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N-HYDROXYAMINOMETHYLPHOSPHONATES: THE REACTION OF HYDROXYLAMINES WITH ALDEHYDES AND SECONDARY PHOSPHITES

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Abstract. *N-Alkyl-N-hydroxyaminomethylphosphonates are prepared by the reaction of N-monoalkyl-substituted hydroxylamines with formaldehyde and sec-phosphites.*

N-Hydroxyaminomethylphosphonates are reported in the literature as intermediates in the synthesis of chiral α-aminoalkylphosphonic acids,[1] and as a new class of herbicides and plant-growth regulators.[2] The EPR spectra of nitroxyl radicals formally derived from N-hydroxyaminoethylphosphonates have been characterized.[3] Known synthetic methodology for the preparation of N-hydroxyaminomethylphosphonates includes the addition of secondary phosphites to nitrones,[1,4] the oxidation of aminomethylphosphonates,[2] the addition of trialkyl phosphites to nitrones,[5] the reduction of nitromethylphosphonates,[6] and the addition of Grignard reagents to nitromethylphosphonates.[6] We report herein the synthesis of N-hydroxyaminoalkylphosphonates by the previously unreported Mannich-type reaction of a secondary phosphite with an aldehyde and hydroxylamine.

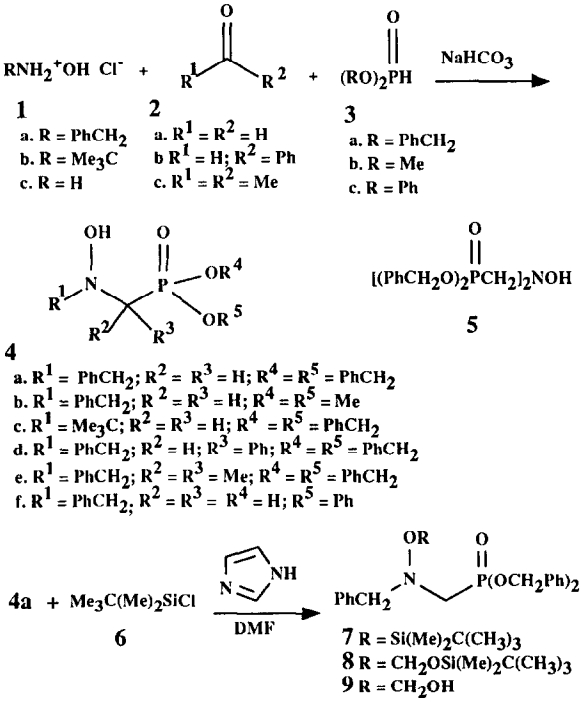
RESULTS AND DISCUSSION

The Mannich reaction of N-monosubstituted hydroxylamines with formaldehyde and secondary amines was initially reported by Hellmann and Teichmann[7] and later by Ulrich and Sayigh.[8] Based upon these studies, the reaction of a N-monoalkyl-substituted hydroxylamine with formaldehyde and a secondary phosphite would be expected to provide a simple route to N-alkyl-N-hydroxyaminomethylphosphonates.[9]

Indeed, the reaction of N-benzylhydroxylamine hydrochloride, **1a**, with paraformaldehyde, **2a**, and

dibenzyl phosphite, **3a**, in tetrahydrofuran (THF) solvent using sodium bicarbonate as a base gave the desired N-hydroxyaminomethylphosphonate **4a** (40%, recrystallized). The reaction of hydroxylamine with **2a** prior to the addition of secondary phosphite is necessary to avoid the formation of unreactive hydroxymethylphosphonate, which is formed by the known reaction of a secondary phosphite with **2a**.[10]

The structure of **4a** is based upon the following spectral data. In the $^{31}P\{^1H\}$ NMR spectrum of **4a**, a resonance was observed at δ 24.6, which is in the region expected for a phosphonate structure.[11] In the ^1H NMR spectrum, a multiplet was observed at δ 5.06 that was assigned to the nonequivalent methylene protons of the benzyloxy groups bonded to phosphorus ($^2J_{HCH}$ = 11.7 Hz; $^3J_{H(a)COP}$ = 8.4 Hz; $^3J_{H(b)COP}$ = 7.8 Hz). At the NMR probe temperature (≈ 26 °C) no evidence was observed for the nonequivalence of the remaining two pairs of methylene protons adjacent to nitrogen because of slow inversion of the lone-pair of electrons on nitrogen or restricted rotation about the nitrogen-oxygen bond, *vide infra*.[12] In the IR spectrum of **4a** absorptions at 3560 cm^{-1} and 3350 cm^{-1} were observed that were assigned to the free and hydrogen-bonded hydroxyl-stretching frequency, respectively. In the MS a molecular ion was observed at m/e 397. The spectral data was fully in accord with the structure **4a** illustrated.



