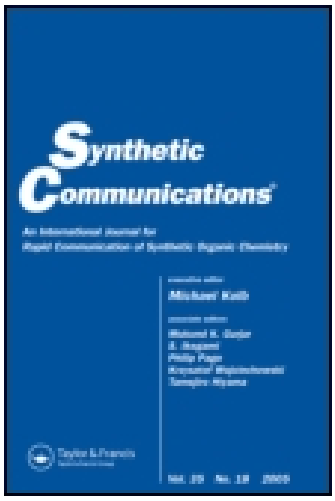


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Efficient Separation Method for Enol Phosphate and Corresponding β-Ketophosphonate from Their Mixtures Under Aqueous Conditions

Cornelis M. Moorhoff [a]

[a] Department of Chemistry , The University of Tasmania , Hobart, Tasmania, Australia

Published online: 17 Aug 2006.

To cite this article: Cornelis M. Moorhoff (2003) An Efficient Separation Method for Enol Phosphate and Corresponding β-Ketophosphonate from Their Mixtures Under Aqueous Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:12, 2069-2086, DOI: 10.1081/SCC-120021033

To link to this article: http://dx.doi.org/10.1081/SCC-120021033

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 12, pp. 2069–2086, 2003

An Efficient Separation Method for Enol Phosphate and Corresponding β-Ketophosphonate from Their Mixtures Under Aqueous Conditions

Cornelis M. Moorhoff *

Department of Chemistry, The University of Tasmania, Hobart, Tasmania, Australia

ABSTRACT

Separation of a mixture β-ketophosphonate **3** and their corresponding enol phosphate **4** is efficiently carried out in aqueous alkaline solutions. Enol phosphate 4 is first extracted with hexanes:dichloromethane (19:1). Acidification of the aqueous layer followed by extraction of the β-ketophosphonate **3** with dichloromethane completes the separation. Thus, when 1-bromo-2,4-pentadione **1a** reacted with triethyl phosphite to give diethyl (2,4-dioxopentyl)phosphonate **3a** (Arbuzov-product) and the corresponding enol phosphate **4a** (Perkow-product), separation of the two compounds was carried out using this method.

*Correspondence: Cornelis M. Moorhoff, Department of Chemistry, The University of Tasmania, GPO Box 252-75, Hobart, Tasmania, 7001 Australia.

DOI: 10.1081/SCC-120021033 0039-7911 (Print); 1532-2432 (Online)

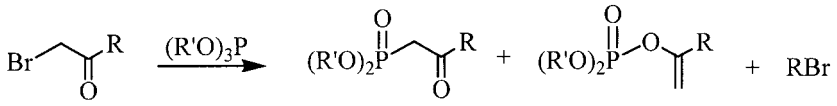
MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

INTRODUCTION

The classical Arbuzov reaction for the preparation of β-ketophosphonate **3** by reacting α-haloketone **1** with trialkyl phosphite **2**, usually leads to the formation of a mixture β-ketophosphonate **3** (Arbuzov-product) and enol phosphate **4** (Perkow-product) (Sch. 1).[1] Protected the carbonyl moiety,[2,3] and other methods[4–7] have been employed but involves at least two or more reactions. While the reaction of α-chloroketones with trialkyl phosphites **2** gives in most cases overwhelmingly the enol phosphates 4,[1,8] a similar reaction using α-iodoketones instead are more likely to lead to the exclusive formation of β-ketophosphonates **3**. However, certain α-iodoketones may not be stable and the best compromise is to use α-bromoketones in this reaction with trialkyl phosphites. Separation of mixtures β-ketophosphonate **3** and enol phosphate **4** may be tedious on a large scale and usually involves chromatographic separation. In this article we give an inexpensive, easy, and fast separation method for mixtures β-ketophosphonates **3** and enol phosphate **4**.

RESULTS

A number of different mixtures β-ketophosphonate **3**—enol phosphate **4** were obtained by reacting α-bromoketones with either trimethyl phosphite or triethyl phosphite. These mixtures **3** and **4** were then "dissolved" in either an aqueous solution of potassium- or sodium carbonate, or potassium- or sodium hydroxide, depending on the stability of the functional groups. For example, separation of substituted phenylacyl bromide derived enol phosphate **4**[9] from the corresponding compound **3**,[9] was carried out in an aqueous solution of potassium hydroxide using petroleum spirits (40–60°C) and dichloromethane (19:1) for extraction. Excellent purities of enol phosphates **4a**, **4b**, **4c**, **4d**, and **4e**,[9]



1 **2** **3** **4**

Scheme 1.

