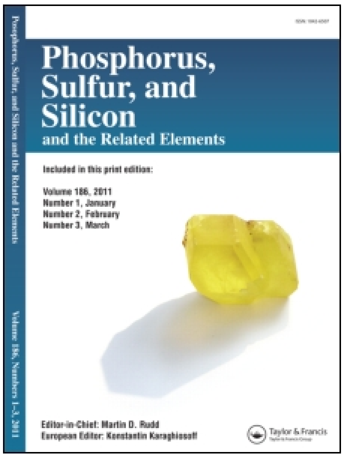

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A design of experiments was conducted to study the transesterification of tris(p-nitrophenyl) phosphate with sodium methoxide. The factorial design was performed to check the experimental conditions that favored ths yield of bis(p-nitrophenyl) methyl phosphate in a semi-batch process. The experiments were performed using a Mettler RC1 calorimeter. The reaction temperature, the addition order of reagents and the time spent in those additions were analyzed at two different levels. The results showed the addition order of reagents as the most important factor to guarantee the improvement of the reaction yielding bis(p-nitrophenyl) methyl phosphate. It was demonstrated that the temperature has a small effect on the reaction yield between 5 and 30°C. An important effect was observed with regard to the addition time of reagents and yield: when the tris(p-nitrophenyl)phosphate is added to the methoxide solution (58% on average) while no effect was observed when the methoxide solution was added to the phosphate (87% on average). Theses results indicated that the addition could be made in times shorter than five minutes under the latter condition.

Keywords Design of experiments; transesterification; triaryl phosphates

INTRODUCTION

The procedures available to synthesize esters of phosphoric acid containing alkyl and aryl groups, employ phosphorus oxychloride,

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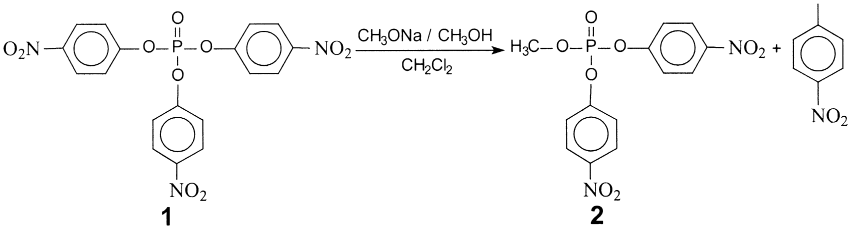
phosphorodichloridates, pyrophosphates and the transesterification of aromatic phosphates.[1]

A procedure, described in the literature, to prepare bis(p-nitrophenyl)methyl phosphates from tris(p-nitrophenyl)phosphate with sodium alkoxides, stated that it is necessary to keep the reaction media at low temperatures and the alkoxide addition should be as slow as possible.[2] Nevertheless, smilar products were obtained in high yields using shorter addition times.[3] This paper intends to clarify the effect of the temperature, addition time and order of reagent addition on the yield of bis(p-nitrophenyl)methyl phosphate.

RESULTS AND DISCUSSION

Bis(p-nitrophenyl)methyl phosphate **2** was prepared by equimolar reaction of tris(p-nitrophenyl)phosphate **1** and a sodium methoxide solution, as shown in Scheme 1.



SCHEME 1

The effects of the temperature, order of reagent addition, and time spent in the additions on the product yields were evaluated through a full three factor-two level design of experiments (DOE) as shown in Table I.

Temperature and the addition time showed negative effects on yield and the order of reagent addition presented a positive result. A synergism between addition order ard addition time factors was observed as mathematically expressed by the Eq. (1)

$$\%\mathbf{2} = +68.48 - 3.02.A - 1.89.B + 17.23.C + 2.03.B.C \qquad (1)$$

where: A = temperature, B = addition time and C = addition order.

Higher yields were always obtained when methoxyde was added to the tris(p-nitrophenyl) phosphate (86.5% on average) instead of the inverse order (57.7%), that favors products of multiple exchanges.

TABLE I Reaction Conditions and Yield of 2

Experiment (standard order)	Experiment (run order)	Factor A temperature (°C)	Factor B addition time (min)	Factor C addition order[a]	2 yield (%)
5	1	−15	30	Phos in mtx	51.2
6	2	−15	30	Phos in mtx	51.0
14	3	−15	30	mtx in phos	88.7
8	4	30	30	Phos in mtx	43.9
9	5	−15	5	mtx in phos	87.3
11	6	30	5	mtx in phos	84.0
4	7	30	5	Phos in mtx	52.2
1	8	−15	5	Phos in mtx	58.0
16	9	30	30	mtx in phos	82.2
7	10	30	30	Phos in mtx	43.1
13	11	−15	30	mtx in phos	89.4
12	12	30	5	mtx in phos	83.2
15	13	30	30	mtx in phos	83.2
3	14	30	5	Phos in mtx	51.9
10	15	−15	5	mtx in phos	87.9
2	16	−15	5	Phos in mtx	58.6

[a] Phos in mtx means: addition of **1** to sodium methoxide solution. mtx in phos means: addition of sodium methoxide to **1**.

