SUPPORTING INFORMATION FOR:

Development of a Safe and Efficient Two-Step Synthesis for Preparing 1-Bromoacetyl-3,3-Dinitroazetidine, a Novel Clinical Anti-Cancer Candidate

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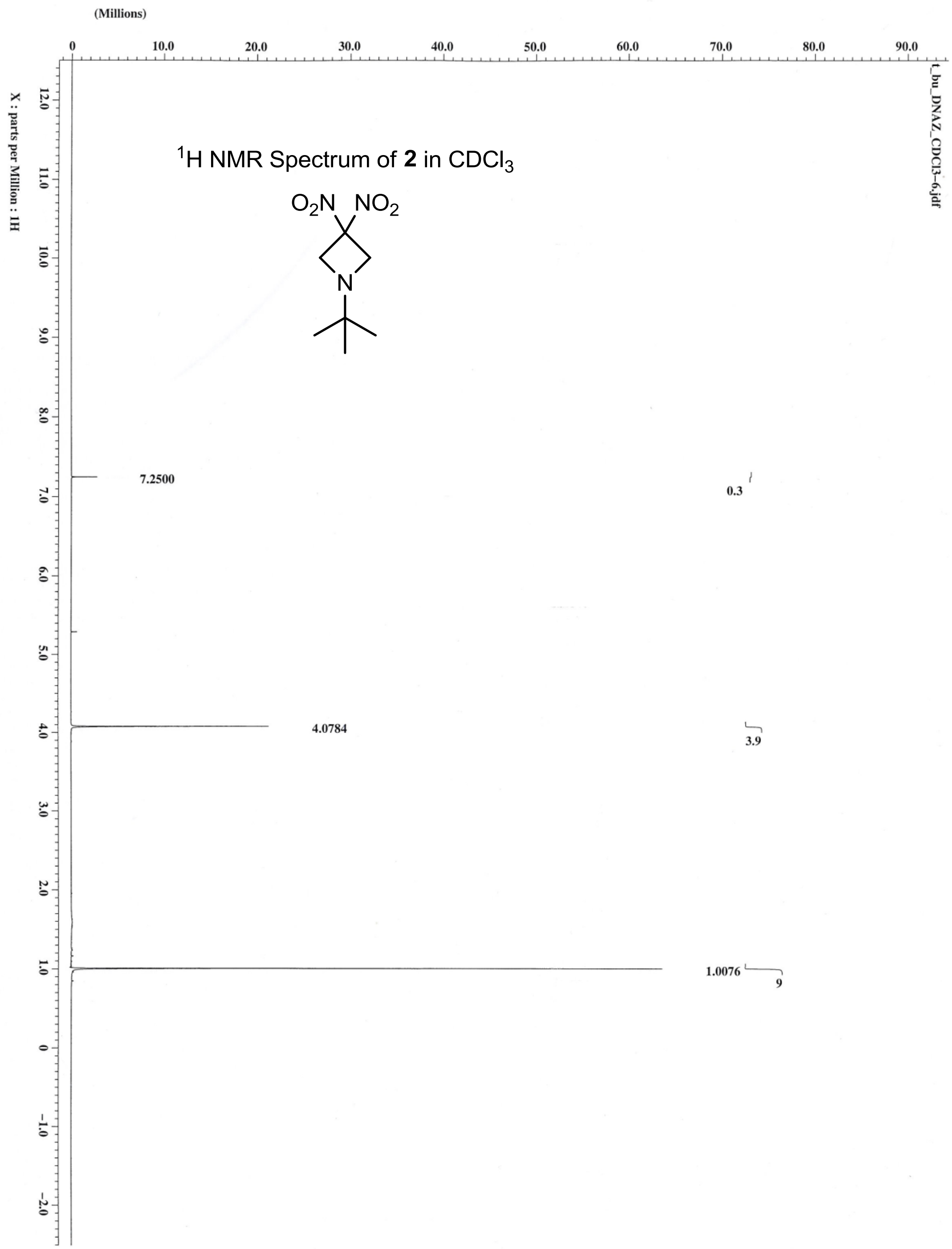
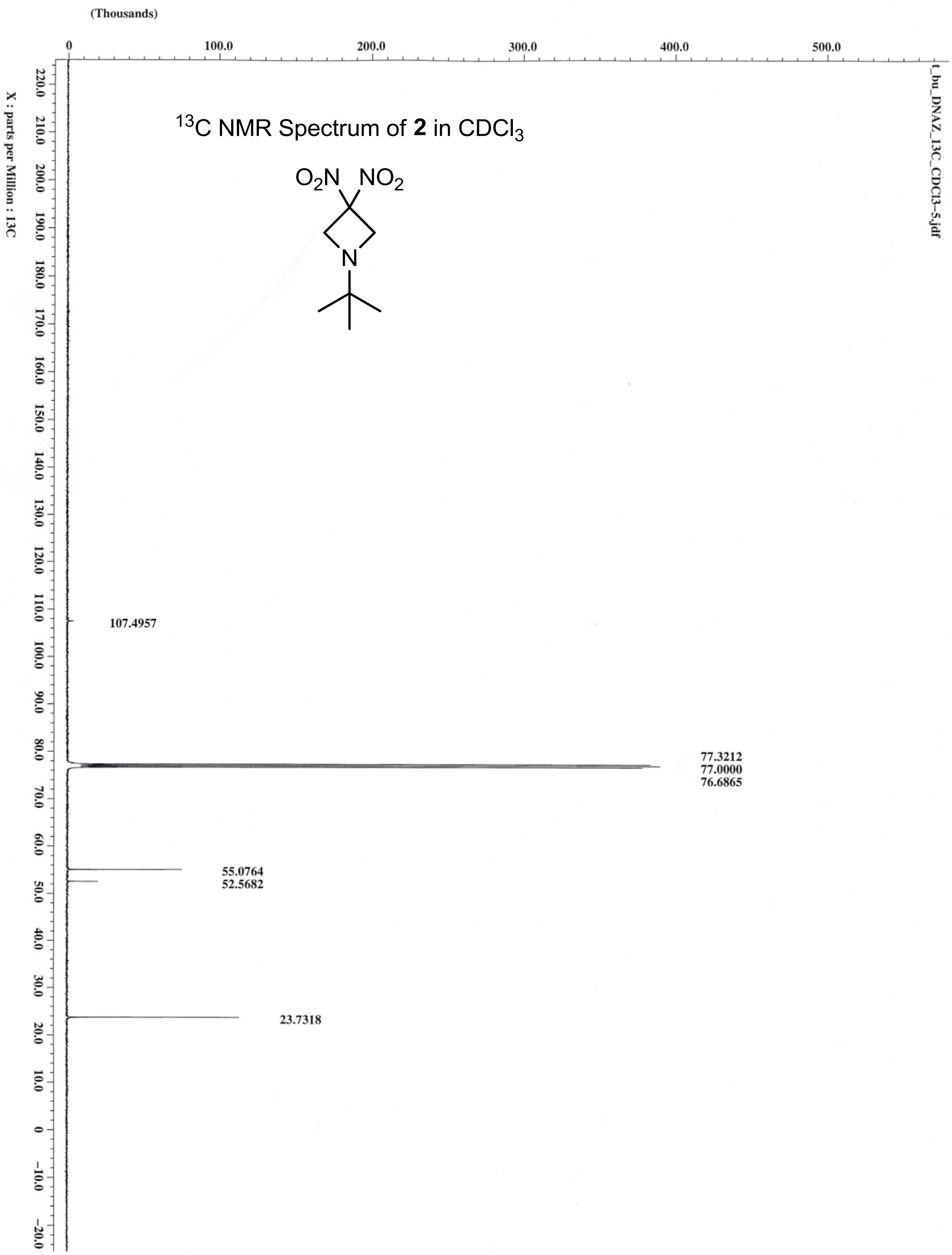
Spectral Data for Compounds 2 and 3

^{1}H and ^{13}C NMR data were collected on a JEOL Eclipse+ 400 MHz spectrometer; the chemical shifts are reported in δ (ppm) relative to residual solvent peaks ($CDCl_3$ δ ^{1}H 7.25; ^{13}C 77.00; d_6-acetone δ ^{1}H 2.05; ^{13}C 29.8).

