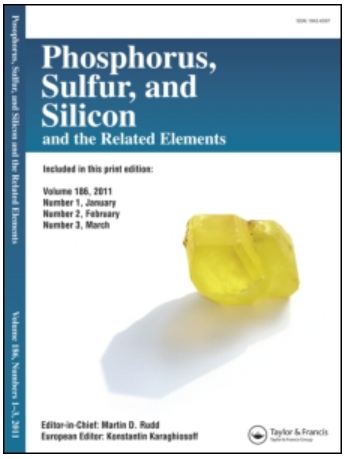

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Phase-Transfer-Catalyzed Michaelis-Becker Synthesis of Dialkyl Methyl Phosphonates

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To cite this Article Fakhraian, Hossein and Mirzaei, Akbar(2006) 'Phase-Transfer-Catalyzed Michaelis-Becker Synthesis of Dialkyl Methyl Phosphonates', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 3, 511 — 518
To link to this Article: DOI: 10.1080/10426500500263789
URL: http://dx.doi.org/10.1080/10426500500263789

Phosphorus, Sulfur, and Silicon, 181:511–518, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500263789

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Phase-Transfer-Catalyzed Michaelis-Becker Synthesis of Dialkyl Methyl Phosphonates

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A liquid–liquid phase-transfer-catalyzed (PTC) Michaelis-Becker reaction was adopted in the preparation of dialkyl methyl phosphonate (R = Me, iPr, nBu, and iBu). This was performed by the reaction of an appropriate dialkyl hydrogen phosphonate with methyl iodide in the presence of benzyl triethyl ammonium chloride and sodium hydroxide as PTC and base, respectively. A liquid–liquid two-phase system (H_2O/CH_2Cl_2) introduced a suitable situation for the preparation of dialkyl methyl phosphonates with bulky alkyl groups (R = iPr, nBu, and iBu), but with R = Me, the hydrolysis of dimethyl hydrogen phosphonate (reagent) reduced the yield to 22%. In this case, a solid–liquid PTC-free system was successfully applied and yield of over 80% was obtained.

Keywords Dialkyl methyl phosphonate; Michaelis-Becker reaction; phase-transfer-catalyzed reaction

INTRODUCTION

Functionalized phosphonic acids and their derivatives have obviously interesting applications as insecticide (Dipterex), herbicide (Glyphosate), and antibiotic (Phosphinothricine).[1,2] Those are generally produced by the hydrolysis of their phosphonic ester homologues.[3]

The Michaelis-Arbuzov (MA) and Michaelis-Becker (MB) reactions are the most widely used methods for the preparation of phosphonic esters such as dialkyl alkyl phosphonates (DAAP:R′P(O)$(OR)_2$).[4] These two reactions occur following different mechanisms using trialkyl phosphite (TAP:$P(OR)_3$) and dialkyl hydrogen phosphonate (DAHP:$(RO)_2P(O)H$) as reagents and an alkyl halide (R′X) as alkylating agent (Scheme 1). The cited reactions have their own advantages and disadvantages regarding the DAAP to be prepared.[5,6]

Received February 24, 2005; accepted May 1, 2005.
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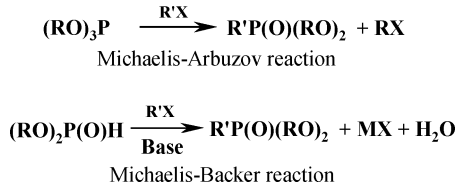


SCHEME 1

With a bulky R′X, the MA reaction requires forcing conditions to proceed and if R′ > R, a mixture of $R'P(O)(OR)_2$ and $RP(O)(OR)_2$ is obtained in which the latest (undesirable) is formed as the main product.[7]

Upon warming TAP (with R = *i*Pr and *t*Bu), olefin elimination was expected to occur readily. The same result was observed when methyl iodide reacted above TAP in low temperature.[8]

The above disadvantages of an MA reaction disappear in an MB reaction, which requires milder conditions to occur and yields the main product regardless of the size of R and R′. The MB proceeds well with a large R′X where MA fails to act. The choice of TAP or DAHP as a principal reagent—in MA and MB reactions, respectively—is resolved in favor of the DAHP (when R > Me) due to their considerably lower cost and more stability.

