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Diastereoselective synthesis of meso-bisphosphonates from dialkyl(aryl) phosphites and activated acetylenes in the presence of NaCN

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Abstract: The facile synthesis of various P–C–C-P compounds is described, based on the reaction of dialkyl (aryl) Phosphite with activated acetylenes in the presence of NaCN. Using this approach, symmetrically substituted 1,2-bisphosphorus compounds can be obtained in good yields.

Keywords: Bisphosphonates, Activated acetylenes, Dialkyl phosphites, Stereoselective synthesis.

Introduction

Organophosphorus compounds are important in a variety of applications, from medicines to pesticides, from ligands in catalysis to extractants and flame-retardants [1].

Among this phosphonates-containing molecules are an important class of active compounds and their use and synthesis have received an increasing amount of attention during the last two decades [2]. Due to such biological importance, phosphonate dreviatives such Bisphosphonates have become the synthetic targets of many organic and medicinal chemist [3–6].

As part of our current studies on the development of new routes in the synthesis of organic molecules [7-10], we now report a diastereoselective synthesis of meso-bisphosphonates through the reaction of dialkyl (aryl) Phosphite and activated acetylenes in the presence of NaCN in good yields.

Results and discussion

As part of our group current studies on the synthesis of alkyl phosphonates, and α aminophosphonates [11-15] Herein we report the results of our studies involving the reaction of diialkyl (aryl) phosphites 1 with acetylenedicarboxylate 2 in the presence NaCN as the catalyst (nucleophile) leads to diialkyl 2,3-bis (dialkoxyphosphoryl) succinates 3a–3f were in good yields (Scheme **1**).

The structures of bisphosphonates 3a–3f were deduced from their elemental analyses and their IR, 1H, 13C, and 31P NMR, and mass spectral data. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values. The 1H NMR spectrum of 3a in CDCl3 showed a singlet at δ = 3.75 for methoxy groupes and a doublet of doublet at δ = 4.34 (2JHP=12, 6 Hz, 2 CH) for the methine protons, along with multiplets at δ = 7.16–7.31 ppm for the aromatic moieties. A single resonance at δ = 166.3 ppm is observed in the 13C NMR spectrum of 3a, which is attributed to the carbonyl groups. The 31P NMR signal of 3a was found at δ = 11.73 ppm. The 1H and 13C NMR spectra of 3b and 3c are similar to those of 3a except for the ester moieties. The 1H NMR spectrum of 3d in CDCl3 showed two doublets at δ =3.45 (3JHP= 8.2 Hz), 3.54 (3JHP= 8.3Hz), for the diastereotopic methoxy groups and a doublet of doublet δ= 4.35 (dd, 2JHP= 11.2, 8.1Hz) for the

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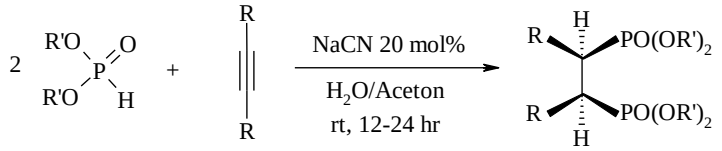
methine moieties, along with a singlet at δ= 3.78 ppm for the two CO2Me groups. The ester carbonyl resonances in the 13C NMR spectra of 3d appear as a singlet at δ = 167.4 ppm in the 13C NMR spectrum. The 31P NMR signal of 3d was found at δ =19.58 ppm. The 1H and 13C NMR spectra of 3e and 3f are similar to those of 3d except for the ester and phosphoranyl moieties moieties respectively.

