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Synthesis of *gem*-bisphosphonates with (3-aryl-4,5-dihydroisoxazol-5-yl)methylamino moiety

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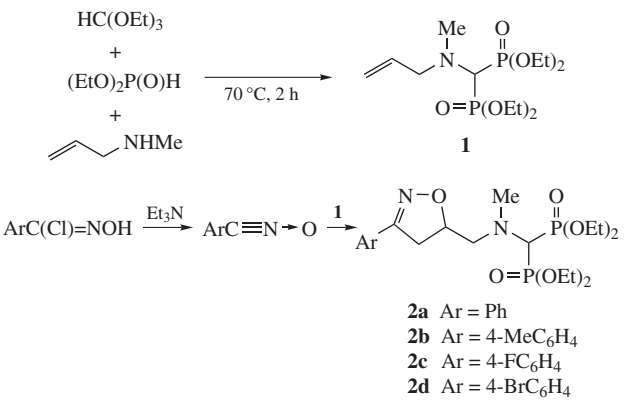
Three-component reaction between *N*-allyl-*N*-methylamine, triethyl orthoformate and diethyl phosphite affords *N*-[bis(diethoxyphosphoryl)methyl]-*N*-methyl-3-arylprop-3-en-1-amine whose cycloaddition with nitrile *N*-oxides gives 5-{*N*-[bis(diethoxyphosphoryl)-methyl]-*N*-methylamino}methyl-4,5-dihydroisoxazoles.

Nitrogen-containing *gem*-bisphosphonates (N-BPs), stable to hydrolysis analogues of pyrophosphates, represent an important class of pharmacologically active compounds.[1] Aminomethylene 1,1-bisphosphonates are powerful inhibitors of the enzyme farnesyl pyrophosphate synthase, a key regulatory enzyme in the mevalonate pathway,[2] and are recognized as therapeutically active molecules for treatment of several human pathologies, *e.g.*, cancer.[3] Due to their exceptional bone affinity, they can also be used as drugs or prodrugs in the treatment of bone diseases, such as osteoporosis, hypercalcaemia, and rheumatoid arthritis.[4] Today some synthetic routes to aminomethylene 1,1-bisphosphonates, including reactions of nitriles with phosphorous acid or phosphites,[5] synthesis from carboxylic acid amides,[6] from imines and related compounds,[7] and three-component reaction involving an amine, triethyl orthoformate and diethyl phosphite,[8] are known.

In this work a strategy for the synthesis of compounds with two pharmacophore sites: aminomethylene 1,1-bisphosphonate fragment and 3-arylisoxazoline moiety is demonstrated. Disubstituted isoxazolines are frequently used in design of pharmaceutical agents and for syntheses of natural products.[9] The use of methodology of three-component reaction made it possible to access aminomethylene 1,1-bisphosphonate with the allylic group which on cycloaddition with nitrile *N*-oxides produced dihydroisoxazole cycle (Scheme 1).

For the synthesis of intermediate **1**, the modified multicomponent reaction[8] was used by mixing stoichiometric amounts of *N*-allyl-*N*-methylamine, triethyl orthoformate, and diethyl phosphite. Unlike described procedure,[8] the reactants were heated at 70 °C under a nitrogen atmosphere in sealed glass ampoules for 2 h. ^{31}P NMR analysis of the reaction mixture revealed some starting diethyl phosphite and product **1**. Column chromatography afforded the desired compound **1** in 72% yield.†



Scheme 1

To prepare nitrile *N*-oxides necessary for isoxazole constructing, a two-step procedure was used. At first an aldoxime was chlorinated with *N*-chlorosuccinimide,[10] and then the obtained hydroximoyl chloride was dehydrochlorinated with triethylamine[11] (see Scheme 1). The [3 + 2] cycloaddition of the resultant nitrile oxides to the double bond of **1** was performed in diethyl ether at –40 °C. In the optimized procedure, a solution of triethylamine in diethyl ether was added dropwise for 2 h to the mixture of hydroximoyl chloride and olefin **1** giving 4,5-dihydroisoxazoles **2a**–**d** in yields of *ca.* 80%.‡ Diesters **2a**–**d** can be easily transformed into the corresponding acids by standard technique.[12]

