Supplementary Material (ESI) for Chemical Communications


# Synthesis of phosphoramidates via a Lewis acid catalyzed phosphorimidate rearrangement

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## Supporting information

### General information

All reagents and solvents were purchased from commercial suppliers and used without further purification. Dry solvents were used as obtained by Acros or Fluka in crown cap bottles over molecular sieve and under inert atmosphere ($H_2O \leq 0.005\%$). All other solvents were reagent grade and used as received. Azides were synthesized, following a literature procedure reported by Alvarez and Alvarez, via a nucleophilic substitution of the corresponding bromide with sodium azide.[1] *α*,*α*-Dimethylbenzyl azide was synthesized starting from α-Methylstyrene following a procedure reported by Balderman and Kalir[2]. Unless otherwise noted, all reactions were carried out under argon using standard Schlenk and vacuum line techniques.

Flash chromatography was performed on silica gel (Acros Silicagel 60 A, 0.035-0.070 mm). TLC was performed on aluminium-backed silica plates (60 $F_{254}$, 0.2 mm) which were developed using potassium permanganate as visualising agent. $^{1}$H-NMR, $^{13}$C-NMR and $^{31}$P-NMR spectra were recorded at Jeol ECX/400 in $CDCl_3$ using the residual solvent signal as internal standard. ESI-MS spectra samples were measured on an Agilent 6210 ESI-TOF, Agilent Technologies, Santa Clara, CA, USA. Solvent flow rate was adjusted to 4 µL/min, Spray voltage set to 4.000 V. Drying gas flow rate was set to 15 psi (1 bar). All other parameters were adjusted for a maximum abundance of the relative $[M+H]^+$.

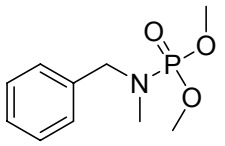
### References

[1] S. G. Alvarez, M. T. Alvarez, *Synthesis*, 1997, **4**, 413.
[2] D. Balderman, A. Kalir, *Synthesis*, 1978, **1**, 24.

**General procedure for the synthesis of Phosphoramidates**

In an oven-dried, two-necked round bottom flask the azide derivative was dissolved in dry benzene (0.6 mmol/mL) and 1.0 equivalents of phosphite was added. The reaction mixture was refluxed for 2 h at 80 °C. After cooling to room temperature 1 mol% of $BF_3$•$EtO_2$, dissolved in 1 mL of dry benzene, was added to the formed phosphorimidate and the rearrangement was allowed to proceed for 2 h at 80 °C. The solvent was removed under reduced pressure to give the crude product. Final purification by flash column chromatography (ethylacetate: hexane 3:1) afforded the pure product in chemical yields between 63-98 %.

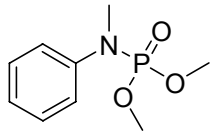
***N*-Benzyl-*N*-methyl-phosphoramidic acid dimethyl ester**




According to the general procedure *N*-Benzyl-*N*-methyl-phosphoramidic acid dimethyl ester was obtained in 98% chemical yield.

IR ($cm^{-1}$): 2950, 2850, 2813, 1455, 1254, 1062, 1029, 822; $^1$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 7.24-7.22 (m, 5 H, Ph), 4.16 (d, $J$ = 8.9 Hz, 2 H, $CH_2$), 3.68 (d, $J$ = 11.0 Hz, 6 H, $CH_3$-O), 2.51 (d, $J$ = 9.7 Hz, 3 H, $CH_3$-N); $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 137.8 (d, $J$ = 4.6 Hz), 128.5, 128.2, 127.4 (Ph), 53.1 (d, $J$ = 5.8 Hz, $CH_3$-O), 53.0 (d, $J$ = 5.0 Hz, $CH_2$), 33.1 (d, $J$ = 3.8 Hz, $CH_3$-N); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 13.59. HRMS (ESI-TOF): Exact mass calculated for $C_{10}H_{17}NO_3P^+$ $[M+H]^+$: 230.0946, $C_{10}H_{16}NNaO_3P^+$ $[M+Na]^+$: 252.0760, Found: 230.0949 $[M+H]^+$, 252.0761 $[M+Na]^+$.

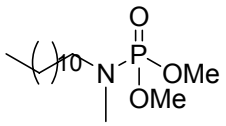
**_N_-Methyl-_N_-phenyl-phosphoramidic acid dimethyl ester**



According to the general procedure *N*-Methyl-*N*-phenyl-phosphoramidic acid dimethyl ester was obtained in 85% chemical yield.

