

## Optimal Synthesis of Enamines from Methyl Ketones. A Comparative Study of Two Different Synthetic Methods

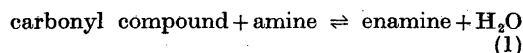
ROLF CARLSON,<sup>a</sup> ROGER PHAN-TAN-LUU,<sup>b</sup> DIDIER MATHIEU,<sup>b</sup> FLORENTIN S. AHOUANDE,<sup>c</sup>  
ANDRÉ BABADJAMIAN<sup>c</sup> and JACQUES METZGER<sup>c</sup>

<sup>a</sup> Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden, <sup>b</sup> Laboratoire de Prospective Réactionnelle et d'Analyse de l'Information, I.U.T., Avenue Gaston Berger, F-13100 Aix-en-Provence, France and <sup>c</sup> I.P.S.O.I., Centre de St Jerome, Rue Henri Poincaré, 13397 Marseille, France

The conditions for optimal synthesis of morpholine enamines from alkyl methyl ketones (alkyl = isobutyl, isopropyl, *tert*-butyl) were studied using two different types of water scavengers, (1) molecular sieves, (2) titanium tetrachloride. The influence of different factors on yield was studied with D-optimal factorial designs. For the molecular sieve method further studies using response surface methodology were necessary to locate optimal conditions. Advantages and disadvantages of each method are discussed.

Most methods for synthesis of enamines from carbonyl compounds have been developed with aldehydes and cyclic ketones.<sup>1</sup> However, when these methods are applied to acyclic aliphatic ketones they sometimes give poor yields and/or undesired side reactions.<sup>2</sup> In a recent paper<sup>3</sup> from these Laboratories we describe a simple one-pot procedure for the conversion of isomer mixtures of some methyl ketone-morpholine enamines into the least substituted isomer. This may extend the scope of enamine chemistry to include regiospecific functionalisation of the methyl group in methyl ketones. Hence it is desirable that methyl ketone enamine syntheses proceed in optimal yield.

The formation of enamine from a carbonyl compound and an amine is described by the overall equilibrium (1).



\* To whom inquiries about the paper should be sent.

The most commonly used technique to enhance enamine formation is to remove water from the reaction mixture and following this principle two different methods of potential general applicability were selected for comparison: Removal of water with (1) molecular sieves<sup>4</sup> and (2) titanium tetrachloride.<sup>5</sup> The choice of these methods needs a comment. Enamine synthesis with molecular sieves has given excellent results with aldehydes and cyclic ketones<sup>4</sup> but its application to acyclic ketones has not been established. Titanium tetrachloride has given good results with acyclic ketones but in the original paper<sup>5</sup> optimum conditions were not determined. To make a fair comparison of the methods optimal conditions in their use must be determined. The generality of each method was tested and compared by applying them on a primary, a secondary and a tertiary alkyl methyl ketone (isobutyl, isopropyl, *tert*-butyl methyl ketone).

### METHODS

We note that a traditional method of optimization, *i.e.* the variation of one variable at a time, does *not* in general lead to an increase in yield due to compensation effects between variables.<sup>6,7</sup> Therefore we resort to a multivariate method, which, though apparently more complicated, leads to the desired optimum.

The general strategy for this investigation

was: Determine the influence of externally controllable variables (factors) like concentration, molar ratio of reactants, rate of agitation *etc.* and the principal possible, previsible, interactions between them, and then perform a synthesis using the most favourable combination of these factors.

If the yield was  $\geq 90\%$  it was stated that a satisfactory result had been obtained and no further refinements were necessary. If the yield was lower a simplex optimisation strategy<sup>8</sup> should be followed by varying the most important factors.

The screening of the influences of the various factors in each method has been restricted to one substrate, isobutyl methyl ketone, with the assumption that conclusions drawn from these experiments could be extended to other ketones. These screenings were performed using D-optimal factorial designs<sup>7,9</sup> to fit the yields to linear models of each method (see below). The experiments were designed to optimize yields, not to give mechanistic information, and no speculations in this direction will be given.

