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DSC - A Valuable Tool in Heterocyclic Synthesis

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Abstract

Many decomposition and ring closure reactions in the azide series (e.g. a cyclization and rearrangement reaction sequence from the azido ester **1** via the ethoxy oxazole **2** to the oxazolone **3**), intramolecular rearrangement reactions (e.g. via a-oxoketenes), self condensation of *p*-octopamine and also reactions with two reactants and the influence of solvents at the reaction conditions were studied using DSC (Differential Scanning Calorimetry).

Keywords: Thermolysis, DSC, cyclization, rearrangement, organic azides

Introduction

DSC (Differential Scanning Calorimetry), which is widely used in material science, quality inspection, polymer and biopolymer chemistry and pharmacy1, has been shown to provide useful information and hints in the stage of planning thermolytical reactions such as ring closure and rearrangement reactions. This information, which can be obtained before the reaction itself is performed, include:

- range of the temperature where the planned reaction can (or must) be performed
- knowledge of subsequent rearrangement and decomposition temperatures
- choice of suitable solvents
- safety precautions in exothermic processes

Of special interest for synthetic organic chemists is the fact that all information can be obtained from 2–5 mg of substance, an amount, which is usually not enough to obtain ^{1}H-NMR spectra. A literature survey covering the last 3 years revealed that only a few applications dealing with synthetic organic chemistry could be found in the literature.

In this survey we present some selected ring reactions which were improved by the assistance of DSC.

Ring closure reactions of *ortho*-aryl and acyl azides

Azidoarenes with reactive substituents in the *ortho* position cyclize to indoles, oxazoles or other fivemembered heterocycles [2]. We were able to show that 3-azido-1-oxoheterocycles with aryl substituents in position 2 represent reactive substrates for such reactions [3].

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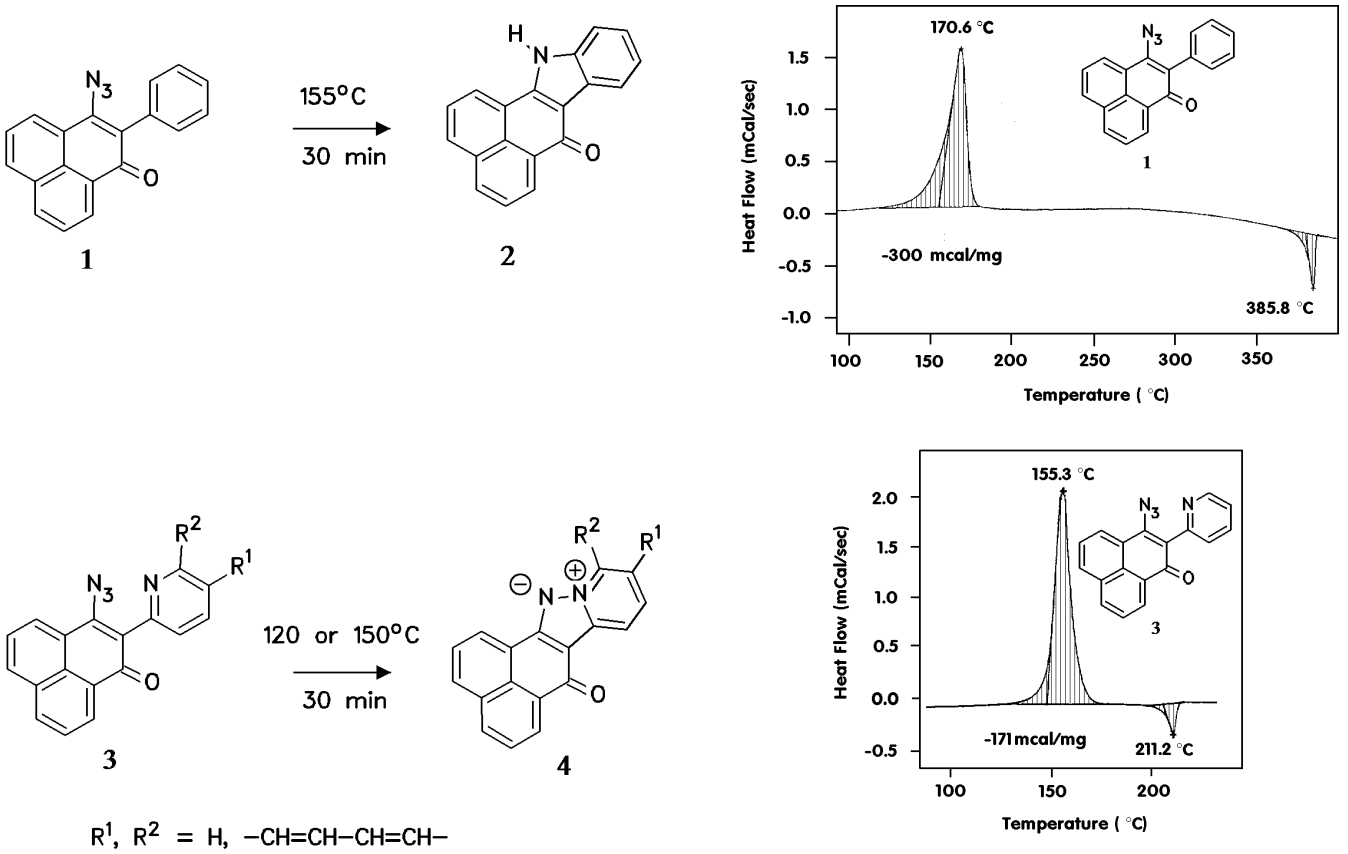


Scheme 1.

