Synthesis of some thieno[3,2-b]thiophene derivatives via alkynylation reaction

Nguyen Hien, Duong Quoc Hoan*
Department of Chemistry, Hanoi National University of Education
Received 1 August 2017; Accepted for publication 20 October 2017

Abstract

Using the Sonogashira cross-coupling reactions synthesized seven new thieno[3,2-b]thiophen derivatives in moderate yield. The procedure was optimized and found that triphenylphosphine (0.2 eq.), Pladium diacetate (0.1 eq.), copper (I) iodide (0.2 eq.), THF, iPr₂NH was the best in these cases of 6a, 6b, 6c, 6d and 6e. The structures of these compounds were elucidated by ¹H and ¹³C NMR and mass spectral analysis.

Keywords. Thieno[3,2-b]thiophen, Sonogashira reaction, cross-coupling reaction.

1. INTRODUCTION

Thieno[3,2-b]thiophene (TT) is a core to construct organic semiconductors of different conjugation lengths [1, 2, 3,4]. The functionalization of thieno[3,2-b]thiophene in particular plays an important role in making organic materials, Figure 1. In 2006, McCulloch et al. reported a liquid-crystalline semiconducting polymer (PBTTT) containing thieno[3,2-b]thiophene moieties with a very high charge-carrier mobility (Figure 1) [5]. Recently, dinaphtho[2,3-b:2',3'-f]thieno[3,2-b]thiophene (DNTT) and alkylated benzothieno[3,2-b][1]benzothiophene (C13BTBT) were shown to demonstrate a very high thin film mobility of 3.1 cm²/Vs and 17.2 cm²/Vs, respectively, in VD-OFETs [6,7]. Shi et al. reported Sn-TIPS as a new high performance semiconductor [8].

Figure 1: Some organic materials containing thieno[3,2-b]thiophene

Recently, the Sonogashira reaction of alkynes and TT has become one of the most popular C-C bond forming processes in organic synthesis that might fill up the band gap of organic semiconducting polymers, extension of the π system by increasing the conjugated length of the molecule is one of the most promising method. It helps not only decreased band gap but also increased charge carrier mobility [9-16]. In order to make a long conjugated system, palladium-assisted C–Br activation appears to be straightforward for functionalization into TT. Taking these facts into considerations, we report here new results that allows selective and controllable C-Br functionalization of 2,3,5,6-tetrameththieno[3,2-b]thiophene to monoalkynyl derivatives.

2. EXPERIMENTAL

2.1. Experimental section

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck were used as received, unless indicated. The ¹H NMR and ¹³C NMR spectra were recorded on the Bruker Avance 500 NMR spectrometer in CDCl₃. Chemical-shift data for each
signal was reported in ppm units. Mass spectra were obtained from Mass Spectrometry Facility of The Vietnam Academy of Science and Technology on LC-MSD-Trap-SL spectrometer.

2.2. Synthetic procedure

2.2.1. General procedure: To the argon degassed solution of THF (6 mL) and iPr₂NH (6 mL) was added 2,3,5,6-tetramethylthieno[3,2-b]thiophene (114 mg, 1 eq.), Ph₃P (13.1 mg; 0.2 eq.), Pd(OAc)₂ (5.6 mg; 0.1 eq.), CuI (10 mg; 0.2 eq.). The resulting solution was refluxed to dissolve all substrates and reagents. The reaction solution was added slowly alkynes (1.2 eq.) then refluxed at 75 °C for 2-3 h. The progress of reaction was monitored by TLC (eluent: n-hexane). The mixture was concentrated in vacuo. The products were purified with column chromatography.

Synthesis of 2,3,6-tris(bromo-5-(2-p-tolylethynyl)thieno[3,2-b]thiophene (6a)
Following the general procedure, using 2,3,5,6-tetramethylthieno[3,2-b]thiophene (114 mg, 0.25 mmol, 456 g/mol), Ph₃P (13.1 mg; 0.2 eq., 262 g/mol), Pd(OAc)₂ (5.6 mg; 0.1 eq., 225 g/mol), CuI (10 mg; 0.2 eq.), 190 g/mol) and 1-ethyl-4-methylbenzene (29.0 mg, 0.25 mmol, 116 g/mol) gave 6a as a white powder (30 mg, 491 g/mol, 25 %), mp. 194 °C; ²³C NMR (CDCl₃, 125 MHz) δ (ppm): 139.6, 138.0, 131.7, 131.5, 129.2, 119.0, 114.8, 107.9, 107.1, 99.9, 80.4, 21.6.

