Improved Synthesis of 1-Methoxy-3-methyl-2-phospholene Oxide Utilising Multivariate Optimization Analysis

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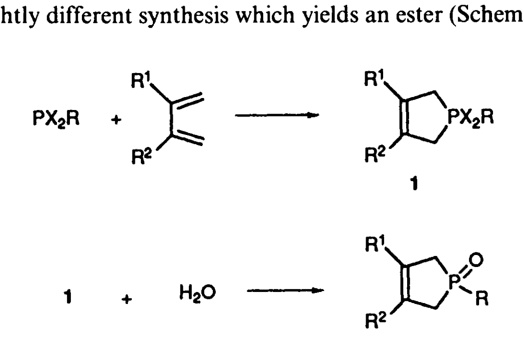
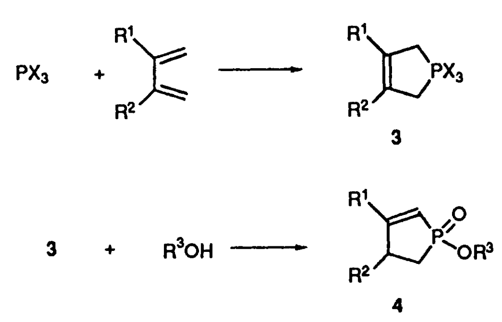
The synthesis of 1-methoxy-3-methyl-2-phospholene oxide from 1,1,1-trichloro-3-methyl-3-phospholene initially gave low yields of around 25%. Attempts to optimise the yield by classic traditional methods, that is, changing only one variable at a time (OVAT) resulted in no significant improvement in the yield. Using multivariate optimization techniques, the yield was rapidly and significantly improved to around 90%. Data was also gathered on the significant variables and the important variable interactions.

Most literature[1-6] concerned with the synthesis of phospholene oxides[2] follows a reaction scheme involving an alkyl phosphorus dihalide and a diene (Scheme 1). This paper refers to a slightly different synthesis which yields an ester (Scheme 2).



Scheme 1 Where X represents halide atoms and R is an organic side chain.



Scheme 2

The desired 1,1,1-trichloro-3-methyl-3-phospholene (Scheme 2; **3** where X = Cl, R^1 = Me, R^2 = H) was prepared from phosphorus trichloride and isoprene by heating the two reactants to 50 °C for 20 h under a gently flowing atmosphere of nitrogen. This gave an 80% yield similar to yields previously reported,[1,2,7,8] but in a fraction of the time, *i.e.* 20 h not 20 days. This is attributed to the reaction being conducted at 50 °C and not ambient temperature, as was the case with earlier workers. 1,1,1-Trichloro-3-methyl-3-phospholene was then reacted with methanol[9] to produce 1-methoxy-3-methyl-2-phospholene oxide (R^1 = R^3 = Me, R^2 = H) in 25% yield.

Attempts to increase this yield further by changing one variable at a time gave no significant improvement in the yield. The reaction is obviously dependent on a number of different variables which are almost surely interactive rather than independent. Therefore, procedures that make it possible to consider the joint influences of all variables simultaneously needed to be applied. Such multivariate techniques are available[10-12] and are in common use in industrial situations, but are rarely applied to fundamental research problems. Rigorous multivariate optimization requires a full factorial analysis, wherein the response of the reaction to all variables is probed. A fractional factorial design would do the job as well. Surprisingly it is necessary to include more factors in a fractional design to make it easier to avoid confounding a main effect with a two-factor interaction. At this early stage of the optimisation, it was deemed vital to investigate fully just three potentially significant variables to develop a firm understanding of these critical variables before progressing to investigate further variables. To use this technique, firstly one assesses the variables governing the experiment and decides which of them is likely to be significant. For this particular reaction, reaction temperature, concentration of 1,1,1-trichloro-3-methyl-3-phospholene **3** (X = Cl, R^1 = Me, R^2 = H) and addition time of methanol were selected. Pre- and post-mixing times, temperature for pre- and post-mixing, solvent choice, and concentration of methanol, were other variables which were considered. However, they were initially deemed less important, and it is helpful to minimise the number of variables to begin with so as to reduce the complexity of interpreting the results. A high and low value for each variable is then chosen giving eight different experimental conditions with the three selected variables at high and low levels ($2^3 = 8$). It is essential that the experiments are performed in a random order. This is necessary, as it is important, for example, not to investigate all the high temperature reactions of a set first and all the lower ones later. If this is done, a change caused by, for example, deterioration of reagent in storage may be ascribed to temperature change. The raw data (in this case percentage yield) is then processed in a pre-specified order. Owing to the design of the experiments four estimates of the effects of variables and variable interaction effects are produced.