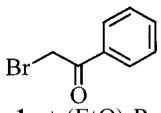
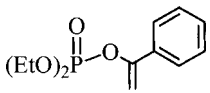
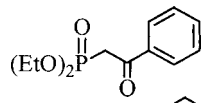
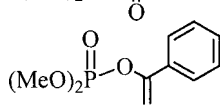
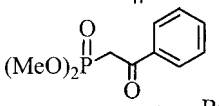
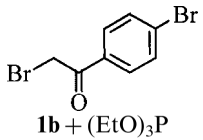
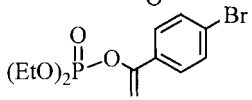
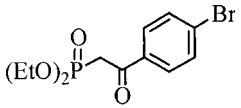
usually >95%, but mostly >99% free from β-ketophosphonate **3**, were obtained. In this series two extractions were normally enough to isolate enol phosphates **4** completely. A third extraction gave little material and actually contained a little β-ketophosphonate **3**. After acidification to ~pH 2 with aqueous hydrochloric acid, the corresponding β-ketophosphonates[1] **3a**, **3b**, **3c**, **3d**, and **3e**[9] respectively, were extracted with dichloromethane and obtained >98% free from enol phosphate **4** (Table 1). Two extractions were found to be sufficient to extract the β-ketophosphonate **3** completely. The success of these separations is probably due to metal enolates of the β-ketophosphonates **3**.[6,10] However, it was found that the dimethyl esters of the enol phosphate **4** and phosphonates **3** were more difficult to separate due to their higher polarity than their diethyl ester derivatives. Another problem encountered was the formation of methylphosphonate: $(MeO)_2P[O]CH_3$. The corresponding dipropyl- or diisopropyl phosphonyl esters were not investigated. Ethyl γ-bromoacetoacetate **1e** reacted also with triethyl- and trimethyl phosphite and gave mixtures of enol phosphate **4f** and **4g**, β-ketophosphonate **3f** and **3g** respectively.[2,7,11–13] In this particular case it became obvious that extraction from aqueous sodium hydroxide was too harsh. No enol phosphate was obtained since it had totally decomposed due to base catalyzed elimination of dialkyl phosphate (eg. Sch. 2).[14]

On the other hand, an aqueous solution of sodium hydrogen carbonate was not able to hold ketophosphonates **3f** and **3g** in the aqueous layer. An aqueous solution of potassium carbonate was able to successfully retain these ketophosphonates **3f** and **3g** without hydrolyzing the ester group or to eliminate diethylphosphate from the enol phosphates **4f** and **4g**. Bromoacetone reacted also with triethyl phosphite.[15,16] These mixtures of enol phosphate **4h** and β-ketophosphonate **3h** were more difficult to separate, and some hydrolysis took place since the yield of the separated compounds was 72%.

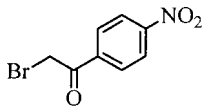
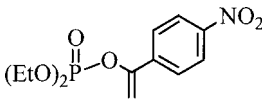
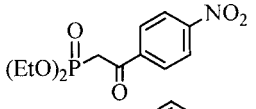
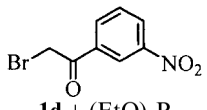
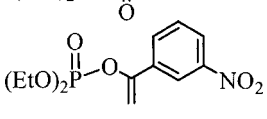
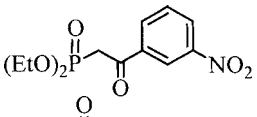
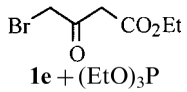
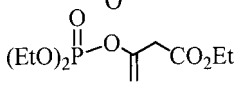
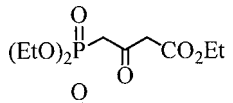
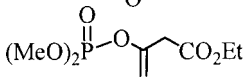
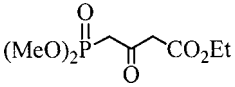
A literature search revealed that the phosphonate **3i** has been prepared in four steps.[17] Although 1-bromo-2,4-pentadione **1g** has been prepared before,[18] we adapted our bromination procedure according to the preparation of ethyl 4-bromo-3-oxobutanoate to **1g**.[19] 1-Bromo-2,4-pentadione **1g** is ~100% enolized ($CDCl_3$) and is unstable at room temperature. The bromodiketone **1g** reacted with triethylphosphite to give a mixture of phosphonate **3i** and enol phosphate **4i** (Sch. 3).

This mixture was added to a saturated aqueous solution of $NaHCO_3$ and the enol phosphate **4i** was extracted with 95:5 petroleum spirits (40–60°C):dichloromethane (twice). Some isomerization of the double

Table 1.

No.	Reactants	Reaction conditions	Enol phosphate and phosphonate		Ratio[a]	Yield[b]	Purity[b]
1	 **1a** + $(EtO)_3P$	90°C for 15 min Workup: aqueous KOH		**4a**[1,9]	18	22%	>95%
				**3a**[1,9]	82	58%	>99%
2	**1a** + $(MeO)_3P$	90°C for 15 min Workup: aqueous KOH		**4b**	28	27%	>99%
				**3b**	78	71%	>99%
3	 **1b** + $(EtO)_3P$	90°C for 15 min Workup: aqueous K_2CO_3		**4c**[9]	36	26%	>91%
				**3c**[9]	64	71%	>99%

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

4	 **1c** + $(EtO)_3P$	90°C for 15 min Workup: aqueous KOH		**4d**[9]	65	57%	>99%
				**3d**[9]	35	23%	>99%
5	 **1d** + $(EtO)_3P$	90°C for 15 min Workup: aqueous NaOH		**4e**	66	64%	>99%
				**3e**	34	35%	98%
6	 **1e** + $(EtO)_3P$	90°C for 15 min Workup: aqueous K_2CO_3		**4f**	57	33% 9%	>99% 1:1 (**4f**:**3f**)
				**3f**	43	28%	>97%
7	**1e** + $(MeO)_3P$	90°C for 10 min Workup: aqueous K_2CO_3		**4g**	79	46%	>97%
				**3g**	21	25%	89%

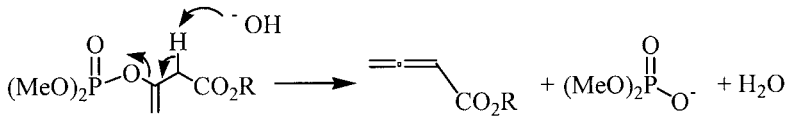
(*continued*)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

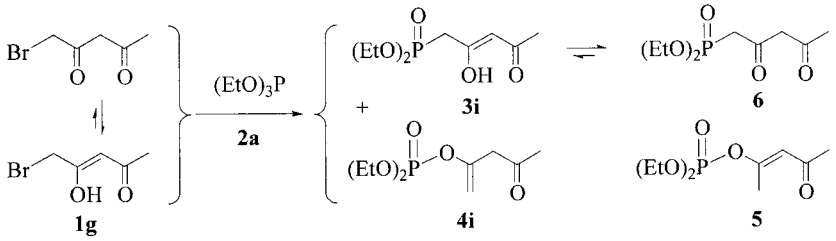
Table 1. Continued.