Synthesis of 2,3,6-tris(bromo-5-(2-(4-methoxyphenyl)ethynyl)thieno[3,2-b]thiophene (6b)
Following the general procedure, using 2,3,5,6-tetramethylthieno[3,2-b]thiophene (114 mg, 0.25 mmol, 456 g/mol), Ph₃P (13.1 mg; 0.2 eq., 262 g/mol), Pd(OAc)₂ (5.6 mg; 0.1 eq., 225 g/mol), CuI (10 mg; 0.2 eq., 190 g/mol) and 1-ethyl-4-methylbenzene (33.0 mg, 0.25 mmol, 132 g/mol) gave 6b as a white powder (32 mg, 507 g/mol, 25 %), mp. 182 °C; ²³C NMR (CDCl₃, 125 MHz) δ (ppm): 160.4, 138.0, 137.1, 133.2, 122.6, 114.6, 114.2, 107.6, 107.0, 99.9, 79.9, 55.3.

Synthesis of 2,3,6-tris(bromo-5-(2-phenylethynyl)thieno[3,2-b]thiophene (6c)
Following the general procedure, using 2,3,5,6-tetramethylthieno[3,2-b]thiophene (114 mg, 0.25 mmol, 456 g/mol), Ph₃P (13.1 mg; 0.2 eq., 262 g/mol), Pd(OAc)₂ (5.6 mg; 0.1 eq., 225 g/mol), CuI (10 mg; 0.2 eq., 190 g/mol) and 1-ethyl-4-methylbenzene (25.5 mg, 0.25 mmol, 102 g/mol) gave 6c as a white powder (50 mg, 477 g/mol, 42 %), mp. 190 °C; ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 137.5, 131.6, 129.2, 128.5, 122.1, 122.0, 115.0, 108.2, 107.1, 99.6, 81.0.

Synthesis of 2,3,6-tris(bromo-5-(2-m-tolylethynyl)thieno[3,2-b]thiophene (6d)
Following the general procedure, using 2,3,5,6-tetramethylthieno[3,2-b]thiophene (114 mg, 0.25 mmol, 456 g/mol), Ph₃P (13.1 mg; 0.2 eq., 262 g/mol), Pd(OAc)₂ (5.6 mg; 0.1 eq., 225 g/mol), CuI (10 mg; 0.2 eq., 190 g/mol) and 1-ethyl-4-methylbenzene (29.0 mg, 0.25 mmol, 116 g/mol) gave 6d as a white powder (44 mg, 491 g/mol, 36 %), mp. 180 °C; ²³C NMR (CDCl₃, 125 MHz) δ (ppm): 138.2, 137.4, 132.1, 130.1, 128.7, 128.4, 122.2, 121.6, 114.9, 108.1, 107.1, 99.9, 80.7, 21.2.

Synthesis of 3-(2-(2,3,6-tris(bromo-5-(2-p-tolylethynyl)thieno[3,2-b]thiophene (6e)
Following the general procedure, using 2,3,5,6-tetramethylthieno[3,2-b]thiophene (114 mg, 0.25 mmol, 456 g/mol), Ph₃P (13.1 mg; 0.2 eq., 262 g/mol), Pd(OAc)₂ (5.6 mg; 0.1 eq., 225 g/mol), CuI (10 mg; 0.2 eq., 190 g/mol) and 3-ethylpyridine (25.75 mg, 0.25 mmol, 103 g/mol) gave 6e as a white powder (35 mg, 478 g/mol, 30 %), mp. 210 °C; ²³C NMR (CDCl₃, 125 MHz) δ (ppm): 153.2, 149.4, 139.7, 130.3, 130.1, 122.1, 121.8, 123.7, 123.0, 116.4, 109.0, 78.2 ; MS (ESI): calcd. for [M+H]+, [C₁₃H₁₃Br₂NS₂]+ 479, found 479; calcd. for [M-H], [C₁₃H₁₂Br₂NS₂]⁻, 477, found 477.

