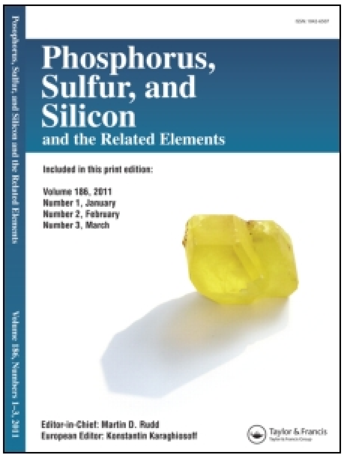

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

"ONE-POT" SYNTHESIS OF TRIARYL PHOSPHATES A REACTION CALORIMETRY APPROACH

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To cite this Article Silva, J. F. Cajaiba Da , Nakayama, H. T. and Neto, C. Costa(1997) '"ONE-POT" SYNTHESIS OF TRIARYL PHOSPHATES A REACTION CALORIMETRY APPROACH', Phosphorus, Sulfur, and Silicon and the Related Elements, 131: 1, 71 — 82

To link to this Article: DOI: 10.1080/10426509708031597
URL: http://dx.doi.org/10.1080/10426509708031597

Phosphorus, Sulfur, and Silicon, 1997, Vol. 131, pp. 71–82
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"ONE-POT" SYNTHESIS OF TRIARYL PHOSPHATES A REACTION CALORIMETRY APPROACH

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(Received 23 April 1997; Revised 5 June 1997; In final form 5 June 1997)

Triaryl phosphates were obtained in yields ranging from 85–96% in a "one-pot" synthesis via an alkaline route: an ethanolic solution of sodium hydroxide was added to a solution of substituted phenol in toluene. The mixture was distilled until all ethanol was removed. Phosphorus oxychloride was then added and the toluene was distilled. The triaryl phosphates were characterized by NMR (^{1}H and ^{31}P), MS and FTIR.

The heat capacity (C_p), the total heat transfer coefficient (U) and the reaction enthalpy (ΔH) were determined for the synthesis of tris(4-chloro-3-methylphenyl), tris(p-cresyl), tris(o-methoxyphenyl) and tris(p-nitrophenyl) phosphates.

Keywords: Phosphate; NMR spectra; heat capacity; phosphorus oxychloride

INTRODUCTION

Two main groups of reagents are usually employed to synthesize esters of phosphoric acid. Phosphorus oxychloride[1] and phosphorochloridates[2] belong to the first group. The second group uses a number of anhydrides[3,4] as phosphorylating reagents. Of all these methods, the most convenient and efficient methods for the synthesis of triaryl phosphates is the one employing phosphorus oxychloride.

Two main routes can be followed to produce aromatic phosphates using phosphorus oxychloride. The acidic route uses the reaction of phenols with phosphorus oxychloride in pyridine[3] and the alkaline route uses the reaction of sodium phenoxide with phosphorus oxychloride in an inert solvent.[4] The first route produces large amounts of HCl (highly corrosive) while in the second, NaCl is formed as by-product. In large scale preparations the second route has decisive advantages.[5,6]

The main difficulty encountered in the alkaline route is the preparation of the anhydrous phenoxide. Laboratory procedures[4] recommend drying the solid under vacuum. The time required to accomplish this step is directly related to the vacuum used.[7] Another concern with this process is the last step, in which the reaction of the phenoxide with phosphorus oxychloride is known to be higly exotermic. This certainly presents a problem for the scaling-up of the process.

Reaction calorimetry is a powerful tool to determine the conditions for the scale-up of a chemical process, as the loss of thermal control is a major hazard in chemical production where large quantities of reactive chemicals are processed.[8,9]

A thermal runaway can be described as the progressive temperature rise of a reaction mixture due to a heat generation rate that constantly exceeds the cooling capacity of the reactor. If the energy release is large enough, gaseous products may be occasionally formed that can lead to overpressurization and possible mechanical destruction of the vessel (thermal explosion).[10]

Automated laboratory reaction calorimeters provide an efficient way to perform safety studies on[11] as well as optimization analyses[12] of chemical processes.

