Carboxamides from Carboxylic Acids by Lewis Acid Catalysis. Use of Principal Properties for Exploring Different Reaction Conditions

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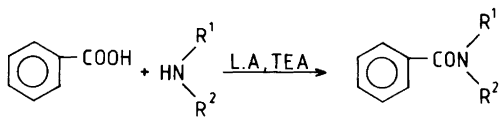
The catalytic effect of Lewis acids on the formation of carboxamides from benzoic acid and primary or secondary amines was studied under different conditions. The results show that the catalyst to be preferred depends on the nature of the amine. The best results were obtained with different catalysts for primary and secondary amines. Directions for preparative runs are given.

There exist a number of different routes to carboxamides.[1] In most of the reactions, a carboxylic acid is converted to a more reactive intermediate, e.g. the acid chloride, which is then allowed to react with an amine. For practical reasons, it is preferable to form the reactive intermediate *in situ*.

A carboxamide-forming reaction of the latter type has attracted our interest in our study of Lewis acid catalysed reactions, viz. the reaction between carboxylic acids and primary or secondary amines, catalysed by Lewis acids and tertiary amines (Scheme 1). There have been some reports on this reaction in the literature,[2] but no systematic study appears to have been undertaken. In this paper we report a study of the reaction with different Lewis acid catalysts and amines, as well as the influence of different reaction conditions.

In a recent paper[3] we proposed a method for selecting suitable Lewis acids catalysts for screening experiments. This strategy is based on a principal component (PC) projection[4] for 116 Lewis acids. The projection describes the systematic variation of 20 physical and chemical properties measured or calculated for the acids. The projection makes it possible to select Lewis acids so that a suitable spread is achieved for all properties considered. The applicability of this method as a tool for exploring synthetic reaction systems has been demonstrated previously.[5]



Scheme 1.

Screening of experimental variables

From earlier reports it is known that the reaction gives acceptable yields with primary amines in toluene under reflux with boron trifluoride etherate/triethylamine (TEA) as catalyst (Sheme 1).[2a] The procedure described in Ref. 2a involves performing the reaction in a Soxhlet apparatus with a drying agent. To obtain information on how different reaction conditions influence the rate and yield, we have selected the reaction between benzoic acid and benzylamine with BF_3 etherate and TEA catalysis as a model system. The reaction was carried out in toluene under reflux and the following experimental variables were studied: (1) relative amount of benzylamine, (2) relative amount of BF_3 etherate, (3) relative amount of TEA, (4) order of introduction of reagents, and (5) presence or absence of drying agent.

A two-level fractional factorial design,[6] 2_{-1}^{5-1}

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Table 1. Levels for the variables in the fractional factorial design.

Variable	− Level	+ Level
(1) Ratio of TEA:substrate[a]/mol:mol	1	3
(2) Ratio of BF_3 etherate:substrate[a]/mol:mol	1	3
(3) Ratio of benzylamine:substrate[a]/mol:mol	1	3
(4) Order of introduction	Lewis acid last	Benzoic acid last
(5) Drying agent[b]	No	Yes

[a]Benzoic acid. [b]Molecular sieves (4Å) in a Soxhlet apparatus were used as drying agent.

was employed for exploring the variation in experimental conditions. Such a design makes it possible to estimate the main effects of each variable and all two-factor interaction effects. Higher-order interaction effects, i.e. between three or more variables, are confounded with two variable interaction and main effects. This does not impose a serious problem, since significant interactions between more than two variables are rare.[6] Levels for the variables are given in Table 1. Experimental design and results are given in Table 2.

Variation of catalyst and amine

The traditional approach to exploring variation of reaction systems, i.e. variation in substrate, reagents, solvents etc., is to study such variables one at a time. This usually involves series of test systems in which, e.g., the reagent is varied while all other parameters are maintained fixed.[7] However, it has been shown that the effects of interaction between "system variables" may play important roles,[8] and like any one-at-a-time procedure, such effects remain undetected in a traditional "systematic" study. Hence, conclusions from such experiments may be false. In the present study an experimental design in both Lewis acid and amine principal properties[§] was employed to

[§]The principal properties of an object are the scores (*t*-values) obtained in PC analyses.