IR ($cm^{-1}$): 2952, 2850, 1600, 1495, 1264, 1190, 1043, 912; $^{1}$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 7.27-7.02 (m, 5 H, Ph), 3.66 (dd, $J$ = 11.3 Hz, $J$ = 3.5 Hz, 6 H, $CH_3$-O), 3.15 (dd, $J$ = 8.8 Hz, $J$ = 3.6 Hz, 3 H, $CH_3$-N); $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 143.9 (d, $J$ = 4.6 Hz), 128.9, 123.9, 122.2 (d, $J$ = 3.8 Hz) (Ph), 53.1 (d, $J_P$ = 5.8 Hz, $CH_3$-O), 37.0 (d, $J$ = 5.0 Hz, $CH_3$-N); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 9.34. HRMS (ESI-TOF): Exact mass calculated for $C_9H_{15}NO_3P^+$ $[M+H]^+$: 216.0784, $C_9H_{14}NNaO_3P^+$ $[M+Na]^+$: 238.0604, Found: 216.0788 $[M+H]^+$, 238.0608 $[M+Na]^+$.

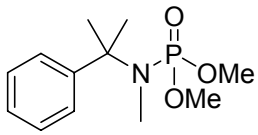
**_N_-Dodecyl-_N_-methyl-phosphoramidic acid dimethyl ester**



According to the general procedure *N*-Dodecyl-*N*-methyl-phosphoramidic acid dimethyl ester was obtained in 89% chemical yield.

IR ($cm^{-1}$): 2925, 2853, 1465, 1377, 1254, 1065, 1032, 826. $^{1}$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 3.63-3.60 (m, 6 H, $CH_3$-O), 2.97-2.90 (m, 2 H, $CH_2$-N); 2.61-2.56 (m, 3 H, $CH_3$-N), 1.50-1.43 (m, 2 H, $CH_2$), 1.20 (m, 14 H, $7CH_2$), 0.84-0.81 (m, 3H, $CH_3$); $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 52.9 (d, $J$ = 5.2 Hz, $CH_3$-O), 49.2 (d, $J$ = 3.8 Hz, $CH_2$-N), 33.4 (d, $J$ = 4.6 Hz, $CH_3$-N); 33.3, 32.0, 29.7, 29.7, 29.7, 29.7, 29.5, 29.4, 28.2, 28.2, 26.7 ($CH_2$), 14.2 ($CH_3$); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 13.91. HRMS (ESI-TOF): Exact mass calculated for $C_{15}H_{35}NO_3P^+$ $[M+H]^+$: 308.2355, Found: 308.2349 $[M+H]^+$.

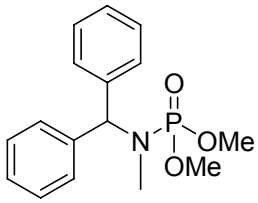
**_N_-Methyl-_N_-(2-phenylpropan-2-yl)-phosphoramidic acid dimethyl ester**




According to the general procedure *N*-Methyl-*N*-(2-phenylpropan-2-yl)-phosphoramidic acid dimethyl ester was obtained in 88% chemical yield.

IR ($cm^{-1}$): 2984, 2950, 1602, 1494, 1250, 1182, 1029. $^{1}$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 7.42-7.19 (m, 5 H, Ph), 3.74 (dd, $J$ = 11.1 Hz, $J$ = 0.8 Hz, 6 H, $CH_3$-O), 2.44 (dd, $J$ = 9.4 Hz, $J$ = 0.7 Hz, 3 H, $CH_3$-N), 1.65 (s, 6 H, $CH_3$); $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 146.7 (d, $J$ = 6.5 Hz), 127.6, 125.8, 124.9 (Ph), 59.7 (d, $J$ = 3.8 Hz, C), 52.2 (d, $J$ = 6.1 Hz, $CH_3$-O), 32.3 (d, $J$ = 4.6 Hz, $CH_3$-N), 27.7 (d, $J$ = 1.5 Hz, $CH_3$); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 13.16. HRMS (ESI-TOF): Exact mass calculated for $C_{13}H_{22}NNaO_3P^+$ $[M+Na]^+$: 280.1073. Found: 280.1088 $[M+Na]^+$.

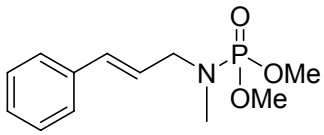
**_N_-Benzhydryl-_N_-methyl-phosphoramidic acid dimethyl ester**




According to the general procedure *N*-Benzhydryl-*N*-methyl-phosphoramidic acid dimethyl ester was obtained in 80% chemical yield.

