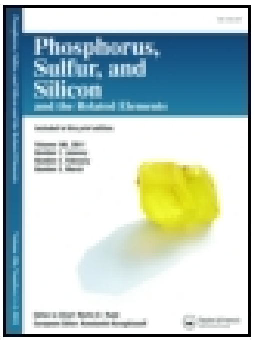

Phosphorus, Sulfur, and Silicon and the Related Elements

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An efficient and green method to prepare bis-α-hydroxy phosphonates using triethylamine as catalyst

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ABSTRACT

An efficient, convenient and environmentally friendly method for the synthesis of bis-α-hydroxy phosphonates *via* a perfectly atom economical Pudovik reaction is described. Using 5 mol% of triethylamine as a catalyst, a series of aromatic/heteroaromatic dialdehydes reacts with dialkyl phosphites to afford the corresponding bis-α-hydroxy phosphonates, particularly the bio-mass based ones, under solvent-free conditions or in a minimum amount of tetrahydrofuran at room temperature with moderate to excellent yields (52–95%).

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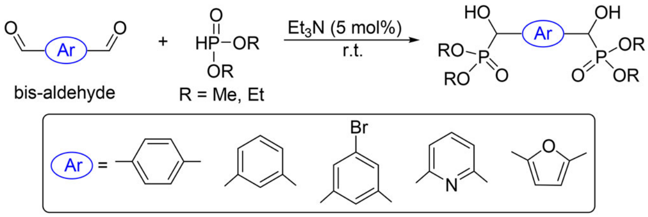
KEYWORDS
Bis-α-hydroxy phosphonate; Pudovik reaction; green syntheses; aromatic dialdehyde; biomass

GRAPHICAL ABSTRACT



Introduction

α-Hydroxy phosphonates have attracted extensive attention because they were found to be biologically active and valuable synthetic precursors for the synthesis of related organophosphonates, such as α-aminophosphonates, alkoxy- and acyloxy-phosphonates, ketophosphonates and halophosphonates.[1] Moreover, bis-α-hydroxy phosphonates can be used as excellent candidates as diol monomers for the synthesis of phosphorus-containing polymers with flame retardant properties.[2] As early as 1988, Mikroyannidis used bis-α-hydroxy phosphonates (1,4-bis[(dialkoxyphosphinyl)hydroxymethyl]benzene) as diols to prepare phosphorus-containing polyurethanes which exhibited a higher fire resistance than that of common polyurethanes.[3] The major synthetic route toward α-hydroxy phosphonates is the atom economic Pudovik reaction.[4] A wide range of catalysts has been explored for the synthesis of α-hydroxy phosphonates, such as lipase,[5] triethylamine (Et_3N),[6] choline hydroxide,[7] $Bi(NO_3)_3{\cdot}5H_2O$,[8] n-BuLi,[9] $Ba(OH)_2$,[10] bimetallic lanthanide bis(amido) complexes,[11] MoO_2Cl_2,[12] MgO[13] and heterogeneous systems,[14] but only a few catalysts were reported for bis-α-hydroxy phosphonates, including a stoichiometric amount of Et_3N[15] and catalytic amount of DABCO,[16] heterogeneous KF/Al_2O_3[17] and Fe_3O_4-immobilized guanidine.[14a] In addition, Failla and coworkers reported the synthesis of three bis-α-hydroxy phosphonates by reacting dialdehyde with trialkyl phosphite under strong acidic conditions (HCl gas) in dry dioxane.[18] Unfortunately, the current protocols for the synthesis of bis-α-hydroxy phosphonates suffer from some inconveniences such as strong acidic conditions (HCl gas), poor activity and low efficiency. Therefore, there is a need to develop an environmentally benign and convenient method for the synthesis of bis-α-hydroxy phosphonates. In this contribution, we report an efficient method to synthesize a series of phosphonate diols (bis-α-hydroxy phosphonates) from aromatic and heteroaromatic dialdehydes under green and mild conditions.

