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Synthetic Use of Thermoanalytical Methods in the Determination of Ringclosure Reaction Conditions and Reaction Mechanisms

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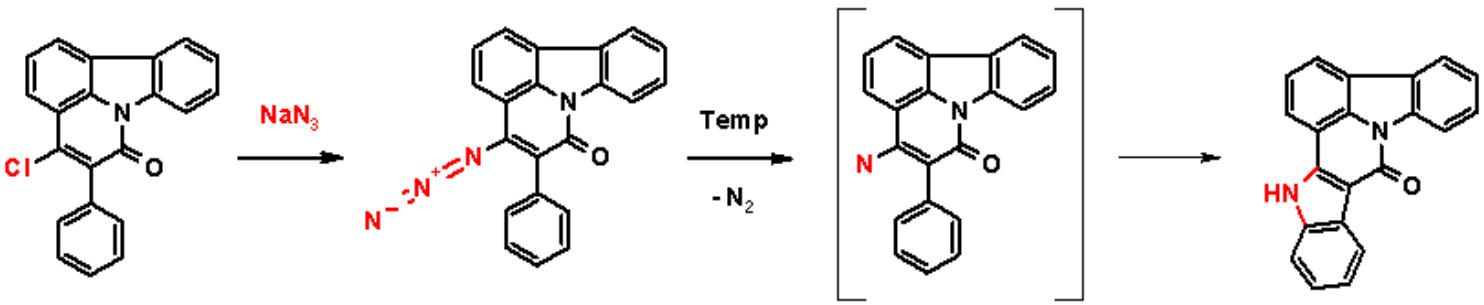
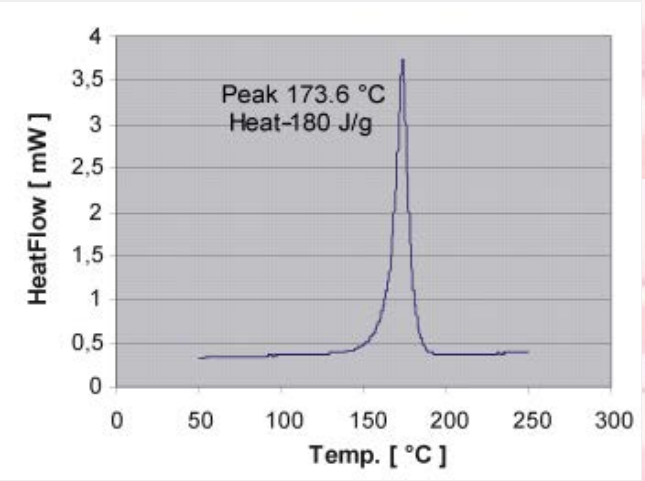
Contents:

General Aspects

Thermal induced synthetic reactions can be planned and elucidated by thermoanalytical methods such as differential scanning calorimetry (DSC) [1] or thermogravimetric analysis (TGA). In this contribution we report about the determination of reaction and cyclization temperatures by DSC methods and the investigation of the reaction mechanism by TGA methods. .

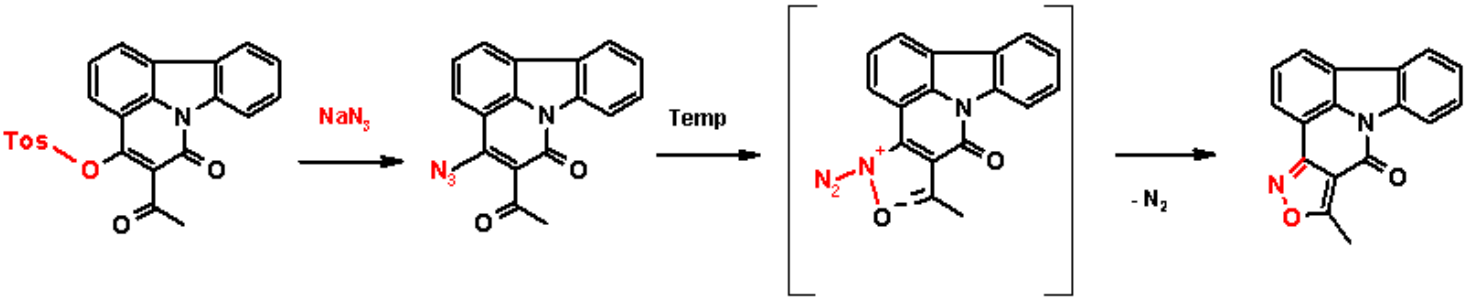
Thermal Cyclization of o-Phenyl Azides to Indoles