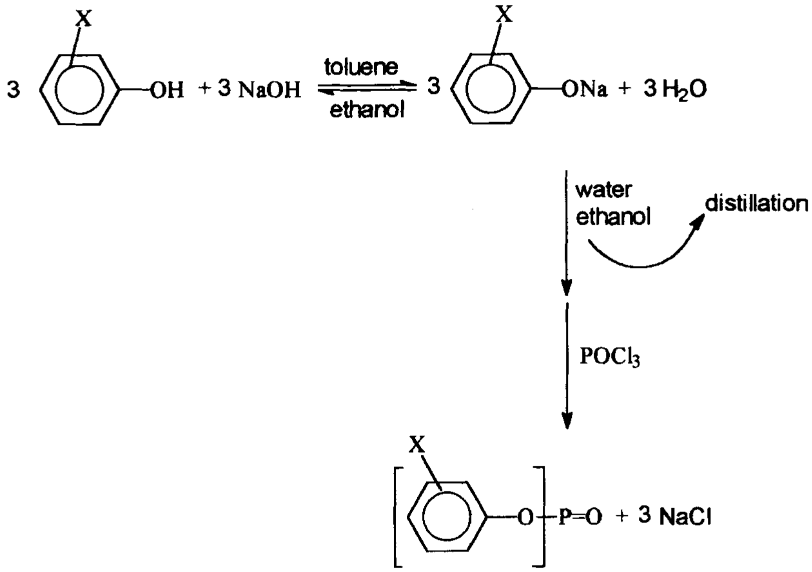
This paper describes a much simpler "one-pot" procedure to prepare triaryl phosphates using the alkaline route and also presents a calorimetric study for this synthesis, in order to verify the safety conditions for the scaling-up of the chemical process.

RESULTS AND DISCUSSION

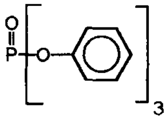
Synthesis

Phenoxides are easily made by reaction of phenols with sodium hydroxide in an excess of ethanol. The mixture can be dried using azeotropic distillation with toluene to remove the ethanol, leaving a suspension of anhydrous phenoxide in toluene. SCHEME 1 shows the reactions used to synthesize substituted triaryl phosphates. In TABLE I the yields obtained for the prepared phosphates, melting points, and the data for ^1H NMR, ^{31}P NMR, IR and MS spectra, are presented.

As a "one-pot" type reaction, this method presents advantages if compared with the conventional procedure to prepare triaryl phosphates,[4] since it does not require preparation of the solid dried phenoxide (a rather cumbersome pro-



cedure) and, overall, it is much less time-consuming. The structures of the preparations are shown below.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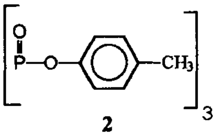
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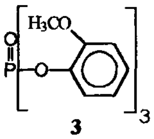
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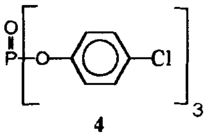
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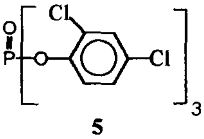
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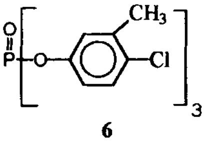
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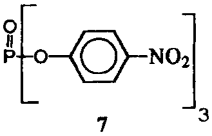
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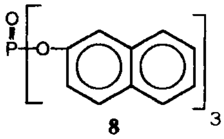
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Calorimetry

The determination of the heat capacity (C_P), total heat transfer coefficient (U) and the reaction enthalpy (ΔH) for the above described phosphates was performed using an automated laboratory reaction calorimeter (Mettler RC1) which is an automatic laboratory reactor with a heat balancing system. Chemical processes or individual steps within them can be performed in a real-world environment on a liter scale. Process variables such as pH, pressure, temperature