Results and discussion

As previously mentioned, Et_3N is a common catalyst for the synthesis of α-hydroxy phosphonates, and Blackburn[15a] and Rangel,[15b] respectively, used a stoichiometric amount to prepare a few bis-α-hydroxy phosphonates from the reaction of dialdehyde and diethyl phosphonate. In our initial study, different amounts of Et_3N were tested for the model reaction between *p*-phthalaldehyde and dimethyl phosphite under solvent-free conditions at room temperature. To a mixture of *p*-phthalaldehyde (1.0 eq.) and dimethyl phosphite (2.1 eq.) was added Et_3N (2–20 mol%) under stirring. The heterogeneous mixture gradually became into a viscous liquid, then into a white precipitate. Washing the resulting

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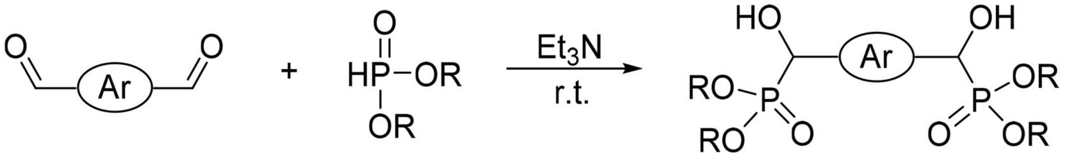
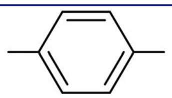
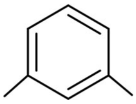
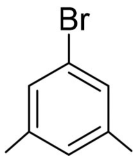
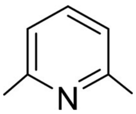
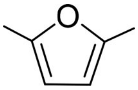
Table 1. Synthesis of bis-α-hydroxy phosphonates catalyzed with Et_3N.[a]



Entry	Ar	R	Solv.	Et3N (mol %)	t/min	Product	Yield (%)[b]
1		Me	Neat	20	5	1a	98
2		Me	Neat	10	5	1a	96
3		Me	Neat	5	30	1a	95
4		Me	Neat	2	60	1a	95
5		Et	Neat	5	30	1b	94
6		Me	THF[c]	5	600	2a	93
7		Et	THF[c]	5	600	2b	87
8		Me	THF[c]	5	120	3a	82
9		Et	THF[c]	5	120	3b	87
10		Me	THF[c]	5	600	4a	94
11		Et	THF[c]	5	600	4b	69
12		Me	neat	5	30	5a	52
13		Et	neat	5	30	5b	69

[a] Reaction conditions: dialdehyde (1.0 mmol), dialkyl phosphite (2.1 mmol), room temperature.
[b] Isolated yield of pure product.
[c] THF (1.0 mL).

Table 2. Significant NMR parameters of the newly obtained bis-α-hydroxy phosphonates (DMSO-d_6).

Compound	^1H NMR δ_{P-CH} (ppm)	$^2J_{PH}$, $^3J_{HH}$ (Hz)	^{13}C NMR δ_{P-C} (ppm)	$^1J_{PC}$ (Hz)	^{31}P NMR[b] δ_P (ppm)
2a	5.00 (dd)	13.3, 5.2	–	–	–
3a	5.07 (dd)	13.8, 5.5	68.3	161.1	23.19, 23.10
3 b	4.97 (dd)	13.9, 5.8	68.6	161.4	21.00, 20.98
4a	5.07 ~ 5.03 (m)	–	70.7	157.3	22.88 (m)
5a	4.96 (dd)	14.4, 6.3	62.9	168.6	21.67 (m)
5 b	4.86 (dd)	14.6, 6.6	63.3	169.1	19.42, 18.83

[b] 202 MHz.

