Supporting Information

Asymmetric organocatalysis and continuous chemistry for an efficient and cost competitive process to pregabalin

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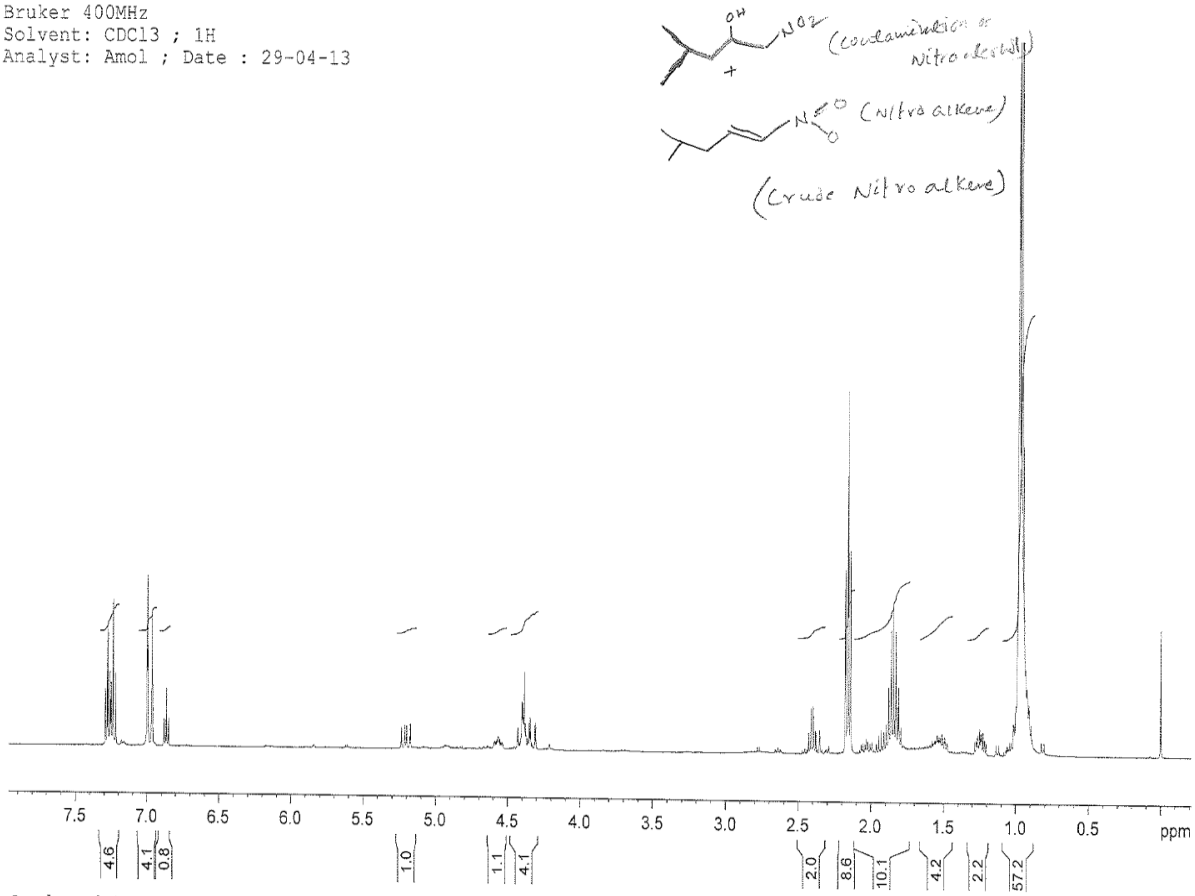
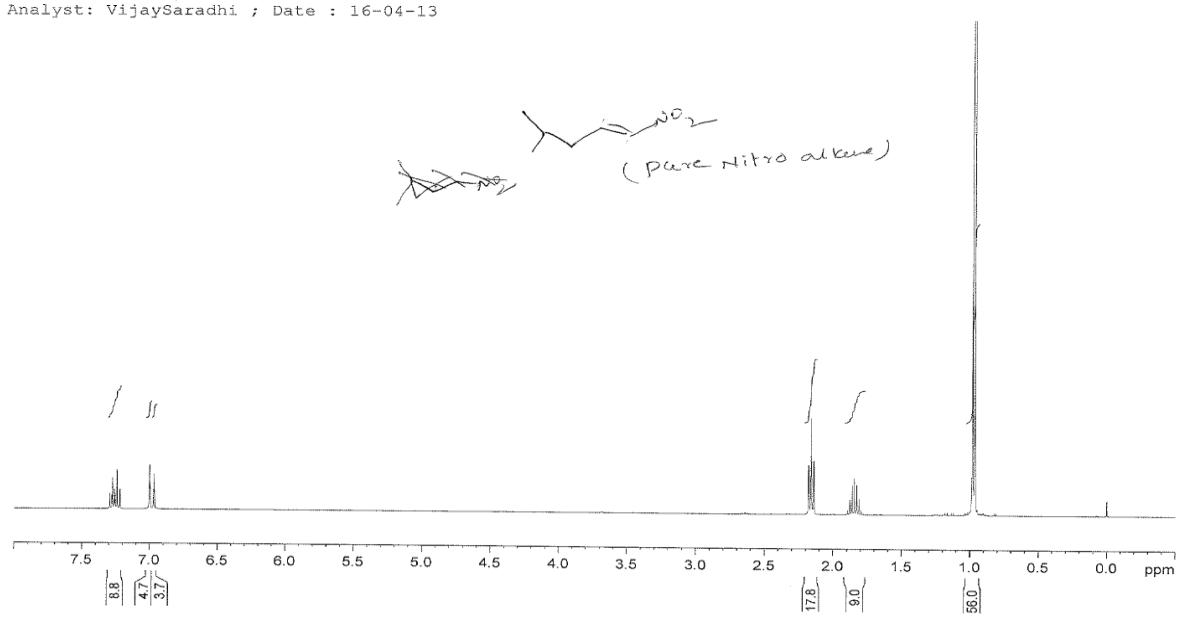
1. NMR of products 4 and 7

