Optimum Conditions for the Willgerodt-Kindler Reaction 2:** A Multivariate Study of the Influence of Different Solvents on the Optimum Reaction Conditions

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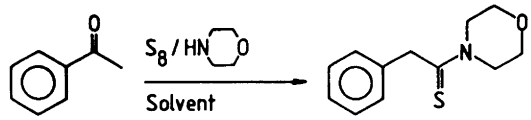
The optimum conditions for synthesis of phenylacetic acid thiomorpholide by the reaction of acetophenone in the presence of morphiline and elemental sulfur have been studied in 13 solvents: *N,N*-dimethylformamide, triethylene glycol, *N*-methylacetamide, ethanol, isopropyl alcohol, isoamyl alcohol, acetonitrile, benzonitrile, pyridine, quinoline, dioxane, benzene and diisopropyl ether. The selection of solvents was based on a principal components analysis of solvent properties. For a subset of the selected solvents, the optimum conditions were determined by response surface technique. By the PLS method, the properties of these solvents were correlated with the established optimum conditions. From the PLS model, optimum conditions for *new* solvents were predicted. The predictions were validated by experimental runs. In triethylene glycol, *N*-methylacetamide, ethanol, isoamyl alcohol, isopropyl alcohol, quinoline, pyridine and benzene, the optimum yields were in the range of 78–96 %. In the other solvents, concurrent reactions lowered the optimum yields.

The Willgerodt-Kindler reaction can be conducted in a variety of solvents and numerous examples can be found in the literature.[1] Common to all these studies, however, is that they have either been performed far from the optimum reaction conditions where side reactions occur, or have been studied by using "standardized reaction conditions" in a series of solvents.[2] The preceeding paper[3] in this series reported that the optimum conditions for the Willgerodt-Kindler reaction are susceptible to variations in substrate structure. It was also shown how these variations can be quantitatively described by a PLS model.[4] In this paper, we have extended the PLS methodology to the study of solvent dependence of the reaction.



Since the mechanism of the reaction is not known, it was desirable that test solvents cover a broad range of solvent properties. In a recent paper[5], we discussed how such a selection of test solvents can be done from a principal components (PC) analysis of property descriptors. To allow for an evaluation of the scope of the reaction with regard to solvent variation, it was essential that the experimental conditions be optimized for *each* solvent considered, otherwise it would not be possible to make a fair comparison. The common method of using "standardized conditions" is questionable since it may lead to erroneous conclusions, (see Ref. 3 for a discussion).

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**Part 1, see Ref. 3.

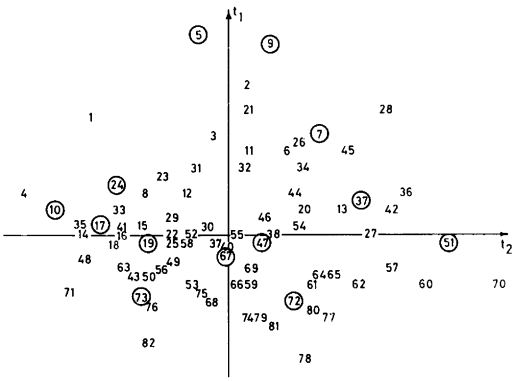

Fig. 1. PC projection of candidate solvents. For identification numbers, see Ref. 5. Selected solvents are encircled.

Methods

Model reaction. The reaction between acetophenone and morpholine in the presence of elemental sulfur was used as a model reaction in all solvents. It was assumed that conclusions from these experiments could be extended to substituted acetophenones as well.[1] The influence of variations in the amine counterpart was considered separately.[6]

Solvent selection. The PC analysis described in Ref. 5 was used to select test solvents. The selection was made so that the test candidates were spread out over the PC projection shown in Fig. 1. The selected solvents were: *N,N*-dimethylformamide (5), triethylene glycol (7), *N*-methylacetamide (9), ethanol (10), isopropyl alcohol (17), 3-methylbutanol (19), acetonitrile (24), benzonitrile (37), pyridine (47), quinoline (51), dioxane (67), benzene (72) and diisopropyl ether (73). These identification numbers are the same as in Ref. 5.

Optimization. Response surface technique[7] was employed to determine the optimum conditions with regard to the following experimental variables[3]: z_1, the amount of sulfur/ketone; z_2, the amount of morpholine/ketone; and z_3, the reaction temperature. Central composite experimental designs[8] or Doehlert uniform shell designs[9] were used to establish second order response surface models. The yields obtained in the optimization experiments were determined by gas-liquid chromatography (GLC) using the internal standard technique. The optimum conditions were validated both by GLC and preparative runs (isolated yields).

