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A Study on the Michael Addition of Dialkylphosphites to Methylvinylketone

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ABSTRACT: *The addition of dialkylphosphites to methylvinylketone giving dialkyl-3-oxobutylphosphonates was studied applying different reagents, such as NaOR/ROH, NaOH/H_2O under PTC, DBU, and R_3Al (R = Me, Et) under different conditions to find the optimum choice regarding efficiency and selectivity. Possible extensions to a few other model compounds were also investigated.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:226–229, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20266

INTRODUCTION

The phospha-Michael (P-Michael) addition is an important tool for P—C bond formation. The nucleophiles may include tervalent P-species, such as phosphines, phosphinites, phosphonites, and phosphites or >P(O)H reagents, such as dialkylphosphites, secondary phosphine oxides, mixed alkyl/phenyl and alkoxy, as well as sulfide and borane derivatives [1–4].

The reaction of α,β-unsaturated ketones and esters with >P(O)H species is usually carried out under basic conditions, either in the presence of a basic catalyst or by using a strong base to give —C(O)—CH_2—CH_2—P(O)< derivatives including γ-oxo-phosphonates [1]. Asymmetric synthesis of β-phosphonomalonates by the reaction of Knoevenagel acceptors and a chiral cyclic phosphite has also been described [5]. The addition of a chiral phosphite to nitroalkenes was also studied [6,7].

Regarding the P-Michael addition in a broader context, the addition of >P(O)H species to α,β-unsaturated C=O or P=O compounds may lead to derivatives that are of potential biological activity [8,9] or that are precursors of bidental P-ligands [10–12]. For this, it seemed to be desirable to examine and to compare the different ways of realizing the Michael additions. Our task was to find the simplest way that is selective, efficient, and environment friendly. The scope and limitations were also investigated.

RESULTS AND DISCUSSION

In our study, the reaction of methylvinylketone (MVK) with diethylphosphite (DEP) was chosen as the model reaction. In the first experiment, MKV was reacted with dialkylphosphites in the presence of 1 equiv. of sodium alcoholate in the corresponding alcohol at reflux for 3 h. The 3-oxobutylphosphonates (**1a** and **1b**) were obtained in ca. 64% yield after the work-up (Scheme 1).

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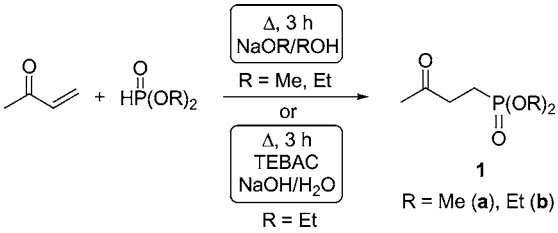


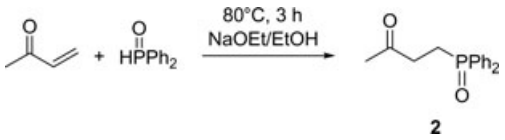
SCHEME 1

A synthesis under L–L phase-transfer catalytic conditions involving 30% aqueous sodium hydroxide and triethylbenzylammonium chloride (TEBAC) in dichloromethane at reflux gave product **1b** in 57% yield after the work-up. The reaction was not, however, entirely selective presumably due to a small extent of hydrolysis of the $P(O)(OEt)_2$ moiety to the mixed ester–acid. Carrying out the reaction under more forcing conditions (using more NaOH and applying a longer reaction time), an increase in the proportion of the by-product (at δ_P 31.6) could be observed.

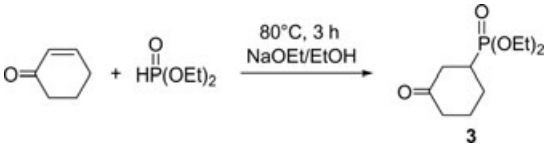
The method activating the >P(O)H reagent with NaOEt/EtOH was successfully extended to the reaction of diphenylphosphine oxide (DPPO) with MVK (Scheme 2) and to that of DEP with cyclohexene-2-on (Scheme 3) leading to phosphine oxide **2** and phosphonate **3**, respectively. The above reactions were found to be chemoselective as the carbonyl group remained intact.

