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ELECTROCHEMICAL GENERATION AND REACTIONS OF ACYLOXYTRIPHENYLPHOSPHONIUM IONS

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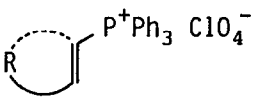
Abstract: Constant-current electrolysis, in an undivided cell, of Ph_3P in the presence of a carboxylic acid in CH_2Cl_2 containing 2,6-lutidinium perchlorate as the supporting electrolyte was shown to generate the corresponding acyloxyphosphonium ion, Ph_3P^+-OCOR, which was converted in situ to esters, amides, and β-lactams under mild conditions.

Triphenylphosphine radical cation [$Ph_3P^{+\bullet}$] (**2**), generated by one-electron oxidation of Ph_3P (**1**), is a strong enough electrophile to react with compounds of weak nucleophilicity at ambient temperature: in the reaction of **2** with benzene, furane, and thiophene, formation of the corresponding phosphonium salts (Ph_3P^+-Ar Y^-) has been demonstrated.[1,2] Thus, electrochemical oxidation of the phosphine **1** in the presence of suitable nucleophiles was expected to afford various phosphonium ions or products derived from them by simple procedures without any special or expensive additives. Quaternary phosphonium ions, either stable or transient, have been proved to occupy an important position in organophosphorus chemistry.

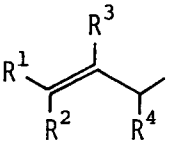
We have so far reported electrochemical one-step preparations of alkylaminotriphenylphosphonium perchlorate (**A**),[3] alkoxytriphenylphosphonium perchlorate (**B**),[4] thioalkoxytriphenylphosphonium perchlorate (**C**),[4,5] 1-alkenyltriphenylphosphonium perchlorate (**D**),[6] allyltriphenylphosphonium tetrafluoroborate (**E**),[7] 2-oxocycloalkyltriphenylphosphonium tetrafluoroborate (**F**),[8] and dioxomethylenetriphenylphosphorane (**G**).[9] Among the products, the alkoxyphosphonium salts **B** can be used as alkylating agents,[4] the phosphonium salts **C** were found to be convenient reagents for the preparation of unsymmetrical

disulfides,[10] the salts F will be useful for Wittig reactions, and the cyclic derivatives of G together with their tributyl analogs (H) will find potential synthetic utility as cycloalkyn-2-one equivalents.[11] Transformations of keto-oximes to amides,[12] amides to nitriles,[13] and ureas to carbodiimides[13] were also achieved by the electrochemical method, though the presumed phosphonium ions were too labile to be isolated.

Ph_3P^+-NHR ClO_4^- (A) Ph_3P^+-OR ClO_4^- (B) Ph_3P^+-SR ClO_4^- (C)



(D)



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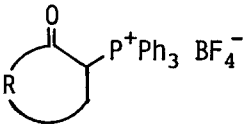
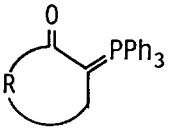
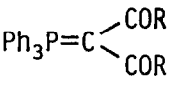
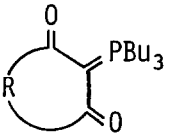


(F) base





(G)



(H)

As a continuation of our work on the application of electrochemically generated phosphonium ions, we turned our attention to acyloxytriphenylphosphonium ions (3), which will be formed by the reaction of the radical cation 2 with carboxylic acids. Acyloxyphosphonium ions including 3 have been suggested as the key intermediates in many synthetically useful reactions.[14-17] However, the counter anions to the phosphonium ions are usually rather strong nucleophiles such as halide ions or RS^-, which might cause unfavorable side reactions. In the electrochemical method, the counter anion to 3 will be ClO_4^- or BF_4^- which show little nucleophilic reactivity.

The preliminary results reported here will implicate the electrochemical generation of 3 by converting the carboxylic acids to esters, amides, and β-lactams.