Table 2. The factorial design (levels for the variables) and yields in the corresponding experiments.

Entry	Variables					Yields (*y*)/%				
	(1)	(2)	(3)	(4)	(5)	1 h[a]	2 h[a]	4 h[a]	8 h[a]	Final[b]
1	−	−	−	−	+	1.3	2.6	6.0	11.1	82
2	+	−	−	−	−	2.4	4.8	9.3	15.9	73
3	−	+	−	−	−	0.5	0.9	1.2	2.0	8
4	+	+	−	−	+	6.3	13.2	25.0	40.2	80
5	−	−	+	−	−	1.1	1.2	1.4	1.9	18
6	+	−	+	−	+	4.6	8.8	15.9	37.4	98
7	−	+	+	−	+	11.7	24.5	41.6	62.6	95
8	+	+	+	−	−	22.3	37.5	56.0	75.7	100
9	−	−	−	+	−	1.4	2.0	2.6	2.8	72
10	+	−	−	+	+	2.8	6.7	14.4	27.4	85
11	−	+	−	+	+	0.0	0.0	0.0	0.0	2
12	+	+	−	+	−	6.3	11.2	21.8	35.6	83
13	−	−	+	+	+	2.8	6.7	9.8	13.8	64
14	+	−	+	+	−	4.7	9.9	21.6	46.3	98
15	−	+	+	+	−	7.6	15.9	28.3	48.3	98
16	+	+	+	+	+	23.1	40.2	58.0	76.2	99

[a]Yield after the time indicated. [b]Yield obtained after 150 h or when no further increase could be obtained.

ensure a simultaneous variation in both acid and amine properties. The principal properties used were taken from the PC study of Lewis acids[4] and from a study on amines in the Willgerodt reaction.[9]

The test candidates were selected to cover a large variation in the principal properties, i.e. a wide spread in the PC projection. However, it would be wasteful not to take previous experience into account. Therefore, two acids known to catalyse the reaction were chosen, viz. BF_3 etherate* and $TiCl_4$. Two other test candidates, $AlCl_3$ and ZnI_2, were also chosen. The following amines were selected: dipropylamine, butylamine and morpholine, for which the selection was based on the PC projection in Ref. 9, and benzylamine, the use of which in the reaction has been described previously. Experiments were made with all combinations of acids and amines, i.e. a complete factorial design.

*The compound used in the PC-projection is BF_3. In the experimental trials, however, the ether complex was used instead because it is easier to handle. The ether complex is weak compared to complexes with amines, so the effect of using the ether complex instead of the pure acid was assumed to be negligible. For complex strengths, see Ref. 12.

Results

The main effects and two-factor interaction effects estimated from the experimental results in Table 2 are summarized in Table 3. Yields were determined at regular intervals so that the effect of the variables on both the rate and final yields could be calculated. The significance of the effects was evaluated by plotting on normal probability paper.[6] As can be seen from Table 3, most of the variables which have significant effects on the yield early in the reaction (effect on the rate) also have an effect on the final yield. It is just the magnitude of the effects which differs. It is worth noticing that the relative amount of BF_3 etherate affects only the rate of the reaction, not the final yield (in the experimental domain). A surprising observation is the strong interaction between variable (1) (relative amount of TEA) and variable (4) (order of introduction of reagents), and between variable (2) (relative amount of BF_3) and variable (4). The presence of drying agent seems to have negligible influence on the final yield.

