Optimum Conditions for the Willgerodt-Kindler Reaction 1: Reaction of Substituted Acetophenones. Prediction of Optimum Conditions for New Substrates by Multivariate Correlation

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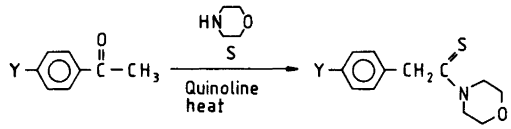
Optimum conditions for the synthesis of *p*-substituted phenyl-acetic acid thiomorpholides by the joint action of elemental sulfur and morpholine on *p*-substituted acetophenones have been studied with the following substrates: *p*-methoxy-, *p*-*N*,*N*-dimethylamino-, *p*-methyl-, *p*-chloro-, *p*-nitro-, *p*-cyanoacetophenone and unsubstituted acetophenone. With the exceptions of *p*-nitro- and *p*-cyanoacetophenone which did not give the desired product, isolated yields of substituted phenylacetic acid thiomorpholides were in the range 86–95 %. Optimization was achieved by using a fractional factorial experimental design combined with response surface methods. Separate response surface models for each substrate were determined. Correlation of established optimum conditions for each substrate with tabulated substituent parameters by the PLS method made it possible to predict optimum conditions for *new* substrates (*p*-methylthio-, *p*-bromo-, *p*-flouroacetophenone). The predictions were confirmed by experiments.

The rather curious oxidation-rearrangement that occurs when aryl alkyl ketones are heated in the presence of elemental sulfur and ammonia is known as the *Willgerodt* reaction.[1] A procedure utilizing primary or secondary amines in place of ammonia is known as the *Kindler* modification.[2] The reaction is of wide scope and can be conducted with a variety of substrates and under different reaction conditions. Several review articles on the reaction have been published.[3] Though the reaction is mentioned in almost every textbook on organic chemistry, it has a rather bad reputation for not being very useful for preparative purposes due to the poor yield and messy reaction mixtures usually obtained.

A detailed reaction mechanism is not known with certainty, although over the years, a number have been proposed.[4] It is thus obvious that optimum conditions for synthesis can not be found from an established reaction mechanism, and



that reaction conditions must be optimized by other methods. However, the common approach to synthesis optimization, adjusting one variable at a time, usually fails to attain a true optimum when the variables are not independent.[5] Since the mechanism of the reaction is not known, one can not exclude interactions between the experimental variables. Therefore, any attempts at optimizing the reaction must make use of multivariate optimization strategies.

In this paper, we present results obtained in optimization studies on the Willgerodt-Kindler reaction of a series of *para*-substituted acetophe-

nones: *p*-methoxy-, *p*-*N*,*N*-dimethylamino-, *p*-methylthio-, *p*-methyl-, *p*-fluoro-, *p*-chloro-, *p*-bromo-, *p*-nitro-, *p*-cyanoacetophenone and unsubstituted acetophenone. The substituents were selected to span a range of different electronic effects that might play a rôle. The reaction was carried out using quinoline as solvent, chosen solely due to its high boiling point which made it possible to study a wide variation in reaction temperatures.

The multivariate methods given below were used to determine the optimum conditions. Details of the underlying principles of these methods are given in the various references.

Methods

Fractional factorial experiment.[6] To identify significant experimental variables and the most important interactions between them, a fractional factorial design was used in a screening experiment. This study was carried out on one substrate (*p*-methylacetophenone) with the assumption that significant variables with this substrate are likely to be important with other substrates.

Response surface methods.[7] Optimum conditions for each substrate were determined by response surface methods. Central composite rotatable designs were used with the following substrates: *p*-methoxy-, *p*-methyl-, *p*-fluoro-, *p*-chloro-, *p*-bromoacetophenone and unsubstituted acetophenone. With *p*-*N*,*N*-dimethylaminoacetophenone a more economic[8] Doehlert uniform shell design[9] was used to establish the response surface model since only a limited amount of this ketone was available.

PLS method.[10] The substrates can be characterized by different descriptors (substituent parameters) for the *para*-substituent, see Table 7. The optimum conditions for each substrate can be characterized by the optimum yield and the adjustment of the experimental variables at the optimum. The PLS method was used to establish quantitative models which correlate the properties of the substituents with the optimum conditions and to predict optimum conditions for new substrates when the substituent parameters were known.

