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Optimisation of Ethyl(2-phthalimidoethoxy)acetate Synthesis with the Aid of DOE

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Abstract:

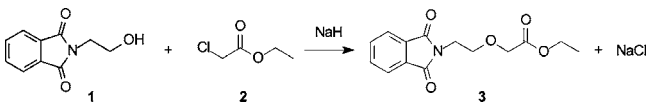
We investigated the reaction of alkylation of 2-phthalimidoethanol with ethyl chloroacetate leading to ethyl(2-phthalimidoethoxy)acetate. The synthesis was successfully optimised by applying factorial design. Major side products have been separated, identified, and characterised. The yield level was increased from 25% to 52%, and a method of decreasing the amount of side products has been proposed.

Introduction

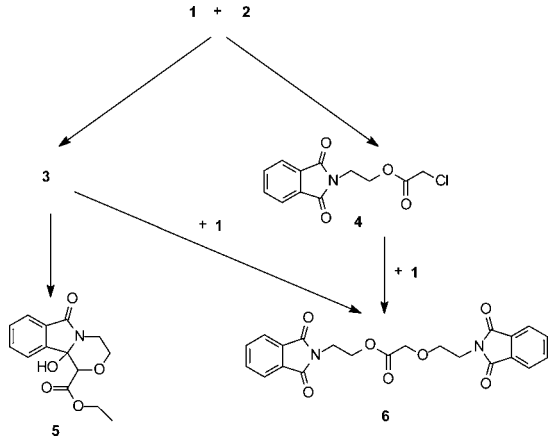
The application of experimental design in organic synthesis is not easy, and the outcome of the results is sometimes far from expectations. There is much resistance to using this approach, and a lot of experimentation is still done with a "one-factor-at-a-time procedure". We want to encourage chemists to use statistical planning and to show them that it is not necessarily complex and can be done with the aid of a spreadsheet. By explaining the logic behind the selection of variables, the experimental scheme, and analysis of the results we will prove that experimental design is not only "black box" research. The more complicated the system the more visible are the advantages of design of experiments (DOEs). For multiparameter systems the traditional "one-factor-at-a-time procedure" leads to many experiments the results of which are difficult to interpret. Mistakes resulting from omitting the interactions of variables are possible. There is no simple way of presenting the results.[1]

We focused our interests on the reaction leading to ethyl-(2-phthalimidoethoxy)acetate (**3**) (Scheme 1), a product important as a useful starting material for our other research.[2]

Scheme 1. **Synthesis of ethyl(2-phthalimidoethoxy)acetate**



Scheme 2. **Impurities resulting from the side and consecutive reactions of the process**



The reaction of an alkoxide anion of **1** with an α-chloroester can lead to some additional products as a result of side and consecutive reactions (Scheme 2).

Mainly due to this fact, we have also found the synthesis of **3** an interesting reaction model for application of factorial experimental design, and herein we present our optimisation approach.

Transesterification, the main competitive reaction, does not influence the process if the alkyl groups in the chloroester and alcohol are identical;[3] if the alkyl groups are different, like in our case, the possibility of side products increases.[4,5]

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The aim of our project was to find the optimal conditions for achieving the best yield for the alkylation of **1** with **2**.

Optimisation. We analysed the reaction of **1** with **2** mediated by sodium hydride, carried out in solvents useful for anionic reactions such as DMF, DMSO and THF. (DMF was previously used to obtain product **3** as a methyl[4e] and *tert*-butyl[4f] ester, and THF, to obtain a deuterated compound.[4d]) The yield of **3** was low (DMF-25%, DMSO-5%, THF-18%), and we observed intense formation of side products. Additionally, we considered that concentrated mixtures of NaH in DMF at elevated temperatures could result in runaway decomposition.[6] The major impurities have been separated and identified, and we proposed the route of their formation.