In conclusion, complex polyfunctional compounds, *gem*-bisphosphonates with (3-aryl-4,5-dihydroisoxazol-5-yl)methylamino

† N-*[Bis(diethoxyphosphoryl)methyl]*-N-*methylprop-3-en-1-amine* **1**. A mixture of *N*-allyl-*N*-methylamine (0.71 g, 0.01 mol), triethyl orthoformate (1.48 g, 0.01 mol) and diethyl phosphite (2.76 g, 0.02 mol) was heated in a sealed glass ampoule at 70 °C for 3 h. The crude product was purified by column chromatography (column: *l* = 30 cm, *d* = 2 cm) using gradient 0 → 3% MeOH in $CHCl_3$ as an eluent. Evaporation of the appropriate fractions afforded product **1** as viscous liquid, yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (t, 12H, 4POCH$_2$*Me*, J_{HH} 7.1 Hz), 2.49 (s, 3H, NMe), 3.31 (d, 2H, NCH$_2$, J_{HH} 6.2 Hz), 3.42 (t, 1H, C*H*[P(O)OEt]$_2$, J_{HP} 25.1 Hz), 4.02–4.06 (m, 8H, 4POCH$_2$), 5.02 (d, 1H, =CH*H*, J_{HH} 10.0 Hz), 5.11 (d, 1H, =C*H*H, J_{HH} 17.2 Hz), 5.66 (ddt, 1H, =C*H*CH$_2$, J_{HH} 10.0 Hz, J_{HH} 17.2 Hz, J_{HH} 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.28–16.40 (m, 4POCH$_2$*Me*), 40.50 (t, NMe, J_{PC} 3.5 Hz), 58.12 (t, NCH, J_{PC} 141.1 Hz), 59.65 (t, NCH$_2$, J_{PC} 5.2 Hz), 62.25 (d, OCH$_2$Me, J_{PC} 3.5 Hz), 62.29 (d, OCH$_2$Me, J_{PC} 6.6 Hz), 62.65 (d, OCH$_2$Me, J_{PC} 3.5 Hz), 62.68 (d, OCH$_2$Me, J_{PC} 3.5 Hz), 118.07 (s, =CH$_2$), 135.97 (s, =CH). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.15. Found (%): C, 43.84; H, 8.23; N, 3.84; P, 7.23. Calc. for $C_{13}H_{29}NO_6P_2$ (%): C, 43.70; H, 8.18; N, 3.92; P, 7.33.

‡ *Compounds* **2a**–**d** *(general procedure)*. Compound **1** (0.35 g, 1 mmol) was dissolved in Et_2O (10 ml). Arylhydroximoyl chloride (1.5 mmol) in Et_2O (5 ml) was added at –40 °C. Triethylamine (0.303 g, 3 mmol) was then added dropwise over 2 h. Stirring was continued at –40 °C until the reaction was complete (TLC control, 2–3 h) and at room temperature for 2 h. The mixture was then quenched with sat. NH_4Cl (10 ml), extracted with Et_2O, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (column: *l* = 30 cm, *d* = 2 cm) using gradient 0 → 7% MeOH in $CHCl_3$ as an eluent. Evaporation of appropriate fractions afforded the desired compounds as viscous oils.

moiety, have been prepared in good yields by simple methods, which may be useful for drug design and fine organic synthesis.