TABLE I Characterization of substituted triaryl phosphates

Compound	*melting point (°C)*		*^1H NMR[a,c] (ppm) Multiplicity and relative peak area*	*^{31}P NMR[b] (ppm) singlets*	*IR (cm^{-1})*		*MS (m/z)*	
yield	*found*	*literature[13]*			*P=O*	*P-O-C*	*M^+*	*base peak*
1 (85%)	50	49–50	7.3 (1H,m)	−19.9	1303	1190, 950	326	326
2 (85%)	78	76–78	2.3 (3H,s) 7.1 (4H,m)	−19.1	1304	1186, 1140, 962	368	368
3 (87%)	91	90–91	3.8 (3H,s), 6.9 (2H,m), 7.2 (1H,m), 7.4 (1H,m)	−18.6	1312	1265, 1167, 1111, 966	416	77
4 (93%)	110	112–113	7.2 (1H,m); 7.3 (1H,m)	−20.1	1301	1197, 1092, 984	428	77
5 (93%)	88	87	7.3 (1H,m); 7.4 (2H,m)	−21.1	1308	1222, 1149, 1014, 978	–	–
6 (84%)	87	–	2.4 (3H,s), 7.2 (2H,m) 7.3 (1H.d)	−19.9	1304	1227, 1149, 1014, 978	472	77
7 (93%)	155	155–156	7.5 (1H,d); 8.3 (1H,d)	−22.2	1308	1191, 1160, 959	–	–
8 (91%)	109	110–111	7.4 (3H,m), 7.8 (4H,m)	−19.6	1291	1210, 1152, 984	476	115

[a] In $CDCl_3$ with TMS as internal standard.
[b] In $CDCl_3$ with 85% H_3PO_4 as extermal standard.
[c] S (singlet), d (doublet), t (triplet), m (multiplet)

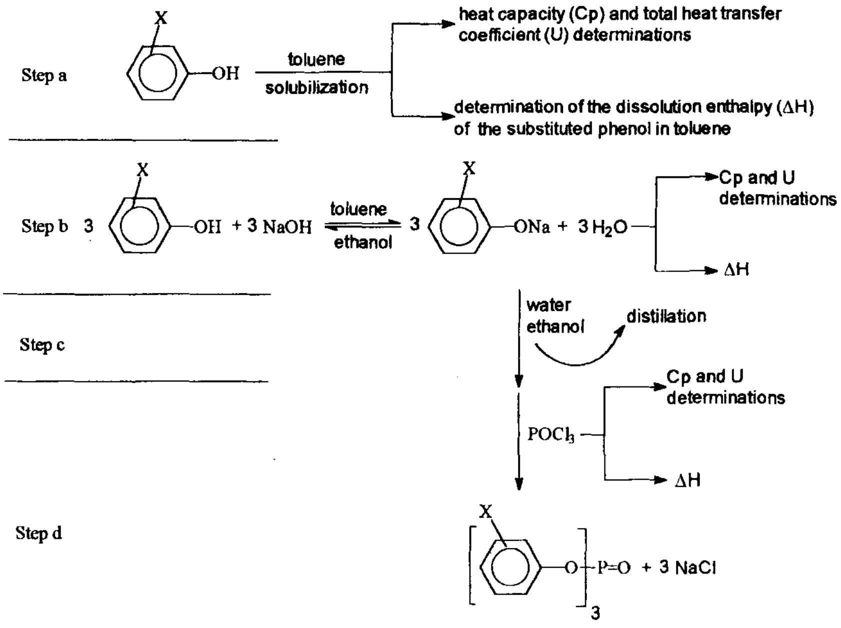
and mixing can be measured and regulated. In addition, however, accurate heat values for chemical and physical conversions can be acquired and heat transport data can be measured. All components of this flexibly expandable system are designed so that results obtained on the liter scale can be transposed to the industrial scale.

