Mechanistic Insights and Safety Evaluation of the Ritter Reaction of Aromatic Nitriles Utilizing *tert*-Butyl Acetate as the *tert*-Butyl Cation Source

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## Supporting Information

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General Experimental Methods

Commercial reagents were used without purification and solvents were used without drying. All reactions were conducted in a 1L MP06 closed-system Mettler-Toledo RC-1e calorimeter (rated to 6 bar) equipped with mechanical stirring, a diaphragm pump, and a DiComp fiber-optic probe (attached to a Mettler-Toledo ReactIR 4000). ARC results were obtained using a Thermal Hazard Technology Enhanced System Accelerating Rate Calorimeter (esARC) and each test was performed in a 10mL hastelloy test cell with magnetic stir bar. The determination of water in strong acids required additional buffering of the Hydranal titrant used in the Metrohm 870 KF Titrino Plus volumetric KF unit used for these studies. RC-1 data was analyzed using the Mettler-Toledo iControl RC-1e v4.0 software and ARC data was analyzed using the Thermal Hazard Technology ARCCal PLUS software. All RC-1 data was evaluated using a linear baseline and the heat accumulation and heat of dosing terms were included in the evaluation, in addition to the typical heat flow term. IR data was analyzed using the Mettler-Toledo iC IR v4.2 software. Individual reference spectra were acquired and used to identify species within the crude reaction mixture. Trends were generated by integrating indicative IR peaks that were selected by overlaying reference spectra with those of the reaction mixture. The IR data was