Correlation of solvent properties to optimum experimental conditions. The PLS method[3,4] was used to establish multivariate correlations between solvent properties and the optimum conditions obtained from the response surface models. The PLS models were determined from a subset of the test solvents and the model was then used to predict the optimum conditions for new solvents. The predictions were checked by experimental runs. The reaction failed to give the desired product, phenylacetic acid thiomorpholide, in some solvents (see below); these solvents were not used for PLS modelling.

Results.

Response surface study. The optimum conditions obtained in different solvents are summarized in Table 1. The reactions were monitored by GLC and the reaction times given in the table are those at which the increase in yield had levelled off.

PLS predictions. The solvents in Table 1 were characterized by the descriptors given in Ref. 5. This constitutes the descriptor matrix, X. The optimum conditions, z_1–z_3, and the predicted optimum yield, y_1, were included in the response matrix, Y. PLS decomposition of X and Y gave the correlations between the PLS components shown in Fig. 2. For details of the PLS method, see Ref. 4. By these correlations, optimum conditions for *new* solvents could be predicted from their corresponding property descriptors. Such PLS predictions of optimum conditions and the experimental results obtained are given in Table 2. The optimum conditions in isopropanol were also determined by response surface methods and these results are also given in Table 2. A projection of the response surface is given in Fig. 3.

Other observations. In two solvents, initially considered, acetonitrile (24) and benzonitrile (37), the reaction afforded very poor yields (<15 %) of the desired product, *1*. In both of these solvents, the main product was phenylglyoxylic acid thiomorpholide, $PhCOCSN\text{-}(CH_2CH_2)_2O$, *2*. This product was also obtained as a major by-product in diisopropyl ether (37) (see Table 1) and in di-

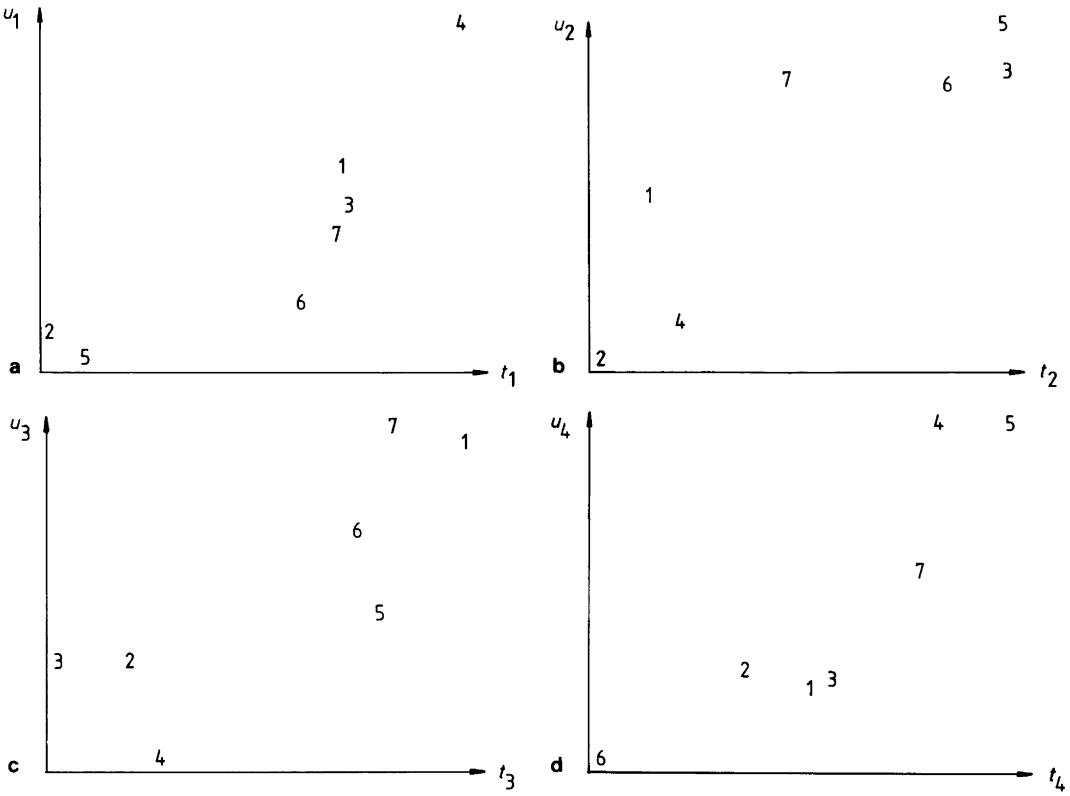

Fig. 2. PLS correlations: u_i are the PLS components of the response matrix, **Y**; t_i are the PLS components of the descriptor matrix, **X**. Identifications: 1 Ethanol, 2 formamide, triethylene 3 benzene, 4 diisopropyl ether, 5 glycol, 6 quinoline, 7 3-methylbutanol.

