On the Roles of Lewis Acid Catalysts and Solvents in the Fischer Indole Synthesis

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The influence of the Lewis acid catalyst and solvent on the Fischer indole reaction has been studied with regard to the distribution of indole isomers in the reaction of phenylhydrazones derived from unsymmetrical ketones. Five ketones, ten solvents and twelve Lewis acids were studied. A multivariate experimental design based on the principal properties of the reactants was used to select test systems (substrate, Lewis acid, solvent). A total of 296 different systems were studied, of which 162 afforded indoles. Analysis of how the properties of these systems are related to the distribution of isomeric indoles was done by PLS modelling. A three-components model was significant according to cross validation and described 87 % of the variance of the isomer distribution. The model showed that the structure of the phenylhydrazone has a dominant influence on isomer distribution; that solvent properties are only weakly involved; and that the properties of the Lewis acid catalyst does not exert any systematic influence on the regioselectivity of the Fischer indole reaction.

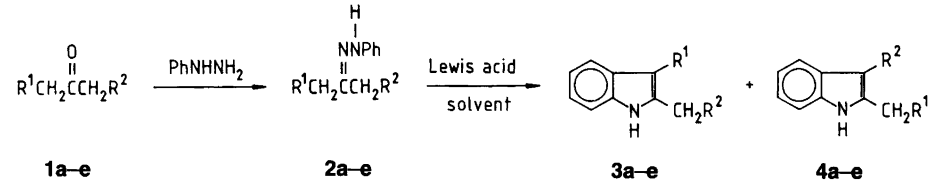
The formation of indoles by rearrangement and ring closure of phenylhydrazones was discovered 1884 by Emil Fischer.[1] The reaction is of wide scope and has become known as the Fischer indole reaction. It has attracted considerable interest and a recent monograph which summarizes more than a century of experience of the reaction contains over 2700 references. The reaction mechanism has been extensively studied and the results have been summarized.[2]

The reaction is catalyzed by acids, and over the years a large number of different catalysts has been used; these include both proton acids and Lewis acids. However, the choice of catalysts seems to be subjective and more a matter of taste rather than based on critical experimentation. The literature is confusing on this point.[3]

A problem with the Fischer indole reaction is that phenylhydrazones derived from unsymmetrical ketones with both α- and α′-methylene groups can give rise to isomeric indoles: see Scheme 1. It has been claimed by some authors that the solution to this problem is to use certain Lewis acid catalysts.[4] One such catalyst is phosphorus trichloride,[5] which was reported to yield only 3-methyl-2-propylindole (**3a**) in the reaction with the phenylhydrazone of 3-hexanone (**2a**). However, all attempts by us to reproduce these findings invariably led to a mixture of the expected isomeric indoles. This prompted us to undertake a more detailed study of the regiocontrol in the Fischer indole reaction when both the Lewis acid catalyst and the solvent are varied. This paper summarizes our findings in this area.

Methods

Substrates. Initial screening experiments were conducted using the phenylhydrazone from 3-hexanone (**2a**) as the substrate. This choice was dictated by previous claims of selectivity, but also upon the assumption that conditions giving regiocontrol with this compound where the two side chains are similar could eventually be extended to more sterically demanding substrates. Four more substrates were then treated, *viz.* the phenylhydrazones from, respectively, 2-hexanone (**2b**), 3-undecanone (**2c**), 1-phenyl-2-butanone (**2d**) and 5-methyl-3-heptanone (**2e**). The selection was guided by the principal properties of the parent ketones, see Fig. 1(a).[6] Each of the hydrazones was prepared in one large batch and purified by distillation. The same sample was used for all experiments.