We wanted to examine whether a saturated ketone reacts with DEP/NaOEt. The interaction of methylethylketone with the reagent under discussion resulted in the formation of α-hydroxyphosphonate **4** in 15% yield after work-up (Scheme 4). A part of the ketone was regenerated.

An attractive way was to accomplish the addition of DEP to the double bond of MVK in the presence of diazabicycloundecene (DBU) in



SCHEME 2



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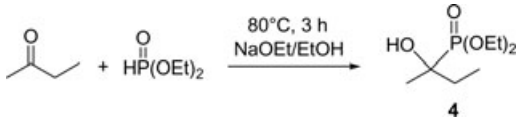


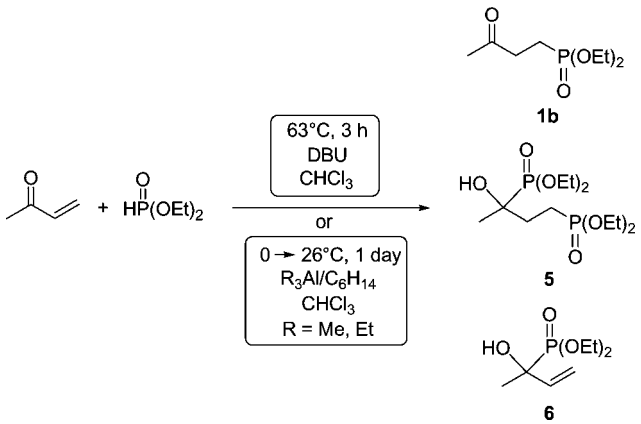
SCHEME 4

chloroform at reflux. The outcome of the reaction was found to be highly dependent on the quantity of the DBU. The use of 0.1 equiv. of DBU led to a low conversion (33%), while the presence of 1 equiv. of the amine caused a rather complex reaction mixture containing only 60% of the desired product **1b**. The optimum quantity of DBU was found to be 0.5 equiv. resulting in an 89:11 mixture of the 3-oxobutylphosphonate **1b** and 3-diethylphosphono-3-hydroxy-butylphosphonate **5** according to ^{31}P NMR spectroscopy (Scheme 5).

A reactive anion can be formed from a >P(O)H species by reaction with trimethylaluminum [13]. Adding MVK in chloroform to the hexane–chloroform solution of the reagent at 0°C and then stirring the contents of the flask at 26°C for 20 h led to a 22:78 mixture of bis-adduct **5** and unsaturated α-hydroxyphosphonate **6** according to ^{31}P NMR spectroscopy (Scheme 5).

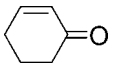
Using triethylaluminum/hexane instead of the trimethylaluminum reagent and adding the $(EtO)_2P(O)H–Et_3Al$ to the solution of MVK dropwise led to a 48:19:33 mixture of **1b, 5**, and **6** as suggested by ^{31}P NMR spectroscopy. It is noteworthy that the desired product (**1b**) was the main component.

In the series of the above experiments, MVK and DEP were heated at 95°C without solvent in a microwave reactor. No reaction could be detected after a reaction time of 1 h. Under similar conditions, DPPO entered, however, in reaction with MVK to give product **2**.



SCHEME 5

TABLE 1 Phospha-Michael Reaction of Some Model Compounds under Different Conditions

Reagents		*Conditions*	*Product(s)*	*Yield (%)*
MVK	DMP	NaOMe/MeOH, Δ, 3 h	**1a**	61
MVK	DEP	NaOEt/EtOH, Δ, 3 h	**1b**	67
MVK	DEP	10 equiv. NaOH/H_2O, TEBAC, Δ, 3 h	**1b**	57
MVK	DPPO	NaOEt/EtOH, Δ, 3 h	**2**	70
	DEP	NaOEt/EtOH, Δ, 3 h	**3**	42
MeC(O)Et	DEP	NaOEt/EtOH, Δ, 3 h	**4**	15
MVK	DEP	0.5 equiv. DBU/$CHCl_3$, Δ, 3 h	**1b** (89%), **5** (11%)	
MVK	DEP	$Me_3Al/C_6H_{14}/CHCl_3$, 0–26°C	**5** (22%), **6** (78%)	
MVK	DEP	$Et_3Al/C_6H_{14}/CHCl_3$, 0–26°C	**1b** (48%), **5** (19%), **6** (33%)	
MVK	DPPO	Microwave	**2**	75