There are a few examples of the application of nonpolar aromatic solvents such as toluene[3e] or xylene[4a] in alkylation reactions. Also in our case, toluene happened to be advantageous for carrying out the second step of the process (alkylation of sodium alkoxide of **1** with **2**). This reduced the yields of the transesterification product **4** (from 8 to 3%), of the product of its conversion **6** (from 10 to 6%), and of the product of cyclisation of **3** to **5** (from 7 to 0%) (Scheme 2, Table 7). However, toluene was not a proper solvent for the preparation of sodium alkoxide due to the very low solubility of sodium hydride. Thus, the final procedure resulting from the above observations consists of carrying out the first step of the process, i.e. preparation of alkoxide in ether, then evaporation of ether, and then alkylation of alkoxide with **2** in toluene.

The formation of the alkoxide from alcohol with sodium hydride is a simple and efficient step and it was assumed to proceed quantitatively (without an excess of NaH); therefore, at first all the optimisation efforts were focused on the reaction of the sodium salt of **1** with **2**. The optimisation criterion was to maximise the yield of **3**, and we decided to apply a factorial design.[1] The first phase was a simple factorial design of 2^3 for checking the influence of temperature, z_1, concentration, z_2 (solvent amount; the relative concentrations of reactants were included as factors in the second DOE), and time, z_3. We expected that checking the influence of those three variables would be enough to obtain a satisfactory level of the yield. The reaction is heterogeneous because the solubility of the alkoxide of **1** in toluene is very low and sodium chloride formed during the reaction is insoluble in toluene. It forced us to check the influence of temperature and concentration which is critical for solubility. The minimum level of concentration, z_2, was set to allow mixing of the suspension at room temperature. The selected maximum and minimum levels of each factor in the factorial design are shown in Table 1. With these variables, a scheme has been set up of 11 experiments with 8 different combinations of maximum and minimum levels of each variable (factorial design 2^3) and of three additional centre point experiments where all levels were chosen at an intermediate value for checking the experiments repeatability (0 in Table 1). Subsequently, the experiments have been performed at random, and for each experiment the HPLC yield has been measured. The experimental matrix of the factorial design, and the results, are shown in Table 2.

Table 1. **Factorial design I: maximum and minimum levels of variables[a]**

z_i	natural variable	(−)	(0)	(+)
z_1	temperature (°C)	24	47	70
z_2	toluene/reactant **1** (mL/g)	24	36	48
z_3	time (h)	3	15	27

[a] All experiments were performed at a scale of 0.02 mol of **1**, variables of the factorial design II were constant ($z_4 = z_5 = 1$, $z_6 = z_7 = z_8 = 0$).

Table 2. **Factorial design I: experimental matrix and results**

	factors of corresponding natural variables			yield of **3** (%)	
trial no.	x_1	x_2	x_3	response y	calculated $\hat{y}$
1	−	−	−	10.1	7.2
2	+	−	−	39.1	34.5
3	−	+	−	4.4	7.2
4	+	+	−	30.1	34.5
5	−	−	+	24.6	24.6
6	+	−	+	36.2	37.5
7	−	+	+	25.1	24.6
8	+	+	+	40.6	37.5
9	0	0	0	23.4	25.9
10	0	0	0	25.9	25.9
11	0	0	0	26.7	25.9

Table 3. **Factorial design I: influence of variables and statistical analysis, test F**

significant coefficients	$F_{calculated}$	$F_{critical}$
$b_0 = -10.12$		
$b_1 = 0.632$	$F_{calculated} = \{s_r^2\}/\{s^2\} = 5.614$	$F_{critical} = 19.247$
$b_3 = 1.033$	residual variance $s_r^2 = 16.638$	degrees of freedom: 4, 2
$b_{13} = -0.013$	variance $s^2 = 2.963$	level of confidence: 95%

The statistical analysis and the significant influences of this factorial design are summarised in Table 3. The coefficients have been calculated using a polynomial function of the three experimental coded variables as given in the following equation:

$$y = b_0 + \sum b_i x_i + \sum b_{ij} x_i x_j + e$$

We decided to analyse the parameters with a significance of 95% (the usual applied level). From the first three factors, x_1 (temperature) and x_3 (time) were significant, i.e., reached this level.[1] On the basis of the data from Table 3, the yield of **3** ($\hat{y}$) could be described, at a 95% confidence level, as a polynomial equation with the significant natural variables:

$$\hat{y} = -10.12 + 0.632 \cdot z_1 + 1.033 \cdot z_3 - 0.013 \cdot z \cdot z_3$$

A good function fitting to the experimental results was proved with the test F: $F_{calculated} < F_{critical}$ (Table 3).