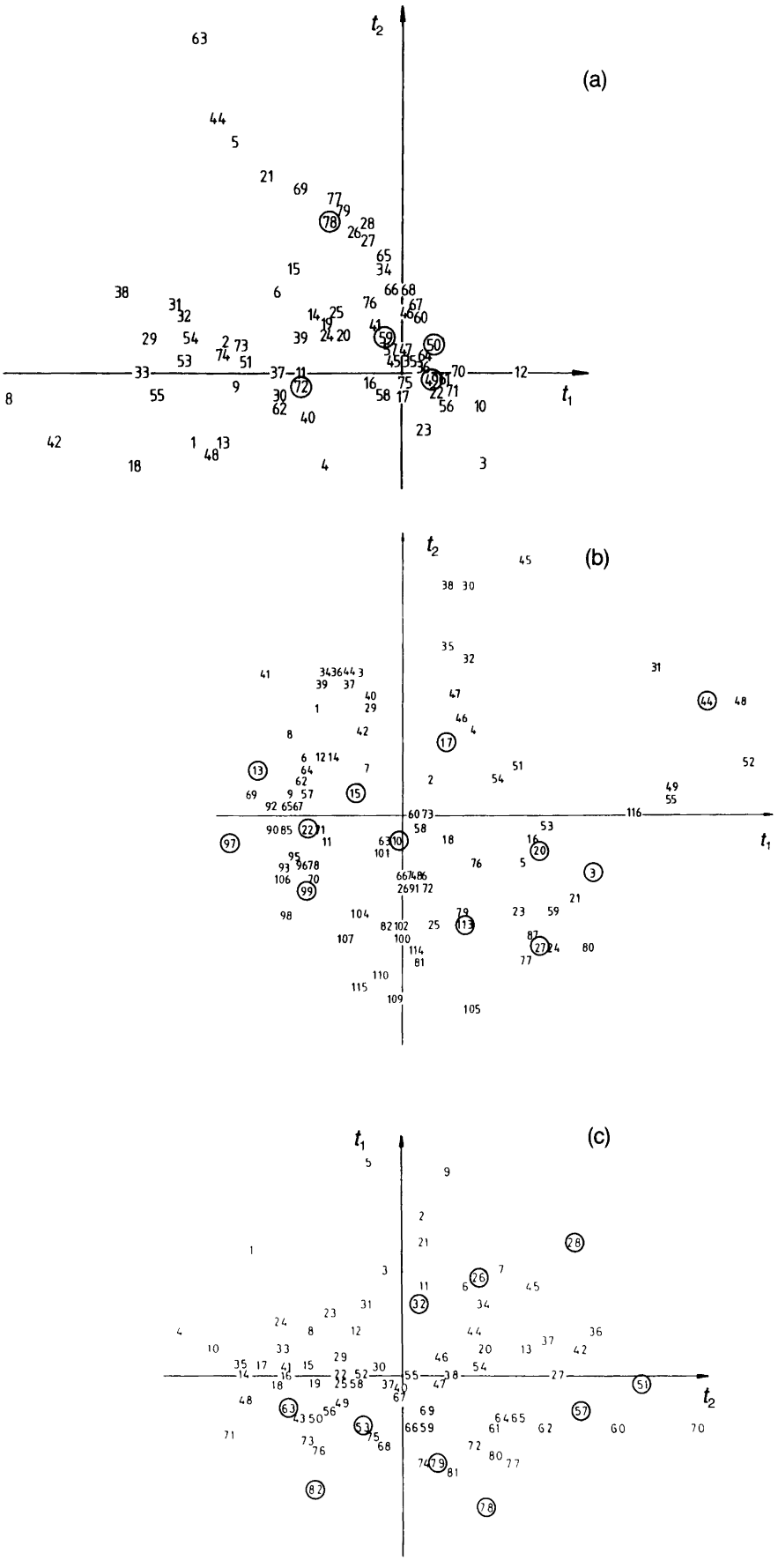


Fig. 1. Plot of principal properties. Selected items have been encircled. (a) *Ketones*, identification numbers: 3-hexanone (50), 2-hexanone (49), 3-undecanone (78), 1-phenyl-2-butanone (72), 5-methyl-3-heptanone (59); (b) *Lewis acids*, identification numbers: BF_3 (44), CuCl (13), ZnI_2 (99), $TiCl_4$ (3), $ZnCl_2$ (15), $SbCl_5$ (27), PCl_3 (113), $FeCl_3$ (10), $SiCl_4$ (20), $AlCl_3$ (17), $SnCl_4$ (22), CuI (97); (c) *Solvents*, identification numbers: sulfolane (28), carbon disulfide (78), *N,N*-dimethylacetamide (32), quinoline (51), 1,2-dichlorobenzene (57), dimethyl sulfoxide (26), carbon tetrachloride (79), chloroform (53), tetrahydrofuran (63), hexane (82).

Catalysts and solvents. The selection of Lewis acids and solvents was also based upon their principal properties, see Figs. 1(b) and (c).[7,8] A general discussion on the use of principal properties for selection of test systems is given in Ref. 9. Fig. 1 shows a selection which assured a uniform spread in all properties considered.

Isomer distribution. The reaction was monitored by high resolution capillary GLC and the isomer distribution was determined from the intergrated peak areas. For two substrates, **2a** and **2b**, the overall yields were also determined by internal standard techniques using phenylcyclohexane as the internal standard. However, analysis by PLS modelling of the total yield variation with respect to the properties of the system did not show any conceivable structure (< 20 % variance explained over four PLS components). There were no significant components according to the cross validation criterion.[10] In these models each substrate was considered separately. This is the main reason why total yields were not determined for the remaining substrates. There were also difficulties in achieving good reproducibility in the yield determination, owing to solubility differences of the internal standard in the various solvents used. The experimental error in GLC determination of the isomer distribution is estimated to be ± 2 %.

Structural assignment of indole isomers. The identity of the isomers was inferred from their mass spectra and from their and ^{13}C NMR spectra.

Multivariate modelling. To analyze quantitative relations between the properties of the reaction system and the observed isomer distribution we used PLS modelling. For details of the PLS method, see Ref. 11. The models were evaluated by cross validation.[11]

To describe the reaction system, the corresponding principal properties (PC scores) were used as independent variables in the X-block. For the ketones, $R^1CH_2COCH_2R^2$, adjusted van der Waals radii, v_i[12] of R^1CH_2 and R^2CH_2 were also used as variables, since the principal properties do not explicitly take steric factors into account. Attempts at using the calculated van der Waals volumes afforded poorer models. The descriptor variables are given in Table 1. In the X-block we also included the squares and the cross products of the descriptors. This was done to take non-linear effects and interaction effects into account, see Ref. 8 for a discussion. The dependent variable used in the Y-block was the regioisomeric excess (%, RE). This is defined analogously to enantiomeric excess, EE, and diastereomeric excess, DE, as the proportion (%) of the more abundant isomer minus the proportion (%) of the less abundant isomer. The RE values were calculated from the isomer distributions given in Tables 2 and 5–8. In the first set of calculations, we used the proportion (%) of the first-eluted (GLC) indole isomer **3a–e** as the dependent variable. By this as much as 97 % of the variance of the dependent variable was described by a three-component model. As pointed out by one Referee, such a procedure, however, runs the risk of being self-fulfilling. This is not possible using RE as the dependent variable.

Attempts to use the isomer ratio, 3:4, as the dependent variable afforded poorer models.

Results

Phosphorus trichloride as the catalyst. Treatment of **2a** with PCl_3 invariably led to mixtures of 3-methyl-2-propylindole (**3a**) and 2,3-diethylindole (**4a**) in an approximately 7:3 ratio. The isomers were readily separated by high resolution GLC. Our findings are in conflict with those reported by Baccolini *et al.*[5] who claim that **3a** is the 'exclusive product.' In our experiments, we used the isolated, purified, phenylhydrazone. This differs from the method of Baccolini in which the phenylhydrazone was treated with PCl_3 without purification.

Screening of catalysts and solvents with the phenylhydrazone from 3-hexanone as the substrate. The results are

Table 1. Descriptors used to characterize the reaction system.