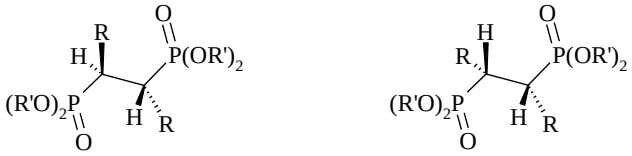


1	R'
a	Ph
b	Me
c	Et

2	R
a	CO_2Me
b	CO_2Et
c	CO2^{t}Bu

3	R	R'	Yield %
a	CO_2Me	Ph	90
b	CO_2Et	Ph	83
c	CO2^{t}Bu	Ph	70
d	CO_2Me	Me	87
e	CO_2Et	Me	80
f	CO_2Me	Et	76

Scheme 1: Synthesis of hydrogen phosphonate derivatives.

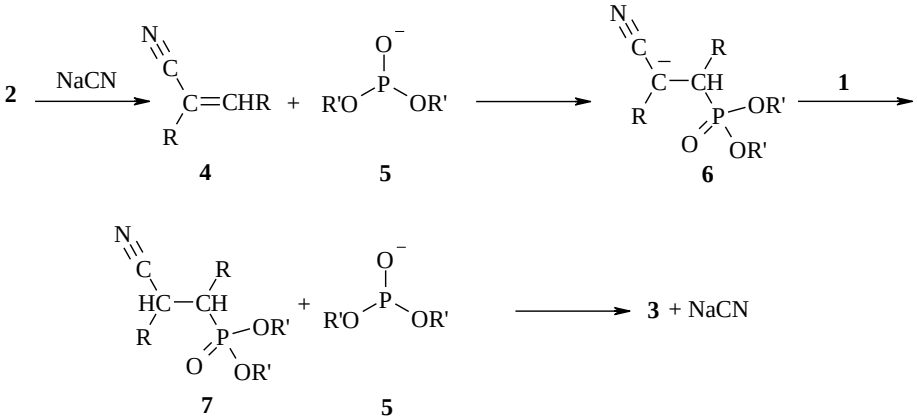


meso-3 dl-3

Scheme 2: meso and dl structure.

Assignment of the meso structure to compounds 3 (Scheme **2**) is based on the ^{13}C NMR spectra [16]. Whereas the P–CH carbon atoms of the meso diastereoisomer exhibits a 5-line pattern (A part of AXX' system; X=X'=phosphorus), a simple doublet is expected for the dl form [11]. The meso structure represents a high field limiting case which does not give a ''first order'' spectrum. Thus, some mixing of the basic functions is involved [17]. The RC=O carbon of the meso form appears essentially as a singlet (fairly small $^{2,3}J_{PC}$ values), but the dl form exhibits a multiplet (a doublet of doublet due to the higher $^{2,3}J_{PC}$ values).

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme **3**).



Scheme 3: Proposed mechanism for the formation of products.

Presumably, the zwitterionic intermediate [18-20] formed from NaCN and dialkyl acetylenedicarboxylates, is protonated by **1** to furnish intermediate **4**, which is attacked by intermediate **5,** to produce **6** This intermediate is protonated by anpther **1,** converted to **7**, which undergoes attack by **5** to produce **3.**

Conclusion

In summary, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but the educts can be mixed without any activation or modification. The simplicity of the present procedure for diastereoselective synthesis of bisphosphonates makes it an interesting alternative to complex multistep approaches.

Experimental

General procedure:

Chemicals were purchased from Fluka and Merck and used without further purification. Melting points were measured on an Electrothermal 9100 aparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. Mass spectra were recorded on a FINNIGAN Scheme MATT 8430 spectrometer operating at an ionization potential of 70eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured with a BRUKER DRX- 500 AVANCE spectrometer at 500.1, 125.8, and 202.4MHz.

