

Short Communication

Effect of Formamide in the Leuckart Reaction

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Reductive amination of carbonyl compounds with ammonium salts of formic acid or with formamide, known as the Leuckart reaction, was first reported in 1885.¹ Modifications to the original reaction were first published by Wallach and co-workers,² but it was work by the group of Ingersoll³ that led to reaction conditions that could serve for preparative purposes. A useful method for the methylation of amines using formaldehyde as the reactant containing the carbonyl functionality is the Eschweiler–Clarke procedure.⁴ The reaction and the modifications have been discussed in review articles⁵ and there are also articles discussing the mechanism.⁶

Recent work dealing with the Leuckart reaction was published by Carlson *et al.*,⁷ who showed that the addition of water to the mixture of ketone and formamide led to higher yields and better reproducibility, and by Bianchini and co-workers⁸ who have used spectroscopic methods to prove a radical mechanism for the reduction of the initially formed (form)imide to (form)amide.

In a project carried out in our laboratory involving the use of different amines, it was decided to use the new optimised reaction conditions for the synthesis of starting materials. Surprisingly it was found that yields were lower than expected and were highly variable, and apparently independent of the carbonyl compound. The only variable that could be identified as differing from the optimised procedure was the brand of formamide, and it was therefore decided to look once more into what controls the course of the reaction. Acetophenone was chosen as the carbonyl compound in order to compare the results with the earlier study. As a simplification, it

was decided to analyse the yield of *N*-(1-phenylethyl)formamide (Scheme 1) by GLC instead of analysing the hydrolysed amine.

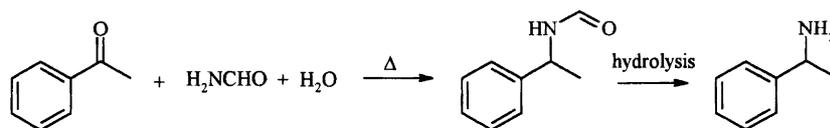
Results and discussion

Five different brands of formamide were chosen for the study. Based on earlier experience it was decided to use a larger excess of the formamide, all other variables being as in the optimised procedure. As can be seen from Table 1, the yields vary considerably between experiments, but in none of them is the yield comparable to those obtained earlier. Experiments using different acetophenones were undertaken but yields were still only affected by what brand of formamide was used.

A screening procedure⁹ with the settings of the experimental variables at two levels was then employed with the range of variation given within brackets: amount of water [no water/water added], and reaction temperature [165 °C/205 °C]. The results are summarised in Table 2.

Table 1. Yield of *N*-(1-phenylethyl)formamide using previously reported optimum conditions with water added [acetophenone/water (w/w), 2.5].⁷

	<i>T</i> /°C	Yield (%)
Aldrich	205	75.5
Baker	205	76.4
Fischer	205	68.3
Fluka	205	73.3
Merck	205	60.0



Scheme 1.

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Table 2. Yield of *N*-(1-phenylethyl)formamide as a function of temperature and added water.

	<i>T</i> /°C	Water	Yield (%)	Water ^a	Yield (%)
Aldrich	165	No	58.3	Yes	70.1
Baker	165	No	16.0	Yes	69.8
Fischer	165	No	57.0	Yes	72.2
Fluka	165	No	40.8	Yes	65.0
Merck	165	No	62.0	Yes	62.8
Aldrich	205	No	10.5	Yes	75.5
Baker	205	No	15.3	Yes	76.4
Fischer	205	No	6.9	Yes	68.3
Fluka	205	No	33.9	Yes	73.3
Merck	205	No	18.7	Yes	60.0

^aAcetophenone/water (w/w), 2.5.

From this table a few points are notable: i, in the absence of water (all other factors being similar), yields vary depending on formamide used; ii, in the absence of water, yields are inversely proportional to temperature; iii, the second effect disappears when the reaction is run in the presence of water.

Although yields were less variable when water was added to the reaction mixture and a lower temperature was used, yields were still not as high as after the earlier optimisation. A new series of experiments was performed where the temperature was kept at the lower level and the amount of water added was varied. The results are shown in Table 3.

As is clearly seen from the table, yields vary with the brand of formamide used if the other variables are kept the same. Yields in excess of 90% can be obtained with all brands of formamide, except the one obtained from Baker.

Table 3. Yield of *N*-(1-phenylethyl)formamide as a function of amount of added water.

	<i>T</i> /°C	Water/ml	Yield (%)
Aldrich	165	0.3 ^a	70.1
	165	0.5 ^b	94.2
	165	0.7 ^c	95.5
Baker	165	0.3	69.8
	165	0.5	83.2
	165	0.7	85.4
Fischer	165	0.3	72.2
	165	0.5	84.4
	165	0.7	95.9
Fluka	165	0.3	65.0
	165	0.5	99.4
	165	0.7	88.4
Merck	165	0.3	62.8
	165	0.5	91.1
	165	0.7	79.0

^aAcetophenone/water (w/w), 2.5. ^bAcetophenone/water (w/w), 1.5. ^cAcetophenone/water (w/w), 1.07.

Experimental

Analytical scale. Acetophenone (0.75 g) and formamide (3.75 g) were magnetically stirred in a 50 ml round-bottomed flask fitted with a reflux condenser. When the reactions were run without the addition of water, a guard tube containing calcium chloride was placed in the top of the condenser. The flask was immersed in an oil-bath and heated to the desired temperature. Heating overnight was followed by addition of 10 ml of water and extraction of the aqueous phase with 3 × 10 ml of diethyl ether. The combined ethereal phases were dried over magnesium sulfate and a 3 ml sample of the solution was then added to approximately 45 mg of phenylcyclohexane internal standard and the mixture was analysed by GLC.

Preparative scale. Acetophenone (Fluka) (4.5 g), formamide (Aldrich) (20 ml) and water (3.6 ml) were stirred in a 100 ml round-bottom flask fitted with a reflux condenser. The flask was immersed in an oil-bath and maintained at 165 °C overnight. The reaction mixture was cooled, after which 30 ml of water were added and the solution was extracted with 50 ml diethyl ether. The aqueous layer was neutralised by addition of solid sodium carbonate and further extracted with two 50 ml portions of diethyl ether. The combined ethereal solutions were washed with saturated sodium bicarbonate and brine and dried over MgSO₄. Solvent removal afforded 4.7 g (84.1%) of an orange oil. Further extraction with 50 ml ethyl acetate gave (after drying and solvent removal) an additional 0.7 g, giving a total of 5.4 g (96.5%). Bulb-to-bulb distillation left 5.12 g of a colourless material (containing traces of formamide) that partially solidified upon standing.

Starting material. The acetophenone used was either from Aldrich (99%) or Fluka (*p.a.*). Formamides used: Aldrich (97%), Baker (*p.a.*), Fisher (>99%), Fluka (*purum*) or Merck (*p.a.*). Phenylcyclohexane was from Aldrich (96%).

Instrumentation. The gas chromatograph used was a Varian 3400 fitted with a 15 m, 0.32 i.d. SPB-5 column supplied by Supelco.

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