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A Rapid, Convenient, Solventless Green Approach for the Synthesis of α-Hydroxyphosphonates by Grinding

DU-LIN KONG[1], REN-DIE LIU[2], GUO-ZHU LI[2], PENG-WEI ZHANG[1,*] and MING-SHU WU[2,*]

[1]School of Pharmaceutical Sciences, Hainan Medical University, Haikou 571199, Hainan Province, P.R. China
[2]College of Chemistry and Chemical Engineering, Hainan Normal University, Haikou 571158, Hainan Province, P.R. China

*Corresponding authors: Tel/Fax: +86 898 66893826, E-mail: zpw0803@163.com; wumingshu@126.com; 173548977@qq.com

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An efficient and convenient approach to the condensation reaction of aromatic aldehydes and diethyl phosphite using Na_2CO_3 as catalyst with grinding at room temperature (without any solvent) is described. This method provides several advantages such as neutral condition, simple work-up procedure, high yields and reduced environmental impact.

Keywords: α-Hydroxyphosphonate, Synthesis, Grinding.

INTRODUCTION

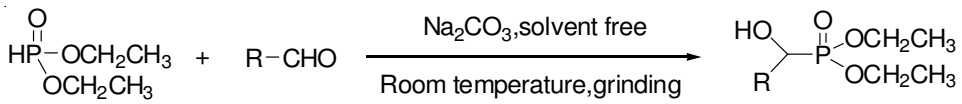
α-Hydroxyphosphonate derivatives are important organophosphorus compounds associated with a wide variety of biological and pharmaceutical activities[1]. These derivatives are extensively used as synthetic intermediates[2] with iterative manipulation of functional groups to α-ketophosphonates[3] and 1,2-diketones[4]. The hydrolyzed products of α-hydroxyphosphonates exhibit a wide range of medicinal properties such as antibacterial[5], antiviral[6] and anticancer activities[7]. A large number of methodologies for the synthesis of various α-hydroxyphosphonates compounds have been extensively developed under various conditions. Recently, the synthesis of α-hydroxyphosphonates with aldehydes and dialkyl (or) trialkyl phosphates using Lewis acids and bases catalysts such as MgO[8], NH_4VO_3[9], alumina[10], quinine[11], lithium diisopropylamine (LDA)[12], $Ti(OPri)_2$[13], $LiClO_4.Et_2O$, TMSCl[14], The majority of these processes suffer some drawbacks such as long reaction times, low yields of the products, requiring a stoichiometric amount of catalysts, costly metal ion and the use of highly toxic catalysts. Therefore, it is still required to develop a more efficient method particularly considering today's environmental concerns combined with economic aspects.

The grinding method is used more and more frequently in organic synthesis[15]. Compared with traditional methods, proposed method is more convenient and easily controlled. A great number of organic reactions can be carried out in higher yields, shorter times or milder conditions by the grinding method. It can even set off some reactions that cannot be carried out under traditional conditions. Herein we reported a simple procedure for the preparation of α-hydroxyphosphonates catalyzed by Na_2CO_3 under grinding at room temperature. (**Scheme-I**).

EXPERIMENTAL

Melting points were uncorrected. Liquid aldehydes were distillated before use. NMR spectra were measured on Bruker Avance 400 (400MHz) spectrometer using TMS as internal reference and $CDCl_3$ as solvent. IR spectra were determined as KBr pellets on Avatar 360 FT-IR spectrophotometer. Elemental analysis was carried out with a Yanaco Chncorder MT-3 analyzer.

General procedure: To 3 mmol of aldehyde, 3 mmol of diethylphosphite and anhydrous sodium carbonate (3 mmol) were added and grinded at room temperature for 10 min. After completion of the reaction, as indicated by thin-layer chromatography the reaction mixture was washed with water (15 mL) then the compounds were extracted with ethyl acetate. The organic layer were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crystallization from acetone-pentane



Scheme-I

afforded products **a-f** white crystals (except for **d** and **f** which were orange crystals; Table-2).

Diethyl (hydroxyl)(phenyl)methylphosphonate (a): white crystals, Yield: 82 %, m.p. 83-85 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.18 (m, 5H), 5.25 (s, 1H), 4.64 (d, $^2J_{P-H}$ = 10.7 Hz, 1H), 4.00-3.90 (m, 4H), 1.26-1.17 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.5 (d, $^2J_{P-C}$ = 3.0 Hz), 134.0, 128.8, 127.1, 70.3 (d, $^1J_{P-C}$ = 157.0 Hz), 62.9 (d, $^2J_{P-C}$ = 7.1 Hz), 16.0 (d, $^3J_{P-C}$ = 6.0 Hz); IR (KBr, ν_{max}, cm^{-1}): 3264 (brs, OH), 1228 (P=O); Anal. calcd. for $C_{11}H_{17}O_4P$: C, 54.10; H, 7.02; Found: C, 53.95; H, 6.90.