Results and Discussion

Prior to using chemometric techniques to optimise the yield, the experiment consisted of slowly adding a known quantity of methanol to a known quantity of 1,1,1-trichloro-3-methyl-3-phospholene **3** (X = Cl, R^1 = Me, R^2 = H) in dichloromethane held at sub-ambient temperature. The mixture was then stirred until ambient temperature was attained and then neutralised with aqueous sodium carbonate solution and the product extracted with dichloromethane.

In applying chemometric techniques, firstly the variables to be investigated are selected. As mentioned previously it was

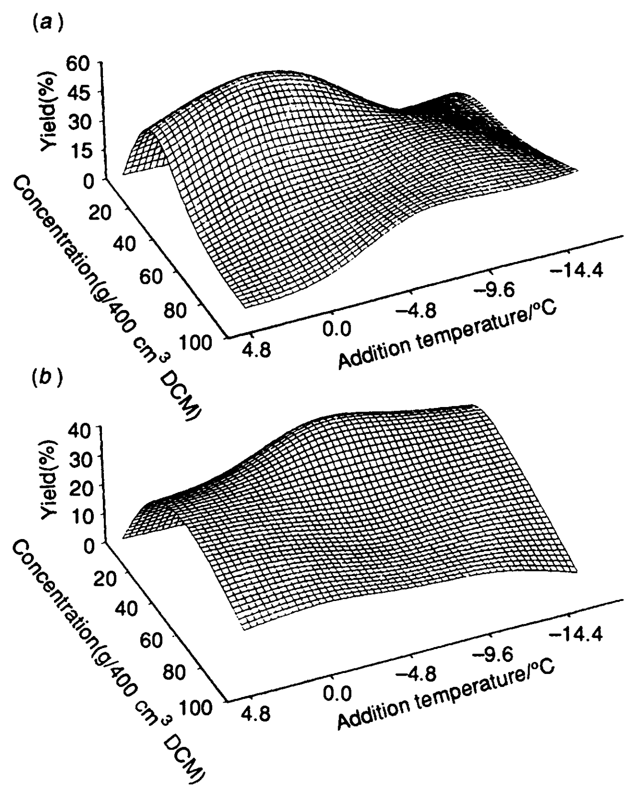


Fig. 1 Three-dimensional response surfaces based on data obtained in full factorial analysis: (*a*) low addition time; (*b*) high addition time

decided to investigate the effects of three variables. The three variables selected for the multivariate analysis were:

A = Addition temperature, − 15 °C or 0 °C;
B = Concentration of 1,1,1-trichloro-3-methyl-3-phospholene, 50 g in 400 cm^3 of dichloromethane or 100 g in 400 cm^3 of dichloromethane;
C = Addition time of methanol, 1 h or 4 h.

The highest yield from these experiments was 42.5%, compared to previous yields of around 25%. Information on the importance of variables and variable interactions was also obtained. The effect of concentration of 1,1,1-trichloro-3-methyl-3-phospholene was highly significant and needed to be lowered. The addition temperature/concentration interaction was important, implying that increasing the addition temperature whilst lowering the concentration will increase the yield. Consequently the addition temperature needed to be increased slightly. The three-fold interaction was also found to be important, although normally three-fold interactions are negligible. It is difficult to draw any conclusions from the three-fold interaction as it is very difficult to visualise the effect of changing the addition temperature on varying concentration and addition time in a physical sense.