System constituent	Principal properties		v_i[a]	
	t_1	t_2	R^1CH_2	R^2CH_2
Ketones				
3-Hexanone	2.34	−0.16	0.68	0.56
2-Hexanone	2.46	−0.15	0.52	0.68
3-Undecanone	−0.52	2.16	0.68	0.56
1-Phenyl-2-butanone	−0.74	−0.42	0.56	0.70
5-Methyl-3-heptanone	0.17	0.74	0.56	1.00
Solvents				
Sulfolane	3.29	2.21		
Carbon disulfide	−3.27	0.98		
N,N-Dimethylacetamide	1.81	0.15		
Quinoline	−0.29	3.13		
1,2-Dichlorobenzene	−0.99	2.27		
Dimethyl sulfoxide	2.54	0.95		
Carbon tetrachloride	−2.49	0.38		
Chloroform	−1.56	−0.59		
Tetrahydrofuran	−1.04	−1.57		
Hexane	−3.0	−1.20		
Lewis acids				
BF_3	7.05	2.80		
CuCl	−3.42	1.33		
ZnI_2	−2.25	−1.77		
$TiCl_4$	4.35	−1.48		
$ZnCl_2$	−1.11	0.79		
$SbCl_5$	3.07	−3.18		
PCl_3	1.32	−2.70		
CuI	−4.00	−0.47		
$FeCl_3$	−0.06	−0.48		
$SiCl_4$	3.18	−0.78		
$AlCl_3$	0.97	1.83		
$SnCl_4$	−2.65	−0.22		

[a] Adjusted van der Waals radii, see Ref. 12.

Table 2. Ratio of isomeric indoles (2,3-diethylindole/2-propyl-3-methylindole), **3a/4a**, and yields[a] obtained in the indolization of **2a**.

Lewis acid[c]	Solvent[b]							
	Sulfolane	Carbon disulfide	Quinoline	1,2-Dichloro-benzene	Dimethyl sulfoxide	Carbon tetrachloride	Chlorform	Tetra-hydrofuran
BF_3OEt_2	nr[d]	25/75 (15)	nr	32/68 (23)	nr	34/66 (36)	28/72 (54)	21/79 (8)
CuCl	nr	nr	nr	nr	nr	28/72 (10)	nr	nr
ZnI_2	21/79 (34)	28/72 (56)	nr	nr	nr	25/75 (34)	28/72 (45)	nr
$TiCl_4$	26/74 (44)	23/77 (17)	33/67 (10)	39/61 (18)	nr	nr	32/68 (49)	21/79 (14)
$ZnCl_2$	24/76 (30)	28/72 (31)	nr	30/70 (29)	nr	28/72 (19)	28/72 (46)	nr
$SbCl_5$	nr	nr	nr	nr	nr	nr	nr	17/83 (10)
PCl_3	24/76 (82)	23/77 (21)	nr	24/76 (31)	nr	29/80 (31)	21/79 (56)	nr
$FeCl_3$	21/79	20/80	nr	23/77	21/79	nr	23/77	21/79
$SiCl_4$	20/80	nr	22/78	nr	nr	22/78	29/71	nr
$AlCl_3$	18/82	20/80	nr	29/71	nr	nr	27/73	21/79
$SnCl_4$	nr	nr	nr	nr	nr	nr	33/67	19/81

[a]Yields (%), when determined, are given within parentheses after the isomer ratio. [b]*N,N*-Dimethylacetamide was omitted from this table since no reaction was observed with any of the catalysts. [c]Copper(I) iodide was omitted from this table since no reaction was observed in any of the solvents. [d]No reaction was observed.

summarized in Table 2. In neither case was it found that only one indole isomer was produced.

The combinations of Lewis acids and solvents that gave the most selective reactions in Table 2 were subjected to repeated experiments to verify the reproducibility. It was also determined whether reversing the order of introduction of the reactants improved the selectivity or not. The results of these experiments are summarized in Table 3.

Lewis acid induced indolization was also compared with a common standard procedure in which the phenylhydrazone is heated in glacial acetic acid.[13] The isomer distribution obtained at different temperatures is shown in Table 4. The reaction temperature did not influence the isomer distribution, although the yield is improved by increasing the temperature. The other phenylhydrazones were also studied in glacial acetic acid at 50 °C to enable a comparison with the Lewis acid induced reaction to be made. The results of these experiments are given in the notes to Tables 5–8.

Table 3. Check on the reproducibility of the most selective combination of acid catalyst and solvent in the indolization of **2a**. Comparison with reversed order of addition of phenylhydrazone to the reaction mixture.

Catalyst/ Solvent	Isomer ratio, **3a/4a**		
	Trial 1	Trial 2	Reversed order[a]
BF_3OEt_2/tetrahydrofuran	21/79	20/80	19/81
CuCl/carbon tetrachloride	31/69	28/71	nd[b]
ZnI_2/sulfolane	21/79	19/81	22/78
$TiCl_4$/tetrahydrofuran	21/79	21/79	20/80
$ZnCl_2$/sulfolane	24/76	28/72	23/77
$SbCl_5$/tetrahydrofuran	20/80	17/83	19/81
PCl_3/carbon tetrachloride	20/80	21/79	22/78
$FeCl_3$/carbon disulfide	20/80	23/77	15/85
$SiCl_4$/sulfolane	20/80	18/82	20/80
$AlCl_3$/sulfolane	18/82	18/82	19/81
$SnCl_4$/tetrahydrofuran	18/82	19/81	19/81

[a]The phenylhydrazone was added to a solution/suspension of the Lewis acid in the solvent. [b]Not determined.

Table 4. Temperature dependence of isomer ratio (2,3-diethylindole/2-propyl-3-methylindole) **3a/4a** in the indolization of **2a** in anhydrous acetic acid.

Temperature[a]/°C	Isomer ratio **3a/4a**	Yield (%)
50	21/79	< 2
70	19/81	< 2
100	19/81	49
140	20/80	61

[a]Temperature of the oil bath.

Experiments with the phenylhydrazone from the other test ketones. The results are summrized in Tables 5–8.