IR ($cm^{-1}$): 2950, 2918, 2847, 1637, 1495, 1258, 1030, 819, 731, 702, 567. $^{1}$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 7.35-7.26 (m, 10 H, Ph), 6.14 (d, $J$ = 9.7 Hz, 1 H, CH), 3.65 (d, $J$ = 11.4 Hz, 6 H, $CH_3$-O), 2.48 (d, $J$ = 9.4 Hz, 3 H, $CH_3$-N); $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 139.1 (d, $J$ = 4.2 Hz), 129.0, 128.3, 127.3 (Ph), 62.3 (d, $J$ = 5.4 Hz, CH), 52.5 (d, $J$ = 5.8 Hz, $CH_3$-O), 28.7 (d, $J$ = 4.2 Hz, $CH_3$-N); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 13.61. HRMS (ESI-TOF): Exact mass calculated for $C_{16}H_{21}NO_3P^+$ $[M+H]^+$: 306.1254, Found: 306.1247 $[M+H]^+$.

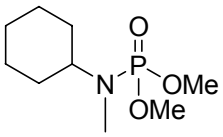
**_N_-Methyl-_N_-(3-phenyl-allyl)-phosphoramidic acid dimethyl ester**




According to the general procedure *N*-Methyl-*N*-(3-phenyl-allyl)-phosphoramidic acid dimethyl ester was obtained in 80% chemical yield.

IR ($cm^{-1}$): 2950, 2848, 1737, 1598, 1578, 1496, 1449, 1253, 1028. $^{1}$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 7.40-7.20 (m, 5 H, Ph), 6.53 (d, $J$ = 15.4 Hz, 1 H, CH), 6.14 (dt, $J$ = 16.1 Hz, $J$ = 6.4 Hz, 1 H, CH), 3.80-3.66 (m, 2 H, $CH_2$), 3.71 (d, $J$ = 10.9 Hz, 6 H, $CH_3$-O), 2.65 (d, $J$ = 9.6 Hz, 3 H, $CH_3$-N); $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 136.4, 133.1, 128.5, 127.7, 126.3, 125.4, 125.4 (d, $J$ = 3.5 Hz) (Ph, CH, CH), 53.02 (d, $J$ = 5.8 Hz, $CH_3$-O), 51.11 (d, $J$ = 4.6 Hz, $CH_3$-N), 33.0 (d, $J$ = 4.2 Hz, $CH_3$-N); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 13.58. HRMS (ESI-TOF): Exact mass calculated for $C_{12}H_{18}NNaO_3P^+$ $[M+Na]^+$: 278.0917, Found: 278.0923 $[M+Na]^+$.

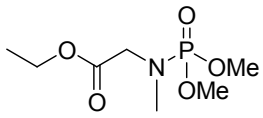
**_N_-Cyclohexyl-_N_-methyl-phosphoramidic acid dimethyl ester**




According to the general procedure *N*-Cyclohexyl-*N*-methyl-phosphoramidic acid dimethyl ester was obtained in 80% chemical yield.

IR ($cm^{-1}$): 2932, 1454, 1389, 1250, 1029, 927, 826, 729. $^{1}$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 3.62-3.58 (m, 6 H, $CH_3$-O), 3.32-3.22 (m, 1 H, CH), 2.50-2.46 (m, 3 H, $CH_3$-N), 1.74-1.70 (m, 2 H, $CH_2$), 1.62-1.55 (m, 3 H, $CH_2$), 1.47-1.37 (m, 2 H, $CH_2$), 1.32-1.20 (m, 2 H, $CH_2$), 1.03-0.91 (m, 1 H, $CH_2$), $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 55.1 (d, $J$ = 4.2 Hz, CH), 52.7 (d, $J$ = 5.8 Hz, $CH_3$-O), 30.9 (d, $J$ = 3.1 Hz, $CH_3$-N), 27.4 (d, $J$ = 3.8 Hz, $CH_2$), 25.9 ($CH_2$), 25.5 ($CH_2$); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 13.77. HRMS (ESI-TOF): Exact mass calculated for $C_9H_{21}NO_3P^+$ $[M+H]^+$: 222.1259, $C_9H_{20}NNaO_3P^+$ $[M+Na]^+$: 244.1073, Found: 222.1251 $[M+H]^+$, 244.1079 $[M+Na]^+$.

**[(Dimethoxy-phosphoryl)-methyl-amino] acetic acid ethyl ester**

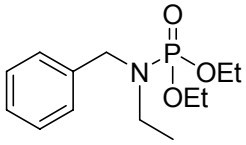


According to the general procedure *N*-Cyclohexyl-*N*-methyl-phosphoramidic acid dimethyl ester was obtained in 78% chemical yield.