further processed and examined using derivitization and principal component analysis. The determination of water in strong acids required additional buffering of the Hydranal titrant with Hydranal-Buffer Acid used in the Metrohm 870 KF Titrino Plus volumetric KF unit.
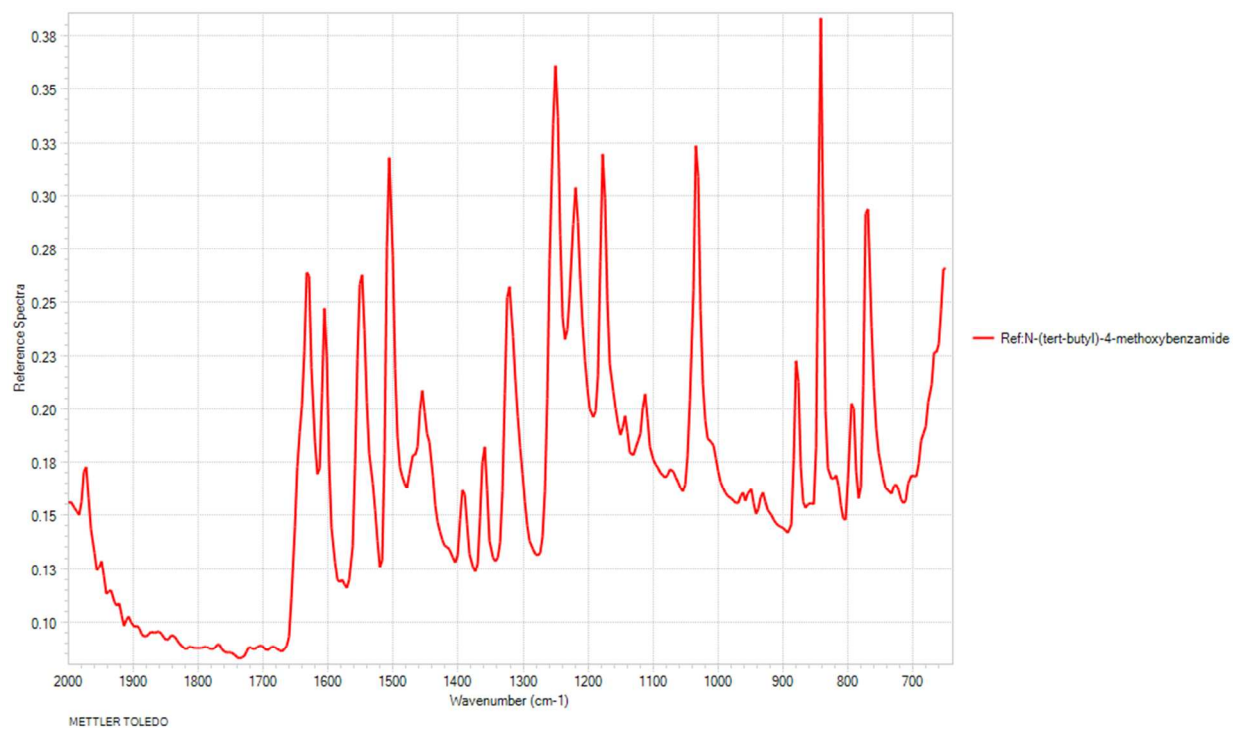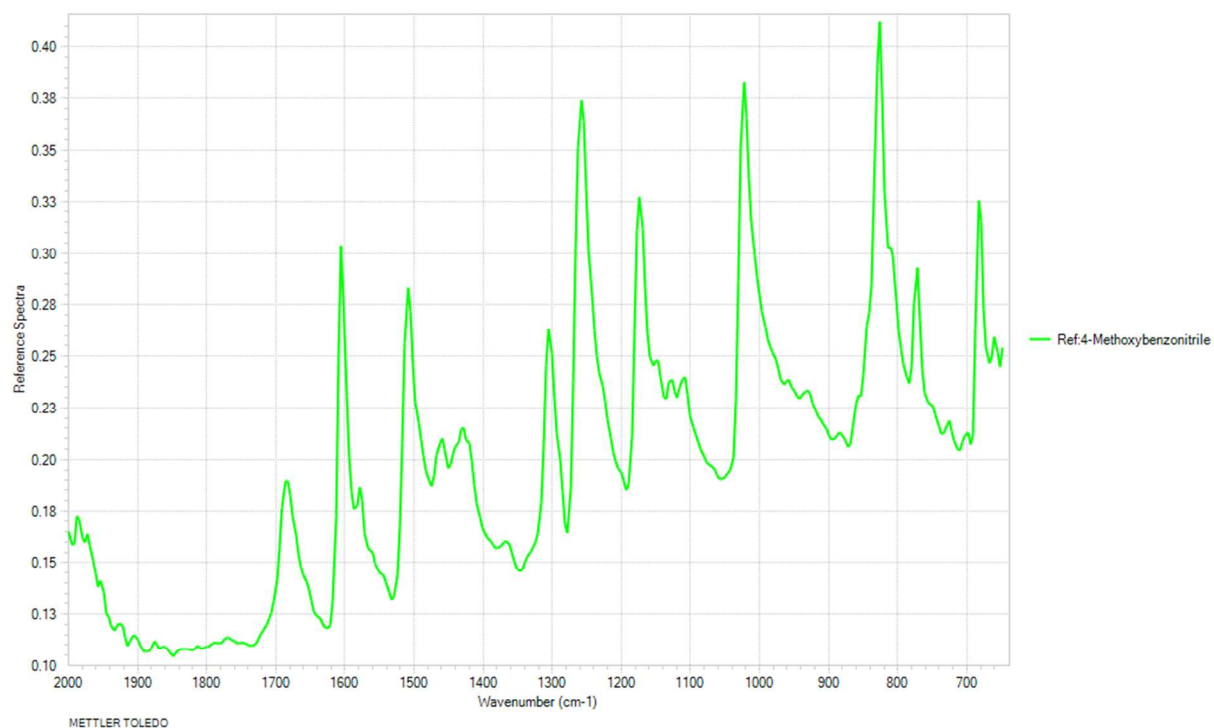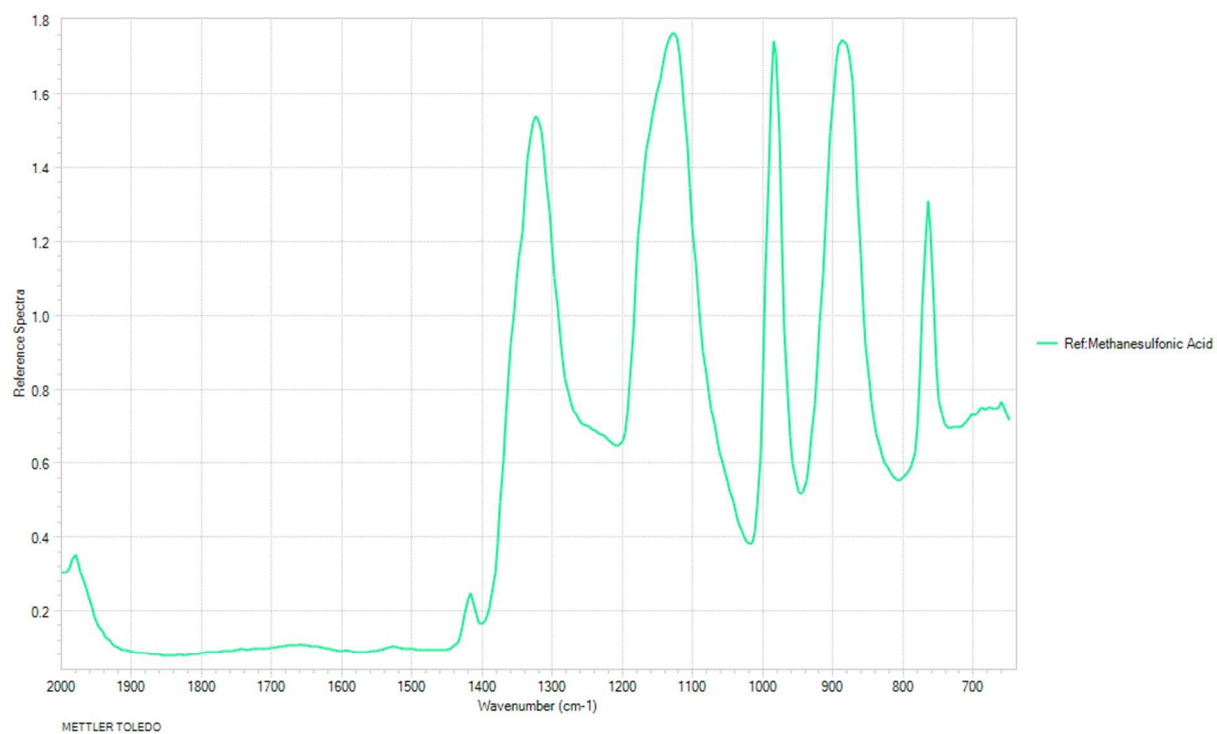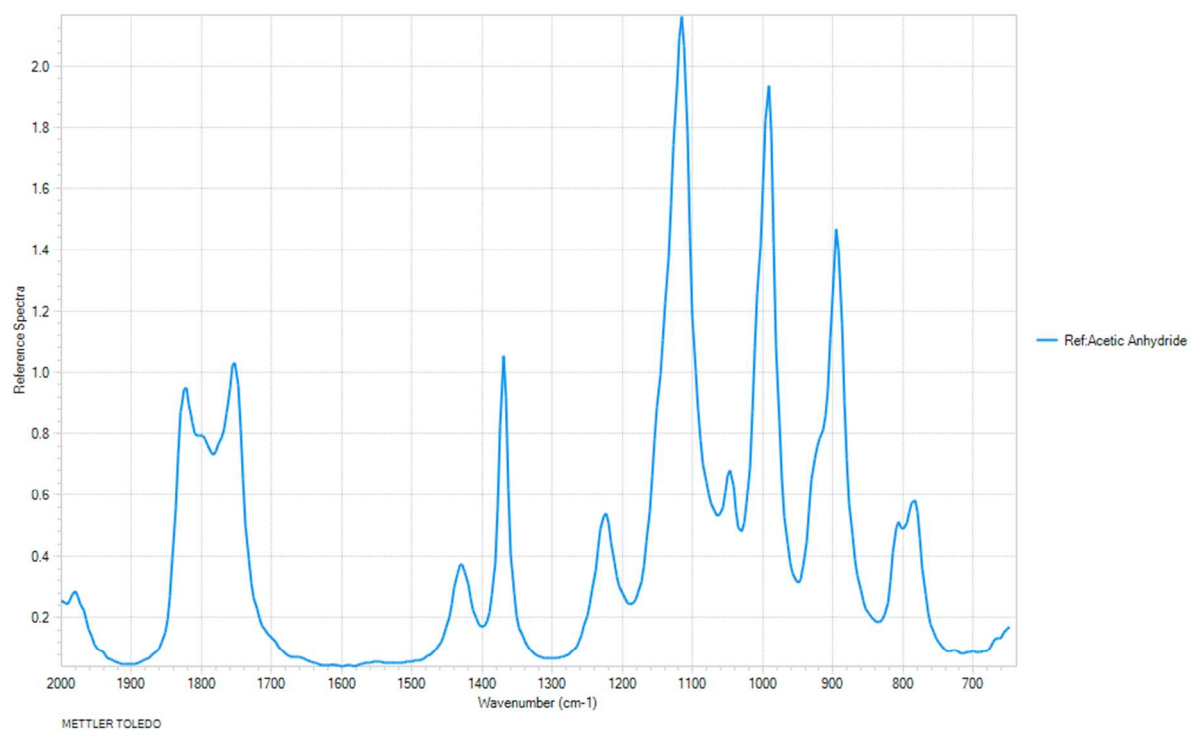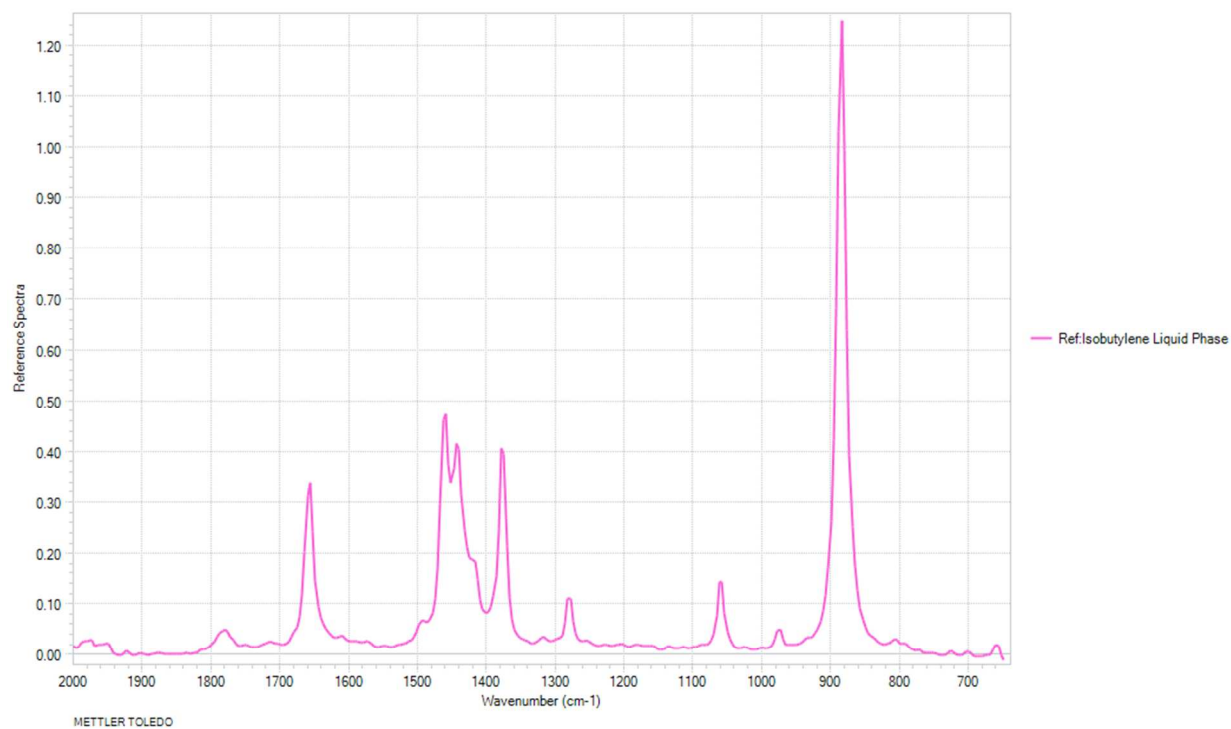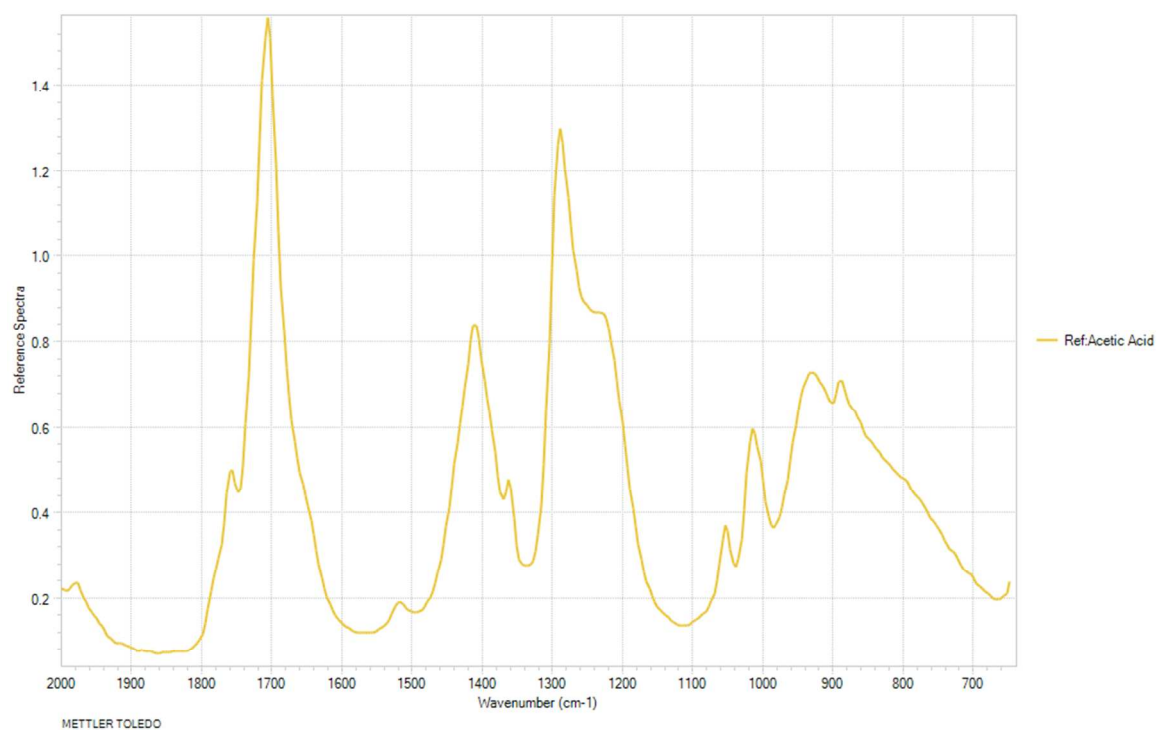
Reference Peak Assignments
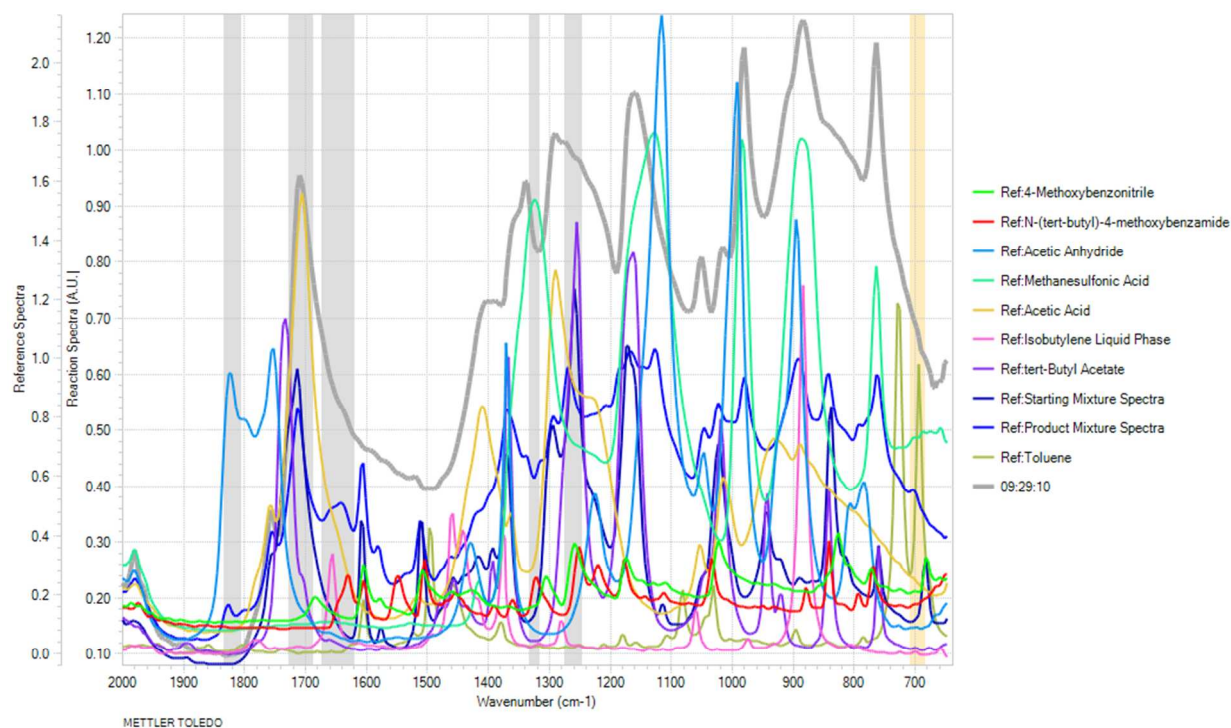
The peak explanations are as follows (see graph above for peaks with reference spectra):
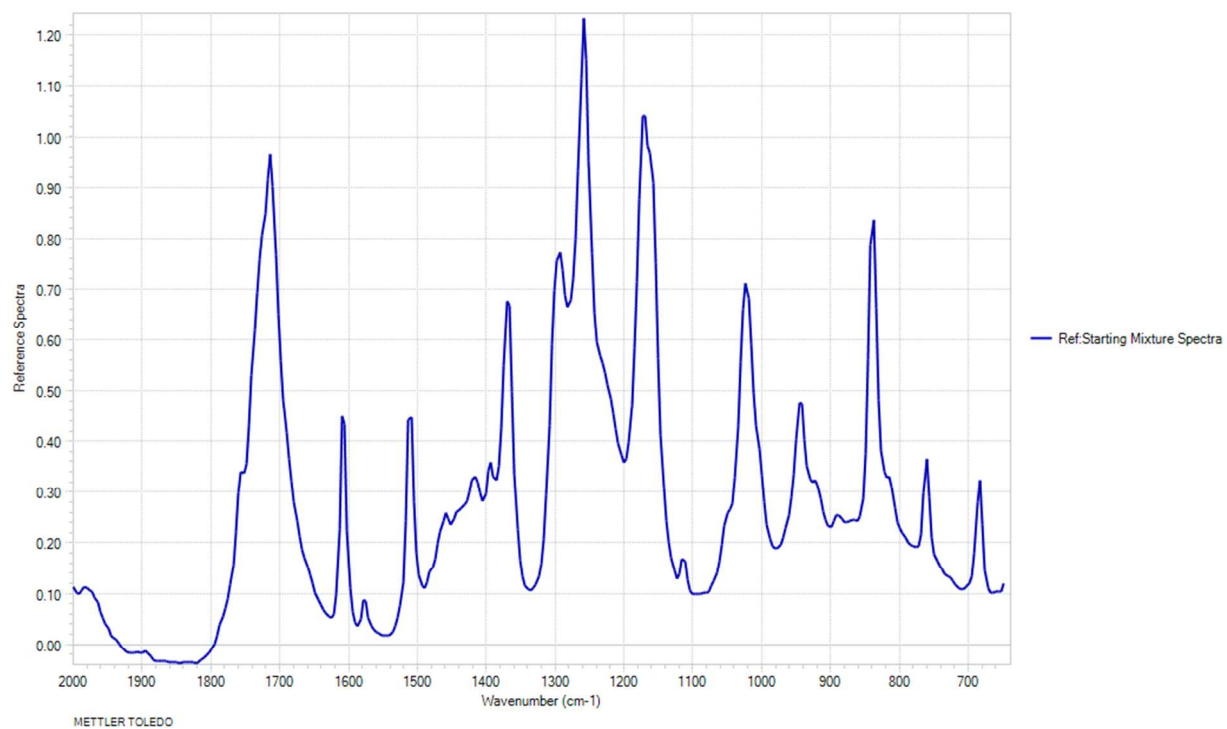
1. **Acetic Anhydride:** This peak was analyzed from 1800-1830 cm^{-1}.
2. **Acetic Acid:** This peak was analyzed from 1690-1725 cm^{-1}.
3. ***N*-(*tert*-butyl)-4-methoxybenzamide:** This peak is analyzed from the 1620-1670 cm^{-1}.
4. **4-Methoxybenzonitrile:** This peak was analyzed from 680-700 cm^{-1}.
5. **Methanesulfonic Acid:** This peak was analyzed from 1320-1330 cm^{-1}.
6. ***tert*-Butyl Acetate**: This peak was analyzed from 1245-1270 cm^{-1}.

