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Flash Vacuum Pyrolysis as a Green, Solvent–Free Technology

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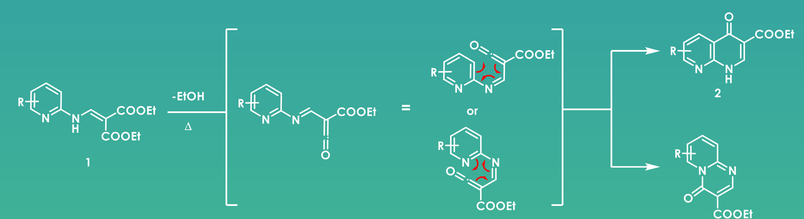
The Gould–Jacobs Reaction

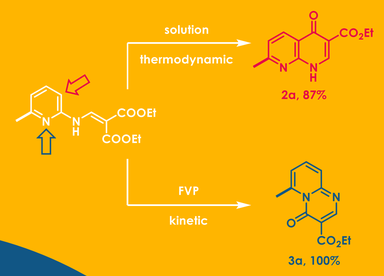
is a well known thermal cyclization for the construction of the 4-quinolone scaffold.[1] An anilinomethylene malonate such as **1** undergoes an electrocyclization via a ketene intermediate and heterocyclic compounds like naphthyridinones **2** or pyridopyrimidinones **3** are generated. The regioselectivity of the cyclization is controlled by steric/electronic factors and therefore highly dependent on the substituent on the pyridine ring.[2,3] The classical thermal cyclization reaction typically requires temperatures >200 °C. Thus, **high boiling solvents** such as **diphenylether** are used, which complicates work-up and product isolation. As a consequence, scientists are always on the search for new techniques for this powerful transformation.

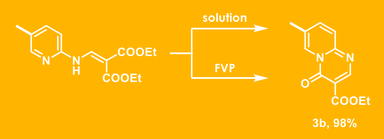


[1] R. G. Gould, W. A. Jacobs, *J. Am. Chem. Soc.* **1939**, *61*, 2890–2895
[2] G. R. Lappin, *J. Am. Chem. Soc.* **1948**, *70*, 3348–3350
[3] Z. Mészáros, I. Hermecz, *Tetrahedron Lett.* **1975**, *12*, 1019–1020

Regioselectivity

Pyridopyrimidinones **3** as kinetic products are favored in FVP because of the extremely short contact time of ~ 0.3 s. In solution phase, the cyclization of the 6-methyl substitued pyridine derivative proceeds with a major preference for the naphthyridinone **2a** due to its steric hindrance and the longer reaction times at temperatures ≥260 °C.

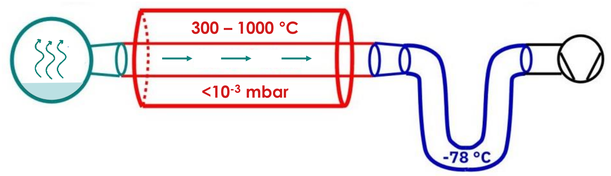


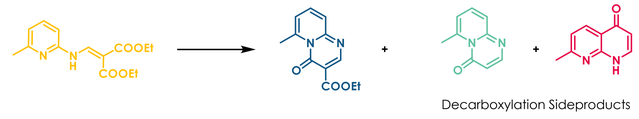


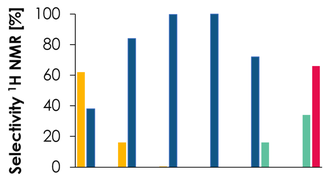
Conditions in solution: 0.12 M in Ph_2O, refluxing for 30 min
Conditions in FVP: 100 mg, 450 °C, 10^{-3} mbar

Flash Vacuum Pyrolysis

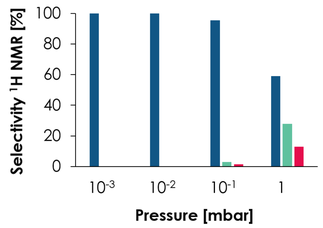
is a **flow technique in gas phase** in which a substrate is sublimed through a hot quartz tube under high vacuum at temperatures of 300 – 1000 °C. Under FVP conditions extremely **short contact times** in the range of **ms–s** can be reached. It is mostly used for reaction discovery and the synthesis of heterocyclic compounds, which cannot be easily obtained by other methods.







Conditions in FVP: 100 mg substrate, 2-4 h, 10^{-3} mbar



Conditions in FVP: 100 mg substrate, 2-6 h, 450 °C

The Contact Time

is the most important parameter in FVP. It can be increased either by adjusting the pressure, packing the tube with e.g. quartz wool, or reducing the inner diameter of the tube.

FVP is also termed

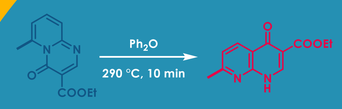
Chemistry without Reagents

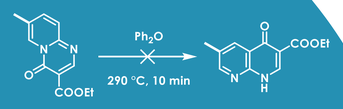
because it is performed in **the absence of a solvent and reagents**. Generally, **intramolecular** transformations such as eliminations, rearrangements or cyclizations occur, which make the reactions highly **atom efficient**. In solution, a high dilution is usually employed for intramolecular transformations to inhibit competing intermolecular processes. Compared to other thermolysis techniques, therefore, considerably **cleaner reaction profiles** are obtained in FVP, which simplifies product isolation and in turn **prevents waste**.

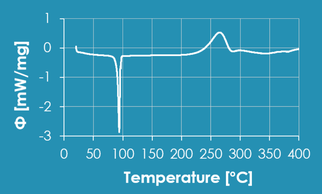
Prevent Waste

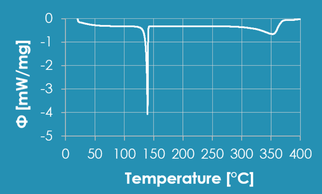
Atom Economy

Rearrangement Studies









In general, **pyridopyrimidinone 2 is initially generated**, but in solution at reaction times of 10–30 min and temperatures ≥260 °C, it **rearranges** to the **thermodynamically** more stable **naphthyridinone 3**, but solely when a **substituent is present at the 6-position**. This rearrangement pathway was also corroborated by DSC analysis.

Heating under FVP conditions at 450 °C only furnished recovered starting material.

Conclusion

Depending on the position of the substituent in the pyridine moiety and the applied thermolysis technique, the regioselectivity of the Gould–Jacobs thermolysis can be controlled either in favor of the kinetic (pyridopyrimidinone) or the thermodynamic (naphthyridinone) product. Under FVP conditions, 6-substituted pyridopyrimidinones were obtained, which were not evidenced previously under standard Gould–Jacobs reaction conditions.
The intramolecular Gould–Jacobs cyclization is highly atom efficient, because only EtOH is generated as by-product. FVP as a solvent-free thermolysis technique provides the products in high regioselectivity. Due to the cleaner reaction profiles and omission of solvents, less waste is produced.

M. Wernik, P. E. Hartmann, G. Sipos, F. Darvas, A. D. Boese, D. Dallinger, C. O. Kappe, *Eur. J. Org. Chem.* **2020**, 7051-7061

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FFG Forschung wirkt.
SFG NEUES DENKEN. NEUES FÖRDERN
Das Land Steiermark