The steps performed on the reaction calorimeter are sumarized in SCHEME II.

The calorimetric studies were performed on the synthesis of the following products: tris(p-cresyl) phosphate **2**, tris(o-methoxyphenyl) phosphate **3**, tris(4-chloro-3-methylphenyl) phosphate **6** and tris(p-nitrophenyl) phosphate **7**.

The heat capacity variation (ΔC_p) and the total heat transfer coefficient variation (ΔU) for the triaryl phosphates synthesized are shown in TABLE II.

The diminution observed in the C_p values is related to the distillation of ethanol (step c in SCHEME II). Ethanol has a C_p value (2430 J/kg.K) higher



SCHEME II

than the toluene C_p value (1760 J/kg.K), since the reaction medium in the final step of the synthetic process is a suspension of dried substituted sodium phenoxide in toluene. This fact explains the C_p diminution observed.

The total heat transfer coefficient (U) increased from the beginning to the end of the experiments due to some sodium phenoxide deposited on the walls of the reaction vessel, causing a decrease in the heat flow through the walls of the reactor.

For the four different steps involved in the process for the preparation of tris(p-cresyl) phosphate, the values of the reaction enthalpy (ΔH) were determined and the variation of the temperature was calculated for each step under adiabatic conditions (ΔT). These results are summarized in TABLE III.

TABLE II Heat capacity variation (ΔC_p) and the total heat transfer coefficient variation (ΔU) for the triarylphosphates synthesis.

Triarylphosphate	*ΔC_p (J/kg.K)*	*ΔU (Watts/m^2.K)*
(1) Tris(p-cresyl) phosphate	1967–1604	144–160
(2) Tris(o-methoxyphenyl) phosphate	2094–1516	160–170
(3) Tris(4-chloro-3-methylphenyl) phosphate	1893–1695	160–180
(4) Tris(p-nitrophenyl) phosphate	2210–1653	160–170

TABLE III Calorimetric data for the tris(p-cresyl) phosphate synthesis

Step	*ΔH (kJ)*	*ΔT (°C)*	*Temperature (°C)*
a) Dissolution of p-cresol in toluene	+5.7	−2.6	30
b) Reaction of p-cresol with the ethanolic solution of sodium hydroxide	+1.0	−0.3	30
c) Ethanol distillation	+526.7	−339.5	fluctuating
d) Reaction of p-cresolate with $POCl_3$	−35.3	+17.5	80

An endothermic process was observed for step (b). This result may seem strange owing to the fact that reactions of acids with bases are usually highly exothermic. In this case, two different processes are taking place simultaneously: the first one, the dissolution of ethanol and p-cresol in toluene (endothermic processes) and the second, the reaction of p-cresol with sodium hydroxide (exothermic process). The absorbed heat in the endothermic step seems to overcome the released heat in the exothermic one. To confirm this hypothesis an experiment was performed inverting the order of steps **a** and **b**. The results obtained are shown in TABLE IV.

From the values from TABLE III and TABLE IV it was possible to calculate the enthalpy changes ($\Delta H_{reaction}$) for the reaction of p-cresol with NaOH:

$$\Delta H_{step\ b'} = \Delta H_{reaction} + \Delta H_{p\text{-cresol dissolution}}$$
$$\Delta H_{reaction} = \Delta H_{step\ b'} - \Delta H_{p\text{-cresol dissolution}}$$
$$\Delta H_{reaction} = -5.8 - (+5.7) = -11.5\ \mathrm{kJ}$$
$$\Delta H_{reaction} = -46.0\ \mathrm{kJ/mol}$$

The same procedure applied to the reaction, where the order of steps **a** and **b** was changed, gives −28.0 kJ/mol for the $\Delta H_{reaction}$.

These results clearly show that the reaction of p-cresol with NaOH is, as expected, exothermic. The observed differences between the $\Delta H_{reaction}$ values for the reaction of p-cresol with sodium hydroxide, arise from the fact that the final enthalpy value is the same from these two experiments, but the initial values are different because the primary reaction medium composition was different.

