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for the Preparation
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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.

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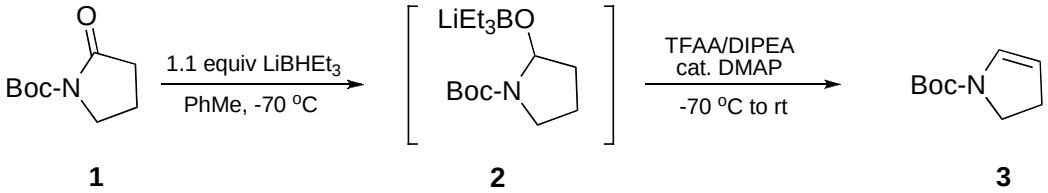
ONE-POT CONVERSION OF LACTAM CARBAMATES TO CYCLIC ENECARBAMATES: PREPARATION OF 1-*TERT*-BUTOXYCARBONYL-2,3-DIHYDROPYRROLE



1 **2** **3**

Submitted by Jurong Yu,[1]* Vu Truc,[1] Peter Riebel,[2] Elizabeth Hierl,[1] and Boguslaw Mudryk. [1]
Checked by Matthias Maywald and Andreas Pfaltz.

1. Procedure

1-tert-Butoxycarbonyl-2,3-dihydropyrrole. To a 500-mL, three-necked, round-bottom flask equipped with a magnetic stirring bar, a rubber septum, a thermometer and a two-tap Schlenk adaptor connected to a bubbler and an argon/vacuum manifold (Note 1) is added *N*-(*tert*-butyloxycarbonyl)pyrrolidin-2-one **1** (14.1 g, 73.6 mmol) (Note 2). The flask is evacuated for 25 min at room temperature (Note 3), then is filled with argon and kept under argon atmosphere during the entire reaction. Through the rubber septum, anhydrous toluene (100 mL) is added via syringe. The flask is cooled to −70 °C (internal temperature) and a solution of lithium triethylborohydride (Super Hydride®, 81.0 mL, 1.0 M in THF, 81.0 mmol, 1.1 equiv) is added dropwise via syringe, while maintaining the temperature below −60 °C (Note 4). After complete addition, the reaction mixture is stirred for one additional hour at −70 °C to allow completion of the reaction (Note 5). Solid DMAP (90 mg, 0.736 mmol, 0.01 equiv) is added in one portion, followed by *N*,*N*-diisopropylethylamine (73.2 mL, 420 mmol, 5.70 equiv) and trifluoracetic anhydride (12.3 mL, 88.3 mmol, 1.20 equiv) which are added, in sequence, dropwise by syringe through the rubber septum at rates that maintain the temperature below −55 °C (Note 6). After complete addition, the cooling bath is removed, and the reaction mixture is allowed to warm to room temperature. The mixture is then stirred for about

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two hours to allow completion of the reaction (Note 7). The reaction mixture is cooled to 0 °C in an ice/water bath and then is quenched by dropwise addition of water (150 mL) via syringe while keeping the temperature below 15 °C (Note 8). The mixture is transferred to a 1-L separatory funnel where the phases are separated. The organic phase is washed twice with water (150 mL each) and then is dried over anhydrous Na_2SO_4 (approximately 5 g). The solution is filtered through a fritted glass funnel with suction and the residue is washed with toluene (2 x 50 mL) and the combined filtrates are evaporated to dryness under reduced pressure (approximately 15 mmHg, water bath temperature 30 °C). The residue (14.1–16.0 g) is purified by silica gel flash chromatography (Note 9) to afford 9.05–9.75 g of product as a light-yellow oil (Note 10). Further purification by bulb-to-bulb distillation (oven temperature 50 °C, 0.06 mmHg) affords 8.71–9.10 g (70–73%) of analytically pure enecarbamate **3** as colorless oil (Note 11).

2. Notes

1. All glassware was oven-dried, quickly assembled and heated with a heat gun under vacuum (0.05 mmHg) prior to use. The submitters used nitrogen as inert gas.

2. Submitters and Checkers used 1-(*tert*-butoxy-carbonyl)-2-pyrrolidinone **1** (97%), lithium triethylborohydride (Super-Hydride®, (1.0 M in THF,), *N*,*N*-diisopropylethylamine (99%) and trifluoracetic anhydride (>99%) as purchased from Aldrich Chemical Co. Submitters used 4-dimethylaminopyridine and toluene, p.a., as purchased from Aldrich Chemical Company, Inc. The Checkers received these chemicals from Fluka.