Multivariate analysis by PLS modelling. Tables 2, 5–8 present 296 different reaction systems of which 162 underwent the indole reaction. These were used in a PLS analysis. We did not include the systems in which no reaction was observed.

Three substrates, **2a**, **c**, **d**, afforded mixtures of isomeric indoles. Attempts to describe the isomer distribution for each of these substrates by separate PLS models did not yield significant models. Less than ca. 20 % of the variance of the dependent variable was described by the models. The PLS components were not significant according to cross-validation. The final analysis taking the roles of the ketones into account was done in two stages. In the first

Table 5. Ratio of isomeric indoles (2-butylindole/2-methyl-3-propylindole) **3b/4b** and yield[a] obtained in the indolization of **2b**.[b]

Lewis acid	Solvent[c]			
	Sulfolane	Carbon disulfide	1,2-Dichloro-benzene	Tetra-hydrofuran
BF_3OEt_2	0/100 (17)	0/100 (5)	1/99 (16)	5/95 (6)
ZnI_2	0/100 (26)	0/100 (31)	0/100 (66)	nr[d]
$TiCl_4$	0/100 (35)	nr	0/100 (5)	8/92 (18)
$ZnCl_2$	0/100 (39)	0/100 (26)	1/99 (55)	nr
$SbCl_5$	nr	nr	nr	0/100 (11)
PCl_3	0/100 (16)	nr	0/100 (34)	6/94 (7)
$FeCl_3$	0/100 (14)	nr	0/100 (19)	4/96 (8)
$SiCl_4$	0/100 (14)	nr	nr	nr
$AlCl_3$	0/100 (37)	nr	0/100 (47)	1/99 (12)
$SnCl_4$	0/100 (9)	nr	nr	11/89 (6)

[a]Yields (%) are given in parentheses after the isomer ratio. [b]An isomer ratio 11/89 was observed in glacial acetic acid at 50 °C. [c]Dimethyl sulfoxide was omitted from this table since no reaction was observed with any of the Lewis acids. [d]No reaction was observed.

run, a calibration set of 124 reaction systems was selected.* These are depicted in Fig. 2. A three-component PLS model was significant according to cross-validation and accounted for 86 % of the variance of the dependent variable. The first two components described 81 % of the variance. The 38 remaining systems were used to validate the model by comparing the observed isomer distribution with the distribution predicted by the PLS model. A correlation coefficient $r = 0.93$ was observed for the correlation between $Y_{Pred.}$ and $Y_{Obs.}$ of the test set. This was assumed to be satisfactory. The final analysis was done with all 162 systems. A three-component model was significant and accounted for 87 % of the variance of the dependent variable.

By analyzing the loadings of the descriptor variables together with the calculated modelling power, we can use the PLS model to determine *which* properties of the reaction system are related to the observed isomer distribution.

A surprising result was that the properties of the Lewis acids are not at all related to the isomer distribution. A loading plot which shows the contribution of the individual variables to the first two PLS components is given in Fig. 3. The most important variables are projected on the periphery of the plot. Variables that do not contribute are projected close to the origin. This is the case for the Lewis acid descriptors. A modelling power close to zero was also found for the interaction of the Lewis acid properties with other descriptors of the system. Although these variables are not at the origin in the loading plot they are close enough to be insignificant.

The most important factors are, not unexpectedly, the properties of the ketones. The first PLS component is mainly composed of the ketone descriptors. The van der Waals radii are dominant, both as linear and square variables and in interaction with other descriptor variables. The principal property descriptors of the ketone are also important. An interesting finding is that the lipophilic and nucleophilic properties of the solvent seem to intervene, since it is the second principal property of the solvent which is most important.

The second and third PLS components are also highly dependent on the descriptors of the ketones and the solvents, although in other combinations. To these components there is also a small contribution from the 'polarity' properties of the solvent.

Stereoisomers of the phenylhydrazones. GLC–MS revealed that the phenylhydrazones form *Z* and *E* isomers. The mass spectra of the isomers were almost identical. For **2a** and **2b** we were able to assign the structures from their ^1H and ^{13}C NMR spectra. We were unable to assign the isomers for **2c–2e**. The following *E*/*Z* ratios were observed: for **2a** 50/50 and for **2b** 5/95. These ratios did not show any tendency to

*A PC decomposition of the matrix formed by the eight descriptors of the 124 selected items afforded eight significant components. This means that the selection gave a full rank variance – covariance matrix and assures that there are not severe collinearities among the design variables.

Table 6. Ratio of isomeric indoles (2-ethyl-3-heptylindole/2-octyl-3-methylindole) **3c/4c** obtained in the indolization of **3c**.[a]

Lewis acid	Solvent					
	Sulfolane	Carbon disulfide	1,2-Dichloro-benzene	Dimethyl sulfoxide	Tetrahydro-furan	Hexane
BF_3OEt_2	38/62	39/61	39/61	34/66	33/67	39/61
ZnI_2	34/66	33/67	35/65	49/51	44/56	36/64
$TiCl_4$	35/65	nr[b]	nr	nr	30/70	nr
$ZnCl_2$	35/65	nr	36/64	43/57	nr	43/57
PCl_3	35/65	34/66	34/66	nr	34/66	34/66
$FeCl_3$	32/68	nr	33/67	39/61	33/67	42/58
$AlCl_3$	32/68	35/65	36/64	nr	31/69	nr

[a]An isomer ratio 29/71 was observed in glacial acetic acid at 50 °C. [b]No reaction was observed.