The N-hydroxyaminomethylphosphonates **4b,c** were prepared in a similar manner by the reaction of the hydroxylamine **1a,b** with **2a** and the corresponding phosphite **3a-c**. In a lone attempt to substitute aqueous **2a** for paraformaldehyde in the reaction of **1a** with **3c**, which is admittedly an easily hydrolyzable phosphite, the

4-hydroxyaminomethylphosphonate **4f** was obtained resulting from the partial hydrolysis of the phosphonate ester.

The extension of this methodology to the use of either an aldehyde or ketone in place of **2a** proved straightforward. For example, the dialkyl-substituted derivative **4e** was prepared as a white crystalline solid (43% recrystallized) by the reaction of acetone, **2c**, with **1a** and **3a** . The bisphosphonate **5** could be prepared by the reaction of **1c** with two equivalents of **2a** and **3a** (80% column chromatographed).

The reaction of the **4a** prepared *in situ* using excess **2a** with *tert*-butyldimethylsilyl chloride, **6**, gave the expected O-silyloxy derivative **7**. Interestingly, the silyloxymethoxy-derivative **8** was also isolated in significant yield. This observation suggests that **2a** and **4a** in solution are in rapid equilibrium with the hemiacetal **9**.[13]

In the ^{1}H NMR spectrum of **7** at probe temperature, both the protons of the methyl group bonded to silicon and the benzylic protons adjacent to nitrogen were observed as very broad singlets. These signals were observed as sharp singlets at 55 °C. A reasonable explanation for this dynamic behavior is that at probe temperature these resonances are near coalescence either because of a reduced inversion rate of the lone pair of electrons on nitrogen or a slowing of rotation about the N-O bond due to increased steric encumbrance within the molecule.

EXPERIMENTAL

All melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1300 spectrophotometer, and reported peak absorptions are estimated to be accurate to ± 10 cm^{-1}. ^{1}H NMR spectra were taken on a Jeol FX-90Q, Varian Model CFT-20, or Varian Model XL-200 spectrometer. ^{13}C NMR spectra were obtained on a Varian Model XL-200 spectrometer. ^{31}P NMR spectra were obtained on a Varian Model FT-80 or XL-200 spectrometer with full proton decoupling. All ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane where a positive sign is downfield from the standard. ^{31}P chemical shifts are reported in ppm relative to 85 % phosphoric acid (external), where a positive sign is downfield from the standard. The abbreviations used for peak multiplicity are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, and dq = doublet of quartets. MS were obtained on a Finnegan Model 8200 mass spectrometer.

Merck 9385 silica gel 60 (230-400 mesh) was used for flash chromatography.[14] Merck pre-coated (0.25 mm) silica gel 60 F-254 plates were used for TLC. Preparative HPLC was carried out with a Waters PREP 500A HPLC.

Reagents were purchased from commercial laboratory supply houses. Solvents were dried prior to use when necessary with appropriate drying agents. THF was distilled immediately prior to use from a deep-blue solution of sodium benzophenone ketyl. Reactions were carried out in flame-dried apparatus under a dry, inert atmosphere of either nitrogen or argon. Elemental analyses were performed by Analytical Research Services, CIBA-GEIGY Corp.