Individual Reference Spectra

Ref:4-Methoxybenzonitrile

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Ref:N-(tert-butyl)-4-methoxybenzamide

METTLER TOLEDO

METTLER TOLEDO

Ref:Acetic Anhydride

METTLER TOLEDO

Ref:Methanesulfonic Acid

Ref:Acetic Acid

METTLER TOLEDO

Ref:Isobutylene Liquid Phase

METTLER TOLEDO

Ref:tert-Butyl Acetate

METTLER TOLEDO

Ref:Starting Mixture Spectra

METTLER TOLEDO

Ref:Product Mixture Spectra

METTLER TOLEDO

Ref:Toluene

METTLER TOLEDO

IR Spectra

Conditions A. IR and calorimetry profiles of nitrile **8** with *tert*-butyl acetate as solvent (relative time axis cropped). Conditions: 1.0 equiv 4-methoxybenzonitrile, 1.0 equiv sulfuric acid, 3.8 vol *tert*-butyl acetate, 45 °C, 30 min addition time.
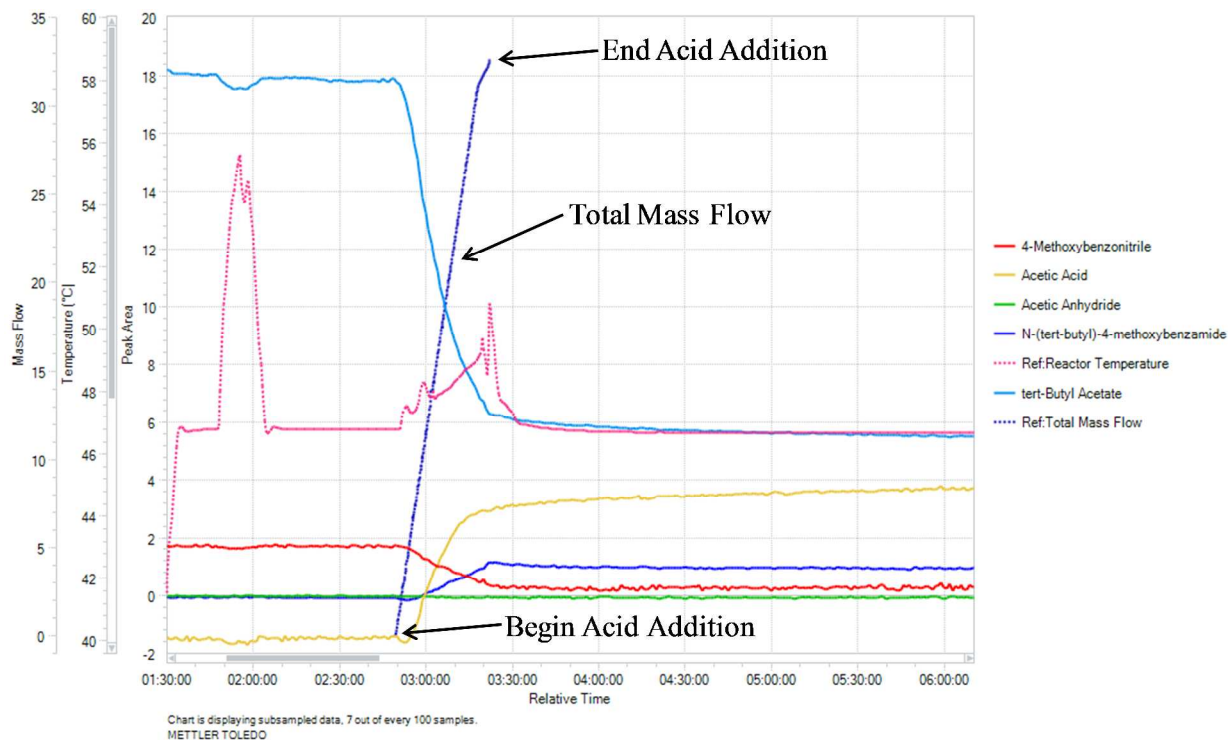
Conditions A. IR and calorimetry profiles of nitrile **8** with *tert*-butyl acetate as solvent and <1 min sulfuric acid addition (relative time axis cropped).

