



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

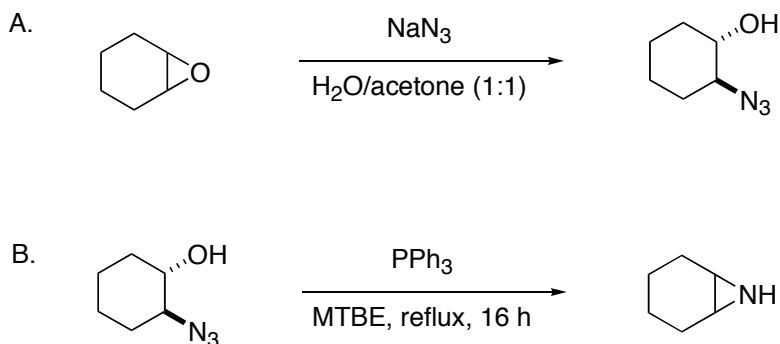
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Copyright © 2010 Organic Syntheses, Inc. All Rights Reserved

CYCLOHEXENE IMINE
(7-AZA-BICYCLO[4.1.0]HEPTANE)



Submitted by Iain D. G. Watson, Nicholas Afagh and Andrei K. Yudin.¹

Checked by Lars Troendlin and Andreas Pfaltz.

1. Procedure

WARNING: Organic azides can be unstable and/or explosive.

A. trans-2-Azido-cyclohexanol. In a 500-mL, one-necked, round-bottomed flask equipped with a magnetic stir bar (4 cm, cylindrical-shaped) is placed sodium azide (25.2 g, 388 mmol, 2.5 equiv) (Note 1). Water (85 mL) is added and the solution is stirred at room temperature until all solid has dissolved. Acetone (60 mL) is added followed by a slow and continuous dropwise addition of cyclohexene oxide (15.5 mL, 153 mmol, 1.0 equiv) in acetone (25 mL) using a pressure equalizing dropping funnel over 30 min (Note 2). The flask is fitted with a reflux condenser and the solution is heated to reflux for 18 h (85 °C), after which acetone is evaporated *in vacuo* and the residual solution is extracted with diethyl ether (3 x 200 mL). The combined organic phases are washed with brine (100 mL) and dried over Na₂SO₄. The solvent is removed *in vacuo* (Note 3) and *trans*-2-azido-cyclohexanol is obtained in 99% yield as a yellow oil (21.6 g, 153 mmol), which is reacted immediately and without further purification (Note 4).

B. Cyclohexene imine. Into a flame-dried, 500-mL, three-necked, round bottomed flask equipped with a magnetic stir bar (4 cm, cylindrical-shaped), reflux condenser, a pressure equalizing dropping funnel, internal thermometer and high-vacuum-argon connection is added the azido alcohol (21.6 g, 153 mmol, 1.0 equiv) followed by freshly distilled methyl *tert*-butyl

ether (MTBE) (40 mL) (Note 5). Triphenylphosphine (40.2 g, 153 mmol, 1.0 equiv) is dissolved in MTBE (100 mL) and the solution is transferred into the dropping funnel. The solution is added slowly and continuously over 45 min (Note 6). The addition is accompanied by the vigorous evolution of nitrogen gas and a temperature increase to 40 °C. After the addition of the triphenylphosphine solution, the dropping funnel is washed with TBME (20 mL). After nitrogen evolution has ceased, the solution is heated to reflux (70 °C) for 16 h under a nitrogen atmosphere. The solution is then transferred in a well ventilated hood to a single-necked, 1-L evaporating flask (Note 7). MTBE is removed at 40 °C under reduced pressure (360 mmHg) on a rotary evaporator (Note 8) leaving an off-white solid (Ph₃PO), within which is trapped the cyclohexene imine product. The cyclohexene imine is distilled *in vacuo* (0.01 mmHg) at 160 °C from the resulting residue using a short path distillation apparatus to afford a clear, colorless liquid (Note 9). Residual MTBE, which will inevitably co-distill with the product, can be removed by freeze-drying the resulting liquid. In this procedure, the flask containing the cyclohexene imine is immersed in a -12 °C sodium chloride/ice cold bath and the flask is rotated such that as cyclohexene imine begins to solidify, it forms a thin coat along the interior of the flask effectively maximizing the surface area and facilitating removal of MTBE. While still immersed in the cold-bath, a spatula is used to scratch the sides of the flask to break up the thin layer of cyclohexene imine to afford fine flakes. The residual MTBE is then removed *in vacuo* (0.13 mbar) while the flask remains immersed in the cold-bath to afford pure cyclohexene imine (13.6 g, 140 mmol) in 91% yield as fine white crystals below 5 °C and a clear colorless liquid above this temperature (Notes 10 and 11; for GC data, see Note 12).

2. Notes

1. All reagents were purchased from Sigma-Aldrich. MTBE was purchased from Sigma-Aldrich; all other solvents were purchased from EMD Chemicals. Sodium azide must be measured with a plastic or glass spoon. Do not allow sodium azide to come in contact with metal or chlorinated solvents.

2. If cyclohexene oxide is added neat, all at once, a white insoluble polymeric material is formed which is deposited on the side of the flask, negatively affecting the isolated yield.

3. It is important that the product is dried as water will negatively affect subsequent synthetic manipulations. After isolation using the rotary evaporator, residual water is removed from the product using a vacuum pump (0.1 mmHg).