Results

Screening experiment. *p*-Methylacetophenone was used as a model substrate. Five variables were considered as potentially important: x_1, the amount of sulfur; x_2, the amount of morpholine; x_3, the reaction temperature; x_4, the particle size of sulfur and x_5, the rate of agitation. The reaction occurs in a heterogeneous system and the two last variables, x_4, x_5, were included to account for effects due to the heterogeneity. It was desired to obtain estimates of all main effects and all possible two-variable interactions. We assumed that interactions between three or more variables were neglible and that the variation in response (yield), y, for screening purposes, could be adequately described by a polynomial in the experimental variables including linear terms, $b_i x_i$, and cross-product (interaction) terms, $b_{ij} x_i x_j$:

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

Table 1. Variables and their levels in the response surface and screening experiments

Variables		Levels				
		−1.68	−1	0	1	1.68
x_1:	Amount of sulfur/ketone (mol/mol)	2.95	5.00	8.00	11.00	13.05
x_2:	Amount of morpholine/ketone (mol/mol)	4.63	6.00	8.00	10.00	11.37
x_3:	Reaction temperature (°C)	86	100	120	140	154
x_4:	Particle size of sulfur (mesh)	–	240	–	120	–
x_5:	Stirring rate (rpm)	–	300	–	700	–

Table 2. Screening experiment

Entry	Variables					Yield (%)
	x_1	x_2	x_3	x_4	x_5	y
1	1	−1	−1	−1	−1	53.8
2	−1	1	−1	−1	−1	55.7
3	−1	−1	1	−1	−1	78.1
4	1	1	1	−1	−1	84.5
5	−1	−1	−1	1	−1	16.5
6	1	1	−1	1	−1	72.6
7	1	−1	1	1	−1	91.4
8	−1	1	1	1	−1	86.2
9	−1	−1	−1	−1	1	11.5
10	1	1	−1	−1	1	75.1
11	1	−1	1	−1	1	88.9
12	−1	1	1	−1	1	77.6
13	1	−1	−1	1	1	43.7
14	−1	1	−1	1	1	38.0
15	−1	−1	1	1	1	79.5
16	1	1	1	1	1	78.6

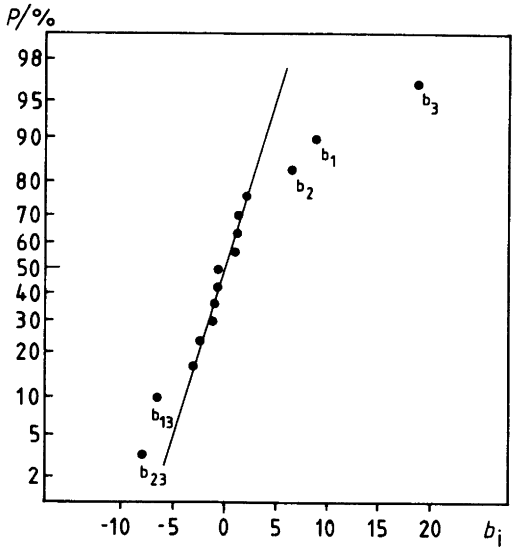


Fig. 1. Normal probability plot of estimated effects in the screening experiment.

A two-level fractional factorial design, 2^{1-5}, was used to obtain estimates of the effects. The experimental domain (levels of variables) is given in Table 1 and the design matrix and the yields obtained after 2 h are given in Table 2. For simplicity, only the yields after 2 h are given. Yields were determined by GLC, using the internal standard technique. The estimated effects were:

Average yield: $b_0 = 64.48$

Main effects: $b_1 = 9.09$, $b_2 = 6.56$, $b_3 = 18.62$, $b_4 = -1.17$, $b_5 = -2.87$

Interaction effects: $b_{12} = -2.43$, $b_{13} = -6.43$, $b_{14} = 0.83$, $b_{15} = 0.87$, $b_{23} = -7.93$, $b_{24} = -1.01$, $b_{25} = -0.84$, $b_{34} = 1.99$, $b_{35} = 0.92$, $b_{45} = -0.49$

A plot of these effects on *normal probability* paper[11] is shown in Fig. 1. It is clearly seen that b_1, b_2, b_3, b_{13} and b_{23} fall off the straight line that fits well all the remaining effects. It was therefore concluded that x_1 (amount of sulfur), x_2 (amount of morpholine) and x_3 (temperature) and the interactions between x_1,x_3 and x_2,x_3 had a strong influence on the yield. The variations in the experimental conditions described by x_4 and x_5 do not seem to have any significance, since their main effects as well as all interaction effects among these variables are normally distributed and can likely be interpreted as estimates of the experimental error. To use this type of plot to evaluate screening experiments, it is essential that the design be randomized so that the assumption of normality and independence of the experimental error is not violated.