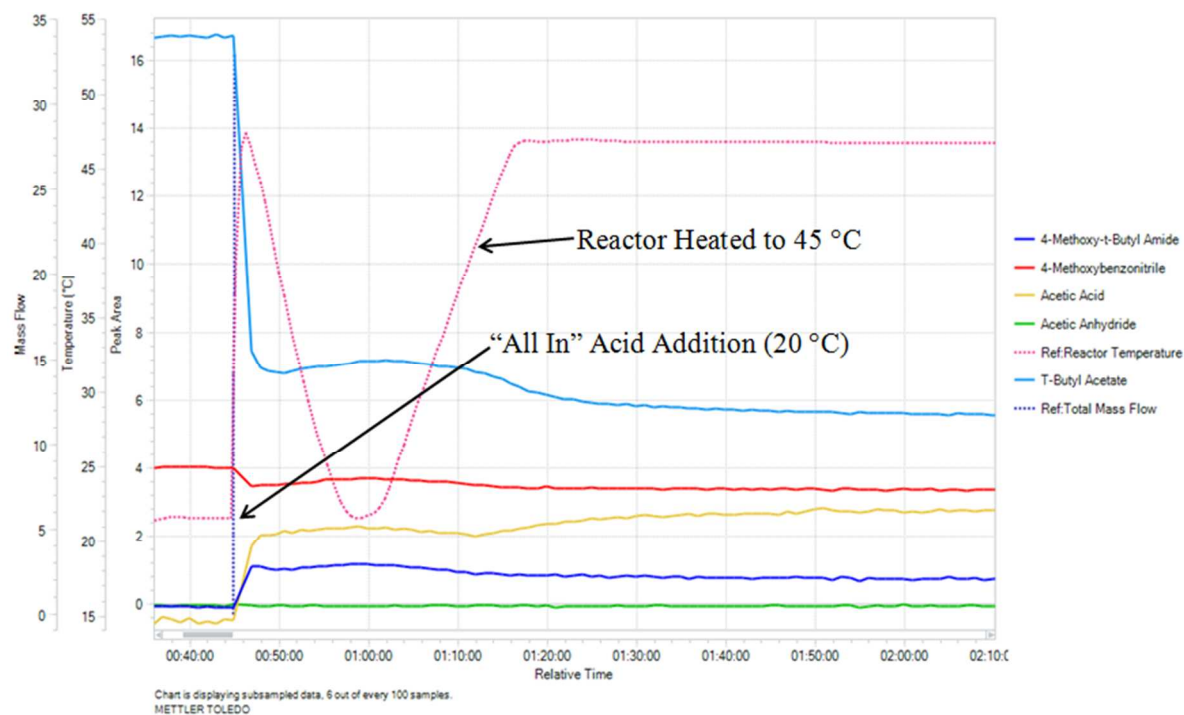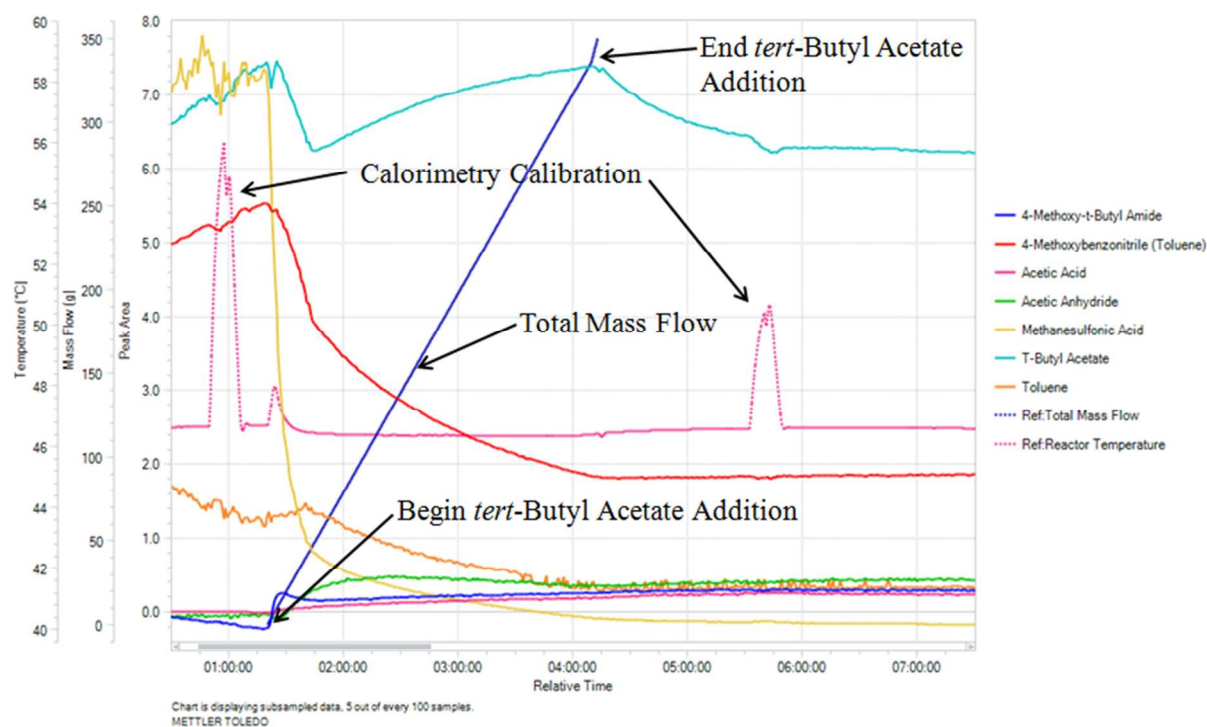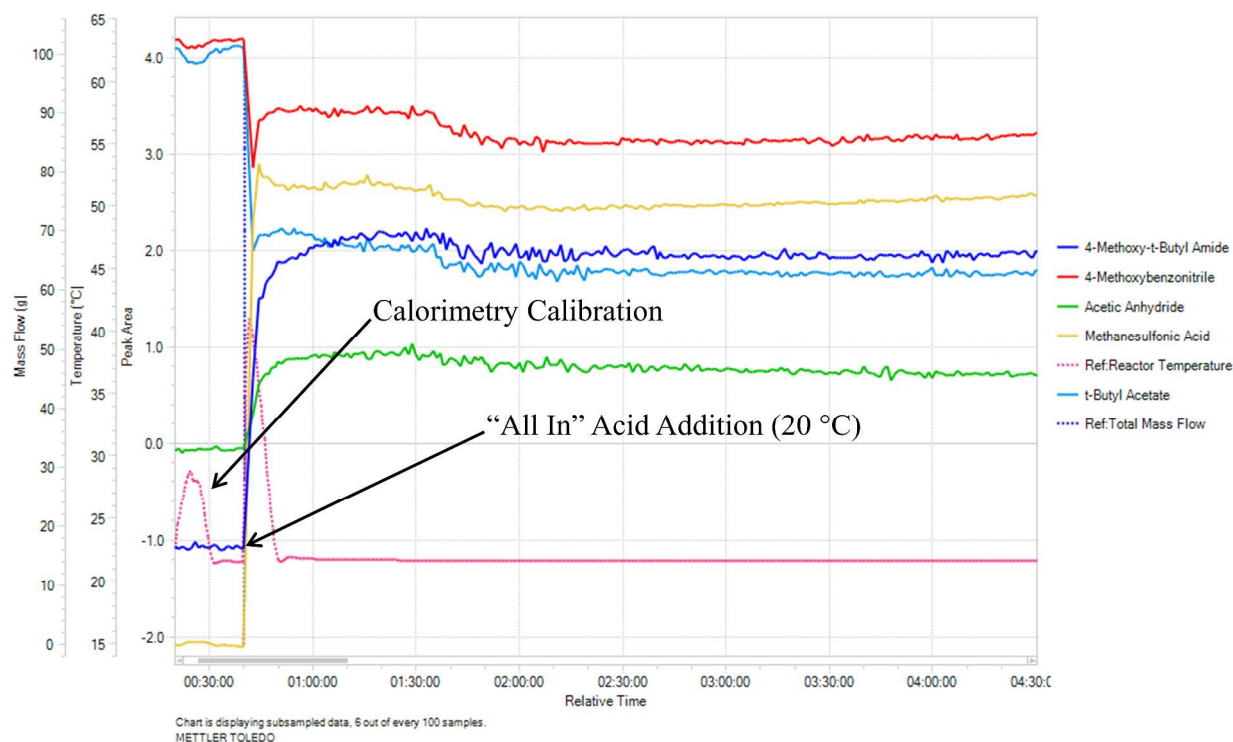**Conditions B**. IR and calorimetry profiles of nitrile **8** with toluene as solvent (relative time axis cropped). Conditions: 1.0 equiv 4-methoxybenzonitrile, 10.0 equiv *tert*-butyl acetate, 3.5 vol toluene, 3.0 equiv MSA, 45 °C, 3h addition time.

Conditions C. IR and calorimetry profiles of nitrile **8** (relative time axis cropped). Conditions: 1.0 equiv 4-methoxybenzonitrile, 2.0 equiv *tert*-butyl acetate (1 vol acetic acid); 3.0 equiv MSA (1.0 vol acetic acid); 20 °C, <1 min addition time.