3. Final pressure: 0.05 mmHg.

4. A dry-ice acetone bath was used. Addition took about 40 minutes.

5. Progress of the reaction was followed by TLC on silica gel with hexane/EtOAc, 1:1. Visualization was accomplished with phosphomolybdic acid reagent (12 g in 250 mL of EtOH). The starting material has an R_f = 0.25 and the product has an R_f = 0.37.

6. Addition took about 10 min for diisopropylethylamine and 15 min for trifluoroacetic anhydride.

7. Progress of the reaction was followed by TLC analysis as described in Note 5. Enecarbamate **3** has an R_f = 0.63.

8. Addition took about 10 min.

9. The residue was dissolved in a minimum amount of dichloromethane, transferred to a 5 × 42 cm column packed with silica gel 60 (Merck, 0.040–0.060 mm) and eluted with 2.5 L of hexane-EtOAc 90:10 containing 0.2% (v/v) triethylamine). Enecarbamate **3** has an R_f = 0.21.

10. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the substance after chromatography showed traces of impurities with very weak signals at δ = 1.13–1.27 (0.30 H), 1.70–1.80 (0.25 H), 3.35–3.42 (0.12 H).

11. Analytical data: IR (film): 3414, 2974, 1703, 1617, 1478, 1409, 1366, 1289, 1257, 1224, 1178, 1135, 1093, 985, 882, 810, 763, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (s, 9 H), 2.54–2.62 (m, 2 H), 3.59–3.70 (m, 2 H), 4.93 (d, J = 18 Hz, 1 H), 6.39/6.52 (br. s, 1 H) (pair of rotamers); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 28.6/29.6, 44.7/45.2, 79.8/79.9, 107.4, 129.7, 151.6/152.3 (pair of rotamers); MS [EI, 70 eV] *m*/*z* (relative intensity): 169 (3), 113 (16), 96 (12), 68 (42), 57 (100), 41 (74); Elemental Analysis Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.62; H, 8.81; N, 8.08. ^{1}H NMR, ^{13}C NMR and MS data were identical to those reported in ref. 4b.

Safety and Waste Disposal Information

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

Cyclic enecarbamates, a class of deactivated enamines, are versatile intermediates for the synthesis of alkaloids and nitrogen-containing heterocycles. Among the available methodologies for their preparation, the reduction of lactam carbamates followed by dehydration of the lactamols is the most straightforward approach. The lactam carbamates can be reduced to lactamols by sodium borohydride ($NaBH_4$),[3] diisobutylaluminum hydride (DIBAL-H), [4] and lithium triethylborohydride (Super-Hydride®).[5] Among them, Super-Hydride® is most widely used in the laboratory, because it typically gives the cleanest reductions and highest yields. Many protocols of dehydrating lactamols to enecarbamates have been developed.[6] In comparison to the other dehydrating methods, dehydration using trifluoriacetic anhydride and a hindered base, such as 2,6-lutidine or diisopropylethylamine, was found to be the most effective. These mild conditions are compatible with a number of protecting groups and are suitable for compounds with epimerizable stereogenic centers.[7]

Recently, we simplified the two-step process by developing an efficient one-pot conversion of lactam carbamates to cyclic enecarbamates by telescoping the reduction with lithium triethylborohydride, and *in-situ* dehydration with trifluoroacetic acid and diisopropylethylamine.[8] The one-pot protocol avoids the isolation of unstable lactamol intermediate, which could undergo a ring-opening to form the tautomeric aldehyde.[9] This one-pot protocol is suitable for different azacycles (5-, 6- and 7-membered rings), and is compatible with a number of protecting groups (Boc, Cbz, Bn). Due to the mild conditions, Boc-protected *L*-pyroglutamate can be converted to its enecarbamate without any epimerization. Results are summarized in Table 1.

In general, the main advantages of this one-pot protocol are its simple operation, higher overall yields, and formation of fewer side products. This methodology has successfully been used for the preparation of enecarbamate **3c** (see Table 1) on greater than 100 kg scale.