oxane (67). In dioxane, 27 % of *1* and 46 % of *2* were obtained under predicted (PLS) optimum conditions: z_1 = 7.7 equivalents of sulfur, z_2 = 10.6 equivalents of morpholine, z_3 = 96 °C. In *N,N*-dimethylformamide, DMF, (5) 43 % of *1* was formed under predicted optimum conditions (PLS): z_1 = 6.7 equivalents of sulfur, z_2 = 9.6 equivalents of morpholine, z_3 = 120 °C. Also in DMF *2* was obtained as a by-product (12 % after 2 h) but it disappeared during the course of the reaction. When the reaction was carried out in DMF at room temperature, comparable amounts of *1* and *2* were formed. The total conversion was, however, low at room temperature.

When isolated *2* was heated with sulfur and morpholine in quinoline under optimum conditions (see Table 1), no trace of *1* could be detected (GLC). The starting material, *2*, was recovered unchanged, even after prolonged heating (24 h).

Discussion

In the present paper, we suggest a new methodology for the study of synthetic reactions with regard to solvent variation. The procedure can be divided into three different steps:

(1) Select test solvents in which the *principal properties*[10] show a sufficient variation over the test set. By *principal properties,* we mean significant principal component (PC) scores revealed by PC analysis of pertinent property descriptor variables, (see Fig. 1).

(2) Determine the optimum conditions for each item in a *subset* of these solvents, (see Table 1).

(3) Relate the solvent properties to the optimum conditions in each solvent by the PLS method. Use the PLS model to predict optimum conditions for *new* test solvents, (see Table 2). The PLS model can be updated for each new item investigated. The PLS method permits systematic variations to be detected.

Table 1. Optimum conditions determined by response surface methods.

Solvent (Number)	Optimum conditions[a]			Yield/%	
	z_1	z_2	z_3	Y_1[b]	Y_2[c]
Triethylene glycol (7)[d]	17.0	9.5	145	92.5	91
N-Methylacetamide (9)[d]	2.0	6.0	120	82.1	80
Ethanol (10)[e]	3.7	13.4	80	86.0	84
3-Methylbutanol (19)[f]	9.5	13.2	130	83.6	82
Quinoline (51)[d]	7.5	10.3	123	94.0	90
Benzene (72)[e]	11.6	12.0	80	85.1	85
Diisopropyl ether (73)[e]	6.5	13.7	70	47.0[g]	45

[a] z_1 = Amount of sulfur/acetophenone (mol/mol), z_2 = amount of morpholine/acetophenone (mol/mol), z_3 = reaction temperature (°). [b] Determined by GLC; [c] Isolated yield in preparative runs; [d] Reaction time 2 h; [e] Reaction time 22 h; [f] Reaction time 5 h; [g] Phenylglyoxylic acid thiomorpholide, 29 %, was also formed.

This methodology can be extended to the study of other variations of the experimental system, such as substrate[3] and reagent variations[6]. Using this strategy, the accuracy of experimental investigations of the scope and limitations of synthetic procedures will be increased.

The reaction system used in the Willgerodt-Kindler reaction is complicated. Elemental sulfur interacts with amines and gives rise to complex mixtures of various species: charge transfer complexes[11], free radicals[12] as well as ionic species[1] have been invoked. In such mixtures, acetophenone is transformed to phenylacetic acid thiomorpholides. A number of mechanisms have been suggested[13] but a generally accepted mechanism is still lacking. Phenylglyoxylic thioamides have been suggested as intermediates in the course of the Willgerodt-Kindler reaction.[14] Our finding that *2* is *not* converted to *1* when subjected to optimum Willgerodt-Kindler conditions rules out *2* as an intermediate. The present study does not reveal the reaction mechanism, but it seems unlikely that a purely ionic mechanism can account for a reaction that shows consistent behaviour in all the solvents in Tables 1 and 2, including some that are *polar* (*N*-methyl-acetamide), *nonpolar* (benzene), *hydrogen bond donors* (alcohols) and *hydrogen bond acceptors* (pyridine, quinoline).

Concurrent reactions, e.g. leading to *2*, may be ionic since *2* is a major product formed in nitrile and ether solvents and a minor product in pyridine and DMF. These solvents are not hydrogen bond donors and this may give clues to future studies of the formation of *2*. Nitriles are however known to take part in other reactions under Willgerodt-Kindler conditions[15] and these may be competitive with the Willgerodt-Kindler reaction path. Although we can not interpret the somewhat puzzling results presented in this paper on a firm mechanistic basis, it is, however, clear that the reaction shows regular behaviour with regard

Table 2. Prediction of optimum conditions by the PLS method.