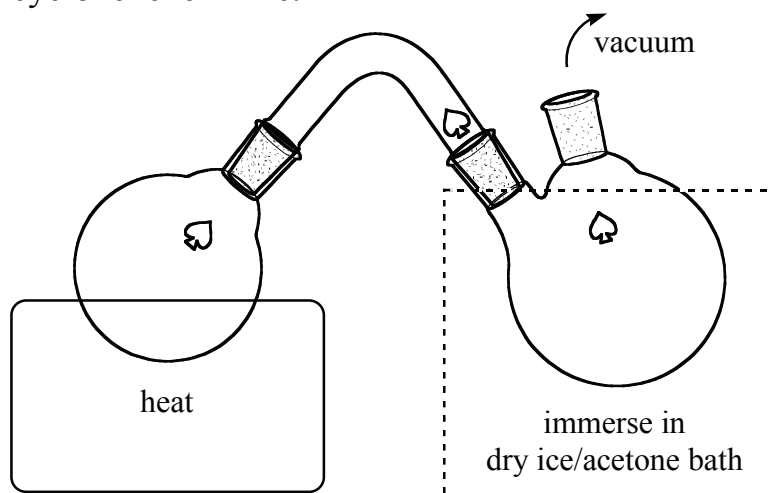
4. *WARNING: organic azides can be unstable and/or explosive.* ^1H NMR (CDCl_3 , 400 MHz) δ : 1.23–1.39 (m, 4 H), 1.71–1.78 (m, 2 H), 1.99–2.08 (m, 2 H), 2.31 (bs, 1 H), 3.15–3.21 (m, 1 H), 3.35–3.40 (m, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 23.8, 24.2, 29.7, 33.0, 67.1, 73.6. If desired, the intermediate *trans*-2-azido-cyclohexanol can be further purified by flash chromatography on SiO_2 (R_f = 0.15, 95:5 hexanes/EtOAc).

5. Anhydrous MTBE was obtained by distillation over 4Å molecular sieves (30 g for 300 mL of MTBE).

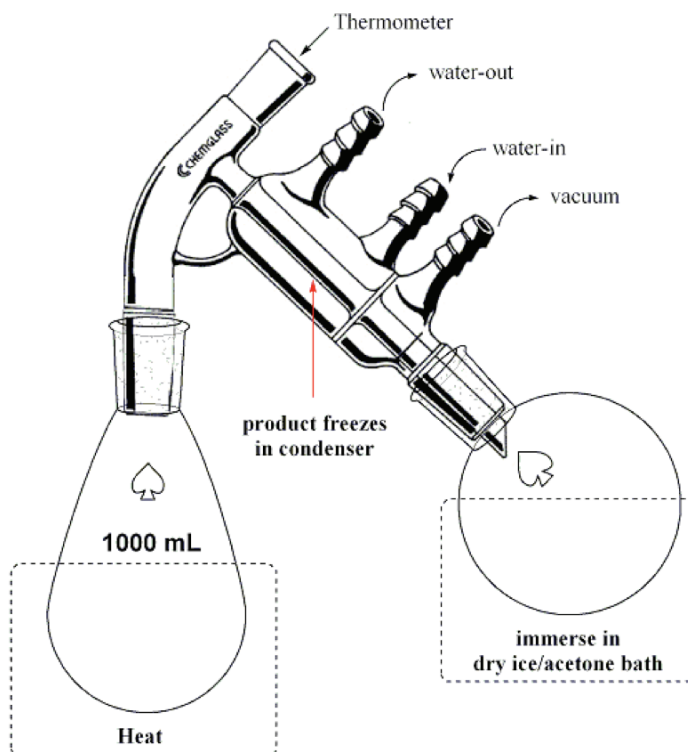
6. The slow, continuous addition of triphenylphosphine under an atmosphere of N_2 was found to be essential in obtaining high yields. The submitters added solid triphenylphosphine using a pressure-equalizing powder addition funnel.

7. Transferring the solution to the larger 1 L evaporating flask avoids complications arising from bumping of the residual solid during the two distillation steps.

8. The checkers used a rotary evaporator for removing the solvent. The submitters performed the distillation in a short path apparatus. The connector between the flasks should have a sharp angle to prevent bumped triphenylphosphine oxide from contaminating the collected product. A piece of glass wool may be optionally inserted into the connector to avoid contamination of the collected product with bumped impurities. The collecting flask must be *completely* immersed in dry ice/acetone to prevent loss of volatile cyclohexene imine.



9. Due to the low melting point of cyclohexene imine, it will occasionally freeze in the condenser (indicated by the arrow) at which point the distillation will arrest. If this occurs, then the vacuum can be temporarily removed and the water flowing through the condenser can be shut off and the condenser area gently heated with a heat-gun to melt the frozen product into the collecting flask. This opportunity can also be used to break up the solid in the evaporating flask using a metal spatula.



10. Cyclohexene imine is stored over KOH pellets (4 pellets for 13.6 g of product) at $-20\text{ }^{\circ}\text{C}$. Aziridines should always be considered as highly toxic compounds and treated with care in ventilated spaces.

11. ^1H NMR (CDCl_3 , 400 MHz) δ : 0.41 (br, 1 H), 1.16–1.36 (m, 4 H), 1.77 (s, 4 H), 2.14 (s, 2 H), 3.21 (d, $J = 2\text{ Hz}$); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 20.4, 24.5, 29.2. MS (ESI) m/z (rel. intensity) 196 ($[\text{2M}]^+$, 75), 98 ($[\text{M}+1]^+$, 100), 65 (30).