DEP, diethylphosphite; DMP, dimethylphosphite; DPPO, diphenylphosphine oxide; MVK, methylvinylketone; TEBAC, triethylbenzylammonium chloride.

Experimental results were summarized in Table 1. It can be seen that regarding the P-Michael reaction of MVK and DEP, the use of NaOEt/EtOH is the method of choice. The phase-transfer catalytic approach is not so efficient, while the use of DBU or R_3Al (R = Me or Et) leads to the formation of unwished byproducts, such as a bis-adduct and a hydroxyphosphonate. The microwave synthesis could not be applied in the case under discussion. Cyclohexene-2-one could be used instead of MVK and DPPO instead of DEP applying NaOEt/EtOH.

Experiences of the above study may promote planning Michael reactions of dialkylphosphites with a variety of —CH=C—C(O)— or —CH= C—P(O)< compounds.

EXPERIMENTAL

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The couplings are given in Hz. Mass spectrometry was performed on a ZAB-2SEQ instrument.

General Procedure for the Preparation of 3-Oxobutyl Derivatives **1–3** *by the Reaction of α,β-Unsaturated Ketones and >P(O)H in the Presence of NaOR/ROH*

To the mixture of 4.29 mmol of the unsaturated ketone and 4.29 mmol of the >P(O)H species, 0.29 g (4.29 mmol) of sodium ethoxide in 10 mL of ethanol was added dropwise, and the mixture was stirred at 60–70°C for 3 h. After cooling to room temperature, 20 mL of chloroform was added, and the organic phase was washed with water (2 × 10 mL) and then dried. The crude product was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 3-oxobutyl derivatives **1–3**.

The following products were thus prepared.

Diethyl-(3-oxobutyl)phosphonate **1b** *by the Reaction of Methylvinylketone and Diethylphosphite.* Yield: 0.60 g (67%); ^{31}P NMR ($CDCl_3$): δ 31.4, δ^{lit} [14] 32.1; ^{13}C NMR ($CDCl_3$): δ 16.3 ($J = 6.1$ Hz, OCH_2CH_3), 19.2 ($J = 144.6$ Hz, PCH_2), 29.5 ($C(O)CH_3$), 36.2 ($J = 3.8$ Hz, $C(O)CH_2$), 61.5 ($J = 6.4$ Hz, OCH_2CH_3), 205.6 ($J = 14.8$ Hz, C(O)); δ^{lit} [15] 16.4 ($J = 6.1$ Hz), 19.4 ($J = 143.7$ Hz), 29.7, 36.3 ($J = 3.6$ Hz), 61.7 ($J = 6.6$ Hz), 205.7 ($J = 15.1$ Hz).

Dimethyl-(3-oxobutyl)phosphonate **1a** *by the Reaction of Methylvinylketone and Dimethylphosphite.* Yield: 0.46 g (61%); ^{31}P NMR ($CDCl_3$): δ 34.1; ^{13}C NMR ($CDCl_3$): δ 18.0 ($J = 144.5$ Hz, PCH_2), 29.3 ($C(O)CH_3$), 35.9 ($J = 3.9$ Hz, $C(O)CH_2$), 52.2 ($J = 6.4$ Hz, OCH_3), 205.3 ($J = 14.2$ Hz, C(O)); δ^{lit} [15] 18.5 ($J = 143.8$ Hz), 29.9, 36.3 ($J = 3.9$ Hz), 52.7 ($J = 6.5$ Hz), 205.8 ($J = 14.5$ Hz).

