Efficient Synthesis of Monosubstituted 3-Alkynylfurans via Suzuki Coupling

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Abstract: A convenient synthesis of monosubstituted 3-alkynylfurans by Suzuki coupling reaction of 3-furanylboronic acid with substituted acetylene bromides is described. The internal alkyne products were attainable in 50–89% yields from substrates free of relatively acidic protons. Our protocol is expected to find applications in the synthesis of structurally related natural products.

Key words: Suzuki coupling, monosubstituted 3-alkynylfurans, 3-furanylboronic acid, bromoalkynes

Conjugated alkynylfurans, especially 3-alkynylfurans, are often present as part of the structure in several natural products and designed bioactive agents, and also used as intermediates in natural product synthesis.

Although polysubstituted 3-alkynylfurans could be easily constructed via Sonogashira coupling of terminal alkynes with the corresponding 3-halofurans, the reaction involving simple 3-halofurans proves to be a dramatically different case based both upon our own observations and upon literature results. For example, no coupling product could be isolated by the reaction of protected propargylamine with 3-bromofuran in the presence of Pd(PPh3)2Cul, or Pd(PPh3)2Cl2/Cul (5–10 mol% of each catalyst) in Et3N–DMF (1:1 to 2:1), or Et2NH alone at 55 °C to reflux temperatures for 8–20 hours. In addition, only few papers describe the Sonogashira coupling reaction of simple 3-halofurans. Among these, the Sonogashira reaction of 3-bromofuran with propargyl alcohol was reported to give the corresponding coupling products in 7% and 25% yield, respectively. In the synthesis of hispanolone, Wong described three cases of Sonogashira coupling of parent 3-halofuran conducted in a large amount of Et3NH used as both base and solvent, in which the alkyne substrate was present in the system at 5–6 mM concentration. Moreover, coupling took place regioselectively at the C-2 position of 2,3-dibromofurans although 200 mol% of the terminal alkynes were added. It seems that highly efficient and practical assembly of monosubstituted 3-alkynylfurans (i.e., no substitutions at other positions of furan) remains a daunting challenge to contemporary organic chemists, although a few sporadic synthetic approaches to them (e.g., from sodium tetraalkynylaluminate, or through Negishi or Stille coupling) have been reported.

Recently we were interested in developing a convenient and general method for the synthesis of monosubstituted 3-alkynylfurans. This paper discloses our investigations centered at fast assembly of these internal alkynes by Suzuki coupling reaction, a powerful transformation that plays a more and more important role in modern organic synthesis.

The search for Suzuki reaction parameters started with the coupling of bromoalkyne 1a (Scheme 1) and 3-furanboronic acid 2 in the presence of Pd(OAc)2 and Na2CO3 in boiling PrOH–H2O (5:1) for two hours. Unfortunately, no desirable product could be obtained in this case. However, when the reaction was run in the presence of Pd(PPh3)4 (10 mol%) and Ba(OH)2·8H2O in boiling DME–H2O (4:1) for 30 minutes, 3-alkynylfuran 3a was formed in moderate yield (50%). Furthermore, no substantial gain in the product yield was observed by increasing the catalyst loading from 10 to 20 mol%. Therefore, the catalyst usage was fixed at 10 mol% for all subsequent experiments.

In order to evaluate the scope of the current method, nine additional 1-bromoalkynes 1b–j (Table 1) were examined using the optimized reaction conditions. As a homologue of 1a, the 1-bromoalkyne 1b (entry 2) coupled with 2 to generate internal alkyne 3b in comparable yield (62%). It is noteworthy that alkynes 1c and 1d (entries 3 and 4), containing a secondary sulfonamide moiety, resulted in

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Figure 1 Protected propargylamine A

![Figure 1](protected-propargylamine.png)
much lower yields of the coupling products due to reduced efficiency of the coupling reaction. These results, in combination with those for 1a and 1b, suggest that the amine nitrogen should be fully protected to ensure better material conversion. For the alkyne components with an ether functionality such as 1e and 1f (entries 5 and 6), the reaction also went reasonably well and the coupling products were obtained in around 60% yields. Finally, the coupling efficiency was greatly enhanced in the case of arylacetylene bromides 1g–j (entries 7–10) where 3-(arylalkynyl)furans 3g–j were formed in high yields (79–89%).