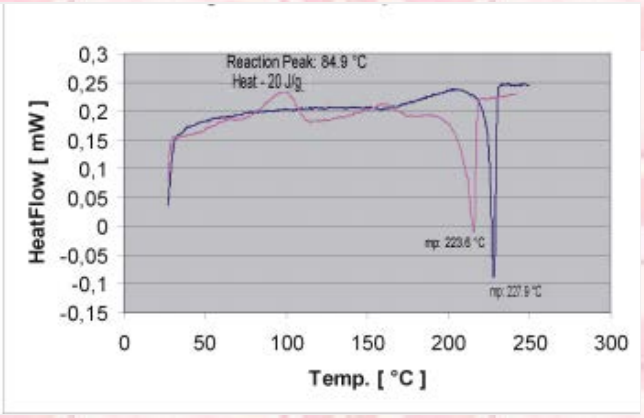




Heteroaryl azides such as 4-azido-pyrido[3,2,1-jk]carbazoles are obtained from appropriate chloro derivatives. On thermolysis nitrogen is evolved and decomposition takes place by formation of nitrenes. These intermediate nitrenes react with aryl-substituents in ortho position and cyclize to indolo fused heterocycles.
The cyclization temperature (onset temperature 149°C) and the reaction enthalpy (-180 J/g) can be determined by DSC.

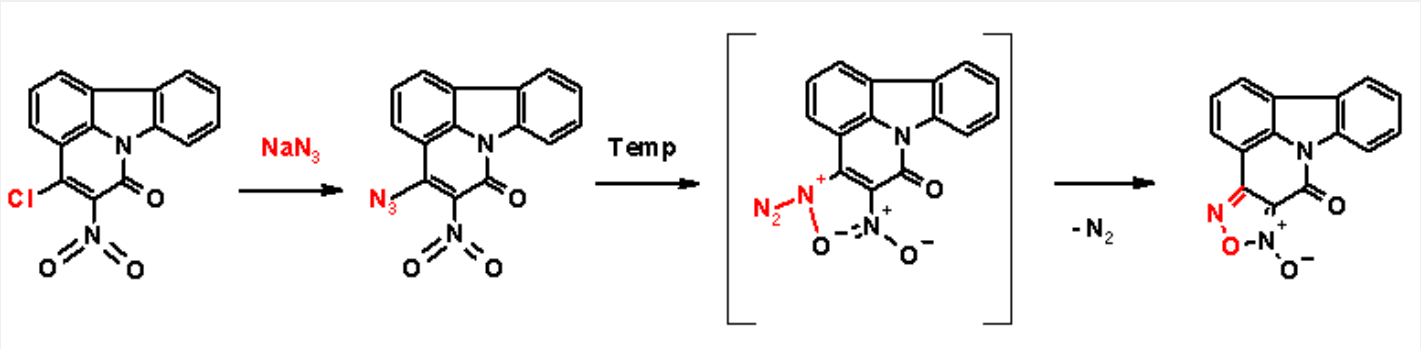
Thermal Cyclization of o-Acyl Azides to Isoxazoles





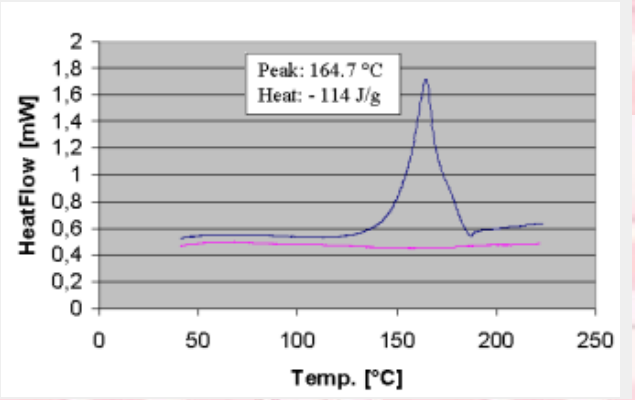
4-Azido-pyrido[3,2,1-jk]carbazoles with acyl groups in ortho-position cyclize on thermolysis via an electrocyclic mechanism. As ring closure product an isoxazolo fused heterocycle is obtained.
The change in the cyclization mechanism is obvious by the lower cyclization temperature (red curve, onset temperature 75°C, maximum 85 °C) and the lower reaction enthalpy (-20 J/g) in the DSC diagram (red curve).

