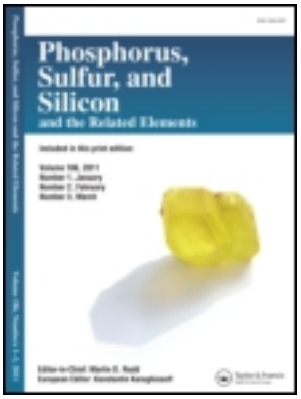

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Solvent-Free Synthesis of Tertiaryα-Hydroxyphosphates by the Triethylamine-Catalyzed Hydrophosphonylation of Ketones

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SOLVENT-FREE SYNTHESIS OF TERTIARYα-HYDROXYPHOSPHATES BY THE TRIETHYLAMINE-CATALYZED HYDROPHOSPHONYLATION OF KETONES

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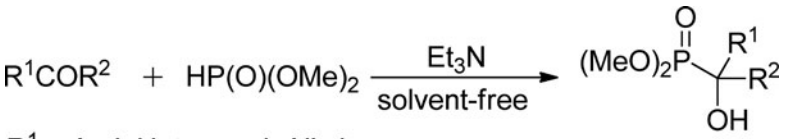
GRAPHICAL ABSTRACT



R^1 = Aryl, Heteroaryl, Alkyl
R^2 = Alkyl, Aryl

Abstract *A new, environmentally benign, convenient, and easy method of synthesizing tertiary α-hydroxyphosphonates by the triethylamine-catalyzed hydrophosphonylation of unactivated ketones was developed. In the presence of triethylamine, aromatic or heteroaromatic ketones can react with phosphite to form tertiary α-hydroxyphosphonates under solvent-free and mild conditions. The proposed method was also suitable for functionalized ketones.*

Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental files:* Additional text and figures.

Keywords Phosphite; hydrophosphonylation; ketone; solvent-free

INTRODUCTION

Hydroxyphosphonates are important compounds because of their remarkable activities.[1,2] These compounds are widely used as enzyme inhibitors,[3] antiviral agents,[4–8] antischistosomal agents,[9] and anti-HIV agents.[10] In addition, α-hydroxyphosphonates are attractive precursors in the synthesis of α-substituted phosphonates and phosphonic acids.[11,12]

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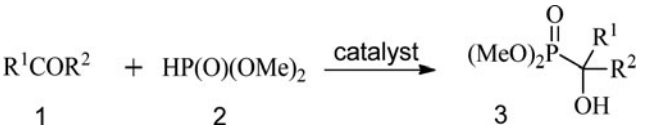
Thus, the synthesis of α-hydroxyphosphonates and their functionalized derivatives is a significant objective.[13,14]

A series of α-substituted phosphonates has been synthesized and examined for their biological activities by our group.[15] Although numerous methods of preparing α-hydroxyphosphonates are available,[16–18] the synthesis of tertiary α-hydroxyphosphonates still attracts considerable attention. The traditional synthesis of tertiary α-hydroxyphosphonates involves a reaction between phosphite and unactivated ketones in the presence of various bases. However, strong basic catalysts potentially exclude the hydrophosphonylation of base-sensitive ketones. Zhou et al.[19] used $(i\text{-PrO})_4$Ti as catalyst in the hydrophosphonylation of ketones with a broad substrate scope. Wang et al.[20,21] and Sarazin et al.[22] used metal amido complexes as catalysts for the hydrophosphonylation of unactivated ketones. Seven et al.[23] prepared tertiary hydroxyphosphonates from organoaluminum reagents and acyl phosphonates. A direct hydrophosphonylation of ketones also proceeds when pyridine 2,6-dicarboxylic acid is used as a bifunctional organocatalyst.[24] However, all existing methods have disadvantages such as environmental pollution caused by organic solvents, extreme reaction conditions, unsatisfactory yields, and complicated operations. Therefore, an efficient and convenient method of constructing this significant scaffold must be developed.

Solvent-free organic synthesis has advantages over its homogeneous counterparts because of the rising concern on the effects of organic solvents on the environment and human health, in addition to economic demands and simple processes.[25] In this article, we describe the solvent-free synthesis of tertiary α-hydroxyphosphonates by the hydrophosphonylation of unactivated ketones (see Scheme 1).