Optimization

Some of the screening experiments gave good yields (~90 %) and it was concluded that optimum conditions probably were to be found within the explored domain. To locate the optimum conditions, response surface models of the significant variables (x_1, x_2, x_3) were determined. *Particle size of sulfur* was not further controlled and flowers of sulfur were used as delivered without particle fractionation. *Stirring rate* was maintained at 700 rpm ($x_5 = 1$). It was assumed that

Table 3. Response surface design and yields obtained

Entry	Variables			Substituents Me- Yields (%)	MeO-	H-	Cl-	F-	Br-
	x_1	x_2	x_3	y_1	y_2	y_3	y_4	y_5	y_6
1	−1	−1	−1	11.5	16.6	37.2	43.7	71.6	67.8
2	1	−1	−1	43.7	34.8	77.8	66.3	91.2	77.3
3	−1	1	−1	38.0	28.9	76.0	55.7	82.4	73.9
4	1	1	−1	75.1	82.9	87.7	39.5	90.2	91.3
5	−1	−1	1	79.5	75.3	62.4	83.9	85.9	82.4
6	1	−1	1	88.9	73.9	88.6	28.0	94.1	93.5
7	−1	1	1	77.6	55.8	86.6	96.9	83.5	85.7
8	1	1	1	78.6	86.7	80.9	55.7	76.7	77.2
9	1.68	0	0	91.5	73.1	87.0	67.0	70.5	89.4
10	−1.68	0	0	48.5	28.0	57.8	50.4	55.1	17.2
11	0	1.68	0	94.7	71.7	89.1	89.8	87.7	61.5
12	0	−1.68	0	58.8	44.4	62.9	40.5	86.5	14.8
13	0	0	1.68	94.1	70.1	85.3	63.8	89.6	74.9
14	0	0	−1.68	14.4	22.4	67.4	25.6	80.0	83.7
15	0	0	0	83.9	90.4	85.6	91.6	92.9	93.9
16	0	0	0	84.2	89.7	83.1	87.7	–	–
17	0	0	0	85.6	90.3	86.0	90.1	–	–
18	0	0	0	82.6	92.2	88.1	89.9	–	–
19	0	0	0	83.2	87.2	85.8	89.5	–	–
20	0	0	0	84.9	92.2	87.2	87.3	–	–

second order models would suffice to describe the response surfaces, i.e.,

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + e.$$

Experimental design and yields obtained are summarized in Tables 3 and 4. With *p-N,N*-dimethylaminoacetophenone a Doehlert design[9] given in Table 4 was employed. Estimated model parameters are summarized in Table 5. The general feature of the response surfaces is illustrated by the projections of the surface obtained from *p*-methylacetophenone in Fig. 2. The response surfaces were all similar and the projections in Fig. 2 are representative.

The optimum conditions for the different substrates were determined by differentiation of the response surface models. These optimum conditions and yields obtained in validation experiments are summarized in Table 6.

The reaction failed to give the expected arylacetic acid thiomorpholide with two substrates, *p*-nitro- and *p*-cyanoacetophenone. With nitroacetophenone, poor to fair yields of *p*-aminophenylglyoxylic acid thiomorpholide was obtained, *p*-$H_2NC_6H_4COCSN(CH_2CH_2)_2O$. With cyanoacetophenone, only tarry products were obtained.

Table 4. Doehlert design used with *p*-dimethylaminoacetophenone

Entry	Variables			Yield (%)
	x_1	x_2	x_3	y
1	0	0	0	87.7
2	1.00	0	0	75.5
3	0.50	0.87	0	81.4
4	0.50	0.29	0.82	87.4
5	−1.00	0	0	64.7
6	−0.50	−0.87	0	69.0
7	−0.50	−0.29	−0.82	66.7
8	0.50	−0.87	0	69.0
9	0.50	−0.29	−0.82	79.2
10	0	0.58	−0.82	54.0
11	−0.50	0.87	0	74.6
12	−0.50	0.29	0.82	65.0
13	0	−0.58	0.82	64.7

