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Preparation of α-ketophosphonates by oxidation of α-hydroxyphosphonates with neutral alumina supported potassium permanganate (NASPP) under solvent-free conditions and potassium permanganate in dry benzene

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Abstract—Various types of α-hydroxyphosphonates were converted to α-ketophosphonates in high yields by potassium permanganate in dry benzene or by neutral alumina supported potassium permanganate (NASPP) under solvent-free conditions.

In the realm of organophosphorus chemistry, phosphonates are interesting complements to phosphates in terms of biological activity and have been well documented in the literature.[1] Within this class of compounds there exists an important subdivision, the α-ketophosphonates. The adjacent phosphorus substituents and carbonyl functional groups in α-ketophosphonates is the main reason that makes them interesting compounds in organic synthesis.[2] The chemical properties of α-ketophosphonates are mainly determined by the phosphorus substituents, but in general are a hybrid between ketones and secondary amides.[3] For instance, it is possible to derive hydrazones,[4] imines[5] and oximes[6] from the carbonyl function; to reduce α-ketophosphonates to the corresponding α-hydroxyphosphonates,[7] or use them in Wittig reactions.[8] The C(O)–P bonds in these compounds are known to be sensitive towards hydrolysis and acidic conditions.[9] Therefore, handling α-ketophosphonates is not so easy and requires special precautions.[9] The Michael–Arbuzov reaction is a general method for the preparation of α-ketophosphonates from acyl chlorides and trialkylphosphites, this method works well for the less complex acyl chlorides.[10] Oxidation of α-hydroxyphosphonates[11] is another method for the preparation of α-ketophosphonates. A literature survey showed that reports of the oxidation of α-hydroxyphosphonates are rare, and most of them suffer from using toxic reagents or low yields of the products.[12] Recently, we have reported a new method for the oxidation of α-hydroxyphosphonates to α-ketophosphonates by zinc dichromate trihydrate ($ZnCr_2O_7{\cdot}3H_2O$) under solvent-free conditions.[13] Avoiding toxicity in using zinc dichromate trihydrate, we decided to apply an inexpensive and environmentally friendly oxidant, potassium permanganate ($KMnO_4$) for the oxidation of α-ketophosphonates with or without solvents. In order to optimize the reaction conditions, we first studied the oxidation reaction of diethyl α-hydroxy-(phenylmethyl) phosphonate to diethyl α-keto-(phenylmethyl) phosphonate in different dry solvents (Table 1).

The reactions in dry benzene were found to be cleaner and also faster with higher yields in comparison with the other solvents. Therefore, the oxidation of different α-hydroxyphosphonates (**1b–o**) were performed in dry benzene, at room temperature, in this study (Schemes 1 and 2, Table 2, method A). [14] This heterogeneous system offers an easy work up that includes only a

Table 1. Oxidation of diethyl α-hydroxy-(phenylmethyl) phosphonate to diethyl α-keto-(phenylmethyl) phosphonate by $KMnO_4$ in various dry solvents

Solvent	Time (h)	Conversion[a] (%)
Acetonitrile	6	25
Dichloromethane	5	10
Diethyl ether	7	5
Benzene	4	100

[a] $KMnO_4$/substrate = 2:1; room temperature.

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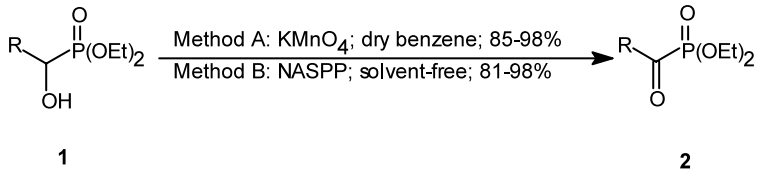
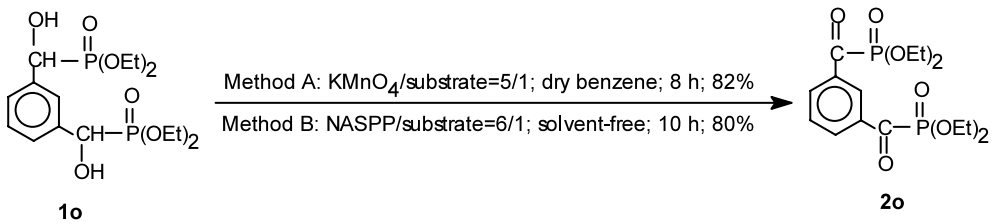


Scheme 1.