Table 7. Ratio of isomeric indoles (2-ethyl-3-methylindole/2-ethyl-3-phenylindole) **3d/4d** obtained in the indolization of **2d**.[a]

Lewis acid	Solvent					
	Sulfolane	Carbon disulfide	1,2-Dichloro-benzene	Dimethyl sulfoxide	Tetrahydro-furan	Hexane
BF_3OEt_2	16/84	6/94	19/81	25/75	20/80	15/85
ZnI_2	28/72	21/79	23/77	nr[b]	11/89	17/83
$TiCl_4$	22/78	4/96	19/81	nr	12/88	22/78
$ZnCl_2$	31/69	15/85	27/73	nr	nr	nr
PCl_3	37/63	19/81	24/76	nr	31/69	26/74
$FeCl_3$	27/73	36/64	5/95	17/83	22/78	17/83
$AlCl_3$	36/64	6/94	29/71	nr	25/75	nr

[a]An isomer ratio 22/78 was observed in glacial acetic acid at 50 °C. [b]No reaction was observed.

Table 8. Ratio of isomeric indoles [2-(2-methylbutyl)-3-methylindole/2-ethyl-3-(2-butyl)indole] **3e/4e** obtained in the indolization of **2e**.[a]

Lewis acid[b]	Solvent[c]				
	Sulfo-lane	Carbon disulfide	1,2-Dichloro-benzene	Dimethyl sulfoxide	Tetra-hydro-furan
BF_3OEt_2	100/0	100/0	100/0	100/0	100/0
ZnI_2	100/0	100/0	100/0	nr[c]	nr
$TiCl_4$	100/0	nr	100/0	nr	100/0
$ZnCl_2$	100/0	nr	100/0	nr	nr
PCl_3	100/0	nr	100/0	nr	100/0
$FeCl_3$	100/0	nr	100/0	100/0	nr
$AlCl_3$	100/0	nr	nr	nr	100/0
$SiCl_4$	100/0	nr	100/0	nr	100/0
$SnCl_4$	100/0	nr	nr	nr	100/0

[a]An isomer ratio 100/0 was observed in glacial acetic acid at 50 °C. [b]Antimony(V) chloride was omitted from this table since no reaction was observed any of the solvents. [d]No reaction was observed.

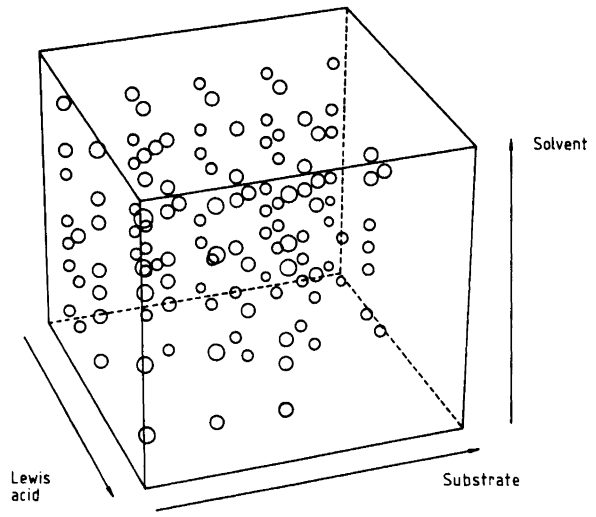


Fig. 2. Graphic illustration of the spread of the selected test systems in the design for PLS modelling. Each 'axis' is actually two-dimensional and defined by the corresponding principal properties.

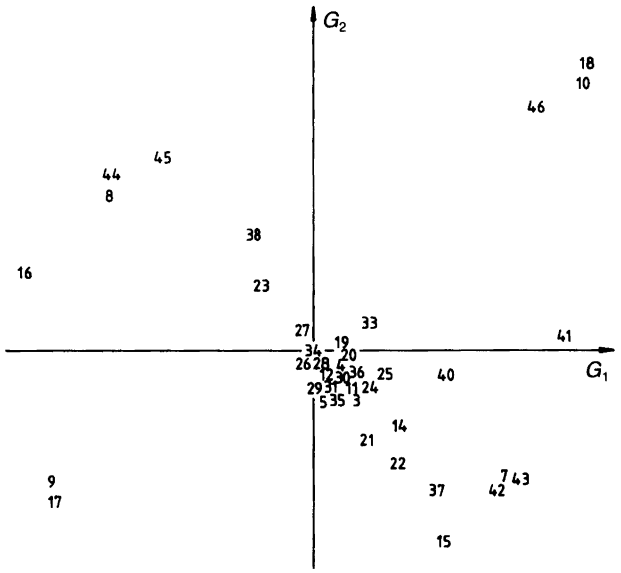


Fig. 3. Loading plot showing the contribution of the individual principal properties to the first two components of the PLS model. Variables: 3–10 are the descriptor variables given in Table 1, 11–18 are the squared variables, 19–46 are the cross-product (interaction) variables.

change with time and remained constant over the series of experiments. It is therefore likely that the observed *E*/*Z* ratios correspond to equilibrium mixtures.

A dynamic NMR experiment was done with **2a** to determine whether or not the isomer distribution was susceptible to variation in temperature and whether the rate of *E*/*Z* interconversion is of importance in the indolization reaction. Although the result was rather imprecise, a barrier to rotation of < 25 kcal mol^{-1} was indicated. This makes a rapid interconversion at moderately elevated temperatures (< 50 °C) less likely. This is also supported by our findings that **2a** and **2b** always gave two peaks in high resolution GLC with peak areas equal to the *E*/*Z* ratio determined by NMR spectroscopy.

Discussion

The literature on the regiochemistry of the indolization of arylhydrazones is bewildering and numerous rationalizations have been attempted to correlate factors to the isomer distribution.[4,14] As the reaction mechanism is rather complex, with many reaction steps, it is likely that a large number of factors are involved which influence both the equilibria and the rates of the elementary steps. It also reasonable to believe that these factors will show interaction effects. Chemical phenomena never depend on single factors, and to detect interaction effects it is necessary to use an experimental design which allows all potentially important factors to be varied simultaneously. In our experiment we have varied the substate, the catalyst and the solvent. The experiments in Tables 2 and 5–8 actually represent a multi-level factorial design. This arrangement made it possible to determine both the direct influence of system variables on isomer distribution and their interaction effects.