No.	Reactants	Reaction conditions	Enol phosphate and phosphonate		Ratio[a]	Yield[b]	Purity[b]
8	**1f** + $(EtO)_3P$	90°C for 5 min Workup: aqueous Li_2CO_3		**4h**[6,7]	38	14% 18%	88% 4:1 (**4h**:**3h**)
				3h	62	40%	96%
9	**1g** + $(EtO)_3P$	60°C for 1 min; then 15 min at 90°C		**4i**	27	14%	>97%
		Workup: aqueous $NaHCO_3$		**3i**	73	59%	>93%

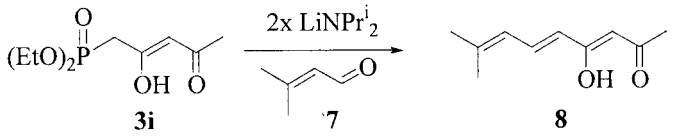
[a]By ^{1}H NMR.
[b]Isolated yield and purity by ^{1}H NMR.



Scheme 2.



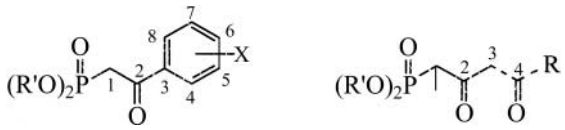
Scheme 3.



Scheme 4.

bond to **5**[20] had taken place and some hydrolysis of the enol phosphate **4i** had occurred. The aqueous layer was acidified with 1M HCl solution and extraction with dichloromethane gave the ketophosphonate **3i**. NMR-analyses revealed that the enol compound **3i** was the dominant tautomer in $CDCl_3$ and that the keto tautomer **6** was only 13% of the mixture (Sch. 4). Condensation of 3-methyl-2-butenal **7** and the dianion of the ketophosphonate **3i**, generated by two mole lithium diisopropylamide in THF at room temperature,[12] gave (2*Z*,4*E*)-4-hydroxy-8-methyl-3,5,7-nonatriene-2-one **8** in 75% yield.

Table 2. Chemical shift δ in ppm; coupling constant J in Hz.



^{13}C	**3a** (X=H)		**3b** (X=H)		**3c** (X=4-Br)		**3d** (X=4-NO_2)		**3e** (X=3-NO_2)		**3f** (R=OEt)		**3g** (R=OMe)		**3h**		**3i** (R=Me)	
no.	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ(enol)	J_{CP}
1	38.00	129.0	36.57	130.3	38.30	128.3	38.64	129.5	38.19	128.3	41.91	126.4	41.88	128.0	42.49	126.3	37.94	129.4
2	191.45	6.5	191.28	6.7	190.63	6.4	190.36	6.7	189.58	6.8	194.16	6.3	194.21	6.2	199.11	6.3	186.71	6.2
3	136.08	2.3	135.71	2.6	134.96	1.6	140.51	—	137.04	1.9	49.13	—	49.39	—	30.61	—	101.10	—
4	128.55	—	128.31	—	130.30	—	123.50	—	127.18	—	166.23	—	166.38	—			189.92	—
5	128.29	—	128.06	—	131.60	—	129.91	—	147.70	—								
6	133.18	—	133.16	—	128.69	—	150.25	—	134.19	—								
7	128.29	—	128.06	—	131.60	—	129.91	—	129.48	—								
8	128.55	—	128.31	—	130.30	—	123.50	—	123.20	—								

$(EtO)_2P[O]$: $\delta = 15.60$–15.95 (d, $J_{CP} = 6.1$–6.3); 62.11–62.65 (d, $J_{CP} = 6.0$–6.4). $(MeO)_2P[O]$: $\delta = 52.45$–52.84 (d, $J_{CP} = 4.6$–6.4). CH_3 (**3i**); $\delta = 23.73$.

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

^{1}H	**3a** (X=H)		**3b** (X=H)		**3c** (X=4-Br)		**3d** (X=4-NO_2)		**3e** (X=3-NO_2)		**3f** (R=OEt)		**3g** (R=OMe)		**3h**		**3i** (R=Me)	
no.	δ	J_{HP}	δ	J	δ	J_{HP}	δ	J	δ	J	δ	J_{HP}	δ	J_{HP}	δ	J_{HP}	δ (enol)	J_{HP}
1	3.479	22.7	3.418	J_{HP} 22.5	3.496	J_{HP} 22.8	3.674	J_{HP} 23.0	3.571	J_{HP} 22.8	3.057	22.6	3.190	22.7	2.946	22.7	2.838	22.6
3											3.451	s	3.529	s	2.142	s	5.582	s
4	7.853	dm	7.725	J_{HH} 8.5	7.499	J_{HH} 7.7	8.099	J_{HH} 9.0	8.583	sm								
5	7.302	m	7.189	m	7.778	J_{HH} 7.7	8.232	J_{HH} 9.0										
6	7.42	m	7.3	"					8.1–8.2	m								
7	7.302	m	7.189	m	7.778	J_{HH} 7.7	8.232	J_{HH} 9.0	7.525	J_{HH} dd, 7.9×2								
8	7.853	dm	7.725	J_{HH} 8.5	7.499	J_{HH} 7.7	8.099	J_{HH} 9.0	8.1–8.2	m								

$(EtO)_2P[O]$: $\delta = 1.07$–1.22 (t, $J_{HP} = 0$ Hz); 3.94–4.10 (dq, $J_{HP} = 7.1$, 8.3 Hz). $(MeO)_2P[O]$: $\delta = 3.48$–3.66 (d, $J_{HP} = 11.3$ Hz). OEt: 1.15; 4.07. CH_3 (**3i**); $\delta = 1.958$.

