Optimum Conditions for the Willgerodt-Kindler Reaction. 3. Amine Variation

Torbjörn Lundstedt,[a] Rolf Carlson[a,*] and Rashad Shabana[b]

[a]Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden and [b]National Research Centre, Dokki, Cairo, Egypt

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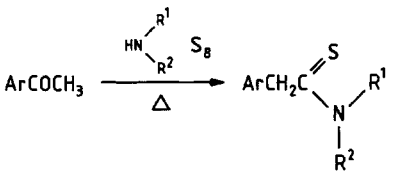
Optimum conditions for the synthesis of phenylacetic acid thioamides by the joint action of elemental sulfur and amines on acetophenones have been studied with the following amines: Morpholine, pyrrolidine, 4-methylpiperidine, isopropylamine, 2-butylamine, octylamine, diethylamine, dipentylamine, diisopropylamine and dipropylamine. With the exception of diisopropylamine, which did not give the desired reaction, isolated yields of thioamides were in the range 62–90 %. Selection of amines was based on principal components analysis of 29 amines characterized by seven property descriptors. The selection was made to achieve a maximum spread in the properties. A multivariate correlation of optimum conditions to amine properties was obtained by the PLS-method. The PLS-model was used to predict the optimum conditions for the amines butylamine and piperidine. The predictions were confirmed by experiment.

Previous papers in this series on the Willgerodt-Kindler reaction have shown that optimum conditions for synthesis are susceptible to variations in substrate structure[1] and to change of solvent.[2] In the present paper we present optimum conditions for the Willgerodt-Kindler reaction of acetophenone in quinoline solvent with a variety of amine reagents (Scheme 1).

Methods

The selection of amines was made from a principal components (PC) analysis of a set of 29 primary and secondary amines characterized by seven property descriptors (see Table 1). Strategies for selection by PC modelling have previously been described for organic solvents[3] and Lewis acids.[4]



Scheme 1.

Optimization of reaction conditions was achieved by response surface methods.[5] Central composite designs[6] were used with the following experimental variables: u_1, the ratio between the amounts of amine and ketone; u_2, the ratio between the amounts of amine and ketone, and u_3, the reaction temperature. The yields in the optimization experiments were determined by gas-liquid chromatography (GLC) using the internal standard technique.

Correlation of amine properties to optimum conditions was carried out by the PLS method.[7] The PLS model was then used to predict optimum conditions for *new* amines.

To validate predictions from response surface and PLS models the yields of isolated thioamide were determined gravimetrically. The products in these preparative scale runs were isolated by flash chromatography on silica gel.[8]

*To whom correspondence should be addressed.

Table 1. Amines and descriptors used in the principal components analysis.

Amine[a]	Descriptors[b]						
	1	2	3	4	5	6	7
1, Methylamine	10.66	−7	0.663	–	210.0	218.4	−1.35
2, Ethylamine	10.81	17	0.683	1.366	213.0	221.4	−0.86
3, Isopropylamine	10.71	35	0.689	1.374	215.3	223.7	−0.38
4, *t*-Butylamine	10.83	46	0.717	1.387	217.3	225.7	−0.23
5, Propylamine	10.71	49	0.717	1.388	214.4	222.8	−0.58
6, *s*-Butylamine	10.56	63	0.725	1.393	216.4	224.8	−0.38
7, Isobutylamine	10.42	68	0.735	1.397	215.4	223.7	−0.38
8, Butylamine	10.77	77	0.741	1.401	214.9	223.3	−0.53
9, Isopentylamine	10.60	97	0.749	1.408	–	–	–
10, Pentylamine	10.59	105	0.754	1.411	–	–	–
11, Hexylamine	10.56	129	0.766	1.418	–	–	–
12, Heptylamine	10.66	155	0.775	1.425	–	–	–
13, Octylamine	10.65	177	0.782	1.429	–	–	–
14, Dimethylamine	10.73	7	–	–	216.6	224.8	−2.66
15, Diethylamine	10.49	56	0.707	1.386	221.0	229.4	−2.30
16, Diisopropylamine	10.96	84	0.717	1.392	225.0	233.2	−1.73
17, Dipropylamine	10.91	110	0.738	1.405	223.2	231.4	−1.84
18, Di-*sec*-butylamine	–	135	0.753	1.411	227.0	235.2	−0.85
19, Diisobutylamine	10.91	137	0.746	1.409	224.8	233.0	−0.74
20, Dibutylamine	11.31	159	0.760	1.418	224.3	232.5	−1.69
21, Diisopentylamine	–	186	0.771	1.423	–	–	–
22, Dipentylamine	–	205	0.777	1.427	–	–	–
23, Pyrrolidine	11.27	89	0.845	1.424	220.4	228.6	–
24, Piperidine	11.12	106	0.861	1.453	221.5	229.7	−2.59
25, 2-Methylpiperidine	–	118	0.844	1.456	–	–	–
26, 3-Methylpiperidine	–	126	0.846	1.447	–	–	–
27, 4-Methylpiperidine	–	128	0.867	1.446	–	–	–
28, Morpholine	8.33	130	1.000	1.455	215.7	223.9	−2.25
29, Piperazine	9.83	146	–	1.446	218.0	226.0	−3.24