precipitate with ethyl ether to remove Et_3N and excessive dimethyl phosphite afforded the desired bis-α-hydroxy phosphonate, 1,4-bis[(dimethoxyphosphoryl)hydroxymethyl]-benzene (**1a**) in excellent yields (Table 1, entries 1–4). Given the reaction time and solution reaction (*vide infra*), 5 mol% amount of Et_3N was employed as standard condition in the following experiments. With the same procedure, 1,4-bis[(diethoxyphosphoryl)hydroxymethyl]benzene (**1b**) was synthesized from *p*-phthalaldehyde and diethylphosphite within 30 min in 94% yield (Table 1, entry 5). This new strategy avoided the use of reaction solvent and strong acidic gas (HCl) in comparison with the described method.[18] When *m*-phthalaldehyde, 5-bromoisophthalaldehyde and 2,6-pyridinedicarboxaldehyde were used as substrates, the reactions proceeded rapidly and exothermally, accordingly, partial substrates (aldehydes) were covered by newly produced precipitate and did not convert completely, and resulted in difficulty in separation and low yields. To circumvent this drawback, dialdehyde and dialkyl phosphite were dissolved in a minimum amount of tetrahydrofuran (THF) (*ca.* 1.0 mL) prior to the addition of Et_3N. In this case, compounds **2a** and **4a** precipitated from reaction solution within 600 min at the cost of decreasing activity, but excellent yields (93% and 94%) and high purity were obtained after simple work-up (Table 1, entries 6 and 10). While compounds **2b**, **3** and **4b** did not precipitate from the reaction solution and were isolated as viscous oils in moderate to good yields (Table 1, entries 7–9 and 11).

Recently, the scientific community has sought biomass-derived molecules as alternatives for replacing building blocks arising from petrochemicals.[19] 5-Hydroxymethylfurfural (HMF), derived from the dehydration of renewable carbohydrates, is considered as one of the most promising platform chemicals.[20] As one important derivative of HMF, 2,5-furandicarbaldehyde was used as dialdehyde to react with

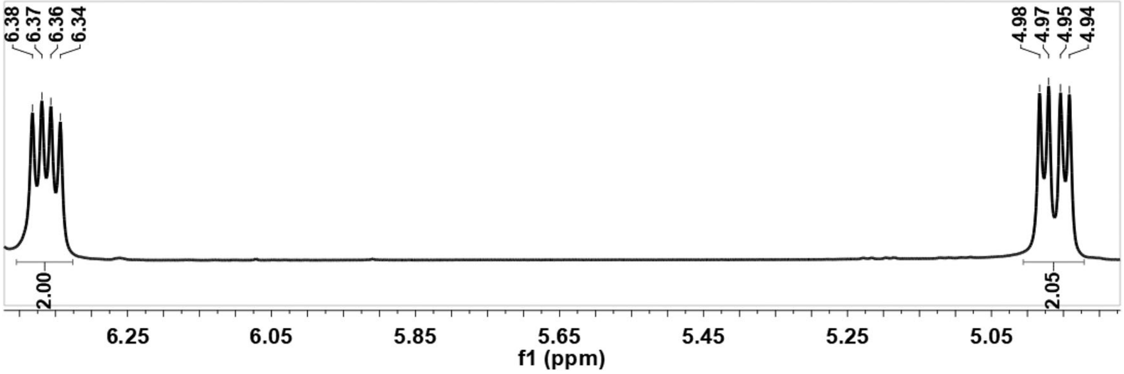


Figure 1. ^1H NMR (500 MHz, DMSO-d_6) spectrum of P–C*H*–O*H* system in **5a**.

dialkyl phosphite. Unlike *p*-phthalaldehyde, the 2,5-furandicarbaldehyde reacted with dialkyl phosphite in the presence of Et_3N under solvent-free condition afforded an orange oil, and precipitate was not observed. Recrystallization from THF/Et_2O solution produced desired biomass-based bis-α-hydroxy phosphonates as pale-yellow solid in moderate yields (Table 1, entries 12 and 13).