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

Table 3. Chemical shift δ in ppm; coupling constant J in Hz.

^{13}C	**4a** (X=H)		**4b** (X=H)		**4c** (X=4-Br)		**4d** (X=4-NO_2)		**4e** (X=3-NO_2)		**4f** (R=OEt)		**4g** (R=OMe)		**4h**		**4i** (R=Me)	
no.	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}	δ	J_{CP}
1	96.99	3.5	97.23	3.5	97.89	3.5	109.97	3.7	99.57	3.4	100.43	4.2	100.47	3.8	97.56	4.8	99.97	3.8
2	152.03	7.7	152.01	7.8	151.36	7.7	150.14	7.3	149.90	7.2	148.07	8.1	147.88	8.2	151.72	8.3	150.39	8.5
3	133.98	6.6	133.80	6.7	133.25	6.8	140.07	7.2	135.90	7.0	40.38	6.2	40.08	6.3	20.25	5.3	40.34	6.2
4	124.89	—	124.93	—	126.78	—	123.50	—	123.47	—	168.54	—	168.35	—			181.48	—
5	128.12	—	128.26	—	131.54	—	125.79	—	148.18	—								
6	128.83	—	129.02	—	123.23	—	147.72	—	130.73	—								
7	128.12	—	128.26	—	131.54	—	125.79	—	129.39	—								
8	124.89	—	124.93	—	126.78	—	123.50	—	119.90	—								

$(EtO)_2P[O]$: $\delta = 15.61$–16.09 (d, $J_{PC} = 6.6$–6.8); 63.76–64.63 (d, $J_{PC} = 5.9$–6.3). $(MeO)_2P[O]$: $\delta = 54.40$ (d, $J_{PC} = 6.2$). EtO: $\delta = 13.63$–13.82; 60.69–60.79. 29.67 (Me).

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

^{1}H	**4a** (X = H)		**4b** (X = H)		**4c** (X = 4-Br)		**4d** (X = 4-NO_2)		**4e** (X = 3-NO_2)		**4f** (R = OEt)		**4g** (R = OMe)		**4h**		**4i** (R = Me)	
no.	δ	J_{HP} J_{HH}	δ	J_{HP} J_{HH}	δ	J_{HP} J_{HH}	δ	J_{HP} J_{HH}	δ	J_{HP} J_{HH}	δ	J_{HP} J_{HH}	δ	J_{HP} J_{HH}	δ	J_{HP} J_{HH}	δ	J_{HP} J_{HH}
1a	5.182	2.6, 2.6	5.164	2.6, 2.6	5.208	2.1, 2.9	5.376	2.1, 3.3	5.336	2.1, 3.2	4.590	2.1, 2.5	4.564	1.2, 1.8	4.366	0.9, 0.9	4.611	1.8, 2.1
1b	5.219	2.6, 2.6	5.253	2.6, 2.6	5.248	2.9, 2.9	5.437	2.1, 3.3	5.403	2.5, 3.2	4.912	1.8, 2.5	4.857	2.6, 1.8	4.579	0.9, 0.9	4.869	2.1, 2.1
3											3.115	s	3.077	s	1.761	s	3.002	s
4	7.53	m	7.52	m	7.38	J_{HH} 9.0	7.689	J_{HH} 9.1	8.361	dd, 4.0×2								
5	7.28	m	7.29	m	7.45	J_{HH} 9.0	8.142	J_{HH} 9.1										
6	,,	,,	,,	,,					7.863	ddm, 7.9, 1.8								
7	,,	,,	,,	,,	7.45	J_{HH} 9.0	8.142	J_{HH} 9.1	7.506	dd, 8.1×2								
8	7.53	m	7.52	m	7.38	J_{HH} 9.0	7.689	J_{HH} 9.1	8.126	ddm, 8.1, 2.2								

$(EtO)_2P[O]$: $\delta = 1.17$–1.31 (dt, $J = 7.1$, 1.1); 3.98–4.18 (dq, $J = 7.1$, 8.1). $(MeO)_2P[O]$: $\delta = 3.66$ (d, $J_{HP} = 11.3$). OEt: 1.10–1.15; 4.01–4.17. CH_3 (**3i**); $\delta = 1.928$.

EXPERIMENTAL

All reactions were carried out in air, except the condensation of ketophosphonate **3i** and 3-methyl-2-butenal (under nitrogen). ^{1}H NMR (δ, ppm, with $SiMe_4$ as an internal standard) and ^{13}C NMR (δ, ppm) were recorded on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz (Table 1). High resolution electron ionization (EI) mass spectra were obtained from a Varian MAT 311 A instrument and high resolution chemical ionization spectra (CI) using ammonia, were obtained from a Kratos Concept ISQ instrument. Infrared spectra were obtained on a Hitachi 270-30 FTIR spectrophotometer (film, NaCl plates). Bulb-to-bulb distillations were carried out on a Büchi GKR-51 apparatus.

