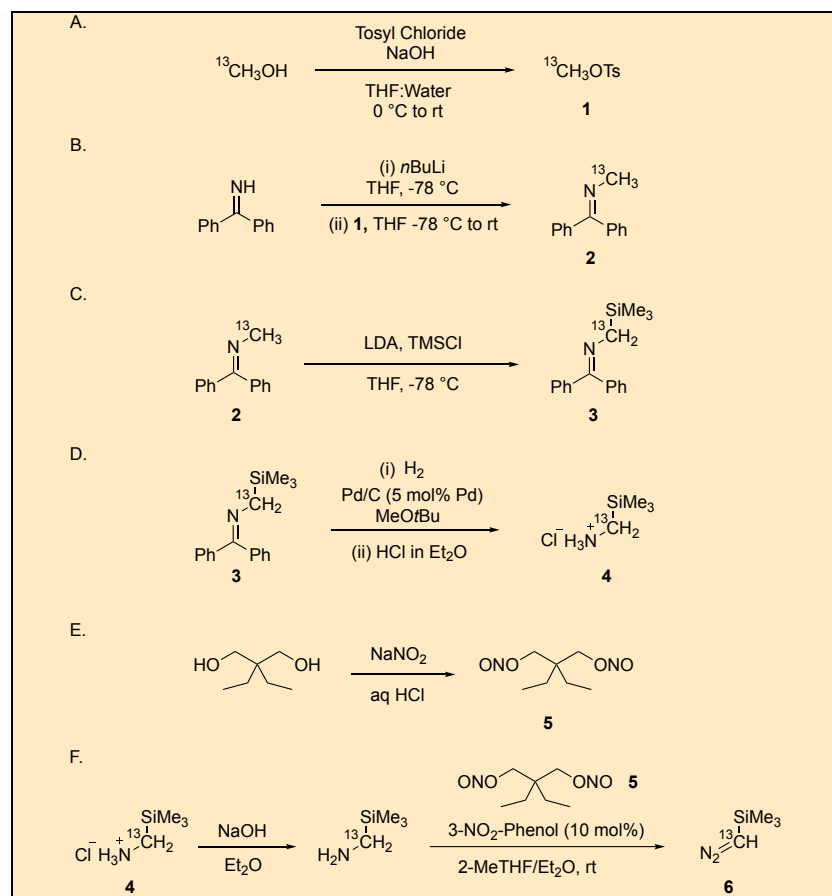


## Trimethylsilyldiazo[<sup>13</sup>C]methane: A Versatile <sup>13</sup>C-Labeling Reagent

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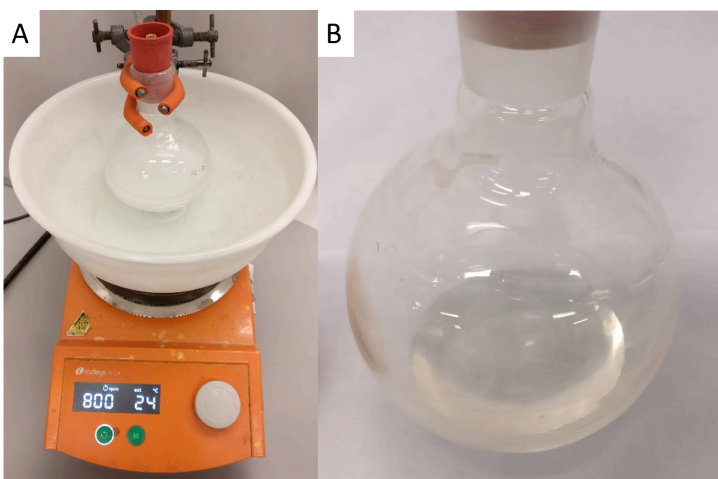
Checked by Bachir Latli and Chris Senanayake



