Microwave-Assisted Hydrolysis of Phosphonates Diesters: An Efficient Protocol for the Preparation of Phosphonic Acids

Petr Jansa,* Ondřej Baszczyński, Eliška Procházková, Martin Dračinský, and Zlatko Janeba*

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo nám. 2, CZ-16610 Prague 6, Czech Republic

jansa@uochb.cas.cz, janeba@uochb.cas.cz

Supporting information

General information. Unless stated otherwise, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 13 Pa. Melting points were determined on a Büchi B-540 and are uncorrected. Analytical TLC was performed on silica gel 60 F254 plates (Merck). Column chromatography was performed on silica gel 60 µm (Merck). Mass spectra were measured on a LTQ Orbitrap XL (Thermo Fisher Scientific) spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on Bruker Avance 500 (¹H at 500 MHz and ¹³C 125.7 MHz) in D₂O (referenced to dioxane as an internal standard δ = 3.75 ppm and δ = 67.19 ppm, respectively). Complete assignment is based on heteronuclear correlation experiments HSQC and H,C-HMBC. Chemical shifts (δ) are in ppm and coupling constants (J) in Hz. Optical rotations were measured on Autopol IV polarimeter (Rudolph Research Analytical, U.S.A.) at 20 °C, [α]D values are given in 10⁻¹ deg cm² g⁻¹, concentrations are given in g/100 mL. The purity of compounds was determined by elemental analysis (C, H, N) measured on Perkin–Elmer CHN Analyzer 2400, Series II (Perkin–Elmer). The microwave-assisted (MW-assisted) reactions were carried out in the following MW syntheses instruments: Type I – CEM Discover®, single-mode cavity with focused MW heating (MW power supply 0-300 W, 1 W increments, IR temperature sensor, open or closed vessel mode, pressure range 0-20 bar, 10 ml or 80 ml vials); Type II – Milestone BatchSYNTH®, single-mode cavity, scale-up (MW power supply 0-1000 W, 10 W increments, internal temperature sensor, batch mode, pressure range 0-30 bar, 250 ml vessel); Type III – Milestone FlowSYNTH®, (MW power supply 0-1000 W, 10 W increments, internal temperature sensor, flow mode, pressure range 0-30 bar, 200 mL reaction cell volume, flow rate 10-100 mL/min). Starting phosphonate diesters were synthesized at the Institute of Organic Chemistry and Biochemistry in Prague, Czech Republic.¹,³,⁹

General procedure for the microwave-assisted hydrolysis of phosphonate diesters.

A mixture of the starting phosphonate diester (1.0 mmol) in the aqueous HCl solution (1.0 or 2.0 mmol of 0.5 M or 1.0 M HCl solution) was placed, with a magnetic stirring bar, into 10 mL
reaction tube and sealed. The reaction mixture was heated in the microwave reactor (Type I) at 130-140 °C until constant pressure (20-30 min). The reaction mixture was cooled down to 0 °C and precipitated product was filtered off, washed (water, EtOH, and acetone), and dried in vacuo. The products can be crystallized from water for better purity.

(R)-(((1-(2,6-Diamino-9H-purin-9-yl)propan-2-yl)oxy)methyl)phosphonic acid (9).\(^1\)

Reaction conditions: a) Microwave reactor Type I, starting compound 1 (1.0 mmol), 130 °C for 10 min, yield 77% of 9; b) Microwave reactor Type II, starting compound 1 (100.0 mmol), 130°C for 10 min, yield 79% of 9.

\[ \text{9} \]

\(^1\)H NMR and \(^{13}\)C NMR spectra correspond to literature.\(^1\) For C\(_9\)H\(_{15}\)N\(_6\)O\(_4\)P (302.1) calculated (%): C 35.77; H 5.00; N 27.81; found (%): C 35.54; H 5.23; N 27.59. MS ESI(-), \(m/z\) (%): 301 [M-] (100). Optical purity (99.2 %) was determined by capillary electrophoresis.\(^2\) Chemical purity was determined by X-ray fluorescence analyzer SPECTRO iQ II and confirmed that compound 9 did not contain silicon or any other elements higher than sodium.

