Investigation of the regioselectivity of thermal cyclisation reactions in gas and liquid phase high temperature flow reactors

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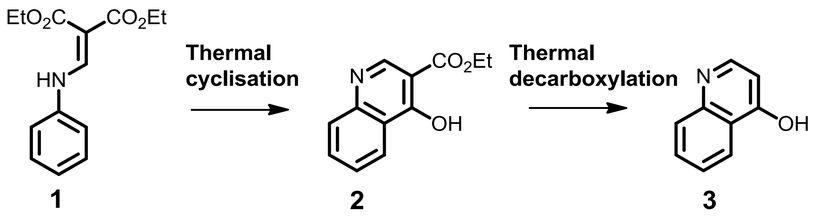
Introduction

Gould-Jacobs type intramolecular thermal cyclisations were previously reported about in a continuous flow reactor at high temperatures (300-360 °C) and pressure (100-160 bar) in liquid phase [1]. The regioselectivity of the ring closure is dependent on the nature and position of the substituents often leading to a mixture of products. We investigated the regiochemical outcome of the cyclisation of substituted amino-pyridine substructures under various conditions in liquid as well as in gas phase, by applying a flow pyrolysis apparatus under high vacuum in solvent-free conditions. Flash vacuum pyrolysis (FVP) allows a rapid exposure to high temperature (200 - 900 °C), which often favours the formation of one regioisomer. Here we compare the outcome of the thermal cyclisation of various unsaturated diesters or analogous substructures (derived from condensation with ethoxymethylenemalonate) performed in both systems.

Thermal cyclisation – the Gould-Jacobs reaction

Alkylidene β-diesters or analogous substructures derived from condensation with Meldrum's acid or electron-withdrawing group containing esters (e.g. malonic ester or cyanoacetic acid esters) readily undergo pericyclic annulation reactions at high temperatures, if they are located in a favourable position relative to aromatic or unsaturated systems (Scheme 1.).

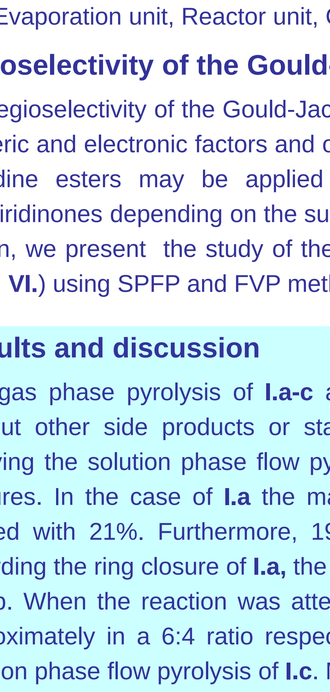


Scheme 1.: The Gould-Jacobs reaction

Typical procedures

The thermal cyclisation of the above-mentioned types is normally carried out in high boiling point solvents (e.g. diphenyl ether). In several cases, the long exposure to high temperature induces side-reactions. The work-up can therefore be difficult. In high temperature/pressure continuous flow systems, such as the Phoenix Flow Reactor (Scheme 2.), low boiling point solvents can be used with high flow rates to avoid side reactions or decomposition. The use of microwave or gas phase techniques can be beneficial as well.

Solution phase flow pyrolisis (SPFP) in the Phoenix Flow Reactor



Scheme 2.: Phoenix Flow Reactor

The Phoenix Flow Reactor system is a high temperature, high pressure flow reactor module. The system works by pumping a continuous-flow of reaction mixture into an exchangeable reaction coil or cartridge at **flow rates of up to 10 mL/min**. The reaction coil or cartridge could be **heated and pressurised up to 450°C and 100 bar** respectively. The reaction mixture is then cooled before eluting into a collection vessel. **Reaction coils are available in various sizes, between 1 mL and 32 mL**. The different size coils may be exchanged to vary the residence time or the throughput of the compound through the reactor.

Flash vacuum pyrolysis (FVP)

Pyrolysis is a thermochemical treatment of organic materials at elevated temperatures in gas phase (~200-900°C). FVP is a technique which involves a vacuum distillation or sublimation of a substrate through an empty or filled hot tube with the products afterwards collected in a cold trap. The major elements of the device are: Evaporation unit, Reactor unit, Condenser unit, Vacuum unit. Typical residence time: ms – s.

Regioselectivity of the Gould-Jacobs reaction

The regioselectivity of the Gould-Jacobs type reactions is another important issue, which is normally governed by steric and electronic factors and often leads to a mixture of products. For example, 2-aminopyridine-derived alkylidine esters may be applied for the synthesis of various pyrido[1,2-*a*]pyrimidon-4-ones and 1,8-naphtiridinones depending on the substituents on the pyridine ring and the other substituents [2].
Herein, we present the study of the ring closure of *N*-(x-methyl-2-pyridyl)aminomethylenemalonate derivates (**I.a-c**, **VI.**) using SPFP and FVP method, as well.