Having identified effects within the chosen parameters a few probing experiments outside of these could then be attempted to confirm initial findings, before attempting the new experiments dictated by the primary experimental investigations. The variable A was raised to 0 °C, B was halved to 25 g of 1,1,1-trichloro-3-methyl-3-phospholene in 400 cm^3 of dichloromethane and C was reduced to 30 min. The recorded yield was 57%, a good increase over the previous highest yield of 42.5%. Three more probing experiments were then performed, with only one variable altered, two with their addition temperatures at +5 °C and −5 °C and one with the stirring time halved to 1 h. In a sense this is a return to the classical research approach, however, one can measure the effect on the response when one factor is varied while the others are held at their optimum levels. This 'fine tuning' technique checks that the optimum has been located accurately for the variable chosen. These experiments gave yields of 42%, 51% and 54% respectively. All but the last of these probing experiments had been designed using evolutionary operations (EVOPS) techniques,[10] but could only incorporate variables previously studied. An indication of the complex variation of yield with the three variables studied is provided by the three-dimensional response surfaces presented in Fig. 1. These show that the highest yield obtained was about 57%, *i.e.* the summit on the low-addition-time surface. In an attempt to increase the yield, further variables were investigated. The new variables selected were concentration of methanol, stirring time and stirring temperature. Now a standard 2^3 experimental design could have been attempted with these variables, the original variables studied being held constant at pre-specified levels. However, it was felt that the interaction effects between 'new' and 'old' variables would be significant and that a study of these would also yield more valuable information on the mechanism of the reaction as well as being time saving. With five variables (fixing the concentration of 1,1,1-trichloro-3-methyl-3-phospholene at 25 g in 400 cm^3 of dichloromethane), 32 experiments (2^5) need to be performed to complete a full factorial analysis. However, by dividing the 32 experiments into four separate blocks of eight experiments, fractional factorial experimental designs[10] may be performed. The principal block is carefully designed to include those variables and variable interactions which are thought to be the most important. If the design is correct then the significant variables and variable interactions will be identified by strong responses. In this manner the proposed important variables and variable interactions are examined efficiently. However, one must also be aware of the fact that these strong responses generated by performing only the principal block will be aliased with certain two-factor interactions. Thus a strong response is associated with two factors, either or both of which may have significance. A good design chooses the appropriate aliases to be examined and thus overcomes the disadvantage that some of the effects are confounded by one another. If it is unclear which of the two factors is significant then further blocks must be performed to clarify the situation.

The highest yield attained from the principal block was 78%. The important variables were found to be the addition temperature (A)/stirring temperature (E) interaction and the methanol concentration and/or the effects with which they are aliased. The addition temperature/stirring temperature interaction, which is aliased with the methanol concentration/stirring time interaction, should be increased. That is, the yield will be increased by lowering the addition temperature and subsequently raising the stirring temperature. It was unclear whether the methanol concentration effect was important or not and so other experiments were performed to ascertain this using simplex EVOPS analysis. From these it was established that the concentration of methanol was of little importance but the two-factor interaction of addition time of methanol with stirring temperature with which it was aliased was of significance. It therefore follows that if the stirring temperature is raised then the methanol addition time must consequently be reduced in order to increase the interaction effect. Initially a yield of 83.5% was obtained with a further experiment leading to a 90% yield. Repeated experiments now have yields of 90 ± 3%. Further yield improvement towards 100% was thought to be too time consuming to investigate and perhaps, in real terms, unobtainable. While these optimum synthesis conditions may only hold for methanol, the information gathered on variable interactions and their significance on yield should be very useful in achieving optimum yields of all esterification reactions of this type.

Table 1 Responses from full factorial design

Order	Treatment combination	Response (% yield)
3	(1)[a]	24.8
6	a	42.5
1	b	39.0
7	ab	18.2
2	c	32.8
4	ac	33.0
8	bc	13.2
5	abc	24.3

[a] Indicates low A, low B, low C.

Table 2 Yates analysis of responses from initial full factorial

Response	1	2	3
24.8	67.3	124.5	227.8
42.5	57.2	103.3	$8.2 = 4\,\text{eff}_a$
39.0	65.8	−3.1	$-38.4 = 4\,\text{eff}_b$
18.2	37.5	11.3	$-27.6 = 4\,\text{eff}_{ab}$
32.8	17.7	−10.1	$-21.2 = 4\,\text{eff}_c$
33.0	−20.8	−28.3	$14.4 = 4\,\text{eff}_{ac}$
13.2	0.2	−38.5	$18.2 = 4\,\text{eff}_{bc}$
24.3	11.1	10.9	$49.4 = 4\text{eff}_{abc}$

Experimental

Instruments.—All infrared spectra were obtained using a Perkin-Elmer 1710 FTIR with the sample in the form of a film. NMR spectra were taken on a Bruker A.C. 300 MHz NMR using $CDCl_3$ solvent. *J*-Values are in Hz. Combined GC/MS analyses were performed using a Varian 3400 GC coupled to a Finnigan 4500 MS. Samples were injected into the GC as solutions in dichloromethane.

