Palladium-Catalyzed Cyanation Reactions of Thiophene Halides

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Abstract: The described method provides an efficient cyanation reaction of thiophene halides using tris(dibenzylidene-acetone)dipalladium(0), 1,1′-bis-(diphenylphosphino)ferrocene) and zinc powder as the catalyst system and Zn(CN)₂ as the cyanide source. Several thiophenes with various substituents are effectively cyanated under these conditions.

Key words: nitriles, thiophene, palladium, catalysis, cyanation

In continuation of the synthesis of thiophene derivatives,¹ we wanted to develop a general procedure yielding thiophene nitriles. Aryl and heteroaryl nitriles are very important intermediates in organic synthesis because they can be transformed to various other functional groups such as acyl, carboxy, formyl, and carbamoyl. Several methods have been reported for the synthesis of aryl and heteroaryl nitriles.² Among them, the following methods for the direct introduction of a cyano group to arenes and heteroarenes are known as classical methods: the cyanation of aryl and heteroaryl halides with copper(I) cyanide (CuCN), the Reissert–Henze cyanation of π-deficient heteroaromatic N-oxides, and the electrophilic cyanation of π-sufficient heteroaromatics. Unfortunately the classic copper-mediated cyanations often involve the use of stoichiometric quantities of copper cyanide at high temperatures (>150 °C) followed by an often difficult workup to remove the copper salts from the product. Therefore the palladium-catalyzed displacement of aryl and heteroaryl halides with cyanide ions to afford the corresponding aryl and heteroaryl nitriles has been reported as a more favorable alternative.³

Three years ago F. Jin and P. N. Confalone⁴ reported the cyanation of some electron-deficient and electron-rich aryl chlorides with a palladium catalyst and Zn(CN)₂ as the cyanide source.⁵

We tried to optimize the method for thiophene halides bearing various substituents. Pd₂(dba)₃ [tris(dibenzyliyden-acetone)dipalladium(0)] and dppf [1,1′-bis-(diphenylphosphino)ferrocene] used as ligand to enhance the reactivity of the palladium complex were reported to show the best results in conversion. Most of the tested thiophene halides gave conversion rates above 54% under these conditions. More than half of the experiments at 120 °C showed modest (26.8%) to very good (86%) conversion in N,N-dimethylacetamide (DMA). Zn(CN)₂ was used as cyanide source.

As Table 1 shows, much higher conversion rates up to 91% could be observed for some of the thiophene halides at 80 °C reaction temperature, when the conversion was very low at 120 °C.

We did temperature studies with 3,4-dibromothiophene 17 (entry 10) because it gave the highest conversion to the corresponding nitriles 18a,b. It can be seen from Figure 1, that the conversion into the thiophenedinitrile 18a rises up to 90% at 80 °C reaction temperature, but decreases with heating to higher temperatures. As a consequence 18b reaches the lowest point of conversion (3.9%) at 80 °C and rises up to 40% with increasing temperature.

Figure 1

To sum up our results, we have optimized the reaction procedure for a palladium-catalyzed cyanation of thiophene halides. Most of the substances tested showed modest to very good conversion rates into the corresponding thiophene nitriles, which can be used in further synthesis.

Cyanation; General Procedure

The thiophene halide (3.0 mmol), Pd₂(dba)₃ (3 mol%), dppf (5.7 mol%), Zn powder (17 mol%) and Zn(CN)₂ (0.86 mmol) were placed in a dry 3-neck flask flushed with argon and dissolved in dimethylacetamide (5 mL) which was added via syringe. The reaction was stirred and heated to 100 °C under an argon atmosphere. The mixture was cooled to r.t., diluted with EtOAc (25 mL) and then washed aq NH₄OH (2 M) and sat. aq NaCl. After drying (Na₂SO₄) the organic layer was concentrated by rotary evaporation. The residue was purified via column chromatography on silica gel (toluene–EtOAc, 8:2).

5-Acetyl-2-thienylcyanide (2)

Table

- 1H NMR: δ = 7.68–7.66 (d, J = 4.1 Hz, 1 H), 7.65–7.63 (d, J = 4.1 Hz, 1 H), 2.64 (s, 3 H).
13C NMR: δ = 188.7, 148.7, 136.7, 130.2, 115.3, 112.3, 26.1. MS: m/z (%) = 151 (M+, 100).

Anal. Calcd for C₇H₅NOS: C, 54.68; H, 3.92; N, 6.84. Found: C, 54.65; H, 4.10; N, 6.88.

Table 1  Palladium(0)-Catalyzed Cyanation of Thiophene Halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp (°C)/Time (h)</th>
<th>Product</th>
<th>Conversion (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>120/48</td>
<td>2</td>
<td>78.7 (32.1)c</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>120/72</td>
<td>4</td>
<td>48.7 (27.5)c</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>120/1.5a</td>
<td>6</td>
<td>32.7 (13.5)c</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>120/27</td>
<td>8</td>
<td>86.0 (n.r.)c</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>130/3a</td>
<td>10a</td>
<td>26.8 (n.r.)c</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>120/23</td>
<td>10b</td>
<td>8.4 (n.r.)c</td>
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<tr>
<td>7</td>
<td>12</td>
<td>80/48</td>
<td>13</td>
<td>83.0</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>80/18</td>
<td>8</td>
<td>90.5</td>
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<tr>
<td>9</td>
<td>15</td>
<td>80/50</td>
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<td>68.4</td>
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<td>17</td>
<td>80/50</td>
<td>18a</td>
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<td>19</td>
<td>80/46</td>
<td>18b</td>
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<td>80/30</td>
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<td></td>
<td></td>
<td></td>
<td>22b</td>
<td>3.9</td>
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</table>

a  The product does not remain stable with heating.
b  Conversion rate detected via GS-MS.
c  Conversion rate at 80 °C reaction temperature (n.r. = no reaction product detected).

References