The yields were determined by gas chromatography using the internal standard technique.

*Molecular sieve method, screening of factors.* Cyclohexane was used as solvent in all experiments.<sup>4b</sup> The experiments were performed at room temperature without stirring and the reason for this was two-fold: (1) *Convenience*, since the reaction mixture could be left without supervision and (2) *economy*, since heat (and agitation) are energy demanding. If acceptable yields could be reached with these restrictions extra advantages of the method would result.

The experimental domain (factors, levels) in the screening experiments is given in Table 1.

The formation of enamines is acid catalyzed. Commercial Silica-Alumina cracking catalyst<sup>4b</sup> as well as protic acids<sup>1</sup> have been used in enamine synthesis. To determine which type of catalyst that gives best results in methyl ketone enamine synthesis, Silica-Alumina LA-3P cracking catalyst (see Experimental for details) and trifluoroacetic acid were chosen as examples from each group.

We assumed that only the interactions  $x_1x_2$ ,  $x_3x_4$  and  $x_2x_6$  exist and the following model was proposed for the screening experiment.

Table 1. Experimental domain in the molecular sieve screening experiments.

Factors	Levels	
	-1	+1
$x_1$ Ratio morpholine/ketone (mol/mol)	1	3
$x_2$ Ratio cyclohexane/ketone (dm <sup>3</sup> /mol)	0.2	0.8
$x_3$ Ratio molecular sieve/ketone (g/mol)	200	600
$x_4$ Type of molecular sieve	3 Å	5 Å
$x_5$ Type of catalyst	SA <sup>a</sup>	TFA <sup>b</sup>
$x_6$ Ratio catalyst/ketone (g/mol)	SA	SA
TFA (drops/mol)	50	200
	10	250

<sup>a</sup> Silica-Alumina. <sup>b</sup> Trifluoroacetic acid.

$$\eta = \sum_{i=0}^6 \beta_i x_i + \beta_{12} x_1 x_2 + \beta_{34} x_3 x_4 + \beta_{56} x_5 x_6 \quad (2)$$

where  $\eta$  is the true value of the yield and  $x_0$  is a dummy variable = 1.

A small number of experiments was desired and it was decided that twelve were sufficient to estimate the parameters ( $\beta_0, \dots, \beta_{56}$ ) in the model.

With  $y_j$  (the experimental yield in the  $j$ th experiment) as estimates of  $\alpha$ , least square estimates of  $\beta_1, \dots, \beta_{56}$  were obtained by the procedure defined by the matrix equation (3).<sup>8a</sup>

$$\mathbf{B} = (\mathbf{X}'\mathbf{X})^{-1} \mathbf{X}'\mathbf{Y} \quad (3)$$

$$\mathbf{Y} = \begin{matrix} y_1 \\ \vdots \\ y_{12} \end{matrix} \quad \mathbf{B} = \begin{matrix} b_0 \\ \vdots \\ b_{56} \end{matrix} \quad \text{and } \mathbf{X}' \text{ is the transposed}$$

factor matrix given in Table 2.  $b_i$  is an estimate of  $\beta_i$  confounded with higher order interaction effects<sup>7</sup> which are assumed to be negligible.

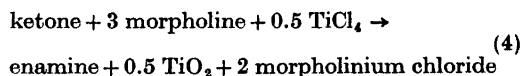
The design matrix was established according to the criterion of maximised determinant  $|\mathbf{X}'\mathbf{X}|$  (D-optimal design) using an algorithm of exchange.<sup>9</sup> However, it cannot be stated that the ultimate, optimal design has been achieved since (due to costs of computation) all possibilities have not been tested, but the designs used in this and the  $\text{TiCl}_4$ -study were the best obtained after about 30 iterative cycles of exchange.