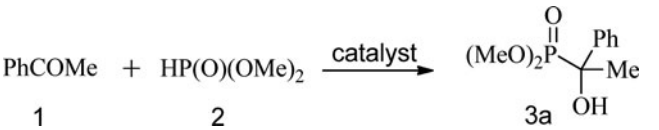
Scheme 1

RESULTS AND DISCUSSION

A preliminary survey revealed that mildly basic triethylamine was a promising catalyst for the hydrophosphonylation of acetophenone (see Table 1, entries 1–8). With 50 mol% triethylamine, the corresponding product was obtained with 35% isolated yield for 4 h without any byproduct. Pyridine was a better catalyst in terms of reactivity. Compared with triethylamine, separating pyridine from the reaction mixture was difficult. If the product contained an extremely small amount of pyridine, a foul smell was emitted. The product was washed with water several times. By contrast, the other tertiary amines gave **3a** with ≤30% yield. The commercially available triethylamine was used as the catalyst. Separating triethylamine from reaction mixtures was easy. Triethylamine was purified using a rotatory evaporator and recycled.

An intensive investigation of the reaction conditions revealed that the triethylamine concentration played a crucial role in the reaction. The results are summarized in Table 1 (entries 9–12). By increasing the triethylamine concentration, the yield improved.

Table 1 Optimization of the reaction conditions



Entry	Catalyst (mol%)	Time (h)	Yield[a] (%)
1	N,N-Dimethylaniline (50)	4	20
2	Tri-*n*-butylamine (50)	4	15
3	Triisobutyamine (50)	4	9
4	Tri-*n*-propylamine (50)	4	16
5	Triisopropylamine (50)	4	7
6	Dimethylheptylamine (50)	4	21
7	Pyridine (50)	4	29
8	Triethylamine (50)	4	35
9	Triethylamine (80)	2	81
10	Triethylamine (100)	2	93
11	Triethylamine (120)	2	93
12	Triethylamine (150)	2	93

[a]The products were purified by silica gel column chromatography (petroleum ether–ethyl acetate, 2:1, v:v).

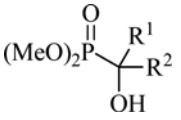
The optimal result was obtained when the model reaction was allowed to proceed at room temperature under solvent-free conditions. The reaction smoothly proceeded with 100 mol% catalyst for 2 h (see Table 1, entry 10). Increased amount of catalyst did not improve the yield. Compared with other catalysts, triethylamine had some advantages such as mild reaction conditions, few side reactions, moisture stability, low toxicity, and simple operation.

A series of ketones with different substituents on the aromatic ring was subjected to the addition reaction from ambient temperature to 40 °C for 2 h. Regardless of the electronic nature and location of substituents on the aromatic ring, the reaction of aromatic ketones showed high reactivities. The current system was extended to the hydrophosphonylation of heteroaromatic and aliphatic ketones, giving the corresponding products in good yields (see Table 2, entries 13–15). The mild alkalinity of triethylamine made it an effective catalyst for the reaction of chloroacetone, which contains a base-sensitive functional group (see Table 2, entry 16). Benzophenone exhibited reduced reactivities because of its intrinsic lower reactivity, but it was also an effective substrate for this reaction system (see Table 2, entry 17).

The corresponding products were isolated in good yields (63%–89%; see Table 2), and the structures of products **3a**–**3q** were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, MS (mass spectrum), and elemental analysis (see Supplemental Materials).

The products exhibited some characteristic peaks at $\delta = 1.24$–2.08 ppm (d or m, 3H or 2H, P−C−CH_3 or P−C−CH_2) and at $\delta = 5.3$–6.7 ppm (s or d, 1H, P−C−OH), respectively, in ^{1}H NMR. The typical carbon resonance was at about $\delta \approx 53$ ppm and $\delta = 69$–78 ppm (d or dd) in the ^{13}C NMR spectra of the products, respectively, which also confirmed the presence of a P−OMe group and a P−C bond. The typical phosphorus resonance was at $\delta = 20$–33 ppm in the ^{31}P NMR spectra of the products.