Table 5. Response surface model parameters

Model parameter	Me-	MeO-	H-	Cl-	Me_2N-	Br-	F-
b_0	84.20	90.00	85.97	89.20	87.70	89.70	82.80
b_1	11.13	13.00	8.72	3.90	2.00	4.07	11.05
b_2	7.77	7.30	7.78	10.41	4.65	−0.70	6.24
b_3	21.20	15.30	5.34	8.62	6.27	1.55	1.14
b_{11}	−5.87	−12.43	−4.79	−9.87	−11.13	−8.52	−5.28
b_{22}	−3.50	−9.77	−3.51	−7.60	−23.20	0.56	−11.02
b_{33}	−11.45	−13.95	−3.39	−14.82	−14.20	−0.20	4.45
b_{12}	−0.44	8.51	−7.99	−3.69	0.89	−3.39	−1.46
b_{13}	−7.36	−5.34	−3.58	−12.93	2.65	−3.21	−3.03
b_{23}	−8.76	−8.39	−3.65	3.08	14.66	−3.74	−4.14

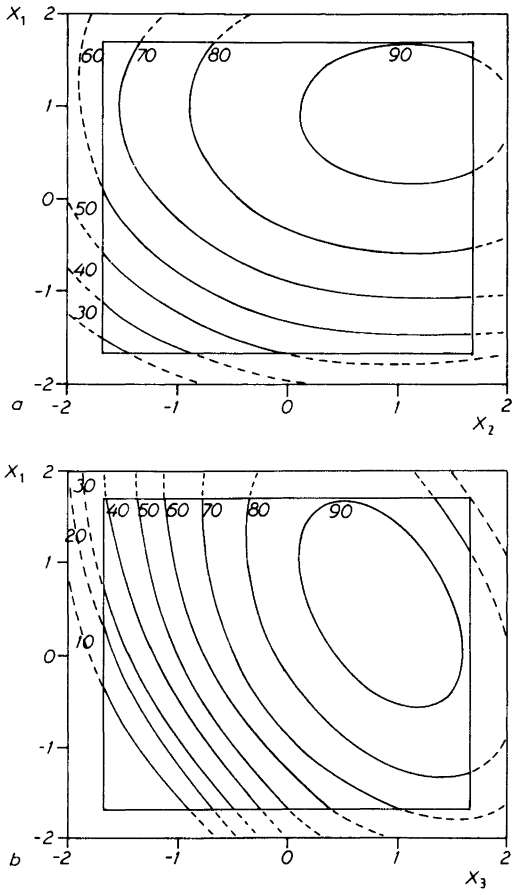


Fig. 2. Response surface projections obtained in the reaction of *p*-methylacetophenone. The isoresponse contours are dashed outside the explored domain. (Published with permission of *Kemisk Tidsskrift.*)

The reaction also failed in polar aprotic solvents (reported in part 2 in this series). For these reasons, polar acceptor substituents were not further considered in this study.

Prediction of optimum conditions for new substrates by the PLS method

For details of this method, see Ref. 10. In a first series of experiments the optimum conditions were determined for *p*-methyl, *p*-methoxy-, *p*-hydrogen,-, *p*-chloro- and *p*-dimethylaminoacetophenone.[12] The predicted yield and optimum conditions from the response surface models for these substrates in Table 6 were included in the response matrix, **Y**, as a learning set. Substituent parameters for the corresponding substituent were included in the descriptor matrix, **X**, see Table 7. PLS decompositions[10] of the matrices af-

Table 6. Optimum conditions and optimum yields

Substituent	Optimum Conditions[a]			Optimum yields			
	z_1	z_2	z_3	Y_{pred1}[b]	Y_{pred2}[c]	Y_{found}[d]	Y_{found}[e]
Me-	9.6	8.4	133	96.0	95.8	96	88
MeO-	9.3	8.9	130	98.2	93.5	100	90
H-	7.5	10.3	123	90.8	91.6	94	90
Cl-	9.7	9.9	119	95.0	96.6	100	95
Me_2N-	8.8	8.3	127	89.0	91.2	89	86
F-	8.3	10.6	116	94.0	95.0	93	88
Br-	10.2	9.5	121	95.0	97.0	95	93
MeS-	10.4	8.4	129	–	97.0	95	89

[a]z_1 = amount of sulfur/ketone (mol/mol); z_2 = amount of morpholine/ketone (mol/mol); z_3 = reaction temperature (°C). [b]Predicted from the response surface model. [c]Predicted from the PLS model. [d]Yield determined by GLC. [e]Isolated yield in preparative run.