TABLE IV Calorimetric data for the second tris(p-cresyl) phosphate synthesis

Step	*ΔH (kJ)*	*ΔT (°C)*	*Temperature (°C)*
a') Dissolution of the ethanolic solution of NaOH in toluene	+8.0	−2.6	30
b') Dissolution of p-cresol and reaction with NaOH in toluene	−5.8	+1.9	30
c') Ethanol distillation	+384.4	−246.3	fluctuating
d') Reaction of the sodium p-cresolate with $POCl_3$	−35.2	+18.6	80

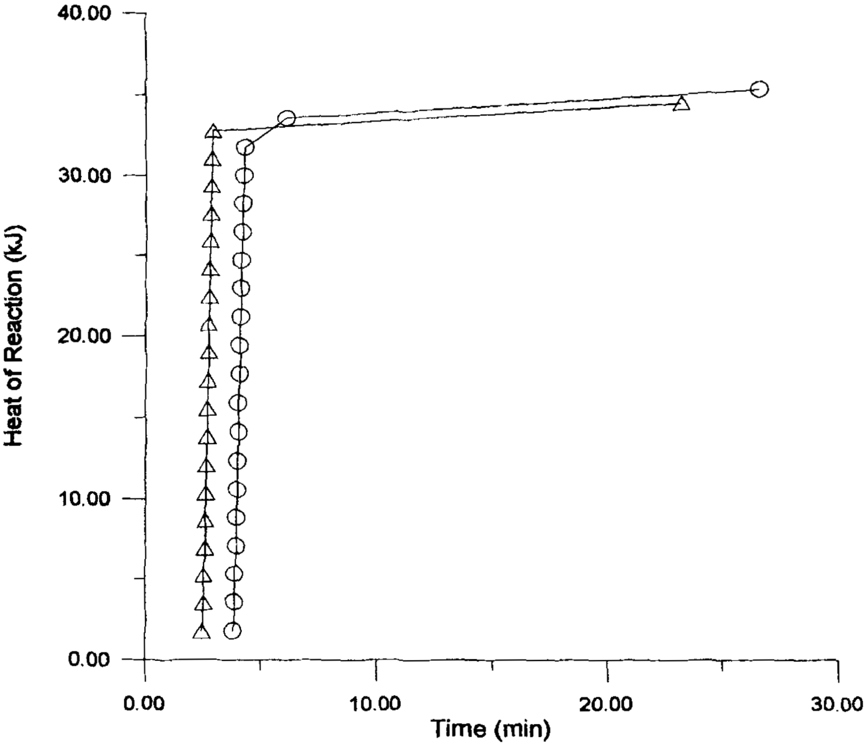


FIGURE 1 Heat produced in the reaction of sodium p-cresolate with $POCl_3$ as function of reaction time (Values from TABLE I and II).

Now, the reaction of sodium p-cresolate with $POCl_3$ should be conducted with great care since this is a highly exothermic process (−420 kJ/mol), that could readily lead to a runaway (loss of thermal control).

By means of the expression $\Delta H = mC_p\Delta T$ and the reaction temperature at the moment of the addition of $POCl_3$ (80°C) the highest possible temperature this reaction could attain under the conditions of this experiment, was calculated. The calculated temperature is 98°C. Since this value is about 12 degrees below the boiling point of the solvent (toluene) used, it minimizes the possibility of a runaway situation since, at this temperature, an overpressurization of the reactor is not very likely to occur.

The reproducibility of experiments on the RC1 calorimeter is very high as it can be shown in FIGURE 1, where the heat profile for the most important step of the above mentioned reactions is reproduced.