Note: The following additions of triethylphosphite to α-bromoketones or vice versa, all produced mixtures of enol phosphate **4** and ketophosphonate **3** during a vigorous, exothermic evolution of ethyl bromide. CAUTION!: Enol phosphates are neurological toxins.

(a) Separation of a Mixture 1-[(Diethoxyphosphinyl)oxo]styrene 4a and 2-(Diethoxyphosphinyl)acetophenone 3a

2-Bromoacetophenone [phenacyl bromide] (2.0 g, 10.05 mmol) was added to triethyl phosphite (1.8 g, 10.83 mmol) at 90°C within 2 min and then stirred for a further 15 min at 90°C with a simultaneous release of ethyl bromide. Excess triethyl phosphite and traces of ethyl bromide were removed under vacuum. The resulting viscous, oily mixture of phosphonate **3a** and enol phosphate **4a** (82:18) was shaken in an aqueous solution of potassium hydroxide (2.0 g KOH mmol, in 150 mL H_2O) and extracted twice with a mixture petroleum spirits (40–60°C) and dichloromethane 19:1 (2×100 mL) and the organic extract dried ($MgSO_4$). After evaporation of the solvents *1-[(diethoxyphosphinyl)oxo]styrene* **4a** (0.562 g, 21.8%, 95% purity) was isolated as a colorless oil. [Found: MH^+(LSIMS), 257.09517. $C_{12}H_{18}O_4P$ requires *M*, 257.094266]; Acidification with concentrated hydrochloric acid to pH 4 followed by extraction with dichloromethane (2×50 mL) gave, after drying of the organic extract ($MgSO_4$) and evaporation of the solvent, enol phosphate free *2-(diethoxyphosphinyl)acetophenone* **3a** (1.489 g, 57.8%) as a colorless oil. [Found: MH^+(LSIMS), 257.09368. $C_{12}H_{18}O_4P$ requires *M*, 257.094266].

(b) Separation of a Mixture 1-[(Dimethoxyphosphinyl)oxo]styrene 4b and 2-(Dimethoxyphosphinyl)acetophenone 3b

2-Bromoacetophenone (1.0 g, 5.025 mmol) was added to excess trimethyl phosphite (0.8 g, 6.45 mmol) under the same conditions as in (a). The resulting viscous oily mixture of phosphonate **3b** and enol phosphate **4b** (72:28) was treated in the same way as described under (a) to give phosphonate free *2*-[(*dimethoxyphosphinyl*)*oxo*]*styrene* **4b** (0.31 g, 27.0%), as a colorless oil. [Found: MH^+(LSIMS), 229.06764. $C_{10}H_{14}O_4P$ requires *M*, 229.062967]. IR: ν_{max} 3020, w; 2956, m; 2855, w; 1676, s; 1596, m; 1581, w; 1535, w; 1448, s; 1351, w; 1258, vs; 1187, m; 1029, vs; 879, m; 808, s; 732, m. Enol phosphate free *2*-(*dimethoxyphosphinyl*)*acetophenone* **3b** (0.81 g, 70.6%) as a colorless oil. [Found: MH^+(LSIMS), 229.06235. $C_{10}H_{14}O_4P$ requires *M*, 229.062967]. IR (cm^{-1}): ν_{max} 3070, w; 2960, s; 2858, m; 1760, m; 1725, s; 1684, m; 1635, s; 1577, m; 1492, s; 1447, s; 1269, vs; 1186, s; 1011, vs; 844, s; 773, s; 705, s.

(c) Separation of a Mixture 2-[(Diethoxyphosphinyl)oxo]-2-[4-bromophenyl]ethane 4c and 2-(Diethoxyphosphinyl)-4′-bromoacetophenone 3c

Triethyl phosphite (1.8 g, 10.83 mmol) was added to 4′-bromo-α-bromoacetophenone [2,4′-dibromoacetophenone or 4′-bromophenacyl bromide] (2.0 g, 7.196 mmol) at 90°C within 2 min and then stirred for a further 15 min at 90°C. The workup of the resulting viscous oily mixture of phosphonate **3c** and enol phosphate **4c** (64:36) proceeded in the same way as described under (a) but with the use of potassium carbonate (2.0 g, K_2CO_3 mmol, in 200 mL H_2O). *2*-[(*Diethoxyphosphinyl*)*oxo*]-*2*-[*4-bromophenyl*]*ethane* **4c** (0.633 g, 26.3%, 91% pure) [Found: MH^+(LSIMS), 335.00537. $C_{12}H_{17}BrO_4P$ requires *M*, 335.004777]; IR (cm^{-1}): ν_{max} 3070, w; 2983, s; 2932, m; 2920, m; 1681, s; 1585, w; 1484, w; 1444, w; 1396, m; 1254, s; 1163, m; 1026, s; 972, s; 806, s. Enol phosphate free *2*-(*diethoxyphosphinyl*)-*4′-bromoacetophenone*. **3c** (1.72 g, 71.5%) as a colorless oil. [Found: MH^+(LSIMS), 335.00382. $C_{12}H_{17}BrO_4P$ requires *M*, 335.004777]. IR (cm^{-1}): ν_{max} 2985, s; 2950, m; 2910, m; 1712, s; 1680, s; 1586, s; 1485, m; 1444, m; 1395, s; 1370, w; 1238, s; 1160, s; 1029, vs; 817, s; 759, m.