Optimum Procedure for Synthesis of 1-*Methoxy*-3-*methyl*-2-*phospholene Oxide.*—To a mixture of isoprene (330 cm^3) and copper stearate (1 g) was slowly added phosphorus trichloride (260 cm^3) under an atmosphere of gently flowing nitrogen. The mixture was then heated to 50 °C for 20 h. The solid product obtained was washed with light petroleum (b.p. 40–60 °C). To dichloromethane (400 cm^3) was added 1,1,1-trichloro-3-methyl-3-phospholene (25 g; 0.125 mol) and the mixture stirred at −10 °C under a flowing atmosphere of nitrogen. Distilled methanol (136 cm^3; 13 mol) was then added over 15 min the temperature being kept at −10 °C, then it was stirred at room temperature for 1 h. The solution was then neutralised with saturated aqueous sodium hydrogencarbonate. The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (5 × 200 cm^3). The organic layers were combined and the solvent removed under reduced pressure, leaving a dark red oil of 90% yield, b.p. 75–79 °C at ambient pressure; ν_{max}/(film)/cm^{-1} 1615, 2850 and 2900; δ_H(270 MHz) 1.95 (5 H, m, Me and CH_2), 2.48 (2 H, d, *J* 42.76, CH_2), 3.72 (3 H, d, *J* 11.24, OMe) and 5.80 (1 H, d, *J* 22.66, CH); δ_C(67.8 MHz) 21.0 (q, Me), 22.6 (s, $\mathit{C}H_2P$), 31.1 (t, CH_2), 53.3 (q, OMe) 116.2 (d, CHP) and 164.2 (d, CHMe); δ_P(36.1 MHz) 76.41; *m*/*z* (EI) (GC/MS) 147 [$(M + H)^+$], 116 [$(M + H)^+$] − Ome; *m*/*z* (CI) (GC/MS) 293 [$(\text{Dimer} + H)^+$] and 147 [$(M + H)^+$].

Optimization of the Synthesis of 1-*Methoxy*-3-*methyl*-2-*phospholene Oxide.*—The optimization procedure employed was completed in the following manner. At first a series of eight experiments (2^3 full factorial design) were run with the three pre-specified variables set at high and low levels, the responses, in this case percentage yields, being recorded as shown in Table 1. Each individual experiment is known as a treatment combination and is expressed in shorthand note form. If the lower case letter of the assigned variable is present it infers that the variable is at its high value, if it is absent, the variable is at its low value. Hence ac means high A, low B, high C.

Table 3 Fractional factorial analysis

Treatment combination	Response (% yield)	Effect	Aliasing effect
(1)	45.1		
ad	60.2	−2.85	A with −BD
bde	62.5	0.2	B with −CE + AD
abe	46.8	3.6	D with −AB
ce	77.8	9.35	C with −BE
acde	49.8	−2.55	AC with −DE
bcd	53.6	−1.8	E with −BC
abc	70.8	19.0	AE with CD

The variables, with their high and low values were as follows: variable A—addition temperature, low −15 °C, high 0 °C; variable B—concentration of 1,1,1-trichloro-3-methyl-3-phospholene, low 50 g in 400 cm^3 of dichloromethane, high 100 g in 400 cm^3 of dichloromethane; variable C—addition time of methanol, low 1 h, high 4 h. In all of these experiments after the addition of 68 cm^3 of methanol over the desired addition time, the mixture was stirred for a further 2 h whilst being brought to ambient temperature. It was then neutralised with aqueous sodium hydrogencarbonate and extracted with dichloromethane. A rapid and simple method of calculating the effects in factorial design is Yates' algorithm[10] which is applicable to both complete and fractional factorial designs. Yates' algorithm was applied to the responses shown in the standard format in Table 1. These responses were then treated in successive pairs as shown in Table 2.

The first four entries in column 1 of Table 2 were obtained by adding the pairs of responses together (*i.e.* 24.8 + 42.5 = 67.3 *etc.*). The lowest four numbers in column 1 were obtained by subtracting the top number of each pair from the lower number (*i.e.* 42.5 − 24.8 = 17.7, *etc.*). Column 2 is then obtained in the same way as was column 1. This was then repeated to obtain column 3 from column 2. Column 3 represents the results of the Yates' analysis. The first number is equal to the total of all the responses and is used as a check that the calculations have been executed correctly. The remaining numbers are equal to each of the effects examined multiplied by four, *i.e.* half the number of experiments performed. Thus the effects of the variables investigated (*i.e.* temperature, concentration and time) together with their interaction effects can be evaluated as follows:

Effect of addition temperature (variable A) = 2.05
Effect of concentration (variable B) = −9.6
Effect of addition time (variable C) = −5.3

Interaction Effects

Effect of A on B on C = 12.35
Effect of A on C = 3.6
Effect of A on B = −6.9
Effect of B on C = 4.55

