SYNTHESIS OF 4-PHENYLPYRIMIDINE FROM ACETOPHENONE AND FORMAMIDE

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Abstract - Employing cuprous chloride as a catalyst in the Leuckart reaction between formamide and acetophenone leads to the formation of 4-phenylpyrimidine in satisfactory yield.

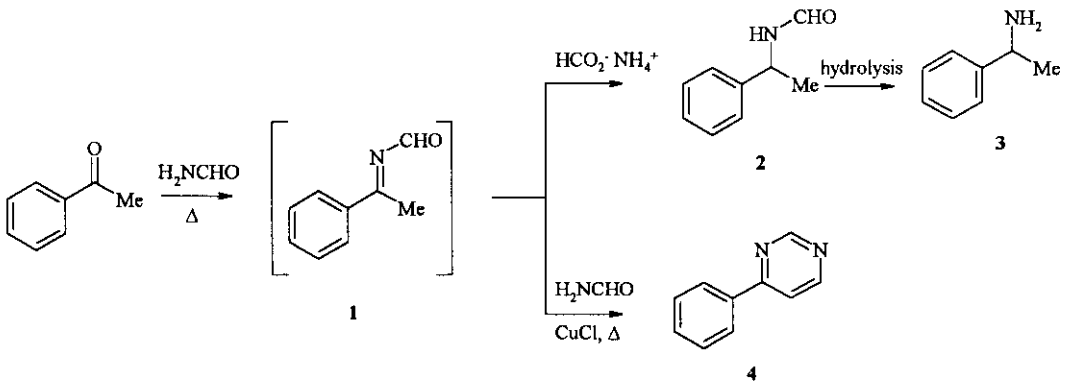
INTRODUCTION

In the Leuckart reaction between acetophenone and formamide, α-methylbenzylamine (**3**) is formed after hydrolysis (Scheme 1), and an optimised procedure for this reductive amination has recently been published.[1] In this reaction variable amounts of a by-product (later identified as 4-phenylpyrimidine (**4**)) was observed by GLC.

Pyrimidines include some of the most important biologically active compounds, and several examples of the use of 4-phenylpyrimidine, and its analogues, are found in the literature. It was reported as early as 1963 that this compound might have cytotoxic qualities, but it has also been used in other chemical research of medical relevance.[2-4]

Published methods for synthesis of pyrimidines are mainly based on the use of ß-dicarbonyl compounds,[5] halogenated compounds[6] or tris(formylamino)methanes.[7] In 1904 it was reported that the condensation of acetophenone with formamide in the presence of zinc chloride gives 4-phenylpyrimidine, but no yield was reported, and later work by Bredereck *et al.*,[7] using the described procedure, only resulted in a 1-2% yield.

The interesting properties of 4-phenylpyrimidine, and the fact that there are no simple synthetic procedures using commercial, low-cost reactants, lead us to further studies of the reaction. In this note we wish to report the results obtained in our attempts to optimise the experimental conditions with respect to yield in the synthesis of 4-phenylpyrimidine from acetophenone and formamide.



Scheme 1

Reaction pathways for the formation of 4-phenylpyrimidine and α-methylbenzylamine.

RESULTS AND DISCUSSION

A mechanism for the Leuckart reaction is proposed in the literature, claiming that the initially formed formyl imide (**1**) is reduced by a formate ion, which arises from water and formamide.[1] The assumption is supported in a recent paper.[9] Since reaction between isolated formyl amide (**2**) and formamide did not produce any 4-phenylpyrimidine, it was concluded that the amide is not an intermediate in the formation of 4-phenylpyrimidine and that the product is formed probably by a reaction between formamide and formyl imide (**1**). The mechanism may be a concerted [4+2] cycloaddition (Diels-Alder reaction) or a 1,4-addition, but mechanistic studies are outside the scope of this paper.

In accordance with the proposed mechanism,[1] the Leuckart reaction depends on the presence of water and the effect of using freshly distilled solvent combined with addition of drying agent or molecular sieves to the reaction mixture was therefore examined. The product was still mainly the reduction product (**2**), indicating that none of the methods removed the water produced quickly enough.

In the paper by Bianchini *et al.*[9] it was concluded that the reduction of Schiff bases by formic acid occurs *via* a free radical mechanism. By adding isoamyl nitrite they were able to inhibit product formation by interruption of the chain process by free-radical capturing. Adding isoamyl nitrite to the reaction mixture still gave the reduction product, indicating that the reaction mechanism is not identical when formate ion is the actual reducing agent. The next attempt was to oxidise the formate ion produced, thus preventing the reduction caused by the hydride transfer. Several oxidation agents, with varying strength and qualities, were tested; CuCl, $CuCl_2$, ZnO, $ZnZl_2$, $KMnO_4$, $K_2Cr_2O_7$, Fe_2O_3, $NaBO_3$

and Na_2O_2. Both amount of formamide and reaction temperature were varied in these experiments, and it was found that CuCl gave the most promising results, and it was decided to perform a screening experiment in order to find which factors influence the reaction.