[a]The numbers are used for identification in Figs. 1a, 2 and 3. [b]Descriptors: (1) pK_a measured in water; (2) boiling point (°C); (3) density (10^3 kg m^{-3}); (4) refractive index; (5) gas-phase basicity (kcal mol^{-1}); (6) proton affinity (kcal mol^{-1}); (7) $T\Delta S_{prot}$ (kcal mol^{-1}), contributes to description of irregular effects on the Gibbs energy of proton transfer to alkylamines compared to reactions in solution (Ref. 13). Descriptors 1–4 were compiled from standard handbooks (Ref. 14), and descriptors 5–7 were obtained from Ref. 13.

Results

PC analysis of amines. Since the mechanism of the Willgerodt-Kindler reaction is still obscure, it is not known with certainty *which* properties of the amine determine its utility. Table 1 contains data for different properties of 29 common primary and secondary amines. Among the descriptors are bulk properties as well as thermodynamic parameters. PC analysis of the data in Table 1 reveals two significant components. The first component describes 51 % of the variance, and with two components 74 % of the total variance is described. Introduction of a third component was not significant according to cross validation.[9] A plot of the PC scores is shown in Fig. 1a. The contribution of the original descriptors to the PC vectors is shown in the loading plot, Fig. 1b.

One feature of the PC projection in Fig. 1a is that primary, secondary and cyclic secondary amines are clustered into three groups. These groups can be described by separate, disjoint PC models (the SIMCA method for multivariate

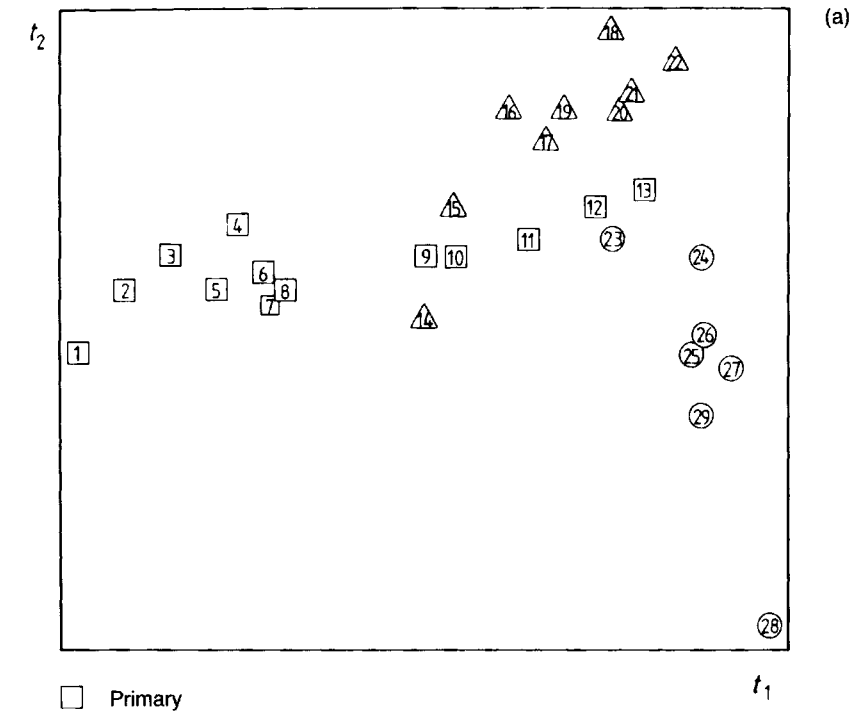


Fig. 1. (a) PC projections of 29 primary and secondary amines; see Table 1 for identification numbers of the amines. (b) PC loading projection showing the contribution of individual descriptors to the PC vectors; see Table 1 for identification number of the descriptors.