The heat profile of the above step shows that it is a very fast reaction. Virtually all heat is liberated in the first minutes of reaction. This behavior clearly indi-

TABLE V Calorimetric data for the tris(o-methoxyphenyl) phosphate synthesis

Step	*ΔH (kJ)*	*ΔT (°C)*	*Temperature (°C)*
a) Dissolution of o-methoxiphenol in toluene	+ 1.3	− 0.5	30
b) Reaction of o-methoxiphenol with the ethanolic solution of sodium hydroxide	+ 1.9	− 0.6	30
c) Ethanol distillation	+ 370	− 256.9	fluctuating
d) Reaction of the sodium o-methoxiphenoxide with $POCl_3$	− 38.4	+ 20.2	80

cates that the reaction of sodium phenoxides with phosphorus oxychloride should be considered as a "feed controlled" reaction. This is an important result since it shows it is not necessary to keep the reaction medium under reflux for two hours after the addition of the phosphorus oxychloride as previously mentioned in the literature.[4,7].

The calorimetric data obtained for the preparation of the studied phosphates are shown on TABLE V, VI, and VII.

It was possible to verify that electron withdrawing groups on the aromatic ring of the triaryl phosphates render the process less exothermic and consequently safer. This behavior could be observed in FIGURE 2 where the released heat of the reaction of the substituted sodium phenoxides with phosphorus oxychloride is shown as function of the time.

A higher electronic density in phenoxides containing electron donating groups makes this species more nucleophilic and consequently the reaction with phosphorus oxychloride is more exothermic.

In the second step of each reaction a 1:10 molar ratio sodium hydroxide ethanol was used. In order to verify the necessity of ethanol in this step, the tris(p-nitrophenyl) phosphate was prepared using a 1:5 molar ratio and in another experiment, ethanol was not used at all. The calorimetric profile of these experiments is shown in FIGURE 3.

As the heat of reaction is directly proportional to the progress of the reaction, the results shown above indicate that similar quantities of heat were released when ethanol was present. A lower final value was observed if the reaction

TABLE VI Calorimetric data for the tris(4-chloro-3-methylphenyl) phosphate synthesis

Step	*ΔH (kJ)*	*ΔT (°C)*	*Temperature (°C)*
a) Dissolution of 4-chloro-3-methylphenol in toluene	+ 6.1	− 2.3	30
b) Reaction of 4-chloro-3-methylphenol with the ethanolic solution of sodium hydroxide	+ 1.1	− 0.4	30
c) Ethanol distillation	+ 336.5	− 226.4	fluctuating
d) Reaction of the sodium 4-choro-3-methylphenoxide with $POCl_3$	− 31.6	+ 19.3	80

TABLE VII Calorimetric data for the tris(p-nitrophenyl) phosphate synthesis

Step	*ΔH (kJ)*	*ΔT (°C)*	*Temperature (°C)*
a) Dissolution of p-nitrophenol in toluene	+5.3	−1.8	30
b) Reaction of p-nitrophenol with the ethanolic solution of sodium hydroxide	+3.6	−1.1	30
c) Ethanol distillation	+286	−178.9	fluctuating
d) Reaction of p-nitrophenoxide with $POCl_3$	−21.8	+13.63	80

proceeded in absence of ethanol. These results also suggest that higher yields are obtained if ethanol is used to prepare the corresponding sodium phenoxide. Indeed, the yield of the isolated products was about 94% when the synthesis was performed with ethanol and 70% without ethanol. The total liberated heat in the latter situation was about 70% of the heat liberated in the former. The heat profiles are in accordance with the yields obtained.