12. GC analysis was conducted immediately after distillation of cyclohexene imine. A sample of cyclohexene imine was dissolved in acetonitrile (HPLC grade) and subjected to GC analysis, which revealed the presence of 4 peaks (relative to MeCN blank). The major peak ($t_R = 9.750\text{ min}$) accounted for 98.9% of the total area of all peaks. Gas-phase chromatography was performed on an HP-6890 series instrument using an HP-5 column (crosslinked 5% phenyl methyl siloxane, 30 m x 0.32 mm x

0.25 μm film thickness). The oven was heated at 30 °C for 5 min followed by a temperature gradient of 5 °C/min to 120 °C. Inlet temperature and pressure were 200 °C and 4.88 psi respectively, with a split ratio of 50:1. Hydrogen was the carrier gas.

The checkers used a Carlo Erba Instrument GC 8000Top, an Restek Rtx-1701 column (14% cyanopropylphenyl - 86% dimethylpolysiloxan, 30 m x 0.25 mm x 0.25 μm film thickness). A sample of cyclohexene imine was dissolved in TBME. The oven temperature was kept at 80 °C for 5 min followed by a temperature gradient of 5 °C/min to 130 °C and then 10 °C/min to 250 °C and, finally, at 250 °C for 5 min. Inlet temperature was 220 °C and the pressure was 60 kPa, helium was the carrier gas. The major peak ($t_{\text{R}} = 10.64$ min) accounted for 96.6% of the total area of all peaks.

Safety and Waste Disposal Information

Sodium azide should not be allowed to come into contact with any metal or chlorinated solvents. The organic azide intermediate should be treated as potentially explosive and reacted immediately. Aziridines should always be considered as highly toxic compounds and to only be used in ventilated fume hoods.

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory;” National Academy Press; Washington, DC, 1995.

3. Discussion

N-Unsubstituted, or NH-aziridines have been used as key substrates in a number of different reactions over the course of our work in this area.² These substrates may be prepared in a number of different ways: by Staudinger, Wenker, Gabriel or conjugate addition strategies.³ Starting materials for NH-aziridines may include epoxides, aminoalcohols, or α,β -unsubstituted carbonyl compounds.

Over the course of the work on the functionalization of aziridines, cyclohexene imine was used extensively as a test substrate (Figure 1). This molecule contains several favorable properties, including relative ease of preparation. It can be distilled below 60 °C under reduced pressure allowing for easy purification. The material is not volatile enough to evaporate while

heating over the course of long reaction times. This aziridine is also less likely to open than monosubstituted aziridines, allowing the use of harsher reaction conditions without loss of selectivity from background ring-opening of starting materials or products.

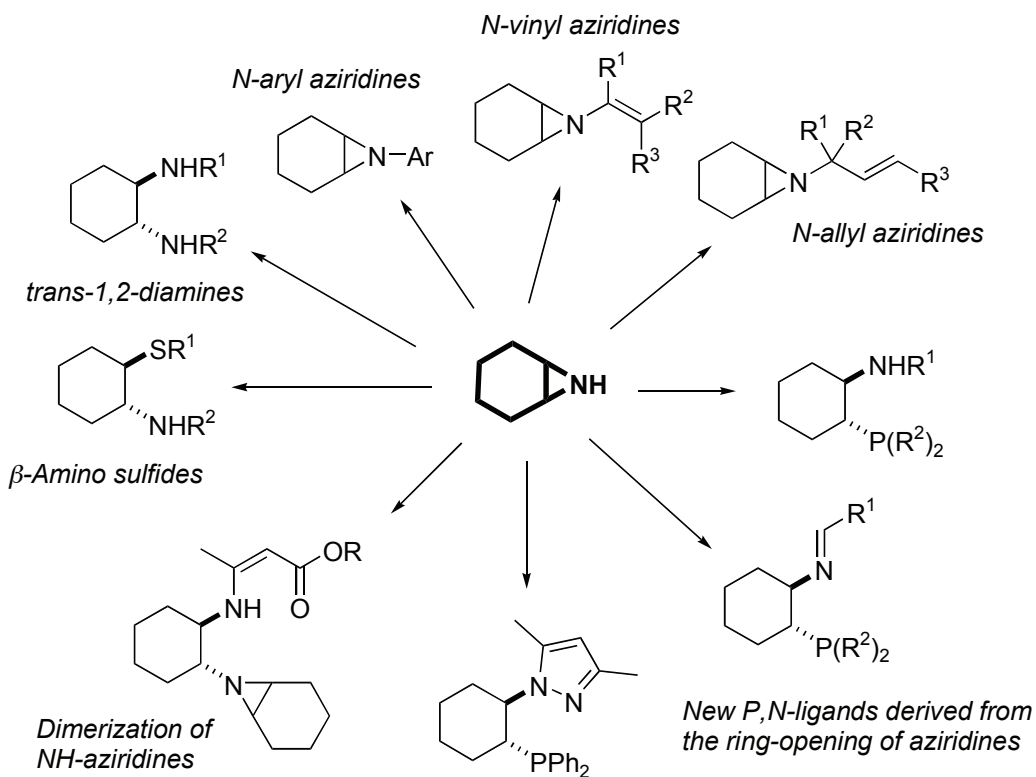


Figure 1. Cyclohexene imine as a precursor for a wide variety of nitrogen containing functionalities.