The addition of dialkyl phosphites to dialdehydes generated two chiral carbon atoms in the corresponding bis-α-hydroxy phosphonates, which accordingly existed in two diastereoisomers (meso- and racemic forms). The newly obtained compounds have been characterized with ^1H, ^{13}C and ^{31}P NMR spectroscopy (DMSO-d_6), and significant NMR parameters are collected in Table 2. For the known compounds such as **1a**, **1b**, **2b** and **4b**, the NMR data (Table S1, see Supplemental Materials) were consistent with those reported in the literatures.[16,18] In the ^1H NMR spectrum of **5a**, the P–C*H*–O*H* system exhibited two doublets of doublets (–C*H*: 4.96 ppm, dd, $J = 14.4$, 6.3 Hz; –O*H*: 6.36 ppm, dd, $J = 12.8$, 6.3 Hz) which resulted from the coupling of P–H and H–H (Figure 1), and in the ^{13}C NMR spectrum (Figure S20, see Supplemental Materials), the resonance of P–*C*H–OH appeared at 62.9 ppm (d, $J_{CP} = 168.6$ Hz). The ^{31}P NMR spectra, which were utilized to determine the diastereomeric purity of bis-α-hydroxy/amino phosphonates,[17,18,21] displayed two singlets or multiplets suggesting that the obtained bis-α-hydroxy phosphonates synthesized with Et_3N were mixtures of diastereoisomers, for example, the major isomer in **5b** is about 72% (Figure S24, see Supplemental Materials).

Conclusion

In summary, a simple procedure has been developed for the synthesis of bis-α-hydroxy phosphonates *via* Pudovik reaction between dialdehyde and 2.1 equivalents of dimethyl phosphite or diethyl phosphite in the presence of a catalytic amount of Et_3N at room temperature, especially the biomass-based bis-α-hydroxy phosphonates. The advantages of this method are mild conditions, high activity and operational simplicity. In the cases of *m*-phthalaldehyde, *p*-phthalaldehyde and 2,6-pyridinedicarboxaldehyde, the desired products precipitated directly from the reaction mixture with excellent yields. Exploring a more efficient approach for biomass-based bis-α-hydroxy phosphonates and application of these bis-α-hydroxy phosphonates to prepare phosphorus-containing polymers are underway in our laboratory.

Experimental section

All reactions were conducted in an argon atmosphere. HMF, *m*-phthalaldehyde, *p*-phthalaldehyde, 2,6-pyridinedicarboxaldehyde, 5-bromoisophthalaldehyde, dimethyl phosphite, diethyl phosphite and triethylamine were purchased from Energy Chemical (Shanghai) and used as received. 2,5-Furandicarbaldehyde was prepared from HMF according to the reported literature.[22] NMR (^1H, ^{13}C, ^{31}P) spectra were recorded on a Bruker Ascend 500 or 400 spectrometer at 25 °C and referenced internally to residual solvent resonances (DMSO-d_6: 2.50 ppm for ^1H NMR, 39.52 ppm for ^{13}C NMR). The Supplemental Materials contain sample ^1H, ^{13}C and ^{31}P NMR for products 1–5 (Supplemental Materials Figures S1–S24).

Synthesis of bis-α-hydroxy phosphonates

1,3-Bis[(dimethoxyphosphoryl)hydroxymethyl]benzene (**2a**): *m*-phthalaldehyde (0.134 g, 1.0 mmol) and dimethyl phosphite (0.231 g, 2.1 mmol) were dissolved in THF (*ca.* 1.0 ml), and Et_3N (5 mg, 50 μmol) was added under stirring, 10 h later, precipitate formed. Removal of solution, washing with ethyl ether, dryness under vacuo at 60 °C for 12 h gave the title compound **2a**. Yield: 0.329 g, 93%. ^1H NMR (500 MHz, DMSO-d_6), δ 7.50 (m, Ph–*H*, 1H), 7.34 (m, Ph–*H*, 3H), 6.31 (dd, $J = 15.1$, 5.4 Hz, –O*H*, 2H), 5.00 (dd, $J = 13.3$, 5.2 Hz, PC*H*, 2H), 3.62 (dd, $J = 10.3$, 1.6 Hz, –OCH_3, 12H), 3.57 ppm (dd, $J = 10.3$, 2.9 Hz, –OCH_3, 3H). HRMS (ESI): *m/z* calcd for $C_{12}H_{20}O_8P_2Na$ $[M + Na]^+$ 377.0531, found 377.0540.

