Novel Approach to the Synthesis of Alkoxycarbonylmethyl- and Bis(alkoxycarbonylmethyl)phosphine Oxides Based on a Reformatsky-Type Reaction

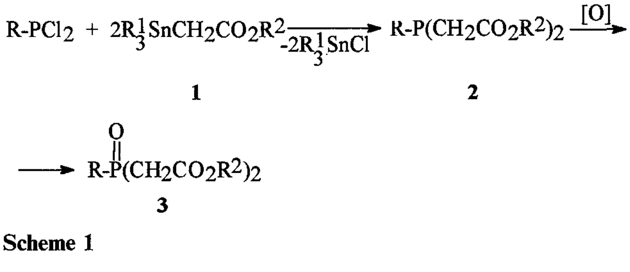
Piotr Kiełbasiński,* Marian Mikołajczyk

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, Sienkiewicza 112, 90-363 Łódź, Poland

Received 28 July 1994; revised 2 September 1994

A new procedure for the preparation of alkoxycarbonylmethyl- and bis(alkoxycarbonylmethyl)phosphine oxides is described, which consists of a Reformatsky-type reaction between chlorophosphines or dichlorophosphines and alkyl bromoacetates in the presence of zinc, followed by oxidation.

In connection with our studies on the enzyme-mediated preparation of optically active heteroorganic compounds having a single chiral centre at the heteroatom,[1,2] we became interested in the synthesis of a new type of prochiral substrate, namely bis(alkoxycarbonylmethyl)phosphine oxides **3**. An inspection of the literature revealed only a few papers devoted to the preparation of these type of compounds.[3] Lutsenko[3a] and others[3b,c] treated phosphorus trichloride or dichlorophosphines with alkyl trialkylstannylacetates **1** and obtained appropriate phosphines **2** which were subsequently oxidized to phosphine oxides **3**.



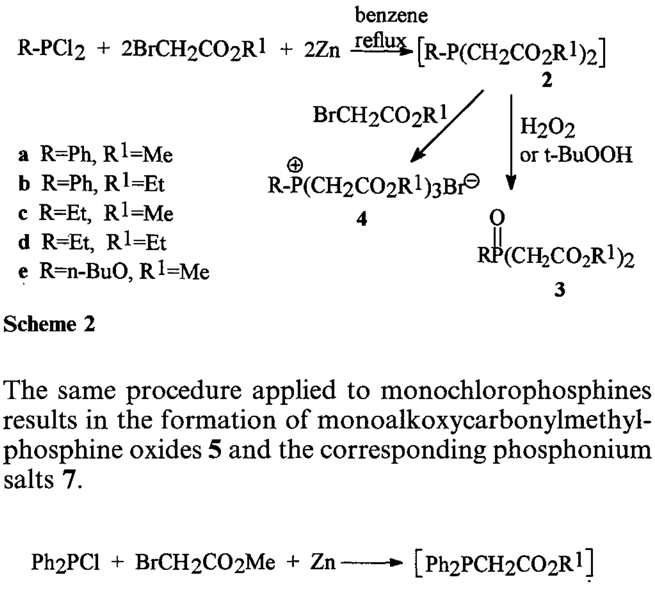
Scheme 1

However, stannyl derivatives are quite unpleasant and difficult to handle due to their toxicity. Moreover, synthesis of **1** is based on a troublesome reaction of trialkylalkoxystannanes with ketene[4] and the weight of trialkylchlorostannanes formed as byproducts in the above reaction is equal to or even higher than the weight of the final products. All these reasons prompted us to look for another general and more convenient approach to the preparation of compounds **3**.

We turned our attention to the Reformatsky-type reaction by which alkyl trimethylsilylacetates can be obtained from alkyl bromoacetates and chlorotrimethylsilane in the presence of zinc dust,[5] in the hope that it could be adapted to our purposes;[6] our assumption was correct and the synthesis of the desired phosphine oxides **3** could be accomplished applying the procedure described.

