Short Communication

An Optimized Procedure for the Reductive Amination of Acetophenone by the Leuckart Reaction

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The formation of saturated amines from carbonyl compounds by treatment with ammonium formate or formamide or mixtures of formamide and formic acid is known as the Leuckart reaction. The reaction was discovered in 1885 by Leuckart.[1] At the beginning of this century, the reaction was further studied by Wallach and coworkers.[2] However, the reaction attracted little interest until preparatively useful conditions were developed by Ingersoll and coworkers[3] and, before the advent of the complex hydride reducing agents, this was the most convenient procedure for the synthesis of saturated amines from carbonyl compounds. Earlier reviews[4] summarized the state of the art. A modification which uses formaldehyde as the carbonyl moiety is known as the Eschweiler–Clarke procedure[5] and has been extensively used for the methylation of amines.

Different reaction mechanisms have been suggested over the years. A generally accepted mechanism[4] is that ammonia (or formamide which is formed in situ) reacts with the carbonyl compound to form a carbinolamine derivative which is dehydrated to an imine (or formyl-imine). This imine derivative is protonated by formic acid to yield an iminium salt after which a hydride shift takes place from the formate ion to yield the saturated amine (or formamide). When secondary amines are used the iminium salt intermediate is formed directly from the carbinolamine. An alternative mechanism which involves a homolytic cleavage of the corresponding carbinolamine formic ester formed by nucleophilic addition of formate ion to the iminium derivative has been suggested.[6] Yet other proposals which involve an initial reduction of the carbonyl compound to yield an alcohol which then acts as an alkylation agent towards the amine (or formamide) have been presented.[7] The last option cannot be a general mechanism since it has been shown that tertiary

enamines are reduced to saturated amines by treatment with stoichiometric amounts of formic acid[8] and that this reaction proceeds via the corresponding iminium salt.[8a,b]

In this communication we report some results obtained in our attempts to optimize the experimental conditions with respect to yield in the Leuckart reaction of acetophenone using formamide as the amine source.

Short background as to why the present study was undertaken. One great advantage of the Leuckart procedure is that the reagents (formamide and formic acid) are cheap. However, the classical Leuckart procedure also has several practical disadvantages. In the original procedure by Leuckart–Wallach, the carbonyl compound was heated with solid ammonium formate without any solvent present in sealed vessels. The reaction liberates one equivalent of carbon dioxide which leads to the build-up of a high internal pressure in the sealed vessels. The procedure developed by Ingersoll[3] used open vessels in which ammonium formate and the carbonyl compound are heated with continuous water separation. By this procedure, however, ammonium carbonate sublimes from the reaction mixture and often clogs the condenser. One possibility to overcome these difficulties would be to conduct the reaction in homogeneous acidic solution so that ammonium carbonate cannot escape from the reaction mixture. It has been reported that a 3 : 1 mixture of formic acid–triethylamine yields a stable (it can even be distilled without decomposition) molecular complex of low viscosity and with interesting solvent properties.[9] Since the mixture can dissolve acetophenone we considered this mixture to be a potentially useful solvent system for the Leuckart reaction.

Results and discussion

To explore the experimental procedure with the formic acid–triethylamine solvent system, a screening experiment

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was planned with the goal of identifying which experimental variables have a significant influence on the yield. The variables are specified in the Experimental section. A two-level fractional factorial design, 2^{5-1} was used.[10] It was assumed that a second-order interaction response surface model would be adequate to describe the variation in yield of α-methylbenzylformamide, y, as a function of the experimental variables, i.e., eqn. (1) where x_i is the

$$y = b_0 + \sum b_i x_1 + \sum \sum b_{ij} x_i x_j$$

setting of variable i.

A cumulative normal distribution plot[10] of the estimated model parameters is shown in Fig. 1. The yield of α-methylbenzylformamide was determined by GLC using the internal standard technique.

The results summarized in Fig. 1 show that the important variables are 1 (the amount of formamide should be at least at its upper level) and 4 [the reaction temperature should be high and possibly further increased from its ($+$)-level]. The other variables have a negligible influence on the yield as long as an excess of formamide is used.

However, when the experimental conditions were adjusted so that 1 and 4 were increased while maintaining the remaining variables at their low levels, poor isolated yields in the range 40–50% were obtained. This was not considered an improvement compared with the original procedure and the formic acid–triethylamine solvent system was not further explored. It might well be that using formic acid–triethylamine as solvent was an unnecessary and useless complication of the experimental procedure.

It is known that the Leuckart reaction can be conducted by heating the carbonyl compound with formamide alone or with a mixture of formamide and formic acid, although highly varying yields have been reported.[4] The next step was therefore to make the maximum simplification of the experimental procedure and to run the reaction with formamide alone for which moderate yields in the range 50–60% have been reported.[11] The result of the screening experiment indicated that a fairly large amount of formamide (6 equiv.) and high temperature (150°C or higher) should be used. Initial experiments

carried out under these conditions afforded 75–80% yield. In these experiments, commercial formamide was used as delivered. The result was encouraging and a careful response surface study was undertaken more precisely to locate the optimum conditions. For this, formamide and acetophenone were dried over molecular sieves and freshly distilled. The yields thus obtained were poor (the best yield was 57%) and highly variable. For instance, replicated runs showed reproducibilities of ±25% with respect to the observed yield. The temperature control in these experiments was achieved by means of a sand bath and the poor repeatability of the results was attributed to difficulties in maintaining a constant reaction temperature. However, a second response surface study using a silicon oil bath afforded equally poor results. Attempts to improve the result by adding Lewis acid catalysts[12] were not beneficial.