1,3-Bis[(dimethoxyphosphoryl)hydroxymethyl]-5-bromobenzene (**3a**): 5-bromoisophthalaldehyde (0.213 g, 1.0 mmol) and dimethyl phosphite (0.231 g, 2.1 mmol) were dissolved in THF (*ca.* 1.0 ml), and Et_3N (5 mg, 50 μmol) was added under stirring for 2 h. Removal of solution, washing with ethyl ether, dryness under vacuo at 60 °C for 12 h gave the title compound **3a** as viscous oil. Yield: 0.355 g, 82%. ^1H NMR (400 MHz, DMSO-d_6), δ 7.51 (s, Ph–*H*, 2H), 7.48 (s, Ph–*H*, 1H), 6.50 (dd, $J = 16.9$, 5.6 Hz, –O*H*, 2H), 5.07 (dd,

$J = 13.8$, 5.5 Hz, PC*H*, 2H), 3.65–3.58 ppm (m, –OCH_3, 12H). ^{13}C NMR (125 MHz, DMSO-d$_6$), δ 140.9, 129.1, 125.2 (m), 120.9, 68.3 (d, $J_{CP} = 161.1$ Hz), 53.7 (m), 53.2 (m) ppm. ^{31}P NMR (202 MHz, DMSO-d$_6$), δ 23.19, 23.10, 22.82. HRMS (ESI): *m/z* calcd for $C_{12}H_{19}BrO_8P_2Na$ [M + Na]$^+$ 454.9636, found 454.9621.

1,3-Bis[(diethoxyphosphoryl)hydroxymethyl]-5-bromobenzene (**3b**): 5-bromoisophthalaldehyde (0.213 g, 1.0 mmol) and diethyl phosphite (0.290 g, 2.1 mmol) were dissolved in THF (*ca.* 1.0 ml), and Et_3N (5 mg, 50 μmol) was added under stirring for 2 h. Removal of solution, washing with ethyl ether, dryness under vacuo at 60 °C for 12 h gave the title compound **3 b** as viscous white solid. Yield: 0.425 g, 87%. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ 7.50 (s, Ph–*H*, 2H), 7.48 (s, Ph–*H*, 1H), 6.38 (dd, $J = 15.1$, 5.8 Hz, –O*H*, 2H), 4.97 (dd, $J = 13.9$, 5.8 Hz, PC*H*, 2H), 4.02–3.89 (m, –OCH_2, 8H), 1.20–1.15 (m, –OCH$_2$CH_3, 12H). ^{13}C NMR (125 MHz, DMSO-d$_6$), δ 140.8, 129.0, 125.2, 120.4, 68.6 (d, $J_{CP} = 161.4$ Hz), 62.4, 62.1, 16.3. ^{31}P NMR (202 MHz, DMSO-d$_6$), δ 21.00, 20.98 ppm. HRMS (ESI): *m/z* calcd for $C_{16}H_{27}BrO_8P_2Na$ [M + Na]$^+$ 511.0262, found 511.0248.