Control Experiments

Acetic Acid:MSA IR Experiment

To a 1L MP06 closed-system RC-1 calorimeter equipped with mechanical stirring, diaphragm pump, and DiComp fiber-optic probe (attached to a Mettler-Toledo ReactIR 4000) was charged acetic acid (300 mL). After thermal equilibration at 20 °C, MSA (220 mL) was charged by diaphragm pump over 15 minutes. After the addition was complete, the mixture was aged overnight at 20 °C. Acetic anhydride was not observed by IR.
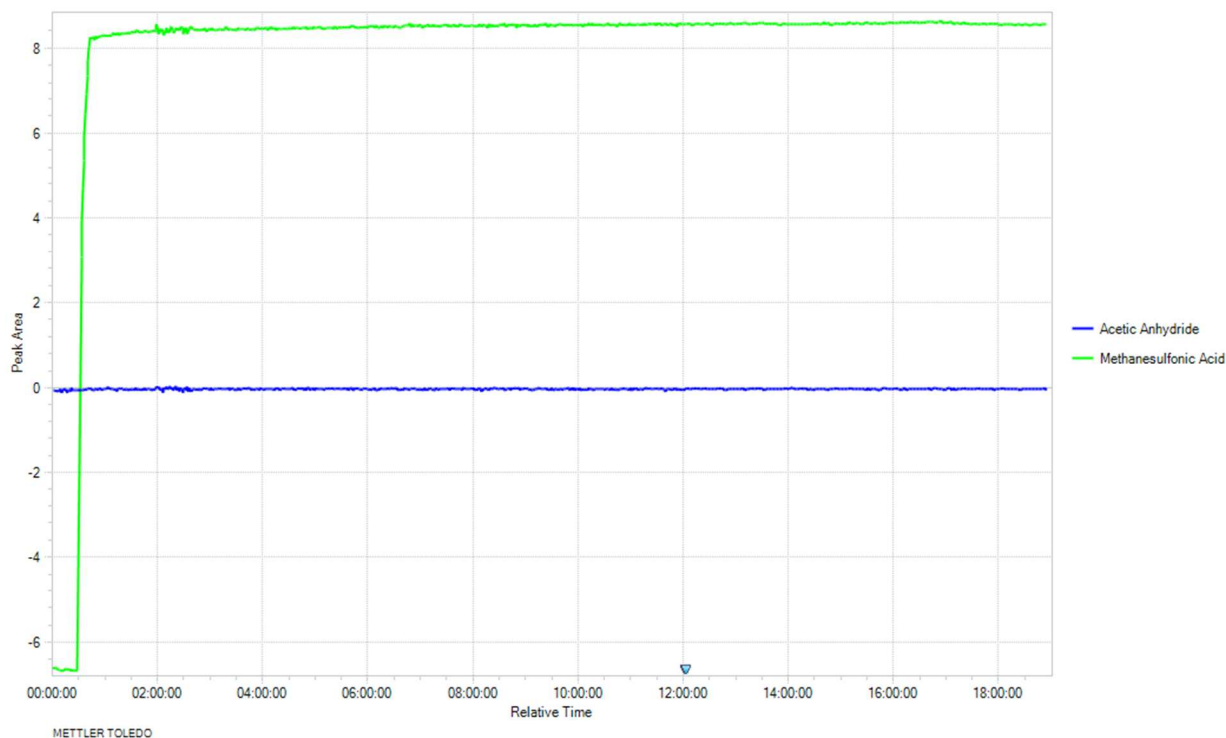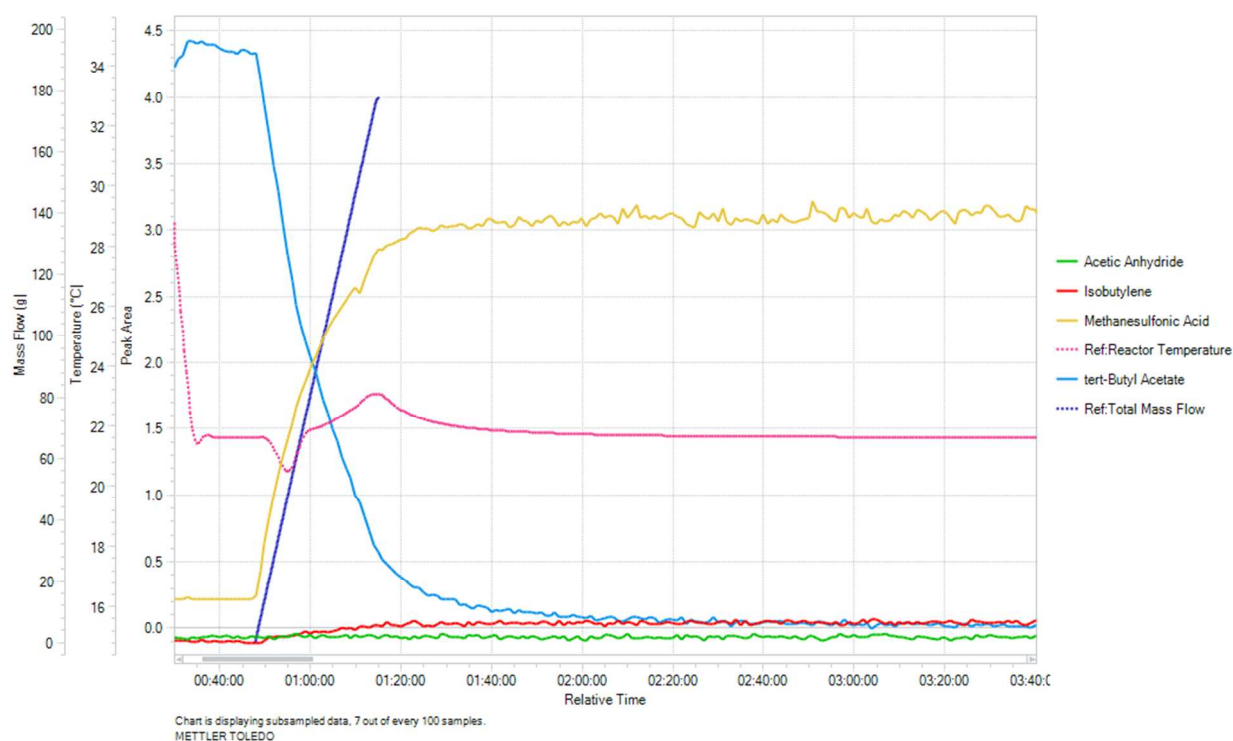
**Acetic Acid:MSA:*tert*-Butyl Acetate IR Experiment**

To a 1L MP06 closed-system RC-1 calorimeter equipped with mechanical stirring, diaphragm pump, and DiComp fiber-optic probe (attached to a Mettler-Toledo ReactIR 4000) was charged acetic ccid (56 mL) and *tert*-butyl acetate (126 mL). After thermal equilibration at 20 °C, an RC-1 heat flow calibration was performed (pre-addition). A pre-mixed solution of acetic acid (56 mL) and MSA (90mL) was charged by diaphragm pump over 27 minutes. After addition was complete, the reaction mixture was held to allow the heat flow to return to baseline, and a RC-1 heat flow calibration was performed. The reaction mixture was aged overnight at 20 °C. After the overnight age, the reactor vent was opened to observe for isobutylene off-gassing. Acetic anhydride was not detected by IR.

Chart is displaying subsampled data, 7 out of every 100 samples.
METTLER TOLEDO

ARC Experiments

Conditions A

To a Hastelloy ARC bomb (10 mL) with stir bar was charged 4-methoxybenzonitrile (1.32 g), *tert*-butyl acetate (5 mL), and sulfuric acid (0.53 mL). The bomb was quickly placed onto the ARC for analysis and the bomb was allowed to self-heat until the temperature (from heat of reaction) equilibrated. The bomb was then cooled and sampled for NMR testing. This test was performed to simulate the first exotherm from conditions A.
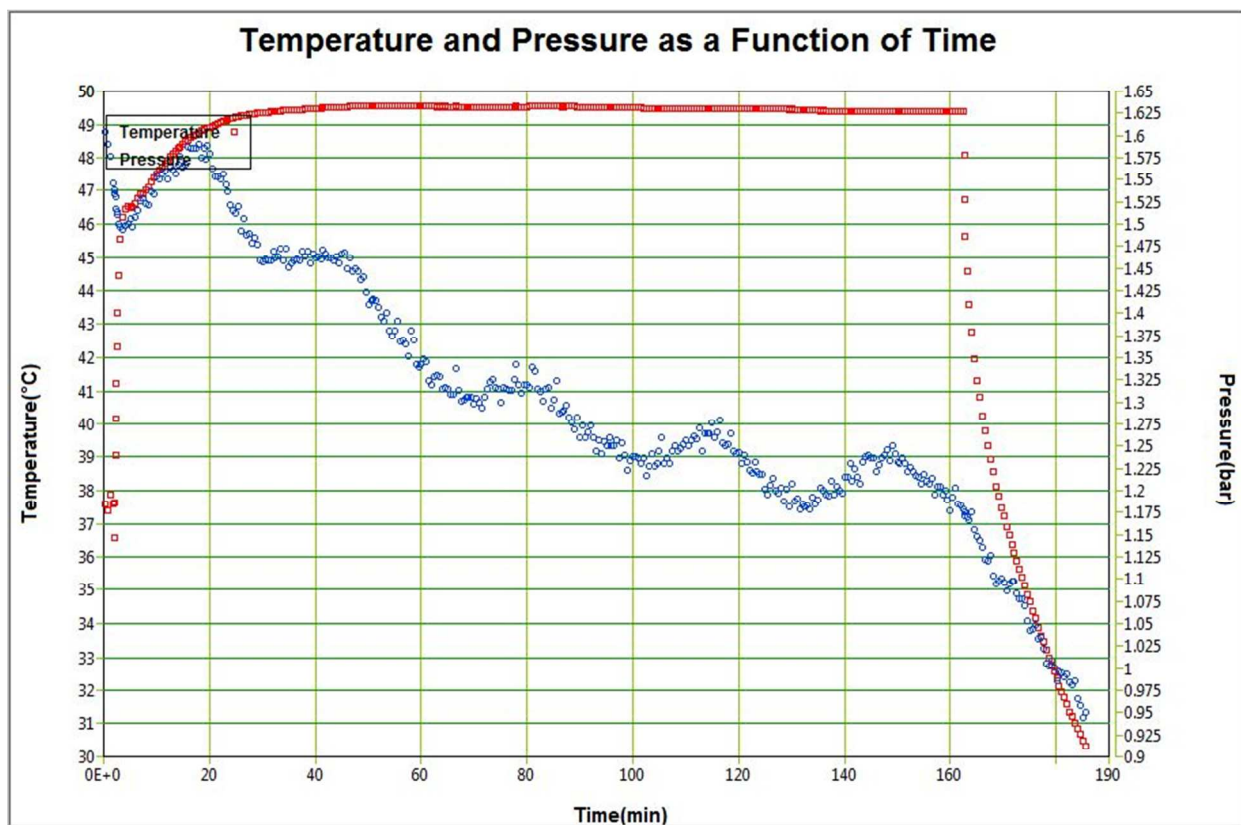
Note: The maximum temperature (50°C) and initial pressure (1.6 bar) were lower than the values depicted in the manuscript for the first exotherm (80°C; 3.15 bar). We believe this is due to lost heat and pressure during bomb preparation and loading onto the ARC.