Table 2. Screening of factors in the molecular sieve method. Factor matrix X and yield matrix Y.

j	X										Y <sup>a</sup>			
	x <sub>0</sub>	x <sub>1</sub>	x <sub>2</sub>	x <sub>3</sub>	x <sub>4</sub>	x <sub>5</sub>	x <sub>6</sub>	x <sub>1</sub> x <sub>2</sub>	x <sub>2</sub> x <sub>4</sub>	x <sub>5</sub> x <sub>6</sub>	y(28)	y(52)	y(76)	y(98)
1	1	-1	-1	1	-1	1	1	1	-1	1	58	66	71	76
2	1	-1	-1	-1	-1	1	-1	1	1	-1	8	13	18	23
3	1	-1	-1	1	1	-1	1	1	1	-1	60	61	65	67
4	1	-1	1	1	-1	-1	-1	-1	-1	1	40	60	69	74
5	1	1	-1	1	-1	1	-1	-1	-1	-1	17	30	40	48
6	1	-1	1	1	1	1	-1	-1	1	-1	80	89	98	99
7	1	1	-1	-1	1	-1	-1	-1	-1	1	32	46	54	64
8	1	1	1	1	1	1	1	1	1	1	47	57	80	82
9	1	1	1	-1	-1	-1	-1	1	1	1	12	15	21	24
10	1	-1	1	-1	1	1	1	-1	-1	1	19	26	40	48
11	1	1	-1	-1	-1	-1	1	-1	1	-1	29	33	45	54
12	1	1	1	-1	1	-1	1	1	-1	-1	25	46	57	60

<sup>a</sup> The figures within parentheses are the reaction times, h.

*Titanium tetrachloride method. Screening of factors.* The stoichiometry of the reaction is given in eqn. (4).<sup>5</sup>



The solvent employed in these reactions was hexane. It has been found that increased yields have been obtained at elevated temperature in some cases<sup>10</sup> and the effect of temperature on yield was to be determined. Adding titanium tetrachloride to an amine solution gives a precipitated TiCl<sub>4</sub>-amine complex which may be involved in the enamine forming reactions. Because of this the efficiency of agitation can influence the yield and this factor was to be accounted for. Table 3 defines the experimental domain in the screening experiments. All factors are quantitative. We assume that only the interactions x<sub>1</sub>x<sub>2</sub>, x<sub>1</sub>x<sub>3</sub>, x<sub>2</sub>x<sub>3</sub>, x<sub>5</sub>x<sub>6</sub> and x<sub>1</sub>x<sub>2</sub>x<sub>3</sub> exist.

The proposed model is shown in eqn. (5),

$$\eta = \sum_{i=0}^6 \beta_i x_i + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{56} x_5 x_6 + \beta_{123} x_1 x_2 x_3 \quad (5)$$

where  $\eta$  is the true yield and  $x_0$  is a dummy variable = 1. Estimates of the parameters ( $\beta_0, \dots, \beta_{123}$ ) were obtained as above. The design matrix is constructed according to the same principles.

For brevity Table 4 shows only the yields and the design matrix, i.e. the columns for the dummy variable  $x_0$  and the interaction products are omitted.

*Validity of the models in the screening experiments.* A minimum number of experiments was desired and any individual experiment was performed without replication. Hence no tests of validity related to estimates of variances were performed. We were not interested in a model of each method *per se*, only a rather qualitative information of the probable directions and magnitudes of the effects of the various factors in order to progress further towards the optimum by further experiments. — The end justifies the means.

Table 3. Experimental domain in the titanium tetrachloride screening experiments.

Factors	Levels	
	-1	1
x <sub>1</sub> Ratio morpholine/ketone (mol/mol)	3	6
x <sub>2</sub> Ratio TiCl <sub>4</sub> /ketone (mol/mol)	0.50	0.80
x <sub>3</sub> Amount of ketone/final volume (mol/dm <sup>3</sup> )	0.30	0.46
x <sub>4</sub> Temperature (°C)	25	~70 (reflux)
x <sub>5</sub> Rate of agitation (rpm)	100	200
x <sub>6</sub> Dilution of TiCl <sub>4</sub> (vol %)	20	50

Table 4. Screening of factors in the  $\text{TiCl}_4$ -method. Design matrix **D** and yield matrix **Y**.