2,6-Bis[(dimethoxyphosphoryl)hydroxymethyl]pyridine (**4a**): 2,6-pyridinedicarboxaldehyde (0.135 g, 1.0 mmol) and dimethyl phosphite (0.231 g, 2.1 mmol) were dissolved in THF (*ca.* 1.0 ml), and Et_3N (5 mg, 50 μmol) was added under stirring, 10 h later, precipitate formed. Removal of solution, washing with ethyl ether, dryness under vacuo at 60 °C for 12 h gave the title compound **4a**. Yield: 0.334 g, 94%. ^{1}H NMR (500 MHz, DMSO-d$_6$), δ 7.87 (t, $J = 7.8$ Hz, Py–*H*, 1H), 7.46 (m, Py–*H*, 2H), 6.45–6.38 (m, –O*H*, 2H), 5.07–5.03 (m, PC*H*, 2H), 3.67 (dd, $J = 10.4$, 2.0 Hz, –OCH_3, 3H), 3.63–3.58 ppm (m, –OCH_3, 3H). ^{13}C NMR (125 MHz, DMSO-d$_6$), δ 156.5, 156.4, 137.2, 121.3, 121.1, 70.7 (d, $J_{CP} = 157.3$ Hz), 53.3 (m), 53.1 (m) ppm. ^{31}P NMR (202 MHz, DMSO-d$_6$), δ 22.88 ppm. HRMS (ESI): *m/z* calcd for $C_{11}H_{19}NO_8P_2Na$ [M + Na]$^+$ 378.0484, found 378.0471.

2,5-Bis[(dimethoxyphosphoryl)hydroxymethyl]furan (**5a**): To a mixture of 2,5-furandicarbaldehyde (0.124 g, 1.0 mmol) and dimethyl phosphite (0.231 g, 2.1 mmol) was added Et_3N (5 mg, 50 μmol), and the mixture was stirred for 0.5 h. The resulting orange oil was recrystallized from THF/Et_2O, and gave the title compound **5a** as pale yellow solid. Yield: 0.179 g, 52%. ^{1}H NMR (500 MHz, DMSO-d$_6$), δ 6.44 (s, furan-*H*, 2H), 6.36 (dd, $J = 12.8$, 6.3 Hz, –O*H*, 2H), 4.96 (dd, $J = 14.4$, 6.3 Hz, PC*H*, 2H), 3.70 (d, $J = 10.4$ Hz, –OCH_3, 3H), 3.62 ppm (d, $J = 10.3$ Hz, –OCH_3, 3H). ^{13}C NMR (125 MHz, DMSO-d$_6$), δ 151.1, 109.9, 62.9 (d, $J_{CP} = 168.6$ Hz), 53.4 (m), 53.0 ppm (m). ^{31}P NMR (202 MHz, DMSO-d$_6$), δ 21.67 ppm. HRMS (ESI): *m/z* calcd for $C_{10}H_{18}O_9P_2Na$ [M + Na]$^+$ 367.0324, found 367.0316.

2,5-Bis[(diethoxyphosphoryl)hydroxymethyl]furan (**5b**): To a mixture of 2,5-furandicarbaldehyde (0.124 g, 1.0 mmol) and diethyl phosphite (0.290 g, 2.1 mmol) was added Et_3N (5 mg, 50 μmol), and the mixture was stirred for 0.5 h. The resulting orange oil was recrystallized from THF/Et_2O, and gave the title compound **5b**. Yield: 0.276 g, 69%. ^{1}H NMR (500 MHz, DMSO-d$_6$), δ 6.43 (s, furan-*H*, 2H, 2H), 6.28 (dd, $J = 12.7$, 6.6 Hz, –O*H*, 2H), 4.86 (dd, $J = 14.6$, 6.6 Hz, PC*H*, 2H), 4.09–3.93 (m, –OCH_2CH$_3$, 8H), 1.20 ppm (dt, $J = 26.5$, 7.1 Hz, –OCH$_2$CH_3, 12H). ^{13}C NMR (125 MHz, DMSO-d$_6$), δ 151.3, 109.7, 63.3 (d, $J_{CP} = 169.1$ Hz), 62.4 (m), 62.2 (m), 16.4 (m) ppm. ^{31}P NMR (202 MHz, DMSO-d$_6$), δ 19.42, 18.83 ppm. HRMS (ESI): *m/z* calcd for $C_{14}H_{26}O_9P_2Na$ [M + Na]$^+$ 423.0950, found 423.0940.

Disclosure statement

No potential conflict of interest was reported by the authors.

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