Table 1. Examples of One-pot Conversion of Carbamate to Enecarbamate

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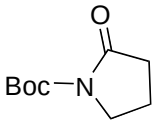
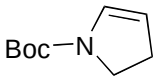
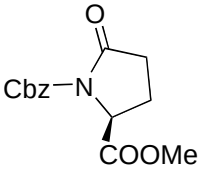
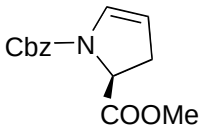
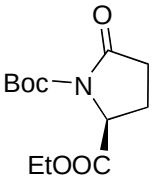
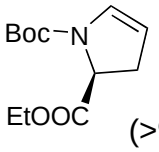
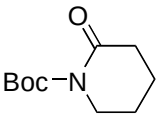
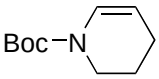
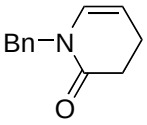
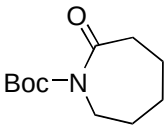
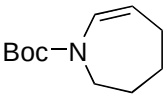
a			81%
b			78%
c		 (>99.5% ee)	95%
d			83%
e			89%
f			90%

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2. ResCom, DSM Pharma Chemicals Regensburg GmbH, D-93055 Regensburg, Germany.

3. (a) Altman, K.-H. *Tetrahedron Lett*. **1993**, *34*, 7721-7724; (b) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem*. **1984**, *49*, 1682-1688; (c) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437-1441; (d) Thomas, E. W.; Rynbrandt, R.

H.; Zimmermann, D. C.; Bell, L. T.; Muchmore, C. R.; Yankee, E. W.; *J. Org. Chem*. **1989**, *54*, 4535-4543.

4. (a) Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77-82; (b) Dieter, R. K.; Sharma, R. R. *J. Org. Chem*. **1996**, *61*, 4180-4184.

5. (a) Shono T. *Tetrahedron* **1984**, *40*, 811-850; (b) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc*. **1982**, *104*, 6697-6703; also see references 4b and 7.

6. Cossy, J.; Cases, M.; Pardo, D. G. *Synth. Commun*. **1997**, *27*, 2769-2776; also see ref 4b and 7 for discussions about dehydration protocols.

7. Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, 64, 6646-6652.

8. Yu, J.; Truc V.; Riebel, P.; Hierl, E.; Mudryk, B.; *Tetrahedron Lett*. **2005**, *46*, 4011-4013.

9. Nagasaka, T.; Tamano, H.; Maekawa, T.; Hamaguchi, F. *Heterocycles* **1987**, *26*, 617-624.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

N-(*tert*-Butyloxycarbonyl)pyrrolidin-2-one; (85909-08-6)

Super-Hydride®: Lithium triethylborohydride; (22560-16-3)

DMAP: *N*, *N*-Dimethyl-4-Pyridinamine: (1122-58-3)

N,*N*-Diisopropylethylamine: *N*-Ethyl-*N*-(1-methylethyl)-2-propanamine; (7087-68-5)

Trifluoracetic anhydride; (407-25-0)

1-*tert*-Butoxycarbonyl-2,3-dihydropyrrole: 1*H*-Pyrrole-1-carboxylic acid, 2,3-dihydro-, 1,1-dimethylethyl ester; (73286-71-2)

