A Study of the Phase-transfer Alkoxycarbonylation of Secondary Alkyl Amines. Application of a Factorial Design

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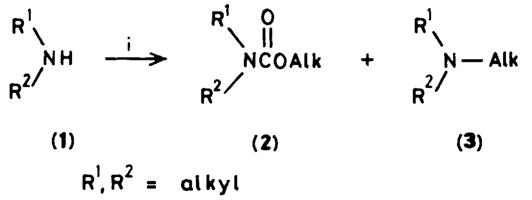
A 2^4 factorial design has been applied to the study of the competitive alkylation *versus* alkoxycarbonylation of secondary alkyl amines under phase-transfer conditions. The relative influence of the experimental variables and their interactions in the course of the reaction have been rationalized. The optimal conditions to obtain high carbamate yields have been established and experimentally corroborated.

In a previous paper[1] we have reported that secondary alkylamines (**1**) can be conveniently alkoxycarbonylated or alkylated to give alkyl carbamates (**2**) or trialkylamines (**3**), respectively, in good to excellent yields, employing a solid–liquid phase-transfer technique, using alkyl halides, potassium carbonate as base, and tetrabutylammonium hydrogensulphate as catalyst.



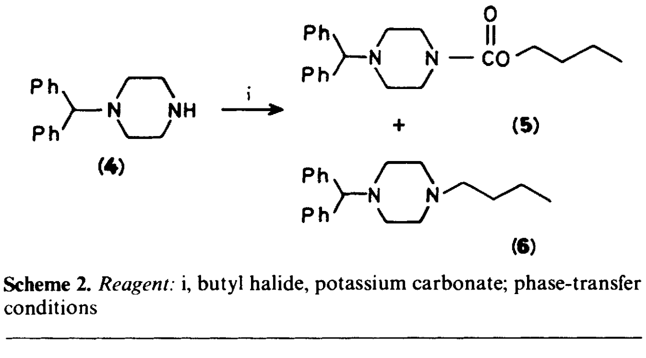
Scheme 1. *Reagent:* i, alkyl halide, potassium carbonate; phase-transfer conditions

The establishment of the optimum operating conditions for obtaining the best yield of (**2**) required the application of the methodology of experimental research to study systematically the competitive alkylation *versus* alkoxycarbonylation under phase-transfer conditions, in an attempt to rationalize the relative influence of different experimental variables and their corresponding interactions.

We describe, herein, the results obtained applying a 2^4 factorial design at two levels.[2,3]

Results and Discussion

2^4 *Factorial Design.*—The reaction of a butyl halide with *N*-diphenylmethylpiperazine (**4**) has been chosen as a model.



Scheme 2. *Reagent:* i, butyl halide, potassium carbonate; phase-transfer conditions

Table 1. Experimental domain. Selected factors and their levels

Factors or variables	High (+)	Low (−)
x_1 ratio of potassium carbonate (mmol per mmol amine)	16	4
x_2 solvent	Acetonitrile	Heptane
x_3 nature of the alkylating agent	Butyl bromide	Butyl chloride
x_4 ratio of tetrabutylammonium hydrogensulphate (mmol per mmol amine)	0.8	0.05

According to our knowledge of the reaction, we have selected as factors or independent variables of the experimental system two quantitative variables (molar ratio of base and catalyst) and two qualitative variables (solvent and alkylating agent) which we thought would have an important influence on the reaction selectivity. Table 1 shows the selected factors and their levels.

On the other hand, temperature (80 °C), volume of solvent (6 ml per mmol amine), reaction time (10 h), and stirring (>350 r.p.m.) were maintained constant in all experiments. The yield of carbamate in the reaction was taken as a response or dependent variable (y) and it was determined by g.c.

We have carried out the experiments indicated in Table 2 according with the design matrix for a 2^4 factorial experiment.[2,3] The order of running was randomized as usual. From these values we have calculated the main effects and interactions of the factors using Yates's algorithm.[2,3] The results are shown in Table 3.