The synthesis of cyclohexene imine was accomplished by a two-step protocol.⁴ First of all, the ring opening of cyclohexene oxide with sodium azide provided the azidoalcohol intermediate in quantitative yield. This intermediate, isolated by extraction, was then reacted without further purification by the addition of one equivalent of triphenylphosphine.

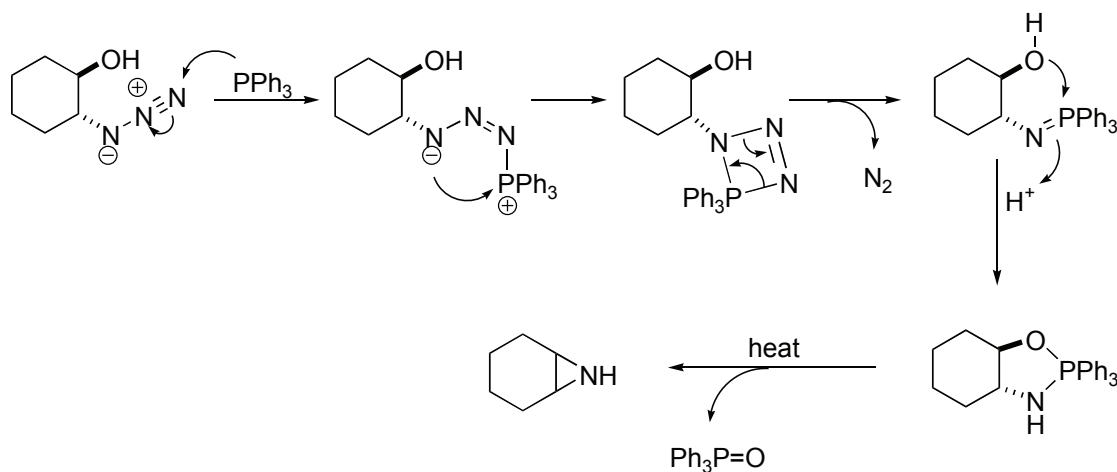


Figure 2. Mechanism of the Staudinger reaction, formation of cyclohexene imine.

The second step of the protocol, the Staudinger reaction, proceeds via initial reduction of the azide group to generate a five-membered intermediate (Figure 2). Decomposition of the intermediate then generates the aziridine by exclusion of triphenylphosphine oxide. Reduction of the azide group occurs immediately upon addition of triphenylphosphine, evident by bubbling caused by the evolution of nitrogen gas. However, heating the solution is necessary for the production of the aziridine. In fact, when the reaction was performed in diethyl ether, yields were much lower than when THF or methyl *tert*-butyl ether were used, owing to the higher boiling points of the latter solvents.

1. Davenport Research Laboratories, Department of Chemistry, The University of Toronto, 80 St. George Street, Toronto, Ontario, Canada, M5S 3H6.
2. (a) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, 39, 194-206. (b) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, 127, 17516 - 17529. (c) Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *J. Am. Chem. Soc.* **2004**, 126, 5086-5087. (d) Alphonse, F.-A.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, 128, 11754-11755. (e) Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2003**, 68, 5160-5167. (f) Dalili, S.; Yudin, A. K. *Org. Lett.* **2005**, 7, 1161-1164. (g) Dalili, S.; Caiazzo, A.; Yudin, A. K. *J. Organomet. Chem.* **2004**, 689, 3604-3611. (h) Sasaki, M.; Dalili, S.; Yudin, A. K. *J. Org. Chem.* **2003**, 68, 2045-2047. (i) Caiazzo, A.; Dalili,

- S.; Yudin, A. K. *Synlett* **2003**, 2198-2202. (j) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, 4, 2597-2600.
3. *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006.
4. (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta.* **1919**, 2, 635-646. (b) Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, 43, 4271-4273. (c) Christoffers, J.; Schulze, Y.; Pickardt, J. *Tetrahedron* **2001**, 57, 1765-1769.

Appendix

Chemical Abstracts Nomenclature; (Registry Number)

Cyclohexene oxide, 98%; (286-20-4)

Triphenylphosphine, 99%; (603-35-0)

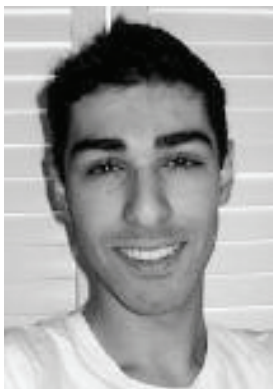
Sodium azide, $\geq 99.5\%$; (26628-22-8)



Professor Andrei K. Yudin obtained his B.Sc. degree at Moscow State University and his Ph.D. degree at the University of Southern California under the direction of Professors G. K. Surya Prakash and George A. Olah. He subsequently took up a postdoctoral position in the laboratory of Professor K. Barry Sharpless at the Scripps Research Institute. In 1998, he started his independent career at the University of Toronto. He received early tenure in 2002 and became Full Professor in 2007. He is a recipient of a number of awards and his research interests are in development and application of novel synthetic methods that enable discovery of functionally significant molecules.