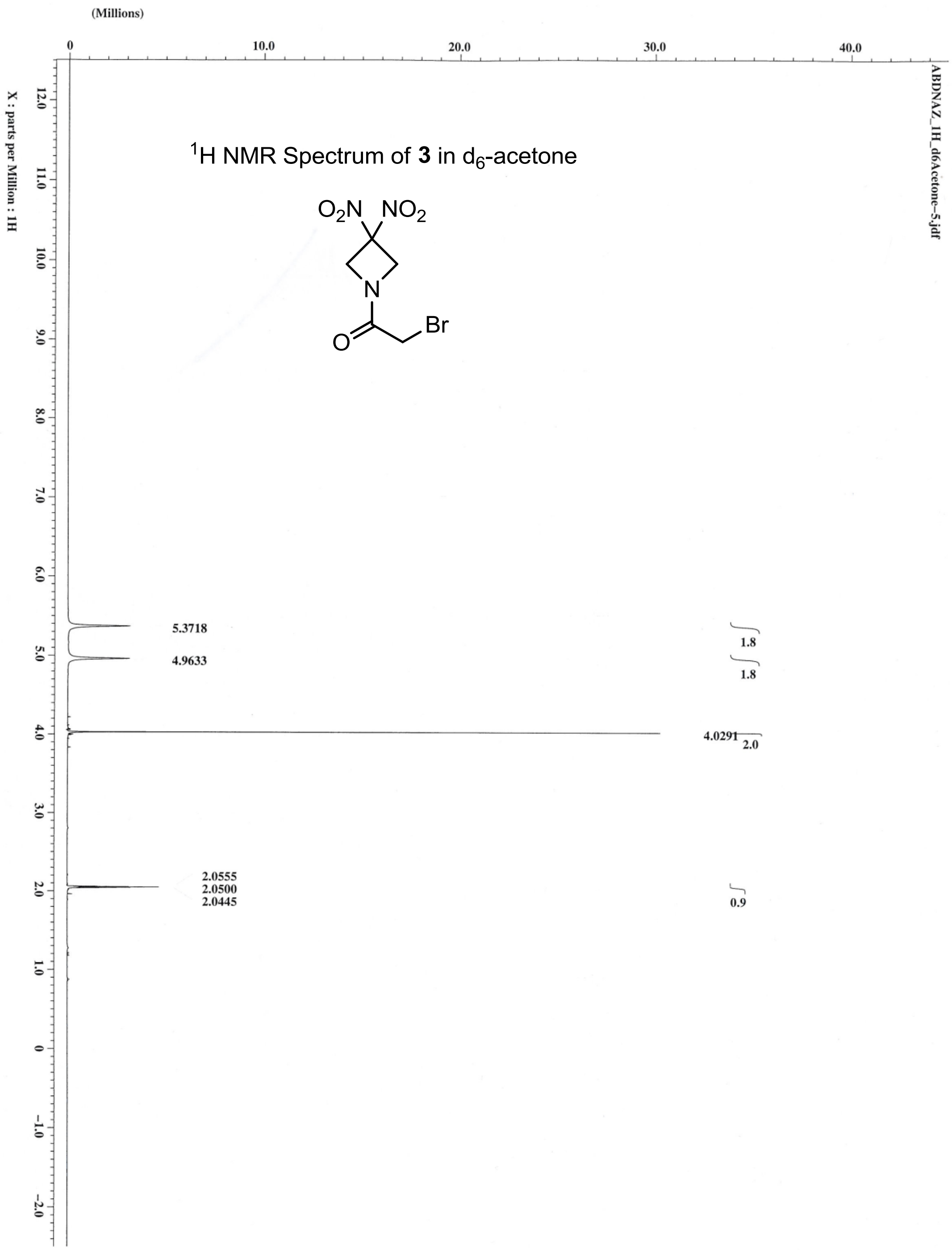
SEE BELOW



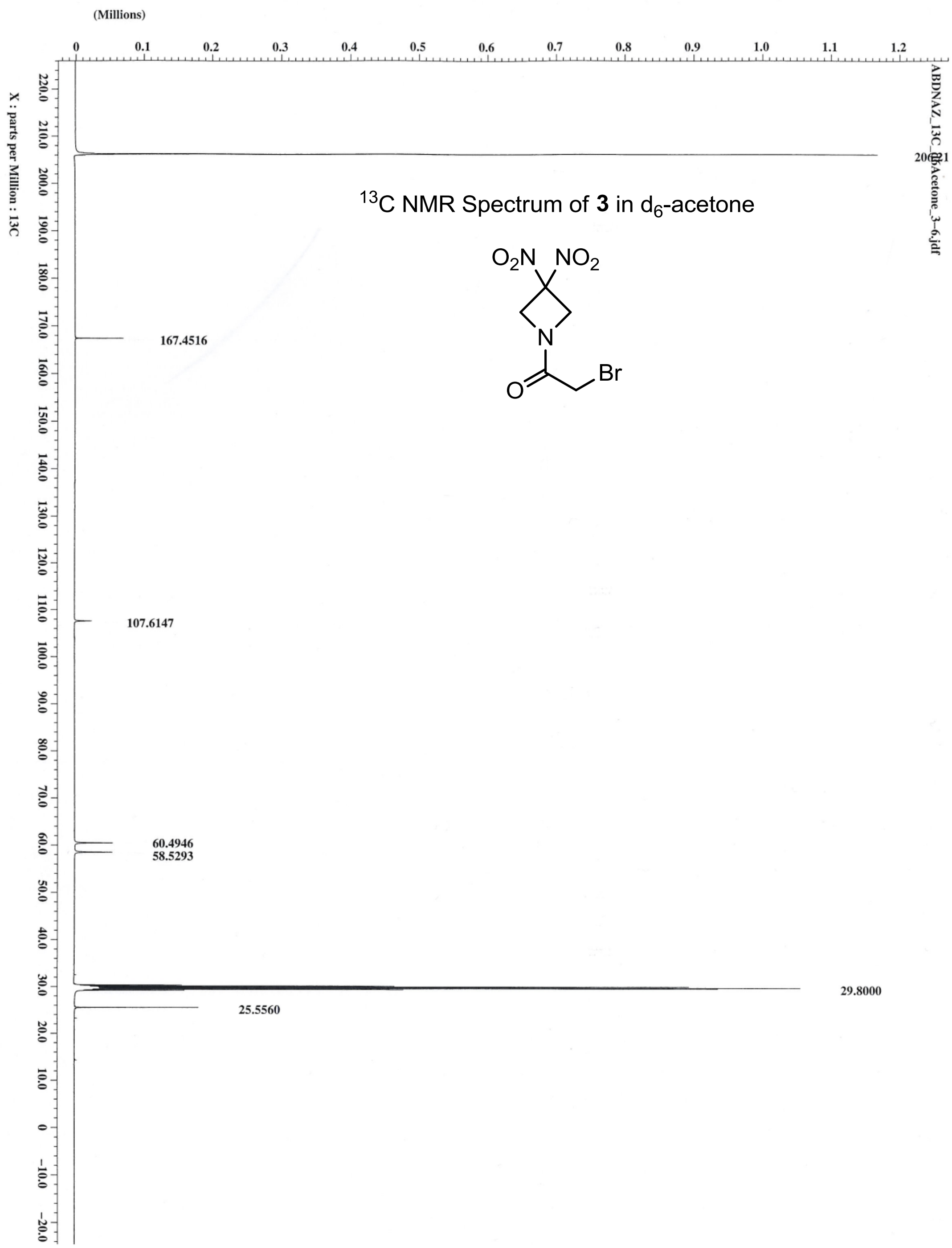
^{1}H NMR Spectrum of **2** in $CDCl_3$
O_2N NO_2
N
(Millions)
0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0
X : parts per Million : 1H
12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0 −1.0 −2.0
7.2500
4.0784
1.0076
0.3
3.9
9
t_bu_DNAZ_CDCl3-6.jdf



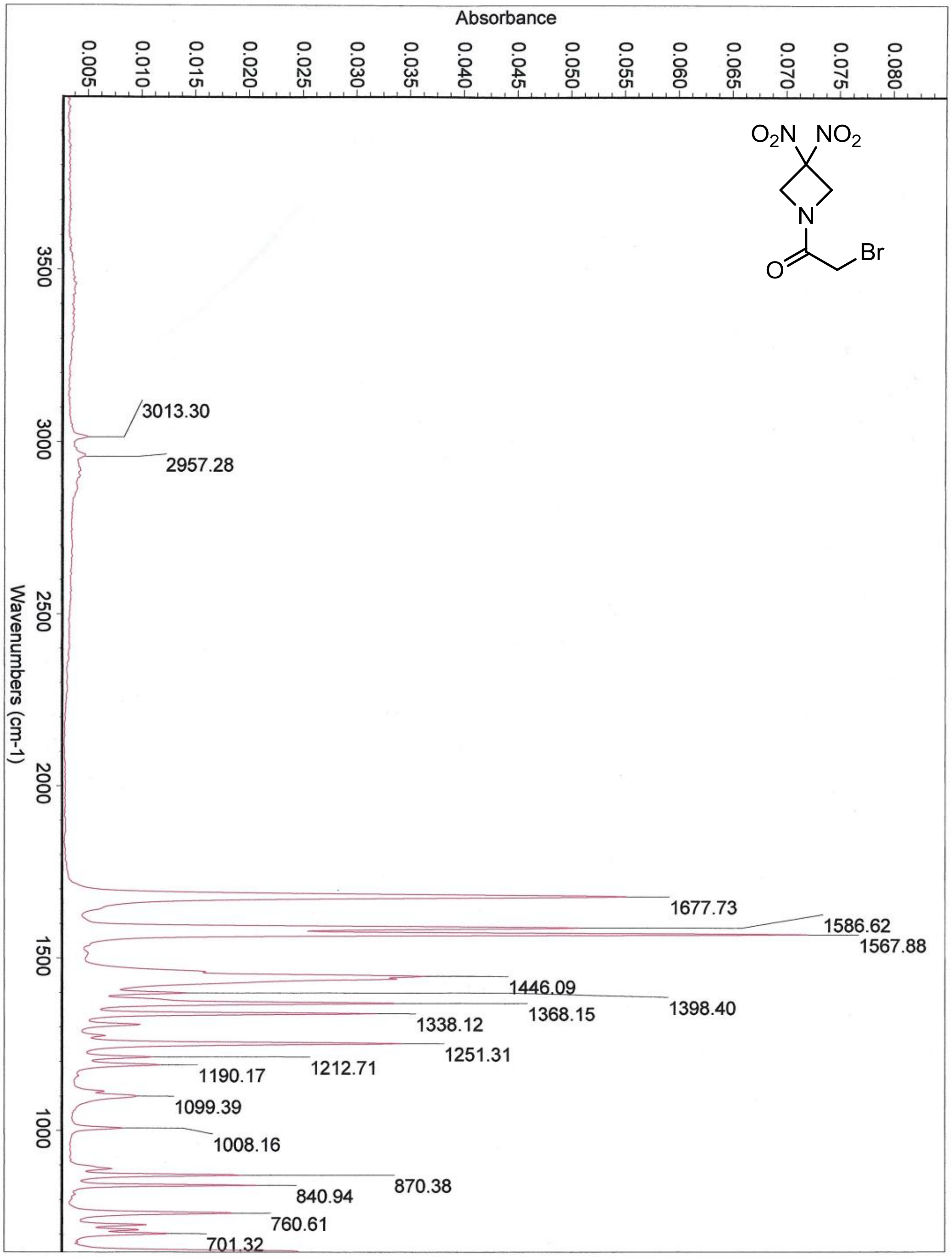
^{13}C NMR Spectrum of **2** in $CDCl_3$