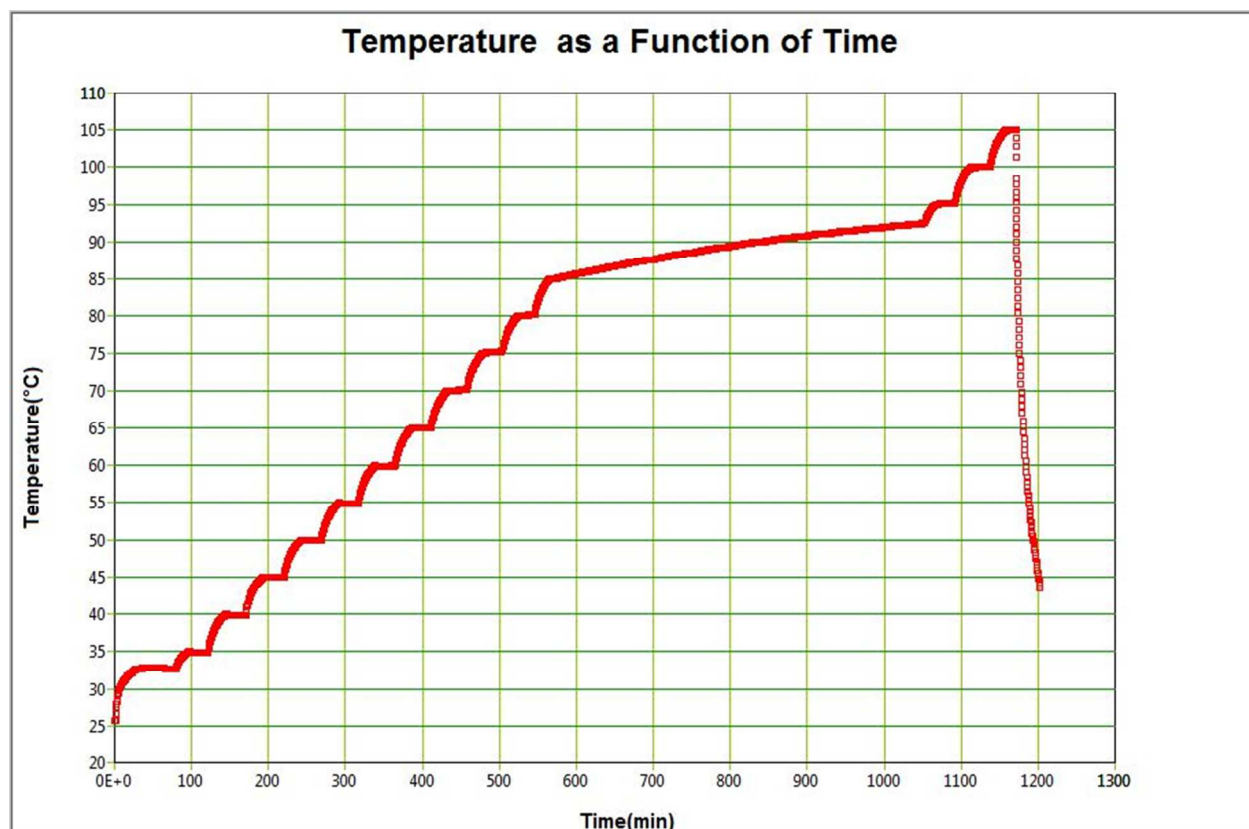| Acquisition Time (sec)	5.1120	Comment	scottr01
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Temperature (degree C)	25.000		

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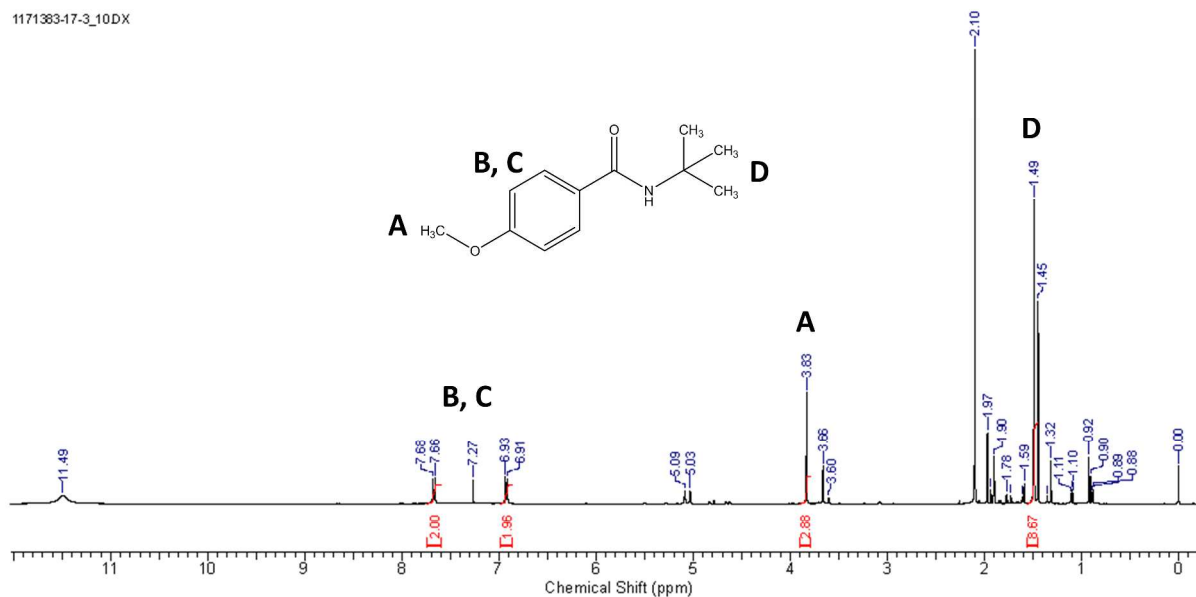
Figure 1. ^{1}H NMR after first exotherm using conditions A.

After the first exotherm sampling, the bomb was re-attached to the ARC and heated to 105°C overnight. The bomb was sampled in the morning for NMR testing. This test was performed to simulate the second exotherm from conditions A.

Temperature as a Function of Time

Note: The exotherm occurred in this test from 85-93°C, which was at a slightly lower temperature than reported in the manuscript (90-100°C).
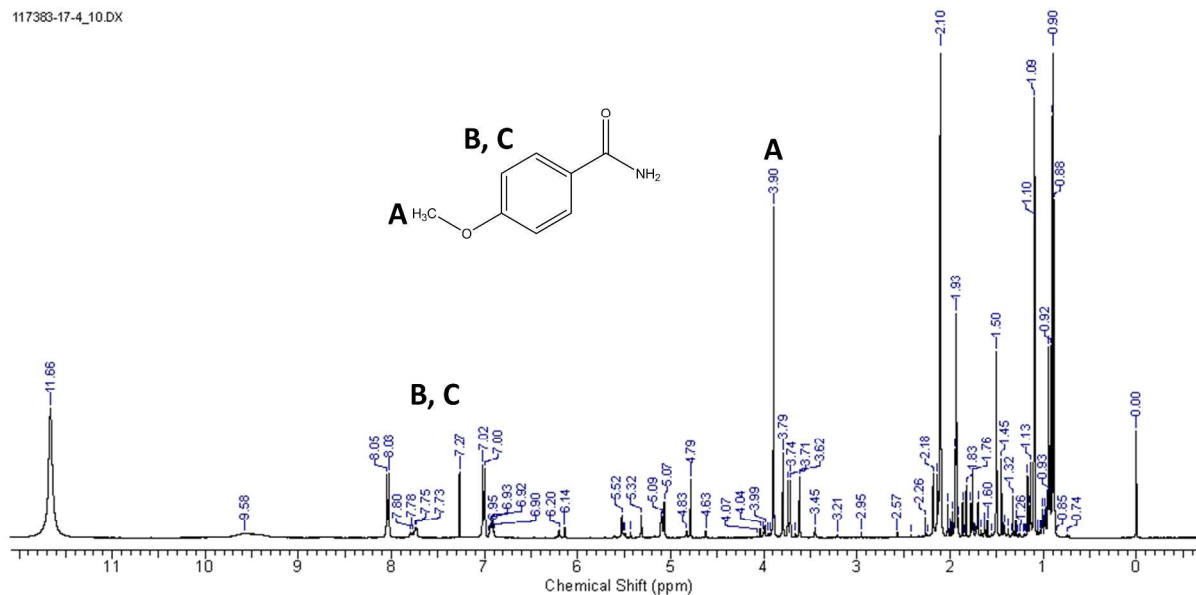
Figure 2. ^{1}H NMR after second exotherm using conditions A.

