Organic Syntheses

Scalable Preparation of *O*-(Diphenylphosphinyl) hydroxylamine (DPPH)

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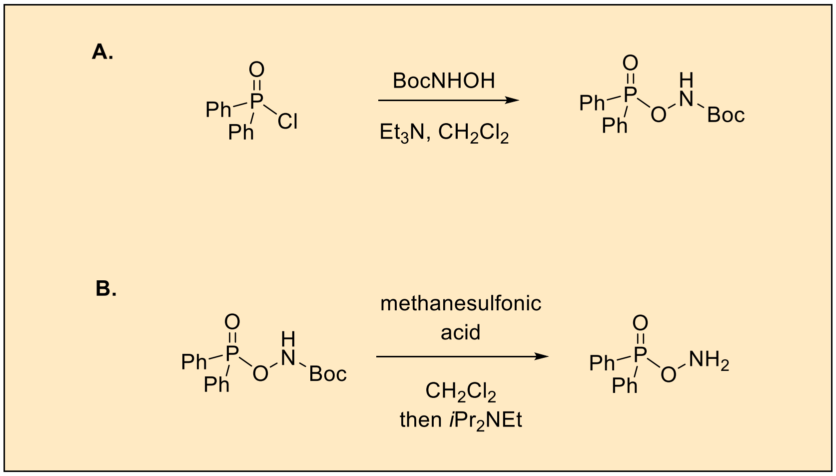

Procedure (Note 1)

A. *tert-Butyl (diphenylphosphoryl)oxycarbamate.* Into a clean and dry 1-L 3- necked flask containing a magnetic stir bar (1.25 in egg-shaped) *tert*-butyl-*N*-hydroxycarbamate (30.9 g, 232 mmol, 1.10 equiv) is added in one portion along with dichloromethane (200 mL) (Note 2) in one portion. Once the charging is completed, the middle neck of the flask is fitted with a 125–mL addition funnel and a nitrogen inlet, followed by placing a temperature probe on the second neck and a septum on the third neck of the flask. After connecting the set-up to a nitrogen inlet, stirring of 200 rpm is initiated, and the contents of the reactor are cooled between –5 °C and –15 °C (internal temperature) using a bath consisting of ice and acetone (Note 3). After about 15 min the solids are completely dissolved, and triethylamine (37 mL, 264 mmol, 1.25 equiv) (Note 2) is added dropwise over 10 min (Note 4). In a separate 250-mL one-necked flask equipped with a septum and a needle to allow a nitrogen atmosphere, diphenylphosphinic chloride (40.4 mL, 50.0 g, 211 mmol, 1 equiv) (Note 2) is mixed in dichloromethane (50 mL) under nitrogen using gentle shaking for about 1 min. The dichloromethane solution of diphenylphosphinic chloride is then transferred to the 125-mL addition funnel using a canula, and the phosphinic chloride solution is added dropwise to the pre-cooled solution of the hydroxylamine using a high nitrogen sweep over 30 min in order to keep the internal temperature below 0 ºC (Note 5). After the reaction completion is determined by ^{1}H NMR (Note 6), the organic phase is warmed above 10 °C by a warm water bath, and the addition funnel is used again to add 5% aqueous citric acid solution (100 mL) over 5 min. After 15 min of stirring, the contents of the reactor are transferred to a 1-L separatory funnel, and the aqueous layer is discarded (Note 7). After the wash, the organic solution is transferred into a 1-L one-necked flask and concentrated on a rotary evaporator setting the vacuum between 225 and 300 mmHg with a bath temperature above 35 ºC until approximately 100–125 mL of total volume remains, at which point the product starts to precipitate spontaneously. To this slurry, hexane (125 mL) (Note 2) is added and concentrated on the rotary evaporator until approximately 100–125 mL remains, at which point another portion of hexanes (125 mL) is added and concentrated to approximately 100–125 mL total volume (Note 8). The resulting slurry is stirred for 12 h at room temperature (Note 9). The solids are collected on a 500-mL sintered glass Büchner funnel with paper filter, and washed with 4:1 hexane:dichloromethane mixture (250 mL) (Note 10). After drying on the frit using 3–4 mmHg vacuum at room temperature, *tert*-butyl (diphenylphosphoryl)-oxycarbamate (67.0 g, 201 mmol, 95%) is isolated as a white solid (Notes 11, 12, 13, and 14).

B. *O-(Diphenylphosphinyl)hydroxylamine.* Using a 100-mL 3-necked flask equipped with an argon inlet, a temperature probe, a magnetic stir bar (0.75 in, egg-shaped), and a 60-mL addition funnel under argon atmosphere, *tert*-butyl-(diphenylphosphoryl) oxycarbamate (10.0 g, 30.0 mmoles, 1 equiv) is suspended in dichloromethane (20 mL) (Note 2) and cooled to –5 °C (internal temperature) (Figure 1) using a cryocool (Note 15). Methanesulfonic

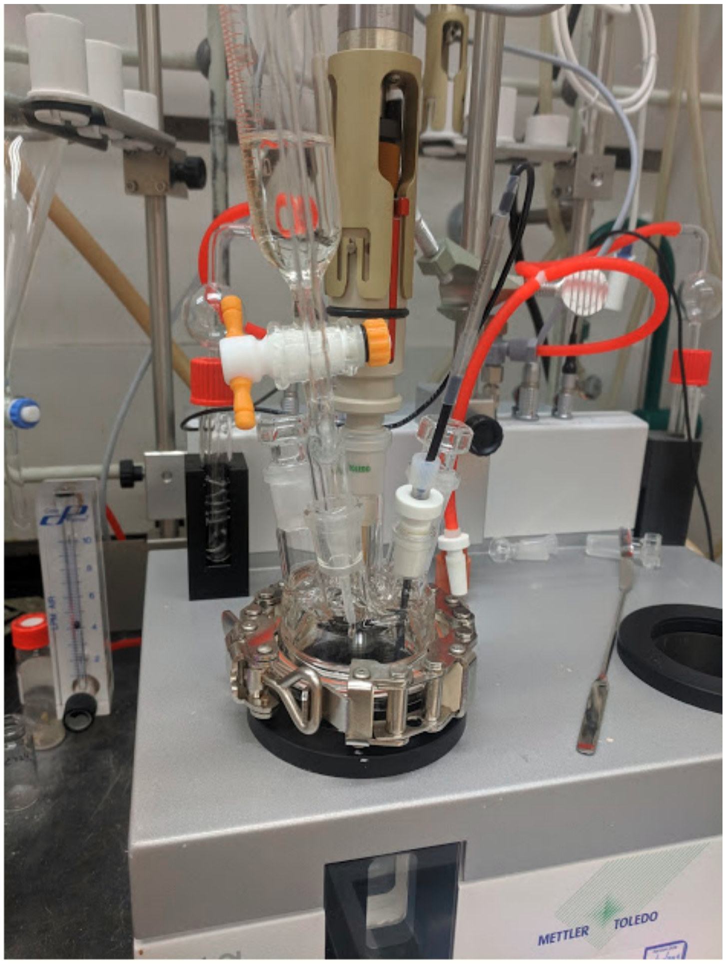

Figure 1. Reaction set-up for Step B (photo provided by submitters)