Scale-up for compound 9 under continuous flow conditions: A mixture of compound 1 (50 mmol, 19.3 g) in the aqueous HCl solution (0.25 M, 400 mL) was heated in the microwave reactor (Type III) at 140 °C at flow rate of 12 mL/min till full conversion. The reaction was monitored by TLC. The reaction mixture was cooled down to 0 °C and precipitated product was filtered off and washed (water). The crude product was crystallized (water), crystals were washed (water, EtOH, and acetone) and dried in vacuo to give 10.9 g (72%) of compound 9.

((2-(2,6-Diamino-9H-purin-9-yl)ethoxy)methyl)phosphonic acid (10).\(^3\)

Reaction conditions: Microwave reactor Type I, starting compound 2 (1.0 mmol), 130 °C for 20 min, yield 78% of 10.
1H NMR and 13C NMR spectra correspond to literature. For C₈H₁₃N₆O₄P (288.1) calculated (%): C 33.34; H 4.55; N 29.16; found (%): C 33.54; H 4.84; N 29.03. MS ESI(-), m/z (%): 287 [M⁻] (100).

(S)-(((1-(2,6-Diamino-9H-purin-9-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphonic acid (11).

Reaction conditions: Microwave reactor Type I, starting compound 3 (1.0 mmol), 130 °C for 20 min, yield 77% of 11.

1H NMR and 13C NMR spectra correspond to literature. [α]D –24.8° (c 0.38, H₂O/NH₃). For C₉H₁₄N₅O₆P (318.1) calculated (%): C 33.86; H 4.42; N 21.94; found (%): C 33.65; H 4.67; N 21.72. MS ESI(-), m/z (%): 317 [M⁻] (100).

((2-(2-Amino-6-oxo-1H-purin-9(6H)-yl)ethoxy)methyl)phosphonic acid (12).

Reaction conditions: a) Microwave reactor Type I, starting compound 4 (1.0 mmol), 140 °C for 10 min, yield 93 % of 12; b) Microwave reactor Type II, starting compound 4 (50.0 mmol), 140°C for 10 min, yield 91% of 12.
1H NMR and 13C NMR spectra correspond to literature. For C₈H₁₂N₅O₅P (289.1) calculated (%): C 33.23; H 4.18; N 24.22; found (%): C 33.43; H 4.37; N 24.16. MS ESI(-), m/z (%): 288 [M-] (100), 310 [M-Na] (21); HRMS ESI(-) calculated (m/z): 288.0502; found: 288.0492.

((2-(6-Amino-9H-purin-9-yl)ethoxy)methyl)phosphonic acid (13). Reaction conditions: a) Microwave reactor Type I, starting compound 5 (1.0 mmol), 140 °C for 10 min, yield 92 % of 13; b) Microwave reactor Type II, starting compound 5 (100.0 mmol), 140°C for 10 min, yield 95% of 13.

1H NMR and 13C NMR spectra correspond to literature. For C₈H₁₂N₅O₄P (273.1) calculated (%): C 35.17; H 4.43; N 25.64; found (%): C 35.28; H 4.59; N 25.43. MS ESI(-), m/z (%): 272 [M-] (100), 294 [M-Na] (17).

(S)-(((1-(6-Amino-9H-purin-9-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphonic acid (14). Reaction conditions: a) Microwave reactor Type I, starting compound 6 (1.0 mmol), 140 °C for 10 min, yield 88 % of 14; b) Microwave reactor Type II, starting compound 6 (50.0 mmol), 140°C for 10 min, yield 92% of 14.
$^1$H NMR and $^{13}$C NMR spectra correspond to literature.$^6$ [α]$_D$ $-13.4^\circ$ ($c$ 0.35, H$_2$O/NH$_3$). For C$_9$H$_{14}$N$_5$O$_5$P (303.1) calculated (%): C 35.65; H 4.65; N 23.10; found (%): C 35.47; H 4.83; N 23.02. MS ESI(-), m/z (%): 303 [M$^-$] (100).