(d) Separation of a Mixture 2-[(Diethoxyphosphinyl)oxo]-2-[4-nitrophenyl]ethane 4d and 2-(Diethoxyphosphinyl)-4′-nitroacetophenone 3d

Triethyl phosphite (1.70 g, 10.23 mmol) was added to 2-bromo-4′-nitroacetophenone (2.0 g, 8.20 mmol) as described under (c). The resulting light-brown viscous oily mixture of phosphonate **3d** and enol phosphate **4d** (35:65) was treated for separation as described in (a) (Note: the aqueous solution became dark yellow to yellow-brown). *2-[(Diethoxyphosphinyl)oxo]-2-[4-nitrophenyl]ethane* **4d** (1.40 g, 56.7%) as a light yellow viscous oil was obtained phosphonate free [Found: MH^+(LSIMS), 302.07913. $C_{12}H_{17}NO_6P$ requires *M*, 302.079345]. IR (cm^{-1}): ν_{max}3120, w; 3080, w; 2991, s; 2940, m; 2920, m; 1694, w; 1632, s; 1599, s; 1522, vs; 1444, m; 1394, m; 1350, s; 1272, vs; 1164, s; 1103, s; 1034, vs; 860, s; 830, s; 760, s; 709, m. Enol phosphate free *2-(diethoxyphosphinyl)-4′-nitroacetophenone* **3d** (0.57 g, 23.1%) as a yellow oil. [Found: MH^+(LSIMS), 302.07809. $C_{12}H_{17}NO_6P$ requires *M*, 302.079345]. IR (cm^{-1}): ν_{max} 3111, w; 2990, s; 2940, m; 2920, m; 1720, s; 1688, s; 1603, s; 1527, s; 1405, s; 1348, s; 1265, vs; 1103, s; 1022, vs; 970, s; 857, s; 835, s; 785, m; 716, m.

(e) Separation of a Mixture 2-[(Diethoxyphosphinyl)oxo]-2-[3-nitrophenyl]ethane 4e and 2-(Diethoxyphosphinyl)-3′-nitroacetophenone 3e

Triethyl phosphite (1.7 g, 10.23 mmol) and 2-bromo-3′-nitroacetophenone (2 g, 8.20 mmol) was reacted and worked up in a similar manner as in the previous example. The resulting light-yellow viscous oily mixture of phosphonate 3e and enol phosphate **4e** (34:66) was worked up as described under (a) but using sodium hydroxide (2.0 g. NaOH mmol, in 150 mL H_2O). *2-[(Diethoxyphosphinyl)oxo]-2-[3-nitrophenyl]ethane* **4e** (1.584 g, 64.2%) as a light yellow viscous oil, b.p. 112 °C/0.5 mm Hg. [Found: MH^+(LSIMS), 302.07955. $C_{12}H_{17}NO_6P$ requires *M*, 302.079345]. IR (cm^{-1}): ν_{max} 3097, w; 2991, s; 2940, m; 2920, m; 1637, s; 1531, vs; 1481, m; 1446, w; 1351, vs; 1263, vs; 1166, m; 1132, s; 1031, vs; 901, m; 831, s; 743, m. *2-(Diethoxyphosphinyl)-1-oxo-3′-nitroacetophenone* **3e** (0.864 g, 35.0%) as a dark yellow solid. m.p. 126°C. [Found: MH^+(LSIMS), 302.0. $C_{12}H_{17}NO_6P$ requires *M*, 302.079345]. IR (cm^{-1}): ν_{max} 3106, w; 2993, s; 2929, s; 2880, m; 1720, s; 1686, s; 1613, s; 1577, s; 1528, s; 1479, s; 1442, s; 1395, s; 1347, vs; 1265, vs; 1030, vs; 965, s; 884, s; 805, s; 732, s.

(f) Separation of a Mixture Ethyl 3-[(Diethoxyphosphinyl)oxo]-3-butenoate 4f and Ethyl 4-(Diethoxyphosphinyl)-3-oxobutanoate 3f

Ethyl 4-bromo-3-oxobutanoate (7.0 g, 33.49 mmol) was added to triethyl phosphite (7.0 g, 42.13 mmol) and treated the same way as described under (a). The resulting viscous oily mixture of phosphonate **3f** and enol phosphate **4f** (43:57) was shaken in an aqueous solution of potassium carbonate (7.0 g. K_2CO_3 mmol, in 200 mL H_2O) (pH ~10) and then extracted three times with a mixture petroleum spirits (40–60°C) and dichloromethane 19:1 (3 × 100 mL) and the organic phase of the first two extractions were combined and dried ($MgSO_4$). After evaporation of the solvents phosphonate free *ethyl 3-[(diethoxyphosphinyl)oxo]-3-butenoate* **4f** (2.9 g, 32.5%), b.p. 112°C/0.5 mm Hg. [Found: $M^{+\cdot}$(EI), 266.0916. $C_{10}H_{19}O_6P$ requires *M*, 266.09193]; $m/z = 221$ ($MH^{+\cdot}$-(CH3)2CH, 45%); 179 ($M^{+\cdot}$-$CH_2CO_2CH(CH_3)_2$, 28%), 155 (100%); 127 ($MH^{+\cdot}$-(EtO)2P[O}OH, 72%), 99 ($MH^{+\cdot}$-69%). (Found: C, 44.81; H, 7.02; P, 11.47. $C_{10}H_{19}O_6P$ requires C, 45.11; H, 7.19; P, 11.63%). IR (cm^{-1}): ν_{max} 2988, s; 2940, s; 2920, s; 1738, s; 1662, s; 1546, w; 1447, m; 1395, m; 1371, m; 1272, s; 1160, s; 1040, s; 867, w; 802, m. The third intermediate extract was kept separate and dried to give after evaporation a mixture of 57% enol phosphate **4f** and 43% phosphonate **3f** (0.83 g, 9.3%). Acidification of the aqueous layer with aqueous hydrochloric acid followed by extraction with dichloromethane gave *ethyl 4-(diethoxyphosphinyl)-3-oxobutanoate* **3f** (2.51 g, 28.2%, 97% pure) as a pale yellow oil b.p. 126°C/0.5 mm Hg. [Found: M^+(EI), 266.0924. $C_{10}H_{19}O_6P$ requires *M*, 266.09193]; $m/z = 221$ ($MH^{+\cdot}$-$(CH_3)_2CH$, 45%); 179 ($M^{+\cdot}$-$CH_2CO_2CH(CH_3)_2$, 28%), 155 (100%); 127 ($MH^{+\cdot}$-$(EtO)_2P[O\}OH$, 72%), 99 ($MH^{+\cdot}$-69%). (Found: C, 44.18; H, 7.16; P, 11.70. $C_{10}H_{19}O_6P$ requires C, 45.11; H, 7.19; P, 11.63%). IR (cm^{-1}): ν_{max} 2986, s; 2940, s; 2920, s; 1750, s; 1716, s; 1446, w; 1393, m; 1369, m; 1257, s; 1029, vs; 973, s; 805, m.