acid (5.85 mL, 8.65 g, 90.0 mmoles, 3.00 equiv) (Note 2) is added dropwise using the addition funnel over 15 min (Note 16). After holding the reaction mixture for 2 h at –5 ºC, a sample of the solution is taken and analyzed by ^{1}H NMR to determine conversion (Note 17). Once the desired conversion is achieved, dichloromethane (20 mL) is added over one minute using the addition funnel, and the bath temperature is adjusted to 0 ºC. Using the addition funnel, diisopropylethylamine (10.5 mL, 60.0 mmoles, 2.00 equiv) (Note 2) solution in dichloromethane (30 mL) is added over one hour while keeping the internal temperature between 0–5 °C (Note 18). Once the quench is completed, the slurry is allowed to warm to 15 °C internal temperature. Once the temperature reaches 15 °C, the slurry is transferred onto a 60-mL sintered glass Büchner funnel with filter paper (Note 10). The cake is then slurry-washed with dichloromethane (3 × 20 mL) on the filter (Note 19). The final product is dried using vacuum at room temperature to obtain O- (diphenylphosphinyl)hydroxylamine (5.32 g, 22.8 mmol, 76%) as a white solid (Notes 20, 21, 22, and 23).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with *tert*-butyl-N-hydroxycarbamate, dichloromethane, triethylamine, diphenylphosphinic chloride, citric acid, hexane, trimethoxybenzene, methanesulfonic acid, sodium hydroxide and diisopropylethylamine.
2. *tert*-Butyl-*N*-hydroxycarbamate (>99%) was purchased from ChemImpex. All other solvents and reagents were purchased from Sigma Aldrich and used as received. These include dichloromethane (>99.8%, anhydrous, contains 40–150 ppm amylene as a stabilizer), triethylamine (>99.5%), diphenylphosphinic chloride (98%), methanesulfonic acid (>99%), and diisopropylethylamine (>99.5%), and hexane (mixture of isomers for HPLC, >98.5%).

3. The submitters used overhead stirring with a two-inch half-moon shaped Teflon stir blade. The checkers found that this was not necessary and employed a magnetic stir bar.
4. During the addition of the triethylamine, a mild (1–2 °C) exotherm occurs.
5. This step is quite exothermic, and a substantial amount of HCl gas is generated. If the nitrogen inlet is located on top of the addition funnel, a needle coming from the septa holding the temperature probe could be a proper outlet. On larger scale, a NaOH scrubber can be employed to neutralize the evolving HCl gas.
6. The conversion was determined by integrating the starting material and product doublets in the 7.7–8.0 ppm region of the ^{1}H NMR in $CDCl_3$. The submitters and checkers observed > 95% conversion fifteen minutes after the completion of phosphinic chloride addition. If the conversion is lower than expected, slow addition of extra phosphinic chloride can be attempted along with checking the reagents and solvents for elevated water content.
7. Upon addition of the citric acid solution, the slurry disappeared from the organic layer, and the homogenous organic solution had a water content of approximately 9600ppm as determined by Karl-Fisher titration. After the prescribed amount of agitation, ^{1}H NMR indicated the citric acid wash removed about >95% of triethylamine from the organic layer, with the pH was measured to be between 4 to 5.
8. The submitters added hexane through the continuous addition port of a rotary evaporator. In the absence of a continuous addition port, portion-wise addition of hexane is sufficient. If appropriate distillation setup is available, the batch concentration can be performed from the three-necked flask or jacketed reactor itself. In this case, the hexane can be added via an addition funnel at a rate that the batch temperature does not dip below 25 ºC. For larger scale, the authors had demonstrated that hexane could be substituted with heptane as the anti-solvent for crystallization.
9. The submitters note that the slurry should be stirred for at least one hour.
10. The submitters used a 60-mL disposable Chemrus disposable filter with a 10 micron frit for the filtration (Figure 2).

Figure 2. Filtration set-up for Step B (photo provided by submitters)

11. Spectroscopic data of the product are as follows: mp 157–159 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.39 (s, 9H), 7.46 (td, J = 7.5, 3.7 Hz, 4H), 7.55 (td, J = 7.5, 1.3 Hz, 2H), 7.96 (dd, J = 7.5, 1.3 Hz, 4H), 8.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.1, 83.2, 128.6 (d, J = 13.3 Hz), 129.5 (d, J = 134.7 Hz), 132.5 (d, J = 10.5 Hz), 132.9 (d, J = 2.7 Hz), 155.9 (d, J = 5.4 Hz). ^{31}P NMR ($CDCl_3$) δ: 39.9 ppm. This compound appears to be stable for at least two years stored in an amber bottle at room temperature.
12. Potency as determined to be 99.3% by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.
13. A second run on half scale provided 32.6 g (93%) of the product.
14. The dichloromethane solution of *tert*-butyl-(diphenylphosphoryl)-oxycarbamate can directly be used in the next step after azeotropic drying, if preferred. However, due to the higher stability of *tert*-butyl-(diphenylphosphoryl)oxycarbamate and little mother liquor losses associated with the isolation of this intermediate, the submitters recommend the isolation strategy described in this procedure.