Conditions A (Control Experiment)

To a Hastelloy ARC bomb (10 mL) with stir bar was charged *tert*-butyl acetate (5 mL) and sulfuric acid (0.53 mL). The bomb was quickly placed onto the ARC for analysis and the bomb was allowed to self-heat until the temperature (from heat of reaction) equilibrated. The bomb was then heated to 150°C overnight. This test was performed to stress the blank from conditions A to see if high-temperature reactivity may have caused the third exotherm from conditions A.
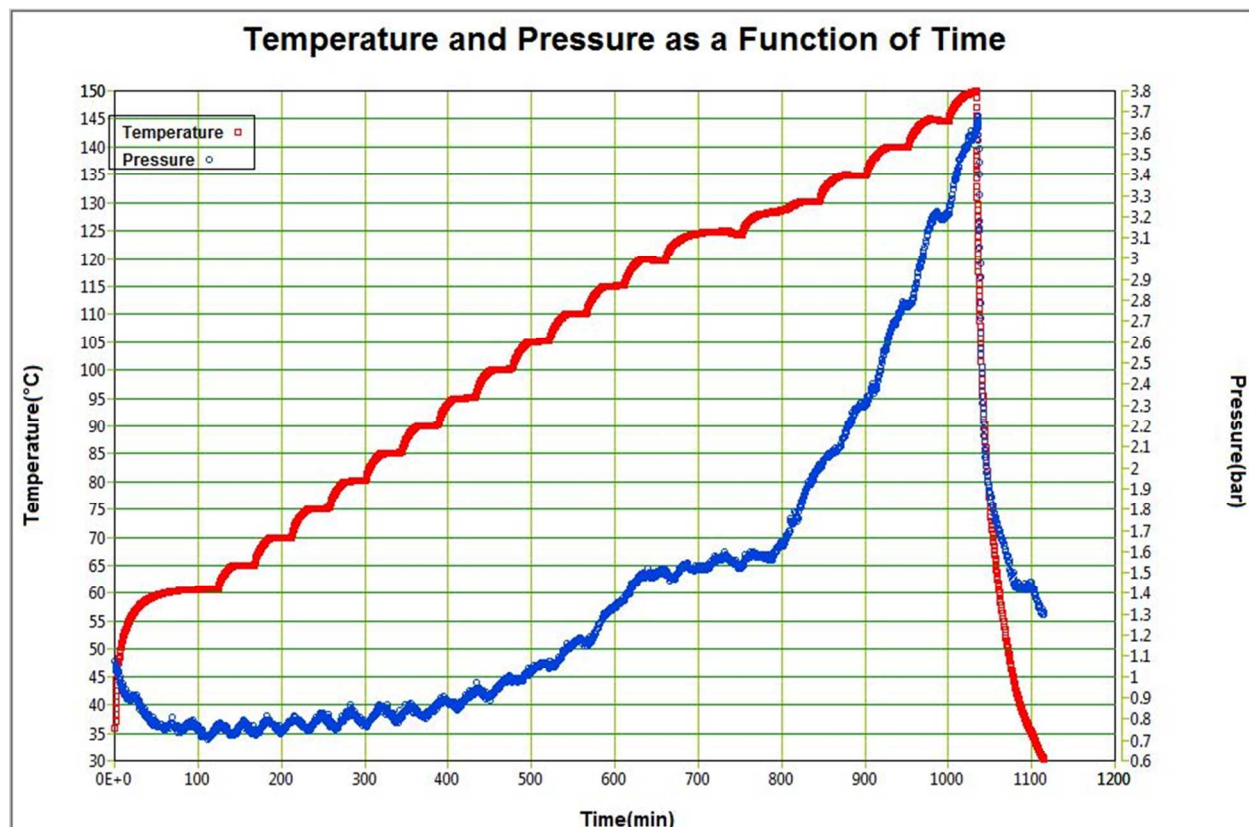
Note: There was no exothermic activity noted during heating to 150°C.

Conditions C

To a Hastelloy ARC bomb (10 mL) with stir bar was charged 4-methoxybenzonitrile (1.03 g), acetic acid (2 mL), *tert*-butyl acetate (2.02 mL), and MSA (1.47 mL). The bomb was quickly placed onto the ARC for analysis and the bomb was allowed to self-heat until the temperature (from heat of reaction) equilibrated. The bomb was then cooled and sampled for NMR testing. This test was performed to simulate the first exotherm from conditions C.

Temperature and Pressure as a Function of Time
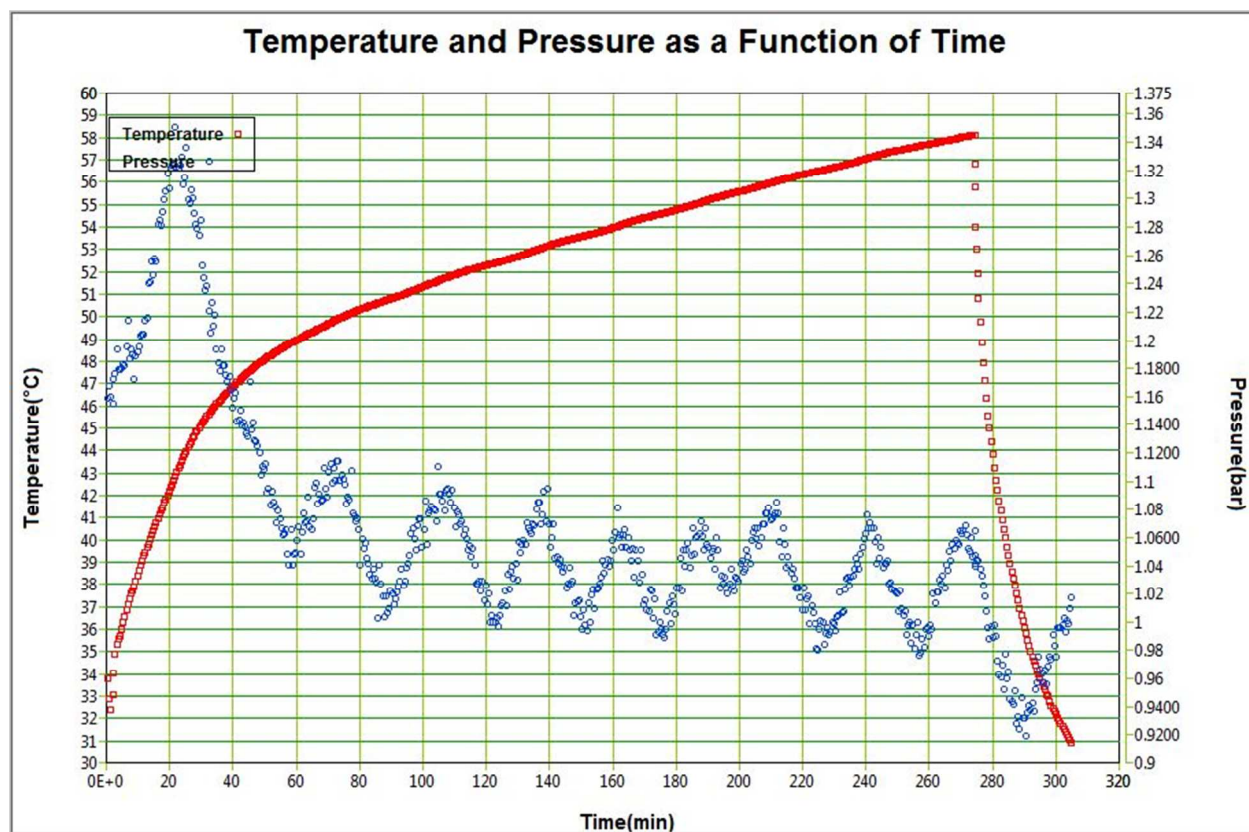
Note: The maximum temperature (58°C) and initial pressure (1.3 bar) were a little higher than the values depicted in the manuscript for the first exotherm (55°C; 1.1 bar).

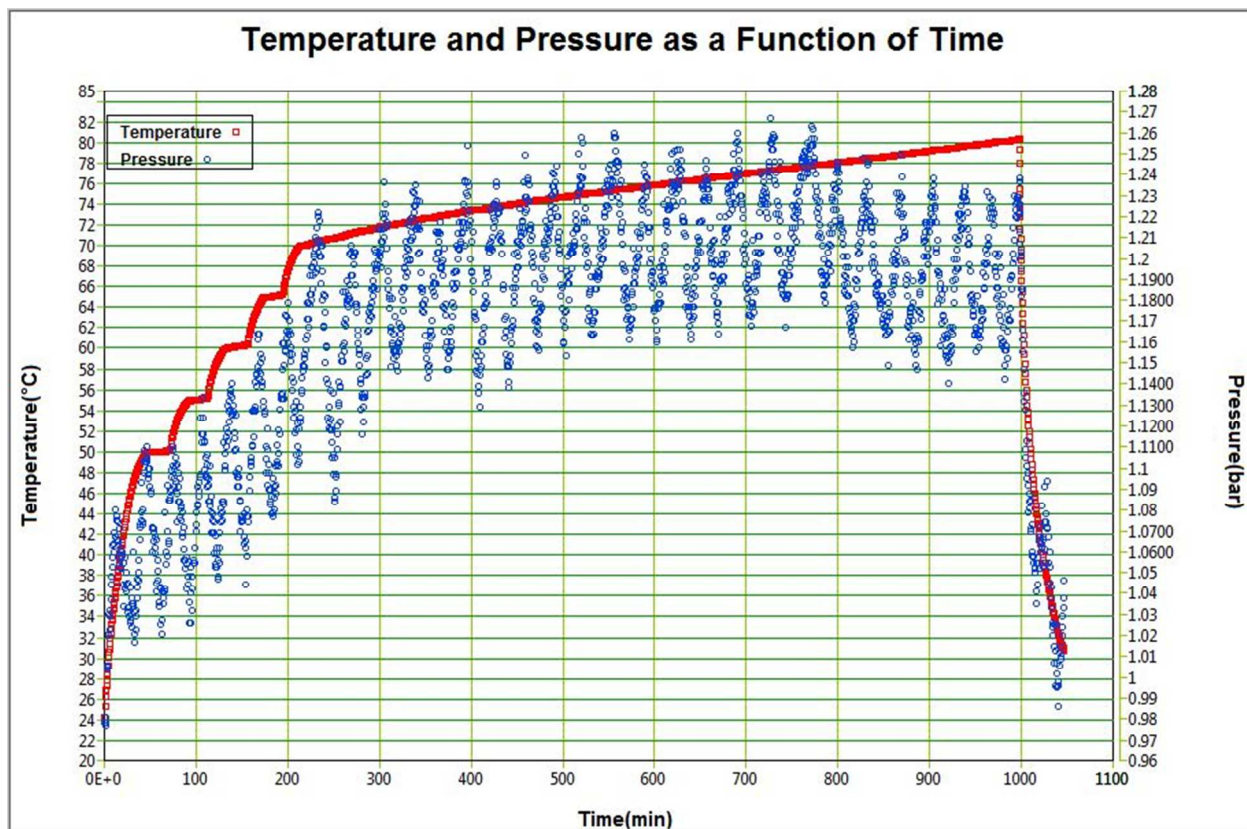| Acquisition Time (sec) | 5.1120 | Comment | scottr01 |
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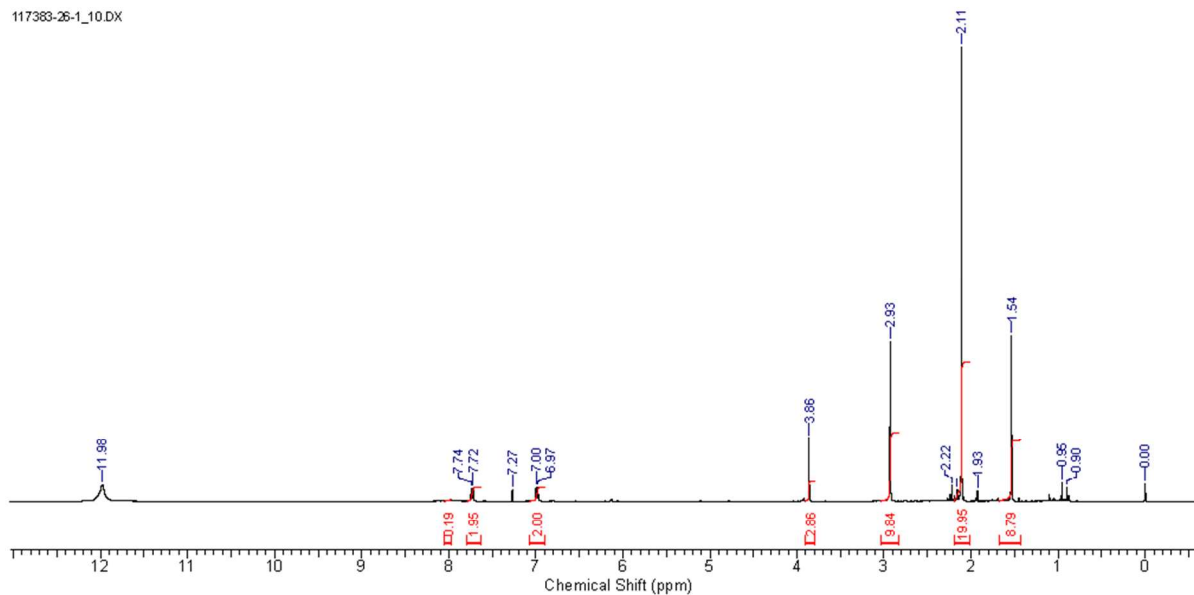
Figure 3. ^{1}H NMR after first exotherm using conditions C. 8.9% Des-*t*-butyl amide present in reaction mixture.