Dibenzyl P-(N-benzyl-hydroxyaminomethyl)phosphonate, 4a

A mixture of 2.0 g (12.5 mmol) of **1a**, 0.75 g (25 mmol) of paraformaldehyde, **2a**, 1.0 g (12 mmol) of sodium bicarbonate, and 40 mL of THF was stirred at 59°C for 1 h. To the resultant mixture was added dropwise over a 3 h period a solution of 3.6 g (13.7 mmol) of **3a** in 40 mL of THF. The reaction mixture was stirred for 14 h at 55 °C. The reaction mixture was concentrated *in vacuo* to 20 mL and 500 mL of ethyl acetate was added. The organic phase was separated and the organic phase was washed sequentially with a saturated solution of sodium bicarbonate and sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel; 20:1 dichloromethane:ethyl acetate eluent) followed by recrystallization from a mixture of dichloromethane, ethyl acetate, and hexane to give 1.95 (40%) of a white solid, mp 62-64 °C; IR ν 3560, 3350 (OH) cm^{-1}; ^{31}P NMR ($CDCl_3$) δ 24.6; ^{1}H NMR ($CDCl_3$)(200 MHz) δ 3.26 (d, CH_2P, $^{2}J_{HCP}$ = 11.4 Hz, 2 H), 3.97 (s, 2 H), 5.06 (AB q, $PhCH_2O$, $^{2}J_{HCH}$ = 11.7 Hz; $^{3}J_{H(a)COP}$ = 8.4 Hz; $^{3}J_{H(b)COP}$ = 7.8 Hz, 4 H), 7.10 (exchangeable s, 1 H), 7.40 (complex m, 15 H); MS m/z 397 $^{+\cdot}$(molecular ion). Anal. Calcd for $C_{22}H_{24}NO_4P$: C, 66.5; H, 6.1; N, 3.5; P, 7.8. Found: C, 66.5; H, 6.2; N, 3.5; P, 8.1.

Dimethyl P-(N-benzyl-hydroxyaminomethyl)phosphonate, 4b

By the procedure used to prepare **4a**, compound **4b** was prepared from 5.0 g (31 mmol) of **1a**, 1.8 g (60 mmol) of **2a**, 4.4 (40 mmol) of **3b**, 2.5g (30 mmol) of sodium bicarbonate, and 350 mL of THF (55 °C for 7 h). The residue was purified by column chromatography (silica gel, dichloromethane:ethyl acetate eluent) to give 6.1g (80%) of a viscous colorless liquid; IR ν 3560, 3350 (OH) cm^{-1}; ^{31}P NMR ($CDCl_3$) δ 26.3; ^{1}H NMR ($CDCl_3$)(200 MHz) δ 3.18 (d, CH_2P, $^{2}J_{HCP}$ = 11.8 Hz, 2 H), 3.72 (d, $^{3}J_{HCOP}$ = 10.7, 6 H), 3.95 (s, 2 H), 6.63 (exchangeable s, 1 H), 7.28 (complex m, 5 H); MS m/z 245 $^{+\cdot}$(molecular ion). Anal. Calcd for $C_{10}H_{16}NO_4P$: C, 49.0; H, 6.6; N, 5.7; P, 12.6. Found: C, 48.6; H, 6.5; N, 5.7; P, 12.6.

Dibenzyl P-(N-*tert*-butyl-hydroxyaminomethyl)phosphonate, 4c

By the procedure used to prepare **4a**, compound **4b** was prepared from 5.0 g (40 mmol) of **1b**, 2.4 g (80

mmol) of **2a**, 9.0 mL (41 mmol) of **3a**, 3.0 g (40 mmol) of sodium bicarbonate, and 200 mL of THF (55 °C for 14 h). The residue was purified by recrystallization from a mixture of dichloromethane and hexane to give 9.2 g (64%) of a white solid, mp 106-107 °C; IR ν 3565, 3360 (OH) cm^{-1}; ^{31}P NMR ($CDCl_3$) δ 27.3; ^1H NMR ($CDCl_3$)(200 MHz) δ 1.07 (s, 9 H), 3.19 (d, CH_2P, $^2J_{HCP}$ = 11.6 Hz, 2 H), 5.11 (AB q, $PhCH_2O$, 4 H), 5.65 (exchangeable s, 1 H), 7.30 (complex m, 15 H); MS m/z 363 $^{+\cdot}$(molecular ion). Anal. Calcd for $C_{19}H_{26}NO_4P$: C, 62.8; H, 7.2; N, 3.8; P, 8.5. Found: C, 62.6; H, 7.1; N, 3.8; P, 8.9.

Dibenzyl P-[1-(N-benzyl-hydroxyamino)-1-phenylmethyl]phosphonate, 4d

By the procedure used to prepare **4a**, compound **4d** was prepared from 15.0 g (94 mmol) of **3a** 10.6 g (100 mmol) of **2b**, 26.7 g (100 mmol) of **3a**, 3.78 g (45 mmol) of sodium bicarbonate, and 300 mL of THF (60°C for 4 h). The residue was purified by column chromatography (silica gel, 2.5:1 hexane:ethyl acetate eluent) followed by recrystallization from a mixture of dichloromethane and hexane to give 5.6g (13%) of a white solid, mp 116-118 °C; IR ν 3550, 3340 (OH) cm^{-1}; ^1H NMR ($CDCl_3$)(200 MHz) δ 3.82 (AB q, $PhCH_2N$, 2 H), 4.38 (d, PhCHP, $^2J_{HCP}$ = 17.6 Hz, 1 H), 4.69 (m, 2 H), 5.14 (m, 2 H), 6.57 (exchangeable s, 1 H), 7.35 (complex m, 20 H). Anal. Calcd for $C_{28}H_{28}NO_4P$: C, 71.0; H, 6.0; N, 3.0; Found: C, 71.2; H, 6.0; N, 2.9.