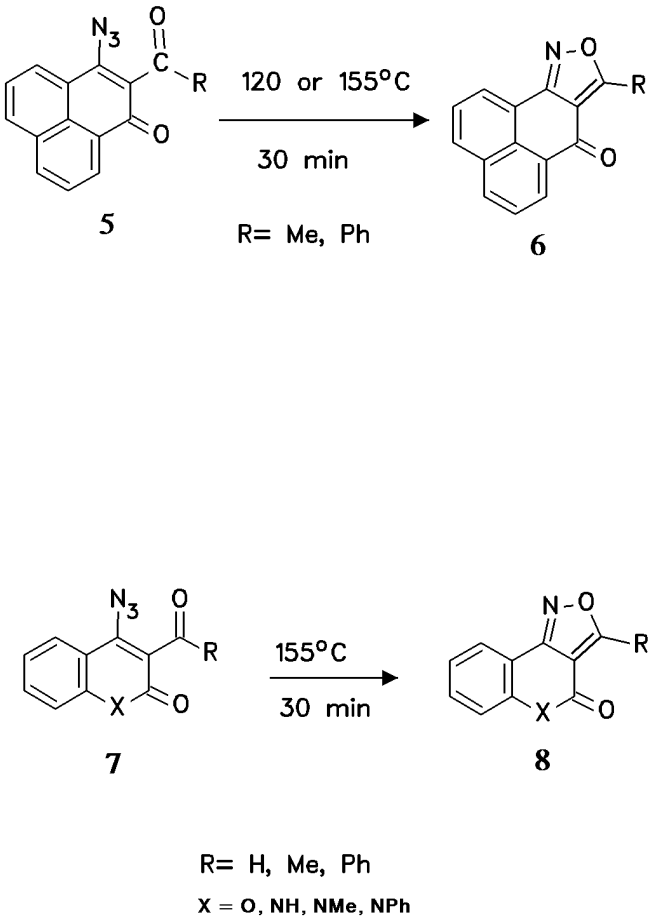
When we investigated the ring closure of 3-azido-2-aryl- or 2-hetaryl-1-phenalenones, the DSC plot (Scheme 1) revealed that an exothermic reaction of 3-azido-2-phenyl-1-phenalenone **1** started (as denoted by the sensitivity of the apparatus) at about 150 °C. This reaction coud be performed in a preparative manner in refluxing DMF (153 °C) to form in 70% yield naphtho[8,1-ab]carbazolone **2** [4]. The DSC scan shows also that higher temperatures bear no danger of decomposition; at about 380 °C the melting range of the cyclization product can be observed.

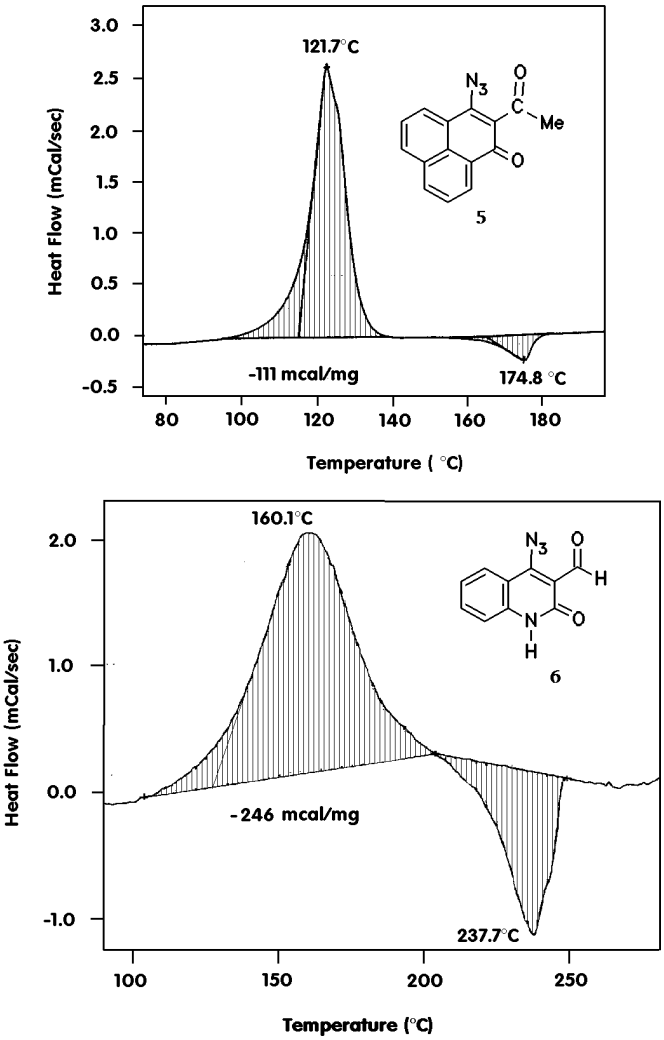
DSC analysis of the pyridyl derivative **3** showed an exothermic peak starting at 148 °C, followed by an endothermic peak at 206 °C, which was the melting point of the cyclized compound. Following hints from the DSC, the pyridyl azide was thermolyzed in refluxing DMF to give the cyclization product**.** The pyridyl ring closure product was also obtained in a one pot reaction starting from the chloro product and excess sodium azide, including as the first step the substitution reaction to the azide followed by cyclization without isolation of the azide. The structure of the pyridyl ring closure product was assigned to the naphtho[8, 1-ab]8a-azonia-9-l^2-azafluoren-7-one **4** according to the ^{13}C-NMR.