15. The submitters used a 100-mL EasyMax reactor. In the absence of such a reactor a simple three-necked flask can be employed with adequate temperature control.
16. The methanesulfonic acid addition was performed under a sweep of nitrogen to address CO_2 off-gassing. In absence of the sweep, the reaction rate can be slower. The rate of methanesulfonic acid addition was controlled so that the temperature during the deprotection remained below 0 ºC.
17. The target conversion is >95% based on integrating the starting material and product doublets in the 7.7–8.0 ppm section of the ^1H NMR using CD_2Cl_2 as the solvent. The water content of the methanesulfonic acid has a large impact on the rate of deprotection; the submitters consistently achieved the target conversion when the water content of the methanesulfonic acid was at or below 0.1% as determined by Karl-Fischer titration. It is critical to dilute the cold sample with CD_2Cl_2 before it warms to room temperature otherwise the conversion can appear artificially high. The starting material is quite soluble in dichloromethane, so it can be efficiently removed in the final crystallization. Addition of the Hünig's base (diisopropylethylamine) solution was always initiated within 2 h of achieving the target conversion.
18. If the quench is performed at lower temperature, the removal of the DIPEA·MSA salt, along with methanesulfonic acid became more problematic.
19. The slurry washes were performed by disconnecting the vacuum source, adding the prescribed amount of dichloromethane to the wet cake, and fully suspending the solids by vigorous agitation for at least one minute using a plastic disposable spatula. The liquids are fully removed via vacuum filtration before the next slurry wash. Typically, two dichloromethane slurry washes can remove the salt content below 5% as determined by ^1H NMR. A third dichloromethane wash can further reduce this impurity below 2%.
20. Spectroscopic properties of the product are as follows: mp 126 ºC; ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.43 (td, J = 5.0, 2.2 Hz, 4H), 7.46–7.51 (m, 2H), 7.69-7.73 (m, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 128.3 (d, J = 12.4 Hz), 130.9 (d, J = 9.9 Hz), 131.0, 135.9 (d, J = 134.5 Hz); ^{31}P NMR (DMSO-d_6) δ: 21.7 ppm. The submitters reported characterization data in methanol-d_4, but the checkers found that the compound was poorly soluble in methanol. Characterization data submitted by the submitters

are as follows: mp 117-119 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ: 7.51 (td, *J* = 7.5, 3.7 Hz, 4H), 7.60 (td, *J* = 7.5, 1.3 Hz, 2H); 7.80 (dd, *J* = 7.5, 1.3 Hz, 4H); ^{13}C NMR (CD_3OD, 125 MHz) δ: 129.72, 129.83, 132.89, 132.97, 133.76; ^{31}P NMR (CD_3OD) δ: 38.52 ppm.

21. Potency was determined to be 99.4% by quantitative ^{1}H NMR using trimethoxybenzene as internal standard.
22. A second reaction on half scale provided 2.85 g (81%) of the white solid.
23. The final DPPH reagent was found to be less stable than the Boc-protected precursor; therefore, DPPH was made on demand and used within 1 month after generation.

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.

Discussion

C-H activation is an attractive platform to rapidly functionalize molecules of high complexity. In recent years, a number of methods have emerged for electrophilic aminations that do not require precious transition metals.[2] These methods, however, require nitrogen sources that contain weak N-X bonds, and the majority of these reagents are highly thermally unstable and even explosive.[3] For a recent preparation of a pharmaceutically relevant intermediate, we wanted to perform a one-step amination on multi-kilogram scale in a safe and reproducible fashion. Based on relevant literature examples,[4] reagent safety, and reaction performance, we selected *O*- (diphenylphosphinyl)hydroxylamine (DPPH) as the aminating reagent.[5] The preparation of DPPH has been described in the literature from diphenylphosphinic chloride and hydroxylamine, typically followed by multiple aqueous re-slurries. Similar to the observations of others,[6] our attempts to replicate this one-step reagent preparation resulted in slow filtration rates with variable yields and quality. Most importantly, our safety evaluation[7] found the amination reagent to be highly energetic (>1,000 J/g), with an onset temperature around 115 °C on Differential Scanning Calorimeter (DSC) testing at 5 °C/min scan rate. Upon prolonged drying necessary to remove water for the success of the subsequent amination, we found that the onset of the exotherm shifted even lower, to around 100 º C. Despite the low onset of exotherm, we found DPPH drop-weight testing impact negative at the 30 Joule level, which indicated this reagent is not shock sensitive. Given the highly energetic nature of this material, we hoped to have a drying temperature with a wider safety margin from the onset temperature, which necessitated eliminating the aqueous conditions described for the generation and isolation of the target compound. Therefore, we devised a procedure that enabled us to successfully prepare DPPH consistently with high yield and purity. In addition to a safe and reproducible preparation, the DPPH prepared with this procedure also demonstrated superior performance in the subsequent amination compared to commercially available DPPH.

References

1. Process Research and Development, Merck & Co., 126 E. Lincoln Ave, Rahway, NJ 07065, tamas.benkovics@merck.com.
2. For selected recent references, see (a) Kattamuri, P. V.; Yin, J.; Siriwongsup, S.; Kwon, D-H; Ess, D. H.; Li, Q.; Li, G.; Yousufuddin, M.; Richardson, P. F.; Sutton, S. C.; Kürti, L. *J. Am. Chem. Soc.* **2017**, *139*, 11184–11196.; (b) Gao, H; Zhou, Z.; Kwon, D-H.; Coombs, J.; Jones, S.; Behnke, N. E.; Ess, D.H.; Kürti, L. *Nature Chemistry* **2017**, *9*, 681–688. For a comprehensive review, see Ciganek, E.; *Organic Reactions*, **2008** *Vol. 72*, 1–366, Edited by Scott E. Denmark
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4. (a) Baldwin, J. E.; Adlington, R. M.; Jones, R. H.; Schofield, C. J.; Zaracostas, C.; Greengrass, C. W. *Tetrahedron* **1986**, *42*, 4879−4888. (b) Smulik, J. A.; Vedejs, E. *Org. Lett*. **2003**, *5*, 4187−4190.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

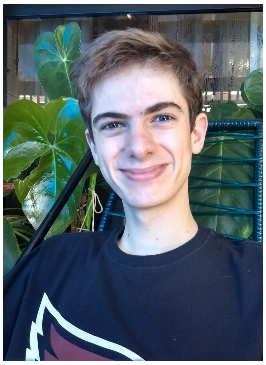
tert-Butyl-N-hydroxycarbamate: N-*tert*-Butoxycarbonylhydroxylamine; (36016-38-3)
Triethylamine: N,N-Diethylethanamine; (121-44-8)
Diphenylphosphinic chloride: Phosphinic chloride, diphenyl-; (1499-21-4)
Citric acid: 2-Hydroxypropane-1,2,3-tricarboxylic acid; (72-99-9)
Trimethoxybenzene; (634-36-6)
Methanesulfonic acid; (75-75-2)
Sodium hydroxide; (1310-73-2)
Diisopropylethylamine: 2-Propanamine, N-ethyl-N-(1-methylethyl)-; (7087-68-5)

Tamas Benkovics, a native of Hungary, obtained his B.S. in chemistry from Colorado State University in 2003. After spending two years with the process group of Amgen in Thousand Oaks, CA, he joined the research group of Professor Tehshik P. Yoon at the University of Wisconsin–Madison. During graduate school, his research was focused on oxaziridine-mediated functionalizetions of hydrocarbons. After receiving his Ph.D. in 2010, he worked in the process chemistry department of Bristol-Myers Squibb, and currently employed in the Merck Process Research in Rahway, NJ.