forded the correlations between u_i (the components of the **Y** bloc) and t_i (the components of the **X** bloc) shown in Figure 3. By entering descriptors for new substituents into the **X** matrix, the PLS model made it possible to predict the corresponding responses (optimum yield and experimental conditions) for these substrates. In this way, predictions of optimum conditions for *p*-fluoro- and *p*-bromoacetophenone were obtained. These results are also given in Table 6. The predicted optima were thereafter validated by determining the response surface models for these substrates, see Tables 5 and 6. These new, validated, results were then included in the training set (matrices **X** and **Y**) and the PLS model was recalculated. Substituent parameters for the *p*-methylthio substituent were now introduced and the yield and optimum conditions for *p*-

Table 7. Substituent descriptors used in the PLS analysis

Descriptors[a]	Substituent							
	Me-	MeO-	H-	Cl-	Me_2N-	F-	Br-	MeS-
1	−0.01	0.3	0	0.47	–	0.54	0.47	0.3
2	−0.17	−0.27	0	0.23	−0.83	0.06	0.23	0
3	−0.04	0.26	0	0.41	0.10	0.43	0.44	0.2
4	−0.13	−0.51	0	−0.15	−0.92	−0.34	−0.17	−0.18
5	−1.24	−0.55	0	−0.97	–	−0.46	−1.16	−1.07
6	0	−0.23	0.32	−0.65	–	−0.14	−0.84	−0.75
7	0.52	0.36	0	0.55	0.43	0.27	0.65	0.64
8	3.00	3.98	2.06	3.52	3.53	2.65	3.83	4.3
9	1.52	1.35	1.00	1.80	1.50	1.35	1.95	1.70
10	1.90	1.90	1.00	1.80	2.56	1.35	1.95	1.90
11	1.90	1.90	1.00	1.80	2.80	1.35	1.95	1.90
12	2.04	2.78	1.00	1.80	2.80	1.35	1.95	3.26
13	5.65	7.87	1.03	6.03	15.55	0.92	8.88	13.83
14	0.56	−0.02	0	0.71	0.18	0.14	0.86	0.61

[a]Descriptors were compiled from Ref. 18. Identification: 1 = σ_I (Taft inductive parameter); 2 = σ_p (Hammett parameter for *para*-substituent); 3 = *F* and 4 = *R* (Swain-Lupton dual substituent parameters); 5 = E_s and 6 = E_sC (Taft steric parameters); 7 = *v* (van der Waals' radii); 8 = *L*, 9 = B_1, 10 = B_2, 11 = B_3, 12 = B_4 (Verloop sterimol parameters); 13 = *MR* (molar refractivity) and 14 = π(Hansch lipophilicity parameter).

methylthioacetophenone predicted. The predicted yield was confirmed by experiment, see Table 6.

