A concise synthesis of
4-imino-3,4-dihydroquinazolin-2-ylphosphonates via
a palladium-catalyzed reaction of carbodiimide,
isocyanide, and phosphite

Guanyinsheng Qiu, Yuan Lu, and Jie Wu*

jie_wu@fudan.edu.cn

Supporting Information

1. General experimental methods (S2).
2. General experimental procedure and characterization data (S2-S8).
3. $^1$H and $^{13}$C NMR spectra of compounds 4 (S9-S36).
General Materials and Methods:

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63µm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr at 25–35°C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II Instrument. The carbodiimides 1 were synthesized according to literature method (1) F. Zeng, H. Alper, Org. Lett. 2010, 12, 3642. 2) F. Zeng and H. Alper, Org. Lett. 2010, 12, 1188.)

General procedure of the synthesis of
4-imino-3,4-dihydroquinazolin-2-ylphosphonates via a palladium-catalyzed reaction of carbodiimide, isocyanide, and phosphite

\[
\begin{align*}
\text{R}_1^1 & \text{H} \hspace{1cm} \text{N} \hspace{1cm} \text{C} \hspace{1cm} \text{N} \hspace{1cm} \text{R}_2^2 \\
\text{O} & \hspace{1cm} \text{H} \hspace{1cm} \text{P} \hspace{1cm} \text{O(OR)}_3^3 \\
\text{R}_1^1 & \hspace{1cm} \text{R}^3_4 \hspace{1cm} \text{N} \hspace{1cm} \text{PO(OR)}_3^3_2 \\
\text{Pd(OAc)}_2^2 & \text{DPPF} (10 \text{ mol } \%) \\
\text{Cs}_2^2 \text{CO}_3 & \text{FeCl}_3 (10 \text{ mol } \%) \\
\text{toluene} & \text{reflux} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1^1 & \text{R}^3_4 \hspace{1cm} \text{N} \hspace{1cm} \text{PO(OR)}_3^3_2 \\
\text{Pd(OAc)}_2^2 & \text{DPPF} (10 \text{ mol } \%) \\
\text{Cs}_2^2 \text{CO}_3 & \text{FeCl}_3 (10 \text{ mol } \%) \\
\end{align*}
\]

Pd(OAc)₂ (10 mol %), DPPF (10 mol %), and FeCl₃ (10 mol %) were added to a solution of carbodiimides 1 (0.2 mmol) in toluene (2.0 mL) under N₂ atmosphere at room temperature. Then phosphite 2 (1.5 equiv) was added. After the mixture was stirred at room temperature for 1 hour, isocyanide 3 (2.0 equiv) and Cs₂CO₃ (2.0 equiv) was added. Then the mixture was stirred at reflux. After completion of reaction
as indicated by TLC (8-12 hrs), the solvent was evaporated and the residue was purified on silica gel to provide the desired product 4.

Diethyl (E)-4-(tert-butylimino)-3,4-dihydro-3-(2-iodophenyl)quinazolin-2-yl-2-phosphonate (4a): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.14 (t, \(J = 7.2\) Hz, 3H), 1.23 (s, 9H), 1.36 (t, \(J = 7.2\) Hz, 3H), 3.66-3.71 (m, 1H), 3.72-3.93 (m, 1H), 4.22-4.28 (m, 2H), 7.01-7.06 (m, 1H), 7.41-7.61 (m, 5H), 7.86 (d, \(J = 8.0\) Hz, 1H), 7.98 (d, \(J = 8.4\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 16.1, 16.3, 31.0, 53.0, 63.0, 64.6, 102.6, 122.3, 125.8, 127.9, 128.8, 128.9, 129.6, 131.6, 132.9, 138.5, 142.6, 146.5, 151.8; HRMS Calcd for C\(_{22}\)H\(_{28}\)IN\(_3\)O\(_3\)P\(^+\) (ESI, M+H\(^+\)): 540.0907; found: 540.0920.

Diethyl (E)-4-(tert-butylimino)-3,4-dihydro-3-phenylquinazolin-2-yl-2-phosphonate (4b): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.14 (t, \(J = 7.2\) Hz, 3H), 1.23 (s, 9H), 1.36 (t, \(J = 7.2\) Hz, 3H), 3.66-3.70 (m, 1H), 3.87-3.91 (m, 1H), 4.24-4.28 (m, 2H), 6.90-6.94 (m, 1H), 7.05-7.28 (m, 7H), 7.61 (d, \(J = 8.0\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 16.1, 16.3, 31.0, 53.0, 62.9, 64.6, 121.1, 122.9, 123.1, 123.7, 124.2, 127.5, 128.6, 130.8, 141.9, 145.6, 148.1, 153.6; HRMS Calcd for C\(_{22}\)H\(_{29}\)N\(_3\)O\(_3\)P\(^+\) (ESI, M+H\(^+\)): 414.1941; found: 414.1940.