Synthesis of 3,6-dibromo-2-(2-p-tolylethynyl)thieno[3,2-b]thiophene (7a)
Following the general procedure, using 2,3,5,6-tetramethylthieno[3,2-b]thiophene (114 mg, 0.25 mmol, 456 g/mol), Ph₃P (13.1 mg; 0.2 eq., 262 g/mol), Pd(OAc)₂ (5.6 mg; 0.1 eq., 225 g/mol), CuI (10 mg; 0.2 eq., 190 g/mol) and 1-ethyl-4-methylbenzene (51.0 mg, 0.50 mmol, 116 g/mol) gave 7a as a pale yellow powder (41 mg, 412 g/mol, 42 %), mp. 130 °C; ²³C NMR (CDCl₃, 125 MHz) δ (ppm): 137.5, 131.6, 129.2, 128.5, 122.0, 122.0, 115.0, 108.2, 107.1, 99.6, 81.0, 21.1; MS (ESI): calcd. for [M+H]+, [C₁₃H₁₂Br₂S₂]+: 413, found 413; calcd. for [M-H], [C₁₃H₁₂Br₂S₂]⁻: 411, found 411.

Synthesis of 3,6-dibromo-2-(2-(4-methoxyphenyl)ethynyl)thieno[3,2-b]thiophene (7b)
Following the general procedure, using 2,3,5,6-tetramethylthieno[3,2-b]thiophene (114 mg, 0.25 mmol, 456 g/mol), Ph₃P (13.1 mg; 0.2 eq., 262 g/mol), Pd(OAc)₂ (5.6 mg; 0.1 eq., 225 g/mol), CuI (10 mg; 0.2 eq., 190 g/mol) and 1-ethyl-4-methoxybenzene (66.0 mg, 0.50 mmol, 132 g/mol)
3. RESULTS AND DISCUSSION

3.1. Synthesis

The 2,3,5,6-tetramethylthieno[3,2-b]thiophene (5) was synthesized following by Wynberg et al. and Turbiez et al. [16,17] with some modifications such as ratio of thieno[3,2-b]thiophene-2-carboxylic acid and bromine. It was found that the best ratio of thieno[3,2-b]thiophene-2-carboxylic acid and bromine was 1:1.8 at ambient temperature 30 °C for 1 hour; 110 °C for 3.5 hours and 70 °C for 12 hours forming 2,3,5,6-tetramethylthieno[3,2-b]thiophene in 60 % yield.

Monoalkylation via the Sonogashira reaction was carried out successfully, Scheme 1 and 2, but the yields were quite low since the diyne products were formed along with. Surprisingly, when the aryl alkynes were increased 2 equivalents gave more monoalkynyl products 7a and 7b with removal of a bromine atom. That observation could be explained that H-insertion happened. The bromine atoms at position 2 or 5 were selective for substitution since they were more reactive than the others [18]. As mentioned above, the formation of diyne products called Glaser products [19] decreased the yield of expected products. Therefore, amount of Cu(I) was changed from 0.05 eq.; 0.1 eq.; 0.2 eq. to 0.3 eq. It was found that amount Cu(I) iodide of 0.2 eq. was the best for 6a. Then other reactions were carried under this condition.

Scheme 1: Monoalkylation via the Sonogashira reaction

Scheme 2: Attempt in synthesis of dialkynylation via the Sonogashira reaction

3.2. Structure determination

Mass spectral data of compounds 6e and 7a gave complicated molecular ion peaks because of the presence of 3 or 2 bromine atoms based on its isotope abundant. So it seemed that MS method was not a good choice for them. Anyway, MS of compound 6e had a peak at m/z 479 indicating that molecular formula of 6e must be C13H13Br3NS2 with molecular weight was 478 g/mol. Compound 7a also gave molecular weight peak at 413 amu that associated with molecular formula C15H15Br3S2.