According to DSC plots the phenalene-acetyl azide **5** (R = Me) should already be cyclized at about 115 °C (Scheme 2). An endothermic peak at 174 °C was also observed, which prompted us not to reach this temperature because of possible decomposition reactions. However, when we thermolyzed it in DMF at 120 °C, side products were formed which we were not able to remove. Though, by lowering the temperature to 65 °C, we obtained 8-methyl-isoxazolo[3, 4-a]phenalen-7-one **6** in 60% yield. The DSC plot of the benzoyl phenalene (**5**, R = Ph) showed an onset point at 161 °C and decomposition reactions at 315 °C. We therfore thermolyzed the azide in refluxing DMF and obtained 8-phenyl-isoxazolo[3,4-a]phenalen-7-one in about 50% yield.

The thermal decomposition of the azido aldehydes **7** is followed immediately by a melting range which corresponds to the melting point of the cyclized species **8**.[5]

The thermolytical decomposition of azides with an ester group in the *ortho* position (**9**) was shown to give two exothermic reaction steps (Scheme 3) [6]. It was subsequently proved by synthesis that the first thermolytical reaction step gave the isoxazoles with the alkoxy group in





Scheme 2.

the isoxazole ring (**10**) as a ring closure product in 50–70% yield, whereas at slightly higher temperatures, a rearrangement to isoxazolones (**11**) with the alkoxy group in the quinoline, coumarin or pyridine ring took place. The structures of the isoxazoles **10** and **11** were elucidated by ^{13}C-NMR spectra.

In azides with *ortho*-chloro groups (**12**) this rearrangement cannot occur and only the isoxazoles **13** are obtained [6, 7].

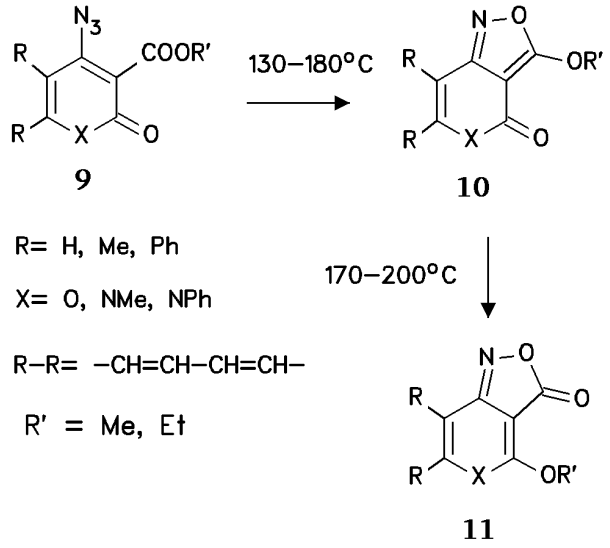
Nitro azides (**14**) cyclize easily to furoxanes (**15**) [8], which can be observed in the DSC plots (Scheme 4) [7, 9]. Also further reactions such as the deoxygenation of the furoxanes **15** to the furazans **16** were investigated by DSC by measuring a mixture of the furoxane and triphenylphosphane in order to find favorable reaction conditions [10].

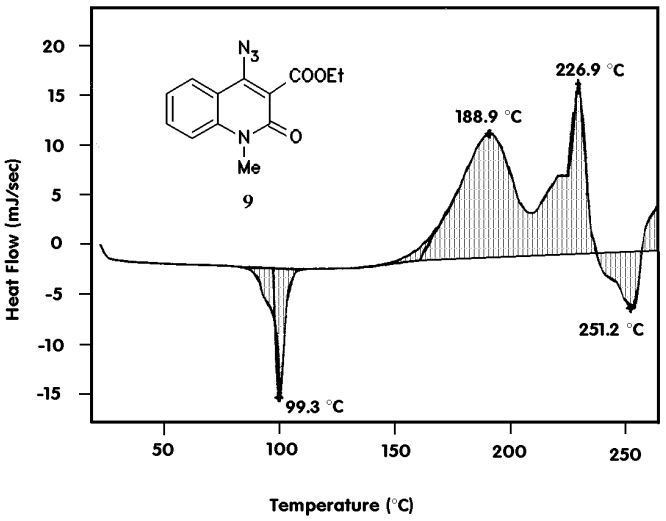
Ring closure reactions of *ortho*-nitro hetarylmalonates