Ph_3P^+-OCOR (3)

Results and Discussion

Phenoxyacetic acid was selected as a model carboxylic acid, and formation of the corresponding acyloxyphosphonium ion (3, R=-CH_2OPh) was examined first. Since the phosphonium ion was thought to be unstable,[18] it was used in situ to react with p-methoxyphenol to afford $PhOCH_2COOPhOMe$-p. The following procedure was found to give favorable results. A solution of 1 (2 eq.), $PhOCH_2COOH$ (1 eq.) and 2,6-lutidinium perchlorate ($LutClO_4$)(2 eq.) in dry CH_2Cl_2 was subjected to constant-current electrolysis (CCE) at a graphite electrode in an undivided electrolysis cell at 40°C under an N_2 atmosphere until 1F per mol of 1 had been passed. After the electrolysis, Et_3N (5 eq.) and p-MeOPhOH (1 eq.) were added to the solution and the mixture was stirred for 30 min at ambient temperature. The ester was obtained in 77% yield based on the carboxylic acid. The use of other trivalent phosphorus compounds such as Bu_3P or $(PhO)_3P$ in the place of 1 gave poor results.

The process for the ester formation will be represented as shown in Scheme 1.

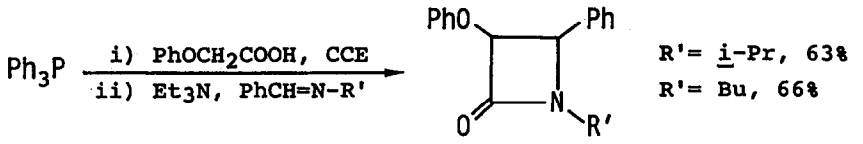
$$\underset{(1)}{Ph_3P} \xrightarrow{-e} Ph_3P^{+\cdot} \xrightarrow[-e,\ -H^+]{RCOOH} \underset{(3)}{Ph_3P^+\text{-}OCOR}$$

$$3 \xrightarrow[Et_3N]{R'OH} RCOOR' + Ph_3PO + Et_3NH^+$$

Scheme 1

On cyclic voltammetry in CH_3CN, oxidation of 1 takes place around 1.0 V vs saturated calomel electrode,[19] while the carboxylic acids used in the present study showed no oxidation peak below 1.8 V. Thus, it is reasonable to assume that the reaction is initiated by one-electron transfer from 1. An alternative process cannot be ruled out, where unreacted carboxylic acid attacks the phsophonium ion to form the corresponding acid anhydride and the latter reacts with the phenol to afford the ester. Actually, in the CCE of 1 with trans-cinnamic acid, formation of cinnamic anhydride (33%) was confirmed at the end of the electrolysis: among the carboxylic acids examined, cinnamic acid gave the

highest yield of anhydride. It was also ascertained that $PhOCH_2COOPhOMe$-p (30%) is produced from $(PhOCH_2CO)_2O$ and p-MeOPhOH in CH_2Cl_2 containing Et_3N at ambient temperature. However, the results of β-lactam formation (Scheme 2) suggest that most of the phenoxyacetate was produced via the phosphonium ion (3, R=-CH_2OPh).



Scheme 2

The β-lactams are considered to be formed by the reaction of the Schiff bases with phenoxyketene, PhOCH=C=O, generated from the phosphonium ion and Et_3N. Synthesis of β-lactams from the ketene has been reported.[20]

When the phosphonium ion (3, R=-CH_2OPh) prepared under the conditions described above was treated with $PhCH_2OH$, $PhCH_2CH_2OH$, and BuOH, $PhOCH_2COOR'$ were obtained in the yields of 69 (R'=-CH_2Ph), 49 (R'=-CH_2CH_2Ph), and 47% (R'=-Bu), respectively. Preparation of p-methoxyphenyl esters of various carboxylic acids was attempted (Table 1), but the yield did not exceed 60%. However, the observed results cannot be ascribed solely to the ineffectiveness of the acids in the formation of acyloxyphosphonium ions at least with the benzoic acids (see below).