Scheme 2.

Table 2. Oxidation of α-hydroxyphosphonates to α-ketophosphonates by $KMnO_4$ in dry benzene (method A), and by neutral Al_2O_3 supported $KMnO_4$ (NASPP) under solvent-free conditions (method B)

Product **2**	R-	$KMnO_4$/benzene (Method A)			$KMnO_4/Al_2O_3$ (Method B)		
		Substrate/oxidant	Time (h)	Yield[a] (%)	Substrate/oxidant	Time (h)	Yield[a] (%)
a	C_6H_5-	1:2	4	98	1:3	6	91
b	4-$CH_3C_6H_4$-	1:2	3.25	97	1:3	5	93
c	4-$CH_3OC_6H_4$-	1:2	6	86	1:3	8	85
d	2,4,6-$(CH_3)_3C_6H_2$-	1:4	7	93	1:3	10	92
e	2-ClC_6H_4-	1:3	3.5	90	1:4	7	84
f	3-ClC_6H_4-	1:4	8	92	1:4	10	81
g	4-ClC_6H_4-	1:2	7	95	1:3	6	96
h	2,6-$Cl_2C_6H_3$-	1:2	3	98	1:2	4	98
i	2-$O_2NC_6H_4$-	1:6	5	93	1:5	15	91
j	3-$O_2NC_6H_4$-	1:4	12	95	1:5	15	92
k	4-$O_2NC_6H_4$-	1:6	12	95	1:6	14	95
l	2-Naphthyl	1:4	10	95	1:4	12	92
m	$C_6H_5CH(CH_3)$-	1:4	9	85	1:5	11	82
n	3-Pyridyl	1:2	5	93	1:3	7	90

[a] Isolated yields; room temperature; ^1H NMR, ^{13}C NMR, IR, MS spectral data are given.[18]

simple filtration to remove the solid material and evaporation of the solvent.

In recent years, solvent-free reactions have received more attention in comparison with their homogeneous counterparts, due to economical and environmental demands and simplicity in processes.[15] Now we report a high yield preparation of α-ketophosphonates by the oxidation of α-hydroxyphosphonates with $KMnO_4$ under solvent-free conditions. We found that $KMnO_4$ with the substrates produced a sticky material and only a minor amount of the substrates were converted to their corresponding α-ketophosphonates. In order to have convenient product isolation and a better reactivity we used neutral alumina supported potassium permanganate[16] (NASPP) with success for this purpose. The work up of the reaction mixtures was clean and not a time-consuming process and the yields of the products were from good to excellent (Schemes 1 and 2, Table 2, method B).[17]

As shown in Table 2, various (α-hydroxyphenylmethyl) phosphonates (**1a–k**) were cleanly converted into the corresponding α-ketophosphonates (**2a–k**) in excellent yields (86–98% by method A, 81–98% by method B). α-Hydroxy-2-naphthyl, an alkyl and 3-pyridyl phosphonate (**1l–n**) were also oxidized efficiently to their corresponding α-ketophosphonates (**2l–n**) in 85–95% yields by method A and in 82–92% yields by method B.

The two hydroxyl groups in (α-hydroxyphenylmethyl)phosphonate **1o** were converted to the corresponding carbonyl groups in 82% yield by method A and in 80% yield by method B (Scheme 2).

In summary, we have presented a non-toxic, inexpensive and environmentally friendly oxidant for the oxidation of sensitive α-hydroxyphosphonates to α-ketophosphonates under mild reaction conditions. The easy work-up, high yields, and also the ability to use the oxidant in solution and also under solvent-free

conditions are worthy of mention for the presented method.