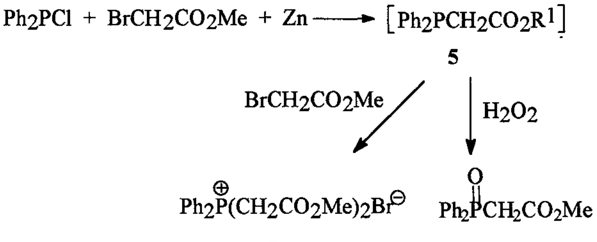
A mixture of an appropriate dichlorophosphine and two equivalents of an alkyl bromoacetate is refluxed in benzene in the presence of two equivalents of zinc dust. Some crystals of iodine are usually added to initiate the reaction. It is crucial for the reaction to maintain fully anhydrous conditions (see Experimental) and to employ vigorous stirring. After refluxing for about four hours the zinc dissolves almost completely and an insoluble, thick oily product appears on the bottom of the flask, which is probably a complex of zinc halides and phosphines **2**. In this way the phosphines are protected from subsequent reactions such as oxidation by air or quaternization. However, attempts to isolate free phosphines **2** have so far been unsuccessful, because after decomposition of the complex by adding water, they react quite rapidly with the remaining bromoacetate to produce phosphonium salts **4** (the salt **4a** has been isolated and characterized; see Table).

For this reason, phosphines **2** were oxidized in situ by adding a solution of hydrogen peroxide in an alcohol to the reaction mixture. In the case of **2e**, *tert*-butyl hydroperoxide was used as oxidizing agent in order to avoid hydrolysis of the butoxy group. Phosphine oxides **3** obtained in this way are finally isolated and purified by column chromatography or distillation.



Scheme 2

The same procedure applied to monochlorophosphines results in the formation of monoalkoxycarbonylmethylphosphine oxides **5** and the corresponding phosphonium salts **7**.



Scheme 3

It is interesting to note that phosphine oxides **3** exhibit very characteristic electron impact (EI) mass spectra. In all cases (except for **3e**), the most abundant peaks are phosphacations $R{-}\overset{+}{P}(O){-}OR^1$ (**10**). Their composition has been established by peak matching in the case of **3a** ($m/e_{\text{found}} = 155.0279$; for $C_7H_8O_2P$ $m/e_{\text{calc.}} = 155.0262$)

Table. Alkoxycarbonylmethylphosphine Oxides **6**, Bis(alkoxycarbonylmethyl)phosphine Oxides **3** and Phosphonium Salts **4** and **7**