Andrew Neel was born Lafayette, IN in 1989. He obtained his B.S. degree in chemistry from the University of North Carolina at Chapel Hill in 2011 and his Ph.D. from the University of California, Berkeley in 2016 under the guidance of Prof. F. Dean Toste. He is currently an Associate Principal Scientist in the Department of Process Research and Development at Merck and Co., Inc. in Rahway, NJ.

Ralph Zhao obtained his B.S. and M. Sc. in Radiation Chemistry from Peking University in China, and Ph.D. in Organic/Polymer chemistry from Virginia Commonwealth University in Richmond, VA under Prof. Raphael Ottenbrite. He did his post-doctoral work under Prof. Richard Wool at Center for Composite Material in University of Delaware. After working for couple specialty chemical companies, he started his pharmaceutical career with Wyeth (now Pfizer) in Chemical and Pharmaceutical Development group in Pearl River, NY. He has worked with Novartis, Pfizer in the past and currently working in Chemical Engineering R&D group at Merck in Rahway, NJ. His career focus is in process safety field.

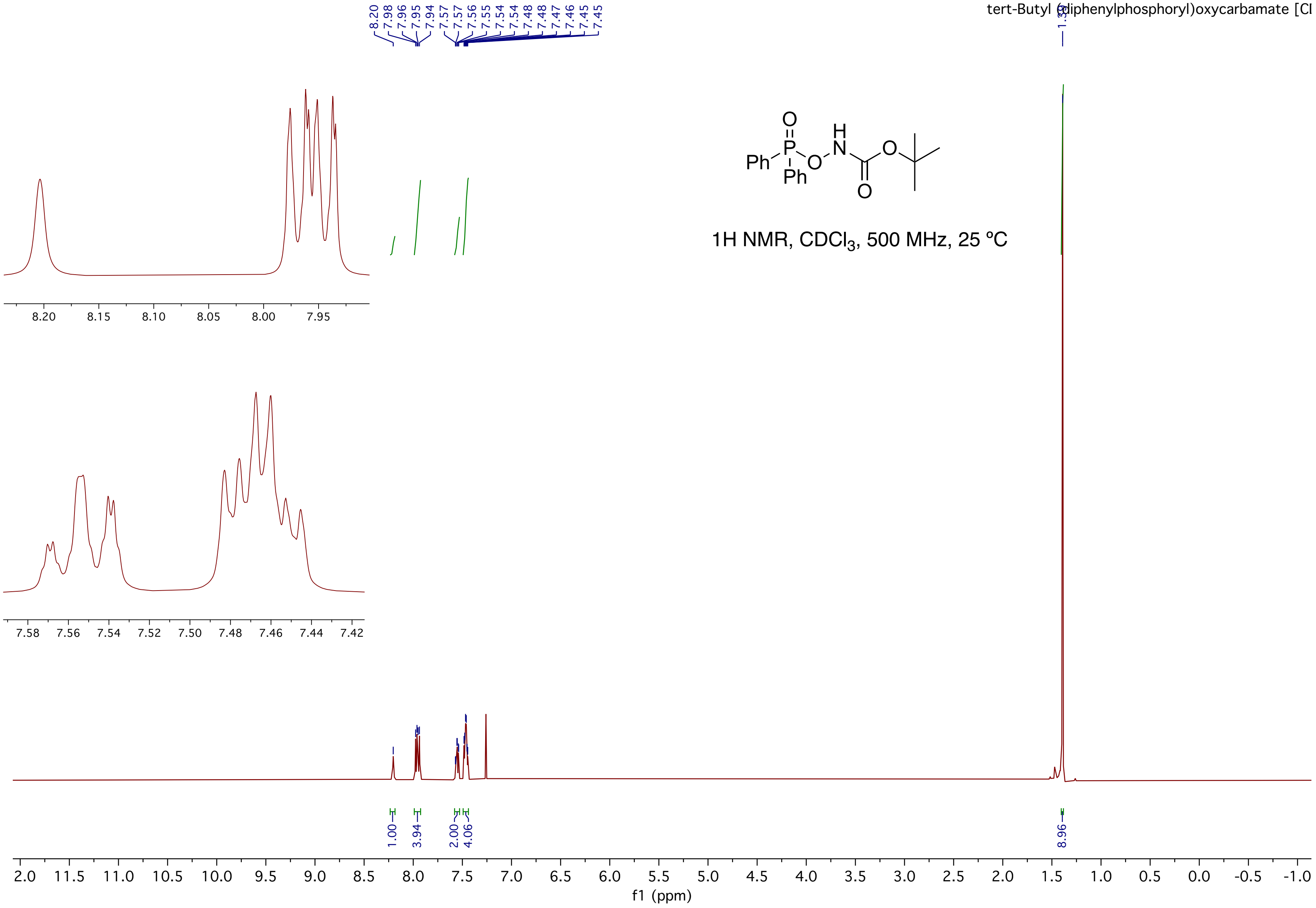
Dr. Hughes completed his undergraduate studies the University of New Brunswick in 1994 and then a Ph.D. in organic chemistry at the University of Toronto. After completing his graduate studies in 2000, Dr. Hughes accepted a postdoctoral fellowship at the Massachusetts Institute. In 2002 he started at Merck Frosst joining a newly formed satellite Process Chemistry group. In 2008 Dr. Hughes relocated to Merck's Rahway site managing a number of enabling technology groups including the catalysis, automation, flow chemistry and biocatalysis groups. In 2013 Dr. Hughes assumed a position as VP of Business Development and Alliance Management at Codexis. In 2016 Dr. Hughes returned to R&D at Merck, assuming his current position as a Principal Scientist in the Process Chemistry organization.