To reach the highest yields of phosphoric acid triaryl esters, prepared by the alkaline route, the reaction medium must be absolutely dry. This can be achieved better when ethanol is used to prepare the dried phenoxide. This result could be

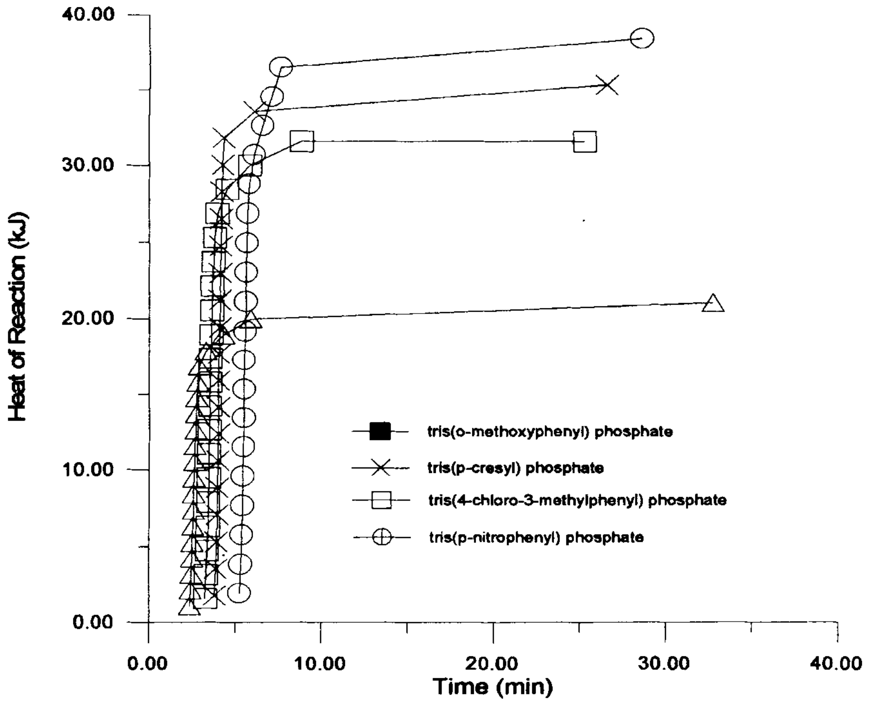


FIGURE 2 Heat of reaction of the substituted sodium phenoxide with $POCl_3$ as function of reaction time for the triarylphosphates synthesis.