j	<b>D</b>						<b>Y</b> <sup>a</sup>				
	$x_1$	$x_2$	$x_3$	$x_4$	$x_5$	$x_6$	y(1)	y(2)	y(3)	y(4)	y(5)
1	-1	1	-1	-1	-1	-1	49	50	51	52	52
2	-1	1	1	1	1	1	70	71	70	70	68
3	1	1	-1	-1	1	1	42	64	72	78	80
4	1	1	-1	1	-1	1	92	96	96	96	95
5	-1	1	-1	1	1	1	64	67	68	67	68
6	-1	-1	1	-1	1	1	48	61	67	70	71
7	1	-1	1	1	1	-1	84	87	87	87	86
8	-1	-1	-1	1	1	-1	74	76	77	78	78
9	1	-1	-1	-1	1	-1	66	78	83	84	85
10	-1	-1	-1	-1	-1	1	38	55	62	66	68
11	1	-1	-1	1	-1	-1	77	84	86	85	87
12	1	1	1	-1	1	-1	95	96	97	95	96

<sup>a</sup> The figures within parentheses are the reaction times (h).

## RESULTS

### Molecular sieve method

*Isobutyl methyl ketone. Screening experiments.* Table 5 shows the effects (model parameters) calculated from the yields given in Table 2. Since the factors are normalized, the influence of the various factors is directly related to the numerical value of the given effect (with the assumption that the model is appropriate).

The average yield,  $b_0$ , increases with time. The effect  $b_1$  is negative and probably important with short reaction time but becomes insignificant with prolonged reaction time. The interaction effect  $b_{11}$  is negative and decreases further with time. The other effects remain fairly constant with time. From Table 5 it can be seen

Table 5. Effects in the molecular sieve method.

	Reaction time (h)			
	28	52	76	98
$b_0$	35.0	45.2	55.0	60.0
$b_1$	-4.3	-3.7	-0.7	-0.3
$b_2$	-1.5	0.8	2.9	1.3
$b_3$	14.5	15.7	16.3	15.1
$b_4$	8.1	8.5	8.9	8.3
$b_5$	-3.7	-4.7	-2.8	-2.2
$b_6$	2.6	1.1	3.3	3.8
$b_{12}$	-3.1	-2.6	-4.2	-6.2
$b_{34}$	1.3	0.3	1.2	0.6
$b_{56}$	1.5	-0.3	0.4	1.2

how further improvement of yield can be obtained. It is necessary to use a molar ratio morpholine/ketone close to 1. This is contrary to what has been reported previously.<sup>4b</sup> Due to the interaction term  $b_{12}$  a dilute solution is suggested. Other than this the influence of concentration on yield is probably negligible. A large amount (600 g/mol of ketone) of molecular sieve and the type of molecular sieve shall be "5Å". Silica-Alumina is preferred to protic acids as catalyst. (This is probably not too important, see, *e.g.*, experiment  $j = 6$  in which a quantitative yield was obtained using a trace of trifluoroacetic acid). The amount of Silica-Alumina of 200 g/mol of ketone is suggested.

*Simplex optimisation. Isobutyl methyl ketone.* Conditions for quantitative yield have already been found ( $j = 6$ , Table 2). However, in order to reduce the time necessary for obtaining high yields a Simplex optimisation strategy<sup>6</sup> was used. The amounts of 5Å molecular sieve,  $x_3$  and of Silica-Alumina,  $x_6$ , were varied while maintaining the other factors at their most favourable levels ( $x_1 = 1$ ,  $x_2 = 1$ ). Taking  $(x_3; x_6) = (1; 1)$  as origin we can define coordinates for the experimental variables by the transformation (6).

$$\begin{aligned} x_3' &= x_3 - 1 \\ x_6' &= x_6 - 1 \end{aligned} \quad (6)$$

The values of  $x_3'$ ,  $x_6'$  and yields obtained in the Simplex experiments are given in Table 6.