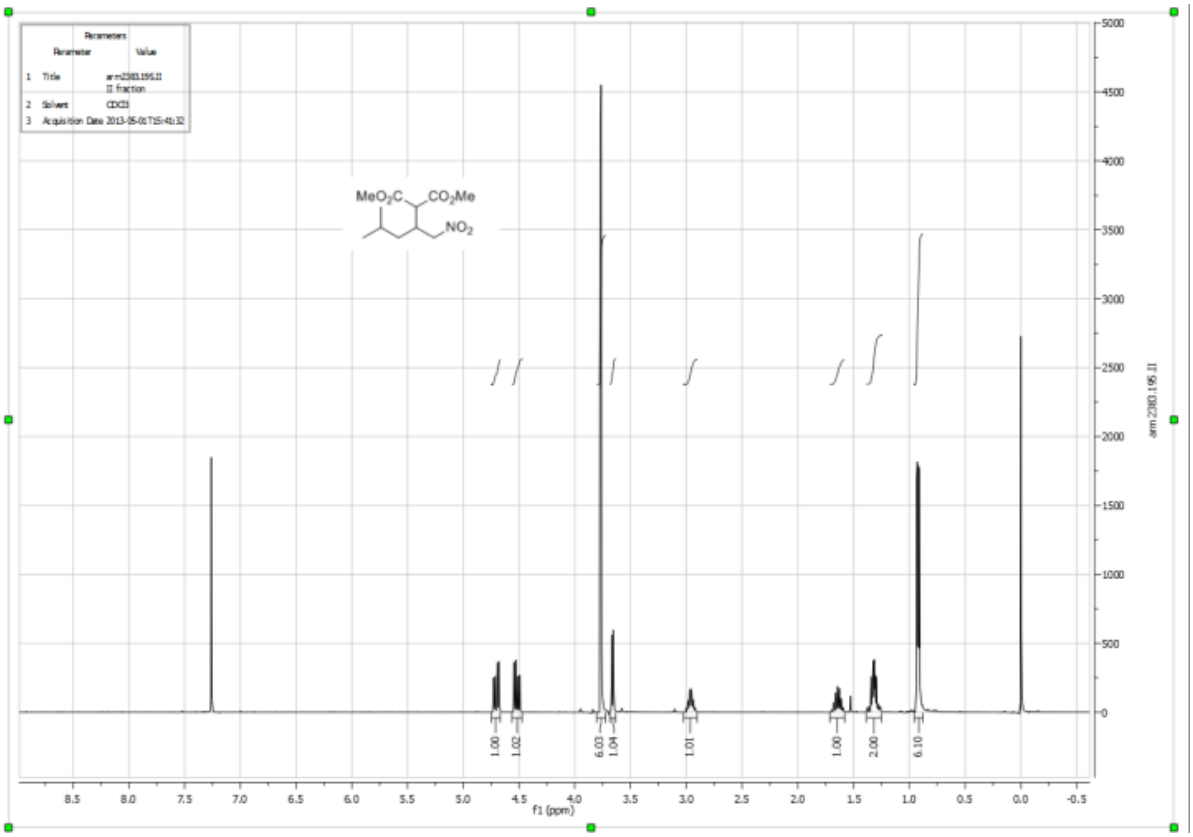
Batch No: PRG/H141/2C/03(R)
AR No: NM0413/402
Bruker 400MHz
Solvent: CDCl3 ; 1H
Analyst: Amol ; Date : 29-04-13



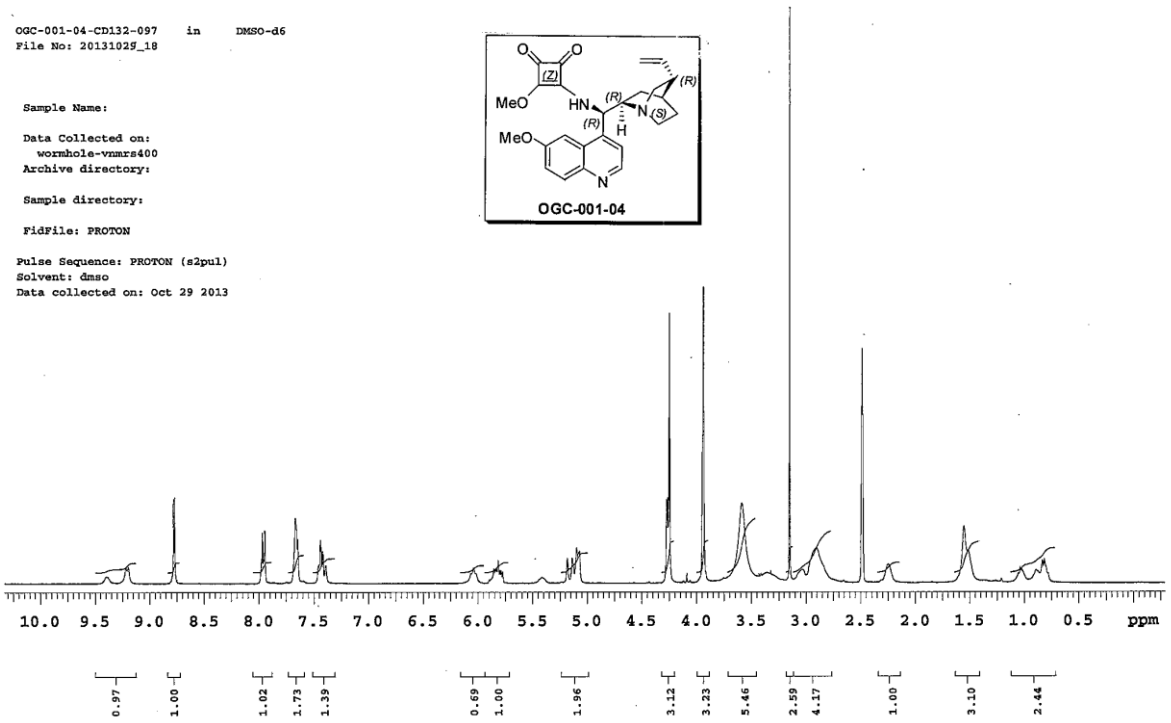
Analyzed By:

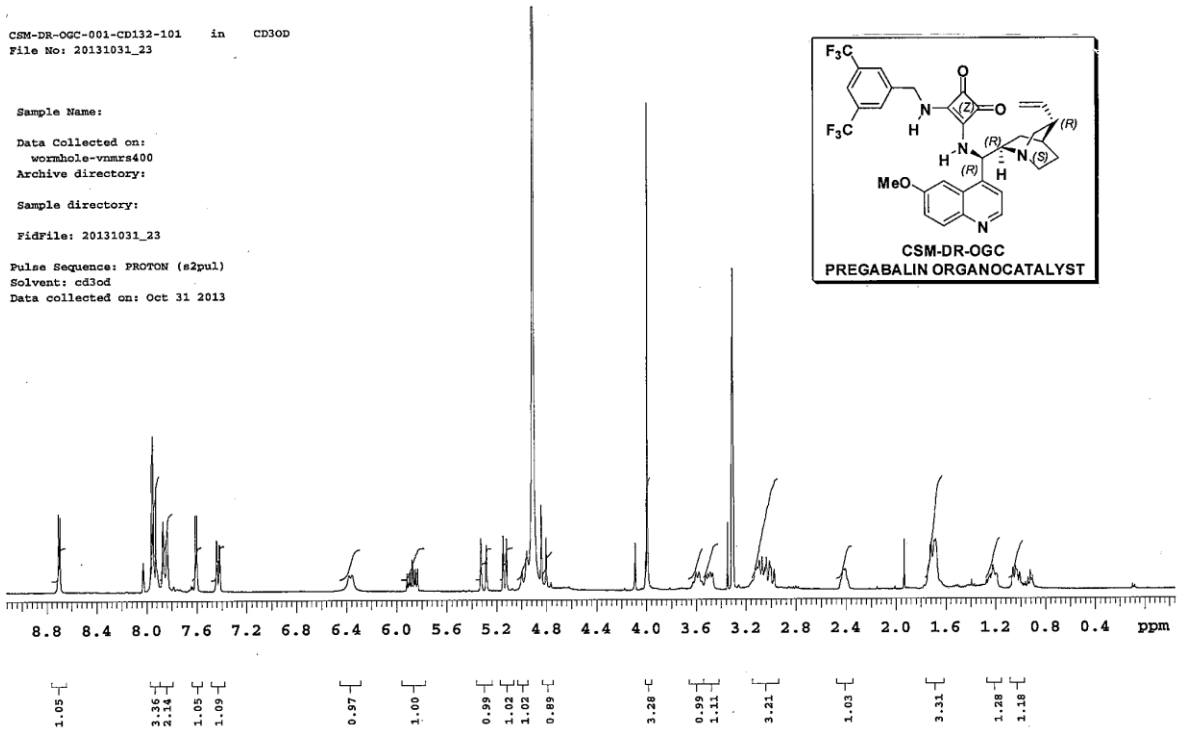
Batch No: PRG/H141/2C/02
AR No: NM0413/208
Bruker 400MHz
Solvent: CDCl3 ; 1H
Analyst: VijaySaradhi ; Date : 16-04-13



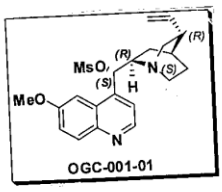

Parameters
Parameter Value
1 Title arm2383.195.II II fraction
2 Solvent CDCl3
3 Acquisition Date 2013-05-01T15:41:32
MeO2C
CO2Me
NO2
1.00
1.02
6.03
1.04
1.01
1.00
2.00
6.10
f1 (ppm)
arm2383.195.II

2. Analytical data of intermediates and catalyst 6a





OGC-001-01-CD121-257 in DMSO-d6
File No.20130926_32



OGC-001-01

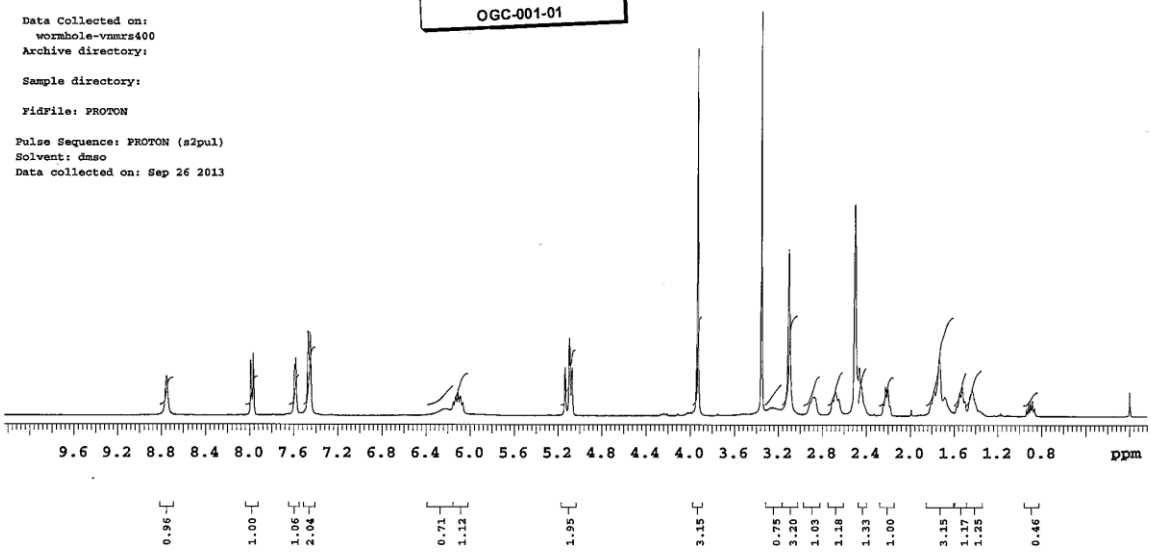
Sample Name:

Data Collected on:
wormhole-vnmrs400
Archive directory:

Sample directory:

FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Sep 26 2013



OGC-001-02-CD121-261 in DMSO-d6
File No.20130927_26

OGC-001-02

Sample Name:

Data Collected on:
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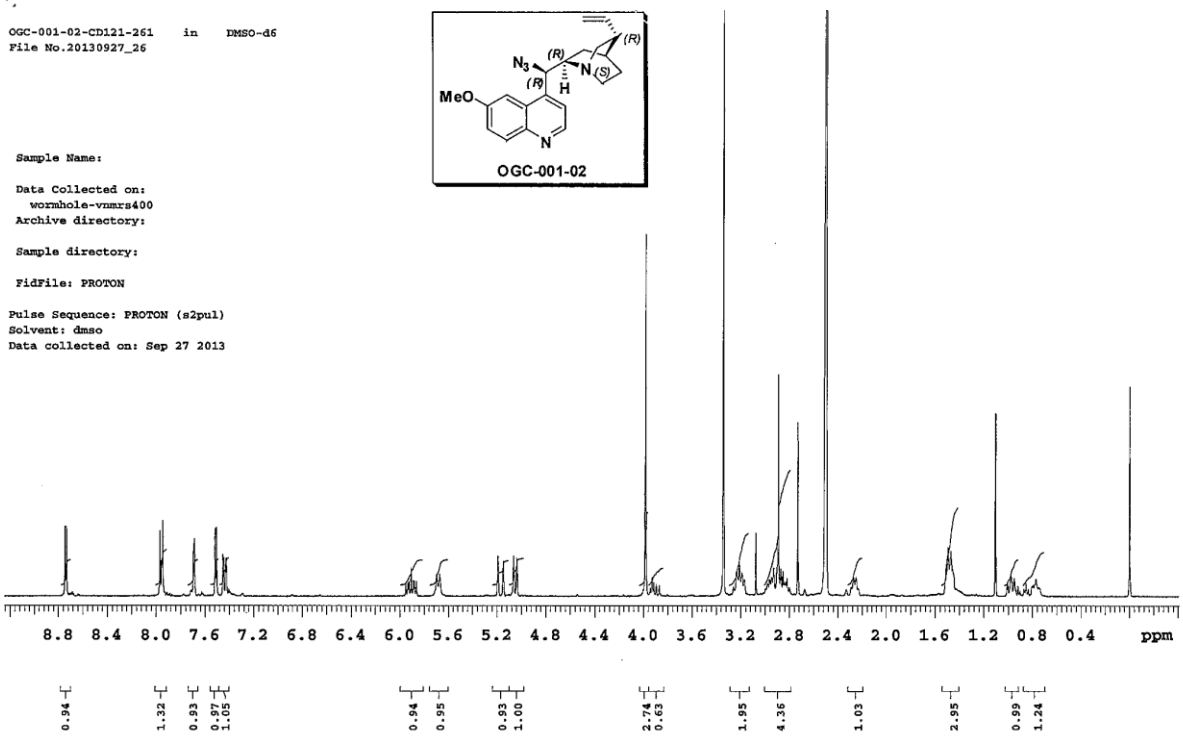
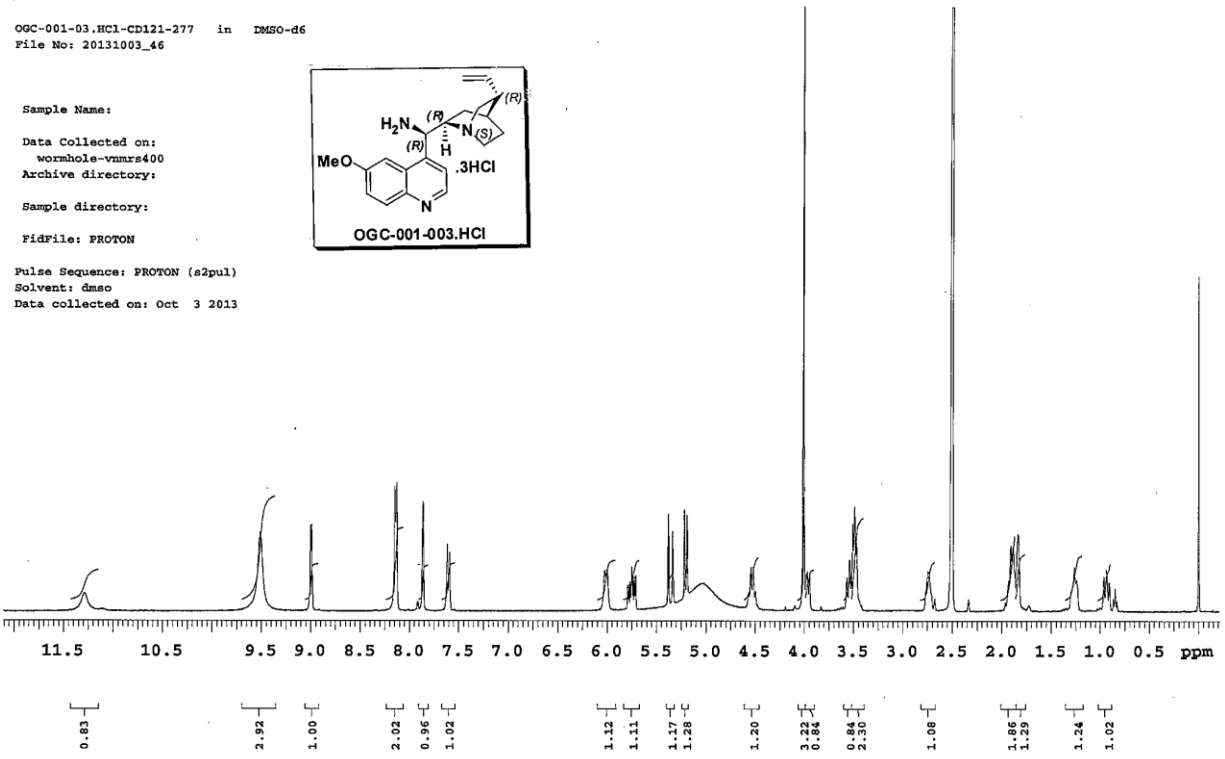
Archive directory:

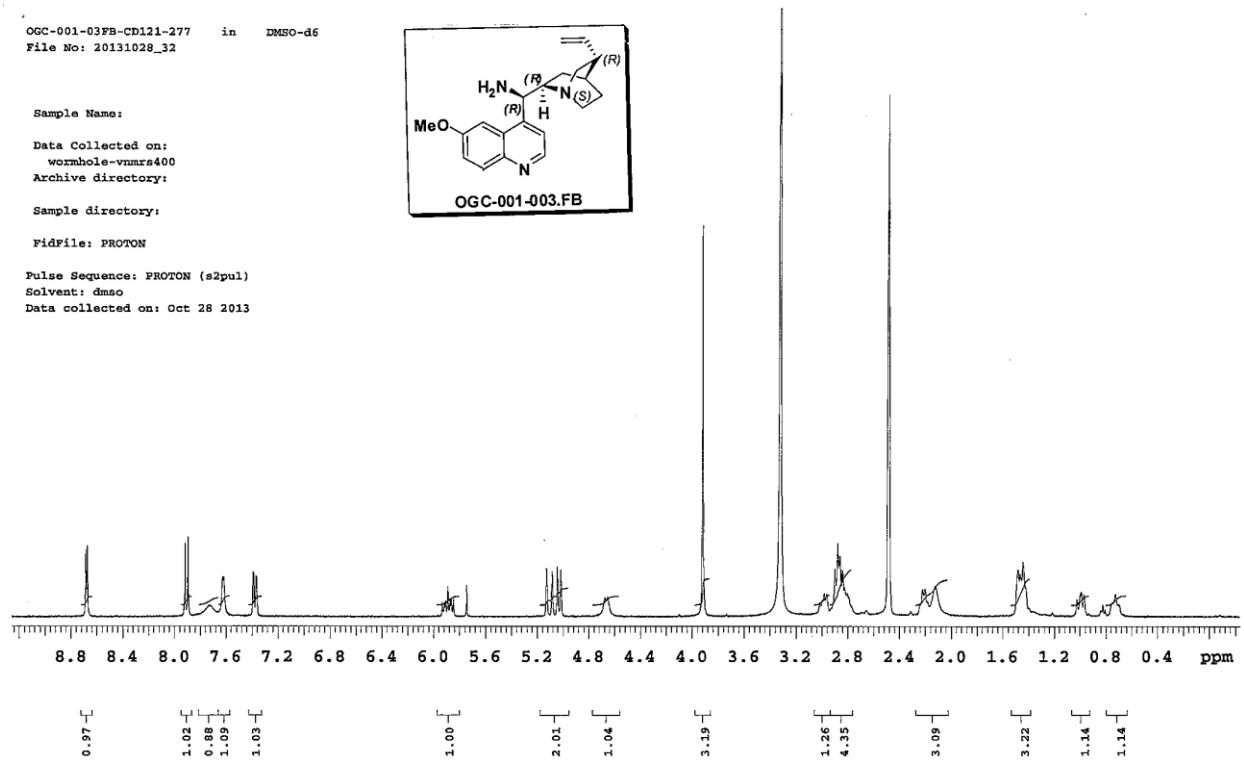
Sample directory:

FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Sep 27 2013




OGC-001-03.HCl-CD121-277 in DMSO-d6
File No: 20131003_46
Sample Name:
Data Collected on:
wormhole-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Oct 3 2013
MeO
.3HCl
OGC-001-003.HCl
11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.83 2.92 1.00 2.02 0.96 1.02 1.12 1.11 1.17 1.28 1.20 3.22 0.84 0.84 2.30 1.08 1.86 1.29 1.24 1.02


OGC-001-03FB-CD121-277 in DMSO-d6
File No: 20131028_32
Sample Name:
Data Collected on:
wormhole-vnmrs400
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Oct 28 2013
MeO
OGC-001-003.FB
8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 ppm
0.97 1.02 0.88 1.09 1.03 1.00 2.01 1.04 3.19 1.26 4.35 3.09 3.22 1.14 1.14

OGC-001-01B-CD132-005 in CDCl3
File No: 20131009_5

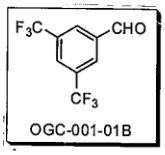
Sample Name:

Data Collected on:
wormhole-vnmrs400
Archive directory:

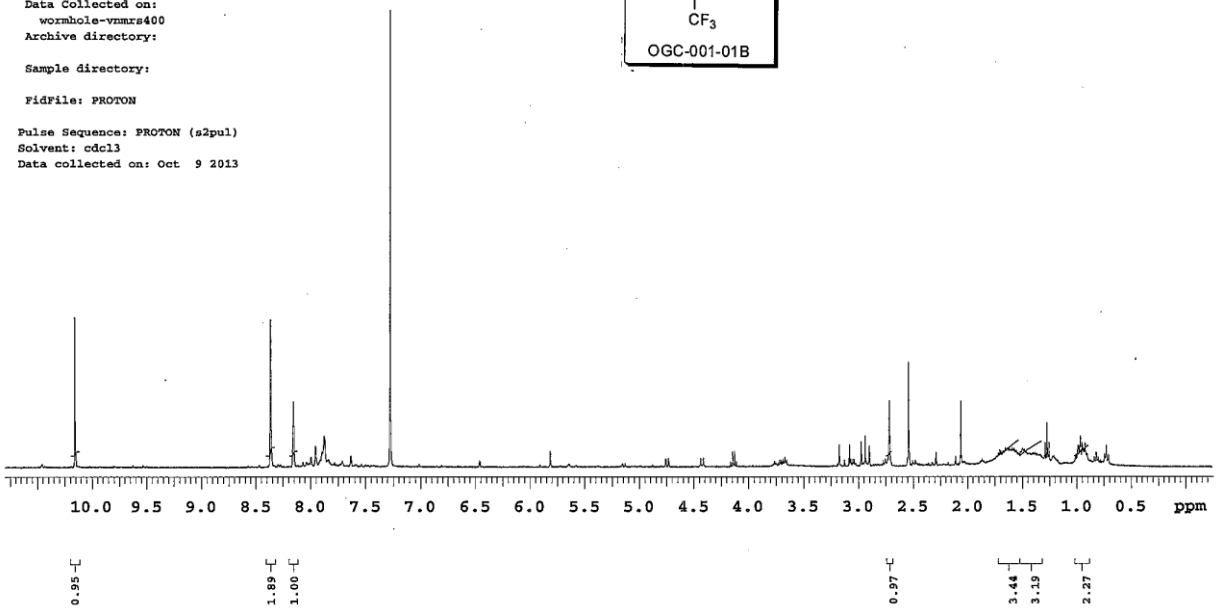
Sample directory:

FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 9 2013



OGC-001-01B



OGC-001-02B-CD132-017 in CDCl3
File No: 20131015_6

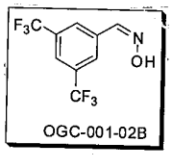
Sample Name:

Data Collected on:
wormhole-vnmrs400
Archive directory:

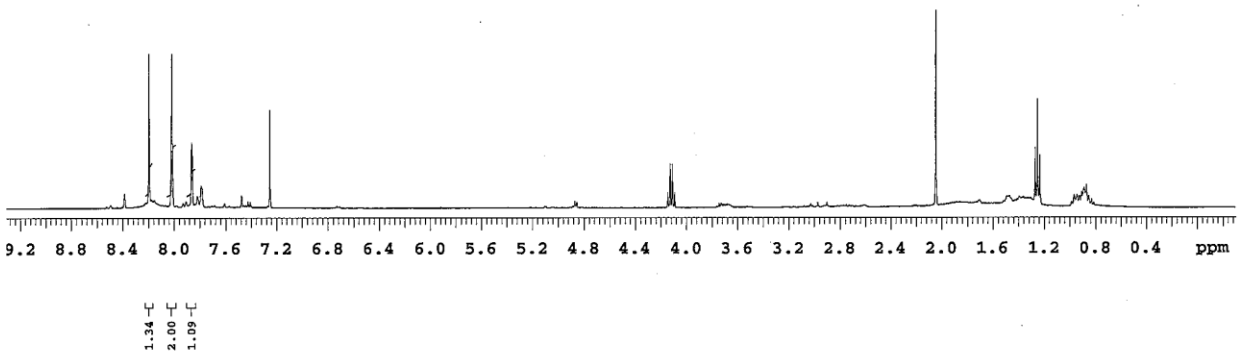
Sample directory:

FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 15 2013



OGC-001-02B



OGC-001-03B-CD132-045 in DMSO-d6
File No: 20131019_3

Sample Name:

Data Collected on:
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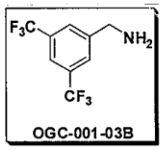
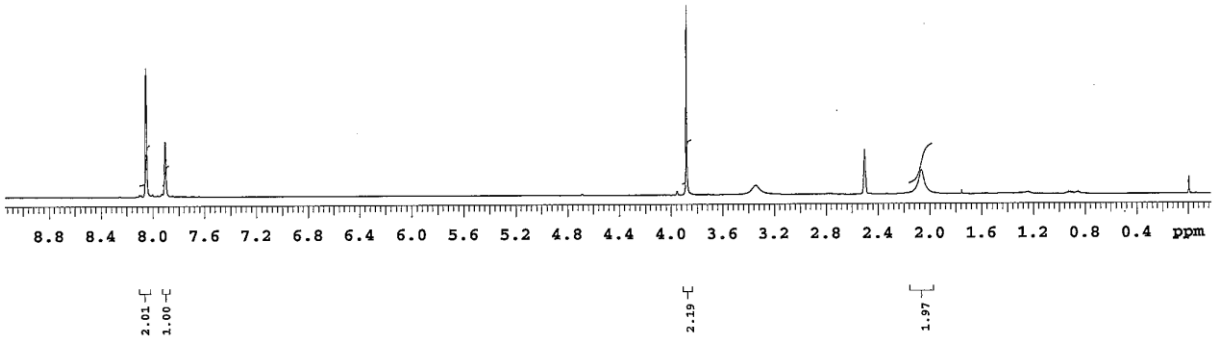
Archive directory:

Sample directory:

FidFile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Oct 19 2013





3. ARC (Advanced Reaction Calorimetry) study on nitroalkene 4

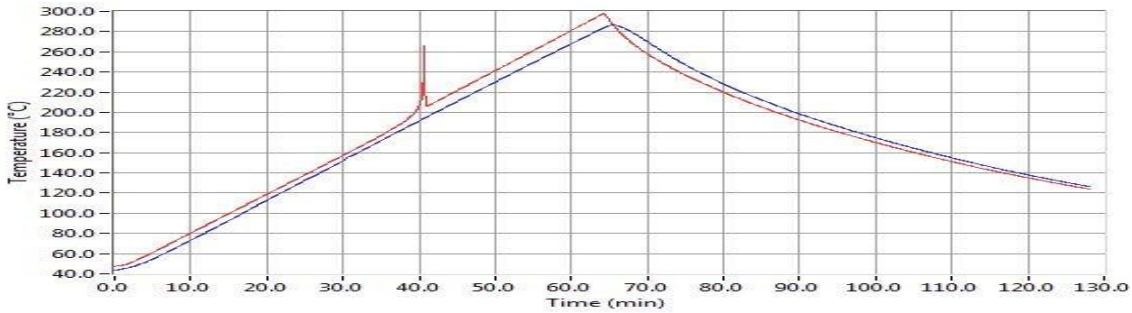
Objective:
The Rapid Screening Device is a safety calorimeter that can screen samples (key starting materials, reaction mass, residues &final compounds) simultaneously to evaluate the risks in handling, processing and storing these potentially hazardous materials.

Data Evaluation:
The RSD is a robust safety calorimeter designed to quickly screen up to 3-4 samples simultaneously (one of the samples is normally a reference sample). It uses temperature ramp methods with isothermal soak options to quickly obtain temperature, pressure and heat of decomposition data. A sealed system makes the pressure data very accurate.

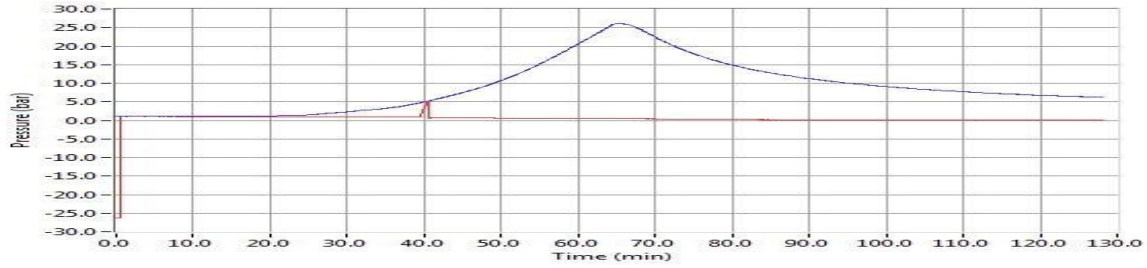
S.No	Test mode	Ramp Rate	End temperature
1	Ramp	4°C/min	350°C