Results and discussion

The gas phase pyrolysis of **I.a-c** at 450°C exclusively led to the formation of pyridopyrimidones (**III.a-c**), without other side products or starting material observed during the course of the reactions. However, applying the solution phase flow pyrolysis method (for the above mentioned substrates) resulted in product mixtures. In the case of **I.a** the main product was **III.a** with 60% conversion, the decarboxylated **V.a** was formed with 21%. Furthermore, 19% of unidentified products also came about. It should be noted that regarding the ring closure of **I.a,** the formation of naphthiridone is not possible due to the position of the methyl group. When the reaction was attempted on substrate **I.b,** two main products: **III.b**. and **V.b** were formed approximately in a 6:4 ratio respectively. Finally, **III.c** and **V.c** developed in a nearly 1:1 ratio during the solution phase flow pyrolysis of **I.c**. Moreover, in the latter case we observed the formation of **II.c** (1%).
Interesting to note that if we carried out the cyclisation reactions of **I.a-c** using higher flow rates (therefore, lower residence time), we observed higher amounts of the decarboxylated compounds (**V.a-c**). Since at the moment we cannot give a logical reason for these results, we would like to extend our studies to understand this phenomenon.

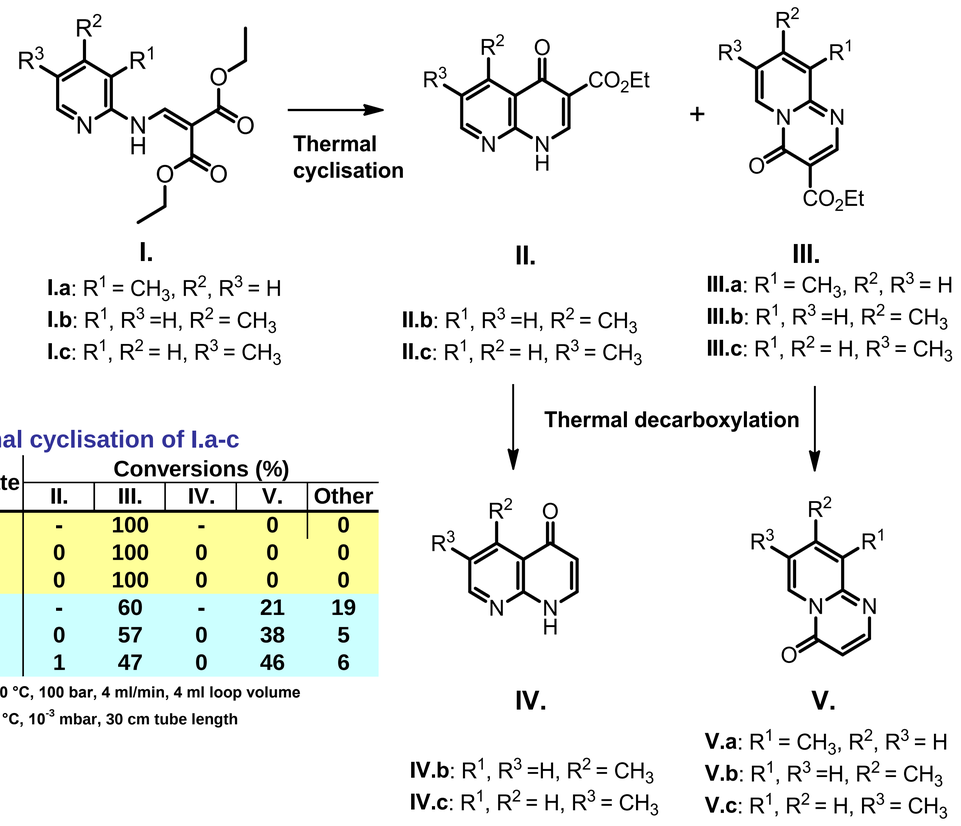


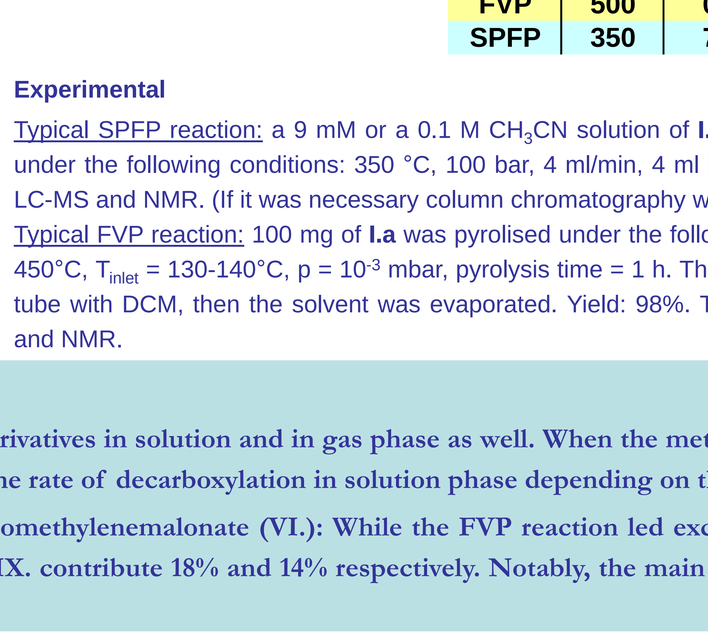
Table 1.: Thermal cyclisation of I.a-c

Method	Substrate	Conversions (%)				
		II.	III.	IV.	V.	Other
FVP	I.a	-	100	-	0	0
FVP	I.b	0	100	0	0	0
FVP	I.c	0	100	0	0	0
SPFP	I.a	-	60	-	21	19
SPFP	I.b	0	57	0	38	5
SPFP	I.c	1	47	0	46	6

Conditions for SPFP: 350 °C, 100 bar, 4 ml/min, 4 ml loop volume
Conditions for FVP: 450 °C, 10^{-3} mbar, 30 cm tube length

Scheme 3.: Pyrolysis of I.a-c

Pyrolysis of *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (VI.)
According to literature data, the thermal ring closure of **VI.** in batch (with microwave or conventional heating) exclusively leads to naphthiridone (**VIII.**) due to the steric hindrance of the methyl group [3]. However, the pyridopyrimidone (**VII.**) can be synthesized in an acid catalysed reaction [4].



Scheme 4.: Pyrolysis of VI.

We found that during the gas phase thermal cyclisation of **VI.** the pyridopyrimidone (**VII.**) was formed as an only product. Unexpectedly, when we carried out the reaction in the X-Cube Flash, compound **X.** was the main product (49%). We also observed the formation of **VIII.** and **IX.**, but we were not able to detect **VII.** in the reaction mixture.