Table 6. Simplex optimisation of isobutyl methyl ketone-enamine synthesis using molecular sieves. Reaction time 22 h.<sup>a</sup>

Exp. number	$x_3'$	$x_6'$	Yield/%
1	0	0	77
2	1.0	0.3	69
3	0.3	1.0	55
4	0.7	-0.7	73
5	-0.3	-1.0	52
6	-1.0	-0.3	59
7	-0.7	0.7	63

<sup>a</sup>  $x_3' = 0$  corresponds to 700 g of molecular sieve/mol of ketone,  $x_6' = 0$  corresponds to 250 g of Silica-Alumina/mol of ketone. One unit of  $x_i'$  corresponds to 100 g/mol of ketone of molecular sieve or Silica-Alumina, respectively.

As seen from Table 6 the Simplex circles the starting point. This can imply that the starting point suggested from the screening experiment is very near to a true optimum which has been enclosed by the experiments 1–5. One possibility to explore this is to reduce the size of the Simplex and progress further towards the true optimum by a new set of experiments. Another possibility is to determine a mathematical model of the response surface<sup>7</sup> by regression using the results already obtained and use the model to predict the location of the optimum. We have chosen the latter method. Using experiments 1–7 the following second degree model (7) was obtained by a least square fit.<sup>8b</sup>

$$\text{Yield (\%)} = 77.0 + 5.7 x_3' + 0.7 x_6' - 8.3 x_3'^2 - 19.8 x_6'^2 - 9.7 x_3' x_6' \quad (7)$$

The features of the calculated response surface are shown in Fig. 1. Differentiation of the response surface function gives a maximum for  $(x_3'; x_6') = (0.415; -0.120)$   $Y(\text{calc.}) = 78.2$ . Eight experiments performed in this point afforded  $79 \pm 3\%$  yields after 22 h and  $98 \pm 3\%$  after 44 h.

*Extension of the molecular sieve method to other ketones: Isopropyl methyl ketone.* Assuming the influence of the various factors to be similar to what is described above, the most favourable combination of molecular sieve and Silica-Alumina was determined. A response surface technique was used directly since it was assumed

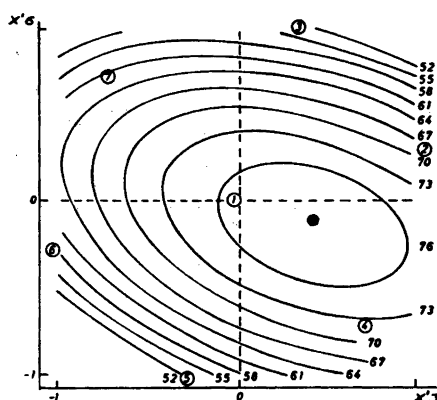


Fig. 1. Response surface obtained in simplex optimisation of isobutyl methyl ketone enamine synthesis. Experimental points are marked with numbered rings. Optimum is marked with a black dot. The numbers at the isoresponse contour lines show the yield (%).

that an optimum was not too remote from what has already been established for isobutyl methyl ketone. It was further assumed that the second degree polynomial below should give a satisfactory description of the response surface. In eqn. (8)  $Y$  is the yield,  $a_0, \dots, a_{12}$  are

$$Y = a_0 + a_1 x_1 + a_2 x_2 + a_{11} x_1^2 + a_{22} x_2^2 + a_{12} x_1 x_2 \quad (8)$$

parameters to be estimated,  $x_1$  is the level of molecular sieve and  $x_2$  is the level of Silica-Alumina.

A rotatable composite design<sup>13</sup> with 13 experiments was used to establish the model; five experiments at the center point and eight experiments equally spaced around. The center point was chosen close to the optimum conditions for isobutyl methyl ketone. The design and the response surface is shown in Fig. 2. The estimated values of the parameters are (95% confidence interval):  $a_0 = 54.86 \pm 0.93$ ,  $a_1 = 2.11 \pm 0.74$ ,  $a_2 = 3.49 \pm 0.74$ ,  $a_{11} = 0.43 \pm 0.79$ ,  $a_{22} = 1.67 \pm 0.79$ ,  $a_{12} = 1.05 \pm 1.04$ .