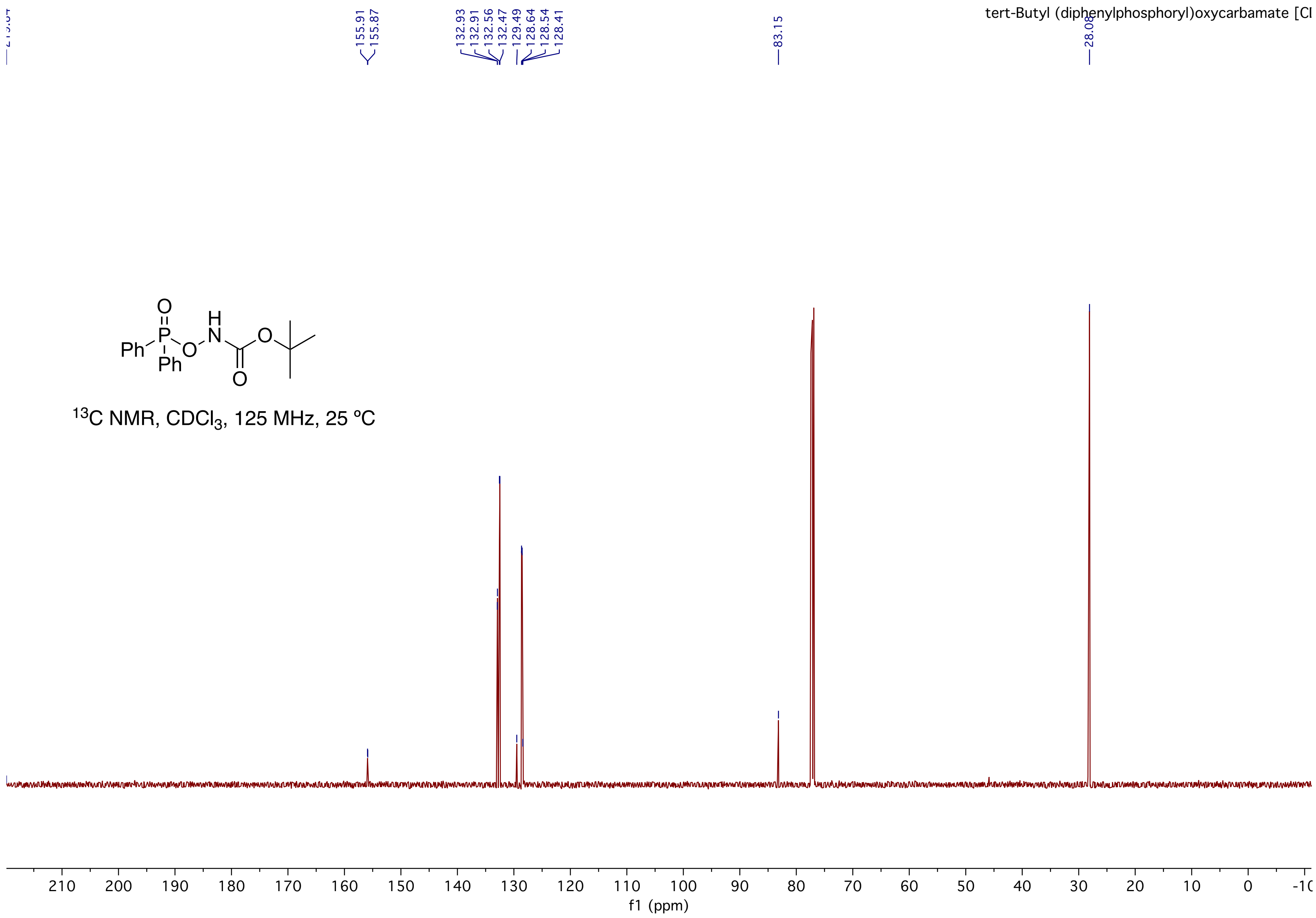


Vinicius Armelin was born in São Bernardo do Campo, Brazil, in 2001. He is currently an undergraduate student at the Massachusetts Institute of Technology pursuing a B.S. degree in Chemistry and conducting undergraduate research in the Movassaghi group.

Tony Scott is originally from New York City. He received his B.S. degree from Yale University in 2017, where he conducted research in the laboratory of Professor Seth B. Herzon. In 2017 he began his graduate studies under the supervision of Professor Mohammad Movassaghi at the Massachusetts Institute of Technology. His research focuses on complex alkaloid total synthesis.