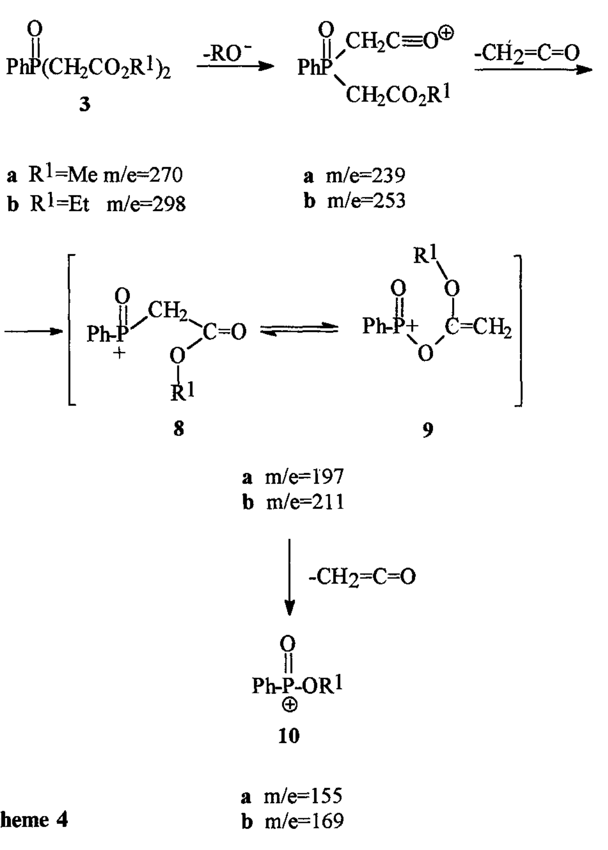
Product	Yield (%)	mp or bp (°C)	^{31}P NMR [δ]	^1H {^{13}C} NMR δ, J (Hz)	MS [m/e]
$PhP(O)(CH_2CO_2Me)_2$ **3a**	64	102–104	28.9	3.41 (d, 4H, $J_{H,P}$ = 15.25, CH_2), 3.56 (s, 6H, CH_3), 7.45–7.75 (m, 5H, Ph), {37.65 (d, $J_{P,C}$ = 63, CH_2), 52.5 (s), 128–132 (Ph), 166.6 (d, $J_{P,C}$ = 4.6, CO)}	270 [M^+], 239 [M^+-OMe], 207 [239-HOMe], 197 [M^+-H_2CO_2Me], 155 $[PhP(O)OMe]^+$
$PhP(O)(CH_2CO_2Et)_2$ **3b**	64	semisolid	29.0	1.14 (t, 6H, $J_{H,H}$ = 7.14, CH_3), 3.39 (d, 4H, $J_{H,P}$ = 15.24, CH_2P), 4.1 (q, 4H, $C\underline{H}_2CH_3$), 7.4–7.9 (m, 5H, Ph)	29.8 [M^+], 253 [M^+-OEt], 211 [M^+-CH_2CO_2Et], 169 $[PhP(O)OEt]^+$, 141 $[PhP(O)OH]^+$
$EtP(O)(CH_2CO_2Me)_2$ **3c**	45	56–59	41.5	1.23 (dt, 3H, $J_{H,H}$ = 7.76, $J_{H,P}$ = 18.77, $C\underline{H}_3CH_2$), 1.97 (dq, 2H, $J_{H,P}$ = 12, $CH_3C\underline{H}_2$), 3.13 (ABX, 4H, $J_{H,P}$ = 15, CH_2P), 3.73 (s, 6H, CH_3O), {5.0 (d, $J_{P,C}$ = 5.57, $\underline{C}H_3CH_2$), 21.97 (d, $J_{P,C}$ = 70.86, $\underline{C}H_2CH_3$), 35.4 (d, $J_{P,C}$ = 58.4, CH_2P), 52.49 (s, CH_3O), 166.75 (d, $J_{P,C}$ = 3.3, CO)}	222 [M^+], 191 [M^+-OMe], 149 [M^+-CH_2CO_2Me], 107 $[EtP(O)OMe]^+$, 161, 151
$EtP(O)(CH_2CO_2Et)_2$ **3d**	48	oil	42	1.12 (dt, 3H, $J_{H,H}$ = 7.76, $J_{H,P}$ = 18.76, $C\underline{H}_3CH_2P$), 1.15 (t, 6H, $J_{H,H}$ = 7.15, $C\underline{H}_3CH_2O$), 1.88 (dq, 2H, $J_{H,P}$ = 12, $CH_3C\underline{H}_2P$), 3.0 (ABX, 4H, $J_{H,P}$ = 15, PCH_2CO), 4.06 (q, 4H, CH_2O)	250 [M^+], 205 [M^+-OEt], 163 [M^+-CH_2CO_2Et], 121 $[EtP(O)OEt]^+$, 93 $[EtPO_2H]^+$
$BuOP(O)(CH_2CO_2Me)_2$ **3e**	62	(80/ 0.4 Torr)	38.7	0.85 (t, 3H, $C\underline{H}_3CH_2$), 1.2–1.4 and 1.5–1.61 (m, 4H, CH_2), 3.1 (d, 4H, $J_{H,P}$ = 18.1, CH_2P), 3.67 (d, 6H, $^5J_{H,P}$ = 0.45, OCH_3), 4.03 (q, 2H, CH_2O)	266 [$M^+ + 1$], 211 $[(HO)_2P(CH_2CO_2Me)_2]^+$, 179 $[HOP(O)CH_2CO_2Me]^+$, 95 $[HOP(O)OMe]^+$
$Ph_2P(O)CH_2CO_2Me$ **6**	63	93–97	27.4	3.48 (d, 2H, $J_{H,P}$ = 14.7, CH_2), 3.54 (s, 3H, CH_3), 7.4–7.9 (m, 14H, Ph)	274 [M^+], 232 $[Ph_2PO_2Me]^+$, 217 $[Ph_2PO_2]^+$, 201 $[Ph_2PO_2]^+$, 155 $[PhP(O)OMe]^+$, 77 $[Ph]^+$
$[Ph_2P(CH_2CO_2Me)_2]^+Br^-$ **7**	68	150–152	20.9	3.58 (s, 6H, CH_3), 5.22 (d, 4H, $J_{H,P}$ = 13.64, CH_2), 7.6–8.1 (m, 14H, Ph)	FAB (+ve): 331 [cation] FAB (−ve): 410.9 [M^+-1], 490.8 [$M^+ + Br^-$-1]
$[PhP(CH_2CO_2Me)_3]^+Br^-$ **4a**	–	125–129	21.8	3.71 (s, 9H, CH_3), 4.88 (d, 6H, $J_{H,P}$ = 14, CH_2), 7.5–7.8 and 8.15–8.3 (m, 5H, Ph)	327 $[PhP(CH_2CO_2Me)_3]^+$

and **3b** (m/e_{found} = 169.0419; for $C_8H_{10}O_2P$ $m/e_{calc.}$ = 169.0418). Moreover, observation of metastable peaks proved that they were daughter peaks of phosphacations **8** or **9**. Such fragmentation seems more likely when one assumes a rearrangement involving an initial isomerization of cations **8** to their enol ester analogues **9** followed by an alkyl group migration and extrusion of ketene via a six-membered transition state. An alternative direct migration of the whole alkoxy group in **8** seems less probable, due to the energetically less favored four-membered transition state.

