

## Synthesis of 4-(*N,N*-dimethylamino)-acetophenone Optimized by a Doehlert Design

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In our studies of substituent effects on the Willgerodt reaction we needed 4-(*N,N*-dimethylamino)-acetophenone as a model substrate. This compound is not commercially available in Europe. Since we needed substantial amounts, a simple synthetic method using cheap and readily available chemicals was desired. Published procedures for synthesis of 4-(*N,N*-dimethylamino)-acetophenone report poor to moderate yields.<sup>1</sup> One method for preparing the ketone by heating 4-chloroacetophenone with aqueous dimethylamine in an autoclave is described in a Japanese patent.<sup>2</sup> However, from the patent description it is not possible to conclude whether or not optimum conditions have been established. The reported yield was 77 % and the method seemed to be promising for further development. We have now established optimum conditions by the response surface technique. The yield can be increased to 89–92 % by proper choice of reaction conditions.

**Experimental design.** The necessity for using multivariate strategies in synthesis optimization has been emphasized.<sup>3</sup> Excellent reviews<sup>4</sup> on experimental design and optimization strategies have been published. Accordingly, we do not propose to discuss the technical details of these subjects.

Two variables were studied:  $x_1$ , the molar ratio dimethylamine–chloroacetophenone, and  $x_2$ , the reaction temperature. To establish a response surface model, it is necessary to vary both variables simultaneously. Central composite designs<sup>5</sup> have been used extensively in response surface modelling. Such designs contain, however, an excess of experiments compared to the number of parameters in the model. However in synthetic chemistry, time and cost for an individual experiment are often limiting factors. In this study we have used a simplex-lattice design suggested by Doehlert,<sup>6</sup> which permits calculation of a response surface model by a minimum of experiments. Therefore, such designs are of

considerable interest for synthesis optimization. Another attractive feature of these designs is that it is possible to explore a neighbouring experimental domain by including only a few more new experiments. To the best of our knowledge, this is the first application of such a design in synthesis optimization. The design is shown in Table 1, entries 1–7. The experiments define a regular hexagon plus a centre point in the  $x_1, x_2$  plane. See Fig. 1.

**Results.** The individual experiments and the yields obtained are shown in Table 1. A second order response surface model calculated from the first seven experiments suggested that the optimum conditions were to be found outside the explored domain. Three more experiments were included to permit a coverage of the calculated optimum domain, entries 8–10. A second order response surface model was fitted to the experimental results by least squares multiple regression:

$$y = 86.9 + 10.0 x_1 + 6.7 x_2 - 3.9 x_1^2 - 8.7 x_2^2 - 2.3 x_1 x_2$$

The general features of the response surface are shown in Fig. 1. Differentiation shows a

Table 1. Experimental design and yield in response surface determination.

Entry	Variables <sup>a</sup>		Yield (%) <sup>b</sup>
	$x_1$	$x_2$	
1	0	0	87
2	1.00	0	93
3	0.50	0.87	88
4	-1.00	0	59
5	-0.50	-0.87	63
6	0.50	-0.87	80
7	-0.50	0.87	74
8	1.50	0.87	90
9	1.50	-0.87	85
10	2.00	0	91
11	1.22	0.22	89
12	1.22	0.22	92
13	1.22	0.22	91 <sup>c</sup>
14	1.22	0.22	92 <sup>c</sup>

<sup>a</sup>  $x_1=0$  corresponds to a molar ratio dimethylamine/ketone=3.00, one unit of variation in  $x_1$  corresponds to a change in molar ratio=1;  $x_2=0$  corresponds to a reaction temperature of 230 °C, one unit of variation in  $x_2$  corresponds to a temperature change of 20 °C. <sup>b</sup> Yields determined by GLC (internal standard technique). <sup>c</sup> Isolated yield.