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14. *Typical procedure for the preparation of α-ketophosphonates from α-hydroxyphosphonates with $KMnO_4$ under heterogeneous conditions (method A)*:
A solution of the α-hydroxyphosphonate 1 (5 mmol) in dry benzene (50 ml) was prepared. Powdered potassium permanganate (0.316–0.948 g, 2–6 mmol) was added and the resulting mixture was stirred at room temperature (3.25–12 h). Then, the reaction mixture was filtered and the solvent was evaporated to give the crude product. The pure product was obtained (82–98% yields) by bulb to bulb vacuum distillation.
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17. *Typical procedure for the preparation of α-ketophosphonates from α-hydroxyphosphonates with NASPP under solvent-free conditions (method B)*:
NASPP was prepared according to the literature.[16] A mixture of the α-hydroxyphosphonate **1** (5 mmol) and NASPP (0.66–1.99 g, 2–6 mmol $KMnO_4$) was stirred vigorously (4–15 h). The reaction mixture was then washed with CH_2Cl_2 (4×10 ml) and dried over Na_2SO_4. The solvent was evaporated to give the desired crude product. The pure product was obtained in 80–98% yields by bulb to bulb vacuum distillation.
18. Spectral data of some α-ketophosphonates: **2a** [^{1}H NMR ($CDCl_3$, TMS): δ 1.37–1.68 (t, 6H, $^2J_{HH}=7$ Hz, 2-$OCH_2C\underline{H}_3$), 4.08–4.28 (dq, 4H, $^2J_{PH}=7.1$ Hz, $^2J_{HH}=7$ Hz, 2-$OC\underline{H}_2CH_3$), 7.28–7.6 (m, 3H), 8.03–8.25 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 16.64 (d, $^3J_{CP}=5.7$ Hz, 2-$OCH_2\underline{C}H_3$), 64.31 (d, $^2J_{CP}=7.5$ Hz, 2-$O\underline{C}H_2CH_3$), 129.15, 130.06, 135.03, 136.29 (-C_6H_5), 199.12 (d, $^1J_{CP}=$ 177.5 Hz, C=O) ppm; IR (neat): ν 1660 (C=O), 1250 (P=O) cm^{-1}; MS: M$^+$ (242)]. **2b** [^{1}H NMR ($CDCl_3$, TMS): δ 1.29–1.42 (t, 6H, $^2J_{HH}=7$ Hz, 2-$OCH_2C\underline{H}_3$), 2.35 (s, 3H, -CH_3), 4.11–4.16 (dq, 4H, $^2J_{PH}=7.1$ Hz, $^2J_{HH}=7$ Hz, 2-$OC\underline{H}_2CH_3$), 7.12–7.21 (m, 2H), 8.04–8.07 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 16.67 (d, $^3J_{CP}=5.7$ Hz, 2-$OCH_2\underline{C}H_3$), 22.18 (-CH_3), 64.24 (d, $^2J_{CP}=7.5$ Hz, 2-$O\underline{C}H_2CH_3$), 127.35, 129.89, 130.31, 146.41 (-C_6H_4), 198.46 (d, $^1J_{CP}=176.6$ Hz, C=O) ppm; IR (neat): ν 1650 (C=O), 1260 (P=O) cm^{-1}; MS: M$^+$ (256)]. **2c** [^{1}H NMR ($CDCl_3$, TMS): δ 1.11–1.29 (t, 6H, $^2J_{HH}=7$ Hz, 2-$OCH_2C\underline{H}_3$), 3.80 (s, 3H, -CH_3), 3.90–4.10 (dq, 4H, $^2J_{PH}=7.1$ Hz, $^2J_{HH}=7$ Hz, 2-$OC\underline{H}_2CH_3$), 6.84–6.90 (m, 2H), 7.42–7.50 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 16.75 (d, $^3J_{CP}=5.7$ Hz, 2-$OCH_2\underline{C}H_3$), 55.59 (-CH_3), 63.46 (d, $^2J_{CP}=7.5$ Hz, 2-$O\underline{C}H_2CH_3$), 114.03, 128.82, 129.21, 159.78 (-C_6H_4), 198.01 (d, $^1J_{CP}=176.2$ Hz, C=O) ppm; IR (neat): ν 1650 (C=O), 1265 (P=O) cm^{-1}; MS: M$^+$ (272)]. **2d** [^{1}H NMR ($CDCl_3$, TMS): δ 1.25–1.32 (t, 6H, $^2J_{HH}=7$ Hz, 2-$OCH_2C\underline{H}_3$), 2.23 (s, 6H, 2,6-diCH_3), 2.27 (s, 3H, 4-CH_3), 4.06–4.17 (dq, 4H, $^2J_{PH}=7.1$ Hz, $^2J_{HH}=7$ Hz, 2-$OC\underline{H}_2CH_3$), 6.83 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 16.81 (d, $^3J_{CP}=5.7$ Hz, 2-$OCH_2\underline{C}H_3$), 21.17 (2,6-diCH_3), 21.38 (4-CH_3), 63.12 (d, $^2J_{CP}=7.5$ Hz, 2-$O\underline{C}H_2CH_3$), 129.74, 130.3, 137.69, 137.75 (-C_6H_2), 199.01 (d, $^1J_{CP}=177.0$ Hz, C=O) ppm; IR (neat): ν 1660 (C=O),