Table 2 Physical constants of compound **3**



No.	R^1	R^2	Appearance	Melting point (°C)	Yield[a] (%)
3a	Me	Ph	White solid	136.9–137.7 (lit.[23]142–143)	82
3b	Me	2-ClPh	White solid	147.3–148.8 (lit.[23]143–144)	81
3c	Me	3-ClPh	White solid	142.0–143.6 (lit.[23]136–137)	84
3d	Me	4-ClPh	White solid	149.5–151.1 (lit.[23]161–162)	86
3e	Me	3-BrPh	White solid	112.6—113.9	85
3f	Me	4-BrPh	White solid	154.2–155.8 (lit.[26]160)	84
3g	Me	2-FPh	White solid	126.1–126.8	86
3h	Me	4-FPh	White solid	129.1–130.6 (lit.[23]157–158)	87
3i	Me	2, 4-Cl_2Ph	White solid	144.2–145.5	85
3j	Me	4-MePh	White solid	138.2–139.7 (lit.[23]156–157)	84
3k	Me	4-MeOPh	White solid	161.6–162.7 (lit.[23]172–173)	76
3l	*n*-Pr	Ph	White solid	113.2–114.6 (lit.[27]127.5–128)	78
3m	Me	2-Furyl	Off-white solid	74.4–75.7	74
3n	Me	2-Thienyl	Off-white solid	78.6–80.1	75
3o	Me	Me	White solid	68.6–70.2 (lit.[28]72)	88
3p	Me	$ClCH_2$	White solid	72.5–73.8 (lit.[29]73–74)	89
3q	Ph	Ph	White solid	149.1–150.6 (lit.[28,30]171)	63[b]

[a]Isolated yield.
[b]Reaction time was 12 h.

CONCLUSION

In summary, an easy, solvent-free approach to the synthesis of tertiary α-hydroxyphosphonates using triethylamine as a catalyst was developed. The mild base catalyst was applied to the hydrophosphonylation of different ketones including benzophenone, giving the corresponding quaternary α-hydroxyphosphonates in satisfactory yields. The proposed method was suitable for functionalized ketones and can be a valuable addition to the existing methods of preparing tertiary α-hydroxyphosphonates.

EXPERIMENTAL

Column chromatography was carried out with Merck silica gel (230–400 mesh). Thin-layer chromatography was performed on silica gel GF-254. Melting points were measured on a WRS-1B electrothermal melting point apparatus and uncorrected. IR spectra were recorded in potassium bromide disks using an AVATAR360 FTIR spectrophotometer. Only the most significant absorption bands were recorded. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 600 MHz spectrophotometer. ^{31}P NMR spectra were recorded on a 400 MHz spectrophotometer using phosphoric acid (85 wt% H_3PO_4) as an internal standard. Chemical shifts (δ) are given in parts per million, and coupling constants (J) are given in hertz. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). MS was performed on a Finnigan TRACE spectrometer and API2000LC/MS. Elemental analyses (C, H, and N) were analyzed on a Vario EL III CHNSO elemental analyzer. The results were within $\pm$ 0.5% of the theoretical values.

General Procedure for the Synthesis of Compounds 3a–3q

A mixture of substituted ketones **1** (11 mmol), phosphite **2** (10 mmol), and triethylamine (10 mmol) were stirred from ambient temperature to 40 °C for 2 h. The crude product was collected by filtration and recrystallized from ethyl acetate to afford pure α-hydroxyphosphonates **3**.

Selected Spectroscopic Data of New Compounds

Dimethyl (1-(3-bromophenyl)-1-hydroxyethyl)phosphonate (3e): ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ 7.70 (s, 1H, Ar–*H*), 7.51 (d, 1H, $J = 7.8$ Hz, Ar–*H*), 7.47 (d, 1H, $J = 7.8$ Hz, Ar–*H*), 7.31 (d, 1H, $J = 7.8$ Hz, Ar–*H*), 6.22 (d, 1H, $J = 10.8$ Hz, P–O*H*), 3.54–3.66 (m, 6H, 2×O–CH_3), 1.66 (d, 3H, $J = 15.6$ Hz, P–C–CH_3); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): δ 145.5, 129.8, 128.8, 128.7, 125.2, 121.2, 73.2, 72.6 (d, $J = 172.8$ Hz), 53.6, 25.4; ^{31}P NMR (160 MHz, DMSO-d_6, ppm): δ 26.3; MS (m/z,%): 308 (M^+ 6.21), 310 (6.12), 199 (10.21), 183 (100), 126 (51.37), 109 (53.21); IR (KBr): 3436, 2956, 1458, 1231, 1068, 783 cm^{-1}; Calcd. for $C_{10}H_{14}BrO_4P$: C 38.86, H 4.57; Found: C 38.64, H 4.67.

