Cross-Coupling Reactions

Synthesis of 5-Substituted 1,2,3-Triazolyl-4-phosphonate through Cross-Coupling Reactions of 5-Iodo-1,2,3-triazolyl-4-phosphonate

Emilie Thiery,[a] Vanny You,[a] Anne-Sophie Mora,[a] and Mohamed Abarbri*[a]

Abstract: Two methods for the preparation of 5-iodo-1,2,3-triazolyl-4-phosphonate were explored. This compound was then functionalized by Suzuki and Stille cross-coupling reaction to obtain 5-aryl-, 5-heteroaryl- or 5-alkenyl-1,2,3-triazolyl-4-phosphonates.

Introduction

Substituted 1,2,3-triazoles are very important heterocyclic compounds because of their numerous applications to material sciences and medicinal chemistry.[1] They are readily prepared by 1,3-dipolar cycloaddition reactions of azides with alkynes.[2] Interest in phosphorus compounds has increased as these groups, especially phosphonates and phosphonic acids, are present in a number of new therapeutic agents for various diseases,[3] such as diabetes, asthma, inflammation, cancer and malaria. Surprisingly, few examples of synthesis in the preparation of 1,2,3-triazolylphosphonates have been described in the literature. In 2002, the synthesis of 1,2,3-triazolyl-4-phosphonate was reported by a metal-free 1,3-dipolar cycloaddition reaction from ethynylphosphonate and azide in toluene. The reaction was not regioselective, and a quantity of isomer 5-phosphonate was observed.[4] More recently, preparation of phosphohistidine analogues through “click” reactions in the presence of Cu or Ru catalysts has been reported. The regioselectivity depends on a catalyst to prepare analogues of 1-pHis or 3-pHis (Figure 1).[5] Artyushin et al. reported the catalyst-free 1,3-dipolar cycloaddition reaction of phosphorylated azides promoted by water.[6] Internal symmetric alkynes were used to avoid the problem of regioselectivity. Li et al. reported the regioselective synthesis of 1,2,3-triazolyl-5-phosphonates by copper(I)-catalysed three-component reaction from azides, alkynes, and H-phosphates.[7] An alternative to the “click” reaction for the synthesis of 1,2,3-triazole was a metal-free three-component reaction from an azide, aldehyde, and nitro group.[8] However, only one 1,2,3-triazolyl-4-phosphonate has been described by using this methodology. We have focused on the synthesis of 5-halo-1,2,3-triazolyl-4-phosphonate for use in a cross-coupling reaction to obtain new 5-aryl- or 5-alkenyl-1,2,3-triazolyl-4-phosphonates. In 2014, 5-bromo-1,2,3-triazolyl-4-phosphonate was synthesized by Ru-catalysed cycloaddition reaction from 1-haloalkyne and organic azides, but this method required the preparation of non-commercial diethyl bromoethynylphosphonate.[9] We propose here two methods of synthesis of 5-iodo-1,2,3-triazolyl-4-phosphonate and its use in Suzuki and Stille cross-coupling reactions.

![Figure 1. 1,2,3-Triazolyl phosphorus compounds.](image)

Results and Discussion

Two pathways can be envisaged to prepare 5-iodo-1,2,3-triazolyl-4-phosphonate. The Click reaction would make it possible to obtain diethyl 1-benzyl-1H-1,2,3-triazol-4-ylphosphonate (2a), which could be iodated in 5-position (Scheme 1, Pathway A). 1,3-Dipolar cycloaddition reaction of organic azides and ethyl ethynylphosphonates takes place in toluene or in water without a catalyst.[4,5b,6] In the case of diethyl ethynylphosphonate and benzyl azide in our studies, total conversion was observed overnight in toluene at reflux temperatures or in water at 60 °C (Scheme 2). Regioselectivity depends on the solvent, but in two cases 1,2,3-triazolyl-4-phosphonate 2a and 5-phosphonate 2b regioisomers were obtained. They could be separated by chromatography with silica gel and isolated to give good yields.
Iodation of 2a was first envisaged with N-iodosuccinimide but without success. Deprotonation with a strong base followed by addition of iodine was then tried. Only 20 % conversion was observed with n-butyllithium and tert-butyllithium was required to obtain 90 % conversion. Compound 3 was isolated in 48 % yield (Scheme 3), and finally compound 3 was prepared in two steps in 31 % yield from compound 1.