Compounds 6a, 6b, 6c, 6d and 6e were recorded 1H NMR and 13C NMR spectra. All compounds were resembled by alkynyl moieties and thieno[3,2-b]thiophen. However, the alkynyl moieties have protons but no protons for thieno[3,2-b]thiophen. Consequently, the 1H NMR spectral analysis was quite simple as shown in the table 1. Compounds 6a, 6b and 6c have two pairs of identical protons that have same chemical shift values. Since ortho protons were split by Hm/Hm’ and Hp with J = 8.0-9.0 Hz and J = 1.5-2.0 Hz their shape were as doublet or doublet doublet shape peaks. Then other aromatic protons were indicated for Hm/Hm’. Apart from these aromatic protons, peak at δ 2.38 ppm (s,
3H) was assigned for methyl group in compound 6a; 3.86 ppm (s, 3H) for methyl group in the methoxy one in the compound 6b. All aromatic protons of compounds 6d and 6e were not identical; thus, they appeared on the $^1$H NMR spectra as separately peaks. For example, in the $^1$H NMR spectrum of compound 6d, the peak at $\delta$ 7.40 ppm (s, 1H) was for $Ho'$, but at $\delta$ 7.37 ppm (d, $J = 8.0$ Hz, 1H) must have been for $Ho$. Because of pyridine ring, $Ho'$ of compound 6e had appearance of a single peak at $\delta$ 8.8 ppm and $Ho$ was a doublet peak at $\delta$ 8.6 ppm with $J = 5.5$ Hz. Both compounds 6d and 6e have only one proton $Hm$. The triplet peak at $\delta$ 7.26 ppm was assigned for $Hm$ of compound 6d, while the multiplet peak at $\delta$ 7.88 showed the appearance of $Hm$ in the structure of compound 6e since splitting with three different protons in the pyridine ring. Compounds 6c, 6d and 6e have para protons that were very specific shape. $Hp$ of compound 6c was a multiplet peak at $\delta$ 7.37 ppm, doublet peak at $\delta$ 7.19 ppm with $J = 7.5$ Hz was for $Hp$ of compound 6d and the doublet peak at $\delta$ 7.35 ppm with $J = 5.5$ Hz was fit with $Hp$ of compound 6e. Similar to compound 6a, the peak at $\delta$ 2.38 ppm must have been for protons of methyl group on the benzene ring.

**Table 1: $^1$H NMR analysis of compound 6a-e ($\delta$ ppm)**

<table>
<thead>
<tr>
<th></th>
<th>Ho/Ho'</th>
<th>$Hm/Hm'$</th>
<th>$Hp$</th>
<th>H11</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>7.46 (d, $J = 8.0$ Hz, 2H)</td>
<td>7.18 (d, $J = 8.0$ Hz, 2H)</td>
<td>-</td>
<td>2.38 (s, 3H)</td>
</tr>
<tr>
<td>6b</td>
<td>7.53 (d, $J = 9.0$ Hz, 2H)</td>
<td>6.92 (d, $J = 8$ Hz, 2H)</td>
<td>-</td>
<td>3.86 (s, 3H)</td>
</tr>
<tr>
<td>6c</td>
<td>7.38 (dd, $J = 8.0, 1.5$ Hz, 2H)</td>
<td>7.58 (dd, $J = 8.0, 7.5$ Hz, 2H)</td>
<td>7.37 (m, 1H)</td>
<td>-</td>
</tr>
<tr>
<td>6d</td>
<td>7.40 (s, 1H)</td>
<td>7.26 (t, $J = 7.5$ Hz, 1 H)</td>
<td>7.19 (d, $J = 7.5$ Hz, 1H)</td>
<td>2.37 (s, 3H)</td>
</tr>
<tr>
<td>6e</td>
<td>8.6 (d, $J = 5.5$ Hz, 1H)</td>
<td>7.86 (m, 1H)</td>
<td>7.33 (d, $J = 5.5$ Hz, 1H)</td>
<td>-</td>
</tr>
</tbody>
</table>