Diethyl (hydroxy)(*p*-tolyl)methylphosphonate (b): white crystals, Yield: 76 %, m.p. 98-100 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.00 (m, 4H), 5.26 (s, 1H), 4.58 (d, $^2J_{P-H}$ = 10.1 Hz, 1H), 4.21-4.02 (m, 4H), 2.32 (s, 3H), 1.27-1.19 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.4, 137.1, 122.2, 121.4, 69.1 (d, $^1J_{P-C}$ = 150.0 Hz), 62.6 (d, $^2J_{P-C}$ = 6.0 Hz), 61.3 (d, $^2J_{P-C}$ = 6.0 Hz), 21.3, 16.0 (d, $^3J_{P-C}$ = 5.8 Hz), 15.4 (d, $^3J_{P-C}$ = 5.8 Hz); IR (KBr, ν_{max}, cm^{-1}): 3264 (brs, OH), 1233 (P=O); Anal. calcd. for $C_{12}H_{19}O_4P$: C, 55.81; H, 7.42; Found: C, 55.77; H, 7.37.

Diethyl (hydroxy)(4-methoxyphenyl)methylphosphonate (c): white crystals, Yield: 75 %, m.p. 119-121 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.01 (m, 4H), 5.19 (s, 1H), 4.63 (d, $^2J_{P-H}$ = 10.4 Hz, 1H), 4.20-4.02 (m, 4H), 3.87 (s, 3H) 1.28-1.19 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.4, 137.3, 122.1, 121.3, 69.4 (d, $^1J_{P-C}$ = 149.0 Hz), 62.4 (d, $^2J_{P-C}$ = 6.1 Hz), 62.1 (d, $^2J_{P-C}$ = 6.1 Hz), 57.3, 16.0 (d, $^3J_{P-C}$ = 6.1 Hz), 15.7 (d, $^3J_{P-C}$ = 5.9 Hz); IR (KBr, ν_{max}, cm^{-1}): 3263 (brs, OH), 1229 (P=O); Anal. calcd. for $C_{12}H_{19}O_5P$: C, 52.55; H, 6.98; Found: C, 52.45; H, 6.92.

Diethyl (hydroxy)(3-nitrophenyl)methylphosphonate (d): orange crystals, Yield: 85 %, m.p. 83-84 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (quasi d, *J* = 8.2 Hz, 2H), 7.49 (quasi d, *J* = 8.2 Hz, 2H), 5.26 (s, 1H), 4.97 (d, $^2J_{P-H}$ = 10.6 Hz, 1H), 4.38-4.26 (m, 4H), 1.41-1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3, 148.9, 129.7, 128.1, 127.7, 126.3, 70.5 (d, $^1J_{P-C}$ = 153.0 Hz), 64.7 (d, $^2J_{P-C}$ = 6.7 Hz), 63.4 (d, $^2J_{P-C}$ = 6.7 Hz), 16.5 (d, $^3J_{P-C}$ = 6.0 Hz), 16.2 (d, $^3J_{P-C}$ = 6.0 Hz); IR (KBr, ν_{max}, cm^{-1}): 3245 (brs, OH), 1210 (P=O); Anal. calcd. for $C_{11}H_{16}NO_6P$: C, 45.68; H, 5.58; N, 4.84; Found: C, 45.56; H, 5.55; N, 4.83.

Diethyl (4-chlorophenyl)(hydroxy)methylphosphonate (e): white crystals, Yield: 78 %, m.p. 71-73 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.23 (m, 4H), 5.15 (s, 1H), 4.79 (d, $^2J_{P-H}$ = 10.9 Hz, 1H), 4.26-3.99 (m, 4H), 1.35-1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.4, 140.3, 129.1, 128.1, 72.4 (d, $^1J_{P-C}$ = 159.0 Hz), 63.79 (d, $^2J_{P-C}$ = 6.8 Hz), 16.9 (d, $^3J_{P-C}$ = 5.8 Hz), 16.4 (d, $^3J_{P-C}$ = 5.8 Hz); IR (KBr, ν_{max}, cm^{-1}): 3215 (brs, OH), 1236 (P=O); Anal. calcd. for $C_{11}H_{16}O_4PCl$: C, 47.41; H, 5.79; Found: C, 47.40; H, 5.66.