(R)-(((1-(6-Amino-9H-purin-9-yl)propan-2-yl)oxy)methyl)phosphonic acid (15).$^7$

Reaction conditions: a) Microwave reactor Type I, starting compound 7 (1.0 mmol), 140 °C for 10 min, yield 91 % of 15; b) Microwave reactor Type II, starting compound 7 (50.0 mmol), 140°C for 10 min, yield 90 % of 15.

![Image](15)

$^1$H NMR and $^{13}$C NMR spectra correspond to literature.$^7$ [α]$_D$ $-19.2^\circ$ ($c$ 0.5, H$_2$O/NH$_3$). For C$_9$H$_{13}$FN$_5$O$_4$P (287.1) calculated (%): C 37.64; H 4.91; N 24.38; found (%): C 37.49; H 5.17; N 24.27. MS ESI(-), m/z (%): 301 [M$^-$] (100).

(R)-(((1-(6-Amino-9H-purin-9-yl)-3-fluoropropan-2-yl)oxy)methyl)phosphonic acid (16)$^{8,9}$

Reaction conditions: Microwave reactor Type I, starting compound 8 (1.0 mmol), 140 °C for 10 min, yield 93 % of 16.

![Image](16)

$^1$H NMR and $^{13}$C NMR spectra correspond to literature.$^{8,9}$ [α]$_D$ $+8.4^\circ$ ($c$ 0.24, H$_2$O/NH$_3$). For C$_{9}$H$_{12}$FN$_5$O$_4$P (305.1) calculated (%): C 35.42; H 4.29; N 22.95; found (%): C 35.63; H 4.48; N 22.81. MS ESI(-), m/z (%): 304 [M$^-$] (100).
(R,S)-((1-Fluoro-3-(6-oxo-1H-purin-9(6H)-yl)propan-2-yl)oxy)methyl)phosphonic acid (23)\(^{8,9}\)

Reaction conditions: Microwave reactor Type I, starting compound 17 (1.0 mmol), 140 °C for 10 min, yield 82 % of 23.

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\begin{align*}
\text{HN} & \text{N} \\
\text{O} & \\
\text{O} & \\
\text{F} & \\
\text{OH} & \\
\end{align*}
\]

\(23\)

\(^1\)H NMR and \(^{13}\)C NMR spectra correspond to literature.\(^{8,9}\) For C\(_9\)H\(_{12}\)FN\(_4\)O\(_5\)P (306.1) calculated (%): C 35.30; H 3.95; N 18.30; found (%): C 35.43; H 4.20; N 18.17. MS ESI(-), \(m/z\) (%): 305 [M\(^-\)] (100). HRMS ESI(-) calculated (\(m/z\)): 305.0451; found: 305.0450.

(R)-((1-(2-Amino-6-oxo-1H-purin-9(6H)-yl)-3-fluoropropan-2-yl)oxy)methyl)phosphonic acid (24)\(^{8,9}\)

Reaction conditions: Microwave reactor Type I, starting compound 18 (1.0 mmol), 140 °C for 10 min, yield 83 % of 24.

\[
\begin{align*}
\text{HN} & \text{N} \\
\text{O} & \\
\text{O} & \\
\text{F} & \\
\text{OH} & \\
\end{align*}
\]

\(24\)

\(^1\)H NMR and \(^{13}\)C NMR spectra correspond to literature.\(^{8,9}\) [\(\alpha\)]\(_D\) +25.3° (c 0.3, H\(_2\)O). For C\(_9\)H\(_{13}\)FN\(_5\)O\(_5\)P (321.1) calculated (%): C 33.65; H 4.08; N 21.80; found (%): C 33.68; H 4.25; N 21.59. MS ESI(-), \(m/z\) (%): 320 [M\(^-\)] (100).

