



Efficient Curtius Rearrangement Using X-Cube Flash™ Continuous Flow Reactor

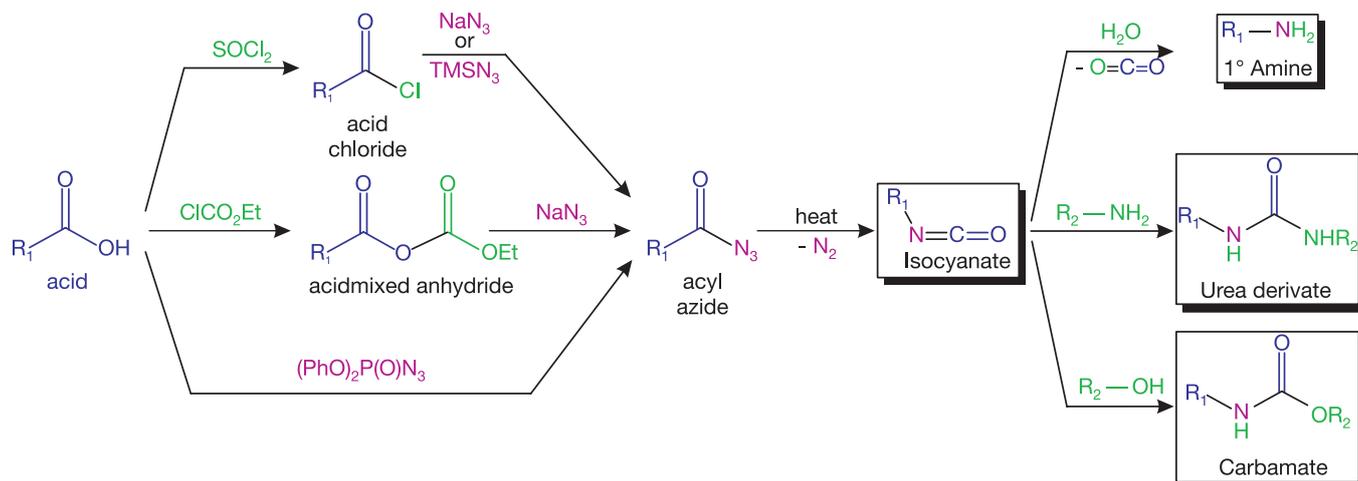


INTRODUCTION

The Curtius rearrangement is the thermal decomposition of carboxylic azides to produce an isocyanate. These intermediates may be isolated or the resulting isocyanate can be trapped by a variety of nucleophiles, including water, which hydrolyze the isocyanate to an amine; amines result in ureas or alcohols leading to carbamates. Traditionally acyl azides are prepared from acid chlorides or mixed anhydrides, however carboxylic acids can be directly converted to acyl azides using diphenylphosphoryl azide. The thermal rearrangement is considered a concerted process and there is no evidence for the formation of a nitrene intermediate.

High temperature readily accelerates the reaction and even if the activation volume is slightly positive (nitrogen is evolved) pressure is also beneficial.

ThalesNano has developed a high pressure/high temperature continuous flow reactor, called X-Cube Flash™, to allow chemists to reach chemistry reaction extremities easier and safer compared to batch. In this application note we will focus on the study of the Curtius reaction (Scheme 1.) from an acyl azide as well as from acids through *in situ* formation of the acyl azide using the X-Cube Flash™ reactor. The detailed reactions involved an initial optimization process in terms of the applied temperature and the appropriate solvent to avoid precipitation of intermediates. For Curtius rearrangement reactions, optimum parameters using the 16 mL loop in the X-Cube Flash™ reactor were a temperature of 150 °C, a pressure of 100 bar and a flow rate of 4 mL/min resulting in the final product after 4 mins residence time.