classification[10]). For the present purpose this is, however, inconvenient and we use one, common PC model for all amines to derive the *principal properties,* i.e. orthogonal measures of systematic variation as measured by significant principal components.[11]

Selection of amines for testing and optimization. The PC projection in Fig. 1a was used to select nine amines for experimental studies. The selection was made so as to obtain an approximately uniform spread in all amine properties, i.e. a uniform spread in the PC projection. Three amines from each subgroup were chosen (see Fig. 2). With these amines the optimum conditions were determined by response surface methods. The results of these experiments are summarized in Table 2.

Diisopropylamine, **16**, was initially chosen as a test candidate but was subsequently replaced by dipropylamine, **17**, since diisopropylamine surprisingly did not undergo the Willgerodt-Kindler reaction. In all cases of the Willgerodt-Kindler reaction, dark, deeply coloured solutions are obtained when amines and elemental sulfur are mixed. When diisopropylamine was used, however, the supernatant liquid was completely clear and colourless, and sulfur and starting ketone were recovered unchanged even after prolonged heating.

Prediction of optimum conditions for new amines. The data in Tables 1 and 2 were used to establish a PLS model which relates amine properties to the optimum conditions. Using this model, optimum conditions for two new amines, butylamine and piperidine, were predicted. These predictions are given in Table 3 together with the experimental yields obtained under these conditions. The PLS correlations are shown in Fig. 3.

Discussion

The results in Tables 2 and 3 show that the Willgerodt-Kindler reaction has a wide scope with regard to amine variation. It is also seen that the optimum conditions differ for different amines. This demonstrates that it is essential to draw conclusions as to the scope of the reaction from *optimized* conditions. Failure to do this may explain why morpholine has long been regarded as a superior reagent in the Willgerodt-Kindler reac-

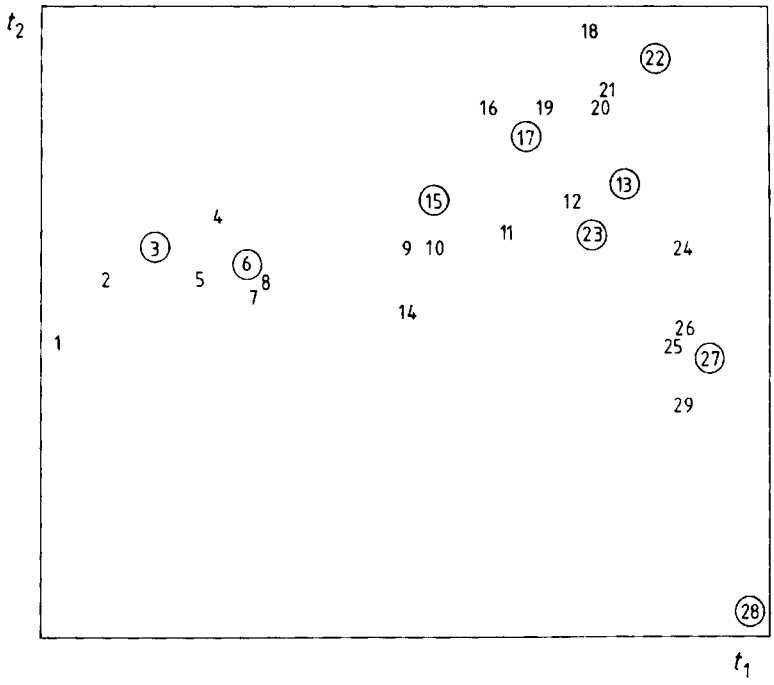


Fig. 2. Amines selected for optimization studies.

Table 2. Optimum conditions and yields determined by response surface methodology.