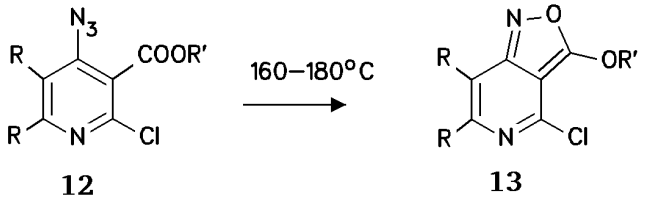
Malonates with hetarylsubstituents having a nitro group in the *ortho*-position gave 2 different reaction products on thermolysis (Scheme 5): diethyl malonates formed the corresponding hetaryl acetates by loss of one ester group (probably by decomposition to CO_2 and ethylene), whereas dimethyl malonates cyclized to isoxazoles by loss of the ester group and reaction with the *ortho*-nitro group (probably by loss of methanol and CO_2) [10].

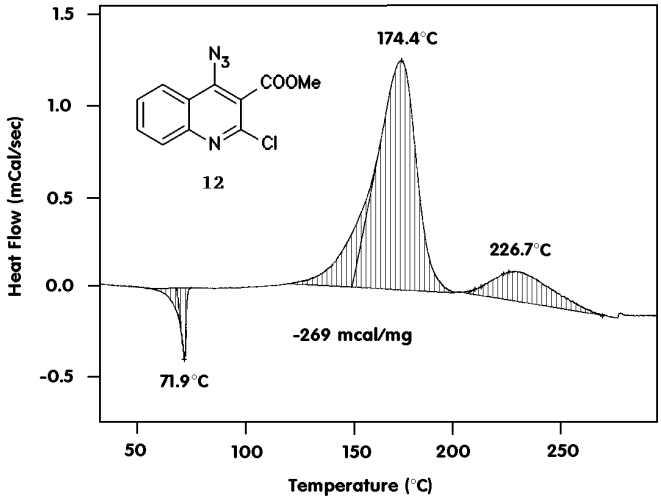
Ring closure reaction of 2-arylaminomethylene-1,3-dicarbonyl-hetarenes

Anilinomethylene compounds of 1,3-dicarbonylarenes or hetarenes (**20**) cyclize either directly to quinolines (**21**) or rearrange and cyclize to give isomeric quinoline derivatives (**22**) [11] depending upon the reaction conditions and structural properties (Scheme 6). The reaction temperatures