However, the general use of an MB reaction is limited by the requirement of a strong anhydrous base (e.g., alkali metal or hydrides) to form a conjugate base.[9] It has been stated that because such bases are reactive toward the alkylating agents, it is necessary to prepare the organophosphorus alkali metal salts in stoichiometric quantities prior exposing it to a alkylating agent. A stepwise procedure such as this results in a high concentration of a strong nucleophile and leads to undesirable side reactions.

Another threshold characteristic of the DAHP metal salt derivatives is their limited solubility in inert organic solvents. A solid–liquid Phase-Transfer Catalyzed (PTC)-free system has been extensively studied to prepare DAAP, but the limitation of the method is not explicitly explained.[10–12]

The PTC system, which is widely and successfully employed in different branches of organic chemistry,[13] was well suited to an MB reaction[14–16] and substantially relieved the limitation previously described. A PTC reaction can be proceed using a liquid–liquid or solid–liquid system in which the mineral base (e.g., NaOH or K_2CO_3) abides in a solid or liquid (aqueous) phase and DAHP with alkyl halide coexists in an organic liquid phase.

A liquid–liquid (organic–aqueous) PTC system with sodium hydroxide as a mineral base and a quaternary ammonium salt (such as methyl tricaprylyl ammonium chloride) was successfully applied to the MB reaction of DAHP with chloroacetamide.[16] The preparation of DAMP has not been deeply investigated by this method.

Despite many advantages, the PTC system has some limitations, one of them being the hydrolytic activity of concentrated aqueous alkali. It is generally known that DAHPs are hydrolyzed in aqueous environments, whether acidic or basic condition. So, attempts have been made to accomplish an MB reaction in a solid–liquid system using quaternary ammonium salt or crown ether as PTC.[14,15]

By this method, diethyl benzyl phosphonate was prepared with a 66% yield using K_2CO_3 (as a base), $C_6H_5CH_2Cl$ (as an alkylating agent), and tetra-*n*-butyl ammonium bromide (as PTC) at 100°C after 3 h.[14]

RESULTS AND DISCUSSION

We attempted to prepare Dialkyl Methyl Phosphonate (DAMP: alkyl = Me, *i*Pr, *i*Bu, *n*Bu) by a solid–liquid PTC-free, solid–liquid, and liquid–liquid PTC MB reaction and compared the yield in three procedures.

An MB reaction was carried-out by DAHP and methyl iodide according to two-phase systems (solid–liquid and liquid–liquid) in the presence or absence of PTC using sodium metal, sodium hydroxide, or sodium carbonate as a basic agent. ^{31}P NMR spectroscopy was utilized to determine the conversion rate of DAHP.

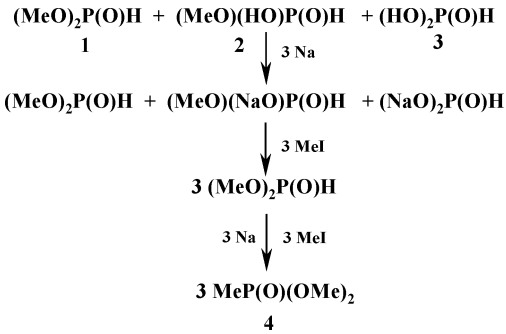
DAHP was prepared by the McCombie method—recently reconsidered[17]—and an MB reaction was performed using DAHP and methyl iodide by the three following two-phase systems:

1. a solid–liquid PTC-free system,
2. a solid–liquid PTC system, and
3. a liquid–liquid PTC system.