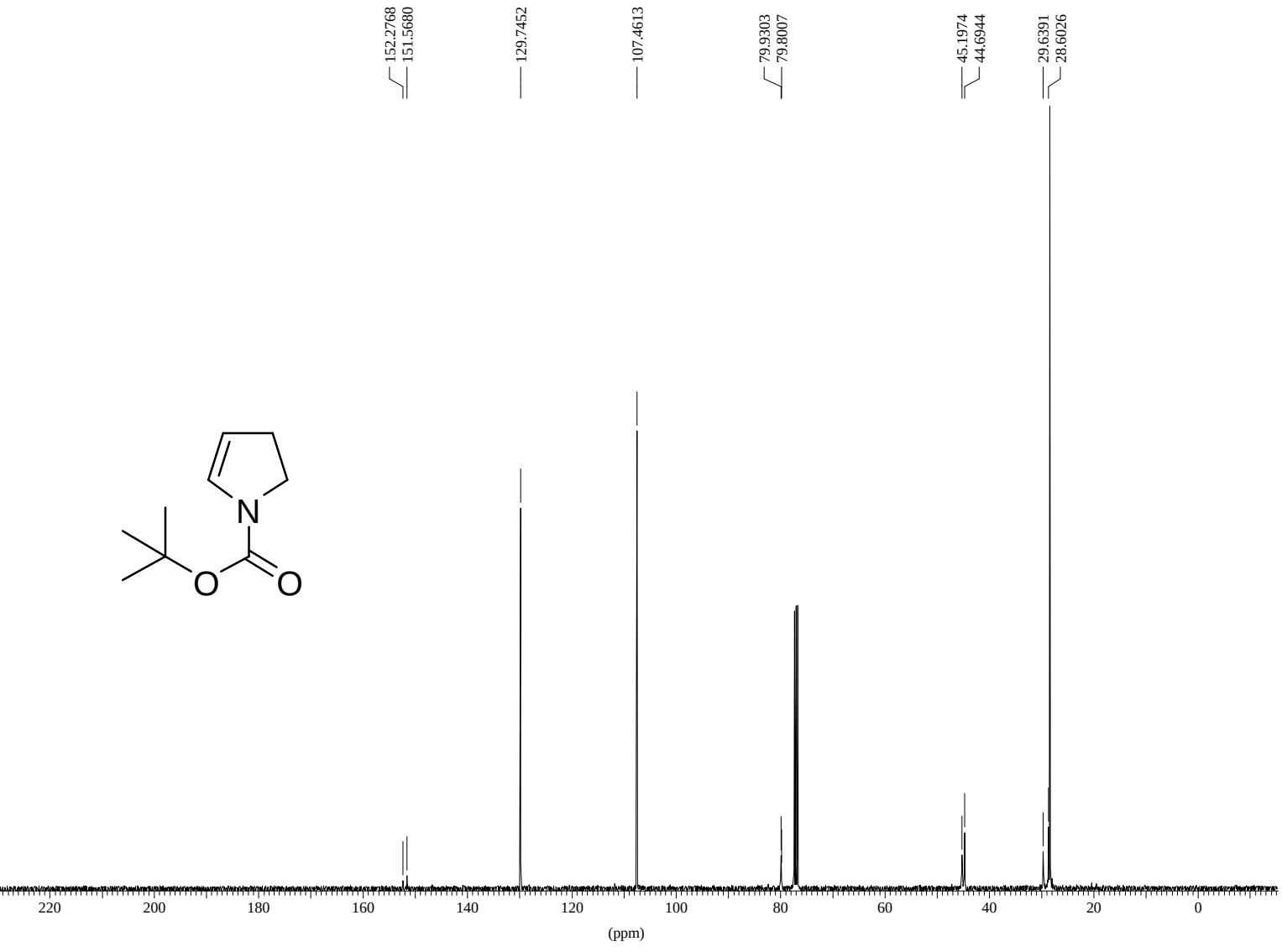
Jurong Yu received his PhD in organic chemistry from Shanghai Institute of Materia Medica, Chinese Academy of Sciences in 1988. After being a research assistant professor for two years, he moved to the United States in 1991. He did postdoctoral research for six years with Prof. J. R. Falck at the University of Texas Southwestern Medical Center at Dallas, where he worked on natural product synthesis and new synthetic methodology development. He joined Bristol-Myers Squibb Process R&D in 1997, and was a Senior Research Investigator before moving back to China in 2007. He is currently the Vice President of R&D at Nanjing Pharmatechs.

Vu Chi Truc obtained his PhD working on the syntheses and conformational analyses of 6- and 7- carbomethoxy-1 and 2-heteradecalin systems with Prof. J. A. Hirsch at Seton Hall University in 1985. He then joined the research group of Prof. M. E. Jung at UCLA for a post-Doc position for more than a year working on the syntheses of Ivermectin, an antiparasitic agent. He is currently a Principal Scientist in the Process Development Department at Bristol-Myers Squibb in New Brunswick, NJ.

Peter Riebel (born 1967 in Munich) studied chemistry at the University of Regensburg and obtained his PhD in 1996 within the workgroup of Prof. Juergen Sauer by contributing with studies on (3+2)-cycloaddition reactions. After a one year post-doc fellowship in the group of Prof. Victor Snieckus (University of Waterloo, Canada), funded by the DFG, he started his career with DSM. He is currently managing director of a site located in Regensburg which is dedicated to the early chemical development activities within DSM Pharma Chemicals (ResCom ®).

Boguslaw Mudryk earned his diploma at the Warsaw Technical University in 1978 under Professor Mieczyslaw Makosza. He completed his PhD thesis on electron transfer reactions of nitroalkanes with enolate anions in 1982 in laboratories of Professor Makosza and of Professor Glen Russell at Iowa State University. He then joined the Institute of Organic Chemistry at the Polish Academy of Sciences where he conducted research on vicarious nucleophilic substitution. In 1987 he joined Professor Thedore Cohen's group at the University of Pittsburgh where he focused his postdoctoral research on reductive lithiations of cyclic ethers. In 1997 he joined Bristol-Myers Squibb where he is now Principal Scientist responsible for developing practical synthetic routes to drug candidates.