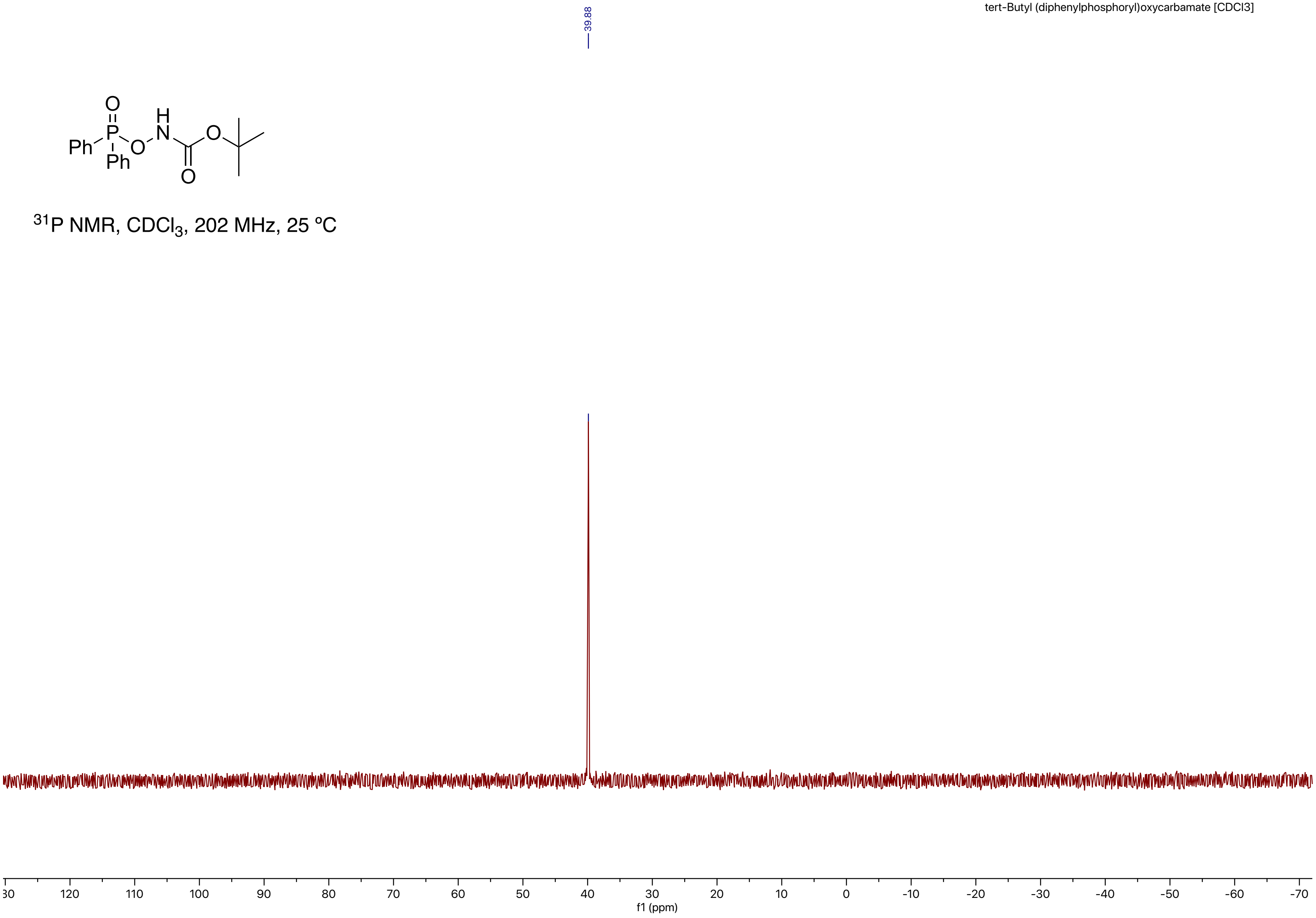
tert-Butyl (diphenylphosphoryl)oxycarbamate [Cl





tert-Butyl (diphenylphosphoryl)oxycarbamate [Cl

^{13}C NMR, CDCl$_3$, 125 MHz, 25 °C


tert-Butyl (diphenylphosphoryl)oxycarbamate [CDCl3]

^{31}P NMR, $CDCl_3$, 202 MHz, 25 ºC

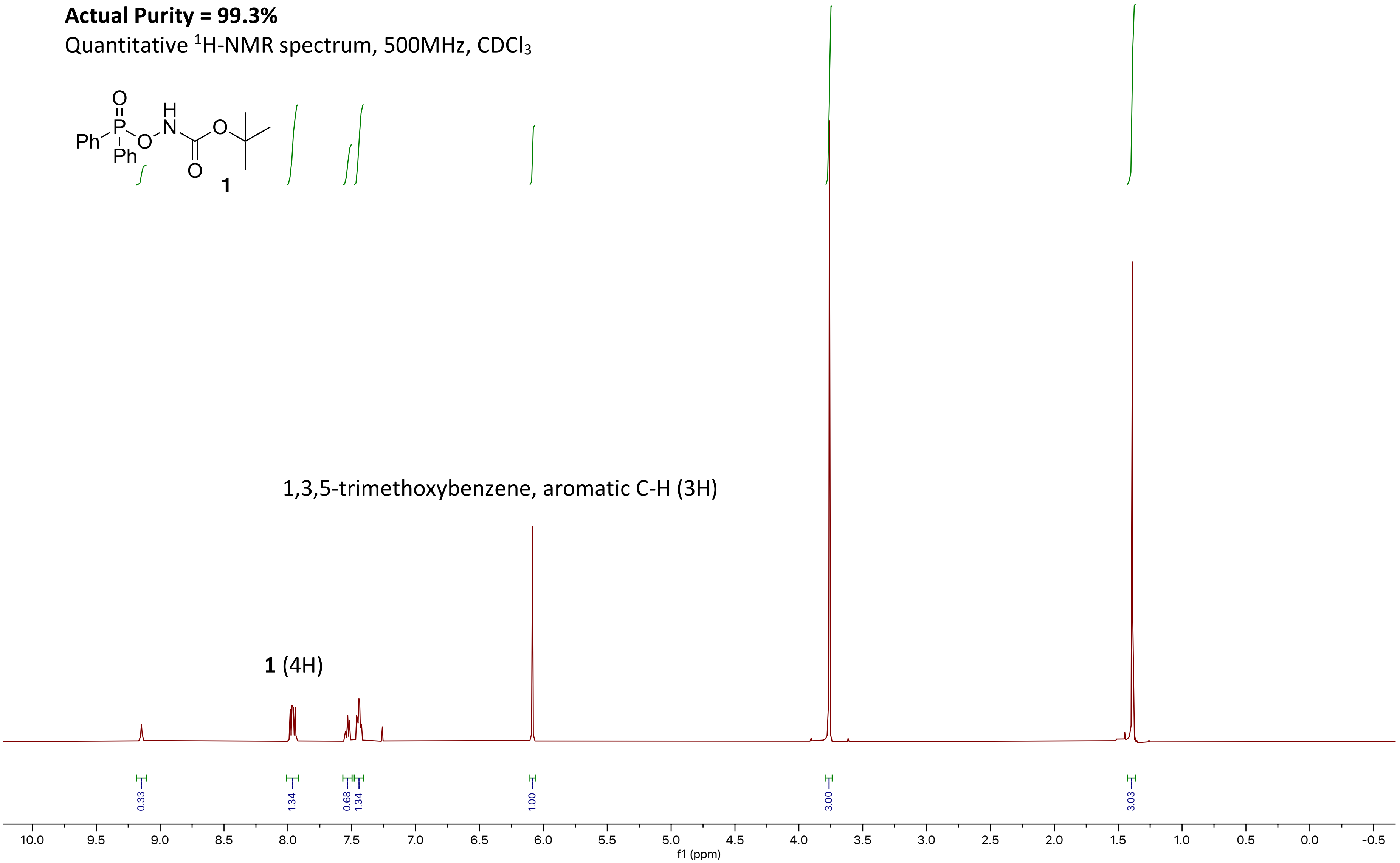
tert-Butyl (diphenylphosphoryl)oxycarbamate [CDCl3]