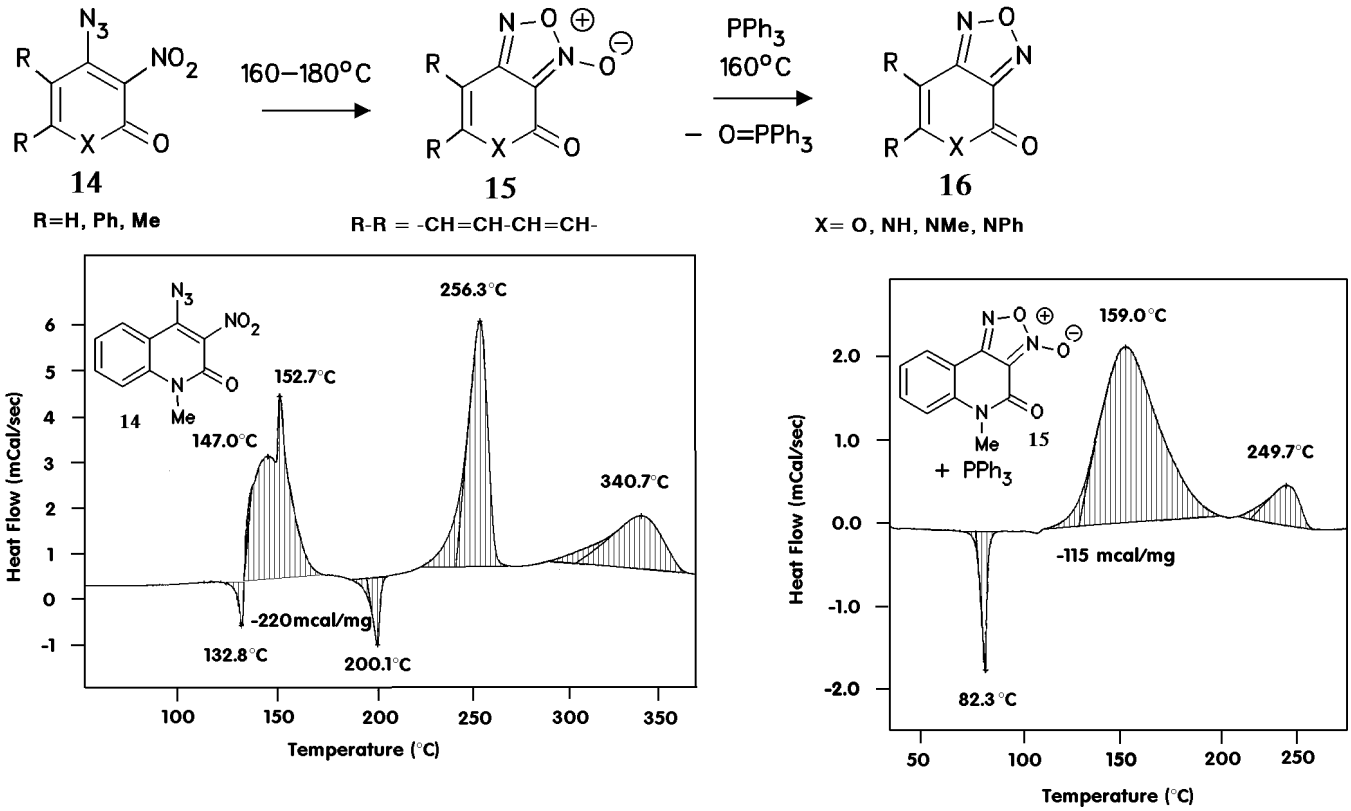


Scheme 3.

range between 100 and 250 °C. DSC plots give exact information for planning this synthesis step to obtain suitable reaction temperatures and prevent decomposition reactions .

Self Condensation of *R,S-p*-Octopamine

The early literature gives two melting points of racemic *p*-octopamine (**23**): 157–158 °C [12] and 250 °C (dec.) [13]. It was shown later [14] that *R,S-p*-octopamine (**23**) melts at 156–158 °C but resolidifies at this temperature and melts under decomposition at temperatures above 250 °C. Pure *R*- and *S-p*-octopamine (**23**) each decomposed between 155–160 °C and formed a high melting compound without ever melting [14, 15]. It was shown that, in general, phenylethanolamines bearing a hydroxy group in *ortho*- or *para*-position undergo self-condensation between 155 °C and 190 °C in which two molecules of amine yield 2,5-diaryl-piperazines (**24**) with the loss of two molecules of water. The preliminary result of a DSC-analysis of this reaction is shown in Scheme 7. It is interesting to observe that in an "open" tube experiment the heat of evaporation



Scheme 4.

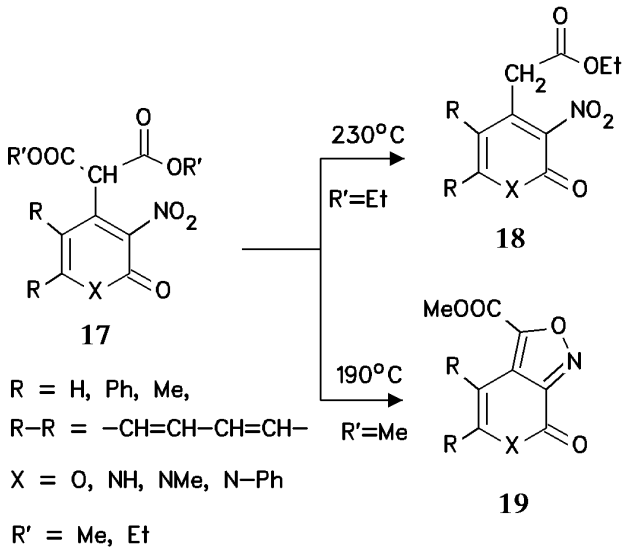
of the water can also be observed. More material has to be collected especially for cases in which melting point and decomposition point are not so close together (for instance *o*-octopamine).