^1H NMR Spectrum of **3** in d_6-acetone


(Millions)
X : parts per Million : 13C
^{13}C NMR Spectrum of **3** in d_6-acetone
O_2N
NO_2
N
O
Br
167.4516
107.6147
60.4946
58.5293
29.8000
25.5560

FT-IR Spectrum of Compound 3 (neat)

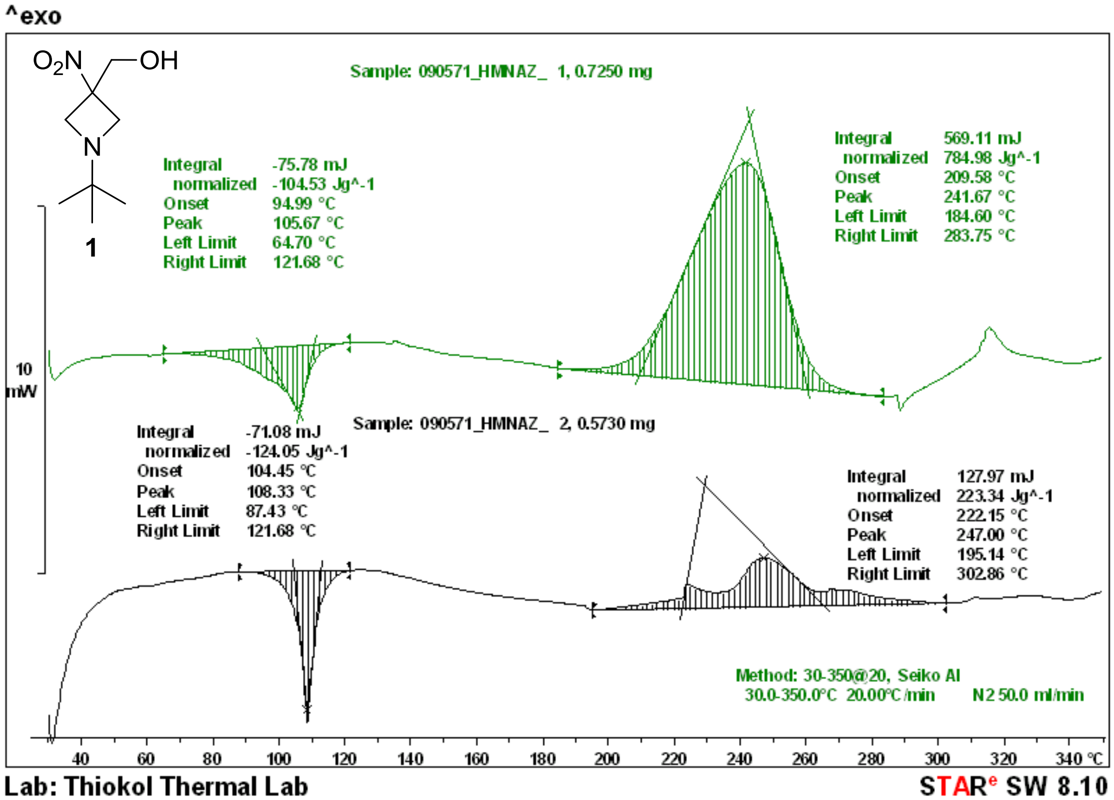


Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) analyses were conducted on powder samples of compounds **1-4** at a heating rate of 20 °C/min in heavy duty 15 µL (~200 mg) aluminum pans (Seiko A115-capsule, Perkin-Elmer part number N-5356003) with a truly hermetic cold-weld metal seal.