Using a probability plot it was seen that concentration, the two-fold interaction of addition temperature on concentration and the three-fold interaction were all significant. Following multivariate simplex EVOPs designs a new treatment combination (probing experiment) was produced by selecting the four treatment combinations that gave the best responses, rejecting the worst of these and then calculating the new treatment combination. This is also moderated by the variable effects generated, *i.e.* since concentration effect is negative then concentration should be lowered and addition temperature increased to allow for the two-factor interaction effect of addition temperature on concentration. The addition time

Table 4

Addition temperature/ °C	Concentration of 1,1,1-trichloro-3-methyl-3-phospholene (g in 400 cm^3)	Addition time of methanol/ h	Concentration of methanol/ cm^3	Stirring time/ h	Stirring temperature[a]/ °C	Yield (%)
−15	50	1	68	2	RT[b]	25
0	50	1	68	2	RT[b]	42
0	25	0.5	136	2	RT[b]	57
−10	25	0.25	272	0.5	RT	78
−10	25	0.5	136	2	−10	83
−10	25	0.25	136	0.5	RT	90
−10	25	0.25	136	1	RT	95

[a] RT is ambient. [b] Indicates mixture stirred for 2 h whilst reaching RT, *i.e.* not stirred at RT for 2 h.

should also be reduced. The three-fold interaction is very difficult to interpret, as mentioned earlier. The new probing experiment generated had the variables set at the levels: addition temperature 0 °C; concentration of 1,1,1-trichloro-3-methyl-3-phospholene, 25 g in 400 cm^3 of dichloromethane; 136 cm^3 of methanol added over 30 min. The remainder of the experiment was as before. The yield was recorded as 57%, a significant increase over the previous highest yield of 42.5%. The multivariate simplex EVOPs exercise was used to generate sequentially three more experiments, with only one variable changed, two with the temperatures of +5 °C and −5 °C and one with the stirring time halved to 1 h. These experiments gave yields of 42%, 51% and 54% respectively, all lower than the 57% level achieved above.

This suggested that other factors were also significantly affecting the yield and needed to be investigated. Five variables were selected and a fractional factorial analysis performed to reduce the number of experiments needed to produce the required information. The primary block is shown in Table 3, the variables defined being: Variable A, addition temperature, low: −10 °C, high: 0 °C; Variable B, addition time of methanol, low: 15 min, high: 30 min; Variable C, concentration of methanol, low: 136 cm^3, high: 272 cm^3; Variable D, stirring time, low: 30 min, high: 2 h; variable E, stirring temperature, low: addition temperature, *i.e.* no change, high: ambient temperature. As mentioned each effect will be aliased with a two-factor interaction which may or may not be significant.

Effects calculated *via* Yates' analysises[10] are:

Effect of addition temperature = −2.85 (aliased with addition time of methanol/stirring time interaction).

Effect of addition time = 0.2 (aliased with concentration of methanol/stirring temperature interaction and addition temperature/stirring time interaction).

Effect of stirring time = 3.6 (aliased with addition temperature/addition time of methanol interaction).

Effect of methanol concentration = 9.35 (aliased with addition time of methanol/stirring temperature interaction).

Effect of addition temperature/methanol concentration interaction = −2.55 (aliased with stirring time/stirring temperature interactions).

Effect of stirring temperature = −1.8 (aliased with addition time of methanol/concentration of methanol interaction).

Effect of addition temperature/stirring temperature interaction = 19.0 (aliased with methanol concentration/stirring time interaction).

The largest effect is due to the addition temperature/stirring temperature interaction, next is the addition time of methanol/stirring temperature interaction and not the methanol concentration with which it is aliased. The latter observation arose from further probing experiments conducted within the set levels of the chosen variables. Using the treatment combination notation, experiment abcd gave a yield of 70%, experiment bc gave a yield of 62%, experiment bd gave a yield of 83.5% and experiment e gave a yield of 90%. On repetition of the latter experiment, yields of 90 ± 3% were recorded. By lengthening the stirring time to 1 h a yield of 95% has been achieved.

Conclusions

Excluding duplications, a total of 28 experiments each having a defined set of fixed variables were completed and the yield of 1-methoxy-3-methyl-2-phospholene oxide was increased from 25% to around 90%. Table 4 shows the changes to those variables giving the best yields after each new approach.

The improvement of the yield to over 90% was only achieved by simultaneous variation of the factors. It was found to be impossible to increase the yield above 25% by varying the individual factors in the classical manner. This clearly shows the power of optimisation by multivariate analysis in the case of syntheses in which multi-parameter interactions are significant.

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