The above-mentioned formation of **X.** means that decarboxylation occurs as the first reaction step. After that, via a ring closure, it may turn into **IX.**. In order to confirm this idea, we pumped through the previously isolated **X.** under the following conditions: 350°C, 100 bar, 4 ml/min, 4 ml loop. The analytical results proved **X.**'s rearrangement into **IX.**

Table 2.: Thermal cyclisation of VI.

Method	T / °C	Conversions (%)					
		VI.	VII.	VIII.	IX.	X.	Other
FVP	250	100	0	0	0	0	0
FVP	350	60	40	0	0	0	0
FVP	400	0	100	0	0	0	0
FVP	500	0	100	0	0	0	0
SPFP	350	7	0	18	14	49	12

Experimental

Typical SPFP reaction: a 9 mM or a 0.1 M CH_3CN solution of **I.a** was pumped through the X-Cube Flash™, under the following conditions: 350 °C, 100 bar, 4 ml/min, 4 ml loop volume. The product was analysed with LC-MS and NMR. (If it was necessary column chromatography was also carried out.)
Typical FVP reaction: 100 mg of **I.a** was pyrolised under the following conditions: 30 cm tube length, $T_{furnace}$ = 450°C, T_{inlet} = 130-140°C, p = 10^{-3} mbar, pyrolysis time = 1 h. The product was washed out from the collection tube with DCM, then the solvent was evaporated. Yield: 98%. The crude product was analysed with LC-MS and NMR.

Summary

We examined the ring closure reaction of all the *N*-(x-methyl-2pyridyl)aminomethylenetemalonate derivatives in solution and in gas phase as well. When the methyl group was in the 3-, 4- or 5-positions, the results of the solution and gas phase methods were roughly the same. The only difference being the rate of decarboxylation in solution phase depending on the applied flow rate.

However, important differences were observed during the cyclisation of *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (VI.): While the FVP reaction led exclusively to the pyridopyrimidone, during the SPFP, a complex product mixture was formed. The expected naphthiridone structures VIII. and IX. contribute 18% and 14% respectively. Notably, the main product, X. made 49%. The latter can be converted to IX. by applying further heating on the substrate.

References: [1] Lengyel L, Nagy T, Sipos G, Dormán G, Jones R, Ürge L, Darvas F, Tetrahedron Letters 53 (2012), pp. 738-743, [2] Morgentin R., Pasquet G., Boutron P., Jung F., Lamorlette M., Maudet M., Plé P., Tetrahedron, 2008, (64), 2722-2782, [3] R. B. Smith, H. Faki, R. Leslie, Synthetic Comm. 2011, 41, 1492-1499., [4] Hermecz I, Horváth Á, Vasvári-Debreczy L, Mészáros Z., Synthesis, 1984, p152-158