Silver-Catalyzed Direct Regioselective Phosphonation of Thiazolo[3,2-b]-1,2,4-triazoles with Dialkyl Phosphites

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A. General method

All reactions were performed for synthesis of products 3a-3p at 80 °C in a Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer (100 MHz for carbon) and respectively referenced to 7.26 and 77.0 ppm for chloroform-d solvent with TMS as internal standard. ESI-MS spectra were measured on Finnigan Mat TSQ 7000 instruments. Elemental analyses were performed on a Heraeus elemental analyzer. TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF254), and visualization was effected at 254 nm.

B. General procedure

Synthesis of 3a: 6-phenylthiazolo[3,2-b]-1,2,4-triazole 1a (0.5 mmol), diethyl phosphonate 2a (1 mmol), AgOAc (10 mol%), K2S2O8 (2.0 equiv) and 3 mL of CH3CN were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 80 °C for 24 h. After completion of the reaction (monitored by TLC), the water (10 mL) was added. The aqueous solution was extracted with ethyl acetate (3×10 mL) and the combined extract was dried with anhydrous Na2SO4. The solvent was removed and the crude product was separated by column chromatography (eluted with petroleum ether/ethyl acetate = 3:1) to give a pure sample of 3a.

C. Analytical data for 3a-3p.

\[
\text{diethyl 6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3a)}
\]

\[1^1H\text{ NMR (400 MHz, CDCl}_3\text{) }\delta 8.22 (s, 1H), 7.89 (m, 2H), 7.56 (m, 3H), 4.17-4.03 (m, 4H), 1.21 (t, J = 7.0 Hz, 6H).\]

\[13^C\text{ NMR (100 MHz, CDCl}_3\text{) }\delta 157.8 (d, J = 8.2 Hz), 157.4, 138.4 (d, J = 17.8 Hz), 131.0, 129.8, 128.6, 126.8 (d, J = 1.8 Hz), 114.1 (d, J = 212.3 Hz), 63.6 (d, J = 5.7 Hz), 16.0 (d, J = 6.6 Hz).\]

\[3^1P\text{ NMR (162 MHz, CDCl}_3\text{) }\delta\]
7.30. (ESI-MS (m/z) 338 [M+H]+. Anal. calcd. C, 49.85; H, 4.78; N, 12.46; Found: C, 49.73; H, 4.72; N, 12.31.

**dimethyl 6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3b)**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.25 (s, 1H), 7.88 (m, 2H), 7.57 (m, 3H), 3.74 (s, 3H), 3.71 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.0 (d, $J$ = 8.0 Hz), 157.8, 139.0 (d, d, $J$ = 16.6 Hz), 131.2, 129.8, 128.6, 126.7, 112.7 (d, d, $J$ = 213.4 Hz), 53.6 (d, d, $J$ = 5.6 Hz). $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 10.31. ESI-MS (m/z) 310 [M+H]+. Anal. calcd. C, 46.60; H, 3.91; N, 13.59; Found: C, 46.49; H, 3.86; N, 13.44.

**dibutyl 6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3c)**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.22 (s, 1H), 7.91 (m, 2H), 7.55 (m, 3H), 4.09-3.97 (m, 4H), 1.56-1.49 (m, 4H), 1.30-1.24 (m, 4H), 0.86 (t, $J$ = 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.8 (d, $J$ = 8.0 Hz), 157.3, 138.3 (d, $J$ = 17.6 Hz), 131.0, 129.8, 128.6, 126.9 (d, $J$ = 2.0 Hz), 114.1 (d, $J$ = 212.0 Hz), 67.2 (d, $J$ = 6.0 Hz), 32.1 (d, $J$ = 6.8 Hz), 18.6, 13.5. $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 7.58. ESI-MS (m/z) 394 [M+H]+. Anal. calcd. C, 54.95; H, 6.15; N, 10.68; Found: C, 54.82; H, 6.11; N, 10.52.