An interesting and crucial observation in these response surface experiments was that the yield of the reaction was highly dependent on the efficiency of the reflux condenser used. With double-mantled condensers the yield was related to the flow rate of water through the condenser. Since the reactions were conducted at high temperature ($>150°C$) it was concluded that one possible explanation was that water is distilled from the reaction mixture and with less efficient condensers the water escapes from the reaction mixture. If the presence of water is essential, one remedy would be to add a small amount of water to the reaction mixture and to use an efficient reflux condenser. An early observation which supports this conclusion was that the yield of α-methylbenzylamine obtained by heating acetophenone with formamide was decreased from 30% to 17% after addition of anhydrous calcium sulfate to the reaction mixture.[13]

A response surface model was established with a view to determining the optimum amount of formamide and the optimum reaction temperature (oil bath) when the reaction was run after addition of water to the reaction mixture. In this study the yields of α-methylbenzylamine was determined by GLC (internal standard technique) after acid hydrolysis the formamide product and aqueous work-up. A projection of the response surface is shown in Fig. 2.
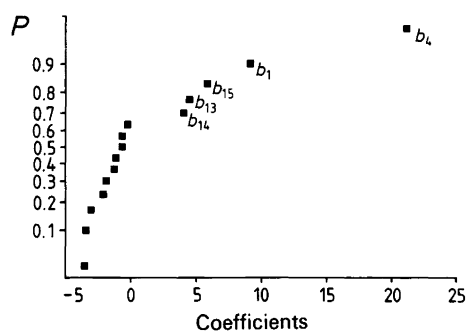

Fig. 1. Cumulative normal probability distribution of estimated model parameters in the screening experiment.
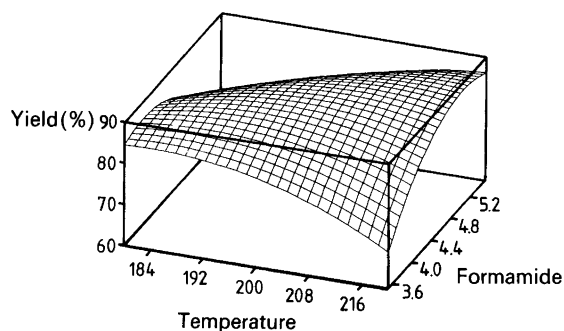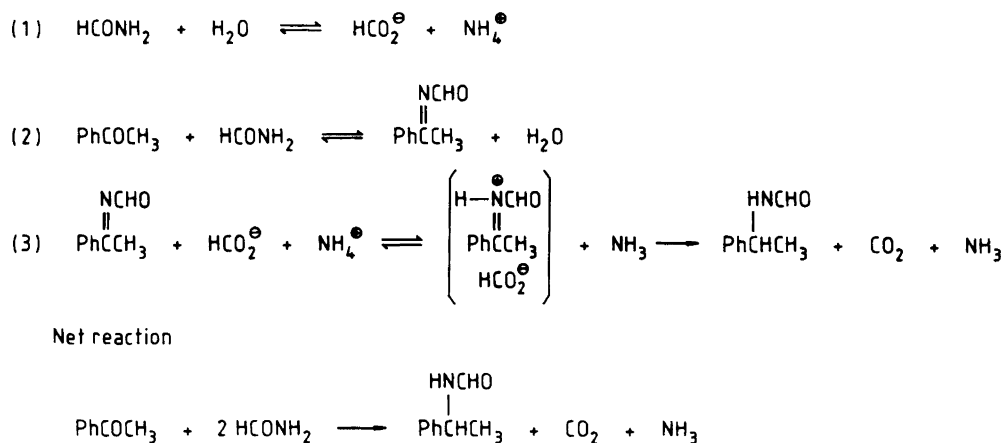

Fig. 2. Projection of the response surface model showing the variation in the yield of α-methylbenzylamine as a function of the amount of formamide/ketone (mol/mol) and the reaction temperature (°C).

$$(1) \quad HCONH_2 + H_2O \ \rightleftharpoons \ HCO_2^{\ominus} + NH_4^{\oplus}$$

$$(2) \quad PhCOCH_3 + HCONH_2 \ \rightleftharpoons \ \underset{\overset{\parallel}{NCHO}}{PhCCH_3} + H_2O$$

$$(3) \quad \underset{\overset{\parallel}{NCHO}}{PhCCH_3} + HCO_2^{\ominus} + NH_4^{\oplus} \ \rightleftharpoons \ \left(\begin{array}{c} H-\overset{\oplus}{N}CHO \\ \overset{\parallel}{PhCCH_3} \\ HCO_2^{\ominus} \end{array} \right) + NH_3 \longrightarrow \underset{\overset{|}{HNCHO}}{PhCHCH_3} + CO_2 + NH_3$$

Net reaction

$$PhCOCH_3 + 2\,HCONH_2 \longrightarrow \underset{\overset{|}{HNCHO}}{PhCHCH_3} + CO_2 + NH_3$$

Scheme 1.