It can be also observed that the temperature effects are independent of the addition order. It was not possible to verify any significant synergic effect between temperature and addition order. Thus, a temperature rise from −15°C to 30°C led to a reduction of the bis(p-nitrophenylmethyl)phosphate yield of about 4–7%, regardless of the addition order. These yield differences do not justify the more expensive conditions of keeping lower temperatures.

The synergic effect between the time and addition order observed in Figure 1 shows that the yields were not significantly affected by the addition time when methoxide was added to the phosphate solution, but if this order was inverted the yields could be increased with shorter addition times. However, the best yield was always obtained by the first addition procedure.

The negligible effect of the addition time on the yield of the reaction when methoxide was added to the aryl phosphate shows that this reaction could be carried out in less time. It suggests that the reaction that led to the first exchange product **2** is faster than the two subsequent exchange reactions. This observation is in accord with a nucleophilic substitution mechanism where the positive charge on the phosphorus decreases when an aryl group is displaced by an alkyl group.[3]

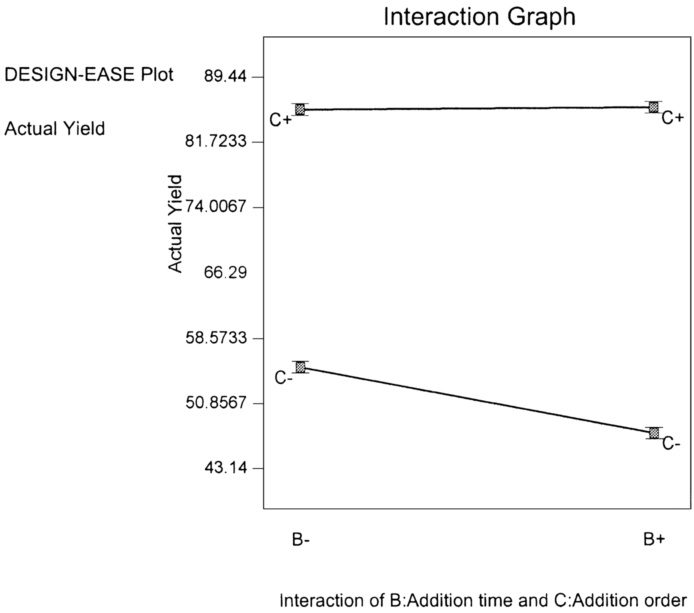
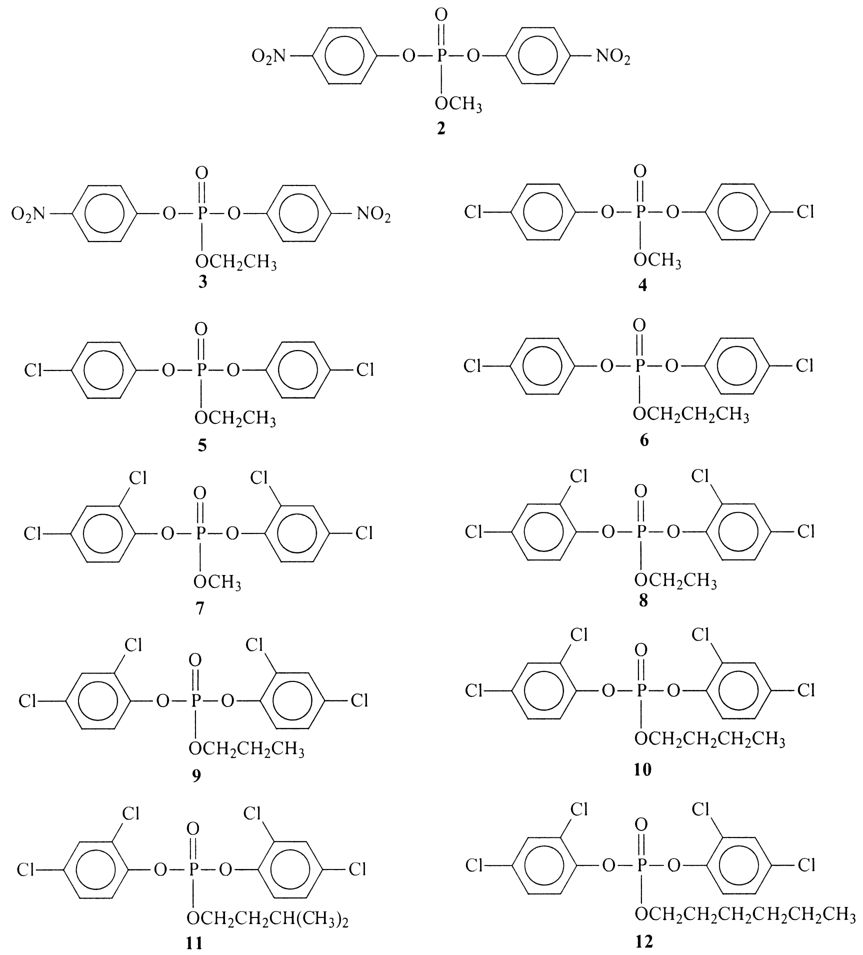


FIGURE 1 The synergic effect between addition time and the addition order factors.