The reaction of the phosphonium ion (3, R=-CH_2OPh) with aliphatic primary amines was examined next. When Et_3N and i-$PrNH_2$ were added to the electrolyzed solution of 1 and $PhOCH_2COOH$ and stirred at ambient temperature for 30 min, $PhOCH_2CONH$-i-Pr was obtained in 72% yield. Since aliphatic primary amines are usually oxidized at potentials more positive than the phosphine 1, it seemed feasible to prepare the corresponding carboxamides in one step instead of the two-step reaction described above. CCE of 1, a carboxylic acid, and an amine in CH_2Cl_2 containing $LutClO_4$ at 40°C gave the amides in good yields (Table 2).

Table 1 RCOOH $\xrightarrow{Ph_3P,\ CCE}$ $\xrightarrow{p\text{-MeOPhOH}}$ RCOOPhOMe-p

R	Yield(%)[a]. of ester	R	Yield(%)[a]. of ester
p-MeOPh-	44	Pr-	48
p-MePh-	48	$CH_3CH_2CH(CH_3)$-	34
Ph-	43	$CH_3(CH_2)_3$-	53
m-MeOPh-	47	$PhCH_2CH_2$-	49
p-BrPh-	48	PhCH=CH-	27
p-ClPh-	46	$PhCH=C(CH_3)$-	39
m-BrPh-	49	$C_2H_5CH=CH$-	49
p-CNPh-	32	$CH_3CH=C(CH_3)$-	27
p-NO_2Ph-	0	$CH_3CH=CH$-	36
Me-	58	$CH_2=C(CH_3)$-	19
Et-	52	$CH_2=CH$-	0
i-Pr-	43		

a. Isolated yield based on RCOOH. CCE procedure is described in the Experimental section.

Table 2 RCOOH $\xrightarrow{Ph_3P,\ R'NH_2,\ CCE^{a.}}$ RCONHR'

R	R'	Yield(%)[b]. of amide	R	R'	Yield(%)[b]. of amide
$PhOCH_2$-	i-Pr-	83	p-MeOPh-	i-Pr-	45[c].
$PhOCH_2$-	Bu-	82	m-BrPh-	i-Pr-	67[c].
$PhOCH_2$-	$PhCH_2$-	74	m-ClPh-	i-Pr-	71[c].
$PhOCH_2$-	$PhCH_2CH_2$-	77	p-CNPh-	i-Pr-	66[c].
Ph-	i-Pr-	61	p-MePh-	i-Pr-	34
		71[c].			56[c].
Ph-	$PhCH_2$-	73[c].	$CH_3(CH_2)_8$-	$PhCH_2$-	61[c].

a. Ph_3P, 6 mmol; RCOOH, 3 mmol; $R'NH_2$, 3 mmol: CCE procedure is described in the Experimental section. b. Isolated yield based on RCOOH. c. $R'NH_2$, 6 mmol.

The process for the one-step preparation of the amides is proposed as shown in Scheme 3.

At the anode

$$Ph_3P \xrightarrow{-e} Ph_3P^{+\bullet} \xrightarrow[-e,\ -H^+]{RCOOH} Ph_3P^+\text{-}OCOR \quad (\underline{3}) \qquad (1)$$

$$Ph_3P^{+\bullet} \xrightarrow[-e]{RCOO^-} Ph_3P^+\text{-}OCOR \quad (\underline{3})$$

In the solution

$$R'NH_2 + LutClO_4 \rightleftharpoons R'NH_3^+ClO_4^- + 2,6\text{-lutidine} \qquad (2)$$

$$R'NH_2 + RCOOH \rightleftharpoons R'NH_3^+RCOO^- \qquad (3)$$

$$\underline{3} \xrightarrow{R'NH_2} RCONHR' + Ph_3PO + H^+ \qquad (4)$$

$$\underline{3} \xrightarrow[\text{or } RCOO^-]{RCOOH} (RCO)_2O + Ph_3PO + H^+ \qquad (5)$$