Our results show that the structure of the ketone is the most important factor involved in the selectivity of the ring closure. A key role is played by steric factors, although our experiments do not allow any safe conclusions to be drawn about the rates of the individual steps of the reaction. Steric effects are likely to intervene in several steps: by analogy with enamine chemistry[15] steric congestion will determine the relative stability of the regioisomeric enehydrazine tautomers of the hydrazone. The more alkylated enehydrazine would be favoured by the sp^3 to sp^2 change in hybridization of the α carbon. An *E* configuration of the enehydrazine would diminish the steric congestion of the side chains. Steric effects will also be involved in determining the transition-state energy of the [3,3]-sigmatropic rearrangement of the enehydrazine. Molecular models indicate that both boat-like and chair-like transition states are possible. A chair-like transition state will give a more efficient overlap and the *E* isomer of the enehydrazine will have all bulky substituents in a pseudo-equatorial position which would be energetically favourable.

The selectivity of the reaction is only slightly dependent on the solvent properties. Lipophilic properties are most important. This suggests that the rather apolar pericyclic step is rate-determining. The tautomerization hydrazone – enehydrazine must involve charged species which would render the reaction highly solvent dependent.

Tables 2 and 5–8, substrate by substrate, show that certain combinations of Lewis acid/solvent gave slightly enhanced selectivity. However, analysis by PLS modelling of all substrates taken together, reveals that the distribution of isomeric indoles is not systematically related to properties of the Lewis acids at all, although we cannot exclude the possibility that some combination of Lewis acid/solvent might have unique properties for certain substrates in the Fischer indole reaction. Our findings show, however, that the probability of finding a combination of a Lewis acid catalyst and solvent which will give general selectivity must be extremely low. The principal properties used as selection criteria in this study cover a large range of a number of individual properties of the Lewis acids and the solvents.

Experimental

GLC–MS characterization of the products was done using a SIL-8 capillary column (0.21 mm i.d., 30 m) coupled to a HP GC/MSD 5830/5970 system. Electron impact, 70 eV, was used for ionization. The same temperature program 100–300 °C, 15° min^{-1} was used for both hydrazones and indoles. ^{13}C NMR spectra were recorded on a Bruker AC 80 instrument.

Preparation of phenylhydrazones: general procedure. Equimolar amounts of phenylhydrazine and the corresponding ketone in benzene solution were refluxed overnight with water separation (Dean–Stark trap). The solution was further dried (Na_2SO_4) and the benzene was evaporated off. The crude phenylhydrazone was distilled under reduced pressure and stored under argon in the freezer.

Physical properties of the phenylhydrazones.

3-Hexanone phenylhydrazone (**2a**): b.p. 146–148 °C/7 mmHg; GLC: two well-separated peaks of area ratio 1:1 were observed, retention times, t_R/min 7.3 and 7.4. MS t_R 7.30: *m/z* [rel. abundance (%)] 191 (7.2), 190 (45.5), 175 (3.6), 161 (7.3), 147 (8.2), 133 (12.7), 120 (18.2), 106 (27.3), 93 (100.0), 65 (68.2), 39 (50). t_R 7.4: 191 (6.1), 190 (45.2), 175 (4.4), 161 (7.0), 147 (8.7), 133 (13.0), 120 (17.4), 106 (26.1), 93 (100.0), 65 (73.9), 39 (56.5). ^{13}C NMR (benzene); δ (assignment): *Z* isomer 119.3 (*para*), 129.1 (*meta*), 113.2 (*ortho*), 150.3 (*ipso?*), 146.8 (N = C ?), 30.3 (CH_2CH_3), 30.0 ($CH_2CH_2CH_3$), 20.1 ($CH_2CH_2CH_3$), 14.1 (CH_2CH_3), 9.5 ($CH_2CH_2CH_3$); *E* isomer 119.3 (*para*), 129.1 (*meta*), 113.2 (*ortho*), 150.3 (*ipso?*), 146.8 (N = C?), 38.5 (CH_2CH_3), 21.4 ($CH_2CH_2CH_3$), 18.7 ($CH_2CH_2CH_3$), 14.4 ($CH_2CH_2CH_3$), 11.1 (CH_2CH_3).

2-Hexanone phenylhydrazone (**2b**): b.p. 148–150 °C/7 mmHg; GLC: two peaks of area ratio 95:5 were observed, t_R 7.46 and 7.6 min. MS t_R 7.46 (*Z* isomer): *m/z* [rel. abundance (%)] 191 (9.2), 190 (57.5), 173 (39.7), 144 (75.3), 133 (62.1), 106 (70.7), 93 (77.0), 65 (100.0), 42 (87.9). t_R 7.60 (*E* isomer): 191 (8.7), 190 (52.2), 161 (3.5), 148 (30.4), 133 (57.4), 106 (65.2), 93 (69.6), 65 (100.0), 42 (91.3). ^{13}C NMR (benzene): *Z* isomer δ (assignment) 119.2 (*para*), 129.1 (*meta*), 113.1 (*ortho*), 146.6 (*ipso*), 146.4 (−N = C), 38.5 (CH_2Pr), 28.9 ($CH_2CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_2CH_3$), 14.1 ($CH_2CH_2CH_2CH_3$), 13.6 (CH_2CH_3); the *E* isomer was detected but was present in such a small concentration that we were able to asssign only the α carbon peaks: δ 29.7 (CH_2Pr), 23.9 (CH_3).

3-Undecanone phenylhydrazone (**2c**): b.p. 185–190 °C/10 mmHg; GLC: one peak was observed in the gas chroma-

togram, t_R 10.9 min. MS *m/z* [rel. abundance (%)] 260 (64.3), 231 (10.0), 207 (7.1), 162 (38.6), 133 (80.0), 108 (100.0), 92 (57.1), 41 (57.0). ^{13}C NMR (benzene) *E* isomer: δ (assignment) 119.9 (*para*), 129.7 (*meta*), 113.7 (*ortho*), 150.4 (*ipso?*), 147.2 (−N = C?), 30.6 CH_2Hept), 27.4 (CH_2CH_2Hex), 14.8 [$(CH_2)_7CH_3$], 21.8 (CH_2CH_3), 9.9 (CH_2CH_3); *Z* isomer: 119.9 (*para*), 129.7 (*meta*), 113.7 (*ortho*), 150.4 (*ipso?*), 147.2 (−N = C?), 37.8 (CH_2CH_3), 28.8 CH_2Hept), 14.8 [$(CH_2)_7CH_3$], 11.6 (CH_2CH_3)? Unassigned peaks: 32.7, 32.6, 30.6, 30.4, 30.3, 30.2, 30.1, 30.0, 25.7, 23.5. An *E*/*Z* ratio of 60/40 was estimated from the NMR spectrum.