**Table 1** Pd(PPh3)4-Catalyzed Suzuki Coupling of Bromoalkynes and 3-Furanboronic Acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Bromoalkyne</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH3N(Ts)Boc</td>
<td>1a</td>
<td>3a</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>(CH3)2N(Ts)Boc</td>
<td>1b</td>
<td>3b</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>CH3NHBs</td>
<td>1c</td>
<td>3c</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>CH3NHNs</td>
<td>1d</td>
<td>3d</td>
<td>31%</td>
</tr>
<tr>
<td>5</td>
<td>CH3OBn</td>
<td>1e</td>
<td>3e</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>(CH3)2OBn</td>
<td>1f</td>
<td>3f</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>1g</td>
<td>3g</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>4-O2NC6H4</td>
<td>1h</td>
<td>3h</td>
<td>80%</td>
</tr>
<tr>
<td>9</td>
<td>4-MeOC6H4</td>
<td>1i</td>
<td>3i</td>
<td>85%</td>
</tr>
<tr>
<td>10</td>
<td>4-MeC6H4</td>
<td>1j</td>
<td>3j</td>
<td>89%</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (120 mol%), 2 (100 mol%), Pd(PPh3)4 (10 mol%), Ba(OH)2·8H2O (500 mol%), DME–H2O (4:1). Bs = benzensulfonyl, Ns = 4-nitrobenzenesulfonyl.

In summary, we have accomplished a convenient synthesis of monosubstituted 3-alkynylfurans 3 by Suzuki coupling reaction of 3-furanboronic acid (2) with substituted acetylene bromides 1. The internal alkynes were attainable as coupling products in 50–89% yields from most substrates except those possessing relatively acidic protons. Our protocol is expected to find applications in the synthesis of structurally related natural products.

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. NMR spectra were recorded in CDCl3 or acetone-d6 (1H at 300 MHz and 13C at 75 MHz) on Bruker DPX-300 and Varian MERCURY 300 spectrometers, using TMS as the internal standard. Analytical samples were obtained by chromatography on silica gel (Shandong Yantai Jiangyou Corp., China; 200–300 mesh).

**Bromoalkynes 1a–g**  
**General Procedure**

In a round-bottomed flask, the respective terminal alkyne (3 mmol) was dissolved in acetone (15 mL). After the addition of N-bromo-succinimide (110 mol%) and AgNO3 (10 mol%), the mixture was stirred for 1 h and diluted with Et2O (20 mL) and H2O (20 mL). The two layers were separated and the aqueous layer was extracted with Et2O (3 × 40 mL). The combined organic layers were washed with brine (30 mL), dried (MgSO4), and concentrated. The residue was purified by column chromatography or distillation to afford the desired product.

1a

Purified by column chromatography (SiO2; EtOAc–PE, 1:10); white solid (82%); mp 118–120 °C.

1b

Purified by column chromatography (SiO2; EtOAc–PE, 1:10); white solid (92%); mp 91–93 °C.

1c

Purified by column chromatography (SiO2; PE–CH2Cl2, 1:3); white solid (71%); mp 88–90 °C.

1d

Purified by column chromatography (SiO2; PE–CH2Cl2, 1:3); white solid (82%); mp 152–153 °C.

1e

Purified by column chromatography (SiO2; PE–CH2Cl2, 1:3); white solid (71%); mp 118–120 °C.

1f

Purified by column chromatography (SiO2; PE–CH2Cl2, 1:3); white solid (82%); mp 152–153 °C.

1g

Purified by column chromatography (SiO2; PE–CH2Cl2, 1:3); white solid (71%); mp 118–120 °C.

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1g Purified by vacuum distillation (60 °C/1 mmHg); light green oil (56%).

1H NMR (300 MHz, CDCl3): δ = 7.30–7.34 (m, 3 H), 7.43–7.45 (m, 2 H).

Bromokynes 1b–j; General Procedure
A solution of CBr3 (200 mol%) in CH2Cl2 (10 mL) was added dropwise to a solution of PPh3 (400 mol%) in CH2Cl2 (5 mL) at 0 °C. After stirring at 0 °C for 20 min, a solution of the corresponding aryl aldehyde (3 mmol) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and filtered. The filtrate was dried (Na2SO4) and concentrated. The residue was purified by silica gel chromatography (CHCl3–PE, 1:5). A mixture of the obtained dibromostyrene (2 mmol) and Bu4NBr (100 mol%) in THF–H2O (4:3) andaq KOH (400 mol%) in a round-bottomed flask was stirred at r.t. for 48 h. The resultant mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated. The residue was purified by column chromatography.

1b Purified by column chromatography (SiO2; CHCl3–PE, 1:5); white solid (95%); mp 178–180 °C.

1H NMR (300 MHz, CDCl3): δ = 6.60 (d, J = 8.7 Hz, 2 H), 6.19 (d, J = 8.4 Hz, 2 H).