(g) Separation of a Mixture Ethyl 3-[(Dimethoxyphosphinyl)oxo]-3-butenoate 4g and Ethyl 4-(Dimethoxyphosphinyl)-3-oxobutanoate 3g

Ethyl 4-bromo-3-oxobutanoate (1.4 g, 6.697 mmol) was added to excess trimethyl phosphite (0.9 g, 7.253 mmol) in a similar manner as in the previous example. The resulting viscous oily mixture of phosphonate **3g** and enol phosphate **4g** (21:79) and (dimethoxyphosphinyl)methane

was worked up in a similar manner as the previous example to give *ethyl 3-[(dimethoxyphosphinyl)oxo]-3-butenoate* **4g** (0.73, 45.7%, 97% pure) [Found: $MH^{+\cdot}$(LSIMS), 239.06769. $C_8H_{16}O_6P$ requires *M*, 239.068447]. IR (cm^{-1}): ν_{max} 2980, s; 2962, s; 2860, w; 1741, s; 1660, s; 1449, m; 1372, m; 1276, s; 1190, s; 1039, s; 954, m; 855, s. *Ethyl-4-(dimethoxyphosphinyl)-3-oxobutanoate* **3g** (0.40 g, 25.1%, 89% pure) as a pale yellow oil. [Found: MH^+(LSIMS), 239.06836. $C_8H_{16}O_6P$ requires *M*, 239.068447]. IR (cm^{-1}): ν_{max} 2961, m; 2860, w; 1740, s; 1720, s; 1449, w; 1405, w; 1369, w; 1266, s; 1030, vs; 813, m. (14% of keto-enol mixture). Note: this compound still had significant impurities of (dimethoxyphosphinyl)-methane.

(h) Separation of a Mixture 2-[(Diethoxyphosphinyl)oxo]-1-propene 4h and 1-(Diethoxyphosphinyl)-2-oxopropene 3h

Bromo-2-oxopropane (1.4 g, 10.22 mmol) was added to excess triethyl phosphite (2.0 g, 12.04 mmol) in the same manner as described under (f). The resulting viscous oily mixture (1.76 g, ~100%) of phosphonate **3h** and enol phosphate 4h (64:36) was shaken in an aqueous solution of lithium carbonate (0.5 g mmol, in 60 mL H_2O) and the extraction and separation procedure followed through as described under (f). After evaporation solvents of the the first two extracts phosphonate free *2-[(diethoxyphosphinyl)oxo]-1-propene* **4h** (0.23 g, 13.5%, 88% pure) was obtained [Found: MH^+(LSIMS), 167.04806. $C_5H_{12}O_4P$ requires *M*, 167.04732]. The third fraction (0.31 g, 18.3%) was a mixture of enol phosphate:phosphonate (4:1). Acidification with aqueous hydrochloric acid to pH 2.5 followed by extraction with dichloromethane gave *1-(diethoxyphosphinyl)-2-oxopropane* **3h** (0.67 g, 39.5%) as a pale yellow oil, containing 4% enol phosphate as an impurity. [Found: MH^+(LSIMS), 167.04657. $C_5H_{12}O_4P$ requires *M*, 167.04732].

(i) Separation of a Mixture 2-[(Diethoxyphosphinyl)oxo]-1-penten-4-one 4i and 5-(Diethoxyphosphinyl)-2,4-dioxopentane(diethyl-2,4-dioxopentylphosphonate) 3i

