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Synthesis of functional bisphosphonates via new palladium-catalyzed bis-hydrophosphorylation reactions

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Abstract

A series of functional bisphosphonates have been synthesized in good isolated yields via new palladium-catalyzed bis-hydrophosphorylation reactions of terminal alkynes and dialkyl phosphites. The scope and mechanism for such a bis-hydrophosphorylation process are also discussed. © 1999 Elsevier Science Ltd. All rights reserved.

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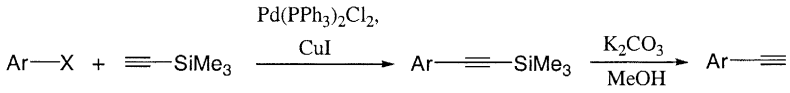
Bisphosphonates have found widespread application both as drugs for the treatment of bone diseases[1] and as ligands for ^{99m}Tc-based bone imaging agents.[2] Intrigued by recent discoveries of facile carbon–phosphorus bond-forming reactions mediated by palladium complexes,[3] we have sought to develop new methods for the synthesis of bisphosphonates containing other functional groups that can readily coordinate to metal centers. Such functional bisphosphonates are useful as novel ligands for well-defined radioactive metal complexes that can be used for both imaging and therapeutic applications.

Herein, we report the synthesis of a series of functional bisphosphonates via new palladium-catalyzed bis-hydrophosphorylation reactions of terminal alkynes and dialkyl phosphites. The terminal alkynes used for this study were synthesized in excellent yields by Heck reactions between aryl halides and trimethylsilylacetylene followed by removal of the trimethylsilyl group under basic conditions (Eq. (1)).[4]



(1)

(Ar = 2-pyridyl, 4-pyridyl, 4-nitrobenzene, 4-benzonitrile, 2-thiazolyl)

Refluxing a mixture of 1 equiv. of terminal alkynes with 3 equiv. of dialkyl phosphites in the presence of 5 mol% $Pd(PPh_3)_4$ in toluene over a period of 19 to 71 h afford a variety of vicinal bisphosphonates via bis-addition of H–P bonds across the triple bonds of terminal alkynes (Eq. (2)).[5] The isolated yields

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after silica-gel column chromatography with appropriate mixtures of acetone and chloroform range from good to excellent (Eq. (2)). The resulting bisphosphonates **1**–**5** have been characterized by ^{1}H, $^{1}H\{^{31}P\}$, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectroscopy.[6] For example, the characteristic signals for the protons on the alkane backbone of **1a** appear as three multiplets at $\sim\delta$ 3.7, δ 2.9, and δ 2.4. Upon decoupling the ^{31}P nuclei, these three proton signals collapse into a doublet, a doublet of doublet, and a doublet with a $^{2}J_{H-H}$ of 15.5 Hz and a $^{3}J_{H-H}$ of 12.2 Hz. The fact that the other vicinal proton–proton coupling constant is negligible is consistent with the *anti* conformation of the two vicinal phosphonate groups. The alkyl protons on the phosphonate groups appear as several complex multiplets because of their diastereotopic nature. The $^{31}P\{^{1}H\}$ NMR spectra of these vicinal bisphosphonates appear as two doublets at $\sim\delta$ 58 and $\sim\delta$ 55 with a $^{3}J_{P-P}$ of ~77 Hz.

Ar =  , **1a**: R = Et, 90%; **1b**: R = ^{i}Pr, 86%

Ar =  , **2a**: R = Et, 89%; **2b**: R = ^{i}Pr, 60% (2)

Ar =  , **3a**: R = Et, 87%; **3b**: R = ^{i}Pr, 47%

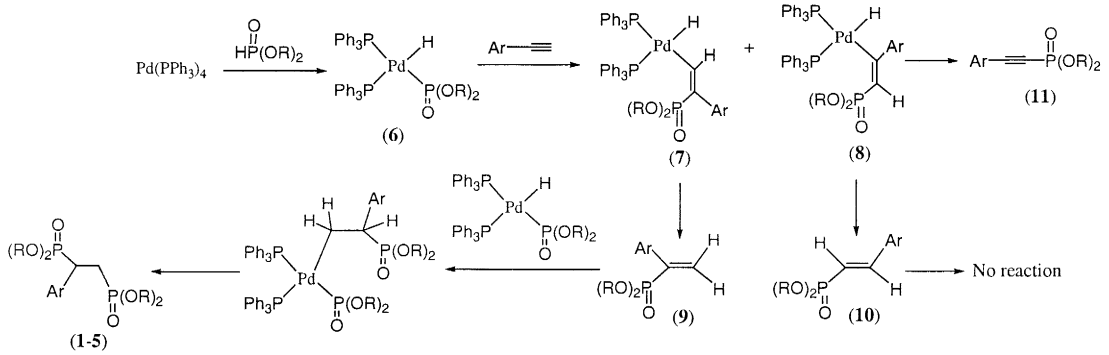
Ar =  , **4a**: R = Et, 87%; **4b**: R = ^{i}Pr, 41%