**Procedure (Note 1)**

A. [ $^{13}\text{C}$ ]Methyl-*p*-toluenesulfonate: (1).<sup>2</sup> A 250-mL, single-necked round-bottomed flask equipped with a Teflon-coated magnetic stirbar (35 mm x 15 mm, oval) is charged with sodium hydroxide (30.3 g, 758 mmol, 5 equiv) (Note 2). The flask is placed in an ice bath and water (50 mL) (Note 3) is added in one portion with stirring. [ $^{13}\text{C}$ ]Methanol (5.00 g, 151.5 mmol, 1 equiv) (Note 4) is weighed in a 12 mL syringe and slowly added to the hydroxide solution at 0 °C. *p*-Toluenesulfonyl chloride (TsCl) (34.7 g, 182 mmol, 1.2 equiv) (Note 5) is weighed into a 250 mL single-necked conical flask equipped with a Teflon-coated magnetic stirbar (30 mm x 15 mm, oval). Tetrahydrofuran (40 mL) (Note 6) is added to this flask and stirred under nitrogen until all the TsCl dissolves. This solution is added over five min via cannulation under nitrogen to the NaOH reaction flask, which is cooled in an ice bath. The conical flask is rinsed with THF (5 mL), which is then added to the round-bottomed flask. The internal sides of the RBF are then rinsed with additional THF (5 mL) via syringe before sealing with a rubber septum and venting with a small needle (Figure 1A). The ice bath is removed and the mixture is allowed to warm to 25 °C with stirring over 20 h (Note 7). The reaction is neutralized by the slow addition of acetic acid (33 mL, 576 mmol, 3.8 equiv) (Note 8) at 0 °C over 5 min. The reaction mixture is left unstirred for 20 min at 0 °C to induce crystallization of sodium acetate (Note 9). The reaction mixture is then filtered through a sintered glass funnel (100 mm tall, 50 mm wide) to remove solid sodium acetate and the filtrate layers of THF and water are separated in a 250 mL separating funnel. The aqueous phase is extracted with ethyl acetate (2 x 60 mL) (Note 10). The filter cake is dissolved in water (150 mL) along with residue in the reaction flask and extracted with ethyl acetate (2 x 60 mL). The organic phases are combined, transferred to a 500 mL separating funnel, washed with sat. aq.  $\text{Na}_2\text{CO}_3$  (100 mL) (Note 11) and sat. aq.  $\text{NaCl}$  (100 mL) (Note 12), dried over  $\text{Na}_2\text{SO}_4$  (~40 g) for 10 min (Note 13), and filtered through a sintered glass funnel (100 mm tall, 50 mm wide) into a 1 L round-bottomed flask. The sodium sulfate is placed on the same sintered glass funnel and rinsed using additional ethyl acetate (40 mL). The organic solvent is concentrated by rotary evaporation at 40 °C (150 to 7 mmHg). A clear, colorless oil is obtained and transferred to a 250 mL round-bottomed flask with diethyl ether rinsings (~50 mL) (Note 14) and

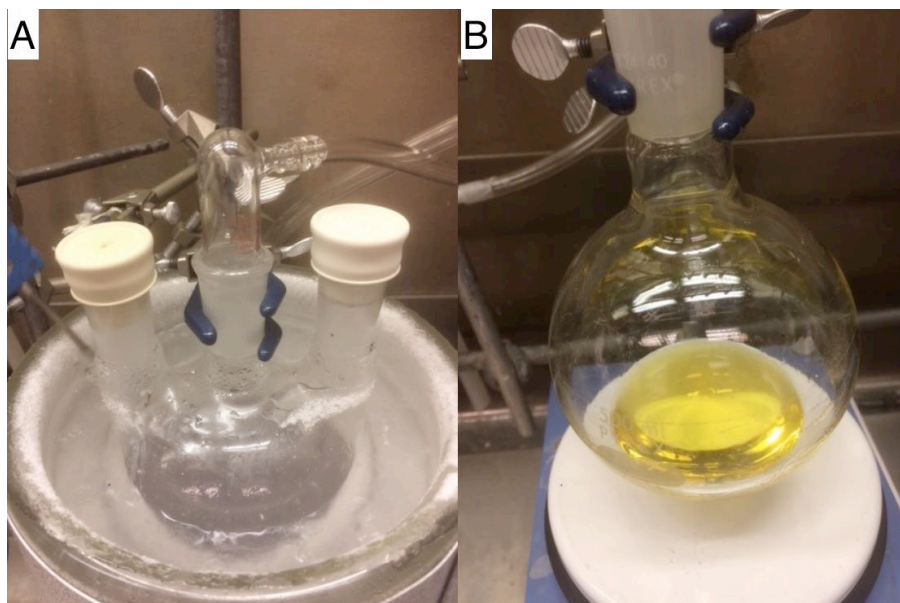
concentrated by rotary evaporation at 40 °C (600 to 7 mmHg). Additional diethyl ether (~50 mL) is added and the concentration repeated to give 27.1 g (96%) of a slightly yellow oil (Figure 1B) (Notes 15 and 16).