Amine	Optimum conditions[a]			Yields /%	
	u_1	u_2	u_3	y_{GLC}[b]	y_{isol}[c]
Isopropylamine	10.25	4.75	133	89	87
sec-Butylamine	9.5	5.5	132	88	85
Octylamine	12.5	11.7	137	65	62
Diethylamine	8.4	3.2	135	86	83
Dipropylamine	12.5	6.6	142	81	80
Dipentylamine	16.5	10.4	138	76	71
4-Methylpiperidine	8.0	7.5	148	80	78
Pyrrolidine	10.0	4.0	135	86	83
Morpholine	7.5	10.3	123	94	90

[a] u_1, the ratio of sulfur/ketone (mol/mol); u_2, the ratio of amine/ketone (mol/mol); u_2, the reaction temperature (°C). [b] Determined by internal standard technique directly on the reaction mixture. [c] Yields of isolated product (flash chromatography on silica gel).

tion. Several other amines afforded isolated yields in the range 80–90 % in the present study.

The methodology followed in this paper for the study of amine variation is general and can be applied to other experimental systems when aspects of systematic variations are to be considered.

The observation that diisopropylamine is inert under conditions that afford high yields with

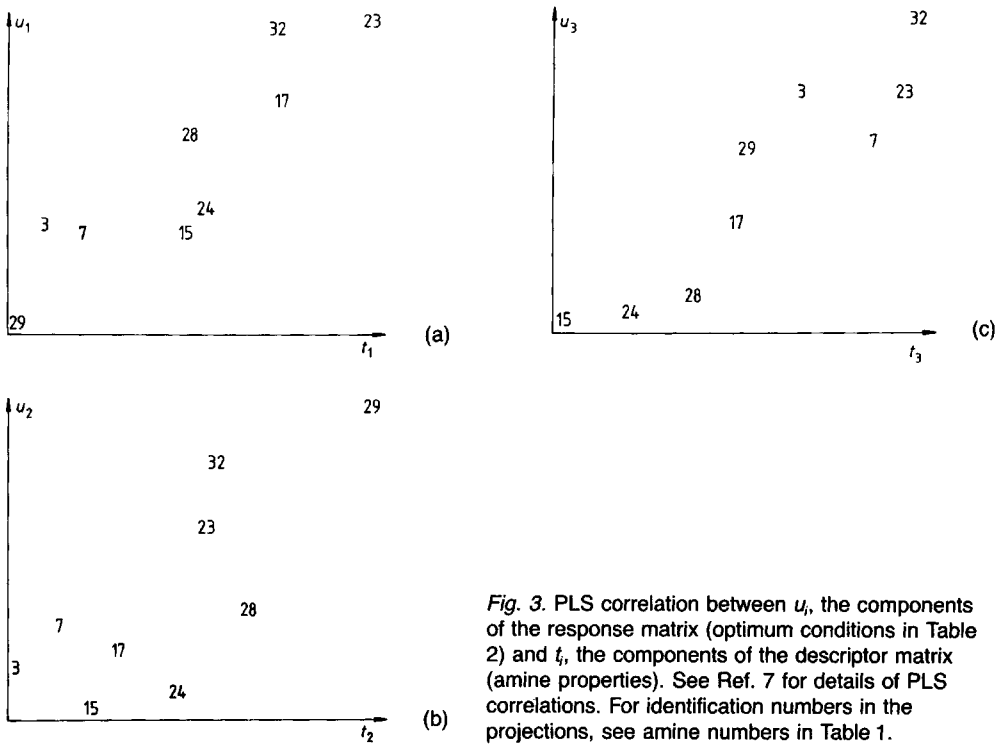


Fig. 3. PLS correlation between u_i, the components of the response matrix (optimum conditions in Table 2) and t_i, the components of the descriptor matrix (amine properties). See Ref. 7 for details of PLS correlations. For identification numbers in the projections, see amine numbers in Table 1.

Table 3. Optimum conditions and yields predicted by PLS and experimental yields obtained in validation of the predictions.

Amine	Predicted optimum[a]				Experimental yield[b]/%
	u_1	u_2	u_3	y_{pred}[c]	
Butylamine	10.6	6.9	133	84	87
Piperidine	11.1	5.5	139	83	79

[a]For definitions of u_1–u_3, see Table 2. [b]Isolated yield obtained by flash chromatography. [c]Yield predicted by the PLS model.

other secondary amines was unexpected. The interactions of elemental sulfur with amines and other nucleophilic reagents are clearly very complicated; charge-transfer complexes and free radicals, as well as ionic species, have been suggested to be involved.[12] The observation that the mixture of sulfur, diisopropylamine and acetophenone remains colourless and unchanged even after prolonged heating in quinoline, and the observation that the Willgerodt-Kindler reaction tolerates a large variation in solvent properties,[2] support an interpretation that an involvement of charge-transfer complexes and/or free radicals is essential for the reaction.