Ar =  , **5a**: R = Et, 72%; **5b**: R = ^{i}Pr, 55%

The above palladium-catalyzed bis-hydrophosphorylation reactions only proceed with electron-deficient terminal alkynes. Without electron-withdrawing functionalities on the aryl groups, alkenyl phosphonates **9** (along with small amounts of **10**) were instead obtained which apparently resulted from mono-hydrophosphorylation. The second addition of dialkyl phosphite to the alkenyl phosphonate did not occur at reflux toluene or xylene. It is interesting to note that the bis-hydrophosphorylation reactions work the best for diethyl phosphite. Diisopropyl phosphite also undergoes bis-hydrophosphorylation reactions albeit at lower isolated yields (Eq. (2)). Reactions with dimethyl phosphite under identical conditions, however, failed to give bis-addition products; only the alkenylphosphonates (mono-addition products) were obtained.

By trapping the alkenyl phosphonate intermediates, we have also been able to shed some light on the mechanism of the bis-hydrophosphorylation reactions. When the hydrophosphorylation reactions were carried out with 1 equiv. of dialkyl phosphites under milder conditions, geminal alkenyl phosphonates (**9**) were the predominant products along with trace amounts of terminal alkenyl phosphonates (**10**) and alkynyl phosphonates (**11**). Interestingly, while **9** readily undergoes the second hydrophosphorylation, **10** fails to react with the second equiv. of dialkyl phosphite under identical conditions. We thus propose that the bis-hydrophosphorylation reactions proceed via the following mechanism (Scheme 1). The active catalyst is the palladium hydride **6**. Oxidative addition of dialkyl phosphite to a zero-valent group 10 metal has been previously established by Tanaka et al.[7] Insertion of alkynes into the Pd–P bonds give

alkenylpalladium intermediates **7** and **8** (Scheme 1). Protonolysis of **7** and **8** by dialkyl phosphites results in alkenylphosphonates **9** and **10** and regenerates the active catalyst **6**. Indirect evidence for the insertion of alkynes into the Pd–P bonds (but not the Pd–H bonds) comes from the isolation of trace amounts of alkynyl phosphonates **11**. Compound **11** can only result from reductive elimination of the alkenylpalladium intermediate **8** (but not from the alkenylpalladium intermediate after the insertion of alkynes into the Pd–H bonds). On the contrary, we believe that the second hydrophosphorylation reaction proceeds via the insertion of geminal alkenylphosphonates **9** into the Pd–H bonds followed by reductive elimination of the products **1**–**5**. This pathway will explain the failure of **10** to react with dialkyl phosphites because of the steric hindrance of the potential insertion intermediate.



Scheme 1. Proposed mechanism for Pd-catalyzed bis-hydrophosphorylation reactions

In summary, we have developed an efficient method for the synthesis of functional bisphosphonates via palladium-catalyzed bis-phosphorylation reactions of alkynes with dialky phosphites. We are currently evaluating the utility of bisphosphonic acids derived from **1-5** as ligands for radionuclides such as ^{99m}Tc and $^{186/188}$Re for imaging and therapeutic applications.

Acknowledgements

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5. A typical experimental procedure for bis-hydrophosphinylation of terminal alkynes: To a mixture of diethyl phosphite (325 μL, 3 mmol) and 2-ethynyl pyridine (100 mg, 0.8 mmol) in toluene was added $Pd(PPh_3)_4$ (66 mg, 5 mol%). The resulting brown solution was stirred at reflux for 26 h. The solvent was removed under reduced pressure to afford a brown oil. The oil was purified by column chromatography (SiO_2, $CHCl_3$:acetone, 3:1) to afford 273 mg (90%) of **1a**.
6. Selected NMR data for **1a**–**5a**. All the spectra were taken in $CDCl_3$ at 400 MHz for ^{1}H, 125 MHz for ^{13}C, and 161 MHz for ^{31}P nucleus, respectively. Compounds **1b**–**5b** exhibit similar NMR spectra except for the regions for the isopropyl groups. Compound **1a**: ^{1}H NMR: δ 8.54 (d, 1H, *J*=4.3 Hz), 7.60 (t, 1H, *J*=7.9 Hz), 7.33 (d, 1H, 7.9 Hz), 7.15 (t, 1H, *J*=6.10 Hz), 4.07–3.74 (m, 8H), 3.70–3.61 (m, 1H), 2.97–2.85 (m, 1H), 2.74–2.35 (m, 1H), 1.24 (t, 3H, *J*=7.3 Hz), 1.16 (t, 3H, *J*=6.7 Hz),