Table 3. Calculated effects[a] of the variables in the factorial design after different times of reaction.

b-term	Value after specified time				
	1 h	2 h	4 h	8 h	Final
b_0	6.18[b]	11.6[b]	19.6[b]	31.1[b]	72.2[b]
b_1	2.88[c]	4.91[c]	8.19[c]	13.3[c]	17.3[c]
b_2	3.54[c]	6.29[c]	9.43[c]	11.5[c]	−1.56
b_3	3.55[c]	6.45[c]	9.52[c]	14.2[c]	11.6[c]
b_4	−0.09	−0.05	0.006	0.23	2.94
b_5	1.89[c]	2.69[c]	3.02	1.09	2.56
b_{12}	1.06	1.11	0.61	0.36	−2.31
b_{13}	0.26	0.52	1.19	1.81	−1.19
b_{14}	2.89[c]	5.14[c]	7.47[c]	8.92[c]	15.81[c]
b_{15}	−0.38	−1.04	−1.97	−2.78	−3.06
b_{23}	−0.09	0.14	0.34	0.65	3.06
b_{24}	0.69	0.62	−0.79	−4.46	−16.1[c]
b_{25}	0.42	0.76	0.47	−0.29	1.81
b_{34}	0.16	0.34	0.38	−0.34	−5.06
b_{35}	−0.26	−0.52	−1.21	−1.55	−2.44
b_{45}	0.39	1.21	1.78	2.51	3.44

[a]The effects are the coefficients in a polynomial model: $y = b_0+b_1x_1+b_2x_2 \ldots + b_{35}x_3x_5+b_{45}x_4x_5$ which was fitted to the experimental data given in Table 2. [b]The average yield coefficients, b_0, were considered significant without justification from normal probability plots. [c]Significant according to normal probability plot.

Table 4. Results of the experiments with different combinations of Lewis acids and amines.

Amine	Lewis acid	Yield/%
Benzylamine	BF_3 Etherate	86
	$TiCl_4$	15
	$AlCl_3$	63
	ZnI_2	0
	$ZnCl_2$	0
Butylamine	BF_3 Etherate	81
	$TiCl_4$	19
	$AlCl_3$	68
	ZnI_2	Trace
	$ZnCl_2$	0
Morpholine	BF_3 Etherate	91
	$TiCl_4$	81
	$AlCl_3$	72
	ZnI_2	0
	$ZnCl_2$	0
Dipropylamine	BF_3 Etherate	45
	$TiCl_4$	44
	$AlCl_3$	8
	ZnI_2	0
	$ZnCl_2$	0

The effect in the beginning of the reaction can be explained as a concentration effect. The reaction is performed in a Soxhlet apparatus and pure solvent therefore accumulates in the upper part of the apparatus, increasing the concentration of the solutes in the reaction vessel.

From the results of the screening study, suitable conditions for the reaction could be determined. If only those factors found significant according to the normal probability plots are considered, the highest yields will be obtained if variables (1), (3) and (4) are held at a high level and variable (2) at a low level. However, the rate will be lower than if all variables are held at a high level. It was therefore concluded that the most suitable conditions would be to have all the variables at high levels [except variable (5), which was excluded from further consideration because of the small influence of that variable]. The conditions were checked experimentally and the results are given in Table 4. One interesting observation is that although BF_3 is the catalyst which gives the highest yields in all the reactions, $TiCl_4$ gives a much higher rate. For the two secondary amines, the difference in yield is much lower than for the primary amines. The failure of ZnI_2 to give more than traces of product raised the question of whether the acids projected in that corner of the PC plot are unsuited as catalysts in the reaction. To check this, $ZnCl_2$ was selected as test candidate since it lies between ZnI_2 and $AlCl_3$ in the plot and is known to function as a catalyst in other Lewis acid catalysed reactions.[10] However, $ZnCl_2$ also failed. This indicates that acids projected in the lower left quadrant in the PC plot (mostly soft acids) are unsuited as catalysts in this reaction.

Attempts to correlate yields and rates of the reactions with the Lewis acid and amine principal properties gave poor correlations (correlation coefficients ca. 0.9). The reasons for this are discussed below.

