

**Amine-Catalyzed Addition of Azide Ion to  $\alpha,\beta$ -Unsaturated Carbonyl Compounds**

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Boston College, Chestnut Hill, Massachusetts 02467-3860***Supporting Information**

**General Procedures.** Proton NMR spectra were recorded on Varian 400 or 300 spectrometers. Proton chemical shifts are reported in ppm ( $\delta$ ) relative to internal tetramethylsilane (TMS,  $\delta$  0.0) or with the solvent reference relative to TMS employed as the internal standard ( $\text{CDCl}_3$ ,  $\delta$  7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on Varian 400 (100 MHz) or 300 (75 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm ( $\delta$ ) relative to TMS with the respective solvent resonance as the internal standard ( $\text{CDCl}_3$ ,  $\delta$  77.0). NMR data were collected at 25 °C, unless otherwise indicated. Infrared spectra were obtained on a Nicolet 210 spectrophotometer. Diagnostic bands are reported ( $\text{cm}^{-1}$ ). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 precoated plates (0.25 mm thickness). TLC  $R_f$  values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with cerium ammonium nitrate (CAM) or  $\text{KMnO}_4$  solutions. Flash column chromatography was performed using Silica Gel 60A (170-400 mesh) from Fisher Scientific.<sup>1</sup> Elemental analyses were performed by Robertson Microlit (Madison, NJ).

All reactions were carried out under an argon atmosphere employing oven- and flame-dried glassware. Methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) and triethylamine ( $\text{Et}_3\text{N}$ ) were distilled from  $\text{CaH}_2$  prior to use. Azidotrimethylsilane ( $\text{TMSN}_3$ ) and 2-Cyclohexen-1-one (**1**) were purchased from the Aldrich Chemical Company and were distilled prior to use and stored under argon.

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<sup>1</sup>) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

*N*-Methylimidazole was distilled and stored under argon at  $-20\text{ }^{\circ}\text{C}$  prior to use. 2-Cyclopenten-1-one (**3**), 4,4-dimethyl-2-Cyclohexen-1-one (**5**), 3-methyl-2-Cyclohexen-1-one (**9**), and 2,4,4-trimethyl-2-Cyclohexen-1-one (**11**), hexamethylphosphoramide (HMPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from the Aldrich Chemical Company and were used without further purification. Glacial acetic acid was purchased from Fisher Scientific and used without further purification. Enone **7** was prepared according to the method of Heathcock.<sup>2</sup> Oxazolidinone **12** was prepared according to the method of Evans.<sup>3</sup>

**Caution:** Organic azides are potentially explosive compounds and should be handled with great care. We encountered no explosive behavior during these studies, however.

#### **General Procedure for the Evaluation of Lewis Bases as Catalysts (Table 1).**

To a solution of  $\text{TMSN}_3$  (0.690 mL, 5.2 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5.0 mL) was added AcOH (0.298 mL, 5.20 mmol) at ambient temperature. After stirring for 20 min, 2-cyclohexen-1-one (0.101 mL, 1.04 mmol) was added dropwise. The neat Lewis basic catalyst (0.21 mmol) was then introduced. After stirring at ambient temperature for 5 h, the reaction mixture was applied directly to a silica plug and eluted with 45% EtOAc/hexane to afford analytically pure product.

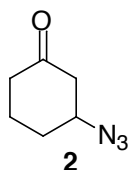
#### **General Procedure for Evaluation of Substrate Scope (Table 2).**

To a solution of 5.0 equiv  $\text{TMSN}_3$  (relative to substrate) dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  was added an equimolar amount of AcOH at ambient temperature. After stirring for 20 min, the substrate (1.0 equiv) was added followed by  $\text{Et}_3\text{N}$  (0.20 equiv). All reactions were performed at a concentration of 0.2-0.3 M in substrate. Reactions were monitored by TLC, and were worked up upon disappearance of starting material (18 to 28 h). The crude reaction mixture was applied directly to a silica plug, eluting with 45% EtOAc/hexane to afford pure product.

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<sup>2</sup>) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132-157.

<sup>3</sup>) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

Data for **Azide-2**.