Typical procedure for preparation of (**3a**):

To a stirred solution of 0.140 DMAD (dimetyl acetylen dicarboxylate) (1mmol) and 0.534 g diphenyl phosphite (2mmol) in 10 cm^3 Aceton/H_2O (2:1) was added 0.001g NaCN (0.2mmol) at room temperature. The reaction mixture was then stirred for 12 h. The solvent was removed under reduced pressure and the viscous residue was purified by preparative TLC on silica gel column chromatography (Merck 230–400 mesh) using n-hexane-EtOAc as eluent to give **3a**

Dimethyl 2,3-bis(diphenoxyphosphoryl)succinate (**3a**):

Colorless crystals, mp 173–175 °C, yield 0.550 g, 90%; IR (KBr) (ν_{max}/cm^{-1}): 2950, 1739, 1581, 1277, 1246, 1184, 1155; Anal. Calcd for $C_{30}H_{28}O_{10}P_2$ (610.48): C, 59.02; H, 4.62 %. Found: C, 59.08; H, 4.76%. ^{1}H NMR (500MHz, $CDCl_3$): δ = 3.75 (6 H, s, 2 MeO), 4.34 (2 H, dd, $^{2}J_{HP}$=12, 6 Hz, 2 CH), 7.16 (4 H, t, $^{3}J_{HH}$= 8.0Hz, 4CH), 7.26 (8 H, d, $^{3}J_{HH}$= 5.4 Hz, 8 CH), 7.31 (8 H, dd, $^{3}J_{HH}$= 8.6, 7.7 Hz, 8 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ= 44.4, 44.7, 45.2, 45.7, 46.0 (5 lines for 2 P–CH), 53.2 (2 MeO), 120.5 (d, $^{3}J_{CP}$= 7.2, 4 CH), 120.6 (d, $^{3}J_{CP}$= 7.3, 4 CH),125.5 (d, $^{4}J_{PC}$= 4.5 Hz, 4 CH), 125.6 (d, $^{4}J_{PC}$= 4.3 Hz, 4 CH), 129.7 (s, 2 CH), 129.8 (s, 2 CH), 150.0 (d, $^{2}J_{PC}$= 9.3 Hz, 2 C), 150.1 (d, $^{2}J_{PC}$= 9.0 Hz, 2 C), 166.3 (2 C=O) ppm; ^{31}P NMR (202MHz, $CDCl_3$): δ=11.73 (P=O) ppm; MS (EI, 70 eV): m/z (%)= 610 (M^+, 6), 579 (20), 517 (100), 485 (10), 318 (10), 285 (80), 223 (58), 140 (46), 94 (40), 77 (100).

Diethyl 2,3-bis(diphenoxyphosphoryl)succinate (**3b**):

Colorless crystals, mp 170–173 °C, yield 0.523 g, 83%; IR (KBr) (ν_{max}/cm^{-1}): 2952, 1738, 1582, 1276, 1246 (P=O), 1183, 1156; Anal. Calcd for $C_{32}H_{32}O_{10}P_2$ (638.54): C, 60.19; H, 5.05 %. Found: C, 60.38; H, 5.16%. ^{1}H NMR (500MHz, $CDCl_3$): δ = 0.8 (6H, d, $^{3}J_{HH}$= 7.2 Hz, 2 CH_3), 3.72 (4 H, q., $^{3}J_{HH}$= 7.2, 2 OCH_2), 4.31 (2 H, dd, $^{2}J_{HP}$=11, 5 Hz, 2CH), 7.18 (4 H, t, $^{3}J_{HH}$= 7.8 Hz, 4CH), 7.29 (8 H, d, $^{3}J_{HH}$= 5.3 Hz, 8 CH), 7.31 (8 H, dd, $^{3}J_{HH}$= 8.9, 7.6 Hz, 8 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ= 14.2 (2 CH_3), 44.2, 44.5, 45.0, 45.5, 45.8 (5 lines for 2 P–CH), 59.2 (2 CH_2O), 119.5 (d, $^{3}J_{CP}$= 7.1, 4 CH), 120.2 (d, $^{3}J_{CP}$= 7.3, 4 CH),125.7 (d, $^{4}J_{PC}$= 3.5 Hz, 4 CH), 125.9 (d, $^{4}J_{PC}$= 3.8 Hz, 4 CH), 129.7 (2 CH), 129.9 (s, 2 CH), 150.2 (d, $^{2}J_{PC}$= 10.4 Hz, 2 C), 150.3 (d, $^{2}J_{PC}$= 9.9 Hz, 2 C), 166.4 (2 C=O) ppm; ^{31}P NMR (202MHz, $CDCl_3$): δ=11.71 (P=O) ppm; MS (EI, 70 eV): m/z (%)= 638 (M^+, 5), 593 (24), 545 (94), 499 (12), 332(8), 285 (70), 237 (68), 140 (45), 94 (44), 77 (100).