Interpretation of Results.—An estimate of error variance is required.[2,3] There was not sufficient background of information on the reactions studied to provide a reliable external estimate of error variance, since only a single replication of the experiment was carried out, but on technical grounds it was thought highly unlikely that the interactions of three or four factors would be appreciable; thereby it was decided to combine the three- and four-factor interactions to give an estimate of error variance. In fact all these interactions (Table 3) are small and it was reasonable to use them as an estimate of error variance. Thus, the error mean square estimated from these interactions is given in Table 4. The analysis of variance table in its conventional form is shown in Table 5.

For one and five degrees of freedom the 5% value of F^4 is 6.61. A mean square based on one degree of freedom is thus significant at the 5% level if it is greater than $6.61 \times 2.93 = 19.37$.

Therefore the main effects *2*—*4* and the interactions *23* and *34* are significant and require interpretation, while the remaining apparent effects could result from the experimental noise.

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Table 2. Matrix for experiments and responses

Experiment	Factor levels x_1	x_2	x_3	x_4	Response y (%)
1	−	−	−	−	72
2	+	−	−	−	58
3	−	+	−	−	9
4	+	+	−	−	11
5	−	−	+	−	2
6	+	−	+	−	1
7	−	+	+	−	0
8	+	+	+	−	0
9	−	−	−	+	91
10	+	−	−	+	89
11	−	+	−	+	34
12	+	+	−	+	35
13	−	−	+	+	15
14	+	−	+	+	12
15	−	+	+	+	8
16	+	+	+	+	6

Table 3. Calculated effects for factors and interactions

	Effect	Estimate
Average		27.69
Main effects	*1*	−2.38
	2	−29.63
	3	−44.38
	4	17.13
Two-factor interactions	*12*	2.63
	13	0.88
	14	0.88
	23	25.63
	24	−1.38
	34	−7.63
Three-factor interactions	*123*	−2.13
	124	−1.63
	134	−1.88
	234	−1.13
Four-factor interactions	*1234*	1.62

Table 4. Estimated error mean square

Interaction	Effect	Effect^2
123	−2.13	4.54
124	−1.63	2.66
134	−1.88	3.53
234	−1.13	1.28
1234	1.62	2.62
Sum of squares		14.63
Degrees of freedom		5
Mean square		2.93

Then, from an empirical point of view, the result means that the carbamate formation yield under phase-transfer conditions can be expressed by equation (*1*).* The calculated values are in

$$\text{Yields}\ (y) = 27.69 - 14.82x_2 - 22.19x_3 + 8.57x_4 + 12.82x_2x_3 - 3.82x_3x_4 \quad (1)$$

total agreement with the experimental ones as shown in Table 6.

Equation (*1*) allows a prediction of the yield of carbamate (**5**) anywhere in the experimental domain. On the other hand, from a chemical point of view, the effects *2*–*4* should be interpreted jointly since mathematically there are appreciable interactions between them, represented by *23* and *34*. However, based on technical grounds and knowledge of the reaction, it was thought that the interactions *23* and *34* might not have chemical significance and their relatively large values arose because the spacing of the levels of the qualitative factor x_3 is clearly too wide. But due to the fact that further experimental work at an intermediate level is not possible, the results must be examined separately.

Table 5. Analysis of variance of data from Table 3

Source of variation	Degree of freedom	Mean square
1	1	5.66
2	1	877.94
3	1	1 969.58
4	1	293.44
12	1	6.92
13	1	0.77
14	1	0.77
23	1	656.90
24	1	1.88
34	1	58.22
Error (high-order interactions)	5	2.93
Total	15	

Table 6. Calculated and experimental carbamate yield

Experiment	Experimental yield (%)	Calculated yield from equation (*1*) (%)	Residual
1	72	65.1	6.9
2	58	65.1	7.1
3	9	9.9	0.9
4	11	9.9	1.1
5	2	2.8	0.8
6	1	2.8	1.8
7	0	−1.3	1.3
8	0	−1.3	1.3
9	91	89.9	2.1
10	89	89.9	0.9
11	34	34.6	0.6
12	35	34.6	0.4
13	15	12.3	2.7
14	12	12.3	0.3
15	8	8.3	0.3
16	6	8.3	2.3

Therefore, we must consider independently (a) the influence of factor x_3 (nature of alkylating agent) and (b) the effects of factors x_2 (type of solvent) and x_4 (ratio of catalyst) and their interaction for each level of factor x_3, *i.e.* when butyl chloride or butyl bromide is employed.