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*5-{*N*-[Bis(diethoxyphosphoryl)methyl]-*N*-methylamino}methyl-3-phenyl-4,5-dihydroisoxazole* **2a**: viscous liquid, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (t, 6H, 2POCH$_2$*Me*, J_{HH} 7.2 Hz), 1.32 (t, 6H, 2POCH$_2$*Me*, J_{HH} 7.2 Hz), 2.75 (s, 3H, NMe), 3.07–3.16 (m, 2H, $CH_{2\ cycle}$), 3.32 (d, 2H, CH_2N, J_{HH} 9.2 Hz), 3.55 (t, 1H, C*H*[P(O)OEt]$_2$, J_{HP} 25.0 Hz), 4.13–4.25 (m, 8H, 4POCH$_2$), 4.87 (ddt, 1H, CH=NO, J_{HH} 3.9 Hz, J_{HH} 5.3 Hz, J_{HH} 9.2 Hz), 7.37–7.39 (m, 3H, H_{Ar}), 7.64–7.65 (m, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.39–16.51 (m, 4POCH$_2$*Me*), 38.03 (s, $CH_{2\ cycle}$), 42.55 (br. s, NMe), 61.15 (br. s, NCH_2), 61.18 (dd, NCH, J_{PC} 143.6 Hz, J_{PC} 145.1 Hz), 62.53 (d, 2O*C*H$_2$Me, J_{PC} 6.6 Hz), 62.57 (d, O*C*H$_2$Me, J_{PC} 6.6 Hz), 63.02 (d, O*C*H$_2$Me, J_{PC} 6.5 Hz), 81.03 (s, CH), 126.63 (s, HC_{Ar}), 128.63 (s, HC_{Ar}), 129.70 (s, C_{Ar}), 129.95 (s, C_{Ar}), 156.80 (s, N=C). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.75 [d, 1P, P(O)OEt, J_{PP} 58.5 Hz], 19.46 [d, 1P, P(O)OEt, J_{PP} 58.5 Hz]. Found (%): C, 50.30; H, 7.07; N, 5.79; P, 13.12. Calc. for $C_{20}H_{34}N_2O_7P_2$ (%): C, 50.42; H, 7.19; N, 5.88; P, 13.00.

*5-{*N*-[Bis(diethoxyphosphoryl)methyl]-*N*-methylamino}methyl-3-(4-methylphenyl)-4,5-dihydroisoxazole* **2b**: viscous liquid, yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (t, 6H, 2POCH$_2$*Me*, J_{HH} 7.2 Hz), 1.34 (t, 6H, 2POCH$_2$*Me*, J_{HH} 7.0 Hz), 2.38 (s, 3H, Ar–*Me*), 2.77 (s, 3H, NMe), 3.08–3.17 (m, 2H, $CH_{2\ cycle}$), 3.31 (dd, 2H, CH_2N, J_{HH} 10 Hz, J_{HH} 5.2 Hz), 3.58 (t, 1H, C*H*[P(O)OEt]$_2$, J_{HP} 25.2 Hz), 4.16–4.25 (m, 8H, 4POCH$_2$), 4.83–4.91 (m, 1H, CH=NO), 7.20 (d, 2H, H_{Ar}, J_{HH} 8.0 Hz), 7.56 (d, 2H, H_{Ar}, J_{HH} 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.42–16.54 (m, 4POCH$_2$*Me*), 21.44 (s, C_6H_4*Me*), 38.22 (s, $CH_{2\ cycle}$), 42.54 (br. s, NMe), 59.71 (br. s, NCH_2), 61.10 (dd, NCH, J_{PC} 143.6 Hz, J_{PC} 145.0 Hz), 62.56 (d, 2O*C*H$_2$Me, J_{PC} 6.6 Hz), 62.60 (d, O*C*H$_2$Me, J_{PC} 6.6 Hz), 63.07 (d, O*C*H$_2$Me, J_{PC} 6.5 Hz), 80.85 (s, CH), 126.59 (s, HC_{Ar}), 126.86 (s, C_{Ar}), 129.35 (s, HC_{Ar}), 140.19 (s, C_{Ar}), 156.77 (s, N=C). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.75 [d, 1P, P(O)OEt, J_{PP} 58.5 Hz], 19.46 [d, 1P, P(O)OEt, J_{PP} 58.5 Hz]. Found (%): C, 51.32; H, 7.51; N, 5.84; P, 12.50. Calc. for $C_{21}H_{36}N_2O_7P_2$ (%): C, 51.43; H, 7.40; N, 5.71; P, 12.63.