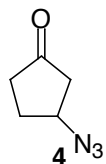
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.89 (apparent septuplet,  $J=4.0$  Hz, 1H), 2.66 (dd,  $J=14.3$  Hz, 4.8 Hz, 1H), 2.43 (dd,  $J=14.3$  Hz,  $J=8.4$  Hz, 1H), 2.35 (m, 2H), 2.09 (m, 2H), 1.85-1.70 (m, 2H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  207.1, 59.4, 46.5, 40.6, 29.7, 21.4;

IR (film,  $\text{cm}^{-1}$ ) 2093, 1715;

TLC  $R_f$  0.31 (20% EtOAc/hexane);

Anal. Calcd. for  $\text{C}_6\text{H}_9\text{N}_3\text{O}_1$ : C, 51.79; H, 6.52; N, 30.20. Found: C, 52.10; H, 6.45; N, 29.98.

Data for **Azide-4**.

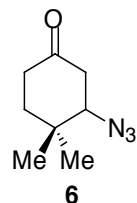
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  4.29 (apparent quintet,  $J=5$  Hz, 1H), 2.44-2.00 (m, 6H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  214.5, 58.9, 44.1, 35.8, 28.9;

IR (film,  $\text{cm}^{-1}$ ) 2102, 1747;

TLC  $R_f$  0.29 (20% EtOAc/hexane);

$^{13}\text{C}$  NMR Spectrum attached to demonstrate purity (Page SI-8).

Data for **Azide-6**.

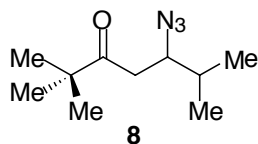
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.50 (dd,  $J=9.4$  Hz, 4.6 Hz, 1H), 2.69 (dd,  $J=14.8$  Hz, 4.8 Hz, 1H), 2.51 (dd,  $J=15.4$  Hz, 9.2 Hz, 1H), 2.34 (m, 2H), 1.81 (ddd,  $J=14.0$  Hz, 6.4 Hz, 6.1 Hz, 1H), 1.52 (ddd,  $J=14.0$  Hz, 5.0 Hz, 5.0 Hz, 1H), 1.16 (s, 3H), 1.08 (s, 3H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  207.5, 68.4, 43.0, 37.6, 35.2, 34.9, 27.1, 21.2;

IR (film,  $\text{cm}^{-1}$ ) 2107, 1720;

TLC  $R_f$  0.26 (10% EtOAc/hexane);

Anal. Calcd. for  $\text{C}_8\text{H}_{13}\text{N}_3\text{O}_1$ : C, 57.46; H, 7.84; N, 25.13. Found: C, 57.64; H, 7.74; N, 25.00.

Data for **Azide-8**.

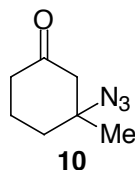
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.82 (ddd,  $J=14.7$  Hz,  $J=8.1$  Hz,  $J=3.5$  Hz, 1H), 2.76 (dd,  $J=17.6$  Hz,  $J=9.5$  Hz, 1H), 2.48 (dd,  $J=17.8$  Hz,  $J=3.1$  Hz, 1H), 1.79 (oct,  $J=5.9$  Hz, 1H), 1.16 (s, 9H), 0.97 (d,  $J=6.6$  Hz, 3H), 0.94 (d,  $J=7.0$  Hz, 3H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  212.8, 63.9, 44.3, 38.7, 32.5, 26.2, 19.4, 17.8;

IR (film,  $\text{cm}^{-1}$ ) 2093, 1709;

TLC  $R_f$  0.44 (5% EtOAc/hexane);

Anal. Calcd. for  $\text{C}_{10}\text{H}_{19}\text{N}_3\text{O}_1$ : C, 60.88; H, 9.71; N, 21.30. Found: C, 61.15; H, 9.71; N, 21.01.

Data for **Azide-10**.

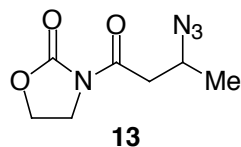
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.49 (d,  $J=14.4$ , 1H), 2.42-2.34 (m, 2H), 2.30-2.22 (m, 1H), 2.05-1.87 (m, 3H), 1.82-1.76 (m, 1H), 1.40 (s, 3H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  207.8, 64.4, 52.0, 40.2, 35.4, 25.8, 21.4;

IR (film,  $\text{cm}^{-1}$ ) 2099, 1715;

TLC  $R_f$  0.31 (20% EtOAc/hexane);

Anal. Calcd. for  $\text{C}_7\text{H}_{11}\text{N}_3\text{O}_1$ : C, 54.89; H, 7.24; N, 27.43. Found: C, 54.73; H, 7.26; N, 27.69.