Diethyl (E)-4-(tert-butylimino)-3,4-dihydro-3-p-tolylquinazolin-2-yl-2-phosphonate (4c): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.12 (t, \(J = 7.2\) Hz, 3H), 1.22 (s, 9H), 1.35 (t, \(J =
7.2 Hz, 3H), 2.40 (s, 3H), 3.64-3.70 (m, 1H), 3.85-3.93 (m, 1H), 4.23-4.26 (m, 2H), 7.00-7.03 (m, 1H), 7.24-7.41 (m, 3H), 7.60 (d, $J = 8.0$ Hz, 2H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.3, 16.5, 20.2, 31.2, 53.1, 63.2, 63.9, 122.5, 126.2, 128.9, 129.3, 129.8, 131.8, 133.2, 138.7, 142.8, 146.9, 149.5, 152.0; HRMS Calcd for C$_{23}$H$_{31}$N$_3$O$_3$P$^+$ (ESI, M+H$^+$): 428.2098; found: 428.2135.

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\begin{array}{c}
\text{Diethyl} \\
(E)-4-(\text{tert-butylimino})-3-(4-chlorophenyl)-3,4-dihydroquinazolin-2-yl-2-phosphonate (4d): \text{H NMR (400 MHz, CDCl$_3$) $\delta$ 1.12 (t, $J = 7.2$ Hz, 3H), 1.21 (s, 9H), 1.34 (t, $J = 7.2$ Hz, 3H), 3.64-3.70 (m, 1H), 3.85-3.89 (m, 1H), 4.23-4.26 (m, 2H), 7.00-7.04 (m, 1H), 7.22-7.41 (m, 3H), 7.50-7.54 (m, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 7.6$ Hz, 1H), 7.97 (d, $J = 8.4$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.1, 16.3, 31.0, 53.0, 62.9, 64.6, 122.3, 126.1, 128.1, 128.8, 129.1, 129.7, 131.2, 132.9, 138.5, 146.5, 149.2, 151.8; HRMS Calcd for C$_{22}$H$_{28}$ClN$_3$O$_3$P$^+$ (ESI, M+H$^+$): 448.1551; found: 448.1553.
\end{array}
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\begin{array}{c}
\text{Diethyl} \\
(E)-4-(\text{tert-butylimino})-3-butyl-3,4-dihydroquinazolin-2-yl-2-phosphonate (4e): \text{H NMR (400 MHz, CDCl$_3$) $\delta$ 0.94 (t, $J = 7.2$ Hz, 3H), 1.25-1.38 (m, 8H), 1.41 (s, 9H), 1.55-1.62 (m, 2H), 4.29-4.36 (m, 6H), 7.25-7.27 (m, 1H), 7.46-7.48 (m, 2H), 7.93 (d, $J = 7.6$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 14.0, 16.3, 16.3, 20.3, 30.1, 31.7, 46.5, 53.3, 64.0, 64.1, 121.2, 125.2, 127.8, 129.3, 131.1, 146.8, 149.8, 152.4; HRMS Calcd for C$_{20}$H$_{33}$N$_3$O$_3$P$^+$ (ESI, M+H$^+$): 394.2254; found: 394.2265.
\end{array}
\]
Diethyl (E)-4-(tert-butylimino)-3-benzyl-3,4-dihydroquinazolin-2-yl-2-phosphonate (4f): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.26-1.37 (m, 15H), 4.22-4.24 (m, 4H), 5.53 (s, 2H), 7.15-7.27 (m, 6H), 7.49-7.53 (m , 2H), 7.84 (d, $J = 7.6$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.0, 31.3, 49.6, 53.2, 64.1, 121.4, 125.4, 126.2, 127.1, 127.7, 127.8, 129.2, 131.2, 138.3, 150.2, 152.7; HRMS Calcd for C$_{23}$H$_{31}$N$_3$O$_3$P$^+$ (ESI, M+H$^+$): 428.2098; found: 428.2098.

Diethyl (E)-4-(tert-butylimino)-3-cyclohexyl-3,4-dihydroquinazolin-2-yl-2-phosphonate (4g): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.38-1.41 (m, 17H), 1.78-1.86 (m, 6H), 2.72-2.78 (m, 2H), 4.29-4.33 (m, 5H), 7.18-7.20 (m, 1H), 7.40-7.41 (m , 2H), 7.72 (d, $J = 8.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.3, 16.4, 25.9, 26.8, 30.7, 31.7, 31.9, 54.3, 63.3, 64.0, 64.1, 122.1, 124.7, 126.6, 128.4, 130.8, 146.7, 150.4, 152.9; HRMS Calcd for C$_{22}$H$_{34}$N$_3$NaO$_3$P$^+$ (ESI, M+Na$^+$): 442.2230; found: 442.2248.