Another pathway was 1,3-dipolar cycloaddition reaction and in situ iodation of diethyl ethynylphophonate and benzyl azide (Scheme 1, Pathway B). Wu et al. reported the synthesis of 5-iodo-4-phenyl-1,2,3-triazole in a one-pot reaction promoted by copper(I) salt,[10] the mechanism of which was recently discussed by Zhu et al.[11] Under similar conditions, 1,3-dipolar cycloaddition reaction of benzyl azide and diethyl ethynylphophonate, catalysed by copper iodide in the presence of triethylamine and iodine in tetrahydrofuran (THF), led to 26 % yield of compound 3 (Table 1, Entry 1). The use of ethyldiisopropylamine and iodine chloride increased the yield to 52 and 61 %.

Table 2. Suzuki reaction optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd] [mol-%]</th>
<th>T [°C]</th>
<th>Time</th>
<th>Conversion %</th>
<th>4a/2a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd2dba3</td>
<td>50</td>
<td>overnight</td>
<td>100</td>
<td>86:14</td>
</tr>
<tr>
<td>2</td>
<td>PdCl2(PPh3)2</td>
<td>50</td>
<td>overnight</td>
<td>55</td>
<td>45:55</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh3)4</td>
<td>50</td>
<td>overnight</td>
<td>56</td>
<td>27:73</td>
</tr>
<tr>
<td>4</td>
<td>PdCl2(MeCN)2</td>
<td>50</td>
<td>overnight</td>
<td>81</td>
<td>66:44</td>
</tr>
<tr>
<td>5</td>
<td>Pd2dba3</td>
<td>MW150</td>
<td>45 min</td>
<td>84</td>
<td>88:12</td>
</tr>
<tr>
<td>6</td>
<td>Pd2dba3</td>
<td>MW180</td>
<td>30 min</td>
<td>86</td>
<td>89:11</td>
</tr>
<tr>
<td>7</td>
<td>Pd2dba3</td>
<td>MW180</td>
<td>45 min</td>
<td>94</td>
<td>89:11</td>
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<tr>
<td>8</td>
<td>Pd2dba3</td>
<td>MW180</td>
<td>45 min</td>
<td>100</td>
<td>86:14</td>
</tr>
</tbody>
</table>

[a] Determined by 1H and 31P NMR spectroscopy.
respectively (Table 1, Entries 2 and 3). In each case we observed the formation of 10–40 % tetraethyl buta-1,3-diyne-1,4-diyldiphosphonate promoted by the presence of copper(I).[12] No literature is available in the field of 5-iodo-1,2,3-triazolyl-4-phosphonate synthesis.

On the basis of previous work,[13] compound 3 was used in Suzuki cross-coupling reactions. It should be noted that the conversion must be complete so that starting material 3 and product 4a can be separated by chromatography with silica gel. To optimize the reaction protocol, we examined a range of palladium catalysts by using the coupling of 3 with phenylboronic acid as the test reaction in the presence of potassium phosphate in toluene at 50 °C for 18 h (Table 2). In each case compound 2a from deiodation was observed by NMR spectroscopy. The use of tris(dibenzylideneacetone)dipalladium(0) as the catalyst provided a more effective reaction than the use of catalysts such as PdCl₂(PPh₃)₂, Pd(Ph₃)₄, and PdCl₂(MeCN)₂ (Table 2, Entries 1–4). Suzuki coupling reactions performed under microwave irradiation (Table 2, Entries 5–8) required a greater quantity of catalyst to obtain complete conversion and did not permit reduction of formation of compound 2a. The use of N,N-dimethylformamide as solvent under microwave irradiation led to degradation of the product. Upon optimization, the best set of reaction conditions was found to be tris(dibenzylideneacetone)dipalladium(0) (5 mol-%) and potassium phosphate (2.0 equiv.) in toluene at 50 °C under conventional heating for 18 h.

A variety of available boronic acids were used to investigate the scope of the Suzuki cross-coupling reaction and the results are summarized in Table 3. As shown in Table 3, the procedure is a general one. It can thus accommodate various aryl and heteroaryl groups with reasonable yields. In the coupling reactions, no significant difference in performance occurred related to the nature of the substituent on the aromatic ring, such as an electron-donating (Table 3, Entries 2 and 4) or an electron-withdrawing group (Table 3, Entry 5).