Data for **Azide-13**.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  4.45 (t,  $J=8.1$  Hz, 2H), 4.06 (m, 3H), 3.22 (dd,  $J=17.8$  Hz,  $J=8.78$  Hz, 1H), 2.99 (dd,  $J=17.6$  Hz,  $J=4.39$  Hz, 1H), 1.36 (d,  $J=6.6$  Hz, 3H);

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  169.9, 153.2, 62.2, 53.6, 42.4, 41.7, 19.7

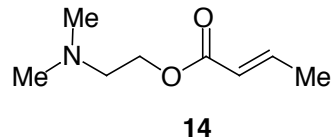
IR (film,  $\text{cm}^{-1}$ ) 2114, 1778, 1696;

TTLC  $R_f$  0.41 (40% EtOAc/hexane);

Anal. Calcd. for  $\text{C}_7\text{H}_{10}\text{N}_4\text{O}_3$ : C, 42.42; H, 5.09; N, 28.27. Found: C, 42.71; H, 5.11; N, 27.99.

Substrates **14** and **16** were prepared in analogy to the method of Halverstadt, et. al..<sup>4</sup>

Data for **Substrate 14**.



<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.76 (dq, J=13.6 Hz, 7.0 Hz, 1H), 5.88 (d, J=15.6 Hz, 1H), 4.22 (t, J=5.6 Hz, 2H), 2.59 (t, J=5.8 Hz, 2H), 2.29 (s, 6H), 1.87 (d, J=7 Hz, 3H);

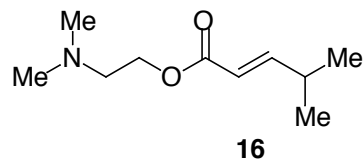
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 166.3, 144.7, 122.4, 61.9, 57.9, 45.8, 18.1;

IR (film, cm<sup>-1</sup>) 1720, 1659;

TLC R<sub>f</sub> 0.42 (10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

Anal. Calcd. for C<sub>8</sub>H<sub>15</sub>N<sub>1</sub>O<sub>2</sub>: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.84; H, 9.33; N, 9.12.

Data for **Substrate-16**.



<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.78 (dd, J=15.7 Hz, J=6.6 Hz, 1H), 5.64 (d, J=15.7 Hz, 1H), 4.05 (t, J=5.9 Hz, 2H), 2.41 (t, J=5.7 Hz, 2H), 2.34 (d-septuplet, J=6.6, 5.5 Hz, 1H), 2.11 (s, 6H), 0.88 (d, J=6.6 Hz, 6H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 166.3, 155.0, 118.0, 61.6, 57.6, 45.4, 30.6, 20.9;

IR (film, cm<sup>-1</sup>) 1721, 1657;

TLC R<sub>f</sub> 0.26 (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>);

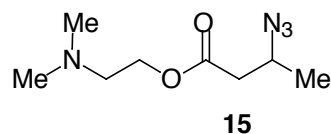
Anal. Calcd. for C<sub>10</sub>H<sub>19</sub>N<sub>1</sub>O<sub>2</sub>: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.89; H, 10.11; N, 7.77.

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<sup>4</sup>) Halverstadt, I. F.; Hardie, W. R.; Williams, A. R. *J. Am. Chem. Soc.* **1959**, *81*, 3618-3628.

**General Procedure for the Preparation of Azides 15 and 17.**

To a solution of TMSN<sub>3</sub> (0.422 mL, 3.18 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added an equimolar amount (0.182 mL, 3.18 mmol) of AcOH. After stirring at ambient temperature for 20 min, substrate **14** (0.100 g, 0.64 mmol) was added, and the reaction was allowed to stir at ambient temperature for 24 h. The reaction mixture was then applied directly to a silica plug and eluted with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was concentrated *in vacuo* to an oil, and then redissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, and washed with saturated sodium bicarbonate solution (2 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to a clear liquid, which was then purified by flash chromatography to yield azide **15** as a clear liquid (0.074 g, 58%).