**diisopropyl 6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3d)**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.12 (s, 1H), 7.85 (m, 2H), 7.45 (br s, 3H), 4.67-4.59 (m, 2H), 1.20 (d, $J$ = 6.0 Hz, 6H), 1.07 (d, $J$ = 6.4 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.6 (d, $J$ = 8.5 Hz), 157.1, 137.7 (d, $J$ = 17.2 Hz), 130.8, 129.9, 128.4, 127.0 (d, $J$ = 2.0 Hz), 115.6 (d, $J$ = 212.6 Hz), 73.0 (d, $J$ = 5.9 Hz), 23.8 (d, $J$ = 4.1
Hz), 23.5 (d, \( J = 5.3 \) Hz). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \( \delta \) 4.96. ESI-MS 366 (m/z) [M+H]\(^{+}\). Anal. calcd. C, 52.59; H, 5.52; N, 11.50; Found: C, 52.49; H, 5.47; N, 11.60.

diethyl 6-o-tolylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3e)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.18 (s, 1H), 7.49-7.30 (m, 4H), 4.12-3.95 (m, 4H), 2.18 (s, 3H), 1.25 (t, \( J = 7.0 \) Hz, 3H), 1.18 (t, \( J = 7.0 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 157.9 (d, \( J = 8.1 \) Hz), 157.5 138.8 (d, \( J = 17.7 \) Hz), 138.2, 131.1, 131.0, 130.4, 126.5, 125.9, 115.2 (d, \( J = 214.7 \) Hz), 63.5 (d, \( J = 5.7 \) Hz), 63.3 (d, \( J = 5.8 \) Hz), 19.6, 16.1 (d, \( J = 6.5 \) Hz), 16.0 (d, \( J = 6.7 \) Hz). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \( \delta \) 6.81. ESI-MS (m/z) 352 [M+H]\(^{+}\). Anal. calcd. C, 51.28; H, 5.16; N, 11.96; Found: C, 51.15; H, 5.11; N, 11.83.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{diethyl-6-o-tolylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate}};
\end{tikzpicture}
\end{center}

diethyl 6-p-tolylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3f)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.16 (s, 1H), 7.74 (d, \( J = 8.0 \) Hz, 2H), 7.31 (d, \( J = 8.0 \) Hz, 2H), 4.13-3.99 (m, 4H), 2.40 (s, 3H), 1.18 (t, \( J = 7.2 \) Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 157.6 (d, \( J = 8.4 \) Hz), 157.2, 141.4, 138.6 (d, \( J = 17.6 \) Hz), 129.7, 129.2, 123.8 (d, \( J = 2.0 \) Hz), 113.3 (d, \( J = 211.9 \) Hz), 63.5 (d, \( J = 5.7 \) Hz), 21.5, 16.0 (d, \( J = 6.6 \) Hz). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \( \delta \) 7.52. ESI-MS (m/z) 352 [M+H]\(^{+}\). Anal. calcd. C, 51.28; H, 5.16; N, 11.96; Found: C, 51.16; H, 5.10; N, 11.81.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{diethyl-6-p-tolylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate}};
\end{tikzpicture}
\end{center}

diethyl 6-(4-methoxyphenyl)thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3g)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{diethyl-6-(4-methoxyphenyl)thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate}};
\end{tikzpicture}
\end{center}
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.21 (s, 1H), 7.89 (d, $J = 8.4$ Hz, 2H), 7.06 (d, $J = 8.4$ Hz, 2H), 4.18-4.05 (m, 4H), 3.89 (s, 3H), 1.24 (t, $J = 7.0$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.6, 157.6 (d, $J = 8.0$ Hz), 157.2, 138.4 (d, $J = 17.7$ Hz), 131.4, 118.9 (d, $J = 1.9$ Hz), 114.0, 112.5 (d, $J = 211.7$ Hz), 63.5 (d, $J = 5.6$ Hz), 55.4, 16.1 (d, $J = 6.6$ Hz). $^{31}$P NMR (162 MHz, CDCl$_3$) δ 7.77. ESI-MS (m/z) 368 [M+H]$^+$. Anal. calcd. C, 49.04; H, 4.94; N, 11.44; Found: C, 48.93; H, 4.88; N, 11.30.