Diethyl (E)-4-(tert-butylimino)-3,4-dihydro-3-(2-iodo-4-methylphenyl)-6-methylquinazolin-2-yl-2-phosphonate (4h): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.14 (t, $J = 7.2$ Hz, 3H), 1.23 (s, 9H), 1.36 (t, $J = 7.2$ Hz, 3H), 2.41 (s, 3H), 2.45 (s, 3H), 3.66-3.70 (m, 1H), 3.87-3.91 (m, 1H), 4.24-4.28 (m, 2H), 7.10 (d, $J = 8.0$ Hz, 1H), 7.33-7.35 (m, 2H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.87 (s, 1H), 7.93 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.1, 16.3, 20.6, 20.6, 31.0, 52.9, 63.0, 64.6, 122.3, 126.0, 128.1, 128.7, 128.8, 129.1,
129.7, 131.7, 133.0, 138.6, 140.4, 142.6, 146.5; HRMS Calcd for C_{24}H_{32}I\textsubscript{3}O_{3}P^{+} (ESI, M+H\textsuperscript{+}): 568.1220; found: 568.1220.

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\text{Diethyl (E)-4-(tert-butylimino)-6-chloro-3-(4-chloro-2-iodophenyl)-3,4-dihydroquinazolin-2-yl-2-phosphonate (4i):} \ \ \ \ ^{1}H \text{ NMR (400 MHz, CDCl}_{3}\text{)} \ \ \ \ ^{\delta} \ 1.16 \ (t, \ J = 7.2 \text{ Hz}, \ 3\text{H}), \ 1.23 \ (s, \ 9\text{H}), \ 1.36 \ (t, \ J = 7.2 \text{ Hz}, \ 3\text{H}), \ 3.78-3.82 \ (m, \ 1\text{H}), \ 3.92-3.98 \ (m, \ 1\text{H}), \ 4.22-4.26 \ (m, \ 2\text{H}), \ 7.31 \ (d, \ J = 7.6 \text{ Hz}, \ 1\text{H}), \ 7.38 \ (d, \ J = 8.0 \text{ Hz}, \ 1\text{H}), \ 7.48-7.52 \ (m, \ 2\text{H}), \ 7.83 \ (s, \ 1\text{H}), \ 7.93 \ (s, \ 1\text{H}); \ ^{13}C \text{ NMR (100 MHz, CDCl}_{3}\text{)} \ \ \ \ ^{\delta} \ 16.0, \ 16.2, \ 30.9, \ 53.2, \ 63.2, \ 63.7, \ 102.5, \ 122.9, \ 128.2, \ 129.2, \ 130.0, \ 131.6, \ 131.9, \ 133.4, \ 133.9, \ 137.8, \ 139.1, \ 140.9, \ 144.8, \ 151.7; \ HRMS \ Calcd for C_{22}H_{26}Cl_{2}I_{3}O_{3}P^{+} \ (ESI, M+H\textsuperscript{+}): 608.0128; \ found: 608.0122.
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\text{Diethyl (E)-4-(tert-butylimino)-3-(2-bromo-4-methylphenyl)-3,4-dihydro-6-methylquinazolin-2-yl-2-phosphonate (4j):} \ \ \ \ ^{1}H \text{ NMR (400 MHz, CDCl}_{3}\text{)} \ \ \ \ ^{\delta} \ 1.14 \ (t, \ J = 7.2 \text{ Hz}, \ 3\text{H}), \ 1.23 \ (s, \ 9\text{H}), \ 1.36 \ (t, \ J = 7.2 \text{ Hz}, \ 3\text{H}), \ 2.40 \ (s, \ 3\text{H}), \ 2.44 \ (s, \ 3\text{H}), \ 3.76-3.79 \ (m, \ 1\text{H}), \ 3.87-3.91 \ (m, \ 1\text{H}), \ 4.31-4.38 \ (m, \ 2\text{H}), \ 7.09 \ (d, \ J = 7.6 \text{ Hz}, \ 1\text{H}), \ 7.27-7.33 \ (m, \ 2\text{H}), \ 7.60 \ (d, \ J = 8.0 \text{ Hz}, \ 1\text{H}), \ 7.86 \ (s, \ 1\text{H}), \ 7.95 \ (s, \ 1\text{H}); \ ^{13}C \text{ NMR (100 MHz, CDCl}_{3}\text{)} \ \ \ \ ^{\delta} \ 16.3, \ 16.5, \ 20.6, \ 21.3, \ 31.2, \ 53.5, \ 63.4, \ 65.0, \ 102.8, \ 123.3, \ 128.5, \ 129.5, \ 130.3, \ 131.9, \ 132.2, \ 133.7, \ 134.2, \ 138.2, \ 141.3, \ 152.1; \ HRMS \ Calcd for C_{24}H_{32}BrN_{3}O_{3}P^{+} \ (ESI, M+H\textsuperscript{+}): 520.1359; \ found: 520.1359.
\]
Dipropyl  