Dimethyl (1-(2,4-dichlorophenyl)-1-hydroxyethyl)phosphonate (3i): ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ 7.85 (d, 1H, $J = 9.0$ Hz, Ar–*H*), 7.51 (d, 1H, $J = 13.2$ Hz, Ar–*H*), 7.44 (d, 1H, $J = 8.4$ Hz, Ar–*H*), 6.32 (d, 1H, $J = 12$ Hz, P–O*H*), 3.60–3.67 (m, 6H, 2×O–CH_3), 1.90 (d, 3H, $J = 15$ Hz, P–C–CH_3); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): δ 138.7, 132.6, 132.2, 131.6, 130.4, 126.6, 73.8 (d, $J = 176.3$ Hz), 53.5, 24.5; ^{31}P NMR (160 MHz, DMSO-d_6, ppm): δ 24.9; MS (m/z,%): 298 (M^+ 7.31), 300 (4.42), 190 (15.26), 175 (63.84), 173 (100), 126 (56.41), 109 (41.78); IR (KBr): 3445, 2954, 1465, 1223, 1070, 861, 798 cm^{-1}; Calcd. for $C_{10}H_{13}Cl_2O_4P$: C 40.16, H 4.38; Found: C 40.28, H 4.52.

Dimethyl (1-hydroxy-1-phenylbutyl)phosphonate (3l): ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ 7.50 (d, 2H, $J = 7.8$ Hz, Ar–*H*), 7.33 (m, 2H, Ar–*H*), 7.24 (m, 1H, Ar–*H*), 5.81 (d, 1H, $J = 5.4$ Hz, P–O*H*), 3.43–3.65 (m, 6H, 2×O–CH_3), 2.07 (m, 1H, PhCCH_2CH$_2$CH$_3$), 1.99 (m, 1H, PhCCH_2CH$_2$CH$_3$), 1.30 (m, 1H, PhCCH$_2$CH_2CH$_3$), 0.78 (m, 4H, PhCCH$_2$CH_2CH$_3$, PhCCH$_2$CH$_2$CH_3); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): δ 140.1, 127.6, 126.6, 126.2, 76.3, 75.8 (d, $J = 168.8$ Hz), 53.4 (d, $J = 8.0$ Hz), 53.3 (d, $J = 8.2$ Hz), 14.9, 14.8, 14.0; ^{31}P NMR (160 MHz, DMSO-d_6, ppm): δ 26.2; MS (m/z,%): 258 (M^+ 25.71), 149 (10.52), 133 (100), 126 (37.41), 109 (46.83); IR (KBr): 3411, 2961, 1450, 1227, 1066, 776 cm^{-1}; Calcd. for $C_{12}H_{19}O_4P$: C 55.81, H 7.42; Found: C 55.73, H 7.61.

Dimethyl (1-(furan-2-yl)-1-hydroxyethyl)phosphonate (3m): ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ 7.63 (s, 1H, 5-Furyl–*H*), 6.43 (m, 1H, 4-Furyl–*H*), 6.41 (m, 1H, 3-Furyl–*H*), 6.11 (d, 1H, $J = 12$ Hz, P–O*H*), 3.60–3.65 (m, 6H, 2×O–CH_3), 1.61 (d, 3H, $J = 15.0$ Hz, P–C–CH_3); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): δ 154.5, 142.4 (d, $J = 15.0$ Hz), 110.4, 107.3, 69.1 (d, $J = 179.5$ Hz), 53.3, 22.7; ^{31}P NMR (160 MHz, DMSO-d_6, ppm): δ 24.7; MS (m/z,%): 220 (M^+ 17.68), 111 (9.36), 109 (37.54), 93 (100); IR (KBr): 3414, 2958, 1456, 1225, 1157, 1049, 841 cm^{-1}; Calcd. for $C_8H_{13}O_5P$: C 43.64, H 5.95; Found: C 43.53, H 6.11.

SUPPLEMENTAL MATERIALS

Data for products **3a–3q** are available. Supplemental Materials associated with this article can be found in the online version.

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