Diethyl (hydroxy)(4-nitrophenyl)methylphosphonate (f): orange crystals, Yield: 83 %, m.p. 83-85 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 5.28 (s, 1H), 4.99(d, $^2J_{P-H}$ = 10.6 Hz, 1H), 4.39-4.25 (m, 4H), 1.40-1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4, 148.8, 128.2, 127.9, 70.8 (d, $^1J_{P-C}$ = 153.0 Hz), 64.9 (d, $^2J_{P-C}$ = 6.7 Hz), 63.5 (d, $^2J_{P-C}$ = 6.7 Hz), 16.9 (d, $^3J_{P-C}$ = 6.0 Hz), 16.5 (d, $^3J_{P-C}$ = 6.0 Hz); IR (KBr, ν_{max}, cm^{-1}): 3240 (brs, OH), 1210 (P=O); Anal. calcd. for $C_{11}H_{16}NO_6P$: C, 45.68; H, 5.58; N, 4.84; Found: C, 45.57; H, 5.57; N, 4.81.

RESULTS AND DISCUSSION

The reaction was optimized using C_6H_5CHO (3 mmol) as the substrate. Different parameters such as the molar ratio of C_6H_5CHO/diethyl phosphite /Na_2CO_3 and reaction time were studied (Table-1). When the molar ratio of $C_6H_5CHO/C_4H_{11}PO_3/Na_2CO_3$ was 1:1:0.5, the yield of oxime was 70 %. Increasing the molar rate to 1:1:1. the yield increase to 82 %. When the molar ratio increased to 1:1:1.5, the yield increase to 83 %. Further increasing the molar ratio, the yield did not increased. When increased the amount of diethyl phosphite to 1:1.2:1, 1:1.4:1, the yield of the α-hydroxyphosphonates was 78 and 81 %, respectively. It seemed that the excess of diethyl phosphite had no pronounced effect to the reaction.

TABLE-1
EFFECT OF THE REACTION CONDITIONS OF α-HYDROXYPHOSPHONATES UNDER GRINDING

Entry	Molar ratio of C_6H_5CHO /diethyl phosphite /Na_2CO_3	Grinding Time (min)	Yield (%)
1	1:1:0.5	12	70
2	1:1:1	10	82
3	1:1:1.5	10	83
4	1:1:2	10	82
5	1:1.2:1	14	78
6	1:1.4:1	14	81
7	1:1:0	a night	0

In the absence of Na_2CO_3, the mixture was ground for 10 min and kept for a night, the yield of the corresponding α-hydroxyphosphonates was 0 %. While in the presence of Na_2CO_3, the yield of the α-hydroxyphosphonates was 82 %. It indicated that Na_2CO_3 was necessary to the reaction.

On the basis of these results, the optimized reaction conditions we chose were: aldehyde (3 mmol), diethyl phosphite (3 mmol) and Na_2CO_3 (3 mmol). Using this reaction system, we performed a series of experiments for α-hydroxyphosphonates of aldehydes by grinding. The results were summarized in Table-2.

TABLE-2
SYNTHESIS OF α -HYDROXYPHOSPHONATES IN GRINDING METHOD

Enty	R	m.p. (°C)	Colour	Yield (%)
a	Ph	83-85	White crystals	82
b	*p*-CH_3Ph	98-100	White crystals	76
c	*p*-CH_3OPh	119-121	White crystals	75
d	*m*-NO_2Ph	83-84	Orange crystals	85
e	*p*-ClPh	71-73	White crystals	78
f	*p*-NO_2Ph	83-85	Orange crystals	83

As shown in Table-2, some aldehydes *via* condensation can give α-hydroxyphosphonates in good yields in free solvent under grinding. Substitution on aromatic aldehyde played a crucial role in governing the product yield as it can be seen from the Table-2. Electron-withdrawing group on benzaldehyde gave a good yield (Table-2, entry **d**), whereas electron-donating group on benzaldehyde gave a lower yield (Table-1, entry **b**) in comparison with benzaldehyde.

Conclusion

In conclusion, a general and highly efficient procedure for the preparation of α-hydroxyphosphonates catalyzed by Na_2CO_3 with grinding method is described. In addition, the procedure offers several advantages including high yields, cleaner reactions, operational simplicity, minimal environmental impact which makes it a useful and attractive process for the synthesis of these compounds. Moreover, it is possible to apply the tenets of green chemistry to the generation of biologically interesting products with grinding method which are less expensive and less toxic than those with organic solvents.

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