((2-(2-Amino-6-oxo-1H-purin-9(6H)-yl)ethoxy)methyl)phosphonic acid (25)\(^3\)

Reaction conditions: Microwave reactor Type I, starting compound 19 (1.0 mmol), 140 °C for 10 min, yield 90 % of 25.
1H NMR and 13C NMR spectra correspond to literature.3 For C8H12N5O5P (289.1) calculated (%): C 33.23; H 4.18; N 24.22; found (%): C 33.17; H 4.43; N 24.07. MS ESI(-), m/z (%): 288 [M-] (100), 310 [M-Na].

(S)-((1-(2-Amino-6-oxo-1H-purin-9(6H)-yl)-3-fluoropropan-2-yl)oxy)methyl)phosphonic acid (26).8,9

Reaction conditions: Microwave reactor Type I, starting compound 20 (1.0 mmol), 140 °C for 10 min, yield 85 % of 26.

(R,S)-((3-(2-Amino-6-oxo-1H-purin-9(6H)-yl)-1,1,1-trifluoropropan-2-yl)oxy)methyl)phosphonic acid (27).

Reaction conditions: a) Microwave reactor Type I, starting compound 21 (1.0 mmol), 140 °C for 10 min, yield 87 % of 27.
1H NMR (D2O): 8.21 s, 1H (H-8’’); 4.43 m, 1H (H-1’a); 4.31 – 4.43 m, 2H (H-1’b, H-2’); 3.84 dd, 1H, \(J_{\text{gem}} = 12.5, J(1,P) = 9.6\) a 3.46 dd, 1H, \(J_{\text{gem}} = 12.5, J(1,P) = 9.3\) (CH2P). 13C NMR (D2O): 173.46 (C-6’’); 156.60 (C-2’’); 153.34 (C-4’’); 137.67 (C-8’’); 123.42 q, \(J(3’,F) = 286.3\) (C-3’); 116.63 (C-5’’); 77.58 qd, \(J(2’,F) = 29.6, J(2’,P) = 12.7\) (C-2’); 71.24 d, \(J(1,P) = 153.1\) (C-1); 42.46 (C-1’). For C8H11O5N5F3P + 1.5 H2O (348.2) calculated (%): C 24.17; H 4.73; N 15.66; F 12.74; found (%): C 24.34; H 4.82; N 15.55; F 12.90%. MS ESI(-), \(m/z\) (%): 356 [M] (100); HRMS ESI(-) calculated (\(m/z\)): 356.0372; found: 356.0368.

((2-(2,6-Dioxo-2,3-dihydro-1H-purin-9(6H)-yl)ethoxy)methyl)phosphonic acid (28).

Reaction conditions: Microwave reactor Type I, starting compound 22 (1.0 mmol), 150 °C for 20 min, yield 80 % of 28.

1H NMR (D2O): 7.84 s, 1H (H-8’’); 4.39 t, 2H, \(J(2’,1’) = 5.0\) (H-2’); 3.95 t, 2H, \(J(1’,2’) = 5.1\) (H-1’); 3.80 d, 2H, \(J(1,P) = 8.5\) (CH2P). 13C NMR (D2O): 158.78 (C-6’’); 151.53 (C-2’’); 141.18 (C-4’’); 138.37 (C-8’’); 115.97 (C-5’’); 71.04 d, \(J(1’,P) = 10.4\) (C-1’); 66.97 d, \(J(1,P) = 159.8\) (CH2P); 44.58 (C-2’). Pro C8H11N4O6P (290.0) vypočteno (%): C 33.11; H 3.82; N 19.31; nalezeno (%): C 33.26; H 4.07; N 19.18. MS ESI(-) \(m/z\) (%): 289 [M] (100), 311 [M+Na].