1.07 (t, 3H, *J*=6.7 Hz), 1.04 (t, 3H, *J*=6.7 Hz); ^{13}C NMR: δ 154.9 (J_{C-P}=8.4 Hz), 148.9 (J_{C-P}=2.3 Hz), 136.2, 124.8 (J_{C-P}=5.3 Hz), 122.1 (J_{C-P}=2.3 Hz), 62.6 (J_{C-P}=6.9 Hz), 62.4 (J_{C-P}=6.1 Hz), 61.4 (J_{C-P}=6.1 Hz), 61.3 (J_{C-P}=6.1 Hz), 41.2 (J_{C-P}=135.4 Hz), 24.1 (J_{C-P}=140.8 Hz), 16.2–15.5 (m); ^{31}P NMR: δ 57.9 (d, J_{P-P}=77.5 Hz), 54.8 (d, J_{P-P}=77.5 Hz). Compound **2a**: ^{1}H NMR: δ 8.54 (d, 2H, *J*=5.50 Hz), 7.31–7.29 (m, 2H), 4.12–4.02 (m, 2H), 3.97–3.80 (m, 6H), 3.79–3.62 (m, 1H), 3.46–3.34 (m, 1H), 2.52–2.35 (m, 1H), 1.29 (t, 3H, *J*=6.7 Hz), 1.14–1.09 (m, 6H), 1.02 (t, 3H, *J*=6.7 Hz); ^{13}C NMR: δ 149.5, 144.4 (J_{C-P}=6.9 Hz), 124.4 (J_{C-P}=6.1 Hz), 63.1 (J_{C-P}=6.9 Hz), 62.5 (J_{C-P}=6.9 Hz), 61.7 (J_{C-P}=6.9 Hz), 61.5 (J_{C-P}=6.9 Hz), 38.5 (J_{C-P}=136.0 Hz), 25.7 (J_{C-P}=142.0 Hz), 16.2–15.8 (m); ^{31}P NMR: δ 56.6 (d, J_{P-P}=79.4 Hz), 54.3 (d, J_{P-P}=79.4 Hz). Compound **3a**: ^{1}H NMR: δ 8.12 (d, 2H, *J*=8.55 Hz), 7.55 (d, 2H, *J*=8.55 Hz), 4.18–4.03 (m, 2H), 3.95–3.74 (m, 6H), 3.72–3.60 (m, 1H), 3.60–3.51 (m, 1H), 2.52–2.40 (m, 1H), 1.29 (t, 3H, *J*=6.8 Hz), 1.12 (q, 6H, *J*=7.3 Hz), 1.02 (t, 3H, *J*=6.8 Hz); ^{13}C NMR: δ 147.2, 143.9 (J_{C-P}=5.3 Hz), 130.4 (J_{C-P}=6.9 Hz), 123.4 (J_{C-P}=3.0 Hz), 63.2 (J_{C-P}=6.9 Hz), 62.6 (J_{C-P}=6.9 Hz), 61.8 (J_{C-P}=6.9 Hz), 61.6 (J_{C-P}=6.9 Hz), 39.2 (J_{C-P}=135.0 Hz), 26.3 (J_{C-P}=143.4 Hz), 16.3–16.1 (m); ^{31}P NMR: δ 56.5 (d, J_{P-P}=79.4 Hz), 54.3 (d, J_{P-P}=79.4 Hz). Compound **4a**: ^{1}H NMR: δ 7.60 (d, 2H, *J*=8.6 Hz), 6.82 (d, 2H, *J*=8.6 Hz), 4.11–4.03 (m, 2H), 3.94–3.73 (m, 6H), 3.69–3.60 (m, 1H), 3.54–3.45 (m, 1H), 2.52–2.33 (m, 1H), 1.28 (t, 3H, *J*=6.7 Hz), 1.15–1.08 (m, 6H), 1.02 (t, 3H, *J*=6.7 Hz); ^{13}C NMR: δ 140.9, 131.9 (J_{C-P}=2.3 Hz), 130.3 (J_{C-P}=6.9 Hz), 118.5, 111.2, 63.1 (J_{C-P}=6.9 Hz), 62.5 (J_{C-P}=6.9 Hz), 61.7 (J_{C-P}=6.9 Hz), 61.6 (J_{C-P}=6.9 Hz), 39.3 (J_{C-P}=135.8 Hz), 26.2 (J_{C-P}=141.9 Hz), 16.3–16.0 (m); ^{31}P NMR: δ 56.6 (d, J_{P-P}=80.0 Hz), 53.5 (d, J_{P-P}=80.0 Hz). Compound **5a**: ^{1}H NMR: δ 7.74 (d, 1H, *J*=3.7 Hz), 7.28 (d, 1H, *J*=3.7 Hz), 4.12–3.85 (m, 9H), 2.86–2.73 (m, 1H), 2.57–2.45 (m, 1H), 1.28 (t, 3H, *J*=7.3 Hz), 1.22 (t, 3H, *J*=7.3 Hz), 1.16 –1.09 (m, 6H); ^{13}C NMR: δ 149.5, 144.4 (J_{C-P}=6.9 Hz), 124.4 (J_{C-P}=6.1 Hz), 63.1 (J_{C-P}=6.9 Hz), 62.5 (J_{C-P}=6.9 Hz), 61.7 (J_{C-P}=6.9 Hz), 61.5 (J_{C-P}=6.9 Hz), 38.5 (J_{C-P}=136.0 Hz), 25.7 (J_{C-P}=142.0 Hz), 16.2–15.8 (m); ^{31}P NMR: δ 56.5 (d, J_{P-P}=70.2 Hz), 51.6 (d, J_{P-P}=70.2 Hz).

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