Dibenzyl P-[1-(N-benzyl-hydroxyamino)-1-methylethyl]phosphonate, 4e

Following the procedure used to prepare **4a**, compound **4e**, was prepared from 5.0 g (31 mmol) of **1a**, 4.4 mL (60 mmol) of **2c**, 8.8 mL (40 mmol) of **3a**, 2.5 g (30 mmol) of sodium bicarbonate, and 200 mL of THF (55 °C for 24 h). The residue was purified by recrystallization from a mixture of dichloromethane and hexane to give 5.6 g (43%) of a white solid, mp 116-117 °C; IR ν 3560, 3350 (OH) cm^{-1}; ^{31}P NMR ($CDCl_3$) δ 29.8; ^1H NMR ($CDCl_3$)(200 MHz) δ 1.50 (d, $C(CH_3)_2$, $^3J_{HCCP}$ = 15.7 Hz, 6 H), 4.08 (s, 2 H), 5.11 (m, 4 H), 5.76 (exchangeable s, 1 H), 7.30 (complex m, 15 H); MS m/z 425 $^{+\cdot}$(molecular ion). Anal. Calcd for $C_{24}H_{28}NO_4P$: C, 67.8; H, 6.6; N, 3.3; P, 7.3. Found: C, 67.6; H, 6.6; N, 3.2; P, 7.2.

Benzyl P-(N-benzyl-hydroxyaminomethyl)phosphonate, 4f

To a solution of 4.63 g (38 mmol) of N-benzylhydroxylamine in 25 mL of acetonitrile was added a solution of 3.05 mL (38 mmol) of a 37% aqueous solution of formaldehyde in 2.0 mL of acetonitrile. The reaction mixture was stirred at room temperature for 5 minutes and then to the resultant mixture was added dropwise over a 5 minute period a solution of 8.81 g (38 mmol) of **3c** in 2 mL of acetonitrile. The reaction mixture was stirred overnight and the resultant precipitate was collected by filtration. The product was

purified by trituration in 150 mL of boiling acetonitrile to give 6.93 g (64%) of a white solid, mp 156-157 °C; IR (KBr) ν 1180 (P=O) cm^{-1}; ^1H NMR (d_6-DMSO)(80 MHz, 80 °C) δ 3.25 (d, $^2J_{HCP}$ = 13 Hz, 2 H), 4.02 (s, 2 H), 6.99 (complex m, 10 H); MS m/z 293 $^+$ (molecular ion). Anal. Calcd for $C_{14}H_{16}NO_4P$: C, 57.3; H, 5.5; N, 4.8; P, 10.6. Found: C, 57.1; H, 5.4; N, 4.9; P, 10.5.

N,N-bis(dibenzylphosphonomethyl)hydroxylamine, 5

By the procedure used to prepare **4a**, compound **5** was prepared from 2.0 g (29 mmol) of **1c**, 3.4 g (114 mmol) of **2a**, 15.0 g (58 mmol) of **3a**, 1.2 g (14 mmol) of sodium bicarbonate, and 200 mL of THF (55 °C for 14 h). The residue was purified by column chromatography (silica gel, 2:1:0.1 ethyl acetate:toluene:ethyl alcohol eluent) to give 8.1 g (49 %) of a white solid, mp 71-73 °C; IR ν 3540, 3350 (OH) cm^{-1}; ^{31}P NMR ($CDCl_3$) δ 23.3; ^1H NMR ($CDCl_3$)(200 MHz) δ 3.51 (d, CH_2P, $^2J_{HCP}$ = 11.8 Hz, 4 H), 3.97 (s, 2 H), 5.06 (AB q, $PhCH_2O$, $^2J_{HCH}$ = 11.8 Hz; $^3J_{H(a)COP}$ = 8.0 Hz; $^3J_{H(b)COP}$ = 8.3 Hz, 8 H), 7.30 (complex m, 20 H); 8.30 (exchangeable s, 1 H); MS (DCI) m/z 582 $^+$ (molecular ion + H); ^{13}C NMR ($CDCl_3$) δ 57.1 (dd, $^1J_{CP(a)}$ = 159.6 Hz; $^3J_{CNCP(b)}$ = 15.0 Hz), 67.3 (d, $^2J_{COP}$ = 6.3 Hz), 127.6 (s), 127.8 (s), 128.0 (s), 135.8 (d, J_{CP} = 6.1 Hz). Anal. Calcd for $C_{30}H_{33}NO_7P_2$: C, 62.0; H, 5.7; N, 2.4; Found: C, 62.3; H, 5.5; N, 2.4.