Attention was next focused on the Stille cross coupling reaction between 3 and vinyltin or heteroaryltin reagents (Scheme 4). Organotin reagents have previously proved to be efficient tools for transfer of the unsaturated unit on both the substrate and the reagent, with a high level of tolerance for numerous functions. To optimize the reaction protocol, we examined various temperature conditions. The reaction from 3 and (E)-trimethyl[2-(tributylstannyl)vinyl]silane in the presence of tris(dibenzylideneacetone) dipalladium(0) (5 %) and toluene as solvent were used as test conditions. Under microwave irradiation (Scheme 4, Condition A) only degradation products were formed. At room temperature (Scheme 4, Condition B) poor conversion was observed after 18 h (conversion 4 %). Complete conversion was obtained by heating the reaction overnight at 50 °C (Scheme 4, Condition C). Compound 5a was isolated in 70 % yield. The reaction between 3 and tributyl(vinyl)stannane, tributyl(furan-3-yl)stannane, or tributyl(thiophen-3-yl)stannane resulted in good yields of expected compounds 5b–5d. The mild experimental conditions of the Stille cross-coupling reaction led to functional dienes 5, and no polymerization products were detected.

### Table 3. Scope of the Suzuki cross-coupling reaction with various boronic acid partners.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>RB(OH)₂</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn-OHB₂</td>
<td>4a</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>MeO-OB₂</td>
<td>4b</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>MeO-OB₂</td>
<td>4c</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>MeS-OHB₂</td>
<td>4d</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>F-OHB₂</td>
<td>4e</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>O-HBO₂</td>
<td>4f</td>
<td>34</td>
</tr>
</tbody>
</table>

[a] Isolated yield.

### Conclusions

In summary, we have developed a new way to produce 5-substituted 1,2,3-triazolyl-4-phosphonate by cross-coupling reaction by using a previously unknown 5-iodo 1,2,3-substituted-4-phosphonate. The use of Suzuki or Stille conditions allowed us to synthesize good yields of 5-vinyl, aryl or heteroaryl 1,2,3-triazolyl-4-phosphonates. Investigations to synthesize new substituted triazolyl phosphate derivatives are currently in progress in our laboratory.
Experimental Section

General Methods: All reactions were carried out under an argon atmosphere. TLC spots were examined under UV light. NMR spectra were recorded at 300 MHz for $^1$H, 121 MHz for $^{31}$P and 75 MHz for $^{13}$C with a BRUCKER AVANCE 300 spectrometer. Chemical shifts are reported relative to the residual chloroform peak (δ = 7.26 ppm). Electrospray ionization mass spectrometry experiments (HRMS) were performed on a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, U. K.) operated in positive mode.

Cycloaddition Reaction – General Procedure: Diethyl ethynylphosphonate (1 mmol, 162 mg) and benzyl bromide (1 mmol, 105 mg) were stirred in toluene under argon at 110 °C for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with silica gel (dichloromethane/ethanol, 98:2 to 95:5). Two regioisomers 2a and 2b were isolated in 40 and 33 % yield, respectively.

Diethyl (1-Benzyl-1,2,3-triazol-4-yl)phosphonate (2a): Yield 76 mg (40 %). White solid, m.p. 76 °C. IR: ν˜ = 3104, 2990, 2912, 1339, 1256, 1213, 1166, 1096, 1011 cm–1. $^1$H NMR (CDCl$_3$, 300 MHz): δ = 7.91 (s, 1 H), 7.37 (m, 3 H), 7.28 (m, 2 H), 5.56 (s, 2 H), 4.17 (m, 4 H), 1.32 (t, J = 7.91 Hz, 6 H) ppm. $^{31}$P NMR (CDCl$_3$, 121 MHz): δ = 8.00 (s, 1 H), 7.37 (m, 5 H), 5.66 (s, 2 H), 4.25 (m, 4 H), 1.38 (td, J = 7.2, 0.6 Hz, 6 H) ppm. $^{13}$C NMR (CDCl$_3$, 75 Hz): δ = 133.6, 130.5 (d, J$_{C-P}$ = 5.8 Hz, 2 C), 54.4, 16.3 (d, J$_{C-P}$ = 6.5 Hz) ppm. HRMS (ESI): m/z calcd. for C$_{13}$H$_{19}$N$_{3}$O$_{3}$P [M+H]+ 296.11585; found 296.11554 (1.0 ppm).

Scheme 4.