IR ($cm^{-1}$): 2956, 2853, 1747, 1645, 1447, 1257, 1026, 960. $^{1}$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 4.22-4.15 (m, 2 H, $CH_2$-O), 3.84-3.80 (m, 2 H, $CH_2$-N), 3.75-3.70 (m, 6 H, $CH_3$-O), 2.72-2.68 (m, 3 H, $CH_3$-N), 1.30-1.25 (m, 3 H, $CH_3$); $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 170.4 (d, $^{3}J_{C,P}$ = 2.7 Hz, C=O), 60.9 ($CH_2$-O), 53.0 (d, $^{2}J_{C,P}$ = 5.4 Hz, $CH_3$-O), 50.7 (d, $^{2}J_{C,P}$ = 6.1 Hz, $CH_2$-N), 34.3 (d, $^{2}J_{C,P}$ = 3.8 Hz, $CH_3$-N), 14.1 ($CH_3$); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 12.59.

HRMS (ESI-TOF): Exact mass calculated for $C_7H_{16}NNaO_5P^+$ $[M+Na]^+$: 248.0658, Found: 248.0662 $[M+Na]^+$.

***N*-Benzyl-*N*-ethyl-phosphoramidic acid diethyl ester**

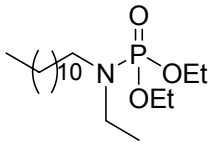


According to the general procedure *N*-Benzyl-*N*-ethyl-phosphoramidic acid diethyl ester was obtained in 98% chemical yield. In this case, TMSOTf was used as catalyst instead of $BF_3$•$EtO_2$. The reaction time was extended to 5 h for the phosphorimidate formation and to 5.5 h for the rearrangement after addition of the catalyst.

IR ($cm^{-1}$): 2979, 2860, 1841, 1603, 1455, 1247, 1026, 960. $^{1}$H-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 7.24-7.23 (m, 5 H, Ph), 4.21 (d, *J* = 9.6 Hz, 2 H, $CH_2$), 4.11-3.97 (m, 4 H, $CH_2$-O), 3.00-2.90 (m, $CH_2$-N), 1.32-1.28 (m, 4 H, $CH_3$-O), 1.06-1.02 (m, $CH_3$-N); $^{13}$C-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) = 138.3 (d, *J* = 3.8 Hz), 128.5, 128.3, 127.3 (Ph), 62.3 (d, *J* = 5.8 Hz, $CH_2$-O), 48.7 (d, *J* = 5.0 Hz, $CH_2$), 39.5 (d, *J* = 3.8 Hz, $CH_2$-N), 16.3 (d, *J* = 7.3 Hz, $CH_3$-O), 13.3 (d, *J* = 1.5 Hz, $CH_3$-N); $^{31}$P-NMR (400 MHz, [$D_1$]-$CHCl_3$): δ (ppm) =

10.79. HRMS (ESI-TOF): Exact mass calculated for $C_{13}H_{23}NO_3P^+$ $[M+H]^+$: 272.1416, Found: 272.1413 $[M+H]^+$.

**_N_-Dodecyl-_N_-ethyl-phosphoramidic acid diethyl ester**




According to the general procedure *N*-Benzyl-*N*-ethyl-phosphoramidic acid diethyl ester was obtained in 63% chemical yield. The reaction time was extended to 12 h at room temperature for the phosphorimidate formation and to 5 h at 80°C for the rearrangement after addition of the catalyst.

IR ($cm^{-1}$): 2925, 2854, 1467, 1389, 1257, 1031, 960, 786. $^1$H-NMR (400 MHz, $[D_1]$-$CHCl_3$): δ (ppm) = 3.63-3.60 (m, 6 H, $CH_3$-O), 2.97-2.90 (m, 2 H, $CH_2$-N); 2.61-2.56 (m, 3 H, $CH_3$-N), 1.50-1.43 (m, 2 H, $CH_2$), 1.20 (m, 14 H, $CH_2$), 0.84-0.81 (m, 3H, $CH_3$); $^{13}$C-NMR (400 MHz, $[D_1]$-$CHCl_3$): δ (ppm) = 52.9 (d, $J$ = 5.2 Hz, $CH_3$-O), 49.2 (d, $J$ = 3.8 Hz, $CH_2$-N), 33.4 (d, $J$ = 4.6 Hz, $CH_3$-N); 33.3, 32.0, 29.7, 29.7, 29.7, 29.7, 29.5, 29.4, 28.2, 28.2, 26.7 ($CH_2$), 14.2 ($CH_3$); $^{31}$P-NMR (400 MHz, $[D_1]$-$CHCl_3$): δ (ppm) = 13.91. HRMS (ESI-TOF): Exact mass calculated for $C_{18}H_{41}NO_3P^+$ $[M+H]^+$: 350.2824, $C_{18}H_{40}NNaO_3P^+$ $[M+Na]^+$: 372.2643, Found: 350.2830 $[M+H]^+$, 372.2642 $[M+Na]^+$.