S.NO	TEST SAMPLE	SAMPLE WEIGHT (g)	CURVE COLOR
1	Nitroalkene **4** crude	4.4	Blue curve
2	Nitroalkene **4** pure	1.3	Red curve

Temperature Plots



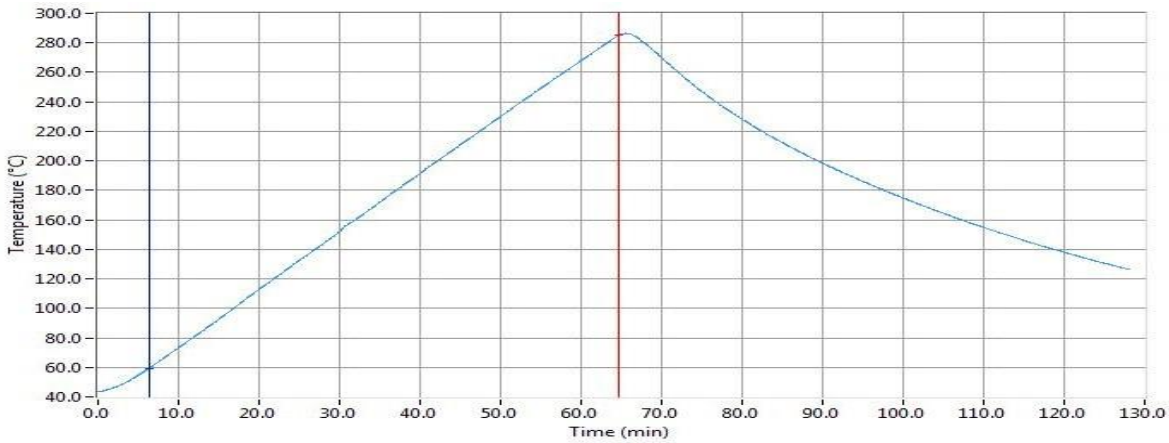
Pressure Plots



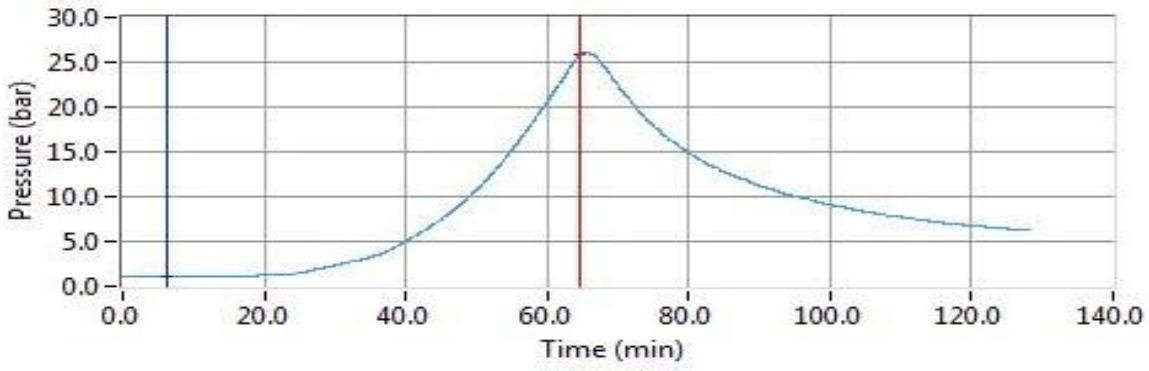
NITROALKENE 4 CRUDE

S.No	Onset temperature	Peak Temperature	Final Temperature	Heat of decomposition
1	103.1°C	202°C	284.9°C	-95.31kJ/kg

Temperature Plot



Pressure Plot



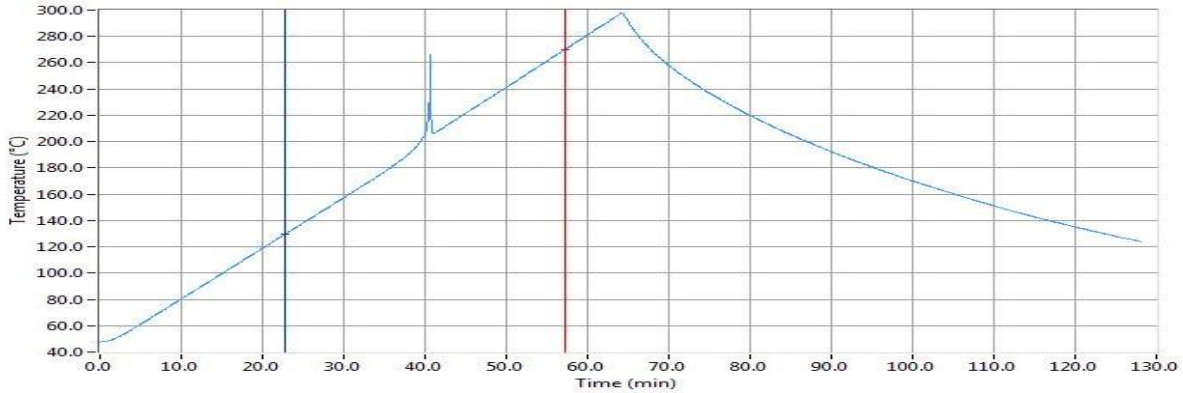
Results

- Nitroalkene crude onset of exothermic event is 103 °C and the pressure rise observed atexothermic event is 1 bar.
- Maximum pressure rise observed after exothermic event is 26 bar.