1250 (P=O) cm^{-1}; MS: M^+ (284)]. **2g** [^{1}H NMR ($CDCl_3$, TMS): δ 1.13–1.42 (t, 6H, $^2J_{HH}=7$ Hz, 2-$OCH_2C\underline{H}_3$), 4.15–4.33 (dq, 4H, $^2J_{PH}=7.1$ Hz, $^2J_{HH}=7$ Hz, 2-$OC\underline{H}_2CH_3$), 7.47–7.50 (m, 2H), 8.21–8.24 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 16.75 (d, $^3J_{CP}=5.7$ Hz, 2-$OCH_2\underline{C}H_3$), 64.49 (d, $^2J_{CP}=7.5$ Hz, 2-$O\underline{C}H_2CH_3$), 129.62, 131.58, 133.72, 141.85 (-C_6H_4), 198.09 (d, $^1J_{CP}=$ 180.0 Hz, C=O) ppm; IR (neat): ν 1660 (C=O), 1260 (P=O) cm^{-1}; MS: M^+ (277), M^++2 (279)]. **2h** [^{1}H NMR ($CDCl_3$, TMS): δ 1.04–1.24 (t, 6H, $^2J_{HH}=7$ Hz, 2-$OCH_2C\underline{H}_3$), 3.95–4.23 (dq, 4H, $^2J_{PH}=7.1$ Hz, $^2J_{HH}=7$ Hz, 2-$OC\underline{H}_2CH_3$), 6.90–7.09 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 16.61 (d, $^3J_{CP}=5.7$ Hz, 2-$OCH_2\underline{C}H_3$), 64.85 (d, $^2J_{CP}=7.5$ Hz, 2-$O\underline{C}H_2CH_3$), 128.06, 128.56, 131.51, 132.07 (-C_6H_3), 204.36 (d, $^1J_{CP}=195.5$ Hz, C=O) ppm; IR (neat): ν 1690 (C=O), 1260 (P=O) cm^{-1}]. **2i** [^{1}H NMR ($CDCl_3$, TMS): δ 1.19–1.27 (t, 6H, $^2J_{HH}=7$ Hz, 2-$OCH_2C\underline{H}_3$), 4.08–4.18 (dq, 4H, $^2J_{PH}=7.1$ Hz, $^2J_{HH}=7$ Hz, 2-$OC\underline{H}_2CH_3$), 7.42–7.47 (m, 1H), 7.64–7.70 (m, 1H), 7.94–8.01 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 16.65 (d, $^3J_{CP}=5.7$ Hz, 2-$OCH_2\underline{C}H_3$), 65.90 (d, $^2J_{CP}=7.5$ Hz, 2-$O\underline{C}H_2CH_3$), 130.62, 131.48, 133.62, 141.50 (-C_6H_4), 197.19 (d, $^1J_{CP}=179.0$ Hz, C=O) ppm; IR (neat): ν 1650 (C=O), 1250 (P=O) cm^{-1}; MS: M^+ (287)]. **2n** [^{1}H NMR ($CDCl_3$, TMS): δ 1.30 (t, 6H, $^2J_{HH}=7$ Hz, 2-$OCH_2C\underline{H}_3$), 4.14 (dq, 4H, $^2J_{PH}=7.1$ Hz, $^2J_{HH}=7$ Hz, 2-$OC\underline{H}_2CH_3$), 7.38–7.43 (m, 1H), 8.45–8.48 (m, 1H), 8.77–8.78 (m, 1H), 9.34 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 16.72 (d, $^3J_{CP}=5.7$ Hz, 2-$OCH_2\underline{C}H_3$), 64.72 (d, $^2J_{CP}=7.5$ Hz, 2-$O\underline{C}H_2CH_3$), 124.11, 137.34, 151.27, 154.90 (-C_5H_5N), 199.18 (d, $^1J_{CP}=195.5$ Hz, C=O) ppm; IR (neat): ν 1660 (C=O), 1260 (P=O) cm^{-1}; MS: M^+ (243)].