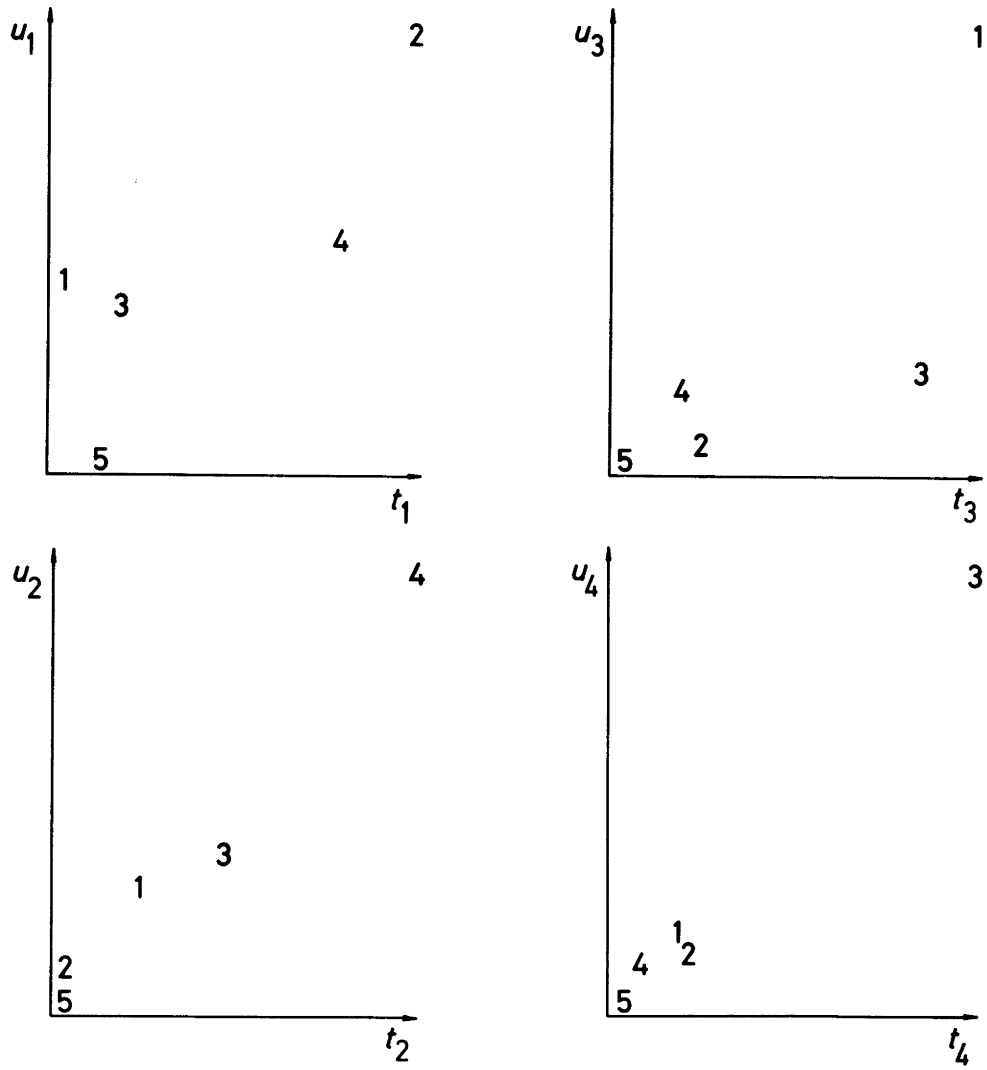
Preparative runs

The optimum experimental conditions predicted by response surface and PLS modelling were confirmed both by GLC analysis (internal standard technique) and by weighing the isolated product in preparative runs. In these experiments, the product was isolated by liquid chromatography on Silica-60 with diethyl ether/light petroleum as eluent. The isolated yields are shown in Table 6.

Discussion

The results given in this paper show that the Willgerodt-Kindler oxidation of substituted acetophenones can give excellent yields of arylacetic

Fig. 3. PLS correlations between u_i (the components of the response matrix **Y**) and t_i (the components of the descriptor matrix **X**). Identification number for the substituents: 1 Me-, 2 H-, 3 MeO-, 4 Me_2N-, 5 Cl-.



acid thiomorpholides. The final yield is, however, strongly dependent on the experimental conditions. In view of our results, we can envisage an explanation of the reasons why previous investigators found such varying results and different "optimum" conditions.[3]

The isoresponse contour surfaces for these reactions form a score of concentric, elongated, ellipsoids in the variable space (see Fig. 2). The center of this score represents the optimum conditions. The main axes of the ellipsoids are tilted from the orientation of the variable axes due to strong interactions between the variables. This is exactly a situation where any attempts to optimize the reaction by adjusting one variable at a time fail. The one-variable-at-a-time procedure will converge to a false optimum (see Ref. 5 for a discussion). The location of this "pseudooptimum" is strongly dependent on the starting conditions of the study.

It is apparent from the results in this paper and previous papers on enamine synthesis from this laboratory[13] that optimum conditions for synthesis may differ with different substrates. Any conclusions on the scope and limitations of a synthetic procedure must therefore be drawn from experiments under optimized conditions. The common practice, however, is not to proceed in this way, but to use standardized conditions for all substrates and record the result (yield, selectivity, or whatever the desired datum may be) from "standardized" experiments.[14] Results from such experiments can be misleading if the optimum conditions are susceptible to changes in substrate structure (see for instance Table 3).

To determine optimum conditions for every new substrate would lead to a prohibitively large number of experiments. (See Table 3 for a modest example.) It is therefore unlikely that this methodology will be accepted and adopted by the community of synthetic chemists. To overcome these difficulties, we suggest a new strategy by which the number of individual experiments can be reduced and yet allow pertinent conclusions to be drawn on the scope of a reaction, the PLS correlation between structural descriptor parameters and the optimum conditions. These models can be established with a rather small set of model compounds. With substituted aromatic substrates, this is an easy task, since many of substituent parameters are available for a large number of substituents. The PLS strategy is iterative and allows the models to be updated and refined when new data become available.