1c Purified by column chromatography (SiO2; CHCl3–PE, 1:5); light yellow solid (93%); mp 39–40 °C.

1H NMR (300 MHz, CDCl3): δ = 3.81 (s, 3 H), 6.83 (d, J = 8.7 Hz, 2 H), 7.38 (d, J = 8.7 Hz, 2 H).

1d Purified by column chromatography (SiO2; CHCl3–PE, 1:5); light yellow oil (96%).

1H NMR (300 MHz, CDCl3): δ = 2.35 (s, 3 H), 7.12 (d, J = 7.5 Hz, 2 H), 7.34 (d, J = 7.8 Hz, 2 H).

Palladium-Catalyzed Suzuki Coupling Reaction of 3-Furanboronic Acid (2) with Various Terminal Bromoalkynes 1; General Procedure
Ba(OH)2·8H2O (500 mol%) was added to a well-stirred mixture containing 3-furanboronic acid 2 (0.5 mmol), bromoalkyne 1 (120 mol%), and Pd(PPh3)4 (10 mol%) in DME (32 mL) and H2O (8 mL) in a two-necked round-bottomed flask under N2 at r.t. The resultant mixture was heated at reflux for 30 min, cooled to r.t., and poured into cold H2O (40 mL). The mixture was extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried (MgSO4), filtered, and concentrated. The residue was purified by column chromatography to afford the desired product.

3a Purified by column chromatography (SiO2; EtOAc–PE, 1:20); white solid; mp 81–83 °C.

1H NMR (300 MHz, CDCl3): δ = 1.35 (s, 9 H), 2.42 (s, 3 H), 4.80 (s, 2 H), 6.41 (s, 1 H), 7.27 (d, J = 7.8 Hz, 2 H), 7.37 (s, 1 H), 7.59 (s, 1 H), 7.93 (d, J = 8.1 Hz, 2 H).

13C NMR (75 MHz, CDCl3): δ = 21.6, 27.8, 36.6, 75.1, 84.8, 86.2, 106.8, 112.4, 128.2, 129.1, 136.6, 142.8, 144.3, 145.9, 150.2.

MS (ESI): m/z = 430 (M + Na + MeOH), 398 (M + Na).

HRMS (ESI): m/z calcd for C10H7NO2S + Na (M + Na): 398.1038; found: 398.1033.

3b Purified by column chromatography (SiO2; EtOAc–PE, 1:20); white solid; mp 94–96 °C.

1H NMR (300 MHz, CDCl3): δ = 1.34 (s, 9 H), 2.44 (s, 3 H), 2.84 (t, J = 7.5 Hz, 2 H), 4.05 (t, J = 7.5 Hz, 2 H), 6.38 (s, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.34 (s, 1 H), 7.53 (s, 1 H), 7.83 (d, J = 7.8 Hz, 2 H).

13C NMR (75 MHz, CDCl3): δ = 20.8, 21.5, 27.8, 45.2, 73.5, 84.4, 87.6, 107.5, 112.5, 127.8, 129.2, 137.1, 142.5, 144.2, 145.3, 150.7.

MS (ESI): m/z = 412 (M + Na), 290 (M − Boc).

HRMS (ESI): m/z calcd for C18H15N3O2S + Na (M + Na): 412.1194; found: 412.1189.

3c Purified by column chromatography (SiO2; EtOAc–PE, 1:10); yellow solid; mp 88–90 °C.

1H NMR (300 MHz, CDCl3): δ = 4.05 (d, J = 6.3 Hz, 2 H), 4.91 (t, J = 5.7 Hz, 1 H, NH), 6.19 (d, J = 1.5 Hz, 1 H), 7.29 (s, 1 H), 7.36 (s, 1 H), 7.48–7.60 (m, 3 H), 7.92 (d, J = 7.2 Hz, 2 H).

13C NMR (75 MHz, CDCl3): δ = 33.7, 76.1, 84.9, 106.3, 112.2, 127.4, 129.0, 132.8, 139.7, 142.7, 145.8.

MS (ESI): m/z = 260 (M − H).

HRMS (ESI): m/z calcd for C18H14N2O2 + Na (M + Na): 284.0365; found: 284.0352.

3d Purified by column chromatography (SiO2; EtOAc–PE, 1:10); white solid; mp 132–134 °C.

1H NMR (300 MHz, acetone-d6): δ = 2.96 (s, 1 H, NH), 4.14 (s, 2 H), 6.23 (s, 1 H), 7.49 (s, 1 H), 7.58 (s, 1 H), 8.19 (d, J = 8.4 Hz, 2 H), 8.40 (d, J = 9.0 Hz, 2 H).

