene</td>
<td>120</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>NaO'Bu</td>
<td>Pd$_2$dba$_3$</td>
<td>Xantphos</td>
<td>Toluene</td>
<td>120</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>DIPEA</td>
<td>—</td>
<td>Xantphos</td>
<td>Toluene</td>
<td>120</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

* Reactions were carried out with [M] catalyst (10 mol%), ligand (10 mol%), base (1.5 equiv.), 1a (0.2 mmol), and ethyl 2-mercaptoacetate 2a (0.4 mmol) in solvent [1 mL] for 24 h under a N$_2$ atmosphere. * Yields were determined by isolation. N.R.: no reaction.

Scheme 2 The conventional synthetic methods to access thieno[3,4-b]thiophene-2-carboxylates and our study.

from commercially available 4-bromothiophene-3-carboxylate and 2-mercaptoacetate (Scheme 2c), which has never been prepared before our study. We demonstrated that this 3-hydroxythieno[3,4-b]thiophene-2-carboxylate can be widely utilized as a chemical building block for modular assembly of structurally diverse 3-substituted thieno[3,4-b]thiophene derivatives via a wide range of hydroxy-based transformations. Moreover, we have evaluated the effect on their photophysical properties of the introduction of the hydroxy group at the C3-position and then developed a series of TT-based conjugated polymer donors.

In our preliminary study, the reaction of butyl 4-bromothiophene-3-carboxylate 1a with ethyl 2-mercaptoacetate 2a was examined under Cu-catalytic conditions. Unfortunately, the developed Cu-catalytic system for the preparation of 3-unsubstituted thieno[3,4-b]thiophene-2-carboxylate was not effective for this conversion (Table 1, entries 1–3). After an extensive screening such as different Pd sources, solvents, reaction times and ligands, we found that treatment of 1a (0.2 mmol) and 2a with Pd$_2$dba$_3$ (5 mol%), xantphos (10 mol%) in toluene (1 mL) at 120 °C for 24 h gave product 3a in 97% yield (Table 1, entry 4). Evaluation of different bases revealed that DIPEA was the best choice (entries 3–7). There is no reactivity at all in the absence of Pd catalyst (entry 8). Finally, we demonstrated that the product 3a can be smoothly cyclized to form the key intermediate 3-hydroxythieno[3,4-b]thiophene-2-carboxylate (entry 4) with 81% yield in the presence of KO'Bu in THF.

As we proposed, the product 3-hydroxythieno[3,4-b]thiophene-2-carboxylate 4a obtained by the method described herein could provide access to structurally diverse 3-substituted thieno[3,4-b]thiophene-2-carboxylates by means of additional hydroxy-based transformations (Scheme 3). First, the hydroxy group of 4a was easily methylated to yield the 3-methoxythieno[3,4-b]thiophene-2-carboxylate 5 using methyl iodide as the methylation reagent. 3-Methoxythieno[3,4-b]thiophene-2-carboxylate 5 could further undergo bromination in the presence of NBS in DMF to yield compound 6 with 60% yield. Furthermore, the hydroxy group of 4a could also be smoothly transformed to –OTf in the presence of Tf$_2$O/pyridine, which is a versatile leaving group in a lot of different types of cross-coupling reactions. For example, the –OTf of 7 can couple with NaSCH$_3$ under Pd-catalytic conditions to produce compound 8 in 91% yield. In addition, the amination of product 7 with diphenylmethanimine in the presence of a Pd catalyst and K$_3$PO$_4$ in toluene also worked smoothly to afford the corresponding 9 in 86% yield. Product 7 could also undergo Suzuki coupling to yield 3-phenylthieno[3,4-b]thiophene-2-carboxylate 10 in 97% yield. Pd-Catalyzed Sonogashira coupling of product 7 and ethynylbenzene also smoothly occurred to access 3-alkynylthieno[3,4-b]thiophene-2-carboxylate 11 with 91% yield.

After development of the modular methodology to access diverse 3-substituted thieno[3,4-b]thiophene-2-carboxylates, we aimed to introduce these building blocks into conjugated polymers.
Following the procedures developed, we synthesized the 3-methoxy and 3-methylthio TbT monomers with a branched alkyl chain to guarantee enough solubility of the polymers. The synthetic route is described in Scheme 4 (upper panel). Furthermore, we found that 4-bromo-6-formyl-3-substituted [3,4-b]thiophene-2-carboxylate 18 could be produced by regioselective mono-formylation and sequential bromination, which can be further utilized in the development of new small molecule donors and acceptors.10 Then, a series of conjugated polymers were prepared by Stille coupling reactions of the TbT monomers and BDT-T or BDT,11 namely P1, P2, P3, and P4 (Scheme 4, lower panel). Detailed synthetic routes and characterizations can be found in the Experimental section of the ESI.†

Table 2  Optical properties of 5, 8, 9, 10, 11 and TT in both the solid state and CH2Cl2 solution

<table>
<thead>
<tr>
<th>Comp.</th>
<th>UV-Vis absorption</th>
<th>Emission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\lambda_{\text{max}}$</td>
<td>$\Phi_{\text{film}}$</td>
</tr>
<tr>
<td>TT</td>
<td>338</td>
<td>352</td>
</tr>
<tr>
<td>5</td>
<td>352</td>
<td>388</td>
</tr>
<tr>
<td>8</td>
<td>368</td>
<td>400</td>
</tr>
<tr>
<td>9</td>
<td>369</td>
<td>400</td>
</tr>
<tr>
<td>10</td>
<td>352</td>
<td>359</td>
</tr>
<tr>
<td>11</td>
<td>378</td>
<td>397</td>
</tr>
</tbody>
</table>

a Absolute quantum yield determined with an integrating sphere system. n.d. = not detected due to the weak emission intensity.