Solvent	Optimum conditions			Yield	
	z_1	z_2	z_3	Y(pred.)	Y(found)[a]
Isopropyl alcohol (17)[b]	5.2	12.7	100	78.3	74
[c]	4.3	14.3	100	78.0	76
Pyridine (47)[d]	11.2	9.8	122	96.0	88[e]

[a] Determined by GLC; [b] Reaction time 22 h; [c] Optimum conditions determined by response surface technique; [d] Reaction time 4 h; [e] Phenylglyoxylic acid thiomorpholide, 5 %, was also formed.

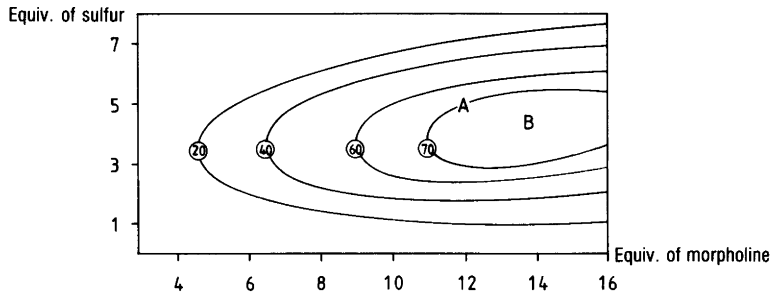

Fig. 3. Response surface obtained with isopropyl alcohol as solvent. The numbers on the isocontour lines show the yield (%). A shows the optimum conditions predicted by the PLS model. B shows the optimum according to the response surface model.

to solvent variation. Otherwise, PLS modelling would fail. Any future suggestions of a reaction mechanism must, therefore, be compatible with these regularities.

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Calculations and experimental

Response surface and PLS models were calculated using a Zampo (8 bit) or Toshiba 1500 (16 bit) microcomputer. Response surface models were determined by the REGFAC program and PLS models by the SIMCA program package (SIMCA 3B version). These programs are available from Sepanova AB, Östrandsvägen 14, S-122 43 Enskede, Sweden. The SIMCA program is also available from Principal Data Components, Shepherd Blvd. Columbia, MO 65201, USA.

All chemicals were commercial *puriss.* or *pro analysi* quality and used as delivered. Quinoline was distilled.

A PYE M64 or PYE Unicam GDC gas chromatograph with flame ionization detector was used. Columns: 2.1 m×4 mm i.d. 5% SE-30 or 5% OV-101 on Chromosorb W-AW 100–120 mesh was used. Anthracene was used as internal standard. Integrated peak areas were used for quantification and a Spectra Physics Minigrator or Milton Roy C-10 integrator was used.

Temperature control was achived by means of a thermostated oil bath. The accuracy was estimated to ±1°.

General procedure for the optimization experiments. The amounts of sulfur, z_1, and morpholine, z_2, and the reaction temperature, z_3, were varied according to a response surface design, (see Ref. 3). For example, a two-necked Erlenmeyer flask was charged with 1.20 g (10 mmol) of acetophenone, an accurately weighed amount (0.35–0.45 g) of anthracene (internal standard) and the given amount of morpholine, z_2, followed by 15 ml of the solvent. The flask was stirred magnetically and heated at temperature z_3 until the internal standard was completely dissolved. The amount of sulfur, z_1, was then introduced in one portion, the reaction mixture stirred at constant rate and maintained at the temperature. Samples were withdrawn at time intervals and analyzed by GLC.

Preparative runs. The procedure was the same as above with the exception that no internal standard was present and the amount of acetophenone was 30 mmol. For work-up, the reaction mixture was transferred to an evaporation flask and 10–20 g of silica gel 60 (Merck) were added. Solvent and excess of morpholine were removed under reduced pressure; for high boiling solvents, finally at oil pump vacuum. The resulting dry powder was applied on the top of a flash chromatography column[16] (silica gel 60) and eluted with light petroleum/diethyl ether.

Synthesis of phenylglyoxylic acid thiomorpholide, 2. Following the procedure for preparative runs using benzonitrile as solvent and 10 mmol of acetophenone yielded 1.45 g of *2* as a greenish crys-

talline product, m.p. 108–110° (lit.[17] 114–118°). IR (KBr) 1660 cm^{-1}; ^1H NMR (100 Mz, $CDCl_3$) 3.60–3.80 (m, 8H), 7.33 (s, 5H); MS (EI, 70 eV) *m/z* (rel. int.) [assignment] 235 (13.2) [$M^{+\cdot}$], 130 (100.0) [$M^{+\cdot} - C_6H_5CO$], 105 (48.0) [$C_6H_5CO^+$], 86 (74.0), 77 (30.0).

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