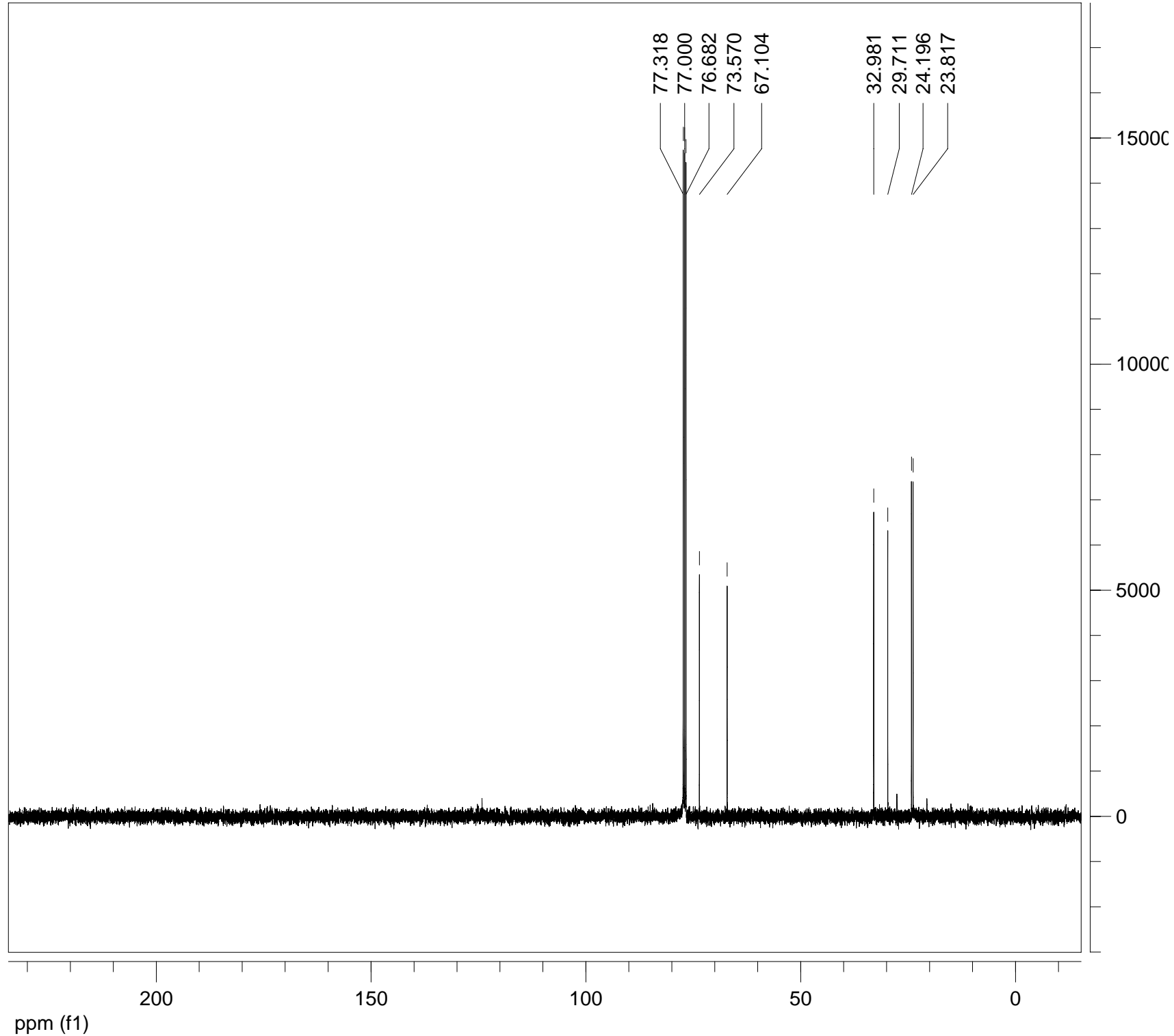
Iain Watson was born in Toronto, Canada. He is a medicinal chemist at the Ontario Institute for Cancer Research (OICR) in Toronto. Iain worked on the development of asymmetric gold(I)-catalyzed cycloisomerization reactions during his postdoctoral studies at the University of California, Berkeley with Professor F. Dean Toste. He received his Ph.D. from the University of Toronto in 2006, working with Professor Andrei Yudin in the fields of amination and palladium catalysis.



Nicholas A. Afagh received a B.Sc. in biochemistry from the University of Ottawa in 2007, working under the supervision of Prof. Robert N. Ben. He is currently a graduate student in the group of Professor Andrei K. Yudin at the University of Toronto, where he is investigating the synthetic applications of *N*-alkenyl aziridines.



Lars Tröndlin was born in 1977 in Lörrach, Germany. He studied Chemistry at the University of Basel where he obtained his M.Sc. in 2006 under the supervision of Prof. Andreas Pfaltz. He began his Ph.D. work in summer 2006 in the group of Prof. Andreas Pfaltz, where he is currently working on synthesis of new chiral ligands for metal-catalyzed reactions.