The experimental procedure used in the experiments mentioned in Tables 2 and 4 is not suitable for preparative runs. The reaction times are too long and large amounts of solvent are consumed. A more practical preparative procedure which reduces the volume of solvent has therefore been adopted. However, when the amount of solvent was decreased as the sole variation, a decrease in yields (ca. 15 %) resulted. Due to interaction effects this could be counteracted by a concomitant lowering of the relative amount of Lewis acid catalyst. Results from these experiments are given in Table 5.

Discussion

Chemical phenomena rarely depend on single factors. To explore variations in reaction systems it is necessary to use methods that allow for the simultaneous variation of all pertinent variables, i.e. to use multivariate methods. This has been emphasized elsewhere[11] and we do not repeat the arguments here.

To cope with discrete variations (catalysts, amines), a design based on principal properties ensured a simultaneous spread in all properties considered. This led to an interesting finding, viz. that carboxamides of primary amines are conveniently prepared with BF_3 as catalyst, whereas $TiCl_4$ is unsuited. However, amides of secondary amines are conveniently prepared with $TiCl_4$ as catalyst; in this case BF_3 gives comparable yields although the reaction is slower. A practical consequence of these findings is that it is possible to adjust the catalyst to the nature of the amine

Table 5. Yields of amides from the preparative runs.

Benzamide		Catalyst	Time/h	Yield[a]/%
R^1	R^2			
$PhCH_2-$	H–	BF_3 Etherate	96	89
$CH_3(CH_2)_3-$	H–	BF_3 Etherate	96	83
$-(CH_2)_2-O-(CH_2)_2-$		$TiCl_4$	10	86
$CH_3(CH_2)_2-$	$CH_3(CH_2)_2-$	$TiCl_4$	10	66

[a]Per cent crude product based on amount of benzoic acid.

counterpart. This demonstrates the utility of a design in principal properties. Thus, these properties are used as tools for exploring discrete variations.

Since the mechanism of the studied reaction is not known in detail, an empirical polynomial model was fitted to the results obtained in the fractional factorial design in the experimental variables. It was assumed, as a working hypothesis, that the conclusions for this model system could be extended to the other systems studied, i.e. that the variables have a similar influence. In this case the experiments (preparative runs) indicate that this assumption is validated.

This study provides an example of how PC projections based on properties which are not related in an obvious way to the problem under study can be used. A thorough discussion of why the principal properties of the Lewis acids are relevant to the problem is to be found in Ref. 3, and will not be repeated here. It suffices to say that the variables used in the PC analysis must in some way be related to the variation of interest, so that the PC scores entail variation of relevance to the problem.

Poor results were obtained on attempting to correlate the yields and rates of the reaction to the Lewis acid and amine PC scores. This is an indication that descriptors related to chemical reactivity of Lewis acids have to be included in the PC analysis before the scores can be used for good quantitative predictions of rate phenomena. There is, however, enough information in the existing PC projection for use in screening experiments.

Summary and conclusions

When examining the scope of a reaction, one has to examine different combinations of reagents and substrate. Unlike experimental variables (e.g. temperature, pressure) there is no single measure that describes variation of chemical compounds completely.

In this paper, a Lewis acid catalysed preparation of carboxamides is described. The exploration of this reaction involved both the study of experimental conditions (experimental variables) and the study of the reaction space (catalyst, substrate). Catalysts and amines were selected with the aid of PC projections to cover a large range of variation, i.e. they were taken from different regions in the PC projection.

Generally it can be said that the use of multivariate designs makes it possible to cover a wide range of variation with a limited number of experiments. Such designs will allow important interactions to be detected and it is concluded that it is necessary to use statistically designed experiments in all aspects of synthetic exploration.

Experimental

The chemicals used in the experiments were of *p.a.* or *puriss.* qualities and were purchased from Fluka, Merck and Aldrich. The Lewis acids were stored in a desiccator over Siccapent (Merck). Amines were distilled and stored over KOH. Toluene, used as solvent in the reactions, was stored over molecular sieves (4Å). Benzoic acid was recrystallized from toluene with azeotropic removal of water.