The response surface model indicates that a maximum yield of 89% should be obtained using 4.5 equiv. of formamide and an oil bath temperature of 205°C. Monitoring the reaction over time showed that the maximum yield was attained after 6 h. Replicated small-scale (4 mmol) runs under these conditions afforded 85–87% yield (GLC) of α-methylbenzylamine after aqueous work-up and this confirmed the conclusions from the response surface study. A preparative-scale run under these conditions using 5 g of actophenone afforded an 80% yield of distilled analytically pure product.

These results show that the presence of water in the reaction mixture is necessary for bringing the reaction under control so that reproducible results can be obtained. The simplest mechanistic explanation is that water is a catalyst when the reaction is carried out with formamide, see Scheme 1. In a first step, water is consumed in a hydrolysis reaction of formamide to yield ammonium formate. In a second step, acetophenone is condensed with formamide to yield the corresponding formylimine after elimination of water. The reduction step is a hydride transfer from the formate ion to the formylimide. In the net reaction water does not appear since it is consumed and regenerated during the course of the reaction.

Experimental

Screening experiment with the formic acid–triethylamine solvent system. The following variables were studied and their ranges of variation are given within brackets [(−)-level, (+)-level]: *1*, the amount of formamide/ketone (mol/mol) [1.0, 6.0]; *2*, the amount of formic acid–triethylamine complex/ketone (mol/mol) [1.3, 4.0]; *3*, amount of formic acid/ketone added during the reaction (mol/mol) [1.00, 5.0]; *4*, the reaction temperature (°C) [120, 150]; *5*, method of introducing the amount of formic acid specified by *3* [dropwise during the course of the reaction, present from the beginning]. The experiments were run with 1.20 g (10.mmol) of acetophenone in 100 ml magnetically stirred Erlennmeyer flasks mounted with reflux condensers. Acetophenone was mixed with the calculated amounts of formamide (variable *1*) and the formic acid–triethylamine complex (variable *2*). The calculated amount of formic acid (variable *3*) was either added in one portion or dropwise over the course of the reaction (variable *5*) and the mixture was heated at the given temperature (variable *4*) for 24 h. After being cooled, the mixture was made slightly acidic with 6 M hydrochloric acid and rapidly extracted with three 30 ml portions of dichloromethane. An accurately weighed amount of anthracene (internal standard) was added to the combined dichloromethane extracts and the amount of α-methylbenzylformamide was determined by GLC using a packed column (1.5 m, 4 mm i.d.) of 5% QF-1 on Chomosorb W at 120°C.

Response surface study of the reaction with formamide in the presence of water. Each reaction was run with 0.5 g (4.17 mmol) of acetophenone in a 25 ml magnetically stirred round-bottomed flask immersed in an oil-bath and equipped with an efficient reflux condenser. A Doehlert uniform shell design[14] was used to vary the amount of formamide over the range of variation 3.5–5.5 equivs. and the oil-bath temperature over the range 180–250°C. After mixing the acetophenone and the calculated amount of formamide, 0.20 ml of distilled water was added to the flask and the resulting mixture was heated at the specified temperature for 6 h. After cooling to ca. 100°C, 10 ml of 6 M hydrochloric acid were added to the flask and the contents were refluxed for 1 h to hydrolyze the formamide product. After being cooled the mixture was extracted with 15 ml of diethyl ether to remove unchanged acetophenone. The ether extract was discarded. The aqueous layer was made alkaline by the addition of 20 ml 5 M sodium hydroxide and extracted with three 10 ml portions of diethyl ether. To the combined ether extracts was added an accurately weighed amount (ca. 0.2 g) of phenylcyclohexane (internal standard) and the yield of α-methylbenzylamine was determined by GLC. A 30 m, 0.54 mm i.d. fused silica SPB-5 column from Supelco was used. Integrated peak areas were used for quantification.

Optimum preparative-scale synthesis of α-methylbenzyl-amine. A round-bottomed flask* equipped with an efficient reflux condenser was charged with a mixture of acetophenone, 5.00 g (41.7 mmol), formamide, 5.81 g (0.188 mol), and 2.0 ml of water. The mixture was heated with magnetic stirring for 6 h at an oil-bath temperature of 205°C. Hydrolysis with 100 ml 6 M hydrochloric acid for 1 h and aqueous work-up analogous to that described above afforded 4.3 g (86%) of crude α-methyl-benzylamine. A purity of >98 % of the crude product was indicated by ^{1}H NMR spectroscopy and GLC but the product was slightly yellowish. Kugelrohr distillation, b.p. 187°C (oven temperature), afforded 4.00 g (80%) of analytically pure α-methylbenzylamine.

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* Actually, a 500 ml flask was used. The size of the flask is not important.