\((E)\)-4-(tert-butylimino)-3-butyl-3,4-dihydroquinazolin-2-yl-2-phosphonate

(4k): 

\(\text{H NMR (400 MHz, CDCl}_3\) \(\delta 0.94 (t, J = 7.6 \text{ Hz}, 3\text{H}), 1.38-1.49 (m, 23\text{H}), 1.68-1.73 (m, 2\text{H}), 4.27 (t, J = 7.2 \text{ Hz}, 2\text{H}), 4.87-4.91 (m, 2\text{H}), 7.23-7.26 (m, 1\text{H}), 7.43-7.47 (m, 2\text{H}), 7.91 (d, J = 8.0 \text{ Hz}, 1\text{H}); \text{^13C NMR (100 MHz, CDCl}_3\) \(\delta 14.0, 20.3, 23.7, 24.2, 24.2, 29.6, 31.8, 46.5, 53.3, 121.2, 125.0, 129.3, 131.1, 146.9, 150.4, 152.9; HRMS Calcd for C\text{_{22}}H\text{_{37}}N\text{_{3}}O\text{_{3}}P\text{^{+}} \text{ (ESI, M+H\text{^{+}}): 422.2567; found: 422.2565.}

Dipropyl  

\((E)\)-4-(tert-butylimino)-3-benzyl-3,4-dihydroquinazolin-2-yl-2-phosphonate

(4l): 

\(\text{H NMR (400 MHz, CDCl}_3\) \(\delta 1.25 (s, 9\text{H}), 1.34 (s, 6\text{H}), 1.35 (s, 6\text{H}), 4.83-4.91 (m, 2\text{H}), 5.52 (s, 2\text{H}), 7.13-7.26 (m, 6\text{H}), 7.46-7.49 (m, 1\text{H}), 7.55 (d, J = 7.6 \text{ Hz}, 1\text{H}), 7.82 (d, J = 8.0 \text{ Hz}, 1\text{H}); \text{^13C NMR (100 MHz, CDCl}_3\) \(\delta 23.4, 24.0, 31.2, 49.8, 53.2, 73.2, 73.3, 121.4, 125.2, 126.1, 127.2, 127.6, 129.2, 131.1, 138.5, 139.5, 146.5, 153.3; HRMS Calcd for C\text{_{25}}H\text{_{35}}N\text{_{3}}O\text{_{3}}P\text{^{+}} \text{ (ESI, M+H\text{^{+}}): 456.2411; found: 456.2413.}

Diethyl  

\((E)\)-3-butyl-4-(cyclohexylimino)-3,4-dihydroquinazolin-2-yl-2-phosphonate

(4m): 

\(\text{H NMR (400 MHz, CDCl}_3\) \(\delta 0.94 (t, J = 6.4 \text{ Hz}, 3\text{H}), 1.25-1.45 (m, 15\text{H}), 1.81-1.83 (m, 5\text{H}), 4.03-4.05 (m, 1\text{H}), 4.30-4.33 (m, 6\text{H}), 7.26-7.26 (m, 1\text{H}), 7.48-7.51 (m, 2\text{H}), 7.78 (d, J = 8.0 \text{ Hz}, 1\text{H}); \text{^13C NMR (100 MHz, CDCl}_3\) \(\delta 13.9, 16.3, 16.4, 20.3, 24.4, 26.1, 29.9, 35.0, 46.5, 56.3, 64.1, 64.1, 120.8, 126.1, 127.3, 128.3,
Diethyl (E)-3-benzyl-4-(butylimino)-3,4-dihydroquinazolin-2-yl-2-phosphonate (4n): 

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)} \delta 0.82 \text{ (t, } J = 7.6 \text{ Hz, 3H), 1.20-1.28 \text{ (m, 8H), 1.47-1.54} \text{ (m, 2H), 3.68-3.71 \text{ (m, 2H), 4.20-4.27 \text{ (m, 4H), 5.63} \text{ (s, 2H), 7.14-7.31 \text{ (m, 6H), 7.50-7.54 \text{ (m, 1H), 7.59} \text{ (d, } J = 8.0 \text{ Hz, 1H), 7.97} \text{ (d, } J = 8.0 \text{ Hz, 1H); \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)} \delta 13.8, 15.9, 16.0, 20.2, 35.1, 49.3, 50.4, 64.0, 64.1, 121.6, 126.0, 126.3, 126.9, 127.7, 128.3, 131.4, 138.0, 143.5, 135.9; HRMS Calcd for C}_{23}\text{H}_{31}\text{N}_3\text{O}_3\text{P}^+ \text{(ESI, M+H}^+)\text{): 428.2098; found: 428.2111.} \]