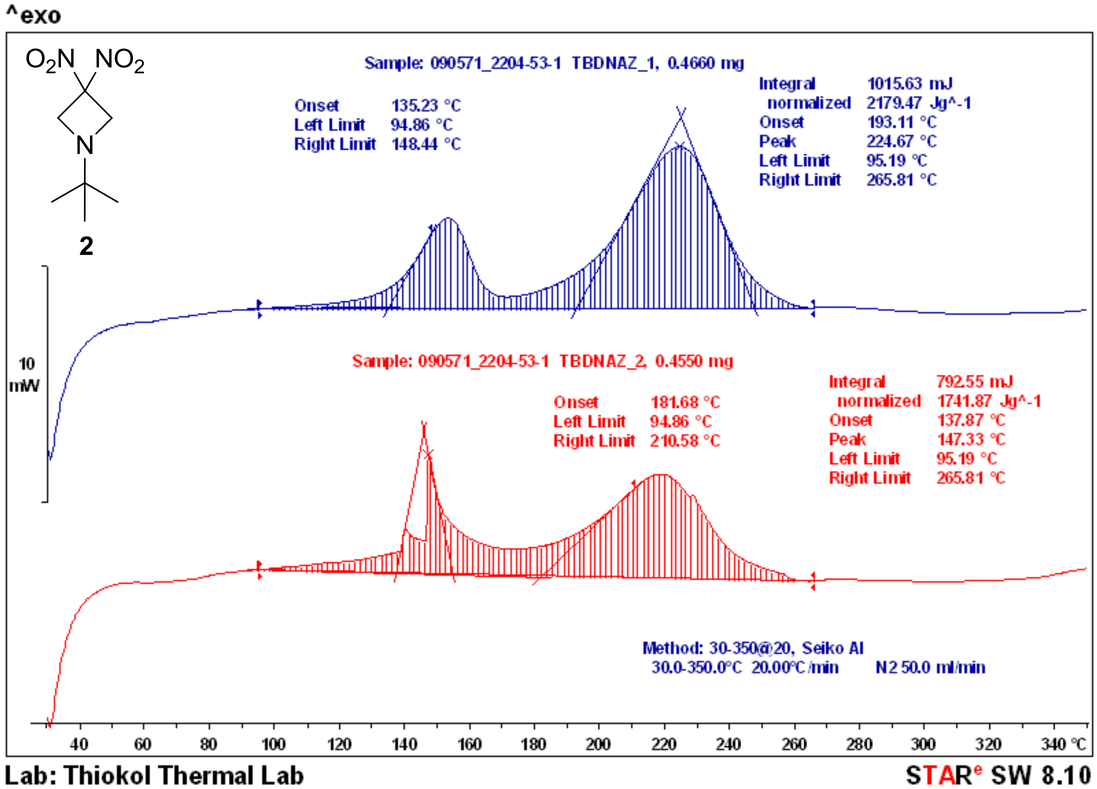
DSC Trace of Compound 1

Ramp rate = 20 °C/min



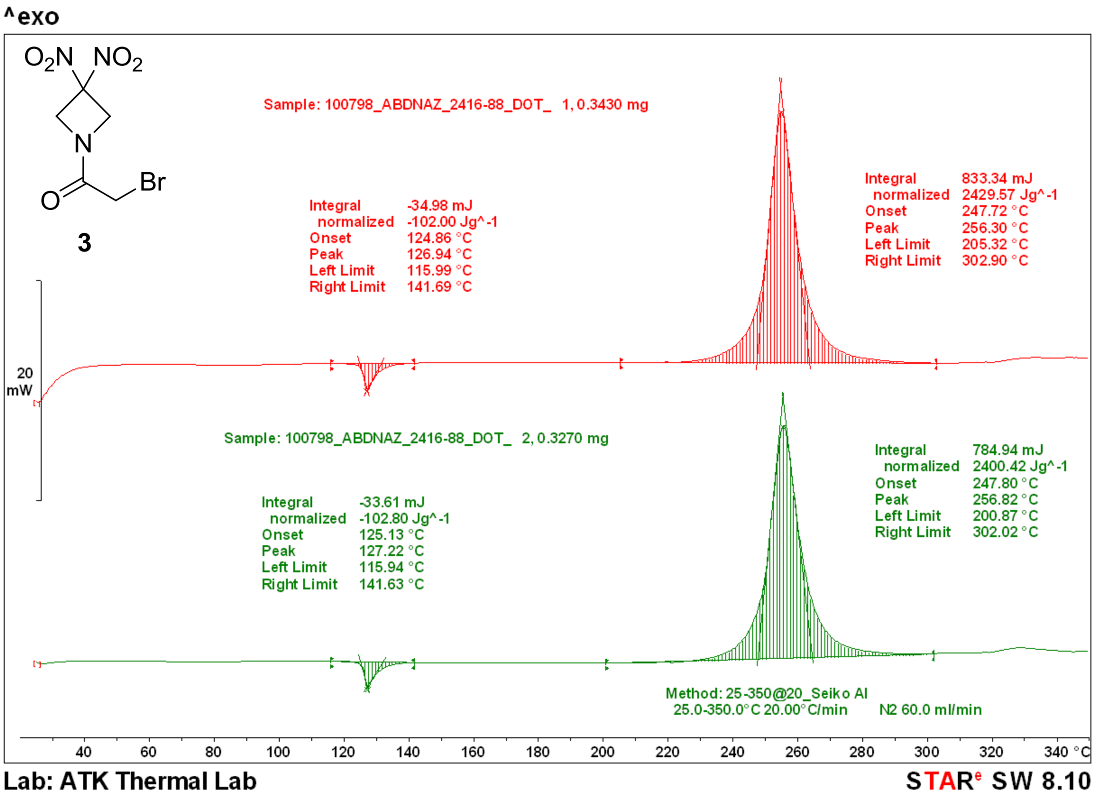
DSC Trace of Compound 2

Ramp rate = 20 °C/min



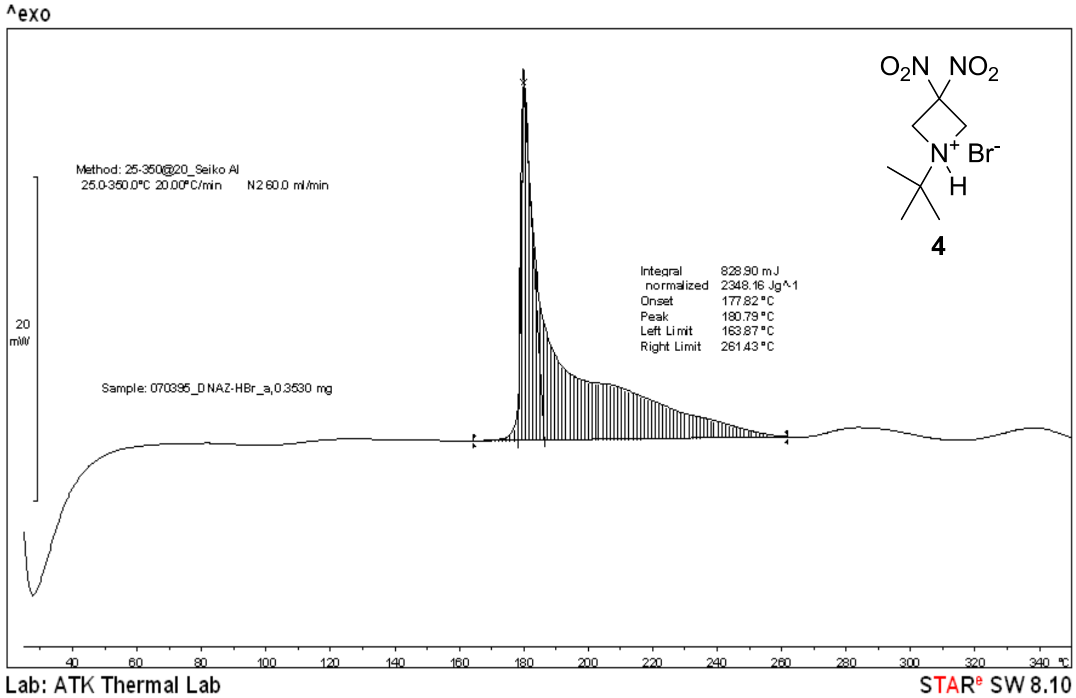
DSC Trace of Compound 3

Ramp rate = 20 °C/min



DSC Trace of Compound 4

Ramp rate = 20 °C/min



<u>Accelerating Rate Calorimetry (ARC)</u>

We have performed thermal stability testing, using accelerating rate calorimetry (ARC), on 1-*t*-butyl-3-hydroxymethyl-3-nitroazetidine (**1**), 1-*t*-butyl-3,3-dintrozetidine (**2**), 1-bromoacetyl-3,3 dinitroazetidine (**3**), and 1-*t*-butyl-3,3-dinitroazetidine hydrobromide (**4**).

ARC is a laboratory calorimetric method designed to simulate the adiabatic self-heating and thermal runaway behavior of bulk quantities of material. In adiabatic mode, the ARC calorimeter walls track the sample container temperature, resulting in a theoretically zero temperature gradient between sample and surroundings. This simulates the poor dissipation of heat in a large mass of decomposing energetic material. Temperature and pressure data are recorded during the experiment.

Samples are heated stepwise in 5 °C increments, with adiabatic holds at each temperature. When the calorimeter detects an exotherm (defined as a self-heat rate in excess of 0.02 °C/min) it remains in adiabatic mode until the exotherm is over or a preset upper temperature, pressure, or self-heat rate limit is reached.

Both the starting material (**1**) and the final product (**3**) show initial ARC exotherms in the vicinity of 115 and 125 °C respectively. These exotherms seem to occur near endotherm (probably melting) temperatures observed in DSC tests. There is no indication from this screening evaluation that that these materials are unstable in ambient storage.

Compound **2** shows a very low ARC initial exotherm temperature (75 °C) and is probably too unstable to store in large quantities in the neat form. Dilution to 6.6% in methylene chloride seems to mitigate the short-term thermal runaway risk. However, if the material is to be stored for long times, the possibility of decomposition and gas evolution under storage conditions should be investigated.

EXPERIMENTAL

Sample Description and Preparation. Five different samples were analyzed: **1**, **2**, 6.6 % **2** in CH_2Cl_2, **3**, and **4**.

ARC Analysis Conditions. With all materials except **2** in CH_2Cl_2, small (~0.3 g) samples were initially run in 1” diameter titanium bombs and allowed to self-heat to thermal runaway and/or autoignition. Then, runs with larger samples and/or smaller bombs (1/2” diameter titanium or stainless steel) were made to increase the sensitivity of the measurements and provide a better representation of bulk thermal runaway behavior. To avoid bomb ruptures, the calorimeters were programmed to turn off before these samples autoignited, with the objective of only measuring the initial part of the exothermic thermal runaway.

Thermal inertia (phi) factors were calculated for all runs and, the lower the phi factor, the more sensitive the measurement. A massless bomb (ultimate sensitivity) would have a thermal inertia or phi factor of 1.

All samples were heated stepwise from 50 °C in 5 °C increments, while monitoring for exotherms at each temperature.

Results for 1. Figures 1 and 2 show typical ARC temperature and pressure vs. time plots for **1** (large bomb/small sample, small bomb/larger sample respectively), while Figure 3 shows self-heat rate vs. temperature plots for exotherms observed during the various runs on **1**. Samples, large and small, start to exotherm in the vicinity of 115 °C (just above the apparent melting point observed in DSC). The acronym HMNAZ refers to **1**.

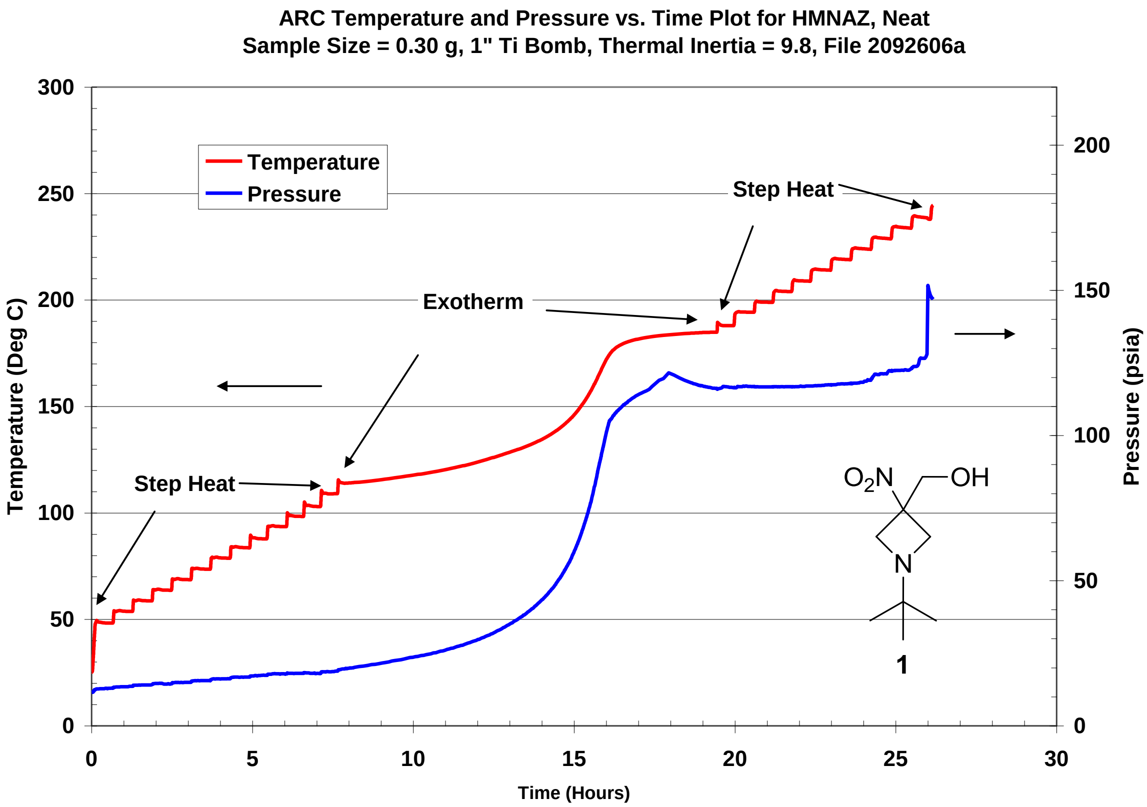


Figure 1. ARC temperature and pressure plot for neat 1 (small sample, large bomb). 1" Ti bomb, sample size = 0.30 g, thermal inertia = 9.8.