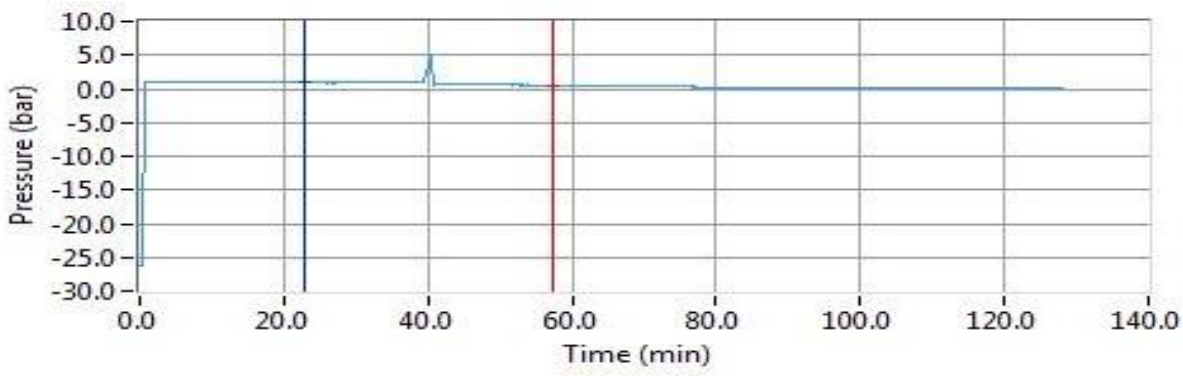
NITROALKENE 4 PURE

S.No	Onset temperature	Peak Temperature	Final Temperature	Heat of decomposition
1	174.9°C	202.8°C	214.6°C	-131.7kJ/kg

Temperature Plot



Pressure as a function of Time



Results

- Nitroalkene pure onset of exothermic event is 174.9°C and the pressure rise observed at exothermic event is 4 bar.
- Immediately after exothermic event the test cell got bursted and the temperature rise observed is 265 °C.

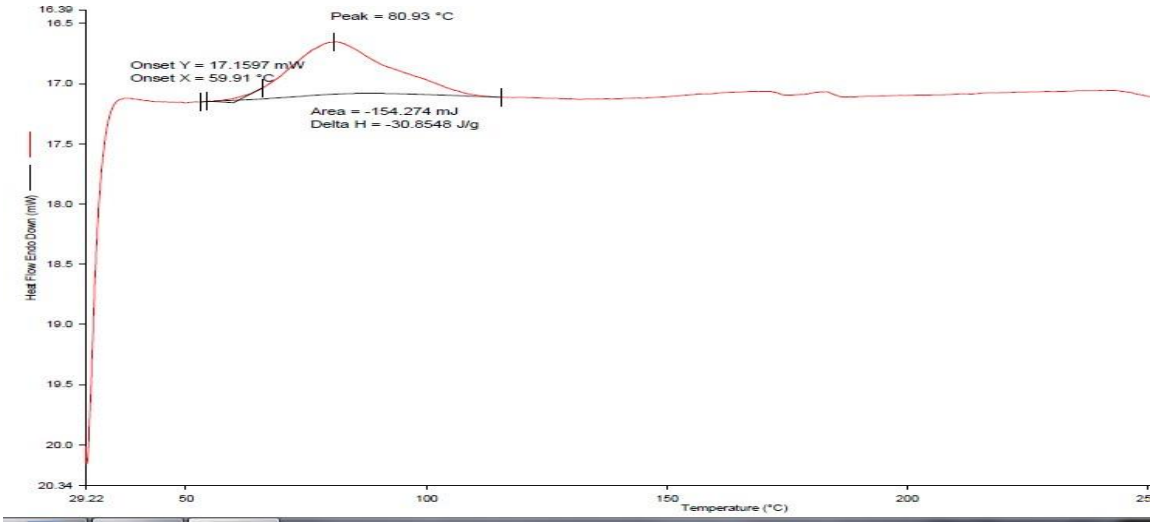
Crude Nitroalkene sample test cell

Pure Nitroalkene sample test cell bursted

DSC Analysis of the Nitroalkene **4** samples

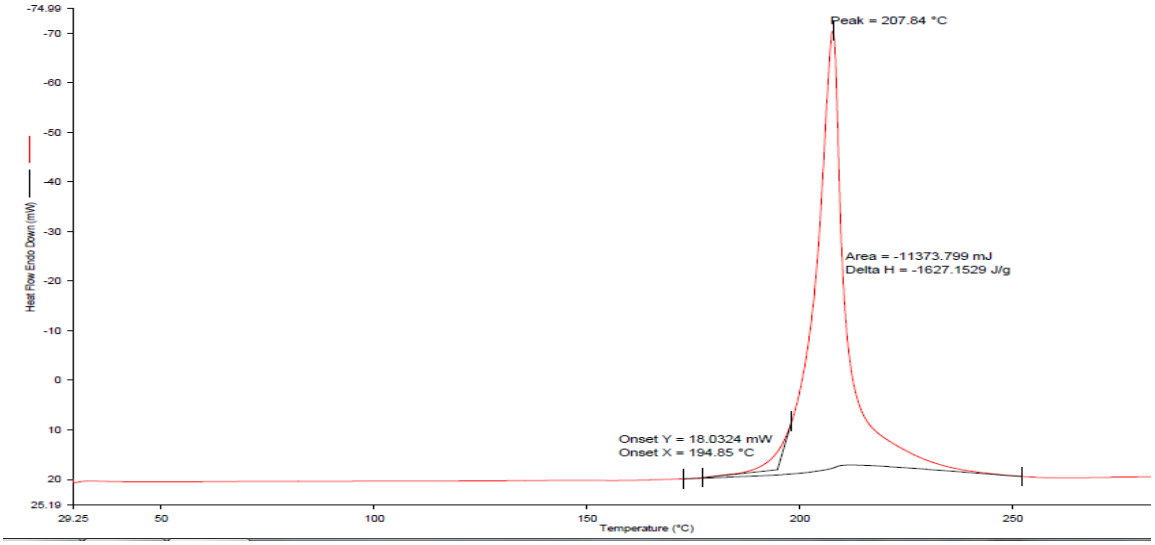
CRUDE SAMPLE

- On set of exothermic event observed at 59.5°C and the heat of exothermic event is 30.85J/g.



PURE SAMPLE

- On set of exothermic event observed at 194.65 °C and the heat of exothermic event is 1627.15 J/g.


Peak = 207.84 °C
Area = -11373.799 mJ
Delta H = -1627.1529 J/g
Onset Y = 18.0324 mW
Onset X = 194.85 °C
Heat Flow Endo Down (mW)
Temperature (°C)
-74.99
-70
-60
-50
-40
-30
-20
-10
0
10
20
25.19
29.25
50
100
150
200
250