$^{13}$C NMR spectral analysis was listed in the experimental section. It is clearly that the framework of the expected structures. For example, all compounds showed 6 carbons of thieno[3,2-b]thiophene part. In addition, compounds 6a, 6b and 6c $^{13}$C NMR spectra showed 4 signals for 6 carbons in the benzene ring due to the para-position substituent themselves. In contrast, compounds 6d and 6e $^{13}$C NMR spectra appeared 6 peaks according to unidentical 6 carbons. Each compounds 6a, 6b and 6d gave an extra at strong field. Those were defined for methyl group attached directly to benzene rings or oxygen atom. Unfortunately, all $^{13}$C NMR spectra of these compounds only showed one signal for C9 and C10. It was thought one might be in the peak blocks of CDCl3.

In attempt synthesizing dialkynyl derivatives, the Sonogashira gave monoalkynation product 7a and 7b. These $^1$H NMR analysis was shown in the table 2. The $^1$H NMR spectrum of compound 7a showed a new peak at $\delta$ 7.40 ppm and $^1$H NMR spectrum of compound 7b showed almost at the same position at $\delta$ 7.39 ppm. This observation indicated that the Sonogashira did proton reductive insertion instead of the second alkylation reaction. Moreover, both compound 7a and 7b contained alkynyl moiety including para-substituted groups. Therefore, protons of ortho or meta positions were doublet with coupling constant from 7.0 Hz to 8.0 Hz indicating the ortho positions each other in the benzene ring [20]. Signals at $\delta$ 2.38 ppm in the $^1$H NMR spectrum of compound 7a illustrated for the presence of the methyl group attached with benzene group. Similarly, the $^1$H NMR spectrum of compound 7b also had a peak at $\delta$ 3.84 ppm of methyl in the methoxy group.

**Table 2: $^1$H NMR spectral analysis of compounds 7a and 7b**

<table>
<thead>
<tr>
<th></th>
<th>H2</th>
<th>Ho</th>
<th>Hm</th>
<th>H11</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>7.40 (s, 1H)</td>
<td>7.47 (d, $J = 8.0$ Hz, 2H)</td>
<td>7.18 (d, $J = 8.0$ Hz, 2H)</td>
<td>2.38 (s, 3H)</td>
</tr>
<tr>
<td>7b</td>
<td>7.39 (s, 1H)</td>
<td>7.52 (d, $J = 7.0$ Hz, 2H)</td>
<td>6.90 (d, $J = 7.0$ Hz, 2H)</td>
<td>3.84 (s, 3H)</td>
</tr>
</tbody>
</table>

Compounds 7a and 7b were also recorded $^{13}$C NMR spectra. The analysis was shown in the experiment section. Compound 7a has 13 signals of carbons; nevertheless its $^{13}$C NMR spectrum showed only 12
signals included 10 aromatic carbon atoms from δ 99.6 ppm to 137.5 ppm; a peak at δ 81.0 ppm was for C9 or C10 (C=C), similarly, one was hidden in the solvent peaks. In addition, the signal at δ 21.0 ppm must be for methyl group. Instantly, the $^{13}$C NMR spectrum of compound 7b was quite similar to that of compound 7a case except the signal at δ 55.4 ppm that belonged to the methyl group of methoxy one.

4. CONCLUSION

Seven new thieno[3,2-b]thiophen derivatives were synthesized successfully via the Sonogashira cross-coupling reactions in moderate yield. The equivalent of CuI was 0.2 that was good for producing monoalkynylation products 6a, b, c, d, e; to reduce diyne products but increasing the equivalence of alkynes monoalkynylation companied by H- insertion to form compound 7a and 7b. The structures of these compounds were confirmed by $^1$H and $^{13}$C NMR and mass spectral analyzes.

REFERENCES


*Corresponding author: Duong Quoc Hoan*
Department of Chemistry, Hanoi National University of Education, 136, Xuan Thuy, Cau Giay, Ha Noi, Viet Nam
E-mail: hoandq@hue.edu.vn Telephone: 0986778213.