1-Phenyl-2-butanone phenylhydrazone (**2d**): b.p. 205–210 °C/10 mmHg. GLC: two peaks were observed, t_R 10.64 and 10.86 min. MS t_R 10.64: *m/z* [rel. abundance (%)] 238 (52.3), 207 (1.9), 182 (5.6), 144 (12.1), 117 (18.7), 93 (100.0), 65 (87.9), 39 (37.4). t_R 10.86: The mass spectrum was almost identical with the spectrum of t_R 10.64. ^{13}C NMR (benzene) *Z* isomer: δ (assignment) 44.2 (CH_2Ph), 21.5 (CH_2CH_3), 10.2 (CH_2CH_3). *E* isomer: 35.8 (CH_2Ph), 31.9 (CH_2CH_3), 11.9 (CH_2CH_3) An *E*/*Z* ratio (40/60) was estimated from the NMR spectrum.

5-Methyl-3-heptanone phenylhydrazone (**2e**): b.p. 155–157 °C/10 mmHg. GLC: two peaks were observed, t_R 8.33 and 8.47 min. MS t_R 8.33: *m/z* [rel abundance (%)] 218 (48.4), 189 (6.1), 162 (36.8), 133 (82.6), 106 (61.6), 93 (100.0), 65 (97.4), 41 (74.7); t_R 8.47: the mass spectrum was almost identical with the spectrum of t_R 8.33. The ^{13}C NMR spectrum was determined on a (50/50) *Z*/*E* mixture in benzene solution: δ (assignment) 149.5, 149.4, 146.8, 129.3 (*meta*) 128.0, 126.8, 121.0 (*para*), 119.5, 113.3 (*ortho*), 43.7, 35.4, 32.4, 32.3, 30.8, 30.1, 29.8, 11.6, 11.2, 9.5.

Indolization experiments.

General procedure for the experiments in Tables 2 and 5–8. To a magnetically stirred solution of the phenylhydrazone (1.00 g) in 50 ml of the solvent at 50 °C, was added an equimolar amount of the Lewis acid. The reaction mixture was maintained at 50 °C and the reaction was followed by GLC over a period of 48 h. In those experiments where the yields were determined by internal standard techniques, an accurately weighed amount (ca. 1 g) of phenylcychlohexane was also added to the reaction mixture.

Reversed order addition experiments (Table 4). These were run as above but the phenylhydrazone was added to a solution/suspension of the Lewis acid.

Indolization in anhydrous acetic acid. A solution of the phenylhydrazone (1.00 g) in anhydrous acetic acid (50 ml) was maintained at 50 °C. The reaction was followed by GLC over a period of 48 h.

Spectral properties of the indoles. These were determined using the resulting mixture of the isomers. We were unable to isolate the pure isomers by preparative chromatography. ^{13}C NMR spectra were recorded in benzene.

2-Propyl-3-methylindole (**3a**): ^{13} C NMR: δ (assignment) 120.9, 119.1, 118.3, 111.1 (protonated aromatic carbons), 135.9, 135.7, 129.8, 106.4 (unprotonated aromatic carbons), 19.3 (3-CH_3), 17.6 (2-CH_2Et), 16.1 (2-$CH_2CH_2CH_3$), 14.8 (2-$CH_2CH_2CH_3$). GLC–MS: t_R 7.24; *m/z* [rel. abundance (%)] 173 (25.9), 144 (100.0), 130 (6.3), 115 (14.3), 102 (3.6), 77 (14.3), 51 (6.3), 39 (6.0).

2,3-Diethylindole (**4a**): ^{13}C NMR: aromatic carbon resonances as for (**3a**); δ (assignment) 28.1 (3-CH_2CH_3), 8.5 (3-CH_2CH_3), 23.2 (2-CH_2CH_3), 13.9 (2-CH_2CH_3). GLC–MS: t_R 7.38; *m/z* [rel. abundance (%)] 173 (32.6), 158 (100.0), 143 (29.2), 130 (9.8), 115 (11.4), 89 (4.5), 77 (8.8), 65 (7.2), 39 (7.0).

2-Butylindole (**3b**): ^{13}C NMR: the presence of **3b** was detected but owing to its low concentration (<0.5 %) we were not able to assign its chemical shifts. GLC–MS: t_R 4.77; *m/z* [rel. abundance (%)] 173 (55.0), 158 (100.0), 144 (40.0), 128 (11.3), 117 (26.3), 116 (11.0), 115 (26.2), 91 (16.3), 77 (28.8), 51 (23.8), 39 (26.0).

2-Methyl-3-propylindole (**4b**): ^{13}C NMR: δ (assignment) 119.1, 118.4 [two resonances], 111.0 (protonated aromatic carbons), 135.6, 131.3, 129.2, 111.6 (unprotonated aromatic carbons), 26.4 (3-CH_2Et), 24.2 (3-$CH_2CH_2CH_3$), 14.1 (3-$CH_2CH_2CH_3$), 10.9 (2-CH_3). GLC–MS: t_R 7.51; *m/z* [rel. abundance (%)] 173 (18.1), 144 (100.0), 128 (5.4), 115 (9.0), 102 (4.5), 77 (10.8), 51 (6.3), 39 (7.2).