13C NMR (75 MHz, acetone-d6): δ = 33.5, 76.0, 86.2, 107.1, 112.5, 124.7, 129.3, 144.0, 146.4, 147.4, 150.6.

MS (ESI): m/z = 305 (M − H).


3e Purified by column chromatography (SiO2; EtOAc–PE, 1:20); light green oil.

1H NMR (300 MHz, CDCl3): δ = 4.36 (s, 2 H), 4.65 (s, 2 H), 6.46 (d, J = 1.5 Hz, 1 H), 7.33–7.38 (m, 6 H), 7.63 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 58.0, 71.7, 77.7, 87.0, 107.1, 112.6, 127.9, 128.1, 128.5, 137.5, 142.8, 146.0.

MS (ESI): m/z = 211 (3, M − H), 105 (83, M − BnO).

HRMS (EI): m/z calcd for C14H12O2: 212.0837; found: 212.0846.

3f Purified by column chromatography (SiO2; EtOAc–PE, 1:20); light yellow oil.

1H NMR (300 MHz, CDCl3): δ = 2.71 (t, J = 6.9 Hz, 2 H), 3.66 (t, J = 6.9 Hz, 2 H), 4.59 (s, 2 H), 6.42 (d, J = 1.8 Hz, 1 H), 7.32–7.38 (m, 6 H), 7.57 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 20.8, 68.2, 72.4, 72.9, 88.4, 107.6, 112.6, 127.7, 128.4, 138.0, 142.5, 145.2 (with one low-field signal absent).

MS (ESI): m/z = 225 (4, M − 1), 105 (27, M − BnO).

3g Purified by column chromatography (SiO2; EtOAc–PE, 1:20); light yellow oil.

1H NMR (300 MHz, CDCl3): δ = 6.51 (d, J = 1.2 Hz, 1 H), 7.30–7.33 (m, 3 H), 7.38 (d, J = 1.2 Hz, 1 H), 7.46–7.50 (m, 2 H), 7.67 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 80.4, 91.0, 107.6, 112.5, 123.1, 128.2, 128.3, 131.4, 142.8, 145.5.

MS (ESI): m/z = 168 (100, M+).

HRMS (EI): m/z calcd for C13H10O: 168.0575; found: 168.0579.

3h Purified by column chromatography (SiO2; EtOAc–PE, 1:10); light yellow solid; mp 148–150 °C.

1H NMR (300 MHz, CDCl3): δ = 6.55 (s, 1 H), 7.45 (d, J = 1.8 Hz, 1 H), 7.62 (d, J = 7.5 Hz, 2 H), 7.76 (s, 1 H), 8.20 (d, J = 7.8 Hz, 2 H).

13C NMR (75 MHz, CDCl3): δ = 85.1, 89.4, 106.9, 112.4, 123.7, 130.2, 132.0, 143.3, 146.5, 146.9.

MS (ESI): m/z = 213 (100, M+).

HRMS (EI): m/z calcd for C13H9NO2: 213.0426; found: 213.0422.

3i Purified by column chromatography (SiO2; EtOAc–PE–AcOH, 1:1:1); colorless oil.

1H NMR (300 MHz, CDCl3): δ = 3.84 (s, 3 H), 6.53 (dd, J = 1.9, 0.7 Hz, 1 H), 6.88 (d, J = 8.4 Hz, 2 H), 7.41 (t, J = 2.1 Hz, 1 H), 7.45 (d, J = 8.1 Hz, 2 H), 7.69 (dd, J = 1.4, 0.4 Hz, 1 H).

13C NMR (75 MHz, CDCl3): δ = 55.3, 79.0, 90.9, 107.8, 112.6, 114.0, 115.3, 132.9, 142.8, 145.3, 159.6.

MS (ESI): m/z = 198 (100, M+), 183 (51, M–Me).

HRMS (EI): m/z calcd for C14H18I0O2: 198.0681; found: 198.0685.

3j Purified by column chromatography (SiO2; EtOAc–PE–AcOH, 1:10); light yellow oil.

1H NMR (300 MHz, CDCl3): δ = 2.35 (s, 3 H), 6.51 (d, J = 1.8 Hz, 1 H), 7.14 (d, J = 8.4 Hz, 2 H), 7.39 (s, 1 H), 7.40 (d, J = 8.1 Hz, 2 H), 7.67 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 21.5, 79.7, 91.1, 107.8, 112.6, 120.1, 129.1, 131.3, 138.4, 142.9, 145.4.

MS (ESI): m/z = 182 (100, M+).

HRMS (EI): m/z calcd for C13H10I0O2: 182.0732; found: 182.0736.

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