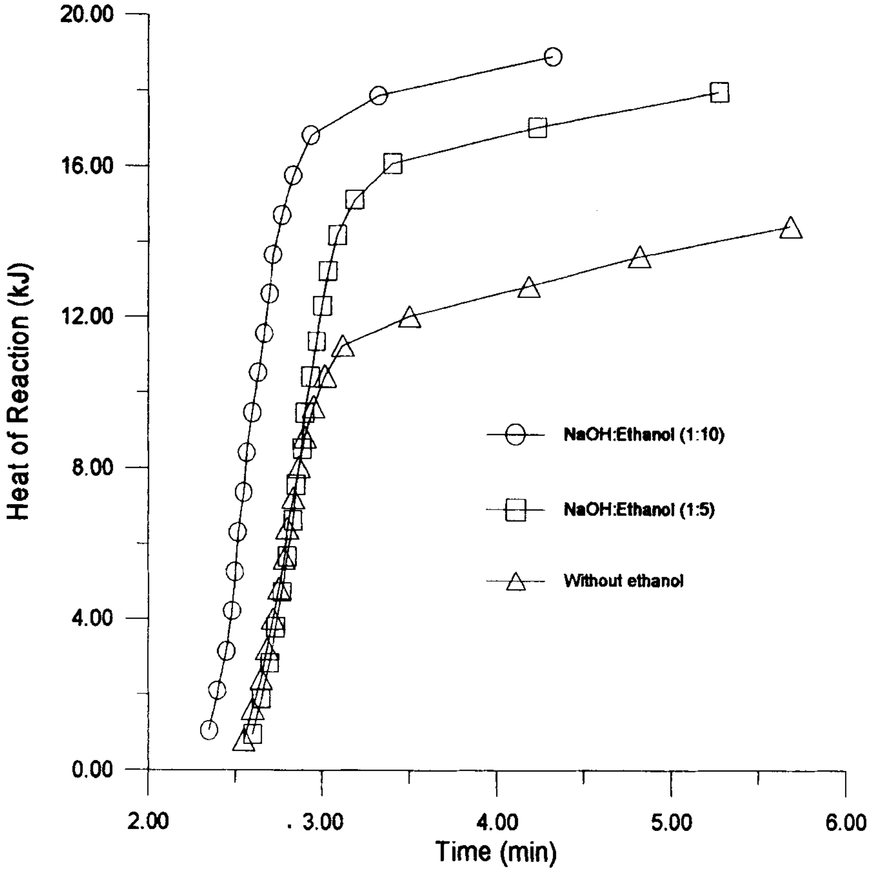


FIGURE 3 Heat of reaction of the sodium p-nitrophenoxide with $POCl_3$.

related to a higher efficiency to remove water from the reaction medium by the ternary toluene-ethanol-water azeotrope rather than by the toluene-water azeotrope.

CONCLUSION

The "one-pot" method developed was very sucessful to prepare triaryl phosphates in high yields (85–96%) both with electron donating or withdrawing groups on the aromatic ring. Calorimetric studies showed that the alkaline route performed under the conditions described in this paper can be considered a safe chemical process, since the loss of thermal control in any of the steps of the process is highly improbable.

EXPERIMENTAL

Infrared spectra were recorded on a Nicolet 740 FTIR spectrophotometer. ^1H NMR and ^{31}P NMR spectra were recorded on a Brucker HC200 at 200 MHz. $CDCl_3$ was used as solvent and chemical shifts were expressed as δ (ppm) units using TMS as internal reference for ^1H spectra and H_3PO_4 as external reference for ^{31}P. Electron impact mass spectra were recorded on a Hewlett-Packard 5790 at 70 eV.

The following experimental procedure illustrates the general "one-pot" method for the synthesis of triaryl phosphates.

Tris-p-nitrophenyl phosphate

In a 1 liter three-necked flask containing 115.2 g (2.5 mol) of ethanol, equipped with a Dean and Stark head, a mechanical stirrer and a dropping funnel, 10 g (0.25 mol) of sodium hydroxide were introduced. To this solution a suspension of 34.8 g (0.25 mol) of p-nitrophenol in 700 ml of toluene was added and fractional distillation of the mixture was started. The toluene-methanol azeotrope (64.5°C) was removed and the distillation was continued until the temperature reached the boiling point (110°C) of toluene. At this point the reaction medium becomes red. The system was then cooled to room temperature and 7.5 mL (0.08 mol) of phosphorus oxychloride were introduced dropwise and the mixture refluxed for 60 minutes. Toluene was removed by distillation. The resulting mixture of solids (sodium chloride and tris(p-nitrophenyl) phosphate) was washed with water to remove the sodium chloride. Tris(p-nitrophenyl) phosphate was then recrystallized from ethyl acetate yielding 34.3 g (93%).

The following experimental procedure illustrates the general "one-pot" method for the synthesis of triaryl phosphates using the Mettler RC1 reaction calorimeter.

Tris(p-cresil) phosphate

1.5 liter of toluene was introduced manually in the RC1 reactor vessel at room temperature (27°C). The reaction medium was stirred at 150 rpm during all the experiment. The toluene temperature was lifted to 30°C and after 7 minutes the first calibration was performed in order to determine the total heat transfer coefficient of the reaction medium. The calibration was completed in ten minutes and ten minutes later 27.0 g (0.25 mol) of p-cresol were automatically added for 1 minute. Twenty minutes later a solution containing 10 g (0.25 mol) of NaOH in 115 g (2.5 mol) of ethanol was added at once. The temperature of the reaction medium was then raised from 30 to 35°C to make it possible to determine the C_p of the reactants and a sequence of U and C_p determinations were performed. The excess of toluene (300 g) was distilled, the reaction temperature was lowered to 80°C for the following addition of 12.4 g (0.25/3.1 mol) of phosphorus oxychloride to be done.

Acknowledgements

We gratefully acknowledge the financial support by CNPq and FINEP.

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