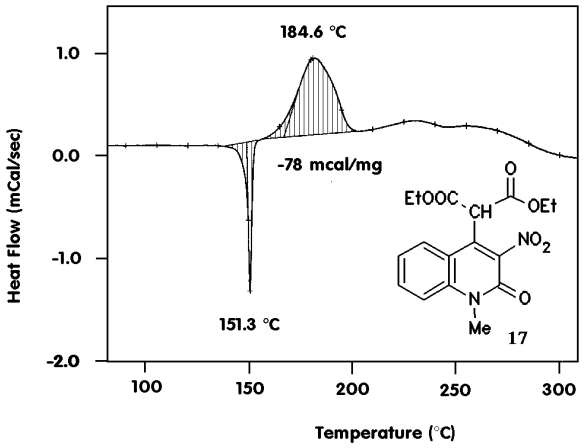
Rearrangement of benzocoumarins

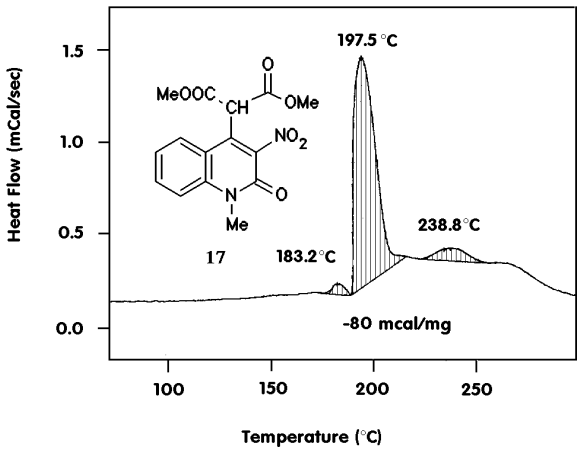
The rearrangement of benzocoumarins (**25**) was first described in 1968 [16]. Many other 2-pyrones with suitable substituents in position 5 react in a similar manner [17]. The reaction proceeds via α-oxoketene intermediates such as **26** [18], which has been demonstrated by flash vacuum pyrolysis experiments [19] DSC gives a useful information as to which temperature range the rearrangement takes place and at which temperatures kinetic measurements should be done (see Table in Scheme 8). Since many cross-conjugated mesomeric heterocyclic betaines containing the malonyl moiety [20] also undergo this type of rearrangement we are currently trying to establish a correlation between kinetic measurements and DSC results [21].

"3,6-Diazidopyridazine"

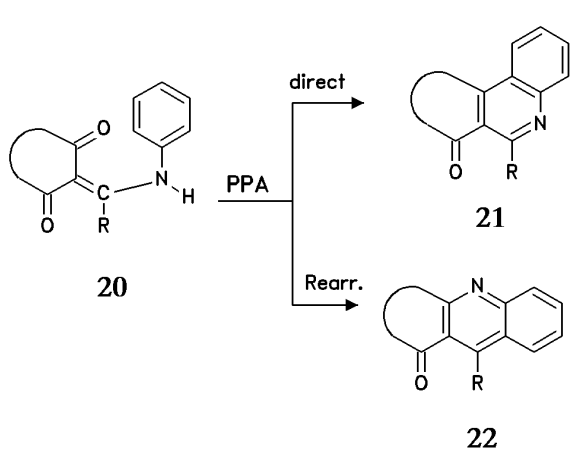
In recent years we have worked with a number of potentially hazardous explosive azido- and especially geminal diazido-compounds [22]. Working with 500 mg of 6-azidotetrazolo[1,5-*b*]pyridazine ("3,6-diazidopyridazine") (**28**) [23] a violent explosion took place (with some injuries to the person involved) when the compound came in contact with one drop of trimethyl phosphite. Moreover, this azide shows a higher impact- and friction-sensitivity than mercury fulminate [24], and therefore the compound should be handled with extreme care! However, the DSC diagram (Scheme 9) shows a relatively high thermal stability: the compound melts at 127 °C, exothermic decomposition starts at 146 °C and reaches its first maximum at 208 °C, a second maximum can be seen at about 250 °C. The total exothermal activity over the two steps is 625 cal/g (average of 4 measurements). Although the DSC gives no hint of the explosive nature of **28** it gives valuable information about the onset point of the decomposition (about 180 °C). Thus, reactions with phosphanes and phosphites were best carried out in refluxing 1,2-dichlorobenzene (bp 180 °C) [23].