The yield of the reaction has been observed in the range between 4.4% and 40.6%, and it has reached its maximum at the upper limit of the investigated range for both

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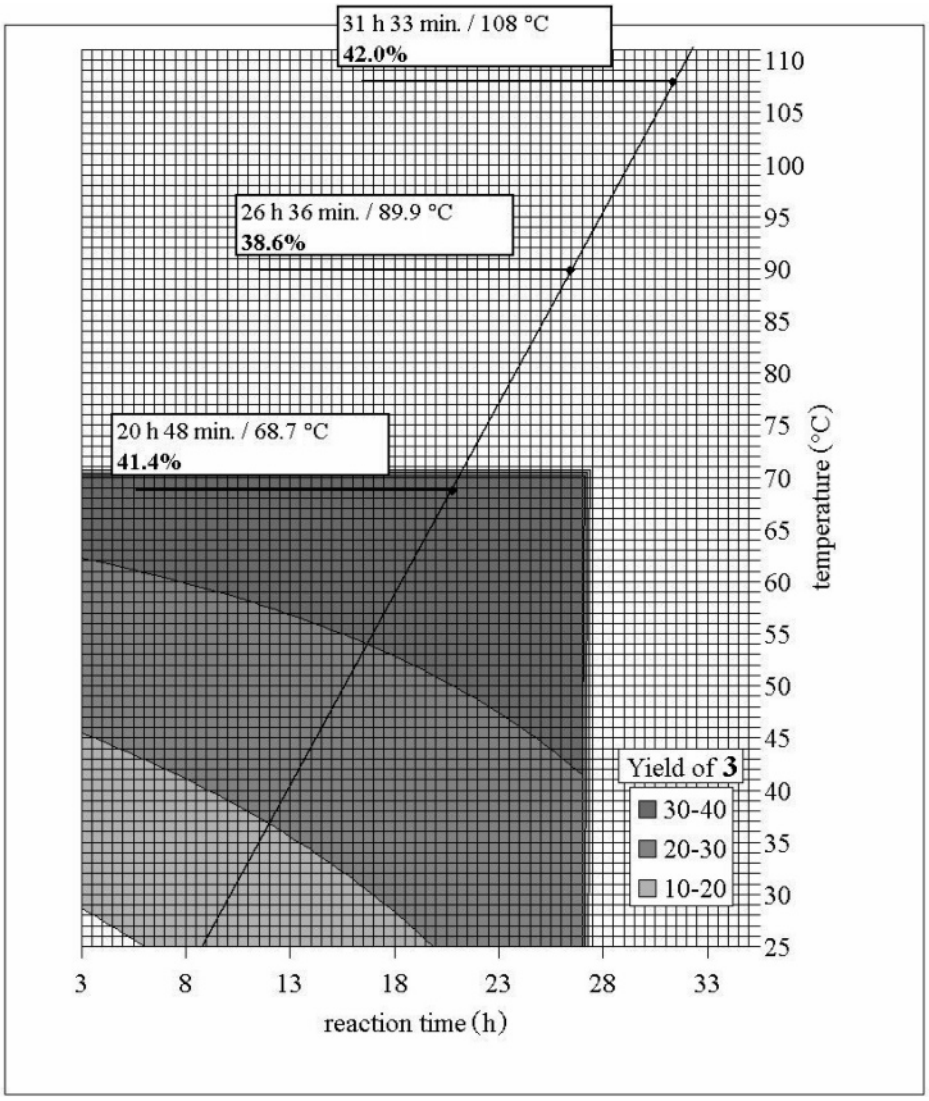

Figure 1. **Factorial design I extended with a steepest-ascent procedure: influence of time and temperature on the yield of 3.**

parameters. Furthermore, both upper levels of z_1 and z_3 extended the experiments into an area with possibly higher yields (z_1 > 70 °C; z_3 > 30 h); thus, we applied the steepest-ascent method along a response surface (Figure 1).[7] A steepest-ascent line has been calculated from the polynomial function without the interaction coefficient, b_{13} (coefficient corresponding to the interaction effect $z_1 \cdot z_3$).