Diethyl (1-Benzyl-5-phenyl-1,2,3-triazol-4-yl)phosphonate (2b): Yield 692 mg (61 %). Yellow solid, m.p. 63 °C. IR: ν˜ = 2987, 2907, 1497, 1453, 1439, 1392, 1253, 1210, 1219 cm–1. $^1$H NMR (CDCl$_3$, 300 MHz): δ = 7.91 (s, 1 H), 7.37 (m, 3 H), 7.28 (m, 2 H), 5.56 (s, 2 H), 4.17 (m, 4 H), 1.32 (t, J = 7.91 Hz, 6 H) ppm. $^{31}$P NMR (CDCl$_3$, 121 MHz): δ = 8.00 (s, 1 H), 7.37 (m, 5 H), 5.66 (s, 2 H), 4.25 (m, 4 H), 1.38 (td, J = 7.2, 0.6 Hz, 6 H) ppm. $^{13}$C NMR (CDCl$_3$, 75 Hz): δ = 133.6, 130.5 (d, J$_{C-P}$ = 33.2 Hz), 129.4 (2 C), 129.2, 128.5 (2 C), 63.5 (d, J$_{C-P}$ = 6.5 Hz, 2 C) ppm. HRMS (ESI): m/z calcd. for C$_{19}$H$_{23}$N$_{3}$O$_{3}$P [M+H]+ 372.14715; found 372.14695 (0.6 ppm).

Suzuki Reaction – General Procedure: A Schlenk flask loaded with 3 (0.25 mmol, 105 mg), tris(dibenzylideneacetone)dipalladium (0.01 mmol, 9 mg), boronic acid (1 mmol), and potassium phosphate (1.5 mmol, 318 mg) was placed under vacuum for 10 min and filled with argon. Then toluene (3 mL), ethyl-diisopropylamine (9 mg), and potassium t-butoxide (0.001 mmol, 2 mg) in toluene (3 mL) were added. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 15 mL). The organic phases were washed with aqueous Na$_2$SO$_4$ solution (20 %, 20 mL) and saturated aqueous NaCl solution (20 mL). The organic phase was dried with MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography with silica gel (petroleum ether/ethyl acetate, 1:1).

Diethyl (1-Benzyl-5-iodo-1,2,3-triazol-4-yl)phosphonate (3): Yield 60 mg (65 %). Clear oil. IR: ν˜ = 2981, 1479, 1455, 1414, 1392, 1244 cm–1. $^1$H NMR (CDCl$_3$, 300 MHz): δ = 7.47 (m, 3 H), 7.28 (m, 5 H), 7.04 (m, 2 H), 5.46 (s, 2 H), 4.12 (m, 4 H), 1.21 (td, J = 7.2, 0.6 Hz, 6 H) ppm. $^{13}$C NMR (CDCl$_3$, 75 Hz): δ = 142.6 (d, J$_{C-P}$ = 241.3 Hz), 133.7, 129.1 (2 C), 128.9, 128.1 (2 C), 86.2 (d, J$_{C-P}$ = 33.7 Hz), 63.5 (d, J$_{C-P}$ = 5.8 Hz, 2 C), 54.5, 16.4 (d, J$_{C-P}$ = 6.5 Hz, 2 C) ppm. HRMS (ESI): m/z calcd. for C$_{13}$H$_{17}$IN$_{3}$O$_{3}$P [M+H]+ 528.00261; found 528.00238 (0.5 ppm).

Copper-Catalysed Cycloaddition Reaction – General Procedure: A Schlenk flask loaded with diethylthiophosphonate (2.7 mmol, 437 mg), benzylazole (2.7 mmol, 359 mg), and copper iodide (2.7 mmol, 513 mg) was placed under vacuum for 10 min and filled with argon. Then toluene (3 mL), ethyldiisopropylamine (3.2 mmol, 528 μL) and diiodide (3.2 mmol, 813 mg) in toluene (5 mL) were introduced at 0 °C and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water (20 mL) and EtOAc (20 mL) and filtered through Celite. The aqueous phase was extracted with EtOAc (2 × 15 mL). The organic phases were washed with aqueous Na$_2$SO$_4$ solution (20 %, 20 mL) and saturated aqueous NaCl solution (20 mL). The organic phase was dried with MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography with silica gel (petroleum ether/ethyl acetate, 1:1).
Diethyl (1-Benzyl-5-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)phosphonate (4d): Yield 80 mg (74%). Clear oil. IR: υ = 2928, 2925, 2925, 2851, 1601, 1487, 1456, 1445, 1307, 1240, 1216 cm⁻¹. 1H NMR (CDCl₃, 300 MHz): δ = 7.27 (m, 5 H), 7.08 (m, 5 H), 7.05 (m, 2 H), 7.44 (s, 2 H), 4.13 (m, 4 H), 3.21 (t, δ = 6.9 Hz, 6 H) ppm. 31P NMR (CDCl₃, 121 MHz): δ = 7.3 ppm. 13C NMR (CDCl₃, 75 Hz): δ = 150.9, 143.4, 136.0, 134.8, 128.9 (C, 2), 128.5, 128.7 (C, 2), 125.7 (C, 2), 121.6, 63.0 (J, C-P = 5.9 Hz, 2 C), 55.5, 52.2, 16.2 (J, C-P = 6.5 Hz, 2 C) ppm. HRMS (ESI): m/z calcd. for C₂₄H₂₇N₃O₄P [M + H]+ 452.17332; found 452.17337 (0.12 ppm).