All substrates were commercially available. NMR spectra were recorded in $CDCl_3$ on a Brüker 200 MHz spectrometer. Mass spectra were recorded on a Finnigan MAT-95 spectrometer. Melting points were uncorrected. Column chromatography: silica gel 60 (70–230 mesh Merck). Satisfactory microanalyses were obtained for compounds **3a**, **3c–e**, **6**, **4a** (C ± 0.5, H ± 0.3, P ± 0.4) and for **3b**, **7** (H ± 0.3, P ± 0.2).

Alkoxycarbonylmethylphosphine Oxides 6 and Bis(alkoxycarbonylmethyl)phosphine Oxides 3; General Procedure:

Benzene (30 mL) and zinc dust (1.308 g, 0.02 mol) were placed in a 100 mL three-neck round-bottom flask equipped with a mechanical stirrer, dropping funnel and condenser arranged for distillation. To ensure dryness, some benzene (~ 5 mL) was distilled off. The condenser was replaced by a reflux condenser with a $CaCl_2$ tube. A solution of an alkyl bromoacetate (0.02 mol) and a dichlorophosphine (0.01 mol for the synthesis of **3**) or chlorophosphine (0.02 mol for the synthesis of **6**) in dry benzene (5 mL) and dry Et_2O (5 mL) was slowly added to the mixture under gentle reflux.



Scheme 4

During the addition, a crystal of I_2 was added to initiate the reaction (the brown colour of iodine disappeared almost immediately). After the additions, the mixture was very vigorously stirred and refluxed until the zinc had dissolved (~ 4 h). An insoluble thick oil separated onto the bottom. The mixture was cooled to r.t. and 30% hydrogen peroxide (1.5 mL) in 10 mL of methanol or ethanol (depending on R^1) was added dropwise, and stirring was continued for the next 30 min. In the case of **3e**, *tert*-butyl hydroperoxide (80% solution in di-*tert*-butyl peroxide, 1.12 mL) was added instead. Finally, brine (slightly acidified with HCl) and $CHCl_3$ (ca. 40 mL) were added to collect all the organic products in the lower layer. The layers were separated and the aq layer was extracted with chloroform (3 × 10 mL). The combined organic layers were first washed with sodium sulfate(IV) (for **3e**) or sodium thiosulfate to remove the rest of oxidation agents (or sometimes free bromine), and then with water and dried ($MgSO_4$). After evaporation, the crude products were purified by column chromatography (for **3a**–**3d**) using a chloroform/methanol gradient as eluent, or by distillation (for **3e**). For analytical purposes, the crystalline products were additionally crystallized from benzene.

Financial support (Grant No 206189101) by the State Committee of Scientific Research is gratefully acknowledged. The authors also thank Ms. Janina Kmieć for her skilful experimental assistance.

(1) Mikołajczyk, M.; Kiełbasiński, P.; Żurawiński, R.; Wieczorek, M.W.; Błaszczyk, J. *Synlett*, **1994**, 127.

(2) Kiełbasiński, P.; Żurawiński, R.; Pietrusiewicz, K.M.; Zabłokka, M.; Mikołajczyk, M. *Tetrahedron Lett.*, **1994**, *35*, 7081.

(3) (a) Proskurina, M.V.; Novikova, Z.S.; Lutsenko, I.F. *Dokl. Akad. Nauk SSSR* **1964**, *159*, 619.
(b) Vinokurova, G.M. *Zh. Obshch. Khim.* **1967**, *37*, 1652.
(c) Ismagilov, R.K.; Razumov, A.I.; Yafarova, R.L. *Zh. Obshch. Khim.* **1972**, *42*, 1248.
(d) Podlahova, J. *Coll. Czech. Chem. Commun.* **1976**, *43*, 57.
(e) Podlahova, J.; Hartl, F. *Coll. Czech. Chem. Commun.* **1984**, *49*, 586.

(4) Lutsenko, I.F.; Ponomarev, S.V. *Zh. Obshch. Khim.* **1961**, *31*, 2025.

(5) Fessenden, R.j.; Fessenden, J.S. *J. Org. Chem.* **1967**, *32*, 3535.

(6) Podlahova, et al.[3a,e] described a similar approach to the synthesis of phosphines **2**. However, their experimental procedure was, in our hands, less effective, particularly for compounds with R^1 = Me.