2-Ethyl-3-heptylindole (**3c**): ^{13}C NMR : we were not able to assign the aromatic carbon signals in **3c** and **4c**. The same applies to signals of the internal methylene groups of the 3-heptyl substituent in **4c** and the 2-octyl substituent in **4c**. δ (assignment) 121.4, 121.3, 119.6, 119.1, 118.8 (two signals), 111.3, 111.1 (protonated aromatic carbons), 130.4, 129.8, 111.8, 106.7 (unprotonated aromatic carbons), 26.7 (2-CH_2CH_3), 15.2 (2-CH_2CH_3), 14.8 [3-$(CH_2)_6CH_3$]. GLC–MS: t_R 10.78; *m/z* [rel abundance (%)] 243 (12.4), 214 (1.9), 168 (1.0), 158 (100.0), 130 (6.7), 93 (2.9), 77 (3.8), 41 (9.5).

2-Octyl-3-methylindole (**4c**): ^{13}C NMR: δ (assignment) 14.8 [2-$(CH_2)_7CH_3$], 9.1 (3-CH_3). For the aromatic signals, see **3c** above. GLC–MS: t_R 11.13; *m/z* [rel. abundance (%)] 243 (19.0), 200 (3.9), 186 (1.0), 144 (100.0), 130 (11.4), 103 (2.9), 77 (5.7), 41 (12.4).

2-Benzyl-3-methylindole (**3d**): ^{13}C NMR: we were not able to assign the aromatic signals. δ (assignment) 33.9 (2-

CH_2Ph), 9.3 (3-CH_3). GLC–MS: t_R 11.18; *m/z* [rel. abundance (%)] 221 (100.0), 206 (37.1), 178 (9.3), 130 (30.1), 102 (13.9), 77 (19.3), 51 (13.0).

2-Ethyl-3-phenylindole, (**4d**): ^{13}C NMR: we were not able to assign the aromatic signals. δ (assignment) 20.4 (2-CH_2CH_3), 15.2 (2-CH_2CH_3). GLC–MS: t_R 11.15; *m/z* [rel. abundance (%)] 221 (90.5), 206 (100.0), 179 (29.5), 144 (21.0), 115 (12.4), 102 (28.6), 77 (19.0), 51 (11.9).

2-(2-Methylbutyl)-3-methylindole (**3e**): ^{13}C NMR: δ (assignments) 121.5, 119.6, 118.8, 110.9 (protonated aromatic carbons), 136.2, 134.5, 130.4, 107.9 (unprotonated aromatic carbons), 34.0 (2-CH_2CHMeEt), 36.2 (2-CH_2CHMeEt), 29.9 (2-CH_2CHMeCH_2CH_3), 19.4 [2-CH_2CH(CH_3)Et], 12.0 (2-CH_2CHMeCH_2CH_3), 9.1 (3-CH_3). GLC–MS: t_R 8.63; *m/z* [rel. abundance (%)] 201 (15.1), 184 (0.9), 156 (2.7), 144 (100.0), 115 (8.0), 91 (2.8), 77 (7.1), 41 (9.8).

2-Ethyl-3-(2-butyl)indole (**4e**): ^{13}C NMR: The presence of **4e** was detected, but owing to its low concentration (< 0.5 %) we were unable to determine and assign its chemical shifts. GLC–MS: t_R 8.24; *m/z* [rel. abundance (%)] 201 (20.0), 173 (13.2), 172 (100.0), 143 (13.0), 115 (7.0), 89 (3.5), 77 (5.3), 39 (5.2).

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References

1. Fischer, E. and Hess, V. F. *Ber. Dtsch. Chem. Ges. 17* (1884) 559.
2. (a) Robinson, B. *The Fischer Indole Synthesis*, Wiley, Chichester, New York, Brisbane, Toronto, Singapore 1982; (b) Robinson, B. *Chem. Rev. 63* (1963) 373; (c) Robinson, B. *Chem. Rev. 69* (1969) 227; (d) Arbuzov, A. E. and Kitaev, Yu. P. *J. Gen. Chem. USSR 27* (1957) 2388.
3. Ref. 2(a), pp. 636–658.
4. Ref. 2(a), pp. 172–393 and references therein.
5. Baccolini, G., Bartoli, G., Marotta, E. and Todesco, P. E. *J. Chem. Soc., Perkin Trans. 1* (1983) 2695.
6. Carlson, R., Prochazka, M. P. and Lundstedt, T. *Acta Chem. Scand., Ser. B 42* (1988) 145.
7. Carlson, R., Lundstedt, T., Nordahl, Å. and Prochazka, M. *Acta Chem. Scand., Ser. B 40* (1986) 522.
8. Carlson, R., Lundstedt, T. and Albano, C. *Acta Chem. Scand., Ser. B 39* (1985) 79.
9. (a) Carlson, R. and Lundstedt, T. *Acta Chem. Scand., Ser. B 41* (1987) 164; (b) Wold, S., Sjöström, M., Carlson, R., Lundstedt, T., Hellberg, S., Skagerberg, B., Wikström, C. and Öhman, J. *Anal. Chim. Acta 191* (1986) 17.
10. Wold, S. *Technometrics 20* (1987) 397.
11. Wold, S., Albano, C., Dunn, W. J., III, Edlund, U., Esbensen, K., Geladi, P., Johansson, E., Lindberg, W. and Sjöström, M. In: Kowalski, B. R., Ed., *Proc. NATO Adv. Study in Chemometrics*, Cosenza, Italy, September 1983, Riedel Publ. Co., Dordrecth, Holland 1984.
12. Seydel, J. K. and Schaper, K. J. *Chemische Struktur und Aktivität von Wirkstoffen*, Verlag Chemie, Weinheim, New York 1979.
13. For an example, see Dave, V. *Org. Prep. Proced. Int. 8* (1976) 41.
14. Lacoume, B., Milcent, G. and Olivier, A. *Tetrahedron 28* (1972) 667.
15. Cook, A. G. *Enamines: Synthesis, Structures and Reactions*, Marcel Dekker, New York, London 1969.

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