Date:
25 Jan 2010

Document's Title:
trans-2-Azido-cyclohexanol-13C.pdf

Spectrum Title:
User/Group Lars Troendlin/Pfaltz
LT422 nach HV
_C13cpd CDCl3 uicon troend 46

Frequency (MHz):
(f1) 100.624

Original Points Count:
(f1) 32768

Actual Points Count:
(f1) 65536

Acquisition Time (sec):
(f1) 1.3042

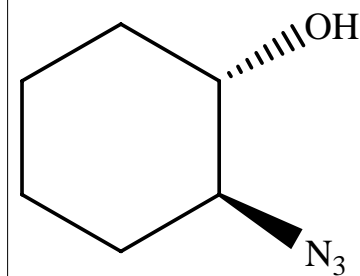
Spectral Width (ppm):
(f1) 249.699

Pulse Program:
ZGDC30

Temperature:
300

Number of Scans:
512

Acq. Date:
Wed Aug 05 09:46:49 PM



Date:
25 Jan 2010

Document's Title:
7-Aza-bicyclo[4.1.0]heptane-13C

Spectrum Title:
User/Group Lars Troendlin/Pfaltz
LT421 nach Dest.1
_C13cpd CDCl3 uicon troend 6

Frequency (MHz):
(f1) 100.624

Original Points Count:
(f1) 32768

Actual Points Count:
(f1) 65536

Acquisition Time (sec):
(f1) 1.3042

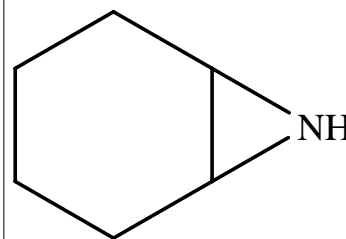
Spectral Width (ppm):
(f1) 249.699

Pulse Program:
ZGDC30

Temperature:
300

Number of Scans:
512

Acq. Date:
Wed Jul 29 09:09:39 PM



77.318
77.000
76.682

29.130
29.098
29.083
24.525
20.015

10000

5000

0

200

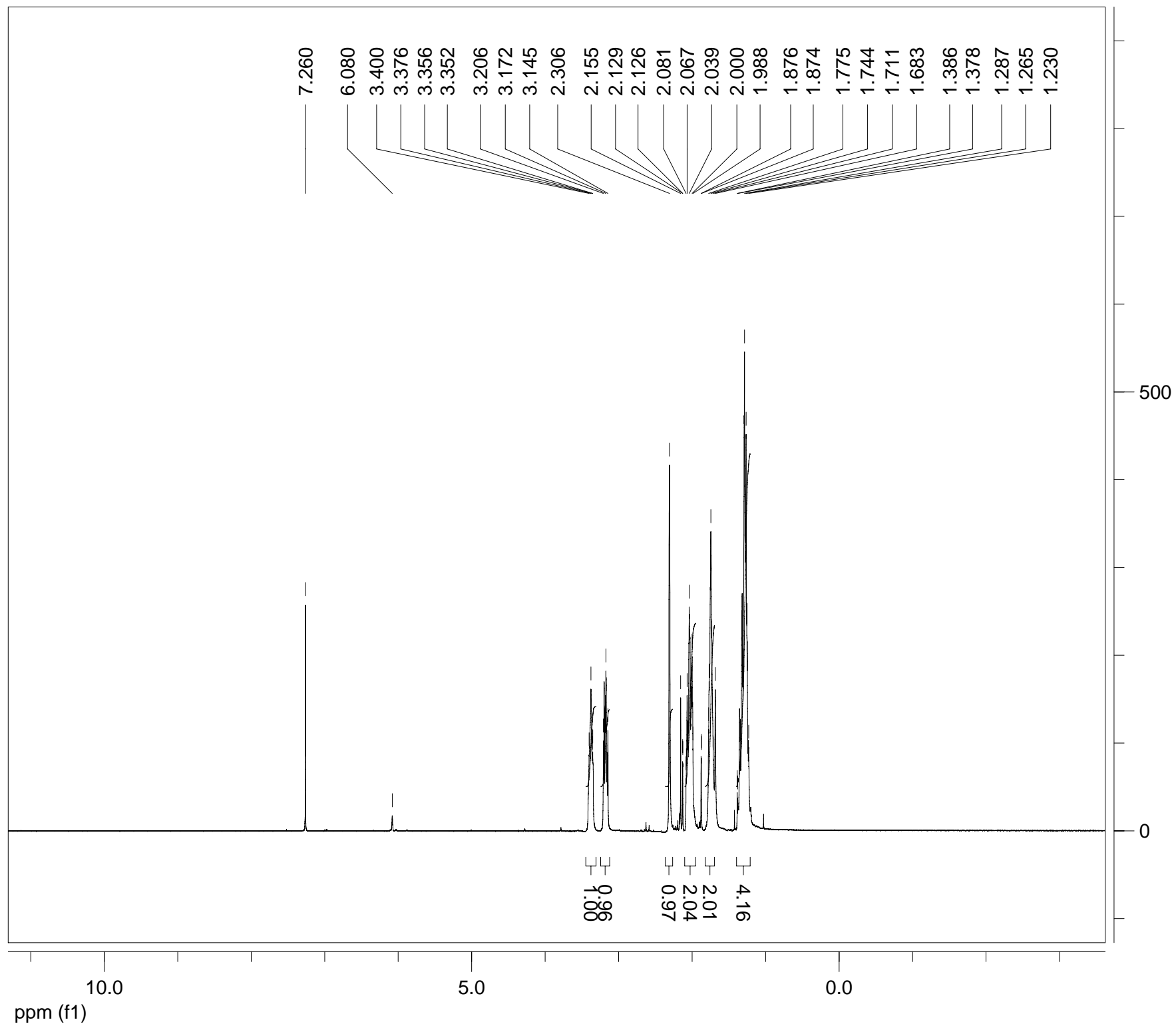
150

100

50

0

ppm (f1)



Date:

4 Nov 2009

Document's Title:

fid

Spectrum Title:

User/Group Lars Troendlin/Pfaltz

LT445 nach Auf.