**Data for Azide-15.**

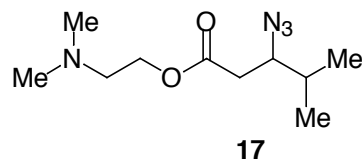
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 4.21 (t, J=5.6 Hz, 2H), 3.97 (apparent sextet, J=6.8 Hz, 1H), 2.58-2.52 (m, 3H), 2.47 (dd, J=16.0 Hz, J=5.6 Hz, 1H), 2.28 (s, 6H), 1.31 (d, J=6.4 Hz, 3 H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 170.3, 62.4, 57.7, 54.2, 45.6, 41.0, 19.5;

IR (film, cm<sup>-1</sup>) 2112, 1748;

TLC R<sub>f</sub> 0.42 (10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

Anal. Calcd. for C<sub>8</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 47.99; H, 8.05; N, 27.98. Found: C, 47.85; H, 7.95; N, 27.89.

**Data for Azide-17.**

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 4.23 (t, J=5.7 Hz, 2H), 3.71 (quintet, J= 4.8 Hz, 1H), 2.58 (m, 3H), 2.48 (dd, J=16.1 Hz, J=9.5 Hz, 1H), 2.28 (s, 6H), 1.82 (m, 1H), 0.97 (d, J=6.6 Hz, 3H), 0.95 (d, J=6.6 Hz, 3H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 171.1, 65.0, 62.5, 57.7, 45.7, 37.1, 32.6, 19.2, 17.9;

IR (film, cm<sup>-1</sup>) 2128, 2097, 1738;

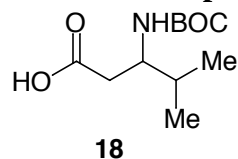
TLC R<sub>f</sub> 0.42 (10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

Anal. Calcd. for C<sub>10</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>: C, 52.61; H, 8.83; N, 24.54. Found: C, 52.38; H, 8.71; N, 24.47.

**Procedure for the conversion of azide **17** to BOC-protected amino acid **18**.**

To a stirred solution of azide **17** (0.146 g, 0.64 mmol) in MeOH (6.0 mL) was added di-*tert*-butyl dicarbonate (BOC<sub>2</sub>O, 0.146 g, 0.67 mmol), followed by a catalytic amount (0.020 g) of 10% palladium on carbon. The reaction mixture was flushed with dihydrogen (3X) and then allowed to stir for 3 h at ambient temperature under an H<sub>2</sub> atmosphere (balloon). The reaction mixture was then filtered through Celite, and the resulting filtrate was concentrated *in vacuo* to give the intermediate BOC-protected amino ester (0.149 g, 77%), which was carried on without further purification.

To a stirred solution of the BOC-protected amino ester (0.149 g, 0.49 mmol) in a 2:2:1 THF/MeOH/H<sub>2</sub>O solvent system (15.0 mL) was added LiOH (0.012 g, 0.52 mmol). The reaction was allowed to stir at ambient temperature for 12 h. The volatiles (THF, MeOH) were evaporated *in vacuo* and the resulting aqueous solution was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 mL). The aqueous layer was then acidified with 10% citric acid solution, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated to a crude solid which was recrystallized from EtOAc/hexane to afford the BOC-protected amino acid **18** (0.067 gm, 59%)

**Data for BOC-protected amino acid-18.**

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 50 °C) δ 4.87 (br s, 1H), 3.75 (m, 1H), 2.53 (m, 2H), 1.85 (apparent octet, J=6.9 Hz, 1H), 1.44 (s, 9H), 0.94 (d, J=6.6Hz, 3H), 0.93 (d, J=6.6 Hz, 3H);