Matthias Maywald (born 1976) received his diploma degree at the University of Göttingen in 2001 where he worked in the laboratory of Professor Armin de Meijere. He completed his Ph. D. thesis on semisynthetic enzymes and high-throughput experimentation in 2005 at the Max Planck Institute for Coal Research in Muelheim/Ruhr under Professor Manfred T. Reetz. In 2006 he began post-doctoral research with Professor Andreas Pfaltz at the University of Basel. His research interests include asymmetric synthesis and the development of new synthetic methods.



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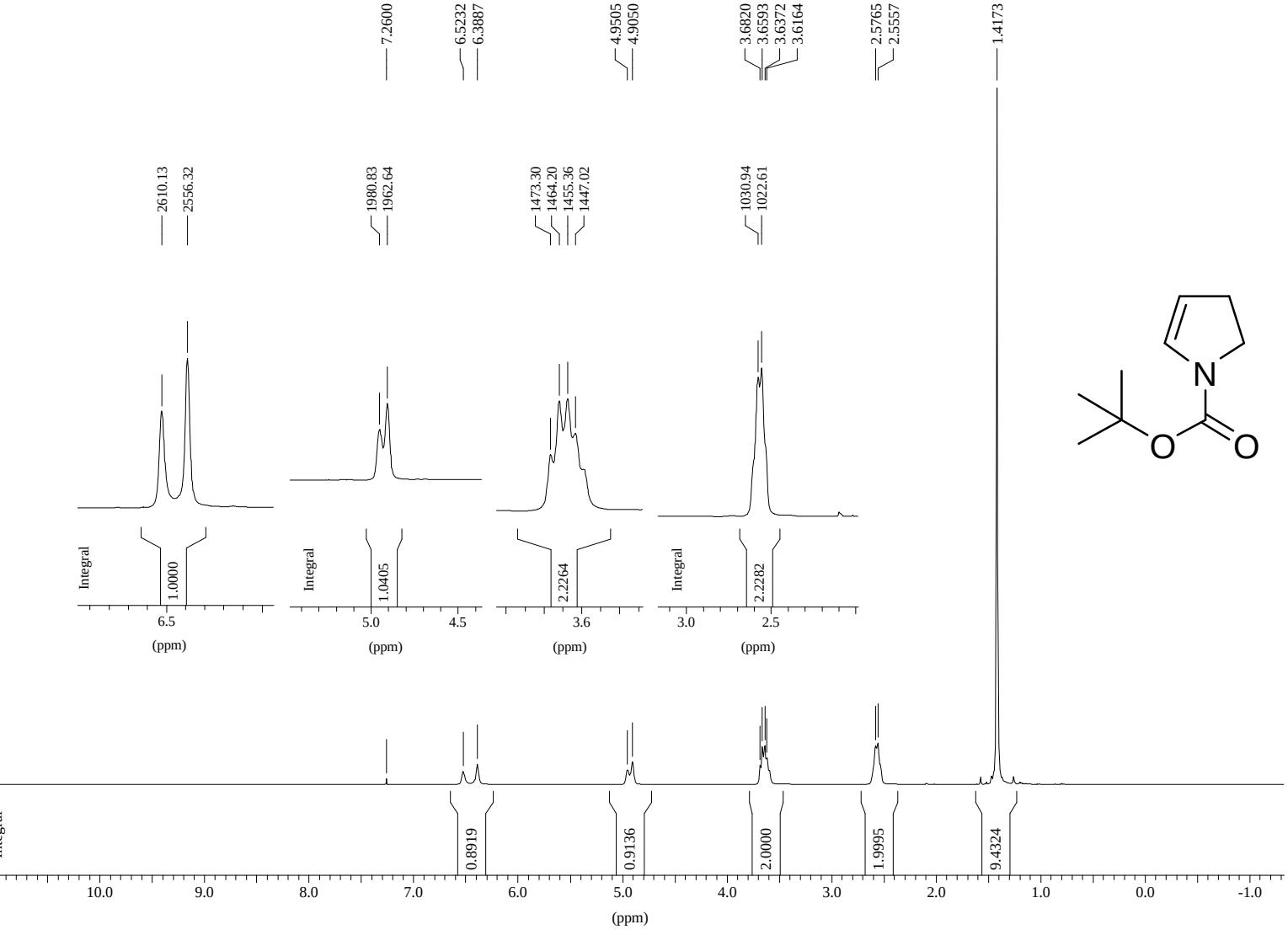

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