To check if the above observations could be applied to the transesterification of other aromatic phosphates with sodium alkoxides, the products showed in Scheme 2 were prepared by simultaneous addition of the aromatic phosphate and the alkoxide in methylene chloride

TABLE II Spectrometric data of the diaryl alkyl phosphates presented in Scheme 2

	NMR		FTIR		MS	
NO	^1H (δ ppm)	^{31}P (δ ppm)	P=O (cm^{-1})	P–O–C (cm^{-1})	Base peak (m/z)	M^{+-} (m/z)
2	4.1, 7.5, 8.3	−14.8	1299	1199, 1053, 951	—	—
3	1.5, 4.5, 7.5, 8.3	−15.8	1291	1201, 1030, 949	—	—
4	4.0, 7.2, 7.3	−13.4	1299	1196, 1051, 958	127	332
5	1.4, 4.3, 7.2, 7.3	14.3	1300	1196, 1042, 962	128	346
6	0.95, 1.7, 4.2, 7.2, 7.3	−14.2	1297	1196, 1015, 954	128	360
7	4.1, 7.2, 7.3, 7.4	−14.2	1305, 1257	1223, 1102, 1065, 940	133	402
8	1.4, 4.4, 7.3, 7.4	−15.2	1312, 1260	1226, 1102, 1065, 940	363	416
9	0, 97, 1.8, 4.3, 7.4	−15.1	1300, 1256	1223, 1101, 1056, 1024	351	430
10	0.91, 1.4, 1.7, 4.4, 7.3, 7.4	−15.1	1305, 1256	101, 105, 1036, 952	351	444
11	0.93, 1.7, 4.4, 7.2, 7.4	−15.1	1305, 1257	1225, 1101, 1058, 1018	243	458
12	0.91, 1.3, 1.7, 4.4, 7.3, 7.4	15.1	1305, 1258	1224, 1101, 1056, 1021	162	472



SCHEME 2

solvent. The diaryl alkyl phosphates were obtained in yields ranging from 79–85%. All compounds were purified by flash chromatograpy using hexane/ethyl acetate (30%) as an eluent. The characterization of the products was achieved using FTIR, CG-MS, and ^{1}H, and ^{31}P NMR as shown in Table II.

CONCLUSION

It was verified that it is not necessary to use low temperatures and long addition times to obtain high yields of diaryl alkyl phosphates through the trasesterification of triaryl phosphates, contrary to what has been mentioned in the literature.

EXPERIMENTAL SECTION

The design of experiments were analysed using the Design Ease program from State Ease Inc. in Minneapolis, USA.

Infrared spectra were recorded on a Nicolet 740 FTIR spectrophotometer. ^{1}H NMR (200 MHz) and ^{31}P NMR (81 MHz) spectra were recorded on a Bruker HC200, $CDCl_3$ was used as solvent and chemical shifts were expressed in δ (ppm) units using TMS as internal reference for ^{1}H spectra and H_3PO_4 (85%) as external reference for ^{31}P. Electron impact mass spectra were recorded on a Hewlett-Packard 5790 at 70 eV.

The symmetrical phosphates used us starting compounds for the preparation of the diaryl alkyl phosphates **2–12**, (tris(p-nitrophenyl) phosphate, tris(p-chlorophenyl) phosphate, and tris(2:4-dichlorophenyl) phosphate) were prepared by a one-pot methodology.

Bis(p-nitrophenyl) phosphate

The experiments were performed using a Mettler Toledo RC1 calorimeter. A complete description of this reactor can be found in the literature.[5] The RC1 vessel was charged with 1.150 L of dichloromethane and 23 g of tris(p-nitrophenyl) phosphate were manually transferred to the vessel. The speed of the anchor agitator was kept constant at 150 rpm. The reaction was initiated when a methanolic solultion of sodium methoxyde (1.15 g of sodium per 75 mL methanol) was added to the tri(p-nitrophenyl)phosphate solution (5 or 30 minutes). The same concentration of reagents (0.05 mol/L) were used in the reactions in which tris(p-nitrophenyl) phosphate was added to methoxide. After the addition, the mixture was transfered to an 1.5 L Erlenmeyer flask and the percipitated sodium p-nitrophenoxide was filtered off. The filtrate was repeatedly washed with cold water until the washings were colorless. The methylene chloride was removed by distillation. The resulting solid bis(p-nitrophenyl)methyl phosphate was recrystallized from ethyl acetate.

Diaryl Alkyl Phosphates

Compounds 3–12

A methanolic solution of sodium methoxide (1.15 g of sodium per 100 mL of methanol) was added in a few seconds to a stirred solution of 0.005 mol of the appropriate triaryl phosphate in 100 mL of methylene chloride at room temperature. The reaction was stirred for 10 minutes and the precipitated sodium phenoxide was filtered off. The filtrate was washed repeatedly with cold water. The methylene chloride was removed by distillation. The yields for the products were between 79–85%.

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