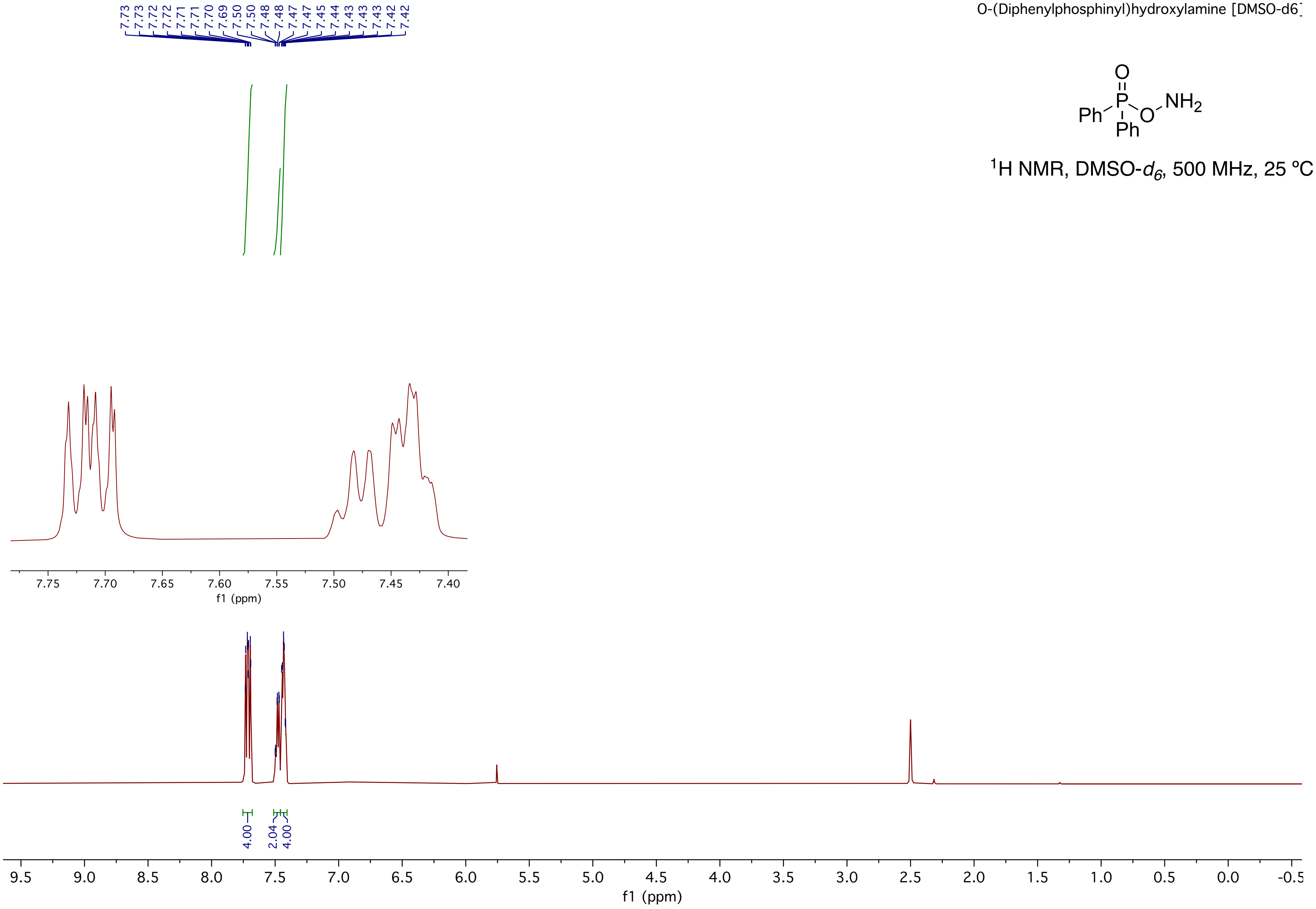
18.2 mg 1,3,5-trimethoxybenzene, 99% purity (MW = 168.19, 0.108 mmol) + 36.3 mg **1** (MW = 333.33, 0.109 mmol)