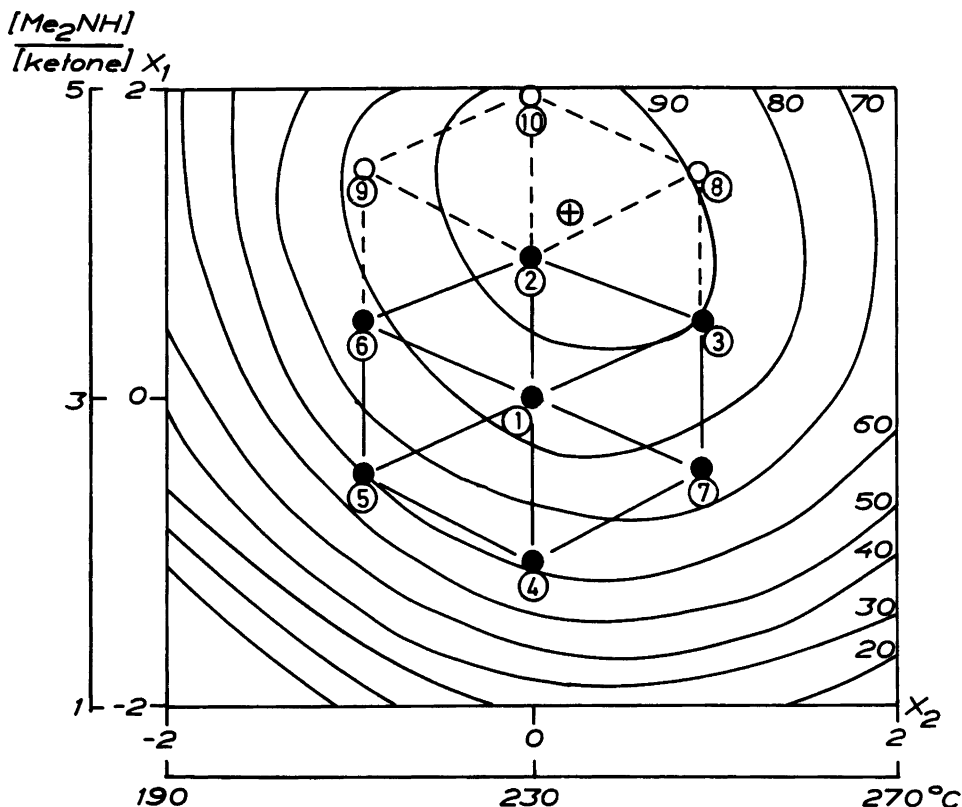


Fig. 1. Response surface obtained by a simplex lattice design. The various experiments are marked with encircled numbers. The figures at the isoresponse contours show the yield (%).

maximum,  $y_{\text{calc}}=95.3$  for  $x_1=1.22$ ,  $x_2=0.22$  which corresponds to a molar ratio dimethylamine–chloroacetophenone=4.22 and a reaction temperature=234 °C. Experiments under these calculated optimum conditions, afforded 89–92 % yield, entries 11–14. A yield of 78.5 % is calculated from the model under the conditions described in the Japanese patent and this is in good agreement with the reported yield, 77 %.

**Experimental. Chemicals.** 4-Chloroacetophenone purum and dimethylamine puriss (40 % aqueous solution) were obtained from Fluka. 4-Nitroacetophenone puriss from EGA was used as internal standard for GLC analysis.

**GLC analysis.** A PYE UNICAM GCD with FID was used. Column: 6 % QF-1 on Chromosorb W-AW 110–120 mesh. Integrated peak areas were used for quantifications.

**Experimental procedure for response surface experiments.** A glass ampoule was loaded with 1.55 g (10 mmol) of 4-chloroacetophenone and the calculated amount,  $x_1$ , of aqueous dimethyl-

amine. The ampoule was sealed and heated for 4 h at the temperature  $x_2$  by means of a thermostated molten metal bath. CAUTION: A safety screen is necessary; two explosions occurred during these experiments. After cooling the ampoule was opened and an accurately weighed amount (of approximately) of 10 mmol 4-nitroacetophenone was added, together with ca. 10 ml of acetone to dissolve the ketones. Samples were withdrawn and analysed by GLC.

**Preparative run.** A stainless steel general purpose bomb, capacity 165 ml, from Parr Instruments was used as reaction vessel. A mixture of 4.65 g (30 mmol) of 4-chloroacetophenone and 14.04 g of 40 % aqueous dimethylamine was heated at  $234 \pm 2$  °C (silicone oil bath) for 4 h. The pressure rose to 220 psi (1.52 MPa) during the reaction. After cooling, the contents were evaporated to dryness on a steam bath. The crude 4-(*N,N*-dimethylamino)-acetophenone, 4.53 g (92 %), showed no impurities on GLC but was slightly yellow. An analytical sample was

obtained by recrystallization from water, m.p. 104 °C (lit.<sup>7</sup> 105 °C). The structure was confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectra.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): δ 2.51 (3H, s), 3.06 (6H, s), 6.64–6.67 (2H, m) and 7.86–7.89 (2H, m). <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ 26.0 (CH<sub>3</sub>CO), 40.0 ((CH<sub>3</sub>)<sub>2</sub>-N), 110.6 (C3, C5), 125.3 (C4), 130.5 (C2, C6), 153.4 (C1) and 196.4 (C=O). MS (EI, 70 eV) *m/e* (relative abundance) (assignment) 163 (66.2) (M<sup>+</sup>) and 148 (100.0) (M<sup>+</sup>-CH<sub>3</sub>).

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