Conclusions

It is essential to draw conclusions on the scope of the reaction from optimized experimental conditions. Multivariate methods such as PC analysis (to characterize systematic variation in properties) and response surface models (to determine optimum experimental conditions) allow general conclusions to be drawn from a limited number of experimental observations. Experiments designed according to these principles also allow PLS models to be developed with which predictions for new systems can be made.

Calculations and experimental

Calculations. Calculations for PC analysis, PLS and response surface modelling were made on a Toshiba T1500 (16-bit) micro-computer. Response surface models were determined by the REGFAC program package, and PC and PLS models by the SIMCA package (SIMCA-3B version). These programs are available from SEPANOVA AB, Östrandsvägen 14, S-12243 Enskede, Sweden. The SIMCA package is also available from Principal Data Components, 2505 Shepherd Blvd., Columbia, Missouri 65201, USA.

Chemicals. Amines, of commercial *puriss.* or p.a. grade, were purchased from Aldrich or EGA and dried over solid KOH. Acetophenone *puriss.* from EGA and sublimed sulfur from KEBO LAB were used as delivered.

Experimental procedures for optimization, preparative runs and GLC analyses were the same as in Ref. 1.

^{1}H NMR spectra were recorded on a BRUKER AC-80 instrument at 80 MHz with deuteriochloroform as solvent.

Physical properties of N-*substituted phenylacetic acid thioamides* are listed in the following under the heading for the corresponding amine:

Isopropylamine: M.p. 70–71 °C; ^{1}H NMR: δ 1.08–1.31 (m, 6H), 2.62 (s, 1H), 4.11 (s, 2H), 4.45–4.91 (m, 1H), 7.26–7.35 (m, 5H).

sec-*Butylamine*: B.p. 176–180 °C/10 mmHg; ^{1}H NMR: δ 0.75–2.56 (m, 8H), 3.70 (s, 1H), 4.08 (s, 2H), 4.22–4.78 (m, 1H), 7.29–7.31 (m, 5H).

Octylamine: M.p. 115–116 °C; ^{1}H NMR: δ 0.81–2.73 (m, 15H), 4.05–4.29 (m, 2H), 4.16 (s, 2H), 7.26–7.39 (m, 5H).

Butylamine: M.p. 81–83 °C; ^{1}H NMR: δ 0.93–1.10 (m, 3H), 1.60–2.21 (m, 4H), 3.42–3.63 (m, 3H), 4.11 (s, 2H), 7.31–7.44 (m, 5H).

Diethylamine: B.p. 180–182 °C/14 mmHg; ^{1}H NMR: δ 0.90–1.35 (m, 6H), 3.40–3.62 (m, 2H), 3.88–4.11 (m, 2H), 4.26 (s, 2H), 7.21–7.49 (m, 5H).

Dipropylamine: B.p. 159–164 °C/8 mmHg; ^{1}H NMR: δ 0.84–1.23 (m, 6H), 1.45–2.08 (m, 4H), 3.56–3.82 (m, 2H), 4.01–4.36 (m, 2H), 4.23 (s, 2H), 7.32–7.43 (m, 5H).

Dipentylamine: B.p. 171–175 °C/1 mmHg; ^{1}H NMR: δ 0.92–1.33 (m, 6H), 1.39–2.74 (m, 12H), 3.45–3.71 (m, 2H), 3.91–4.21 (m, 2H), 4.31 (s, 2H), 7.21–7.35 (m, 5H).

Pyrrolidine: M.p. 68–69 °C; ^{1}H NMR: δ 3.33–3.56 (m, 4H), 3.66–3.77 (m, 2H), 4.02–4.21 (m, 2H), 4.18 (s, 2H), 7.18–7.86 (m, 5H).

4-Methylpiperidine: M.p. 75–76 °C; ^{1}H NMR: δ 0.73–0.91 (m, 3H), 1.16–1.90 (m, 5H), 2.91–3.25 (m, 2H), 4.06–4.39 (m, 2H), 4.59 (s, 2H), 7.31–7.59 (m, 5H).

Piperidine: M.p. 72–74 °C; ^{1}H NMR: δ 1.05–1.41 (m, 2H), 1.46–2.04 (m, 4H), 3.48–3.86 (m, 2H), 4.18–4.39 (m, 2H), 7.45–7.53 (m, 5H).

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