Three experiments carried out along the path of steepest ascent did not help to increase the yield. Considering this and the additional bad fitting of the function for experiments 2 and 4 (Table 2), we decided to check the influence of time in an additional kinetic experiment. This has been done at a high level of temperature (z_1) and low level of concentration (z_2) (toluene/reactant **1**) and proved that increasing time (z_3) over 3 h did not result in an increase in the yield of **3**. We also observed that increasing the reaction time at 70 °C resulted in darkening of the reaction mixture.

Unsatisfied with the yield obtained during the first phase of optimisation, in the second step we decided to investigate higher number of variables. On the basis of our experience from the first step of optimisation and the kinetic experiment, we fixed the temperature, concentration, and time of reaction at 70 °C (maximal not causing darkening of the reaction mixture), 24 mL/g (quite big but the minimal to allow mixing), and 3 h (based on the kinetic experiment), respectively, and we did one-fourth replication (2^{5-2}) to check the significance of five different variables. Application of the fractional factorial design gives the opportunity to examine a large number of parameters in a low number of experiments, (in our case, 8 instead of $2^5 = 32$ as in a full factorial experiment). Excesses of reactants (z_4, z_5) were checked in the range from 1 to 1.2. From our previous experience we knew that the application of a larger amount of sodium hydride could result in intense formation of **5**. We also considered the influence of mixing with an ultrasonic bath (z_6), and tetrabutylammonium bromide as PTC catalyst (z_8)—the reaction is heterogeneous, and of KI (z_7) as a catalyst for the Williamson substitution—possible influence from the Finkelstein reaction.[8] The selected maximum and minimum levels of each factor in the factorial design are shown in Table 4. With these variables, a fractional factorial design

(7) All calculations were done with MS Excel.

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Table 4. **Factorial design II: maximum and minimum levels of variables[a]**

z_i	natural variable	(−)	(0)	(+)
z_4	NaH/reactant **1** (mol/mol)	1	1.1	1.2
z_5	reactant **2**/reactant **1** (mol/mol)	1	1.1	1.2
z_6	time of ultrasonic bath work/ time of experiment (h/h)	0	0.5	1
z_7	KI/reactant **1** (mol/mol)	0	0.025	0.05
z_8	ammonium salt/reactant **1** (mol/mol)	0	0.025	0.05

[a] All experiments were performed at a scale of 0.02 mol of **1**, variables of the factorial design II were constant (z_1 = 70 °C, z_2 = 1 mL/g, z_3 = 3 h).

Table 5. **Factorial design II: experimental matrix and results**

	factors of corresponding natural variables					yield of **3** (%)	
trial no.	x_4	x_5	x_6	x_7	x_8	response y	calculated $\hat{y}$
12	−	−	−	−	+	36.7	37.9
13	+	+	+	+	+	45.8	46.7
14	+	+	−	−	−	51.7	50.7
15	−	−	+	+	−	37.8	41.9
16	−	+	+	−	+	40.5	37.9
17	+	−	+	−	−	51.0	50.7
18	−	+	−	+	−	44.6	41.9
19	+	−	−	+	+	46.2	46.7
20	0	0	0	0	0	40.3	44.3
21	0	0	0	0	0	42.3	44.3
22	0	0	0	0	0	41.6	44.3

Table 6. **Factorial design II: influence of variables and statistical analysis, test F**

significant coefficients	$F_{calculated}$	$F_{critical}$
$b_0 = -1.987$	$F_{calculated} = \{s_r^2\}/\{s^2\} = 6.689$	$F_{critical} = 19.296$
$b_4 = 43.875$	residual variance $s_r^2 = 6.889$	degrees of freedom: 5, 2
$b_8 = -79.5$	variance $s^2 = 1.03$	level of confidence: 95%

has been set up of 11 experiments with 8 different combinations of maximum and minimum levels of each variable, and three additional centre point experiments where all levels were chosen at an intermediate value (0 in Table 4). Subsequently, the experiments have been performed at random, and for each experiment the yield has been measured. In Table 5 the experimental matrix of the factorial design is shown, including the results. Factor x_7 replaced the interaction effect $x_4 \cdot x_5 \cdot x_6$, and x_8 replaced the interaction effect $x_5 \cdot x_6$ which we expected to have the lowest possibility of existence.