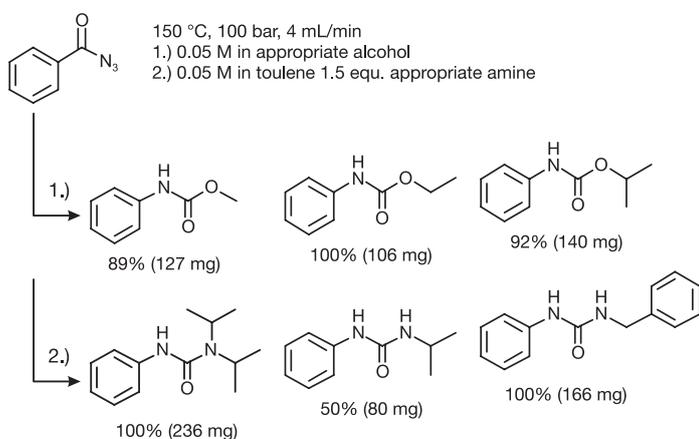


GENERAL PROCEDURE

Solvent was passed through the X-Cube Flash™ reactor while it reached the optimum parameters (4 mL/min, 100 bar, 150 °C), then it was changed to the solution of starting material(s). Products were collected after ca. 6 mins according to the dead volume of the system, then the solvent was evaporated (for the carboxylic acid starting material column chromatography was also needed for purification) and the yield was determined. Purity was confirmed by ¹H-NMR and in all cases it was nearly 90%.

RESULTS OF CURTIUS REARRANGEMENT REACTIONS FROM BENZOYL AZIDE

Benzoyl azide was dissolved in the appropriate solvent and was passed through the instrument to form carbamate derivatives. In order to form ureas benzoyl azide was dissolved in toluene in the presence of 1.5 equ. of the appropriate amine. In each case the product was then evaporated and the yield determined. Products and corresponding yields can be seen in Scheme 2. showing an average yield of 94% and 83% for the carbamate and urea derivatives, respectively.

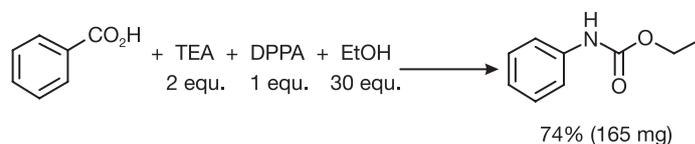


Scheme 2.: Synthesis of carbamides and ureas from benzoyl azide

RESULTS OF CURTIUS REARRANGEMENT REACTIONS FROM BENZOIC ACID

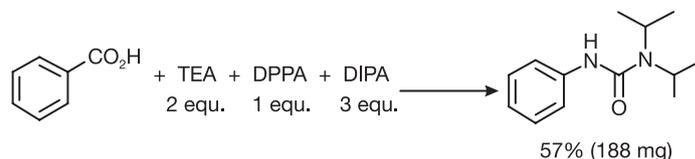
In the synthesis of ethyl phenylcarbamate from benzoic acid (Scheme 3.), a high excess of ethanol was needed to avoid the formation of sideproducts in the presence of 1 equ. diphenylphosphoryl azide to form the azide

intermediate and 2 equ. triethylamine. Product was collected and purified by column chromatography resulting in the desired product in 74% yield.



Scheme 3.: Synthesis of carbamate from benzoic acid in one-step

In the synthesis of *N,N*-diisopropyl-*N'*-phenylurea (Scheme 4.), the solvent system has to be changed to acetonitrile:toluene (2:1) because precipitation occurred during the reaction using only toluene, which blocked the reaction line. Furthermore, only just 3 equ. diisopropanolamine was needed to produce the corresponding urea in 57% after column chromatography.



Scheme 4.: Synthesis of urea from benzoic acid in one-step

CONCLUSION

Various carbamates and ureas were prepared from an acyl azide and directly from an acid using the thermal Curtius rearrangement reaction in a flow reactor under homogenous conditions. High temperature and pressure radically shortened the effective reaction time. When the rearrangement reaction was carried out with previously formed acyl azides, the reaction was clean and in most cases simple evaporation resulted in the products in > 90 % yield and in satisfactory purity. In the reactions where carboxylic acids were converted, *in situ*, to the acyl azide chromatography purification was required to isolate the carbamates and ureas in >60-70% yield. This one step procedure can be considered as a highly efficient and safe procedure which is suitable for scale-up.

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