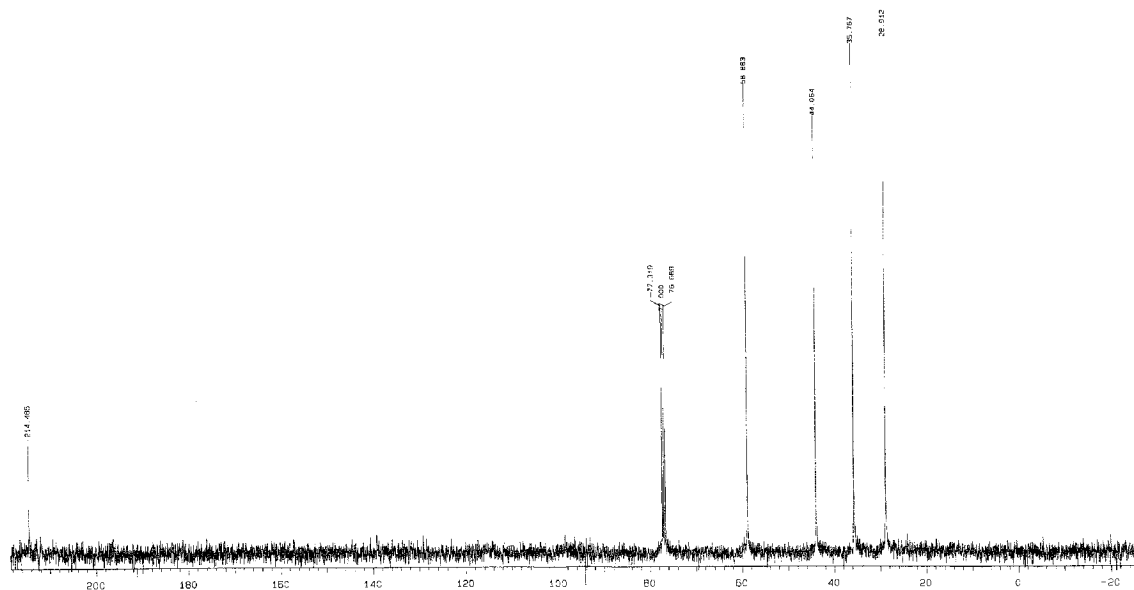
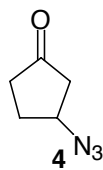
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 176.9, 155.6, 79.4, 52.9, 37.2, 31.8, 28.4, 19.5, 18.7;

IR (film, cm<sup>-1</sup>) 3322, 1719;

TLC R<sub>f</sub> 0.37 (50% EtOAc/hexane);

Anal. Calcd. for C<sub>11</sub>H<sub>21</sub>N<sub>1</sub>O<sub>4</sub>: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.03; H, 9.20; N, 6.03.

$^{13}\text{C}$  NMR Spectrum attached to demonstrate purity.





**Differential Scanning Calorimetry** (DSC) measurements were performed at Science Resources, Inc. Laboratory (2029 Washington Ave., Suite 201, Evansville, IN 47714).<sup>5</sup> The summary of the results obtained is as follows:

### **Summary**

Samples of azide **2** and azide **6** produced DSC endothermic transitions with onset temperatures of 130.4 and 190.7°, respectively, followed by exothermic transitions. A sample of compound **13** produced two exothermic events where the onset temperature for the first event occurred at 200.1°C. The individual thermal curves appear below. The final curve is a comparison plot for all three samples normalized by sample weight for direct comparison of the size of the transitions. The peak apex for the larger exotherm for sample azide **13** is “squared-off” suggesting that this transition exceeded the detector range, consequently, the enthalpy of  $-769$  J/g is underestimated.

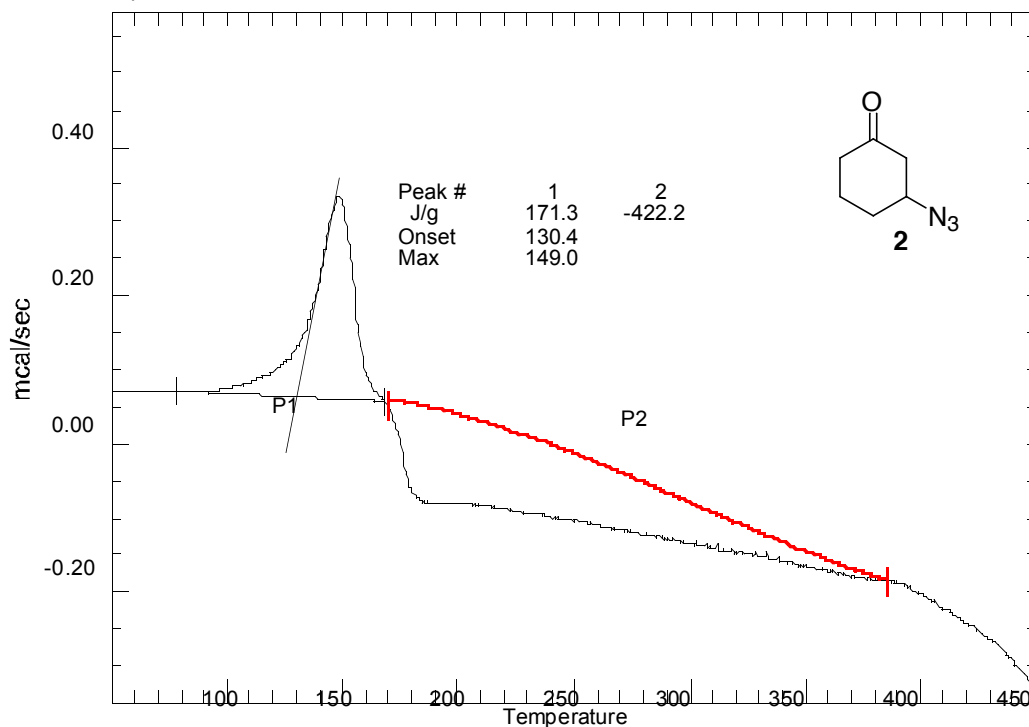
The results are shown below.