diethyl 6-(4-fluorophenyl)thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3h)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.11 (s, 1H), 7.86 (m, 2H), 7.15 (m, 2H), 4.11-3.95 (m, 4H), 1.15 (t, $J = 7.0$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.3, 162.8, 157.5 (d, $J = 8.7$ Hz), 157.3, 137.2 (d, $J = 17.4$ Hz), 132.2, 132.1, 122.8 (d, $J = 2.2$ Hz), 115.8, 115.6, 114.0 (d, $J = 211.3$ Hz), 63.6 (d, $J = 5.7$ Hz), 16.0 (d, $J = 6.5$ Hz). $^{31}$P NMR (162 MHz, CDCl$_3$) δ 7.10. ESI-MS (m/z) 356 [M+H]$^+$. Anal. calcd. C, 47.32; H, 4.26; N, 11.83; Found: C, 47.20; H, 4.21; N, 11.69.

diethyl 6-(4-chlorophenyl)thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3i)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.16 (s, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 4.14-4.02 (m, 4H), 1.21 (t, $J = 6.8$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 157.6 (d, $J = 8.4$ Hz), 157.4, 137.1 (d, $J = 23.4$ Hz), 131.2, 128.9, 125.2 (d, $J = 2.0$ Hz), 114.6 (d, $J = 210.9$ Hz), 63.7 (d, $J = 5.6$ Hz), 16.1 (d, $J = 6.5$ Hz). $^{31}$P NMR (162 MHz, CDCl$_3$) δ 7.01. ESI-MS (m/z) 372 [M+H]$^+$. Anal. calcd. C, 45.23; H, 4.07; N, 11.30; Found: C, 45.12; H, 4.02; N, 11.16.
diethyl 6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate (3j)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.18 (s, 1H), 4.25-4.13 (m, 4H), 2.77 (s, 3H), 1.36 (t, $J$ = 7.0 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 157.6 (d, $J$ = 7.9 Hz), 157.2, 137.7 (d, $J$ = 19.6 Hz), 111.5 (d, $J$ = 212.2 Hz), 63.3 (d, $J$ = 5.4 Hz), 16.2 (d, $J$ = 6.6 Hz), 12.4. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 8.07. ESI-MS (m/z) 276 [M+H]$^+$. Anal. calcd. C, 39.27; H, 5.13; N, 15.27; Found: C, 39.14; H, 5.07; N, 15.11.

diethyl 2,6-dimethylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate (3k)

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.27-4.11 (m, 4H), 2.76 (s, 3H), 2.56 (s, 3H), 1.38 (t, $J$ = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.6, 157.7 (d, $J$ = 8.6 Hz), 137.7, (d, $J$ = 19.7 Hz), 109.7 (d, $J$ = 213.6 Hz), 63.3 (d, $J$ = 5.4 Hz), 16.2 (d, $J$ = 6.6 Hz), 15.0, 12.4. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 8.56. ESI-MS (m/z) 290 [M+H]$^+$. Anal. calcd. C, 41.52; H, 5.57; N, 14.53; Found: C, 41.40; H, 5.51; N, 14.39.

diethyl 6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate (3l)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.18 (m, 2H), 7.47 (m, 3H), 4.29-4.16 (m, 4H), 2.83 (s, 3H), 1.39 (t, $J$ = 7.0 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.9, 158.1 (d, $J$ = 8.7 Hz), 137.9 (d, $J$ = 19.7 Hz), 130.4, 130.2, 128.7, 126.9, 110.5 (d, $J$ = 212.8 Hz), 63.4 (d, $J$ = 5.4 Hz), 16.3 (d, $J$ = 6.5 Hz), 12.5. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 8.40. ESI-MS (m/z) 352 [M+H]$^+$. Anal. calcd. C, 51.28; H, 5.16; N, 11.96; Found: C, 51.16; H, 5.11; N, 11.82.