The visible melting point in the DSC diagram of the azide (225 °C, red curve) derives from the already formed isoxazole, as can be seen in the blue curve, which shows the DSC diagram of the already cyclized isoxazolo product (mp 228 °C).



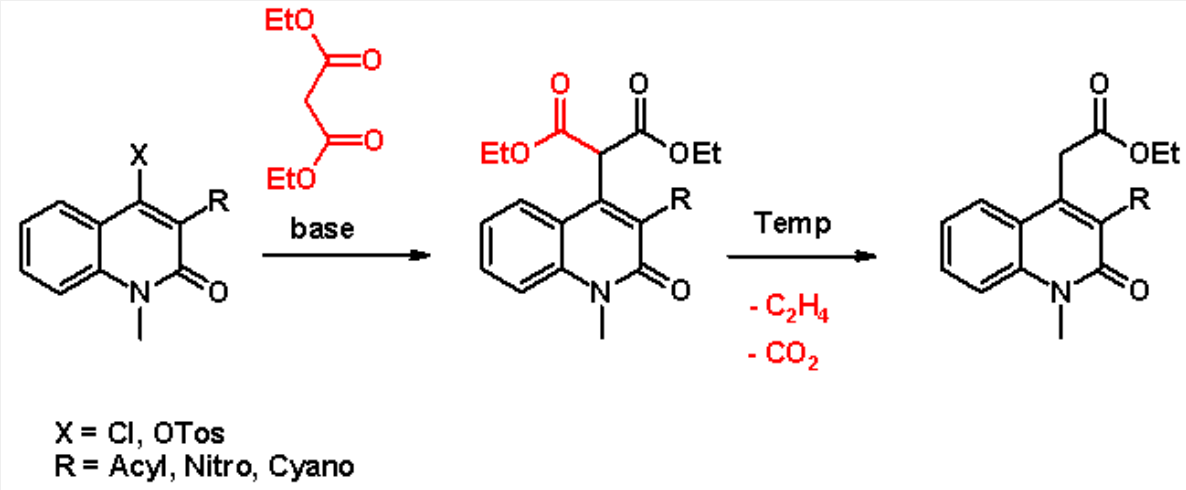
4-Azido-pyrido[3,2,1-jk]carbazole with a nitro group in ortho-position cyclizes on thermolysis also via an electrocyclic mechanism. As ring closure product a furoxan fused heterocycle is obtained.
The cyclization temperature (blue curve, onset temperature 140°C, maximum 165 °C) is similar as observed in the indole reaction; the reaction enthalpy (- 114 J/g) is higher than in the isoxazole reaction, but lower than in the indole reaction. The red curve shows the DSC diagram of the cyclized furoxane).

DSC measurements in solution reveal that solution effects lower the

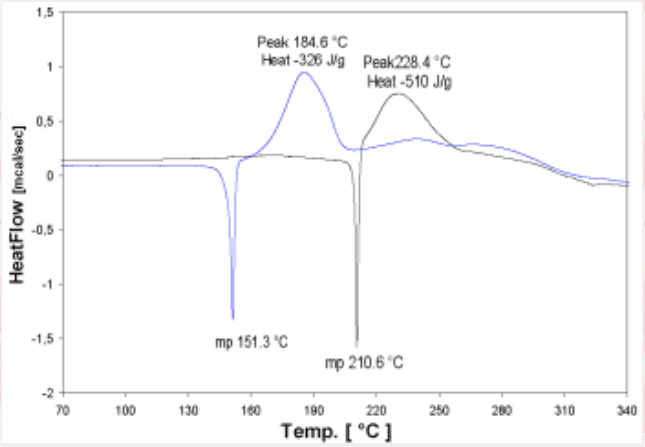


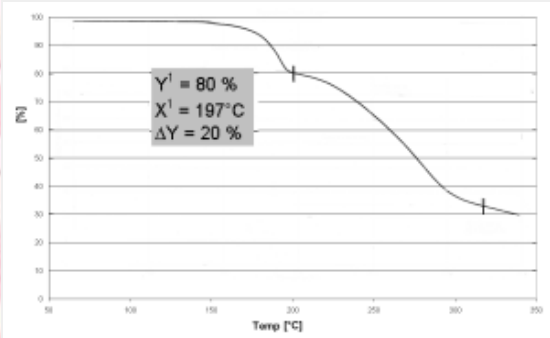
cyclization temperature for 30-50 °C.