We first evaluated the effect of the substitution at the C3-position of thieno[3,4-b]thiophene-2-carboxylate on their photophysical properties. The absorption maxima, photoluminescence (PL) emission maxima, and PL quantum yields ($\Phi_{\text{PL}}$) of compounds TT, 5, 8, 9, 10 and 11 in both the solid state and CH2Cl2 solution are listed in Table 2, whereas the corresponding absorption and emission spectra are depicted in Fig. 1 and Fig. S1 (ESI†). It is worth noting that all these compounds were stable to light, humidity and air. As shown in Fig. 1, the substitution at the C3-position was observed to greatly influence the molecular absorption and fluorescence. By incorporation of functional groups into the C3-position, all of the absorption and emission peaks of these derivatives were obviously red-shifted and their PL efficiencies were also enhanced in comparison with the ethyl[3,4-b]thiophene-2-carboxylate (TT) in both the solid state and CH2Cl2 solution. This might stem from the restriction of intramolecular rotation (RIR) of the ester group at the C2-position and substitution at the C3-position. Fig. 1b and c reveal that the
emission peaks of these monomers in thin films are different from their emissions in CH₂Cl₂. This likely indicates that these monomers involved different intermolecular interactions and molecular aggregation in the solid state and in the dilute solution state.

The optical properties of these conjugated polymers bearing 3-methoxy and 3-methylthio TbT units in solution and in thin films were then also characterized by UV-Vis absorption spectroscopy as shown in Fig. 2. The corresponding spectroscopic data are summarized in Table 3. In general, the absorption maxima of these polymers bearing 3-methoxy or 3-methylthio[3,4-b]thiophene-2-carboxylate in solution and in films showed blue-shifts compared with the related polymers, which did not have substitution at the C3-position. This means that the steric hindrance of these substitutions at the C3-position likely disrupted the conjugation of the polymer chain. Thiomethylation of the polymers lead to larger blue-shifts in the absorption spectra compared with the related polymers, which did not have substitution at the C3-position. The results indicated that we can efficiently tune the energy levels, the optical bandgaps and absorption spectra by introducing different functional groups at the C3-position. Finally, gel permeation chromatography (GPC) was also measured to obtain the molecular weights. It showed average Mₙ of 14.4, 10.8, 21.2, and 12.3 kDa for P₁, P₂, P₃, and P₄, respectively. The polydispersity index (PDI) of these polymers was determined to be about 1.8–2.1. Notably, all the polymers are soluble in chloroform (CHCl₃), chlorobenzene (CB), and 1,2-dichlorobenzene (DCB).

From the absorption onset in films, the optical bandgaps are determined from the onset wavelength of the optical absorption: $E_g^\text{opt} = 1240/\lambda_{\text{max}}^\text{opt}$ (eV). In acetonitrile solution with 0.1 M N-Bu₄NPF₆ as a supporting electrolyte, the molecular weights measured using gel permeation chromatography (against polystyrene standards) in chlorobenzene at 80°C.

Conclusions

In conclusion, we have developed the first Pd-catalytic method for the preparation of 3-hydroxythieno[3,4-b]thiophene-2-carboxylate, which has never been prepared before our study. Furthermore, we demonstrated that 3-hydroxythieno[3,4-b]thiophene-2-carboxylate can be employed as a versatile chemical building block for modular assembly of structurally diverse 3-substituted thieno[3,4-b]thiophene derivatives via hydroxy-based transformations. Additionally, the optical and electrochemical properties of these 3-substituted thieno[3,4-b]thiophene derivatives were also investigated. The results revealed that the photoluminescence (PL) properties of thieno[3,4-b]thiophene-2-carboxylate can be efficiently modulated by introducing different functional groups at the C3-position. Finally, several conjugated polymers bearing 3-methoxy and 3-methylthio TbT units were also synthesized and characterized. The results indicated that we can efficiently tune the energy levels, the optical bandgaps and absorption spectra by introducing 3-substituted thieno[3,4-b]thiophene derivatives into polymers. The device fabrication, measurements and optimization are currently underway in our lab.
Conflicts of interest
There are no conflicts to declare.

Acknowledgements
We are grateful for the financial support from the National Natural Science Foundation of China (21871146 and 21602115), 1000-Talent Youth Program (020/BF180181), the National Science Foundation of China (21871146 and 21602115), the Fundamental Research Funds for the Central Universities and Nankai University.

Notes and references