3-Oxobutyl-diphenylphosphine Oxide **2** *by the Reaction of Methylvinylketone and Diphenylphosphine Oxide.* Yield: 0.80 g (70%); ^{31}P NMR ($CDCl_3$): δ 32.7, δ^{lit} [10] 30.2 (C_6H_6); ^{13}C NMR: δ 22.8 ($J = 73.7$ Hz, PCH_2), 29.2 ($C(O)CH_3$), 34.7 ($C(O)CH_2$), 128.4 ($J = 11.7$ Hz, C_β)*, 130.3 ($J = 9.4$ Hz, C_γ)*, 131.6 (C_δ), 131.9 ($J = 99.5$ Hz, C_α), 205.7 ($J = 13.2$ Hz, C(O)) (*: may be reserved); δ^{lit} [16] 23.6 ($J = 73.5$ Hz), 29.5, 35.3 ($J = 2.9$ Hz), 128.5–135.2, 205.5 ($J = 11.8$ Hz).

Diethyl-3-oxocyclohexylphosphonate **3** *by the Reaction of Cyclohexene-2-one and Diethylphosphite.* Yield: 0.42 g (42%); ^{31}P NMR ($CDCl_3$): δ 29.1; ^{13}C NMR: δ 16.5 ($J = 5.8$ Hz, OCH_2CH_3), 24.5 ($J = 4.5$ Hz, C_6), 26.1 ($J = 18.8$ Hz, C_5), 36.0

($J = 146.1$ Hz, PCH_2), 40.6 ($J = 5.0$ Hz, C_2)*, 41.2 ($J = 0.9$ Hz, C_4)*, 62.1 ($J = 7.0$ Hz, OCH_2CH_3), 62.2 ($J = 6.9$ Hz, OCH_2CH_3), 209.1 ($J = 16.5$ Hz, C(O)) (*: may be reserved); δ^{lit} [15] 16.4 ($J = 5.3$ Hz), 24.3 ($J = 4.6$ Hz), 25.9 ($J = 19.1$ Hz), 35.8 ($J = 145.7$ Hz), 40.5 ($J = 5.3$ Hz), 41.0 ($J = 2.0$ Hz), 61.8 ($J = 4.0$ Hz), 61.9 ($J = 4.0$ Hz), 208.8 ($J = 16.5$ Hz).

Diethyl-2-hydroxy-2-butylphosphonate **4** *was Prepared from Ethylmethylketone and Diethylphosphite by the Method Shown Above Applying a Reaction Time of 6 h.* Yield: 0.12 g (15%); ^{31}P NMR ($CDCl_3$): δ 27.8; ^{13}C NMR ($CDCl_3$): δ 7.1 ($J = 8.2$ Hz, CH_2CH_3), 16.7 ($J = 5.5$ Hz, OCH_2CH_3), 21.4 ($J = 4.4$ Hz, $C(OH)CH_3$), 30.1 ($J = 4.4$ Hz, $C(OH)CH_2$), 62.9 ($J = 7.0$ Hz, OCH_2CH_3), 72.1 ($J = 161.0$ Hz, PC).

Alternative Methods for the Synthesis of Diethyl-3-oxobutylphosphonate **1b**

Under Phase-Transfer Catalytic Conditions. To the solution of 0.35 mL (4.29 mmol) of methylvinylketone, 0.55 mL (4.29 mmol) of diethylphosphite, and 0.10 g (0.44 mmol) of TEBAC in 10 mL of dichloromethane, 1.71 g (43.0 mmol) of sodium hydroxide in 5.7 mL of water was added dropwise. After a reflux of 3 h, the phases were separated and the aqueous phase was washed with chloroform. The combined organic phase was dried and the crude product obtained after evaporation was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 0.51 g (57%) 3-oxobutyl derivative **1b** (^{31}P NMR ($CDCl_3$): δ 31.4).