HPLC analyses were performed with an LKB 2150 HPLC pump and LKB 2151 variable wavelength monitor. For GLC analyses, a PYE UNICAM GCD with a flame ionization detector was used. Peak areas were used for quantification using the internal standard technique. A Milton

Roy CI-10 integrator was used. NMR spectra were recorded on a Bruker AC-80 FT-NMR spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard. Mass spectra were obtained with an HP 5890 capillary gas chromatograph equipped with an HP 5970 MSD.

Procedure for screening of experimental variables. When the acid catalyst was to be introduced last, the following procedure was used: 5 mmol of benzoic acid, the calculated amounts of benzylamine and TEA, and an accurately weighed amount of *o*-dichlorobenzene (internal standard) were dissolved in 170 ml of toluene in the reaction flask. The flask was equipped with a reflux condenser with a $CaCl_2$ drying tube. The mixture was stirred magnetically and heated. When the mixture started to boil under reflux, the reaction was started by the rapid introduction of the calculated amount of BF_3 etherate dissolved in 30 ml of toluene. When the benzoic acid was to be introduced last, the only modification was that the reaction was started with the introduction of 5 mmol of benzoic acid dissolved in 30 ml of toluene to a solution of the reagents boiling under reflux. When drying agent was used, the reflux condenser was replaced with a Soxhlet apparatus. The extraction thimble was charged with 14 g of 4Å molecular sieves.

Analysis. A few drops of the reaction mixture were withdrawn and dissolved in 15 ml of methanol. 10 ml of water were added to the solution. This solution was analysed by HPLC using 71/29 (*v/v*) methanol/water mixture as eluent and a 15 cm × 4.6 mm Supelcosil LC-18 column. Peaks were detected by UV absorption at 254 nm.

Procedure for variation of amine and catalyst. 15 mmol of amine, TEA and Lewis acid catalyst and an accurately weighed amount of octadecane or triphenylmethane (internal standard) were dissolved† in 170 ml of toluene. The mixture was stirred magnetically and heated. When the mixture started to boil under reflux, a solution of 5 mmol of benzoic acid in 30 ml of toluene was rapidly added.

†$AlCl_3$, ZnI_2 and $ZnCl_2$ are not soluble in toluene. In those cases where they were used as catalysts they were slurried in the solvent.

Analysis. A small sample was withdrawn and subjected to GC without further treatment. The analyses were performed with a 1.5 m × 4 mm (i.d.) glass column packed with 6% QF-1 on Chromosorb W-AW (100–120 mesh).

Preparative procedure. 15 mmol of amine, TEA and 5 mmol of Lewis acid catalyst were dissolved in 15 ml of toluene and the mixture was stirred magnetically and heated. When the mixture had reached a temperature near the boiling point, 5 mmol of benzoic acid was added in one portion and rinsed down with 5 ml of toluene. The reaction mixture was maintained under reflux for the length of time indicated in Table 5.

Work up: BF_3 as catalyst. The reaction mixtures were washed consecutively with aqueous 1M NaOH, 2M HCl, 10% $NaHCO_3$ and water. After drying over Na_2SO_4, the solvent was evaporated *in vacuo* to yield the crude products.

$TiCl_4$ as catalyst. The reaction mixtures were poured into aqueous 1M NaOH and thoroughly mixed. Precipitated TiO_2 was removed by filtering through a glass filter. The *N,N*-dipropylbenzamide was then worked up as for the other amides. In the work-up of *N*-benzoylmorpholine, the washing fractions were back-extracted twice with toluene; otherwise the work-up procedure was as for *N,N*-dipropylbenzamide. The purity of the crude benzamides obtained using these procedures was >95%. Further purification of the amides can be achieved by chromatography on silica gel 60 (Merck) using elution with a stepwise gradient of ethyl acetate/petroleum ether (boiling point 30–50 °C). The compounds were identified by ^1H NMR, ^{13}C NMR and mass spectrometry. Purity was checked by TLC and GC.

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