**Figure 1. (A) Reaction Assembly for Step A; (B) Product after work-up and concentration (photos provided by submitters)**

B. *N*-[<sup>13</sup>C]Methyl benzophenone imine (**2**). A dry 500 mL, two-necked round-bottomed flask equipped with a Teflon-coated magnetic stirbar (35 mm x 15 mm, oval), a nitrogen inlet and a rubber septum, is filled with a nitrogen atmosphere and maintained this way over the course of the reaction. The flask is charged with anhydrous THF (175 mL) (Note 17) and cooled to -78 °C (Note 18). *n*-Butyllithium (68 mL, 2.45 M in hexanes, 167 mmol, 1.10 equiv) (Notes 19 and 20) is added to the cooled THF with efficient stirring (Note 21). Benzophenone imine (29 mL, 174 mmol, 1.15 equiv) is dissolved in THF (40 mL), and the solution is added via cannulation over a period 10 min to give a blue solution (Note 22). The benzophenone imine flask is rinsed with THF (10 mL) and added to the reaction flask (Figure 2A). [<sup>13</sup>C]Methyl *p*-toluenesulfonate (**1**) is dissolved in THF (40 mL) and added via cannulation using a double-ended needle over 10 min to the cold (-78 °C) solution. The methyl *p*-toluenesulfonate flask is rinsed with THF (10 mL), which is added to the reaction flask. The stir-rate is increased to facilitate a mild vortex (Note 23) and the flask is transferred to a large ice-bath and allowed to warm to 0 °C over 20 min (Note 24). The flask is placed in a large water bath at 23 °C for a further 45 min. The

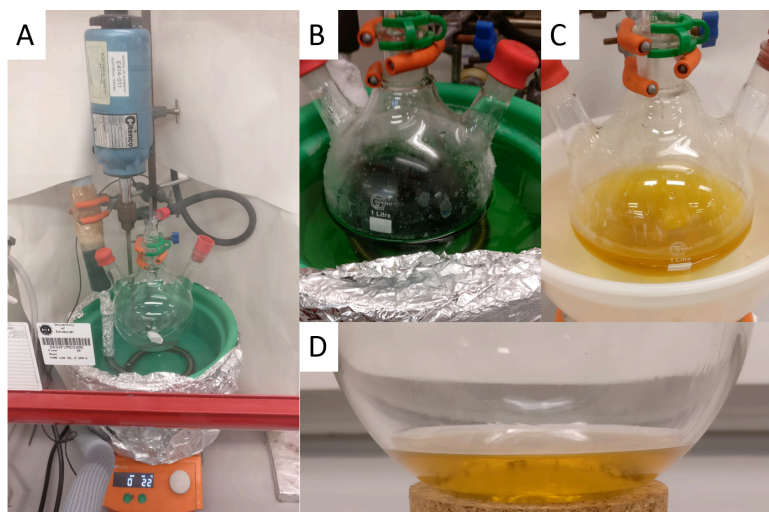
reaction is quenched with water (5 mL), transferred to a 1 L separatory funnel and partitioned with water (200 mL) and Et<sub>2</sub>O (200 mL) (Note 25). The layers are separated and the aqueous layer is back extracted with Et<sub>2</sub>O (50 mL). The combined organic layers are washed with sat. aq. Na<sub>2</sub>CO<sub>3</sub> (100 mL), sat. aq. NaCl (100 mL), dried with Na<sub>2</sub>SO<sub>4</sub> (~40 g) for 10 min, and filtered through a sintered glass funnel (100 mm tall, 50 mm wide) into a 1 L round-bottomed flask. The sodium sulfate is washed in the same sintered glass funnel using additional Et<sub>2</sub>O (40 mL). The bright yellow solution is concentrated *in vacuo* (600 to 7 mmHg, 40 °C) to give a yellow oil (35 g). The oil is treated with petroleum ether (250 mL, bp 35–60 °C) (Note 26) to give a cloudy solution, which is placed in a fridge (4 °C) for 20 h. A short pad of Celite™ 545 (3 cm deep) (Note 27), which is first wetted with 50 mL of petroleum ether, is prepared in a 60 mL glass funnel (medium frit). The mixture is then filtered through the Celite™ into a 500 mL round-bottomed flask using petroleum ether (150 mL). The solution is concentrated *in vacuo* (40 °C, 500 to 120 to 7 mmHg) to give a yellow oil (32 g) (Figure 2B) (Note 28). This material is used directly in the next reaction without further purification (Note 29).