To the best of our knowledge, this is the first example of a strategy by which a quantitative relation between optimum experimental conditions and the nature of the reacting substrate has been determined. We can envision two important fields of synthetic chemistry where this new strategy will be beneficial: (A) *Natural product synthesis* where critical steps often are studied by reactions performed on simplified model compounds. The strategy for this is to first select model compounds which span the variation in structure around the reaction center in an interesting, but precious, synthetic intermediate and determine the optimum conditions for these model compounds. Then establish a PLS correlation and predict more precisely the optimum conditions for the interesting compound. (B) *Synthesis of new compounds for pharmacological screening* which often give rise to large series of similar compounds. For this, the strategy is to determine the optimum conditions for some of the initial syntheses and establish a PLS model. Then use this model to predict suitable conditions for synthesis of later candidates.

Conclusion

Microcomputers are readily accessible to any laboratory today. Computerized tools are being applied more and more to all branches of chemistry. In this paper, we have presented a new computer-assisted strategy by which multivariate optimization of reaction conditions in synthesis procedures, and multivariate correlation by the PLS method of the optimum conditions to structural descriptors of the substrate, may allow for efficient optimization for series of new, similar, substrates. By this method, preparatively useful conditions for Willgerodt-Kindler oxidation of acetophenones were established.

Calculations and experimental

Calculations for response surface and PLS modelling were performed on Zampo (8-bit), Cromemco (16-bit) or Toshiba T1500 (16-bit) microcomputers. Response surface models were obtained by the REGFAC program package and PLS models by the SIMCA package (SIMCA-3B

version). These programs are available from Sepanova AB, Östrandsvägen 14, S-122 43 Enskede, Sweden. The SIMCA package is also available from Principal Data Components, 2505 Shephard Blvd., Columbia, MO 65201, USA.

Chemicals: *p*-methylthioacetophenone was prepared by Friedel-Crafts acetylation of thioanisole using standard procedures.[15] The *para* isomer was separated by flash chromatography, m.p. 69.0–69.5 °C, IR(KBr) (cm^{-1}) 1680 (s); ^1H NMR (60 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.37 (s, 3H), 7.05–7.83 (m, 4H). *p-N,N*-Dimethylaminoacetophenone was prepared by heating *p*-chloroacetophenone with aqueous dimethylamine.[8] The other ketones were commercial of *puriss.* or *p.a.* qualities and purchased from Fluka or Ega. Sublimed sulfur from Kebo Lab was used. Particle size fractionation for the screening experiment was achieved by sieving through brass screens. Morpholine, *puriss.* from Fluka or *perum* from Kebo Lab, and quinoline from BDH were dried over KOH and distilled.

GLC analyses: PYE Unicam® M64, PYE Unicam® GCD or Intersmat gas chromatographs equipped with flame ionization detectors were used. A 1.5 m × 4 mm i.d. glass column packed with 1 % OV-101 on DMCS-treated Chromosorb® W AW, 100–120 mesh, was employed. Triphenylmethane or naphthalene was used as internal standard. Integrated peak areas were used for quantification. A Spectra-Physics Minigrator® or Milton Roy C-10 integrator was used.

Temperature control in the experiments was achieved by means of a thermostated oil bath. The accuracy was estimated at ±1 °C.

General procedure for the screening experiment in Table 2. A 200 ml two-necked flask was charged with 1.34 g (10 mmol) of *p*-methyl acetophenone, the amount of sulfur given, x_1, of particle size x_4, and the amount of morpholine, x_2, followed by 15 ml of quinoline. An accurately weighed amount (~1 g) of triphenylmethane (internal standard) was then added. The reaction mixture was magnetically stirred at rate x_5 and heated at temperature x_3. Samples were withdrawn at various time intervals and the yield determined by GLC.

Procedure for the response surface modelling experiment. The experiments were carried out as above with the exception that sulfur was used as delivered, without particle size fractionation, and the stirring rate was maintained at 700 rpm. Triphenyl methane or naphthalene was used as internal standard for GLC analyses.

Procedure for preparative runs. The reaction was conducted under the optimum conditions given in Table 6 using 30 mmol of substrate. The procedure was the same as for the response surface experiments, but without addition of internal standard. The reaction time in all runs was 2 h. *Work-up:* The reaction mixture was transferred to an evaporation flask and 10–20 g of silica gel 60 (Merck) was added. The excess of morpholine and the solvent were removed under reduced pressure. The residual dry powder was applied on a silica gel 60 column (20 cm × 5 cm) and eluted with diethyl ether/light petroleum (50/50) (w/w). The fractions were monitored by TLC.