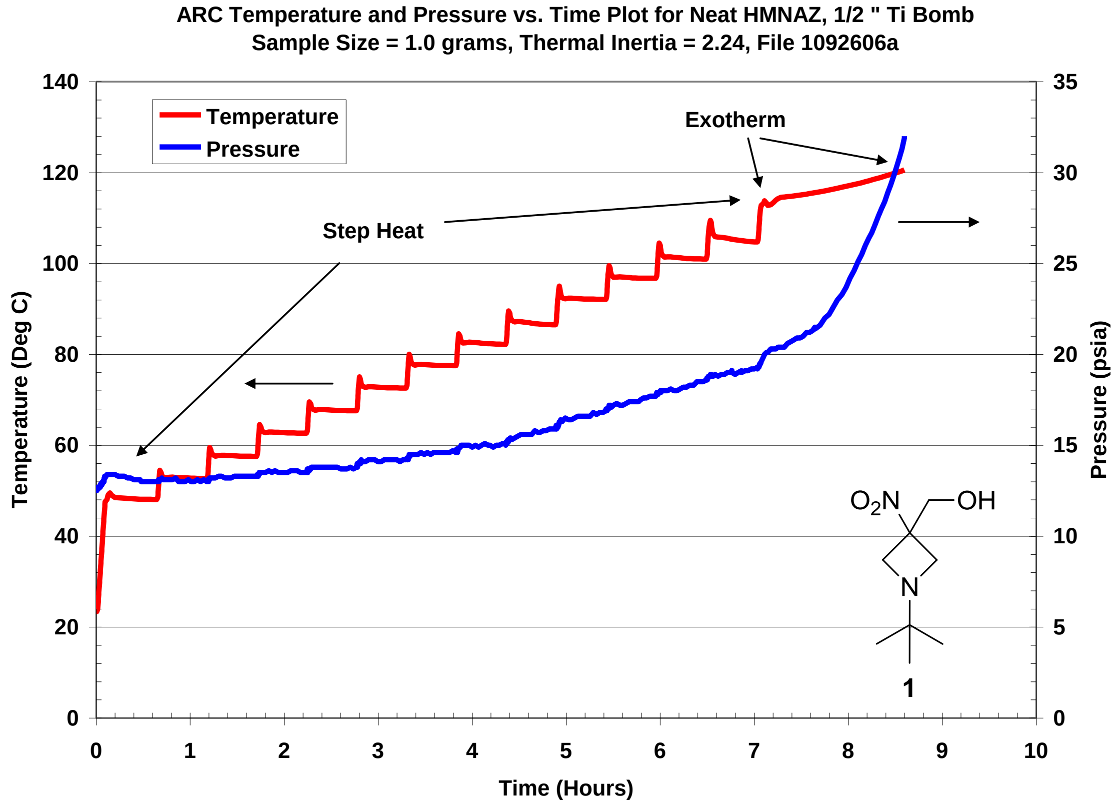


Figure 2. ARC temperature and pressure vs. time plot for neat 1 (larger sample, small bomb). 0.5" Ti bomb, sample size = 1.0 g, thermal inertia = 2.24

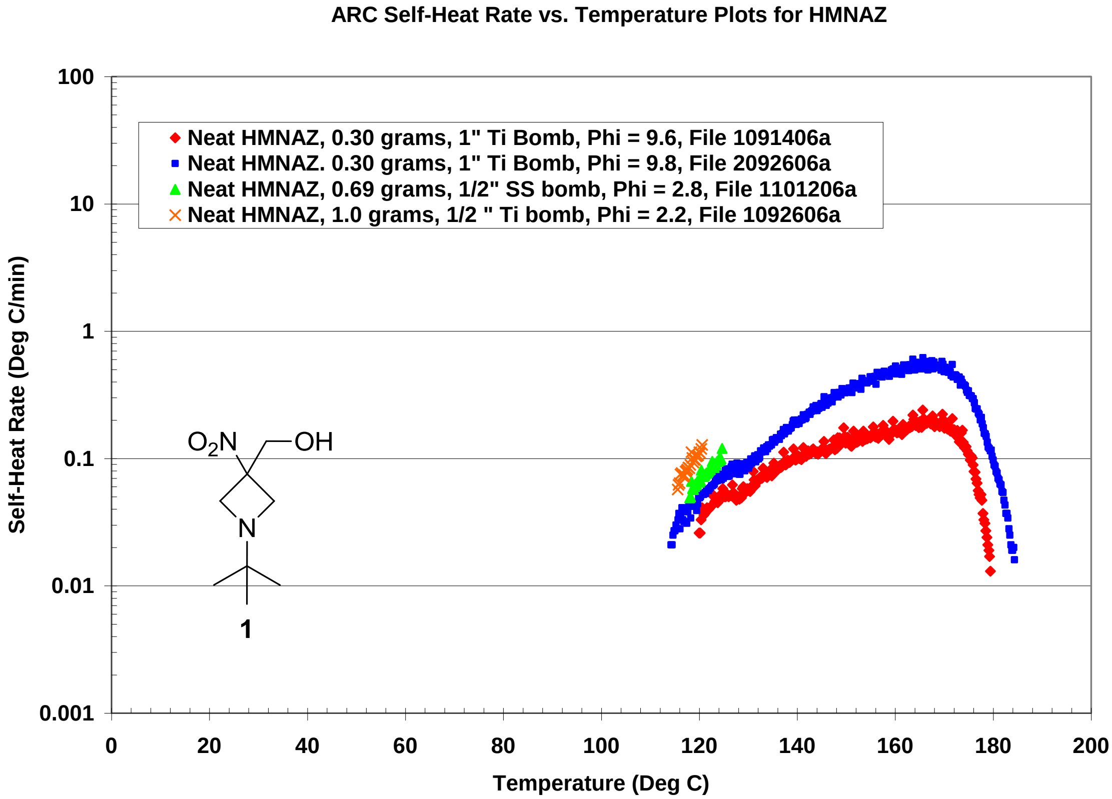


Figure 3. ARC self-heat rate vs. temperature for exotherms observed in tests on 1.

Results for 2. Figures 4 and 5 show ARC temperature and pressure vs. time plots for neat **2**, while Figure 6 is a temperature and pressure vs. time plot for 6.6 % **2** in CH_2Cl_2. Figure 7 shows ARC self-heat rate vs. temperature plots for the exotherms observed in the tests described in Figures 4-6. The acronyms t-Butyl DNAZ and TBDNAZ refer to **2**.

Neat **2** shows its initial exotherm in the vicinity of 75 °C (Figures 4, 5, 7). As such, this material is probably too unstable to store in large quantities for extended periods of time. When it is diluted to 6.6 % with CH_2Cl_2 (Figures 6 and 7) the exothermic activity is very much reduced and the initial exotherm is observed at 135 °C.

There is, with the CH_2Cl_2 mixture, some significant negative temperature drift above 100 °C (Figure 6) that might be due to endothermic processes such as the CH_2Cl_2 refluxing inside the apparatus, or a small bomb leak. This negative drift could mask some lower level exothermic activity. We do not believe there was a significant bomb leak because the system was still holding a large amount of gas pressure after it had cooled down to ambient. When the fitting on the calorimeter lid was loosened, there was a gas pressure release with significant entrained solvent, so weighing of the bomb (normal procedure after a run) could not be used to determine whether or not there had been a leak.

The ARC tests suggest that mixing **2** with CH_2Cl_2 greatly reduces the thermal runaway hazard and this may be a viable method for short-term storage of **2**. There may be some risk of decomposition with gas buildup in storage with this material and it is recommended that these issues be investigated if long term storage is envisioned.

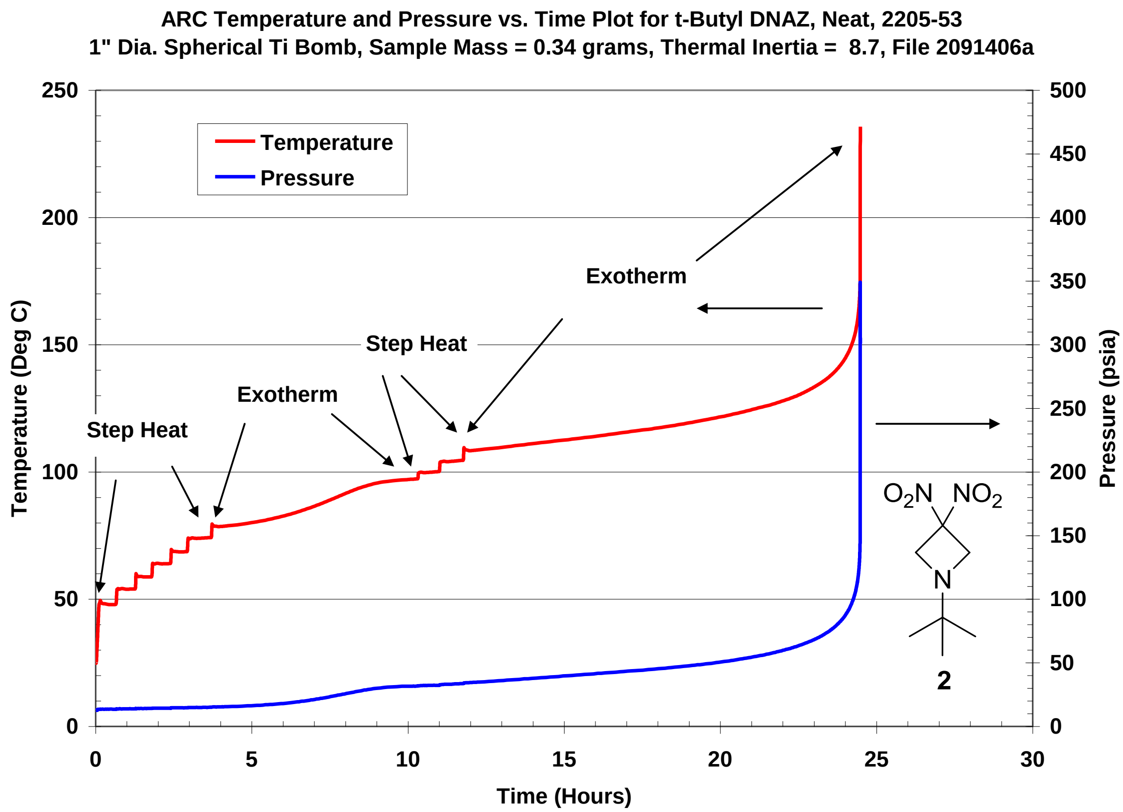


Figure 4. ARC temperature and pressure plot for neat 2 (small sample, large bomb). 1" Diameter spherical Ti bomb, sample mass = 0.34 g, thermal inertia = 8.7.