The statistical analysis and the significant influences of variables from the factorial design II are summarised in Table 6. The coefficients have been calculated using the polynomial function of the five experimental variables. On the basis of data from Table 6, the yield can be described, at a 95% level of confidence, as a polynomial equation with the significant natural variables:

$$\hat{y} = -1.987 + 43.875 \cdot z_4 - 79.5 \cdot z_8$$

A good function fitting to the experimental results was proved with the test F: $F_{calculated} < F_{critical}$. Two of the examined variables occurred to be significant. An excess of sodium hydride (z_4) resulted in an increase of yield up to 52%—probably due to influence on the formation of alkoxide of **1**. On the contrary, the addition of phase transfer catalyst (z_8) resulted in a decrease of yield and an increase of the amount of side products. Three other variables did not cause any effect. An excess of **2** (z_5) was not significant probably due to the irreversibility of the reaction. Mixing with an ultrasonic bath (z_6) was probably not necessary in the presence of good mechanical stirring. An influence of KI (z_7) was not observed even in the presence of tetrabutylammonium bromide, which was a surprise for us, probably because of the bad conditions for the Finkelstein reaction, which was usually carried out in acetone.

Table 7. **Products distribution before and after optimisation**

	yield[a] (%)	
cmpd	preliminary reaction in THF	optimised reaction in toluene
4	8	3
3	18	52
6	10	6
1	34	17
5	7	0
unidentified products	23	22

[a] The yield of the identified products was measured basing on the calibration curves, unidentified products is the rest to 100%.

In conclusion, the obtained moderate yields are more the result of intensity of the side and consecutive reactions than the low reactivity of **1** in reaction with **2**. A careful examination of the reaction conditions has resulted in a two-stage process: synthesis of sodium alkoxide of **1** in diethyl ether and alkylation of the alkoxide of **1** with **2** in toluene, respectively, with the following optimal parameters: z_1 temperature = 70 °C, z_2 toluene/**1** = 24 mL/g, z_3 reaction time = 3 h, z_4 NaH/**1** = 1.2, z_5 **2**/**1** = 1, z_6 time of ultrasonic bath = 0, z_7 KI/**1** = 0 and z_8 ammonium salt/**1** = 0. The investigation described has enabled improving the yield from 25% up to 52%, shortening the reaction time, and lowering the amount of side products (Table 7). The yield of 52% of the synthesis procedure carried out with optimal parameters is in very good agreement with the results obtained with the aid of DOE. We emphasise that it is the first and only information concerning the synthesis of **3**. The isolated side products **4** and **5** and their analogues are under our special consideration.[5,2]

Experimental Section

Commercially available solvents and reagents were used without further purification. Solvents and reagents were preserved against humidity. Reactions were carried out under argon. HPLC was performed with a Hewlett-Packard 1050 chromatograph on a Si-60 column with eluent CH_2Cl_2/CH_3-CN, 70/30, UV detector. Infrared spectra were obtained using Carl Zeiss Jena spectrophotometer Specord M80.

Representative Procedure for the Synthesis of 3 (Optimal Conditions Presented). 1 (19.12 g; 0.1 mol) was

added to a mixture of sodium hydride (4.8 g; 60% in oil; 0.12 mol) in 160 mL of diethyl ether, the mixture was stirred for 30 min. at 30 °C. The temperature was raised to 40 °C, and the ether slurry was concentrated by evaporation of the solvent supported with the flow of inert gas. Toluene (460 mL) was added to the vigorously stirred mixture to suspend the alkoxide. In 2 h the temperature was raised to 70 °C, and **2** (12.26 g; 0.1 mol) was added. The reaction was carried out for 3 h and then cooled to room temperature. Acetic acid was added to neutralise the excess of sodium hydride. In the case of experiments carried out for the factorial design I and II samples of the solution were taken for the HPLC analysis. In the case of the synthesis procedure, further purification followed. The organic solution was washed twice with 200 mL of water and dried with $MgSO_4$, toluene was evaporated off, the raw product was washed first with cold ethanol and later with hexane. After evaporation of the remainder of the solvents, 16.74 g of an oil containing 86.2% of **3** was obtained (yield 52.0%).