Di(tert-butyl) 2,3-bis(diphenoxyphosphoryl)succinate (**3c**):

Colorless crystals, mp 168–170 °C, yield 0.486 g, 70%; IR (KBr) (ν_{max}/cm^{-1}): 2953, 1741, 1579, 1277, 1244 (P=O), 1185, 1153; Anal. Calcd for $C_{36}H_{40}O_{10}P_2$ (694.65): C, 62.25; H, 5.80 %. Found: C, 62.43; H, 5.96%. ^{1}H NMR (500MHz, $CDCl_3$): δ = 1.45 (18 H, s, 2 CMe_3), 4.45 (2 H, dd, $^{2}J_{HP}$=11.6, 6 Hz, 2 CH), 7.15 (4 H, t, $^{3}J_{HH}$= 8.1Hz, 4CH), 7.27 (8 H, d, $^{3}J_{HH}$= 5.5 Hz, 8 CH), 7.34 (8 H, dd, $^{3}J_{HH}$= 8.6, 7.5 Hz, 8 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ= 27.9 (2 CMe_3, 6 CH_3), 44.3, 44.6, 45.1, 45.6, 45.9 (5 lines for 2 P–CH), 83.7 (2 OCMe$_3$), 120.8 (d, $^{3}J_{CP}$= 7.3, 4 CH), 120.9 (d, $^{3}J_{CP}$= 7.1, 4 CH),125.3 (d, $^{4}J_{PC}$= 4.2 Hz, 4 CH), 125.5(d, $^{4}J_{PC}$= 4.3 Hz, 4 CH), 129.6 (2 CH), 129.8 (2 CH), 150.3 (d, $^{2}J_{PC}$= 10.3 Hz, 2 C), 150.5 (d, $^{2}J_{PC}$= 11.0 Hz, 2 C), 166.3 (2 C=O) ppm; ^{31}P NMR (202MHz,

$CDCl_3$): δ=11.73 (P=O) ppm; MS (EI, 70 eV): m/z (%)= 694 (M^+, 3), 621 (18), 601 (90), 527 (12), 360 (10), 285 (87), 265(59), 140 (43), 94 (41), 77 (100).

Dimethyl 2,3-bis(dimethoxyphosphoryl)succinate (**3d**):

White powder, mp 72–74°C, yield 0.315 g, 87 IR (KBr) (ν_{max}/cm^{-1}): 2922, 1720, 1583, 1259 (P=O), 1154, 1024 cm^{-1}; Anal. Calcd for $C_{10}H_{20}O_{10}P_2$ (362.20): C, 33.16; H, 5.57%. Found: C, 33.30; H, 5.88%. ^{1}H NMR (500MHz, $CDCl_3$): δ = 3.45 (6 H, d, $^3J_{HP}$= 8.2 Hz, 2 MeO), 3.54 (6 H, d, $^3J_{HP}$= 8.3Hz, 2 MeO), 3.78 (6 H, s, 2 MeO), 4.35 (2 H, dd, $^2J_{HP}$= 11.2, 8.1Hz, 2 CH) ppm; ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 43.3, 43.7, 44.1, 44.4, 44.8 (5 lines for 2 P–CH), 52.6 (d, $^2J_{CP}$= 4. Hz, 2 $POCH_3$), 53.8 (d, $^2J_{CP}$= 3.8 Hz, 2 $POCH_3$), 54.1 (2 OCH_3), 167.4 (2 C=O) ppm; ^{31}P NMR (202MHz, $CDCl_3$): δ = 19.58 (P=O) ppm; MS (EI, 70eV): m/z (%)= 362 (M^+, 5), 331 (35), 253 (20), 181 (48), 110 (100), 31 (78).