_Proton CDCI3 uicon troend 14

Frequency (MHz):

(f1) 400.132

Original Points Count:

(f1) 24576

Actual Points Count:

(f1) 65536

Acquisition Time (sec):

(f1) 2.9688

Spectral Width (ppm):

(f1) 20.689

Pulse Program:

ZG30

Temperature:

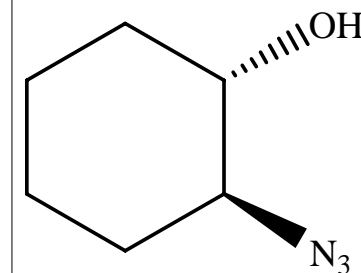
300

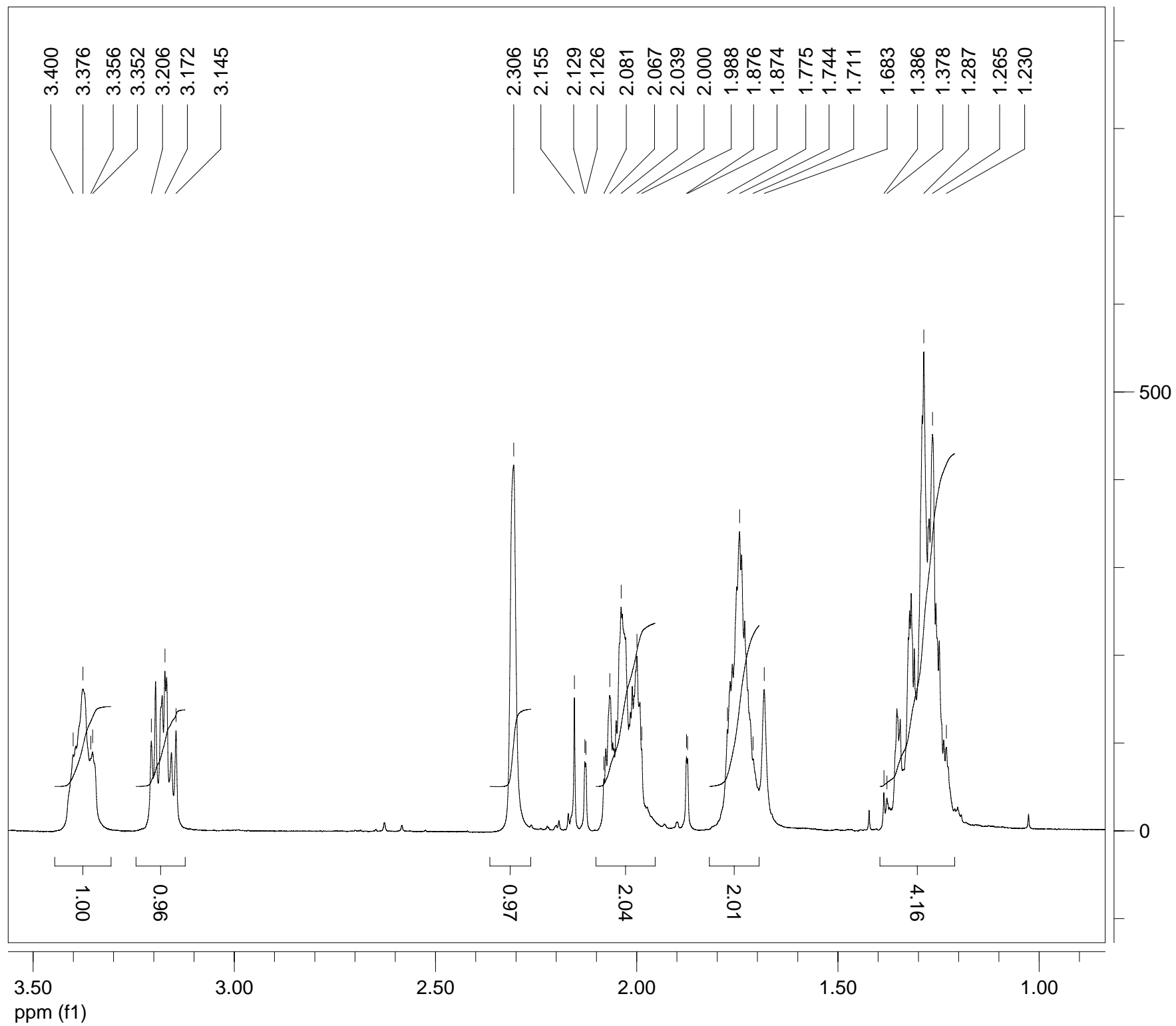
Number of Scans:

16

Acq. Date:

Tue Oct 06 02:59:21 PM



**Date:**

4 Nov 2009

Document's Title:

fid

Spectrum Title:

User/Group Lars Troendlin/Pfaltz

LT445 nach Auf.