Isolation and Identification of Major Byproducts. A raw reaction mixture, before the step of washing with water, was concentrated and dissolved in a minimal amount of *n*-hexane/acetone, 1/1. Column silica gel chromatography of this solution (eluent: hexane/acetone, 1/1) provided in the order of elution samples of **4**, **3**, **6**, **1**, **5**. HPLC retention times **cmpd** (min): **4**(3.56), **3**(4.14), **6**(5.02), **1**(11.60), **5**(23.15).

Spectroscopic and analytical data: ^{1}H NMR, IR: (KBr). ***3***, *ethyl(2-phthalimidoethoxy)acetate:* ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.74 (m, 4 H, ar), 4.12 (q, 2 H, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 4.07 (s, 2 H, $OC\underline{H}_2CO$), 3.92 (t, J = 5.4 Hz, 2 H, $NC\underline{H}_2CH_2O$), 3.80 (t, 2 H, J = 5.4 Hz, $NCH_2C\underline{H}_2O$), 1.19 (t, 3 H, J = 7.1 Hz, $OCH_2C\underline{H}_3$); IR: $\nu_{C=O}$ 1776, 1760, 1710 cm^{-1}, γ_{Ph-H} 720 cm^{-1}.

4, *2-phthalimidoethyl chloroacetate:* ^{1}H NMR(200 MHz, $CDCl_3$): δ = 7.77 (m, 4 H, ar), 4.41 (t, 2 H, J = 5.2 Hz, $NCH_2C\underline{H}_2O$), 4.03 (s, 2 H, $COC\underline{H}_2Cl$), 3.96 (t, 2 H, J = 5.2 Hz, $NC\underline{H}_2CH_2O$); IR: $\nu_{C=O}$ 1770, 1752, 1708 cm^{-1}, γ_{Ph-H} 722 cm^{-1}.

5, *ethyl 10β-hydroxy-1,3,4,10β-tetrahydro[1,4]oxazino-6-oxo[3,4-a]isoindole-1-carboxylate:* ^{1}H NMR (500 MHz, CD_3OD): δ = 7.82−7.77 (m, 2 H, ar), 7.65 (m, 1 H, ar), 7.60 (m, 1 H, ar), 4.36 (m, 2 H, $OC\underline{H}_2CH_3$), 4.14 (m, 2 H, $NCH_2C\underline{H}_2O$), 3.99 (s, 1 H, $OC\underline{H}COO$), 3.51 (m, 2 H, $NC\underline{H}_2$-CH_2O), 1.37 (t, J = 7.2 Hz, 3 H, $OCH_2C\underline{H}_3$); IR: $\nu_{C=O}$ 1676, 1728 cm^{-1}, ν_{O-H} 3264 cm^{-1}.

6, *2-phthalimidoethyl (2-phthalimidoethoxy)acetate:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (m, 8 H, ar), 4.32 (t, 2 H, J = 5.3 Hz, $NCH_2C\underline{H}_2OCO$), 4.07 (s, 2 H, $COCH_2O$), 3.93 (t, 2 H, J = 5.3 Hz, $NC\underline{H}_2CH_2OCO$), 3.90 (t, 2 H, J = 5.6 Hz, $NC\underline{H}_2CH_2OCH_2$), 3.80 (t, 2 H, J = 5.6 Hz, $NCH_2C\underline{H}_2OCH_2$); IR: $\nu_{C=O}$ 1760, 1720, 1709 cm^{-1}, γ_{Ph-H} 728, 716 cm^{-1}.

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