Based on the results above variables and convenient levels for a 2-level factorial design[10] were chosen. These are given in the experimental section. The result of the screening experiment is summarised in the equation:

$$y = 30.00 + 4.16x_1 - 11.69x_2 - 0.76x_3$$

The coefficients indicate that variable 1, amount of CuCl, and variable 2, the reaction temperature, are most important. The amount of CuCl should be high and the temperature low. Variable 3, amount of formamide, has only a minor effect on the yield and a low level was therefore used in the following experiments.

Complementary experiments were then performed to complete a Central Composite Design to determine the optimum reaction conditions. The projected response surface is shown in Figure 1.

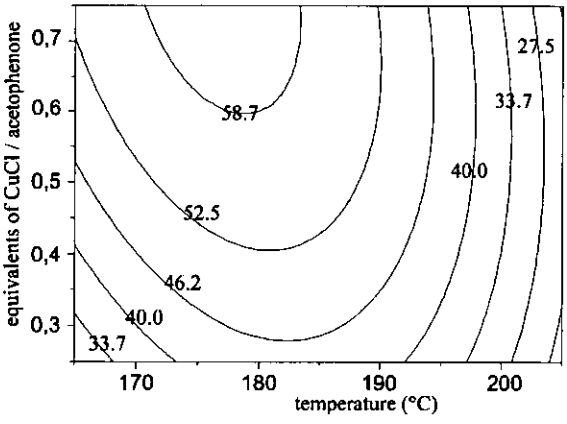


Figure 1

Yield of 4-phenylpyrimidine as a function of reaction temperature and amount of catalyst (equivalents of CuCl / acetophenone)

A simplex optimisation[10,11] gave the optimum reaction conditions,[12] predicting a yield of 61% when using 0.7 equivalents of catalyst and a reaction temperature of 179 °C. The validity of the model was tested by three experiments at the theoretical optimum leading to 50 - 59% yield by GLC and 46 - 48% isolated yield.

EXPERIMENTAL

Screening and response surface modelling

The following variables were studied in a two-level factorial design. Their ranges of variation are given within brackets [(-)-level, (+)-level]; *1*, the amount of CuCl/ketone (mol/mol) [0.25 , 0.75]; *2*, the reaction temperature (°C) [165 , 205]; *3*, the amount of formamide/ketone (mol/mol) [13 , 27]. The results from the two-level factorial design (showing that only temperature and amount of catalyst were of importance within the experimental domain) were complemented by further experiments at the four axial points and at the centerpoint. The experimental error of the resulting Central Composite Design was tested by two additional experiments at the centerpoint, and the validity of the model was then verified by performing experiments under the predicted optimum conditions.

Experimental conditions

Acetophenone (0.75 g, 6.2 mmol), CuCl[13] and formamide[13] were reacted for about 17 h (overnight) in a round-bottomed, 25 mL, flask, immersed in an oil-bath, and fitted with a reflux condenser and a calcium chloride drying tube. The product mixture was hydrolysed with concentrated HCl (20 mL) in an oil-bath kept at 120° C for about 2 h. The mixture was then extracted with ether (50 mL) and the organic phase was discarded. NaOH pellets were added to the aqueous phase to pH=10, and the aqueous phase was then extracted with ether (2x50 mL). The combined organic phases were then concentrated to 30 mL. Internal standard (cyclohexylbenzene) was added and the amount of 4-phenylpyrimidine was determined by GLC using a 30 m fused silica SPB-5 column from Supelco with 0.32 id.

Optimised procedure for synthesis of 4-phenylpyrimidine.

Acetophenone (0.75 g, 6.2 mmol) was treated with CuCl catalyst (0.4 g, 4.0 mmol) and formamide (3.75 g, 83.2 mmol) for about 17 h at 179 °C.[14] The work-up was performed as above. The product mixture was purified by flash chromatography with ether as eluent. The product was in all respects identical to commercial material.

ACKNOWLEDGEMENTS

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12. Analysis of optimum conditions by canonical analysis led to approximately the same result.
13. Cuprous chloride and formamide were used at both high and low level.
14. Monitoring the reaction by GLC showed that all starting material was consumed within 6 hours and there was no indication that the product decomposed over time. It was also observed that **2** is formed parallel to **4**, which probably explains why the yield does not exceed 60%.

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