_Proton CDCI3 uicon troend 14

Frequency (MHz):

(f1) 400.132

Original Points Count:

(f1) 24576

Actual Points Count:

(f1) 65536

Acquisition Time (sec):

(f1) 2.9688

Spectral Width (ppm):

(f1) 20.689

Pulse Program:

ZG30

Temperature:

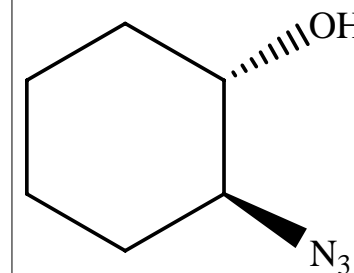
300

Number of Scans:

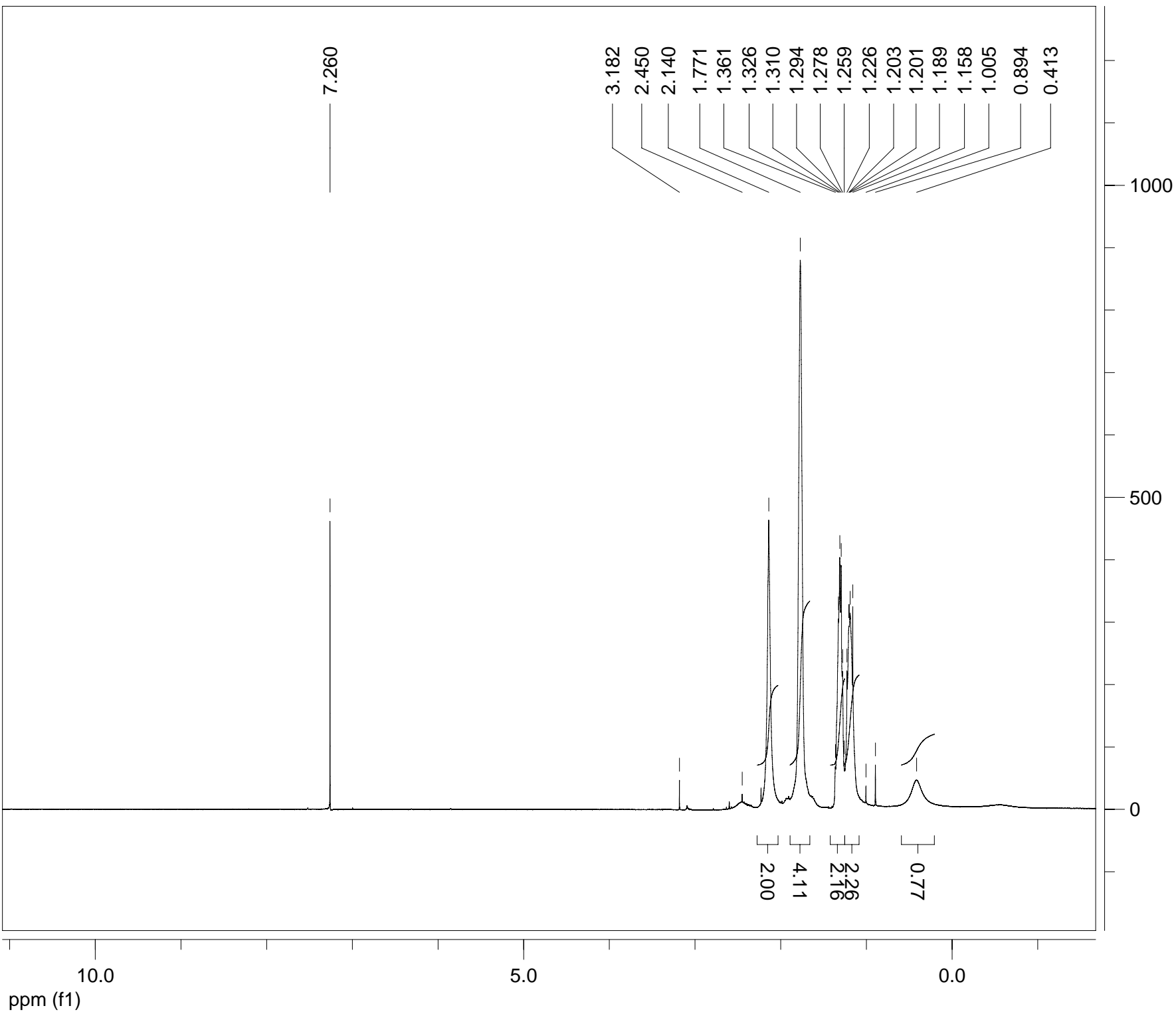
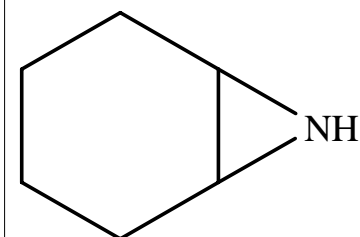
16

Acq. Date:

Tue Oct 06 02:59:21 PM



Date:
 4 Nov 2009
Document's Title:
 fid
Spectrum Title:
 User/Group Lars Troendlin/Pfaltz
 LT446
 _Proton CDCl3 uicon troend 60
Frequency (MHz):
 (f1) 400.132
Original Points Count:
 (f1) 24576
Actual Points Count:
 (f1) 65536
Acquisition Time (sec):
 (f1) 2.9688
Spectral Width (ppm):
 (f1) 20.689
Pulse Program:
 ZG30
Temperature:
 300
Number of Scans:
 16
Acq. Date:
 Fri Oct 09 01:46:00 AM



Date:
 4 Nov 2009
Document's Title:
 fid
Spectrum Title:
 User/Group Lars Troendlin/Pfaltz
 LT446
 _Proton CDCl3 uicon troend 60
Frequency (MHz):
 (f1) 400.132
Original Points Count:
 (f1) 24576
Actual Points Count:
 (f1) 65536
Acquisition Time (sec):
 (f1) 2.9688
Spectral Width (ppm):
 (f1) 20.689
Pulse Program:
 ZG30
Temperature:
 300
Number of Scans:
 16
Acq. Date:
 Fri Oct 09 01:46:00 AM