In our previous study, we showed that in the synthesis of dimethyl hydrogen phosphonate (DMHP) by esterification of phosphorus trichloride with methanol, the hydrogen chloride cleavage of the formed product is an undesirable side reaction and is difficult to control.

In the first experiment (Table I, entries 1–4), we intently tried to perform the MB reaction according to the method 1 on the phosphorus trichloride-methanol reaction mixture in the worst unfavorable conditions in which a large amount of HCl cleavage products were formed (Scheme 2). So a dropwise addition of phosphorus trichloride

to methanol at 25°C afforded the mixture of **1** (57%), **2** (35%), and **3** (5%) (Table I, entry 1).



SCHEME 2

Succeeding the esterification of phosphorus trichloride with methanol, a molar addition of sodium and methyl iodide did not vary considerably the composition of the reaction mixture (Table I, entries 2 and 3), and a minor amount of **4** (6–10%) was obtained.

The second molar addition of sodium and methyl iodide caused the presence of a considerable amount of **4** (79%) (Table I, entry 4). It can be deduced that the sodium salts formation of **2**,**3**—and their transformation to **1** by methyl iodide—appeared before the sodium salt formation of **1** and the production of **4** (Scheme 2). So the formation of **2** and **3** by the hydrogen chloride cleavage of **1** increased the amount of sodium and methyl iodide necessary to produce **4**.

When the esterification process was conducted under optimized conditions during which pure DMHP was synthesized, the sodium salt of DMHP formed a very sticky viscous material that was very difficult to

TABLE I Proportional Composition (%)[a] of the Phosphonic Acid Derivatives After the Esterification of PCl_3 with methanol and MB Reaction According to Solid-Liquid PTC-Free System (Method A)

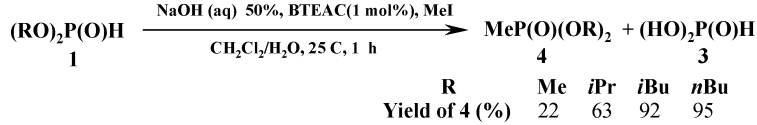
Entry	PCl_3 (mol, mL)	MeOH (mol, mL)	Na (mol, g)	MeI (mol, mL)	$CHCl_3$ (mL)	Time (h)	Temp (°C)	**1**	**2**	**3**	**4**	Deriv.
1	0.05, 4.4	0.15, 5.5	—	—	10	0.5	25	57	35	5	—	3
2	—	—	0.05, 1.15	—	10	40	reflux	35	35	2	6	22
3	—	—	—	0.05, 3.1	—	15	reflux	42	18	1	10	29
4	—	—	0.05, 1.15	0.05, 3.1	—	10	reflux	—	—	—	79	21

[a]Based on ^{31}P NMR spectroscopy.

be mixed with methyl iodide. The same phenomenon was observed with other DAHP.

For reducing the reaction time, we repeated the same reaction using K_2CO_3 or NaOH as a mineral base and Benzyl Triethyl Ammonium Chloride (BTEAC) as PTC (method b). So, the dropwise addition of the DMHP solution (in CH_2Cl_2) to a suspension of a base (K_2CO_3 or NaOH) in CH_2Cl_2 containing BTEAC (1 mol%) and methyl iodide prevented the coagulation of the formed precipitate, but in these conditions, the conversion of DMHP to dimethyl methyl phosphonate (DMMP) was not observed after several hours at a reflux temperature (40°C). In spite of this, we obtained a very pure and stable DMHP, which was not further subjected to the hydrogen chloride cleavage. We presume that in such conditions, hydrogen chloride is neutralized and sodium salt of **2** ((MeO)(NaO)P(O)H) and **3** ($(NaO)_2P(O)H$) are transformed to **1** by methyl iodide. This is perhaps the method for obtaining pure and stable HCl-free DMHP.