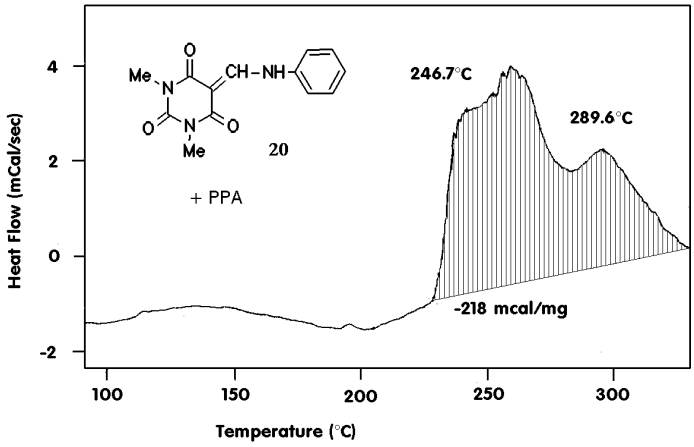


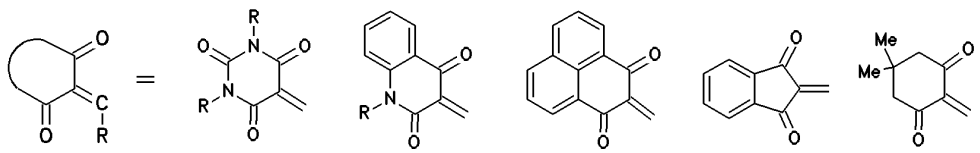




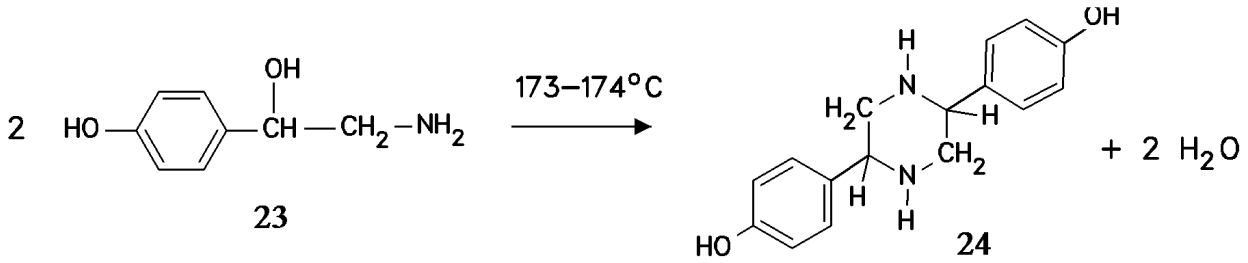
Scheme 5.

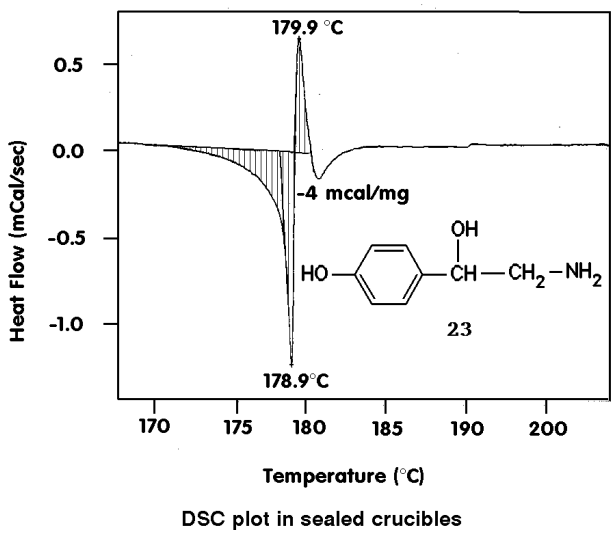




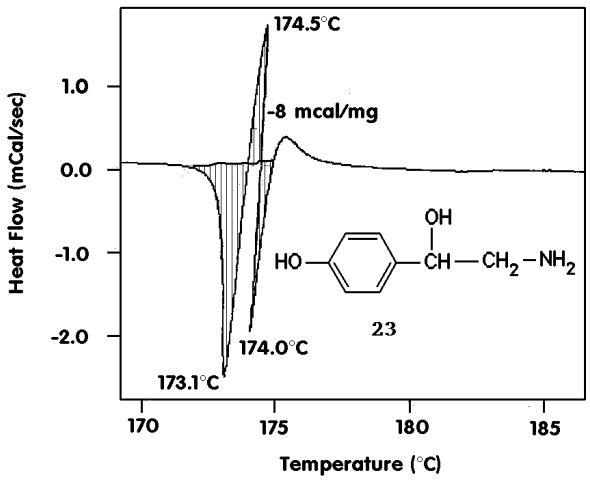


Scheme 6.





DSC plot in sealed crucibles



DSC plot in "open" crucibles

Scheme 6.

Diazidobarbituric Acids

As one of the smallest geminal diazido heterocycles we have investigated the energetic properties of 5,5-diazidobarbituric acid (**29**), and its 1,3-dimethyl derivative (**30**) [22, 25]. Surprisingly, the dimethyl derivative **30** shows a higher exothermic value than the *N,N*-unsubstituted derivative **29**. The melting point of the dimethyl derivative is 46 °C and far away from the region of decomposition. The appearance of the decomposition region in the DSC diagram (Scheme 10) of the unsubstituted compound looks as if endothermic and exothermic processes are overlapping, resulting in less total energy measured. We were not able to observe a friction or impact sensitivity of these azides, however, both compounds exploded when they came into contact with trimethyl phosphite.

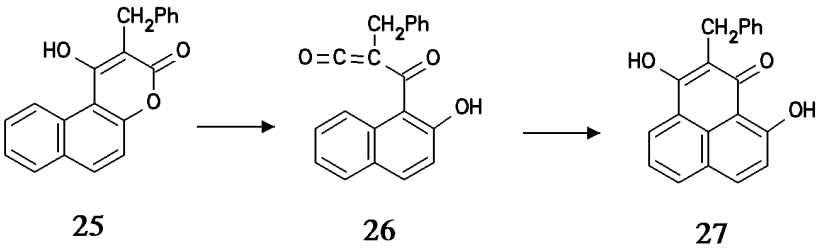
Experimental Methods

DSC data were obtained on a Rheometric Scientific DSC-Plus instrument with the DSC software V5.42. This instrument was sensitive enough for our purposes and offered the advantage to use temperatures up to 600 °C. The DSC plots were recorded between 25–500 °C with a heating rate of 2–10 °C/min. In general only a small amount (ca. 1.5–3 mg) of material in sealed aluminium crucibles (11 bar) was used which was necessary due to the explosive nature of the organic azides involved.

Typical experimental procedures for the preparation of organic azides used in these experiments can be found in recent publications [4, 26].