Diethyl (1-Benzyl-5-(4-fluoro-3-methylphenyl)-1H-1,2,3-triazol-4-yl)phosphonate (5e): Yield 54 mg (59%). Clear oil. IR: υ = 3038, 2927, 2925, 2851, 1601, 1487, 1456, 1445, 1307, 1240, 1216 cm⁻¹. 1H NMR (CDCl₃, 300 MHz): δ = 7.29 (m, 3 H), 7.05 (m, 5 H), 5.43 (s, 2 H), 4.14 (m, 4 H), 2.24 (d, J = 1.5 Hz, 3 H), 1.24 (td, J = 7.2, 0.6 Hz, 6 H) ppm. 31P NMR (CDCl₃, 121 MHz): δ = 7.2 ppm. 19F NMR (CDCl₃, 376 MHz): δ = -114.2 ppm. 13C NMR (CDCl₃, 75 Hz): δ = 164.2 (d, J, C-F = 248.1 Hz), 142.5 (d, J, C-F = 329.6 Hz), 136.1 (d, J, C-F = 239.0 Hz), 134.8, 133.3 (d, J, C-F = 5.8 Hz), 129.3 (J, C-F = 8.6 Hz), 128.9 (C, 2), 128.5, 127.6 (C, 2), 125.6 (J, C-F = 17.8 Hz), 123.1 (d, J, C-F = 3.8 Hz), 115.5 (d, J, C-F = 23.0 Hz), 62.9 (d, J, C-F = 5.9 Hz, 2 C), 52.2, 16.2 (J, C-F = 6.5 Hz, 2 C), 145 (d, J, C-F = 3.5 Hz) ppm. HRMS (EI): m/z calcd. for C₁₉H₁₅F₂N₂O₃P [M + H]+ 453.1120; found 453.1120 (0.01 ppm).

Diethyl (1-Benzyl-5-(4-fluoro-3-methylphenyl)-1H-1,2,3-triazol-4-yl)phosphonate (4e): Yield 54 mg (54%). Clear oil. IR: υ = 3038, 2927, 2925, 2851, 1601, 1487, 1456, 1445, 1307, 1240, 1216 cm⁻¹. 1H NMR (CDCl₃, 300 MHz): δ = 7.29 (m, 3 H), 7.05 (m, 5 H), 5.43 (s, 2 H), 4.14 (m, 4 H), 2.24 (d, J = 1.5 Hz, 3 H), 1.24 (td, J = 7.2, 0.6 Hz, 6 H) ppm. 31P NMR (CDCl₃, 121 MHz): δ = 7.2 ppm. 19F NMR (CDCl₃, 376 MHz): δ = -114.2 ppm. 13C NMR (CDCl₃, 75 Hz): δ = 164.2 (d, J, C-F = 248.1 Hz), 142.5 (d, J, C-F = 329.6 Hz), 136.1 (d, J, C-F = 239.0 Hz), 134.8, 133.3 (d, J, C-F = 5.8 Hz), 129.3 (J, C-F = 8.6 Hz), 128.9 (C, 2), 128.5, 127.6 (C, 2), 125.6 (J, C-F = 17.8 Hz), 123.1 (d, J, C-F = 3.8 Hz), 115.5 (d, J, C-F = 23.0 Hz), 62.9 (d, J, C-F = 5.9 Hz, 2 C), 52.2, 16.2 (J, C-F = 6.5 Hz, 2 C), 145 (d, J, C-F = 3.5 Hz) ppm. HRMS (EI): m/z calcd. for C₁₉H₁₅F₂N₂O₃P [M + H]+ 453.1120; found 453.1120 (0.01 ppm).

Keywords: Synthetic methods · Click chemistry · Cyclodaddition · Cross-coupling · Nitrogen heterocycles


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