$$(RCO)_2O + R'NH_2 \longrightarrow RCONHR' + RCOOH \qquad (6)$$

At the cathode

$$2H^+ + 2e \longrightarrow H_2 \qquad (7)$$

Scheme 3

The primary amine is considered to be a stronger nucleophile than the carboxylic acid; but most of the amine will be protonated by the acid and/or $LutClO_4$, and the amount of the free base must be negligible at the electrode. Thus, it is unlikely that the amide formation proceeds *via* alkylaminophosphonium ion, Ph_3P^+-NHR', which can be produced in the absence of the carboxylic acid,[3] although some contribution of acid anhydride to the process (eqs. 5 and 6) cannot be rigorously ruled out. This conclusion is supported by the following observation: (i) After a solution of 1, $BuNH_2$, and $LutClO_4$ in CH_2Cl_2 was subjected to CCE, p-$MeOPhCO_2H$ was added to the solution and the mixture was stirred for 30 min at ambient temperature; (ii) A mixture of Ph_3P^+-NHBu, prepared by the reported method,[3] and p-$MeOPhCO_2H$ in CH_2Cl_2 was stirred for 3h at ambient temperature; (iii) The aminophosphonium salt and the acid were

refluxed in toluene for 1h. In the three experiments, the formation of p-MeOPhCONHBu was not observed.

The present study shows that acyloxytriphenylphosphonium ions 3 can be generated easily from Ph_3P and carboxylic acids under mild conditions. The counter anion to the phosphonium ion, ClO_4^-, is a very weak nucleophile, and 2,6-lutidine, if it is liberated in the system from $LutClO_4$ used as the supporting electrolyte, will exhibit little nucleophilic reactivity.[21] Consequently, reactions of various nucleophiles with the phosphonium ions are expected. In addition, there might be a possibility that the optimal conditions for the CCE are dependent on the reactivity of the particular carboxylic acid employed. Further study on this point is required. One obvious limitation in the CCE method is that carboxylic acids with functional groups whose oxidation potentials are less positive than the phosphine 1 can not be used.

Experimental

Melting points are uncorrected. IR and ^1H NMR spectra were measured with Nippon-Bunko A202, and Hitachi R-20A (60 MHz) or R-22 (90 MHz) spectrometers, respectively.

Materials: Ph_3P was recrystallized from hexane. $LutClO_4$, the supporting electrolyte, was prepared by adding 70% $HClO_4$ (160 g) dropwise to 2,6-lutidine (110 g) at 0°C. The crystals deposited were filtered, recrystallized from AcOEt-EtOH, dried under reduced pressure at ambient temperature, and stored over P_2O_5. CH_2Cl_2 was distilled from P_2O_5 and stored over molecular sieves. The Schiff bases were prepared according to the reported method.[22] Other chemicals were obtained from commercial sources and were purified, if necessary, by distillation or recrystallization.

Electrochemical equipment: CCE was performed using a Hokuto Denko HA-301 potentiostat/galvanostat, but the use of a conventional DC power supply (50 V - 2 A) was also effective. A 50 ml sample tube (diameter, 3.5 cm; height, 7.5 cm) fitted with a silicon stopper was employed as the undivided electrolysis cell. A graphite plate anode (2 x 10 cm) and a platinum plate cathode (1 x 10 cm) were placed in the cell at a distance of ca. 1 cm through the stopper. A magnetic bar (0.5 ϕ x 2 cm) was also placed in the cell to achieve stirring

during the electrolysis and the following reaction.

Electrolysis: Typical procedures for the electrochemical preparation of esters, β-lactams, and amides are described.