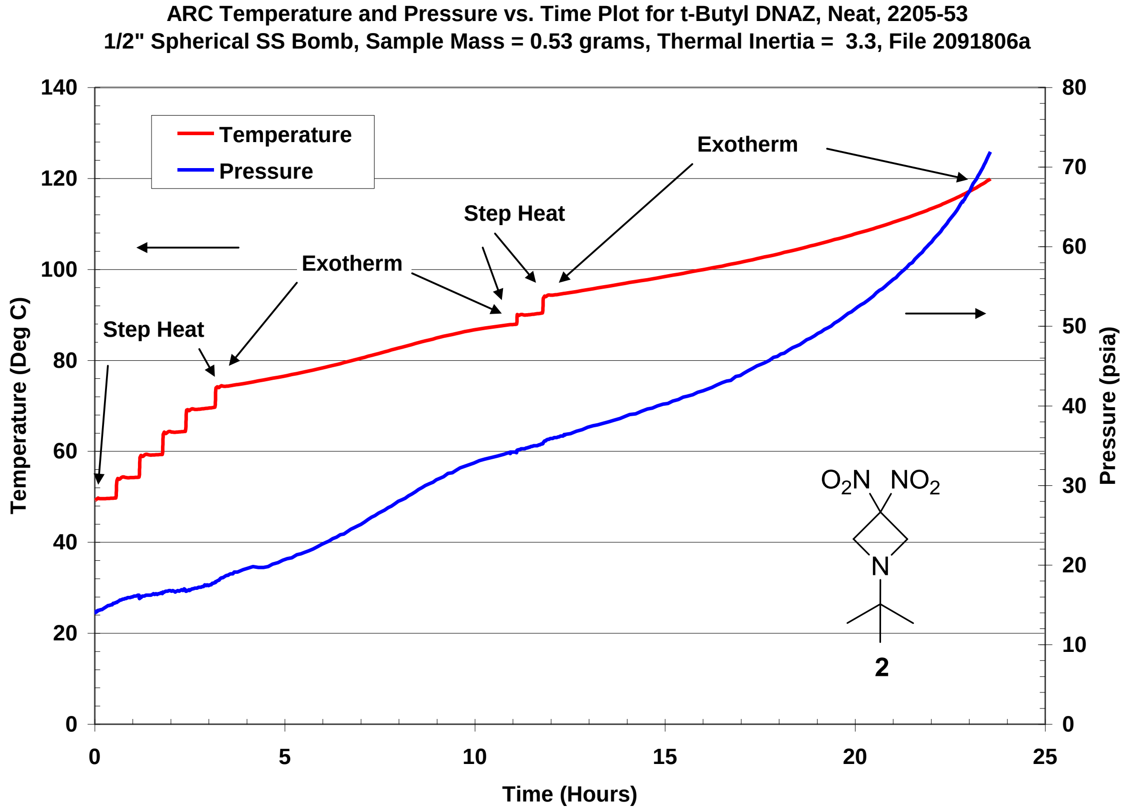


Figure 5. ARC temperature and pressure plot for neat 2 (larger sample, small bomb). 0.5" Spherical SS bomb, sample mass = 0.53 g, thermal inertial = 3.3.

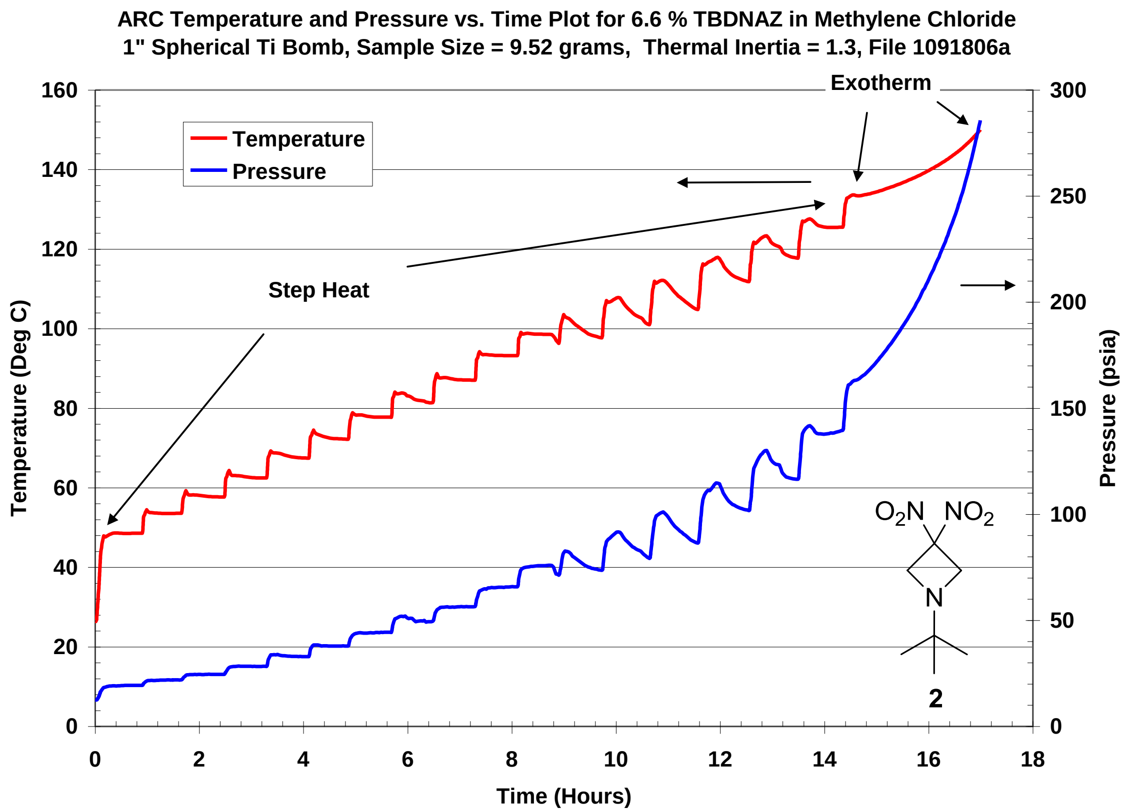


Figure 6. ARC temperature and pressure plot for 6.6 % 2 in CH_2Cl_2 (large sample, large bomb). 1” Spherical Ti bomb, sample size = 9.52 g, thermal inertia = 1.3.

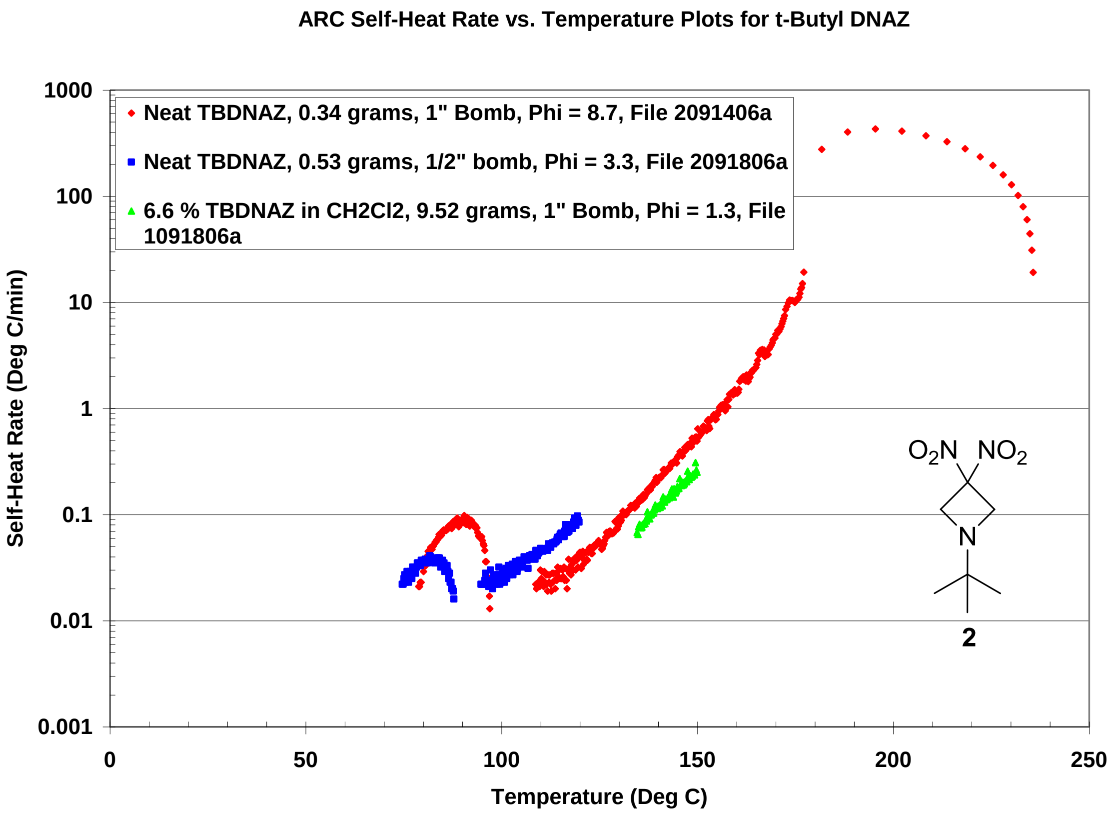


Figure 7. ARC self-heat rate vs. temperature for exotherms observed in tests on 2.

Results for 3. Figures 8 and 9 show ARC temperature and pressure vs. time results for **3** (large bomb/small sample and small bomb larger sample respectively). Figure 10 shows a self-heat rate versus temperature plot for the small sample run of Figure 8. The acronym ABDNAZ refers to **3**.

The small sample run showed an exotherm, leading to autoignition, at about 125 °C. The larger sample/smaller bomb run showed no exotherms up to 117 °C. As with **1**, the decomposition as measured by ARC seems to occur near the apparent melting point of the material as measured by DSC.