Diethyl 2,3-bis(dimethoxyphosphoryl)succinate (**3e**):

White powder, mp 70–72°C, yield 0.312 g, 80%; IR (KBr) (ν_{max}/cm^{-1}): 2921, 1723, 1584, 1258 (P=O), 1153, 1025 cm^{-1}; Anal. Calcd for $C_{12}H_{24}O_{10}P_2$ (390.25): C, 36.93; H, 6.20%. Found: C, 34.10; H, 6.23%. ^{1}H NMR (500MHz, $CDCl_3$): δ = 0.8 (6H, d, $^3J_{HH}$= 7.1 Hz, 2 CH_3), 3.40 (6 H, d, $^3J_{HP}$= 7.9 Hz, 2 MeO), 3.48 (6 H, d, $^3J_{HP}$= 8.1Hz, 2 MeO), 3.78 (4 H, q., $^3J_{HH}$= 7.1 Hz, 2 OCH_2), 4.30 (2 H, dd, $^2J_{HP}$= 10.9, 8.2 Hz, 2 CH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.3 (2 CH_3), 43.0, 43.3, 43.8, 44.3, 44.6 (5 lines for 2 P–CH), 52.7 (d, $^2J_{CP}$= 4. Hz, 2 $POCH_3$), 53.8 (d, $^2J_{CP}$= 3.7 Hz, 2 OCH_2), 54.3 (2 OCH_2), 167.5(2 C=O) ppm; ^{31}P NMR (202MHz, $CDCl_3$): δ = 19.8 (P=O) ppm; MS (EI, 70eV): m/z (%)= 390 (M^+, 4), 345 (45), 281 (24), 195 (45), 110 (100), 45 (65).

Dimethyl 2,3-bis(diethoxyphosphoryl)succinate (**3f**):

White powder, mp 70–72°C, yield 0.326 g, 76%; IR (KBr) (ν_{max}/cm^{-1}): 2921, 1723, 1584, 1258 (P=O), 1153, 1025 cm^{-1}; Anal. Calcd for $C_{14}H_{28}O_{10}P_2$ (306.36): C, 40.20; H, 6.75%. Found: C, 40.42; H, 6.83%. ^{1}H NMR (500MHz, $CDCl_3$): δ = 1.1 (6H, dt., $^3J_{HH}$= 7.1 Hz, $^4J_{HP}$= 0.6 Hz, 2 CH_3), 1.2 (6H, dt., $^3J_{HH}$= 7.2 Hz, $^4J_{HP}$= 0.6 Hz, 2 CH_3), 3.52 (4 H, dq., $^3J_{HP}$= 7.9 Hz, $^3J_{HH}$= 7.1 Hz 2 OCH_2), 3.57 (4 H, dq., $^3J_{HP}$= 8.0 Hz, $^3J_{HH}$= 7.2 Hz 2 OCH_2), 3.70 (6 H, 2 MeO), 4.25 (2 H, dd, $^2J_{HP}$= 10.8, 8.1 Hz, 2 CH) ppm; ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 16.1 (d, $^3J_{CP}$= 4.1 Hz, 2 CH_3), 16.3 (d, $^3J_{CP}$= 4.2 Hz, 2 CH_3), 43.2, 43.5, 44.0, 44.3, 44.6 (5 lines for 2 P–CH), 54.3 (2 OCH_3), 62.7 (d, $^2J_{CP}$= 4.6 Hz, 2 OCH_2), 53.8 (d, $^2J_{CP}$= 4.7 Hz, 2 OCH_2), 167.6 (2 C=O) ppm; ^{31}P NMR (202MHz, CDCl3): δ = 20.1 (P=O) ppm; MS (EI, 70eV): m/z (%)= 418 (M^+, 5), 387 (38), 281 (20), 209 (45), 138 (100), 31 (72).

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