In the Presence of DBU. A solution of 0.12 mL (1.43 mmol) of methylvinylketone, 0.18 mL (1.43 mmol) of diethylphosphite, and 0.05 mL (0.72 mmol) of DBU in 2 mL of chloroform was stirred at the boiling point for 3 h. Then the mixture was washed with 5 mL of 5% HCl, the organic phase was dried and the crude product was obtained after evaporation passed through a small layer of silica gel applying 3% methanol in chloroform to give 0.22 g of an 89:11 mixture of 3-oxobutyl derivative **1b** (~66%, ^{31}P NMR ($CDCl_3$): δ 31.3) and bis-adduct **5** (^{31}P NMR ($CDCl_3$): δ_1 26.3 and δ_2 32.8, $(M + H)^+ = 347$).

By a Trimethylaluminum-Mediated Reaction. To 0.55 mL (4.29 mmol) of diethylphosphite in 5 mL of dry chloroform, 2.14 mL (4.29 mmol) of 2 M trimethylaluminum in hexane was added at 0°C. After stirring a period of 20 min, 0.35 mL (4.29 mmol) of methylvinylketone in 5 mL of chloroform was added dropwise. After complete addition, the cooling bath was removed and the mixture was stirred for 20 h. Then the mixture was hydrolyzed with 20 mL of 5% HCl and the organic phase was separated and dried. The crude product was passed through a small layer of silica gel applying 3% methanol in chloroform to furnish 0.74 g of a 22:78 mixture of bis-adduct **5** (^{31}P NMR ($CDCl_3$): δ_1 26.5 and δ_2 33.0, $(M + H)^+ = 347$) and hydroxyphosphonate **6** (~65%, ^{31}P NMR ($CDCl_3$): δ 24.0, $(M + H)^+ = 209$).

Using triethylaluminum/hexane instead of trimethylaluminum/hexane, a 48:19:33 mixture of **1b, 5**, and **6** was obtained.

Microwave Synthesis of 3-Oxobutyl-diphenylphosphine Oxide **2**

A mixture of 0.11 mL (1.42 mmol) of methylvinylketone and 0.10 g (1.42 mmol) of diphenylphosphine oxide is heated at 95°C under N_2 atmosphere in a CEM Discovery microwave reactor (applying ca. 50 W) for 1 h. The crude product was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 0.15 g (75%) 3-oxobutyl derivative **2** (^{31}P NMR ($CDCl_3$): δ 32.3).

REFERENCES

[1] Enders, D.; Saint-Dizier, A.; Lannou, M-I.; Lenzen, A. Eur J Org Chem 2006, 29.
[2] Tanaka, M. J. Top Curr Chem 2004, 232, 25.
[3] Alonso, F.; Beletskaya, I. P.; Yus, M. Chem Rev 2004, 104, 3079.
[4] Pudovik, A. N.; Konovalova, I. V. Synthesis 1979, 81.
[5] Tedeschi, L.; Enders, D. Org Lett 2001, 3, 3515.
[6] Enders, D.; Tedeschi, L.; Bats, J. W. Angew Chem 2000, 112, 4774.
[7] Enders, D.; Tedeschi, L.; Bats, J. W. Angew Chem Int Ed 2000, 39, 4605.
[8] Jackson, P. F.; Slusher, B. S. Curr Med Chem 2001, 8, 949.
[9] Harsányi, K.; Domány, Gy.; Greiner, I.; Forintos, H.; Keglevich, Gy. Heteroatom Chem 2005, 16, 562.
[10] Keglevich, Gy.; Sipos, M.; Imre, T.; Ludányi, K.; Szieberth, D.; Tőke L. Tetrahedron Lett 2002, 43, 8515.
[11] Keglevich, Gy.; Sipos, M.; Szieberth, D.; Nyulászi, L.; Imre, T.; Ludányi, K.; Tőke, L. Tetrahedron 2004, 60, 6619.
[12] Keglevich, Gy.; Sipos, M.; Szieberth, D.; Petőcz, Gy.; Kollár, L. J Organomet Chem 2004, 689, 3158.
[13] Green, K. Tetrahedron Lett 1989, 30, 4807.
[14] McClure, C. K.; Jung, K-Y. J Org Chem 1991, 56, 867.
[15] Christopher, A.; Verbicky, C. A.; Zercher, C. K. J Org Chem 2000, 65, 5615.
[16] Mikolajczyk, M.; Zatorski, A. J Org Chem 1991, 56, 1217.