Conclusion

All these findings reveal, that DSC can be used as a valuable tool in preparative organic chemistry and this will develop in the future to a standard method along with other methods such as TLC, NMR- or IR-spectroscopy. Especially for intramolecular thermolytic reactions, DSC plots allow us to choose the suitable reaction temperature and to predict side reactions, although, in the case of sensitive compounds, the preparative results must not correspond completely with the DSC data. A rather new useage of DSC can be found in the investigation of reaction mixtures for the determination of suitable reaction conditions. This area of research is currently being pursued in more detail in our laboratories.



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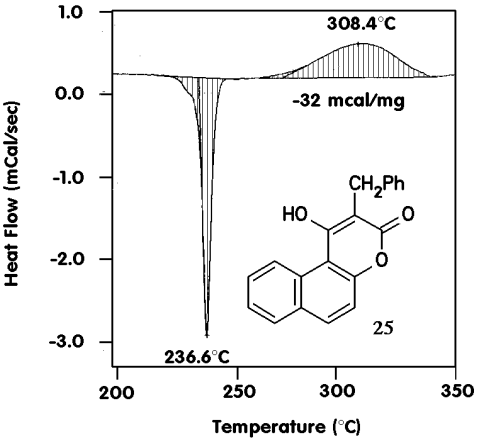
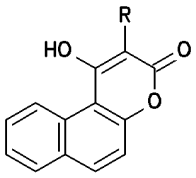


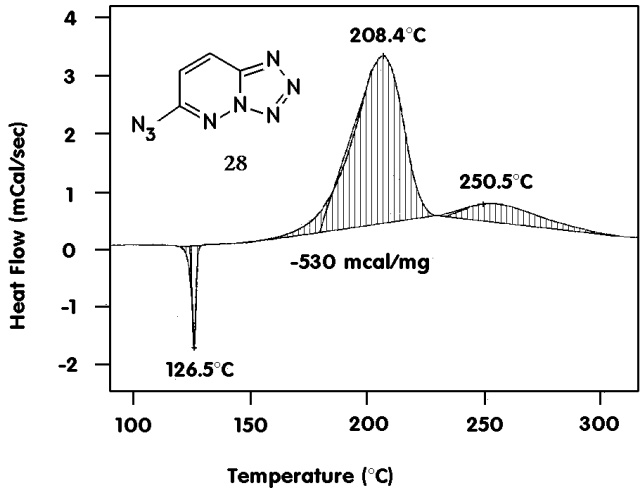


	E_A	$\Delta H^{\neq}$	$\Delta S^{\neq}$
R = Ph	41.1[a]	38.9[a]	-5.0[b]
= CH_2Ph	40.3	37.8	-5.3

$t_{1/2}$ [sec]	250°	260°	270°C
R = Ph	14.000	6.900	3.500
= CH_2Ph	4.700	2.370	1.180

Rearrangements in 2,4,6-trichlorophenol. - a) [kcal . mol^{-1}] b) [kcal . K^{-1} . mol^{-1}]

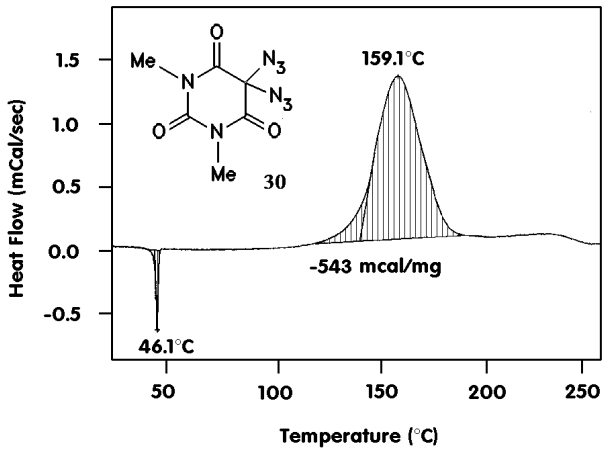
Scheme 8.

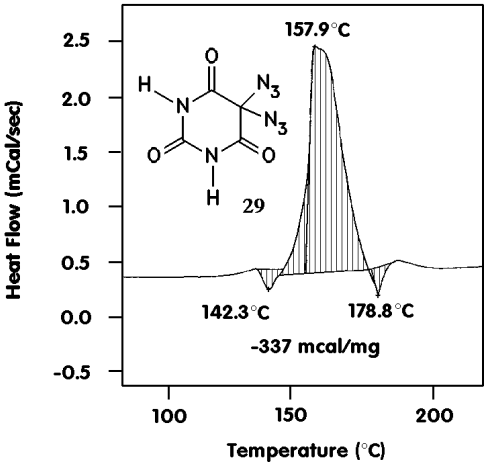


	Impact-Sensitivity	Friction-Sensitivity
"diazidopyridazine"	0.3 J	5 N
mercury fulminate	1-2 J	3 N
$Pb(N_3)_2$	2.4 - 4 J	1 N

(Dynamit Nobel)

Scheme 9.





Scheme 10.

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