Expected integral ratio for 100% purity = 1.0000 : 1.3489

Actual Purity = 99.3%

Quantitative ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

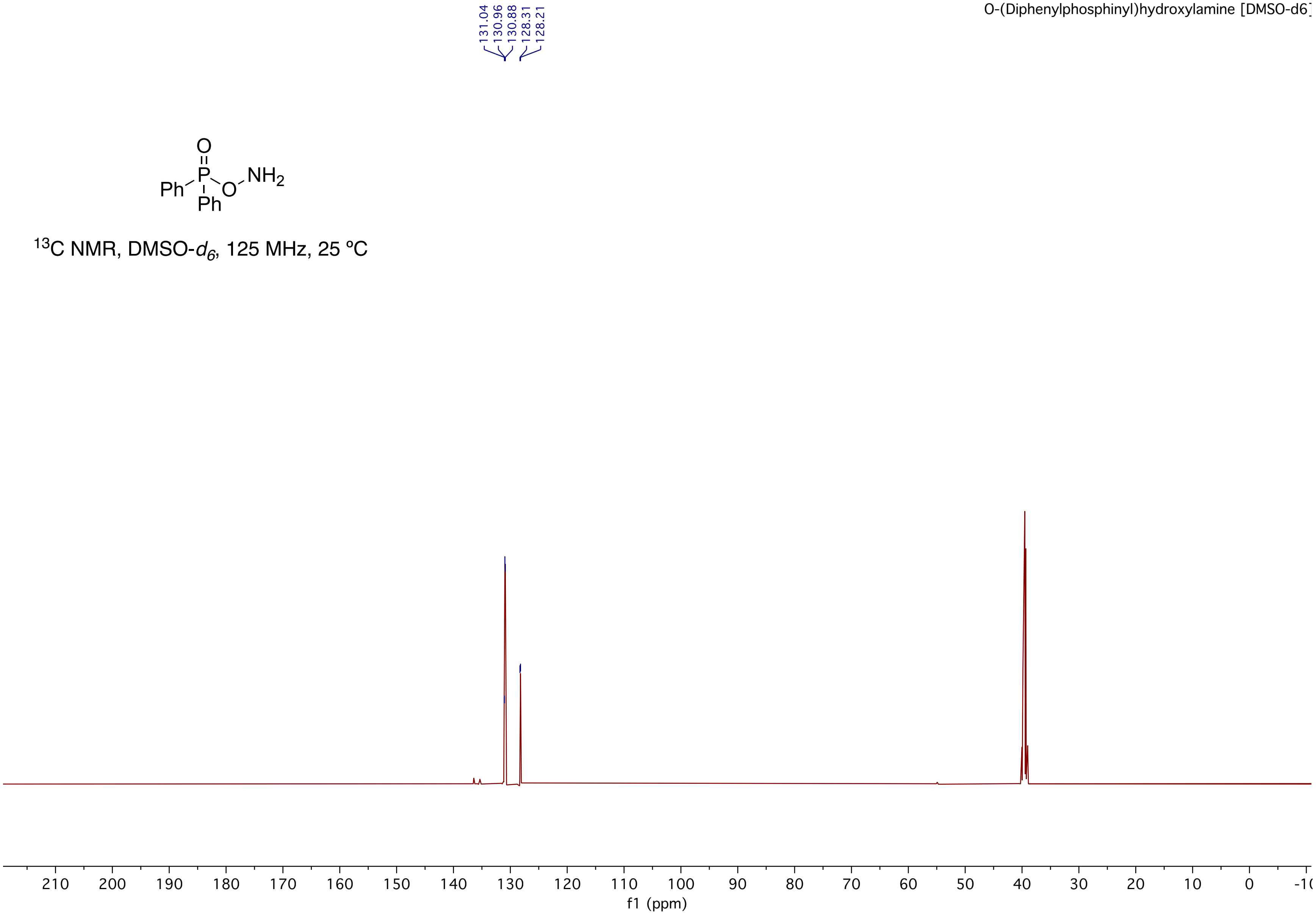




O-(Diphenylphosphinyl)hydroxylamine [DMSO-d6]

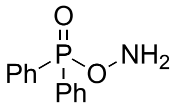
^{1}H NMR, DMSO-d_6, 500 MHz, 25 ºC

O-(Diphenylphosphinyl)hydroxylamine [DMSO-d6]

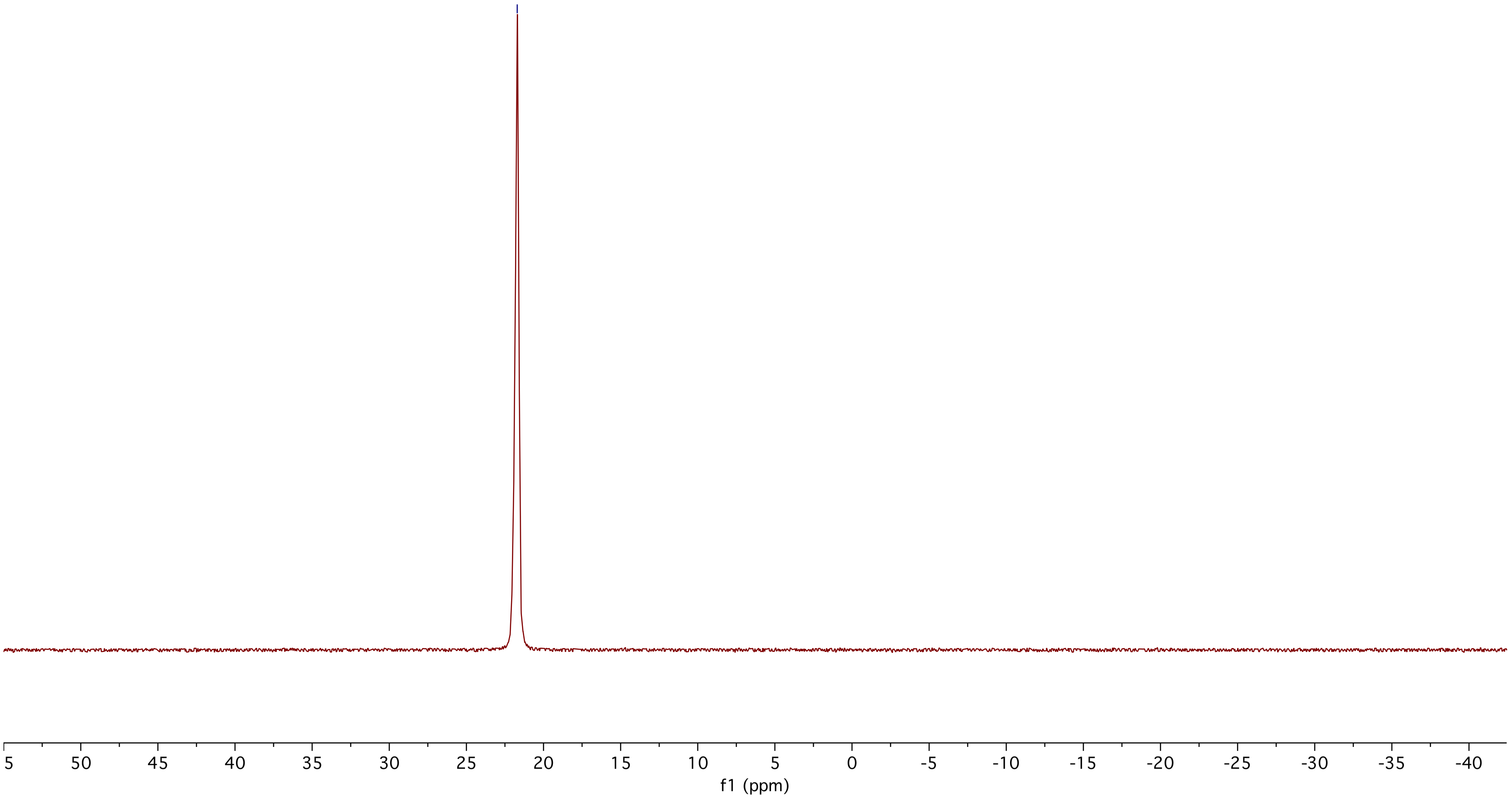


^{13}C NMR, DMSO-*d*$_6$, 125 MHz, 25 ºC

O-(Diphenylphosphinyl)hydroxylamine [DMSO-d6]



^{31}P NMR, DMSO-*d*$_6$, 202 MHz, 25 ºC



17.3 mg 1,3,5-trimethoxybenzene, 99% purity (MW = 168.19, 0.102 mmol) + 23.9 mg **2** (MW = 233.46, 0.102 mmol)

Expected integral ratio for 100% purity = 1.0000 : 1.3485

Actual purity = 99.4%

Quantitative ^{1}H-NMR spectrum, 500 MHz, DMSO-d_6