Dibenzyl P-(N-benzyl-tert-butyldimethylsilyloxyamino-methyl)phosphonate, *7*, and dibenzyl P-(N-benzyl-tert-butyl-dimethylsilyloxymethyloxyaminomethyl)phosphonate, *8*

To a mixture of 10.0 g (62 mmol) of **1a**, 3.2 g (125 mmol) of **2a**, 3.4 g (40 mmol) of sodium bicarbonate, and 200 mL of THF at 60 °C was added dropwise over a 2 h period a solution of 16.5 g (63 mmol) of **3a** in 50 mL of THF. The reaction mixture was stirred for 4 h at 60 °C. The reaction mixture was concentrated in vacuo to a volume of 50 mL and 500 mL of ethyl acetate was added. The organic phase was separated and it was washed sequentially with a saturated solution of sodium bicarbonate and sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was dissolved in 150 mL of dimethylformamide and to the resultant solution was added 16.8 g (248 mmol) of imidazole. To the resultant reaction mixture at room temperature was added dropwise 18.9 g (125 mmol) of **6**. The reaction mixture was stirred for 10 h at room temperature. To the reaction mixture was added 1 L of ethyl acetate and the solution was washed sequentially with a saturated solution of sodium bicarbonate and sodium chloride. The organic phase was dried over anhydrous magnesium sulfate and the solvent removed in vacuo. The residue was purified by column chromatography (silica gel; 3:1 hexane:ethyl acetate eluent) followed by HPLC (3:1 hexane:ethyl acetate eluent) to give two compounds. **7**: 5 g (24%) as a white solid, mp 65-66°C; ^1H NMR ($CDCl_3$)(200 MHz)(55 °C) δ -0.14 (s, $Si(CH_3)_2$, 6 H), 0.85 (s, $C(CH_3)_3$, 9

H), 3.32 (d, $^2J_{HCP}$ = 12 Hz, 2 H), 4.14 (s, 2 H), 5.12 (AB q, OCH_2Ph, 4 H), 7.30 (complex m, 15 H); MS m/z 511 $^+$ (molecular ion). Anal. Calcd for $C_{28}H_{38}NO_4PSi$: C, 65.7; H, 7.5; N, 2.7; P, 6.0. Found: C, 65.7; H, 7.5; N, 2.6; P, 6.1. **8**: 8.1 g (24%) as a colorless liquid; ^1H NMR ($CDCl_3$)(200 MHz) δ 0.08 (s, $Si(CH_3)_2$, 6 H), 0.91 (s, $C(CH_3)_3$, 9 H), 3.39 (d, $^2J_{HCP}$ = 12 Hz, 2 H), 4.19 (s, 2 H), 4.91 (s, OCH_2O, 2 H), 5.07 (m , OCH_2Ph, 4 H), 7.35 (complex m, 15 H); MS m/z 541 $^+$ (molecular ion). Anal. Calcd for $C_{29}H_{40}NO_5PSi$: C, 64.3; H, 7.4; N, 2.6; P, 5.7. Found: C, 64.2; H, 7.3; N, 2.5; P, 5.5.

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13. In an attempt to prepare a bisadduct by the reaction of two equivalents of **3a** and **2a** with **1c**, an mixture was obtained whose ^{1}H NMR spectrum (d_6-DMSO) was consistent with the desired bisadduct $[(PhCH_2O)_2P(=O)CH_2]_2NOH$, **10**, and $[(PhCH_2O)_2P(=O)CH_2]_2NOCH_2OH$, **11**, which could not be isolated in pure form. A doublet resonance at δ 4.86 and a triplet resonance at δ 6.49 ($^3J_{HCOH}$ = 7.5 Hz) were observed that were tentatively assigned to the OCH_2O methylene and hydroxyl protons of **11**, respectively. The observation of ^{3}J coupling of the hydroxyl to the methylene protons clearly indicates that **2a** and **10** are not in rapid equilibrium with **11** on the NMR time scale. See, Abragam, A. *The Principles of Nuclear Magnetism*; Clarendon: London, 1961, p. 308.

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