By the variable transformation, eqn. (9),

$$x_1 = 0.973 z_1 + 0.230 z_2 - 0.187 \quad (9)$$

$$x_2 = 0.230 z_1 + 0.973 z_2 - 0.791$$

the model is reduced to its canonical form [cf. eqn. (10)]<sup>7</sup>

$$Y = 56.04 + 0.56 z_1^2 + 2.86 z_1 - 1.79 z_2^2 \quad (10)$$

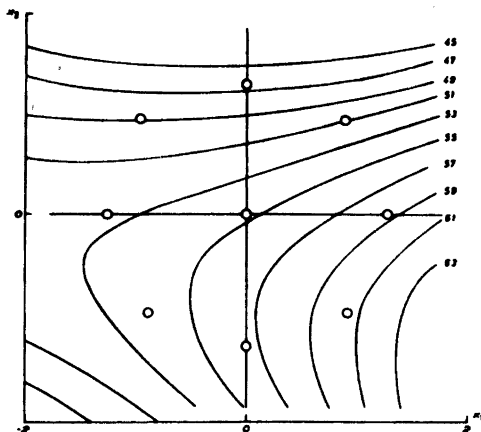


Fig. 2. Response surface obtained in optimisation of isopropyl methyl ketone enamine synthesis. Experimental points are marked with rings. The numbers at the isoresponse contour lines show the yield (%) after a reaction time of 120 h.  $x_1=0$  corresponds to 750 g of molecular sieve/mol of ketone and  $x_2=0$  corresponds to 250 g of Silica-Alumina/mol of ketone. One unit of  $x_1$  corresponds to 100 g.

To improve the yield it is necessary to progress in the positive direction along the  $x_1$ -axis while maintaining  $x_2=0$ . By this procedure the explored domain is departed from and the model becomes uncertain. Only a minor improvement was found by this procedure, 69% yield, ( $x_1=2$ ) and for larger  $x_1$ -values the yields decreased. At this point no further studies of the molecular sieve method with this ketone were undertaken, since excellent results had been obtained with the titanium tetrachloride method (see below).

*tert-Butyl methyl ketone* afforded less than 0.5% yield after 150 h of reaction (5 experiments under the conditions of optimal transformation of isobutyl methyl ketone), and the method was not further studied with this ketone.

#### Titanium tetrachloride method

*Isobutyl methylketone. Screening experiment.* The calculated effects are given in Table 7. The time-related changes in some of the effects involving the temperature and the relative amount of reagents are probably explained by the fact that increased concentrations and

Table 7. Effects in the titanium tetrachloride method.

	Reaction time/h				
	1	2	3	4	5
$b_0$	69.0	74.9	76.9	77.6	77.8
$b_1$	3.7	7.0	8.4	8.7	9.4
$b_2$	7.3	3.4	1.5	0.6	0.0
$b_3$	6.4	3.7	2.5	1.9	1.3
$b_4$	13.9	9.5	7.5	5.9	5.4
$b_5$	-1.4	0.1	0.7	1.1	1.2
$b_6$	-5.0	-1.3	0.4	0.8	1.5
$b_{12}$	3.9	4.0	4.6	4.5	5.0
$b_{13}$	-2.9	-2.2	-1.5	-1.4	-0.7
$b_{23}$	0.9	1.4	1.7	1.4	1.9
$b_{56}$	-9.6	-6.8	-5.1	-4.4	-3.4
$b_{123}$	7.3	5.3	4.7	3.5	3.6

temperature augment the reaction rate. As seen from Table 4 the yields level off after ca. 3 h. To give directions for further improvement of yield, the factors,  $x_1-x_6$ , should be maintained at favourable levels, *i.e.*  $x_1$  has a very strong and positive influence and should be maintained  $\geq 1$ .  $x_2$  has probably no direct influence on the final yield, but the interaction effects  $b_{12}$ ,  $b_{13}$  and  $b_{212}$  are positive and a at least slight excess of  $\text{TiCl}_4$  ( $x_2 \geq 0$ ) is therefore suggested.  $x_3$  has only a small influence. The interaction effects,  $b_{13}$  and  $b_{213}$ , are small and have opposite signs, and the variation in the total concentration of ketone in the experimental domain is too small to cause real effects on yield. For economical reason a small amount of solvent is suggested.  $x_4$  has a strong and positive effect and the reaction should be run at reflux temperature.  $x_5$  and  $x_6$  have only small and probably negligible effects on the yield, or their variations are too small to have any influence. However, the interaction effect  $b_{56}$  is important with short reaction time but becomes less important with time. This implies that the requirement on the type of stirring equipment is not too demanding.