Thermolysis of o-Nitro Malonates

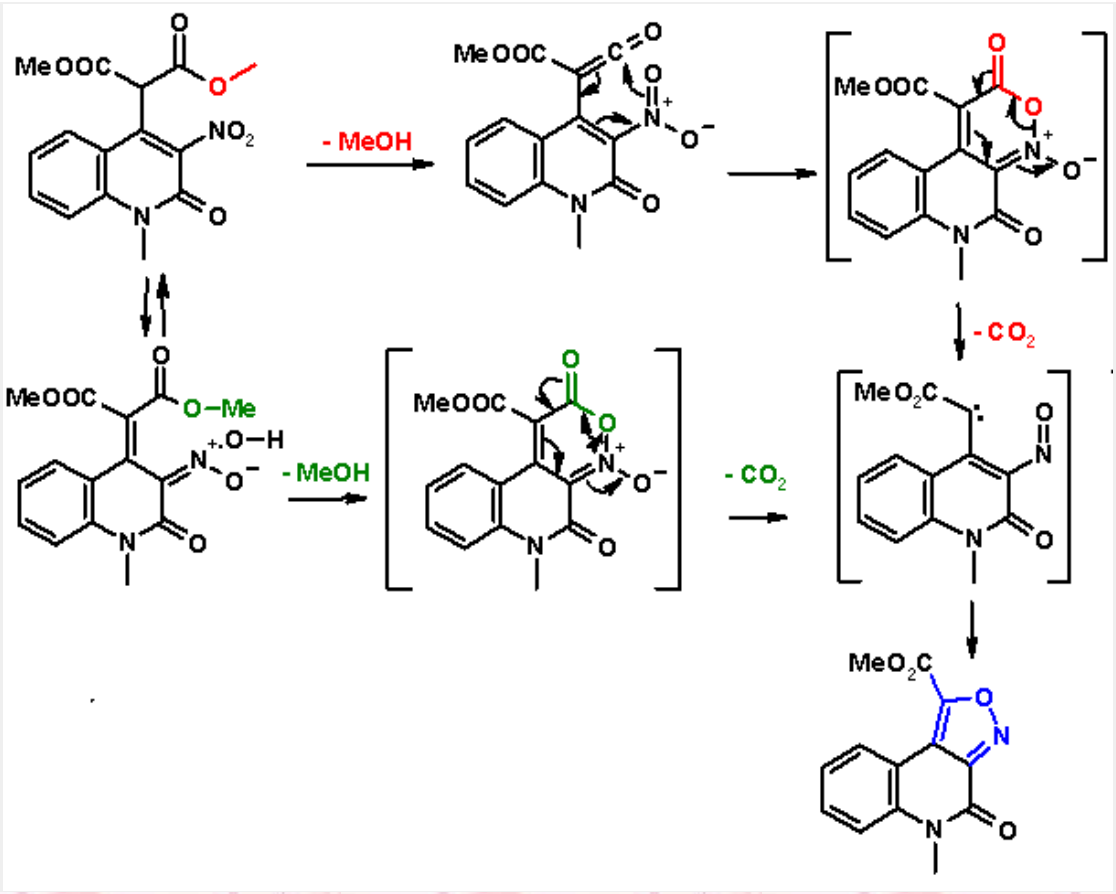


Heterocyclic diethylmalonates can be obtained by reaction of diethyl malonate with quinolones having a reactive leaving group such as chloro or tosyl in 4-position and an electron withdrawing group in position 3. Thermolysis of such heterocyclic diethyl malonates results in the loss of one ester group by elimination of ethene and carbon dioxide.