Triethyl phosphite (6.0 g, 36.11 mmol) was added to 1-bromo-2,4-dioxopentane (5.0 g, 27.93 mmol) at 60°C within one minute and then stirred for a further 10 min at 90°C. The separation procedure for the viscous oily mixture of phosphonate **3i** and enol phosphate **4i** (73:27) was

then followed through as described under (f), but an aqueous solution of sodium hydrogencarbonate (3.0 g. $NaHCO_3$ 35.7 mmol, in 100 mL H_2O) (pH ~8) was used. *2-[(diethoxyphosphinyl)oxo]-1-penten-4-one* **4i** (0.95 g, 14.4%, 97% pure). IR (cm^{-1}): ν_{max} 2988, s; 2928, s, 2850, m; 1657, s; 1444, m; 1395, m; 1368, m; 1272, vs; 1165, s; 1030, vs; 950, s; 809, m. 5-(*Diethoxyphosphinyl*)-2,4-*dioxopentane* **3i** (3.9 g, 59.1%, 93% pure) as a pale yellow oil (87% enolised in $CDCl_3$). IR (cm^{-1}): ν_{max} 2991, m; 2930, m; 2910, m; 1730, m; 1704, m; 1619, s; 1445, m; 1392, m; 1255, vs; 1150, m; 1030, vs; 970, s; 825, w; 786, w. Significant ^{1}H NMR signals of the keto isomer **6** (13% of keto-enol mixture). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.134$ (s, 3H), 3.128 (d, $J_P = 22.7$ Hz, 2H), 3.712 (s, 2H). Distillation (Bulb-to-bulb: 120°C at 0.1 mm Hg) of the ketophosphonate **3i** improved the purity to 98%. [Found: MH^+(LSIMS), 237.08966. $C_9H_{18}O_5P$ requires *M*, 237.08919].

Condensation of the Dianion of the Phosphonate 3i and 3-Methyl-2-butenal

Phosphonate **3i** (2.0 g, 8.46 mmol) in dry THF (10 mL) was added to a freshly prepared solution of lithium diisopropylamide (19.8 mmol) in THF (22 mL) at room temperature. 3-Methyl-2-butenal (1.0 g, 11.9 mmol) in THF (2 mL) was added within 2 min at room temperature and stirred for 30 min. The solution became warm. A solution of brine (50 mL) was added then acidified to ~pH 3 and extracted with ether. The extract was dried, then filtered over silica gel and the solvent evaporated. The residue chromatographed with petroleum:diethyl ether (9:1) to give 4-hydroxy-8-methyl-3,5,7-nonatriene-2-one (1.05 g, 75%). ^{13}C NMR ($CDCl_3$, 20 MHz): δ (3*Z*,5*E*-isomer) = 196.59, 177.85, 145.18, 136.20, 124.31, 123.25, 100.17, 26.24, 25.67, 18.58. ^{1}H NMR ($CDCl_3$, 80 MHz): $\delta = 1.886$ (sm, 3H), 1.904 (s, 3H), 2.121 (s, 3H), 5.515 (s, 1H), 5.799 (d, $J = 15.1$ Hz, 1H), 5.997 (dm, $J = 11.7$ Hz, 1H), 7.490 (dd, $J = 15.1$, 11.7 Hz, 1H), ~15 (s, OH) and dimer aldehyde.[12]

ACKNOWLEDGMENTS

The expertise of Mr. Marshall Hughes and Dr. Noel Davies (University of Tasmania) for mass spectral analyses is gratefully acknowledged. A preliminary investigation into the separation of the

vinylenolphosphate **4f** and β-ketophosphonate **3f** was carried out at the University of Stellenbosch.

REFERENCES

1. Battacharya, A.K.; Thyagaran, G. Chem. Rev. **1981**, *81*, 415.
2. Moorhoff, C.M.; Grosse, A.C. Heteroatom Chemistry **1997**, *8*, 361. And references cited.
3. Yuan, C.; Xie, R. Phosphorus, Sulfur, Silicon, Relat. Elem. **1994**, *90*, 47.
4. Kim, D.Y.; Kong, M.S.; Rhie, D.Y. Synth. Commun. **1995**, *25*, 2865. And references cited.
5. Kim, D.Y.; Kong, M.S.; Kim, T.H. Synth. Commun. **1996**, *26*, 2487. And references cited.
6. Corbel, B.; L'Hostis-Kervella, I.; Haelters, J.-P. Synth. Commun. **1996**, *26*, 2561.
7. Fouqué, D.; About-Jaudet, E.; Collignon, N. Synth. Commun. **1992**, *22*, 219.
8. Borowitz, I.J.; Anschel, M.; Firstenberg, S. J. Org. Chem. **1967**, *32*, 1723.
9. Bianchini, J.P.; Gaydou, E.M. Hebd. Seances Acad. Sci. Ser. C **1975**, *280* (25), 1521.
10. Belcuig, M.P.; Modro, A.M.; Modro, T.A.; Wessels, P.L. J. Phys. Org. Chem. **1992**, 5, 787.
11. Jagodic, V. Croat. Chem. Acta **1977**, *49*, 487.
12. Moorhoff, C.M.; Schneider, D.F. Tetrahedron Lett. **1987**, *28*, 559.
13. DuPisani, C.; Schneider, D.F.; Venter, P.C.R. Synth. Commun. **2002**, *32*, 305.
14. Moorhoff, C.M. Ph.D. thesis, Stellenbosch 1986. Unpublished results.
15. Pudovik, A.N.; Avery'anova, V.P. Zhur Obschei Khim. **1956**, *26*, 1426.
16. Lichtenthaler, F.W. Chem. Ber. **1961**, *61*, 607.
17. Öhler, E.; Kang, H.-S.; Zbiral, E. Synthesis **1988**, *9*, 623.
18. Tavares, D.F.; O'Sullivan, W.I.; Hauser, C.R. J. Org. Chem. **1962**, *27*, 1251.
19. Duthaler, R.O. Helv. Chim. Acta **1983**, *66*, 1475.
20. Sakamoto, M.; Fukuda, Y.; Kamiyama, T.; Kawasaki, T. Chem. Pharm. Bull. **1994**, *42,* 1919.

Received in the USA October 1, 2002