Esters: A solution of Ph_3P (1)(6 mmol), $PhOCH_2COOH$ (3 mmol), and $LutClO_4$ (6 mmol) in dry deoxygenated CH_2Cl_2 (35 ml) was placed in the electrolysis cell, and equilibrated at 40°C in a thermostated water bath. The system was subjected to CCE (25 mA; current density, ca. 0.83 mA/cm^2) under an N_2 atmosphere until 1F per mol of the phosphine 1 (579 C, ca. 6.5 h) had been consumed: the N_2 gas was supplied from a balloon connected to the electrolysis cell by a hypodermic needle. To the electrolyzed solution, Et_3N (15 mmol) and p-MeOPhOH (3 mmol) were added, and the mixture was stirred for 30 min at ambient temperature followed by concentration to ca. 3 ml under reduced pressure. Water (100 ml) was added to the residue, and the mixture was extracted with $CHCl_3$ (50 ml x 4). The organic layer, after being dried over anhydrous $MgSO_4$, was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel with hexane-EtOAc as an eluant to give $PhOCH_2COOPhOMe$-p in 77% yield (597 mg) based on the carboxylic acid: mp 87-88°C (EtOH-hexane). IR($CHCl_3$) 1780 cm^{-1}. ^1H NMR($CDCl_3$) δ 3.75(3H, s) 4.8(2H, s), 6.75-7.4(9H, m).

The esters listed in Table 1 were obtained by essentially the same procedure and showed the expected IR and ^1H NMR spectra.

β-Lactams: To the electrolyzed solution of 1 and $PhOCH_2COOH$, Et_3N (12 mmol) and PhCH=N-i-Pr (3 mmol) were added, and the mixture was stirred at 40°C for 24 h. Work-up of the resulting solution as described above, including chromatographic separation, gave 1-isopropyl-3-phenoxy-4-phenylazetidine-2-one in 63% yield (based on the Schiff base): mp 141-142°C (EtOH-hexane). IR($CHCl_3$) 1750 cm^{-1}. ^1H NMR($CDCl_3$) δ 1.07(3H, d, J=7Hz), 1.29(3H, d, J=7Hz), 3.85(1H, q, J=7Hz), 4.84(1H, d, J=5Hz), 5.25(1H, d, J=5Hz), 6.4-7.5(10H, m).

1-Butyl-3-phenoxy-4-phenylazetidne-2-one was obtained similarly from PhCH=NBu in 66% yield: mp 102-104°C (EtOH-hexane). IR($CHCl_3$) 1755 cm^{-1}. ^1H NMR($CDCl_3$) δ 0.6-1.8(7H, m), 2.55-3.75(2H, m), 4.82(1H, d, J=5Hz), 5.22(1H, d, J=5Hz), 6.4-7.55(10H, m).

The values of coupling constants J=5Hz for C_3 and C_4 protons of the β-lactams indicate that these protons are cis to each other.[23] Formation of the

corresponding trans-isomers was not observed.

Amides: To the electrolyzed solution of 1 and $PhOCH_2COOH$, Et_3N (15 mmol) and i-$PrNH_2$ (3 mmol) were added, and the mixture was stirred at ambient temperature for 30 min. Work-up of the resulting solution as described above gave $PhOCH_2CONH$-i-Pr in 72% yield (based on the amine): mp 65-67°C (hexane). IR($CHCl_3$) 3420, 1665 cm^{-1}. ^1H NMR($CDCl_3$) δ 1.18(6H, d, J=7Hz), 3.8-4.35(1H, m), 4.37(2H, s), 6.3(1H, bs), 6.6-7.4(4H, m).

One-step preparation of amides: A solution of 1 (6 mmol), $PhOCH_2COOH$ (3 mmol), i-$PrNH_2$ (3 mmol), and $LutClO_4$ (6 mmol) in dry deoxygenated CH_2Cl_2 (35 ml) was placed in the electrolysis cell, and the system was subjected to CCE (25 mA) at 40°C under an N_2 atmosphere until 1F per mol of 1 had been consumed (ca. 6.5 h). The electrolyzed solution was concentrated to ca. 3 ml under reduced pressure followed by the work-up performed on the preparataion of $PhOCH_2COOPh$-OMe-p including the chromatographic separation gave $PhOCH_2CONH$-i-Pr in 83% yield (based on the amine).

The amides listed in Table 2 were obtained by essentially the same procedure and showed the expected IR and ^1H NMR spectra.

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