diethyl 6-methyl-2-p-tolylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate (3m)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.07 (d, $J$ = 8.0 Hz, 2H), 7.28 (d, $J$ = 7.2 Hz, 2H), 4.28-4.16 (m, 4H), 2.82 (s, 3H), 2.41 (s, 3H), 1.39 (t, $J$ = 7.2 Hz, 6H). $^{13}$C NMR (100
MHz, CDCl$_3$) δ 168.5, 158.2 (d, $J = 8.8$ Hz), 140.3, 138.0 (d, $J = 19.6$ Hz), 129.5, 129.4, 126.9, 109.8 (d, $J = 213.7$ Hz), 63.4 (d, $J = 5.4$ Hz), 21.5, 16.3 (d, $J = 6.5$ Hz), 12.5. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 8.13. ESI-MS (m/z) 366 [M+H]$^+$. Anal. calcd. C, 52.59; H, 5.52; N, 11.50; Found: C, 52.46; H, 5.46; N, 11.34.

![diethyl 2-(4-chlorophenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3n)](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.12 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H), 4.29-4.16 (m, 4H), 2.83 (s, 3H), 1.39 (t, $J = 7.0$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.3, 158.3 (d, $J = 8.8$ Hz), 137.8 (d, $J = 19.3$ Hz), 136.1, 129.3, 129.0, 128.2, 110.5 (d, $J = 212.7$ Hz), 63.3 (d, $J = 5.2$ Hz), 16.3 (d, $J = 6.5$ Hz), 12.5. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 8.29. ESI-MS (m/z) 386 [M+H]$^+$. Anal. calcd. C, 46.70; H, 4.44; N, 10.89; Found: C, 46.59; H, 4.39; N, 12.31.

![diethyl 2,6-diphenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3o)](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.17 (m, 2H), 7.97 (m, 2H), 7.57 (m, 3H), 7.43 (m, 3H), 4.17-4.03 (m, 4H), 1.21 (t, $J = 7.0$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.3, 158.4 (d, $J = 8.3$ Hz), 138.5 (d, $J = 17.5$ Hz), 130.9, 130.7, 130.1, 130.0, 128.6, 128.5, 127.0, 112.7 (d, $J = 212.3$ Hz), 63.6 (d, $J = 5.7$ Hz), 16.1 (d, $J = 6.6$ Hz). $^{31}$P NMR (162 MHz, CDCl$_3$) δ 7.75. ESI-MS (m/z) 414 [M+H]$^+$. Anal. calcd. C, 58.10; H, 4.88; N, 10.16; Found: C, 57.98; H, 4.82; N, 10.02.

![diethyl thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3p)](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.17 (s, 1H), 7.84 (s, 1H), 4.14-4.01 (m, 4H), 1.21 (t, $J = 7.0$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 157.6 (d, $J = 8.1$ Hz), 157.1, 118.5 (d, $J = 8.1$ Hz), 157.1, 118.5 (d, $J = 8.1$ Hz), 157.1
= 20.4 Hz), 111.4 (d, \( J = 212.2 \) Hz), 63.3 (d, \( J = 5.4 \) Hz), 16.1 (d, \( J = 6.4 \) Hz). \(^{31}\text{P} \) NMR (162 MHz, CDCl\(_3\)) \( \delta \) 7.97. ESI-MS (m/z) 262 [M+H]\(^+\). Anal. calcd. C, 36.78; H, 4.63; N, 16.08; Found: C, 36.66; H, 4.58; N, 15.93.
D. NMR spectra

diethyl 6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3a)
dimethyl 6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3b)
dibutyl 6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate (3c)
diisopropyl 6-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3d)
diethyl 6-o-tolythiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3e)
diethyl 6-p-tolythiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3f)
diethyl 6-(4-methoxyphenyl)thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3g)
diethyl 6-(4-fluorophenyl)thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3h)
diethyl 6-(4-chlorophenyl)thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3i)
diethyl 6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3j)
diethyl 2,6-dimethylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3k)
diethyl 6-methyl-2-phenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3l)
diethyl 6-methyl-2-p-tolylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate (3m)
diethyl
2-(4-chlorophenyl)-6-methylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3n)
diethyl 2,6-diphenylthiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3o)
diethyl thiazolo[3,2-b][1,2,4]triazol-5-yl-5-phosphonate(3p)