((2-(2-Chloro-6-oxo-1H-purin-9(6H)-yl)ethoxy)methyl)phosphonic acid (29).

Reaction conditions: Microwave reactor Type I, starting compound 22 (1.0 mmol), 150 °C for 10 min, yield 40 % of 29.
$^1$H NMR (D$_2$O): 8.05 s, 1H (H-8$''$); 4.32 m, 2H, $J$(2$'$$'$-1$'$$'$) = 5.3 (H-2$'$$'$); 3.92 m, 2H, $J$(1$'$$'$-2$'$$'$) = 5.3 (H-1$'$$'$); 3.48 d, 2H, $J$(1,P) = 8.4 (CH$_2$P). $^{13}$C NMR (D$_2$O): 168.21 (C-6$''$); 154.39 (C-2$''$); 151.28 (C-4$''$); 141.97 (C-8$''$); 122.61 (C-5$''$); 70.73 d, $J$(1$'$$'$-P) = 9.9 (C-1$'$$'$); 69.53 d, $J$(1,P) = 150.0 (CH$_2$P); 40.01 (C-2$'$). Pro C$_8$H$_{10}$ClN$_4$O$_5$P (308.0077) calculated (%): C 31.13; H 3.27; N 18.15; found (%): C 30.94; H 3.25; N 17.86. MS ESI(-), m/z (%): 307. 309 [M$^-$] (100). HRMS ESI(-) calculated (m/z): 306.9999; found: 307.0006.

(2-Chloroethyl)phosphonic acid (33).$^{10}$

**Method A:** Reaction conditions: a) Microwave reactor Type I, starting compound 30 (10.0 mmol) and HCl (30 mmol), 100 °C for 10 min, yield 84 % of 33. b) Microwave reactor Type I, starting compound 30 (10.0 mmol) and HCl (30 mmol), 120 °C for 4 min, yield 87 % of 33. c) Microwave reactor Type I, starting compound 30 (10.0 mmol) and HCl (30 mmol), 150 °C for 2 min, yield 85 % of 33.

$^1$H NMR and NMR according to the literature.$^{10}$ For C$_2$H$_6$ClO$_3$P (144.0) calculated (%): C 16.62; H 4.19; Cl 24.54; found (%): C 16.53; H 4.32; Cl 24.67. MS ESI(+), m/z (%): 145 a 147 [M$^+$] (100).

**Method B:** Reaction conditions: Microwave reactor Type I, starting compound 31 (10.0 mmol) and HCl (30 mmol), 100 °C for 25 min, yield 79 % of 33.

$^1$H NMR and $^{13}$C NMR spectra correspond to literature.$^{10}$ For C$_2$H$_6$ClO$_3$P (144.0) calculated (%): C 16.62; H 4.19; Cl 24.54; found (%): C 16.78; H 4.26; Cl 24.71. MS ESI(+), m/z (%): 145 a 147 [M$^+$] (100).
(2-(6-Amino-9H-purin-9-yl)ethoxy)methyl)phosphonic acid (13).\(^5\)

Reaction conditions: Microwave reactor Type I, starting compound \(32\) (1.0 mmol) and HCl (2 mmol), 140 °C for 20 min, yield 78% of \(13\).

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\begin{align*}
\text{1H NMR and 13C NMR spectra correspond to literature.} & \quad \text{For C}_{8}\text{H}_{12}\text{N}_{5}\text{O}_{4}\text{P (273.1) calculated (\%): C 35.17; H 4.43; N 25.64; found (\%): C 35.35; H 4.60; N 25.38. MS ESI(-), } m/z (\%): 272 [M'] (100), 294 [M'Na] (14).}
\end{align*}
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References:

2. V. Šolínová, V. Kašička, P. Sázelová and A. Holý, Electrophoresis 2009, 30, 2245.