*5-{*N*-[Bis(diethoxyphosphoryl)methyl]-*N*-methylamino}methyl-3-(4-fluorophenyl)-4,5-dihydroisoxazole* **2c**: viscous liquid, yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, 6H, 2POCH$_2$*Me*, J_{HH} 7.0 Hz), 1.31 (t, 6H, 2POCH$_2$*Me*, J_{HH} 7.0 Hz), 2.70 (s, 3H, NMe), 3.08–3.16 (m, 2H, $CH_{2\ cycle}$), 3.30 (d, 2H, CH_2N, J_{HH} 9.2 Hz), 3.52 (t, 1H, C*H*[P(O)OEt]$_2$, J_{HP} 25.0 Hz), 4.10–4.22 (m, 8H, 4POCH$_2$), 4.82–4.90 (m, 1H, CH=NO), 7.04–7.08 (m, 2H, H_{Ar}), 7.62–7.65 (m, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.38–16.49 (m, 4POCH$_2$*Me*), 38.05 (s, $CH_{2\ cycle}$), 42.62 (br. s, NMe), 59.42 (br. s, NCH_2), 61.20 (dd, NCH, J_{PC} 143.2 Hz, J_{PC} 145.0 Hz), 62.53 (d, 2O*C*H$_2$Me, J_{PC} 6.4 Hz), 62.54 (d, O*C*H$_2$Me, J_{PC} 6.4 Hz), 62.98 (d, O*C*H$_2$Me, J_{PC} 6.5 Hz), 81.16 (s, CH), 115.74 (d, HC_{Ar}, J_{CF} 21.9 Hz), 126.01 (d, C_{Ar}, J_{CF} 3.0 Hz), 128.54 (d, HC_{Ar}, J_{CF} 8.0 Hz), 155.85 (s, C=N), 163.63 (d, C_{Ar}, J_{CF} 248.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.74 [d, 1P, P(O)OEt, J_{PP} 58.5 Hz], 19.46 [d, 1P, P(O)OEt, J_{PP} 58.5 Hz]. Found (%): C, 48.65; H, 6.77; N, 5.84; P, 12.40. Calc. for $C_{20}H_{33}FN_2O_7P_2$ (%): C, 48.58; H, 6.73; N, 5.67; P, 12.53.

*5-{*N*-[Bis(diethoxyphosphoryl)methyl]-*N*-methylamino}methyl-3-(4-bromophenyl)-4,5-dihydroisoxazole* **2d**: viscous liquid, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, 6H, 2POCH$_2$*Me*, J_{HH} 7.1 Hz), 1.34 (t, 6H, 2POCH$_2$*Me*, J_{HH} 7.0 Hz), 2.80 (s, 3H, NMe), 3.07–3.18 (m, 2H, $CH_{2\ cycle}$), 3.31 (dd, 2H, CH_2N, J_{HH} 10.2 Hz, J_{HH} 5.2 Hz), 3.56 (t, 1H, C*H*[P(O)OEt]$_2$, J_{HP} 25.0 Hz), 4.16–4.25 (m, 8H, 4POCH$_2$), 4.82–4.90 (m, 1H, CH=NO), 7.15 (d, 2H, H_{Ar}, J_{HH} 8.0 Hz), 7.36 (d, 2H, H_{Ar}, J_{HH} 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.35–16.43 (m, 4POCH$_2$*Me*), 38.72 (s, $CH_{2\ cycle}$), 42.56 (br. s, NMe), 59.41 (br. s, NCH_2), 61.16 (dd, NCH, J_{PC} 143.0 Hz, J_{PC} 145.0 Hz), 62.56 (d, 2O*C*H$_2$Me, J_{PC} 6.6 Hz), 62.60 (d, O*C*H$_2$Me, J_{PC} 6.6 Hz), 63.07 (d, O*C*H$_2$Me, J_{PC} 6.5 Hz), 80.85 (s, CH), 125.69 (s, HC_{Ar}), 126.86 (s, C_{Ar}), 128.35 (s, HC_{Ar}), 147.4 (s, C_{Ar}), 156.73 (s, N=C). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.77 [d, 1P, P(O)OEt, J_{PP} 58.8 Hz], 19.43 [d, 1P, P(O)OEt, J_{PP} 58.5 Hz]. Found (%): C, 52.85; H, 7.25; N, 6.04; P, 13.52. Calc. for $C_{20}H_{33}BrN_2O_7P_2$ (%): C, 52.76; H, 7.30; N, 6.15; P, 13.60.