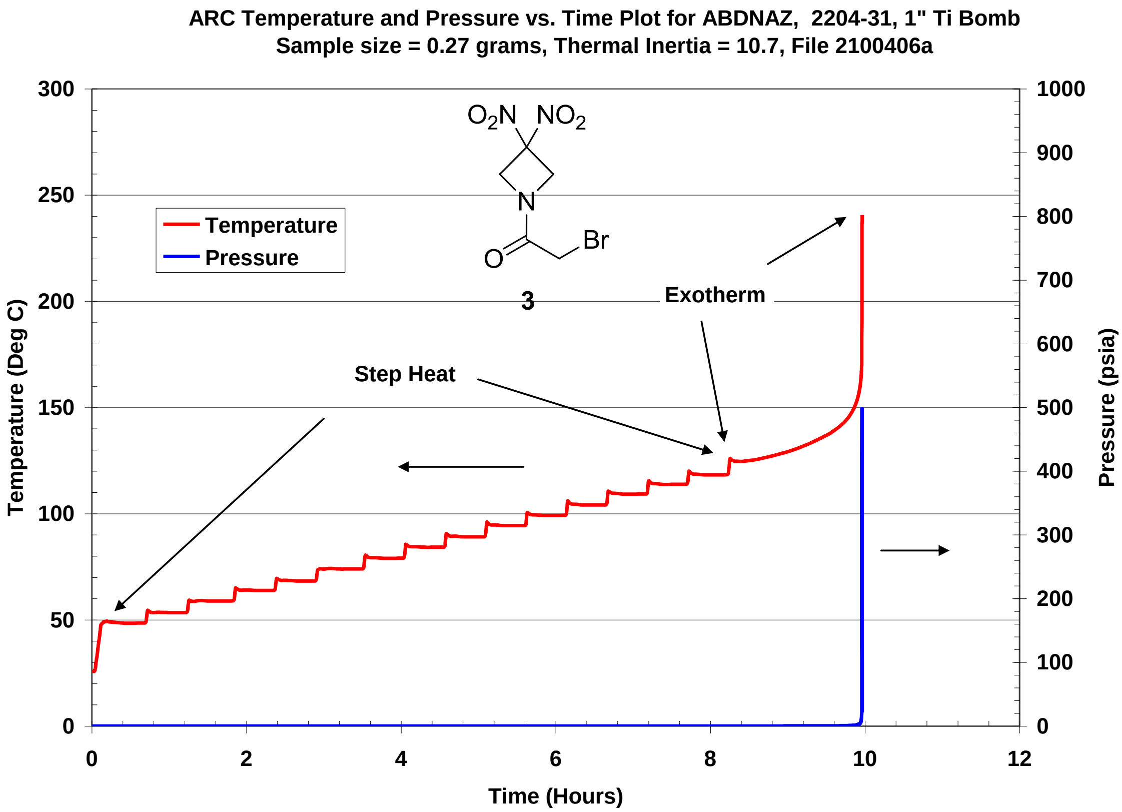


Figure 8. ARC temperature and pressure plot for neat 3 (small sample, large bomb). 1" Ti bomb, sample size = 0.27 g, thermal inertia = 10.7.

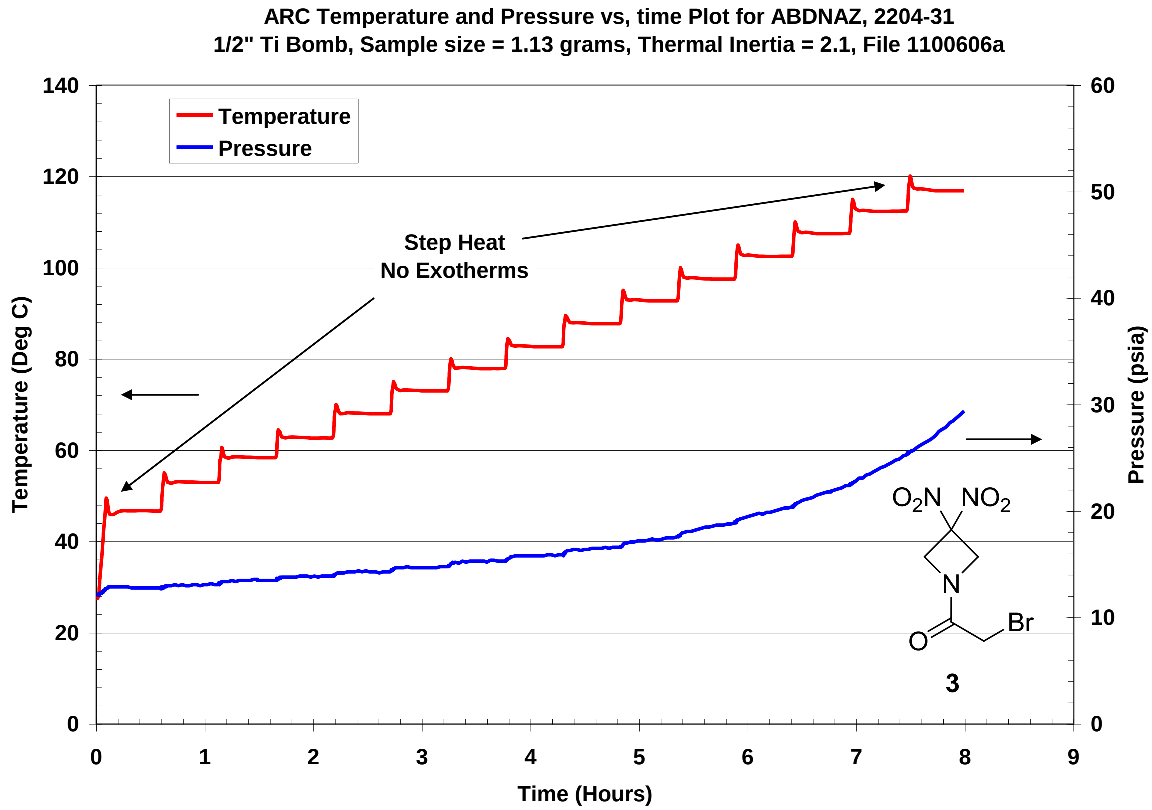


Figure 9. ARC temperature and pressure plot for neat 3 (larger sample, small bomb). 0.5" Ti bomb, sample size = 1.13 g, thermal inertia = 2.1.

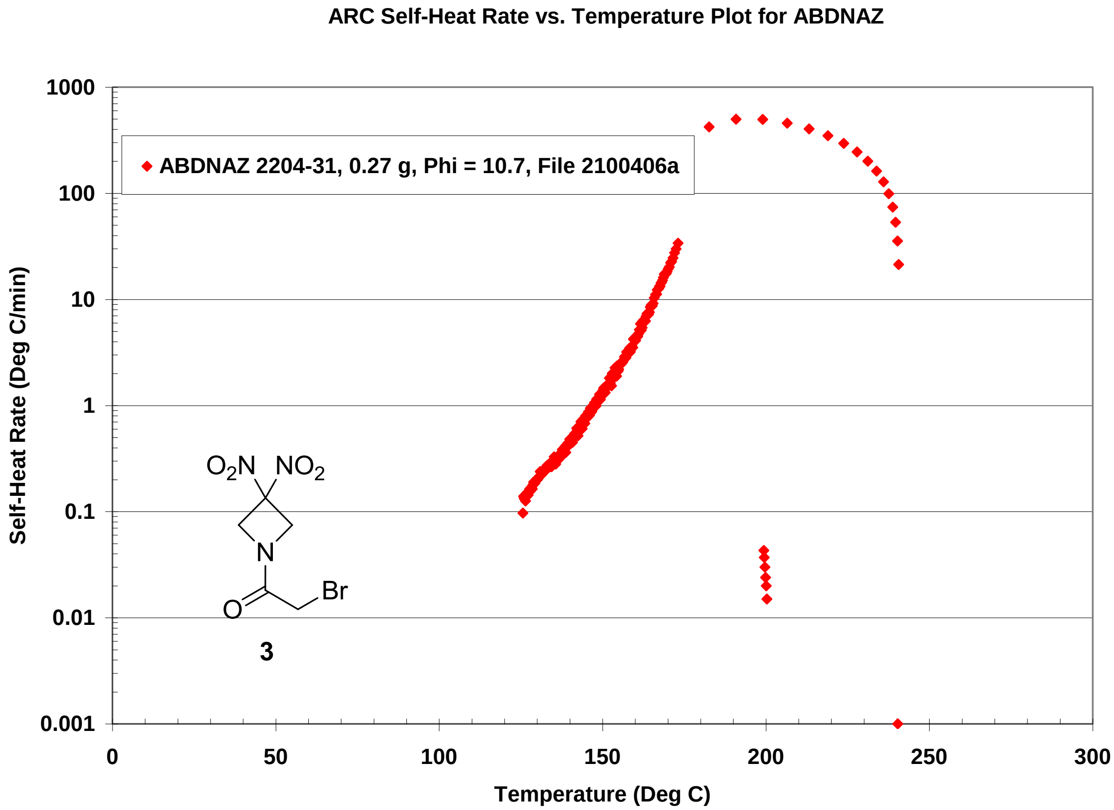


Figure 10. ARC self-heat rate vs. temperature for exotherms observed in tests on 3.

Results for 4. Figures 11 and 12 show the temperature and pressure versus time and self-heat rate versus temperature plots respectively for compound **4**. The acronym DNAZ-HBr refers to **4**.

With ARC, the initial exotherm for **4** is detected at a lower temperature (125 °C) than was the case with DSC. If the material were to be handled/stored in large quantities for an extended period of time, it would probably be advisable to run an ARC experiment with a larger sample (lower phi factor). However, for the conditions under which the material is being produced and handled, the testing done here is adequate.