Physical data of para *substituted phenyl acetic acid thiomorpholides:*

p-MeO-: m.p. 73–74 °C (lit.[16] 71 °C); IR(KBr) (cm^{-1}) 1515 (s), 1495 (s), 1113 (s); ^1H NMR (100 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.45–3.70 (m, 6H), 4.28 (s, 2H), 4.28–4.37 (m, 4H), 6.79–6.90 (m, 2H), 7.20–7.50 (m, 2H); MS (EI, 70 eV) *m/z* (rel. int. %) 251 (88.0), 218 (10.1), 164 (46.4), 130 (96.9), 121 (100.0), 86 (66.0).

p-Me_2N-: m.p. 135 °C; IR(KBr) (cm^{-1}) 1530 (s), 1505 (s), 1113 (s); ^1H NMR (100 MHz, $CDCl_3$) δ 2.90 (s, 6H), 3.40 (m, 2H), 3.60–3.70 (m, 4H), 4.25 (s, 2H), 4.25 (m, 2H), 6.70–7.20 (m, 4H); MS (EI, 70 eV) *m/z* (rel. int. %) 264 (36.8), 177 (27.6), 134 (100.0).

p-Me-: m.p. 105–106 °C (lit.[16] 103 °C); IR(KBr) (cm^{-1}) 1515 (s), 1503 (s), 1110 (s); ^1H NMR (100 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.40–3.80 (m, 6H), 4.30 (s, 2H), 4.35 n(m, 2H), 7.20 (s, 4H); MS (EI, 70 eV) *m/z* (rel. int. %) 235 (94.1), 202 (46.9), 149 (39.2), 130 (100.0).

p-H-: m.p. 79–80 °C (lit.[17] 79 °C); IR(KBr) (cm^{-1}) 1495 (s), 1112 (s); ^1H NMR (100 MHz, $CDCl_3$) δ 3.30–3.80 (m, 6H), 4.30 (m, 2H), 4.40 (s, 2H), 7.30 (s, 5H); MS (EI, 70 eV) *m/z* (rel. nint. %) 221 (93.1), 188 (24.4), 134 (45.5), 130 (61.7), 91 (100.0), 86 (66.0).

p-Cl-: m.p. 91–92 °C; IR(KBr) (cm^{-1}) 1495 (s), 1115 (s); ^1H NMR (100 MHz, $CDCl_3$) δ 3.40–3.80 (m, 6H), 4.35 (s, 2H), 4.30–4.40 (m, 2H), 7.30 (s,

4H); MS (EI, 70 eV) *m/z* (rel. int. %) 257 (20.2), 255 (52.3), 224 (7.6), 222 (13.1), 170 (10.7), 168 (29.2), 130 (100.0), 127 (18.6), 125 (52.9), 86 (65.0).

p-Br-: m.p. 79–80 °C; IR(KBr) (cm^{-1}) 1495 (s), 1115 (s); ^1H NMR (100 MHz, $CDCl_3$) δ 3.36–3.45 (m, 2H), 3.58–3.80 (m, 4H), 4.30–4.47 (m, 2H), 4.36 (s, 2H), 7.26–7.31 (m, 4H); MS (EI, 70 eV) *m/z* (rel. int. %) 301 (25.9), 299 (25.5), 268 (8.1), 266 (7.0), 214 (16.5), 212 (16.6), 171 (25.6), 169 (26.0), 134 (27.7), 130 (100.0), 102 (26.6), 86 (73.0).

p-F-: m.p. 79–80 °C, IR(KBr) (cm^{-1}) 1497 (s), 1115 (s); ^1H NMR (60 MHz, $CDCl_3$) δ 3.33–3.36 (m, 2H), 3.47–3.66 (m, 4H), 4.18 (s, 2H), 4.14–4.27 (m, 2H), 6.70–7.81 (m, 4H); MS (EI, 70 eV) *m/z* (rel. int. %) 239 (100.0), 206 (17.8), 152 (46.1), 130 (44.9), 109 (82.0), 86 (60.7).

p-MeS-: m.p. 91–92 °C; IR(KBr) (cm^{-1}) 1505 (s), 1120 (s); ^1H NMR ($CDCl_3$) δ 3.45–3.59 (m, 2H), 3.66–3.72 (m, 4H), 3.79 (s, 3H), 4.28 (s, 2H), 4.28–4.41 (m, 2H), 6.79–6.90 (m, 2H), 7.18–7.20 (m, 2H).

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