After sampling for Part 1, the bomb was re-attached to the ARC and heated to 80°C overnight. The bomb was cooled and sampled in the morning for NMR testing. This test was performed to simulate the second exotherm from conditions C.

Temperature and Pressure as a Function of Time

Note: The exotherm occurred in this test from 70-80°C, which was a larger range than reported in the manuscript (75-79°C).

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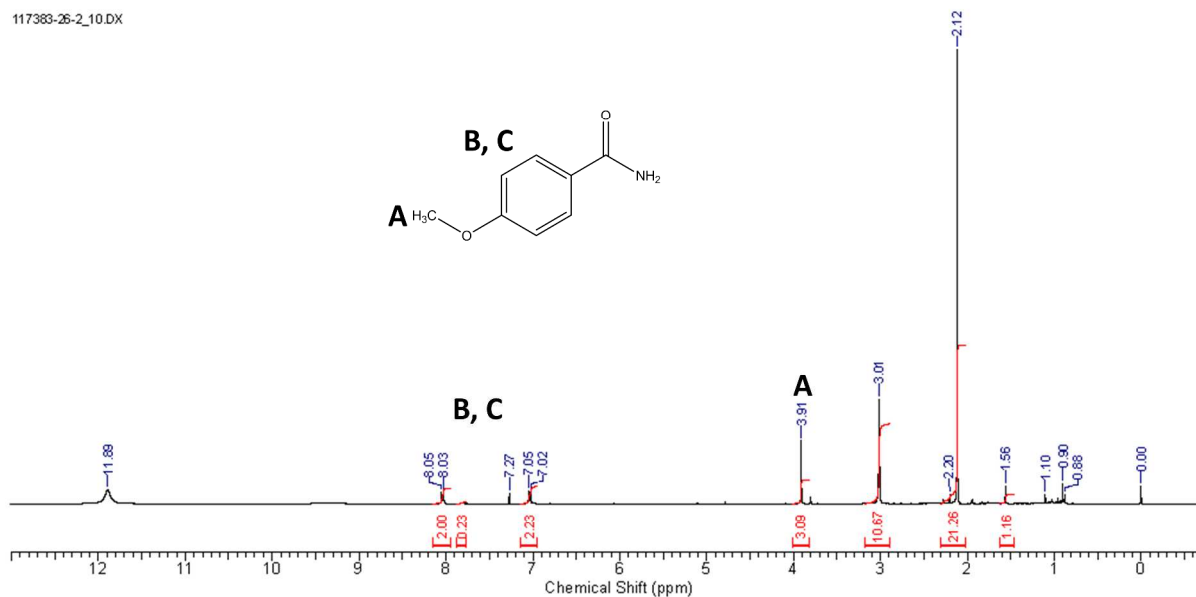
Figure 4. ^{1}H NMR after first exotherm using conditions C. 10.3% *N*-(*tert*-butyl)-4-methoxybenzamide present in reaction mixture.

Conditions C (Control Experiment)

To a Hastelloy ARC bomb (10 mL) with stir bar was charged acetic acid (2 mL), *tert*-butyl acetate (2.02 mL) and MSA (1.47 mL). The bomb was quickly placed onto the ARC for analysis and the bomb was allowed to self-heat until the temperature (from heat of reaction) equilibrated. The bomb was then heated to 150°C overnight. This test was performed to stress the blank from conditions C to see if high-temperature reactivity may have caused the third exotherm from conditions C.

Temperature and Pressure as a Function of Time
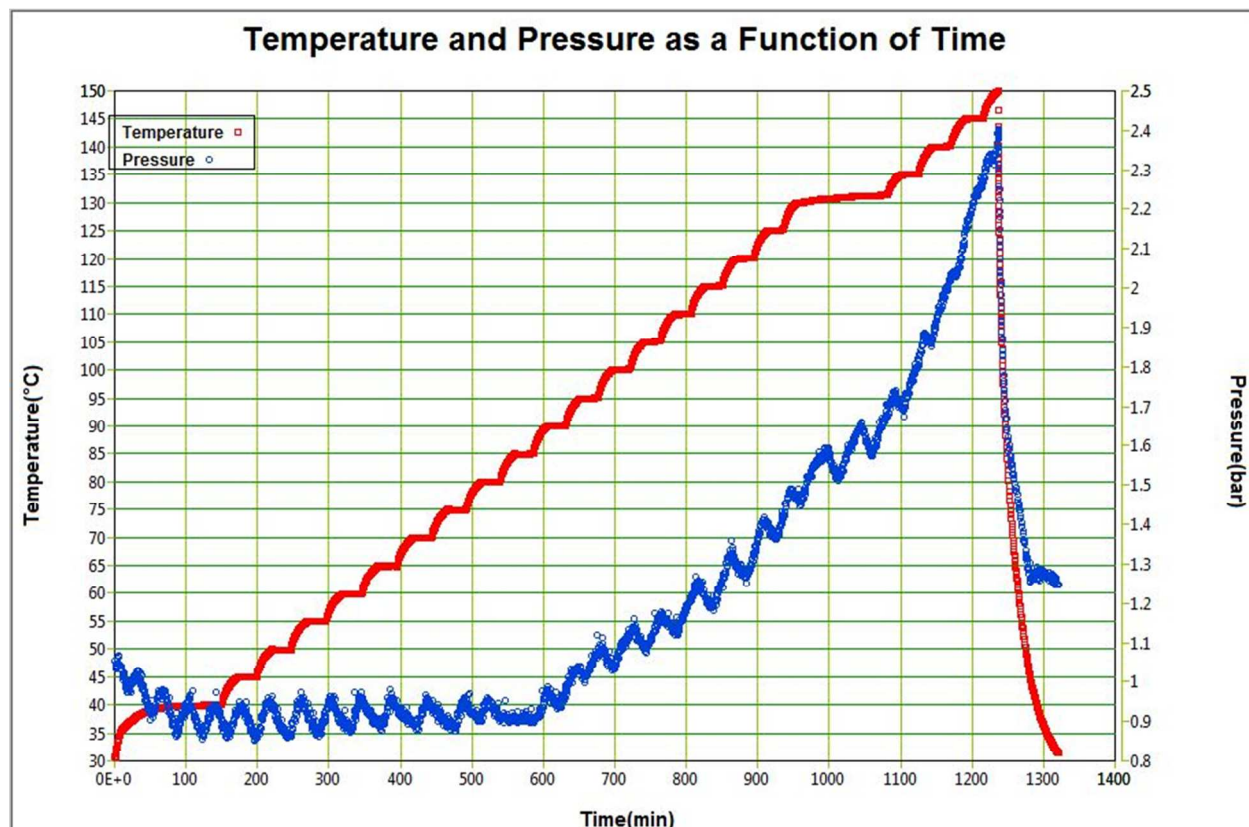
Note: There was a small exotherm noted (from 130-131°C), but this was much smaller than the third exotherm reported in the manuscript (135-150°C).

Closed System Calculations

The calculation of pressure from the addition of a liquid into a closed system is based on the compression of the headspace inside the system. In this case, the headspace was air (headspace not purged prior to each experiment), so the Ideal Gas Law can be used for this calculation:

$$PV = nRT$$

Before and after the addition, the nRT term will remain the same (same moles of air and minimal temperature change). Therefore, the following equation can be deduced:

$$P_1V_1 = P_2V_2$$

Solving for P_2, the pressure after the addition:

$$P_2 = \frac{P_1V_1}{V_2}$$