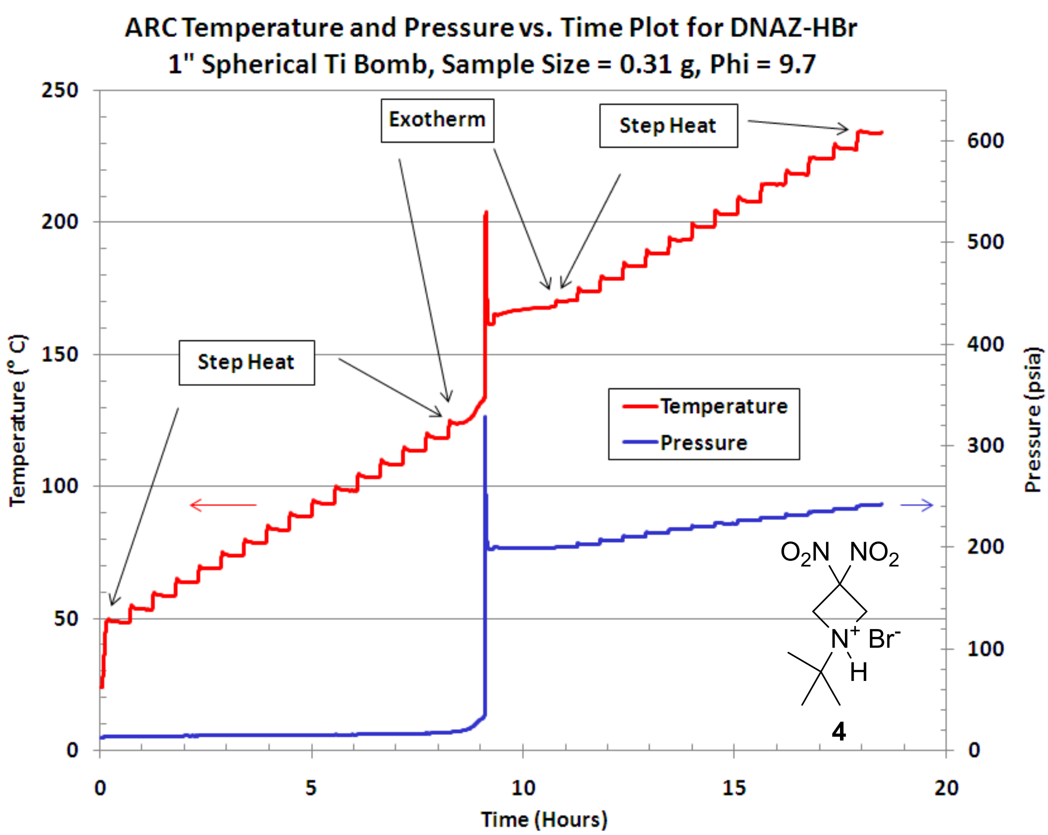


Figure 11. ARC temperature and pressure vs. time plot for 4.

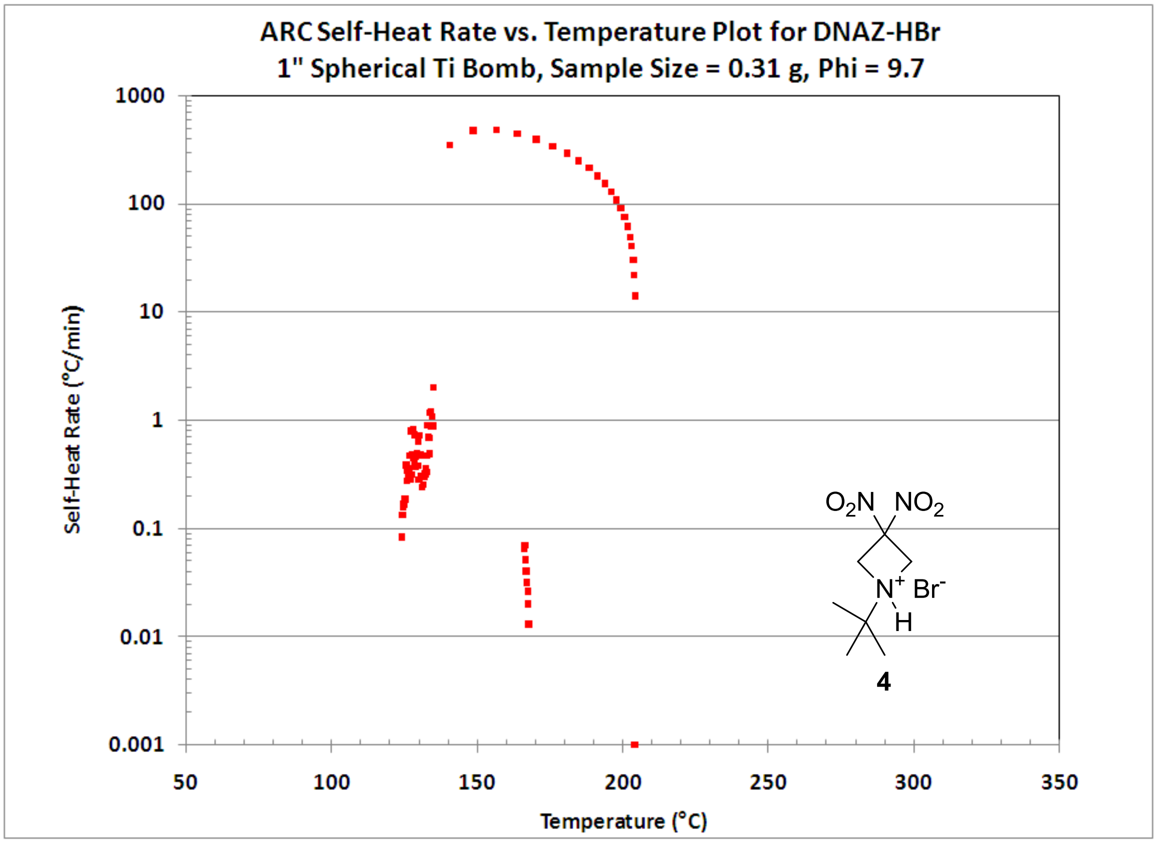


Figure 12. ARC self-heat rate vs. temperature plot for exotherm observed during decomposition of 4.

Reaction Calorimetry

The synthesis reaction of **2** was studied in a stirred reaction calorimeter to obtain quantifiable heat flow data to assess potential hazards in scale-up. The following steps were employed to represent the synthesis:

1. Add H_2O (68 mL) to the reactor and allow to equilibrate at 25 °C.
2. Add NaOH (1.93 g) and allow to dissolve.
3. Add **1** (4.53 g) and allow to dissolve via formation of the nitronate salt.
4. Cool the reactor contents to 10 °C.
5. Add a solution containing $K_3Fe(CN)_6$ (0.79 g), $NaNO_2$ (6.64 g), and H_2O (18 mL).
6. Add $Na_2S_2O_8$ (8.15 g) and allow to react for approximately 40 minutes at 10 °C.
7. Heat the reactor to 25 °C and stir for 16 h to allow the reaction to go to completion.

The reaction calorimeter heat flow curve for the entire synthesis of **2** is shown in Figure 13.

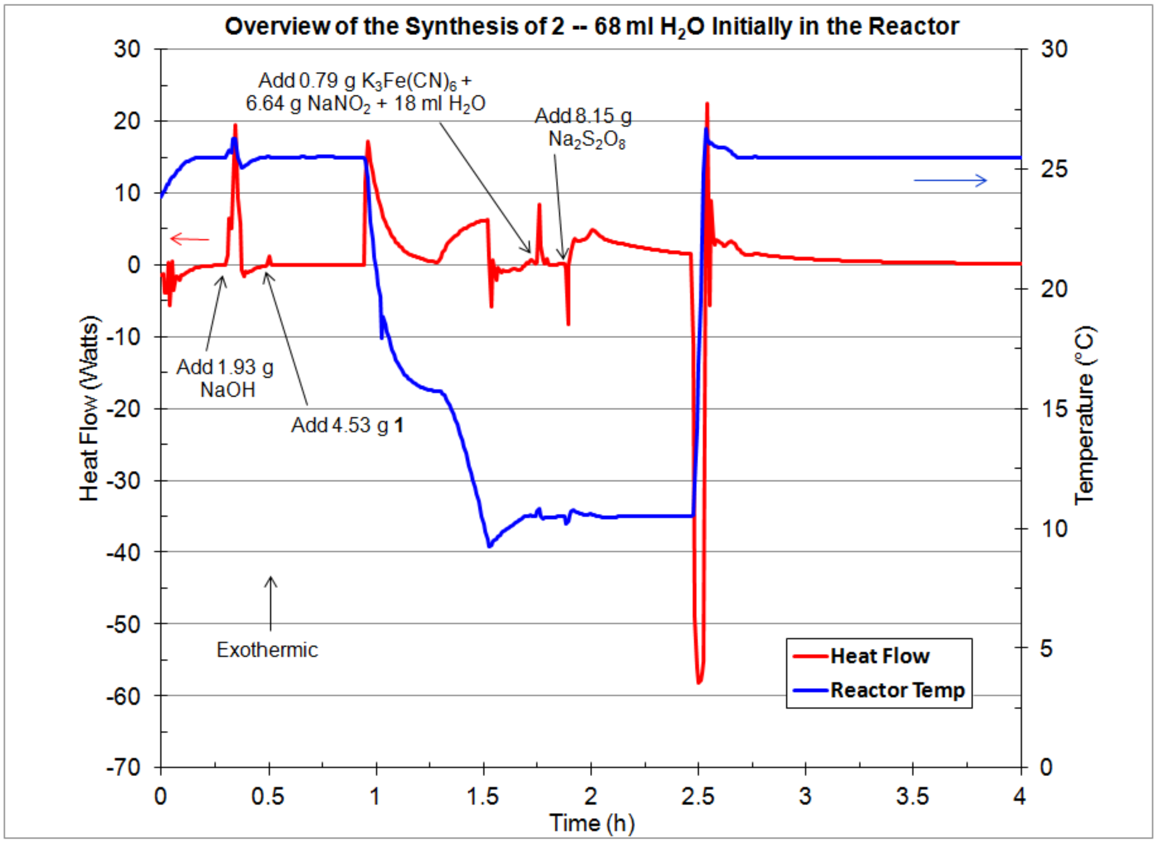


Figure 13. Reaction calorimeter heat flow curve for the entire synthesis of 2.