The syntheses performed with isobutyl methyl ketone under the conditions given above afforded 94–100% yields of enamine after 4–5 h.

*Extension of the titanium tetrachloride method to other ketones.* Isopropyl methyl ketone afforded 95–97% yields of enamine within 3 h under the conditions given above. This is an improve-

ment from the 55 % yield given in Ref. 5. *tert-Butyl methyl ketone* afforded 80–87 % of enamine. However, the reaction is considerably slower compared to the other ketones and a reaction time of 10–12 h was necessary. After 5 h yields in the range 65–70 % were obtained.

## DISCUSSION

Enamine from isobutyl methyl ketone can be prepared in almost quantitative yields by either method and for this ketone any of the methods fulfilling different criteria of convenience are satisfactory. *The molecular sieve method* affords the enamine almost free from unreacted starting material since stoichiometric amounts of ketone and morpholine are used. The procedure is a mere mixing of reagent at room temperature. No supervision is required. The product is collected by filtration and solvent stripping. However, the reaction is rather slow and the molecular sieve and catalyst have to be activated prior to use. Unfortunately, the molecular sieve method seems to be of limited scope since *tert-butyl methyl ketone* failed to give enamine and isopropyl methyl ketone afforded only moderate yields. For unhindered ketones, however, it may be the method of choice.

*The titanium tetrachloride method* seems to be of general scope. It is rapid and neither special equipment nor pretreatment of chemicals is necessary. However, one disadvantage is that the crude product contains the excess of morpholine which must be removed by distillation prior to further use. Moderate excess of titanium tetrachloride is not detrimental, since this excess is removed by filtration as an amine–TiCl<sub>4</sub> complex.

## EXPERIMENTAL

*GC-analyses.* PYE M 64 and Intersmat 16 gas chromatographs with FID were used with 5 % PEG 20 M+0.5 % KOH on Chromosorb W-AW 60–80 mesh columns. (1.5 m, 4 mm i.d. glass or 1.5 m, 3 mm i.d. copper columns). Phenylcyclohexane *puriss.* was used as internal standard. Accuracies in the GC-analyses can be estimated to  $\pm 3$  % (errors of FID response calibration and of weighting). Integrated peak areas were used in calculating yields. The reproducibilities of peak area ratios were  $\pm 1$  %.

The yields given are the average of three analyses of each sample. The samples were analysed in random order.

*Chemicals.* Ketones and morpholine were commercial *puriss.* or *p.a.* products. Cyclohexane *p.a.* was employed in the molecular sieve experiments. Hexane and titanium tetrachloride were technical grade and used without purification. *Molecular sieves* Union Carbide 3 Å or 5 Å 3 mm pellets purchased from FLUKA were heated at 400 °C for 5 h prior to use. *Silica-Alumina LA-3P* purchased from AKZO-CHEMIE (Amsterdam) with the specified composition (%): Alumina 13.900, silica 83.871, sodium oxide 0.089, sulfate 0.130, Fe 0.010 (no specification of the nature of sulfate or Fe) was treated prior to use as is described for the molecular sieves.

*Screening of factors. Molecular sieve method. General procedure.* To eliminate time dependent trends, all experiments were performed simultaneously. With 0.100 mol of ketone the amounts of solvent and of the various reagents specified in Tables 1–2 were mixed together in 250 ml bottles: 10.00 g of phenylcyclohexane was added to each mixture. The bottles were stoppered and left on the laboratory bench with occasional shakings. At the time given *ca.* 0.5 ml samples were withdrawn, diluted with cyclohexane and analysed by GC.

