THALESNano

Thermal Cyclisation Leading to Important Heterocyclic Carbonyl Intermediates Using X-Cube Flash™ Reactor

INTRODUCTION

Heterocyclic carbonyl compounds e.g. quinolones, pyridopyrimidinones, naphthyridinones are important structural motifs in various biological active compounds (e.g. norfloxacin, nalidixic acid). One of the most practical approaches for their synthesis is the thermal cyclisation of the appropriate open chain intermediates containing a suitably substituted 3 carbon extension on the nitrogen. Such intermediates derive either from a condensation product of formaldehyde acetal and a CH-acidic methylene containing precursor (e.g. malonic ester, Meldrum's acid, or cyano-acetic acid ester by Gould-Jacobs type of reaction, Table 1 Entry 1-3)[1-9] or from a direct condensation with acetyl acetic acid esters by Conrad-Limpach reaction (Table 1 Entry 4)[10-11]. The cyclisation normally requires high temperature (> 350 °C) and short exposure time to avoid side-reactions.

In practice, high boiling point solvents are used (e.g. diphenyl ether) or the reaction is carried out using neat (solvent free) conditions. In both cases the work-up can be difficult due to uncontrolled precipitation of either the high boiling solvent or the product. Although MW heating is a method of choice it is not suitable for scale-up and a high temperature/pressure procedure in continuous flow is a viable alternative. In the present study we investigated using an alternative low boiling point solvent at high temperature/pressure with high flow rate to avoid side-reactions or decompositions.

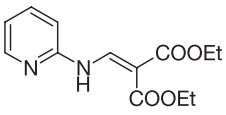
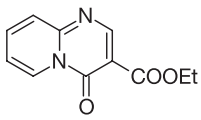
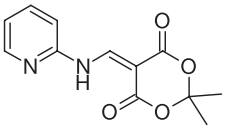
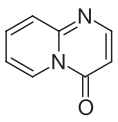
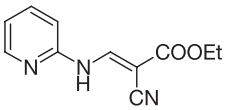
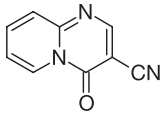
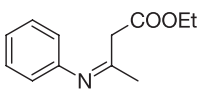
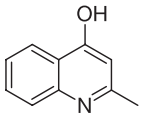
Entry	Starting material	Product	Conversion / %	Isolated yield / %	NMR purity / %
1			100	70	90
2			100	89	98
3			100	75	98
4			100	92	98

Table 1: Reaction data and results of cyclisation reactions
T = 350 °C, p = 100 bar, Loop = 4 mL, Flow rate = 3 mL/min, c = 0.1 M, Solvent: THF

EXPERIMENTAL PROCEDURE

X-Cube Flash™ reactor was preheated to 350 °C while pumping THF through the reactor at 3 mL/min flow rate and 100 bar pressure. After stabilization of the system, a 0.1 M THF solution of the starting materials was pumped through the 4 mL loop. At the end of the reaction the resulting solution was evaporated and after the solid residue was washed with diethyl-ether. The filtrate was then concentrated under reduced pressure to recover the appropriate product as pure crystals. The pure product was identified using ^{1}H-NMR.

RESULTS AND CONCLUSION

We successfully carried out high temperature related thermal ringclosing reactions (Gould-Jacobs and Conrad-Limpach) to pyridopyrimidinones and quinolones (or their hydroxy tautomers) in excellent conversion and good to high yield in a continuous flow system with a very short residence time (1.33 min). We successfully replaced the high boiling solvents with a low boiling point solvent (THF). Additional advantages of performing this procedure in flow with a common low boiling point solvent are that it allows easy work-up, supports automation, and is suitable for process development and scale-up.

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