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<sup>5</sup> We thank Robert J. Behme of Science Resources, Inc. for performing the DSC measurements.

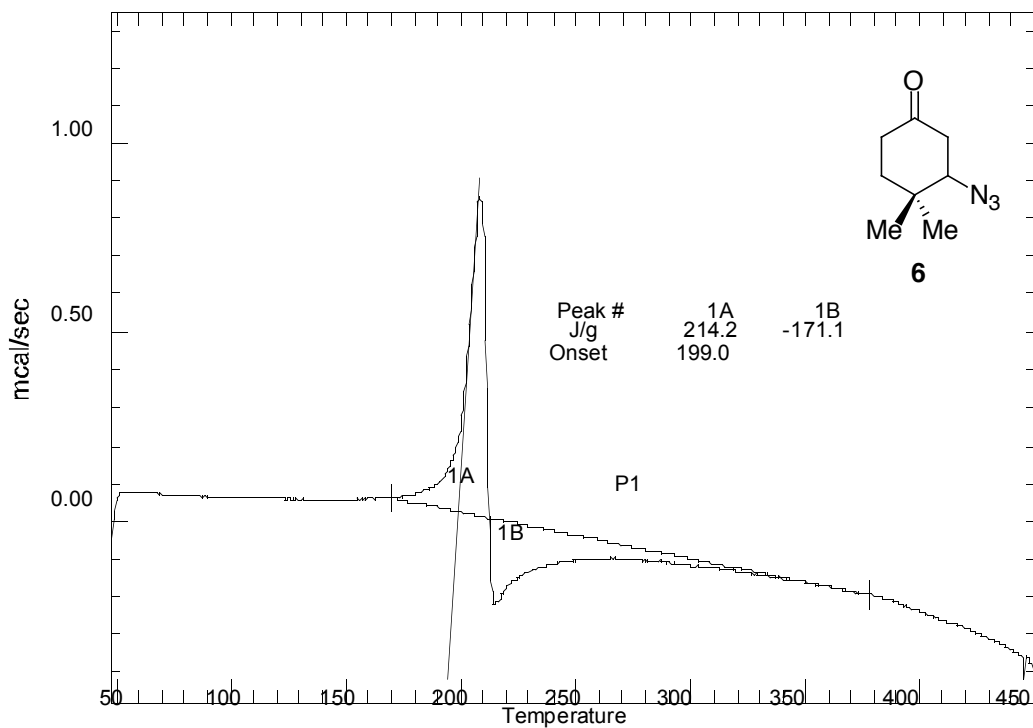
File Name : 9239b  
 Size : 1.802 mg  
 Date : 8/27/99 9:26.14  
 Notes : Boston College  
 : Sample DJG-I-277A

Operator : SMD  
 Scan Rate : 20. deg/min  
 Sample rate: 1.00 pts/sec  
 Gas : nitrogen  
 Instrument : Perkin-Elmer DSC4



File Name : 9239c  
 Size : 2.087 mg  
 Date : 8/27/99 10:00.44  
 Notes : Boston College  
 : Sample DJG-I-260B

Operator : SMD  
 Scan Rate : 20. deg/min  
 Sample rate: 1.00 pts/sec  
 Gas : nitrogen  
 Instrument : Perkin-Elmer DSC4



File Name : 9239d  
 Size : 1.843 mg  
 Date : 8/27/99 10:29.48  
 Notes : Boston College  
 : Sample DJG-I-261A

Operator : SMD  
 Scan Rate : 20. deg/min  
 Sample rate: 1.00 pts/sec  
 Gas : nitrogen  
 Instrument : Perkin-Elmer DSC4