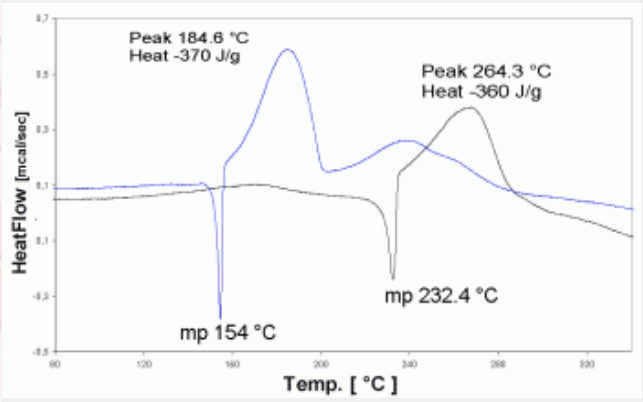


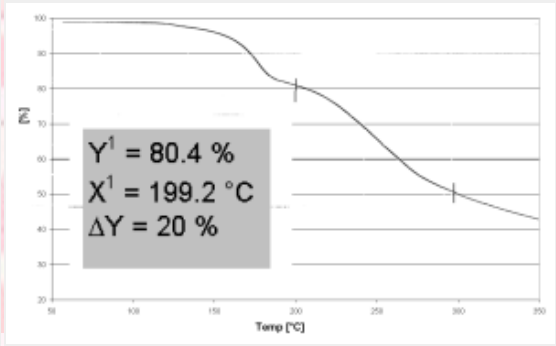


The optimized conditions could be found by DSC investigation (R = nitro, blue curve, onset temperature at 169 °C, max. 185 °C). The DSC of the monoester product (R = nitro, black curve) showed also a sharp decomposition signal, however it could not be used synthetically. Thermogravimetric investigations showed a step at 197 °C with a mass loss of 20% which is consistent with the cleavage of C_2H_4 and CO_2.



Thermolysis of heterocyclic dimethyl malonates with ortho-nitro groups gave surprisingly a ringclosure reaction to an isoxazolo ester. The two outlined reaction mechanisms include both the elimination of methanol and carbon dioxide, so a differentiation by thermoanalytical ways was not possible.





The optimized conditions could be found by DSC investigation (blue curve, mp 154 °C, onset temperature 162 °C, maximum 185 °C). The DSC of the cyclized product (black curve) showed again after the mp at 264 °C a sharp decomposition signal, which could not be used synthetically. Thermogravimetric investigations reveiled a step at 199 °C with a mass loss of 21% which is consistent with the formation of methanol and CO_2.

Experimental

Synthesis of 4-azido-pyrido[3,2,1-jk]carbazoles: To a solution of the appropriate chloro- or tosyloxy derivative in dimethylformamide sodium azide was added and stirred at temperatures between 20 and 60 °C. Then water was added and the resulting precipitate filtered by suction.
Thermal cyclization of 4-azido-pyrido[3,2,1-jk]carbazoles: The appropriate azido derivative was heated in a suitable solvent (mainly DMF) at the temperature obtained from DSC experiments (onset) until no nitrogen gas was evolved. Then the solution was taken to dryness and purified by recrystallization or dry flash column chromatography.
Synthesis of heterocyclic substituted dimethyl- and diethylmalonates: A mixture of the appropriate 4-chloroquinolone, malonate and anhydrous potassium carbonate in dimethylformamide was stirred at room temperature, poured into ice and acidified. The formed precipitate was filtered.
Thermolysis of heterocyclic substituted dimethyl- and diethylmalonates: A solution of the heterocyclic substituted dimethyl- or diethylmalonate in

dichlorobenzene was heated under reflux, then taken to dryness, the residue treated with hexane and the solid product filtered by suction.

DSC measurements: Rheometric Scientific DSC Plus, Software Orchestrator 6.22, aluminium crucibles (11 bar), 1-5 mg sample, heating rate: 5-10 °C/min, 50-750 °C

TGA measurements: Perkin Elmer Thermogravimetric Analyzer TGA7, platinum crucibles, nitrogen, 5-10mg sample, heating rate: 10 °C/min, 30-450 °C

Acknowledgement

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References

[1] Kappe Th., Stadlbauer W., *Molecules*, **1** (1996) 255-263;
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