(a) The remarkably negative value obtained for *3* (coefficient of variable x_3) (Table 3) means that the use of butyl bromide (x_3 in level +) produces a dramatic decrease in yields of carbamate (**5**) resulting almost exclusively in trialkylamine (**6**), whereas if butyl chloride is employed the yield of carbamates are increased. These facts should be due to the higher nucleofugacity of bromide ion, which enhances the rate of *N*-alkylation while the slower incorporation of the CO_2 moiety mediated by the catalyst becomes unlikely in this case.

(b) To study the influence of factors x_2 and x_4 and their interaction at each different level of x_3 we have restructured the original experimental matrix in two blocks: one for x_3 in level + and another for x_3 in level −. We have also considered that each

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* The coefficients of factors and interactions are half the corresponding estimates for the effects (Table 3), since these are referred to an experimental domain two units large.[2]

Table 7. Reduced experimental matrix for x_3 in level +

	Factor levels		Response	
Experiment	x_2	x_4	y(%)	$\bar{y}$(%)
5, 6	−	−	2, 1	1.5
13, 14	−	+	15, 12	13.5
7, 8	+	−	0, 0	0
15, 16	+	+	8, 6	7

Table 8. Reduced experimental matrix for x_3 in level −

	Factor levels		Response	
Experiment	x_2	x_4	y(%)	$\bar{y}$(%)
1, 2	−	−	75, 58	65
9, 10	−	+	91, 89	90
3, 4	+	−	9, 11	10
11, 12	+	+	34, 35	34.5

pair of experiments, where x_2 and x_4 remain unchanged and x_1 alternately takes level + or −, are replicates of each other, since this last factor does not have a significant influence. Then the two blocks become as shown in Tables 7 and 8.

In the case of butyl bromide (x_3 in level +) the low values for carbamate yields do not allow any conclusion about alkoxycarbonylation; on the other hand, when butyl chloride (x_3 in level −) is used, from the values of Table 8, effects *2′* and *4′*, and their interaction *24′*, are calculated as above, and they are as follows: *2′* −27.63; *4′* 12.38; *24′* −0.13.

The large values for *2′* and *4′*, negative and positive respectively, denote that when heptane (x_2 in level −) and an almost quantitative amount of catalyst and amine (x_4 in level +) are used the yields of carbamates are notably enhanced, whereas the value close to zero for *24′* indicates negligible interaction between variables x_2 and x_4.

In summary, to obtain high carbamate yields from secondary amines the optimum conditions are: an alkyl chloride as alkylating agent, heptane as solvent, and a near equimolecular amount of tetrabutylammonium hydrogensulphate, independently of the molar excess of potassium carbonate.

Experimental

The response values (y) (Table 2) corresponding to the ratio (**5**):[(**5**) + (**6**)] were determined by g.l.c. from the crude reaction mixtures. Analyses were carried out on a Hewlett–Packard model T-5830A gas chromatograph. A 2 m, 4 mm internal diameter, 3% carbowax 20M on 80—100 Chromosorb glass column with nitrogen as carrier gas was used.

Reaction of N-*Diphenylmethylpiperazine* (**4**) *with Butyl Halides.*—Experiments 1—16 were carried out according to the factors levels indicated in each case (Table 2) and specified in Table 1. The following procedure corresponding to experiment 10 is typical.

A mixture of *N*-diphenylmethylpiperazine (**4**) (252 mg, 1 mmol), butyl chloride [$x_3(-)$] (222 mg, 2.4 mmol), tetrabutylammonium hydrogensulphate {272 mg, 0.8 mmol [$x_4(+)$]}, and finely powdered anhydrous potassium carbonate {2.2 g, 16 mmol [$x_1(+)$]} in n-heptane [$x_2(-)$] (6 ml) was magnetically stirred at 80 °C for 10 h, to give a mixture of carbamate (**5**) and trialkylamine (**6**). Carbamate (**5**) relative yield (y): 89%.

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