In order to overcome this anomaly in the MB reaction, we adopted method c to facilitate the reagent mixing. In a liquid–liquid PTC system, a high saturated sodium hydroxide aqueous solution (50%) served to prepare the salt of DMHP, which was transferred to the organic phase (CH_2Cl_2) for further reaction with methyl iodide. These sequences of reactions occurred readily at room temperature (RT) in 1 h (Table II). Nevertheless, the yield was not more than 22% and a major part of the reagent (DMHP) was hydrolyzed to **3** (Scheme 3).



SCHEME 3

Performing the same procedure for other DAHPs with more bulky alkyl groups (R = *i*Pr, *i*Bu, and *n*Bu), afforded a satisfactory yield (63–95%) (Scheme 3). So there was a considerable reduction of reaction

TABLE II Reaction Time and Yield of DAMP (Alkyl = Me, *i*Pr) in a Solid–Liquid PTC-Free (Method A) and Liquid–Liquid PTC MB Reaction (Method C)

DAMP	Solid-liquid PTC-free time, yield	Liquid–liquid PTC time, yield
DMMP	65 h, 84%	1 h, 22%
D*i*PrMP	40 h, 33%	1 h, 63%

TABLE III ^{31}P and ^{1}H NMR Spectra of Dialkyl Methyl Phosphonate DAMP (Alkyl = Me, *i*Pr, *n*Bu, *i*Bu)

DAMP	^{31}P NMR δ(ppm)	^{1}H NMR δ, J (ppm, Hz)
$MeP(O)(OMe)_2$	34.1 (m)	1.4 (d, CH_3P, 17.5), 3.75 (d, CH_3O, 10)
$MeP(O)(OiPr)_2$	29.5 (m)	1.09 (d, CH_3, 7), 1.15 (d, CH_3P, 7.5), 4.5 (m, CH)
$MeP(O)(OiBu)_2$	31.7 (m)	0.91 (d, CH_3P, 6.7), 0.95 (d, CH_3, 6.7), 1.9 (m, CH), 3.8 (m, CH_2O)
$MeP(O)(OnBu)_2$	30.7 (m)	0.91 (d, CH_3P, 7.2), 0.94 (t, CH_3 , 6.7), 1.4 (m, CH_2), 1.6 (m, CH_2), 4.1 (m, CH_2O)

time and a favorable yield in the preparation of DAMP with bulky alkyl groups by the implementation of a liquid–liquid PTC system (Scheme 3 and Table II). The only disadvantage of this process was the time-consuming phase-separation procedure. Effectively, the aqueous phase was very viscous, making it difficult to separate from the organic phase.

^{1}H NMR spectrum of the DMMP showed a large $^{2}J_{H\text{-}P}$ value (17.5 Hz), whereas the $^{2}J_{H\text{-}P}$ values in the other DAMP with more bulky alkyl groups (R = *i*Pr, *i*Bu, and nBu) are ~7 Hz (Table III).

CONCLUSIONS

A liquid–liquid PTC system was successfully applied to prepare a high yield of pure DAMP with bulky alkyl groups (e.g., *i*Pr, *n*Bu, and *i*Bu) in a short time (1 h). This system was not adequate for the preparation of DMMP, in which the reagent (DMHP) was hydrolyzed to $(HO)_2P(O)H$. According to the solid–liquid PTC-free system, a high yield of pure DMMP were obtained by the use of an excess amount of sodium metal and methyl iodide after 65 h at reflux temperature. An excess amount of sodium metal and methyl iodide were consumed to convert the hydrogen chloride cleavage products of DMHP after the esterification process (i.e., $(HO)_2P(O)H$ and $(MeO)(HO)P(O)H$ to DMHP). So this can be accounted for producing pure DMHP, which is free from the hydrogen chloride cleavage.

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX-250 instrument (250 MHz for ^{1}H and 100 MHz for ^{31}P). CDCl3 was used as a solvent; chemical shifts were reported in δ (ppm) from TMS (^{1}H) and 85%H_3PO_4 (^{31}P), with downfield shifts being positive.