*Simplex optimisation for isobutyl methyl ketone given in Table 6 and response surface determination for isopropyl methyl ketone given in Fig. 2.* To the amounts of molecular sieve (5 Å) and silica-alumina given, were added the ketone (0.100 mol), morpholine (0.100 mol), phenylcyclohexane (10.00 g) and cyclohexane (100 ml). Analyses were performed as above.

*Screening of factors. Titanium tetrachloride method. General procedure.* The experiments were performed in random order. The reaction vessel was a 500 ml three-neck flask equipped with a dropping funnel, reflux condenser and a teflon blade stirrer. Stirring rate was calibrated with a stroboscope. The reactor was purged with dry nitrogen prior to introduction of chemicals and protected from moisture. 0.0909 mol of isobutyl methyl ketone was used in all experiments. Using the combination of factors specified in Tables 3–4 the reactions were performed as follows: phenylcyclohexane (10.00 g), isobutyl methyl ketone (9.11 g) and morpholine were dissolved in the calculated amount of hexane. After cooling to 0 °C the TiCl<sub>4</sub>-solution was added dropwise with stirring. When the addition was completed the temperature was fixed at the level  $x_4$  by means of a thermostated oil bath. 0.5 ml samples were withdrawn at the time given (time at level  $x_4$ ), filtered, diluted with hexane and analysed by GC.

*Optimal synthesis with titanium tetrachloride. General description.* The procedure as described above was used with the following combination of factors: 0.1 mol of ketone, 0.6 mol of morpho-

line in 150–200 ml of hexane. 0.06–0.007 mol of  $\text{TiCl}_4$  in 10–20 ml of hexane was added. The mixture was refluxed after the  $\text{TiCl}_4$  was added.

*Acknowledgements.* A grant from C.N.R.S. (France) to R.C. and financial support from The Swedish Natural Science Research Council are gratefully acknowledged. The authors are indebted to Professor W. J. Dunn for linguistic criticism.

## REFERENCES

1. For a review see Haynes, L. W. in Cook, A. G., Ed., *Enamines*, Dekker, New York 1969, pp. 55–96.
2. a. Jacquier, R., Petrus, C. and Petrus, F. *Bull. Soc. Chim. Fr.* (1966) 2845; b. Madsen, P. and Laweson, S.-O. *Recl. Trav. Chim. Pays-Bas* 85 (1966) 753; c. Bianchetti, G., Croce, P. D. and Pocar, D. *Tetrahedron Lett.* (1965) 2039; d. Hickmott, P. W., Hopkins, B. J. and Yoxall, C. T. *J. Chem. Soc. B* (1971) 205; e. Munk, M. E. and Kim, Y. K. *J. Am. Chem. Soc.* 86 (1964) 2216.
3. Carlson, R., Nilsson, L., Rappe, C., Babadjamian, A. and Metzger, J. *Acta Chem. Scand. B* 32 (1978) 85.
4. a. Taguchi, K. and Westheimer, F. H. *J. Org. Chem.* 36 (1971) 1570; b. Roelofsen, D. P. and van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* 91 (1972) 605.
5. White, W. A. and Weingarten, H. *J. Org. Chem.* 32 (1967) 231.
6. a. Spendley, H. G. R., Hext, G. R. and Himsforth, F. R. *Technometrics* 4 (1962) 441; b. Deming, S. N. and Morgan, S. L. *Anal. Chem.* 45 (1973) 278 A.
7. a. Davies, O. L., Ed., *Design and Analysis of Industrial Experiments*, Oliver & Boyd, London 1963; b. Meyers, R. M. *Response Surface Methodology*, Allyn and Bacon Inc., Boston 1971.
8. a. Draper, N. R. and Smith, H. *Applied Regression Analysis*, Wiley, New York 1966, pp. 58–67; b. *Ibid. cf.* pp. 128–130.
9. Mitchel, T. J. *Techometrics* 16 (1974) 203.
10. Carlson, R. and Rappe, C. *Acta Chem. Scand. B* 31 (1977) 488.
11. Box, G. E. P. and Hunter, J. S. *Ann. Math. Stat.* 28 (1957) 195.

Received February 13, 1978.