Solid–Liquid Phase-Transfer-Catalyzed-Free Michaelis-Becker Synthesis of DMMP

Small pieces of alkali metal sodium (1.15 g, 0.05 mol) and $CHCl_3$ (10 mL) were placed in a 100-mL three-necked flask. Then DMHP was obtained by the esterification of phosphorus trichloride (4.4 mL, 0.05 mol) with MeOH (5.5 mL, 0.15 mol), diluted by 10 mL $CHCl_3$, and added dropwise to the flask. The reaction was continued at a reflux temperature for 40 h. Then methyl iodide (3.4 mL, 0.055 mol) was added and the reaction was continued for another 15 h. An incomplete reaction led us to add another equivalent amount of Na and methyl iodide and to continue the reaction for another 10 h at a reflux temperature. The product was centrifuged and a clear liquid was obtained. The evaporation of the solvent left 5.2 g (0.042 mol, 84%) of DMMP with 80% purity.

The previously mentioned procedure was repeated for the synthesis of D*i*PrMP. So D*i*PrHP was obtained by the esterification of phosphorus trichloride (4.4 mL, 0.05 mol) with *i*PrOH (11.5 mL, 0.15 mol) was diluted by 25 mL of heptane, and was added dropwise to a solution of 25 mL of heptane and 1.15 g of Na (cut to small pieces). The reaction was continued at reflux temperature for 30 h. Then methyl iodide (6.2 mL, 0.1 mol) was added to the mixture and the reaction was continued for another 10 h. After the evaporation of the solvent, 3 g (0.017 mol, 33%) of D*i*PrMP with 95% of purity was obtained.

Liquid-Liquid Phase-Transfer-Catalyzed Michaelis-Becker Synthesis of DMMP

A solution of methyl iodide (12.4 mL, 0.2 mol), BTEAC (0.23 g), 50% sodium hydroxide (25 g NaOH and 25 mL H_2O), and 25 mL of CH_2Cl_2 was placed in a 200-mL three-necked flask immersed in an ice bath and equipped with a stirring device and an inert gas fitting. Then a solution of DMHP (11.2 g of 85% purity, 0.085 mol), BTEAC (0.23 g), and CH_2Cl_2 (25 mL) was added dropwise (for 20 min) to the flask. Then the organic layer was separated and centrifuged and the solvent was vacuum stripped. The pure product as a clear liquid weighed 2.3g (0.018 mol, 22%).

The previously mentioned procedure was repeated for the preparation of another DAMP (R = *i*Pr, *n*Bu, and *i*Bu) (^{1}H and ^{31}P NMR characteristics are in Table III).

The liquid–liquid PTC MB reaction in the solution of diisopropyl hydrogen phosphonate (23.8 mL, 0.1 mol), methyl iodide (6.2 mL, 0.1 mol), and CH_2Cl_2 (50 mL) in the presence of BTEAC (0.23 g, 0.001 mol)

and 50% sodium hydroxide (25 g NaOH and 25 ml H_2O) afforded 11.4 g (0.06 mole, 63%) of diisopropyl methyl phosphonate.

A liquid–liquid PTC MB reaction in the solution of di-n-butyl hydrogen phosphonate (18.3 mL, 0.094 mol), methyl iodide (6 mL, 0.094 mol) and CH_2Cl_2 (50 mL) in the presence of BTEAC (0.23 g, 0.001 mol) and 50% sodium hydroxide (25 g NaOH and 25 ml H_2O) afforded 18.6 g (0.09 mole, 95%) of di-n-butyl methyl phosphonate.

A liquid–liquid PTC MB reaction in the solution of diisobutyl hydrogen phosphonate (9.7 g, 0.05 mol), methyl iodide (3.1 mL, 0.05 mol) and CH_2Cl_2 (50 mL) in the presence of BTEAC (0.23 g, 0.001 mol) and 50% sodium hydroxide (25 g NaOH and 25 ml H_2O) afforded 9.5 g (0.046 mole, 92%) of diisobutyl methyl phosphonate.

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