**Figure 2. (A) Reaction Assembly for Step B; (B) Product after work-up and concentration (photos provided by checkers)**

C. *N*-[<sup>13</sup>C]Methyl(trimethylsilyl)-benzophenone imine (3). A dry 1 L, three-necked round-bottomed flask equipped with a Teflon-coated magnetic stirbar (35 mm x 15 mm, oval), a nitrogen inlet and two rubber septa is placed under a nitrogen atmosphere and maintained this way over the course of the reaction (Figure 3A). The flask is charged with anhydrous THF (240 mL) and diisopropylamine (30.3 mL, 216 mmol, 1.5 equiv) (Note 30) before being cooled to -78 °C (Note 31). *n*-Butyllithium (88.1 mL, 2.45 M in hexanes, 216 mmol, 1.5 equiv) is added with stirring to the diisopropylamine solution. After 5 min stirring at -78 °C, chlorotrimethylsilane (29.2 mL, 230 mmol, 1.6 equiv) (Note 32) is added over 3 min followed immediately by *N*-[<sup>13</sup>C]methyl benzophenone imine (2) that is dissolved in THF (40 mL), which is added over the course of 5 min. The flask that contained compound 2 is rinsed with THF (10 mL), which is added to the three-necked flask. A dark solution is formed, which can be dark green to dark red depending on slight changes in the amount of unreacted benzophenone imine. Figure 3B shows the dark green color of the reaction mixture. The reaction mixture is allowed to stir at -78 °C for 15 mins, at which time the dry ice/acetone bath is removed and a dry ice/CHCl<sub>3</sub> bath (-60 °C) is added (Note 33). The reaction is maintained at this temperature for 5 h. The reaction is quenched at -60 °C by the slow addition of acetone (6.3 mL, 86 mmol, 0.6 equiv) (Note 34) and the resulting quenched solution left to stir for 10 min at this temperature (Note 35). The reaction mixture is transferred to a large 23 °C water bath and allowed to warm over 15 min to give a yellow-orange solution (Figure 3C). The solution is transferred to a 1 L single-necked, round-bottomed flask, and the three-necked flask is rinsed with petroleum ether (50 mL), which is added to the single-necked, round-bottomed flask. The solution is concentrated by rotary evaporation at 40 °C (500 to 120 to 7 mmHg). The residue is suspended in petroleum ether (150 mL), filtered through a 3 cm plug of Celite™ 545 filter aid (Note 36) into a 1 L round-bottomed flask with petroleum ether (70 mL) and concentrated by rotary evaporation at 40 °C (500 to 120 to 7 mmHg).

The residue is once more dissolved in petroleum ether (150 mL), cooled in an ice-water bath for ~20 min, filtered through a ~3 cm pad of Celite™ 545 with additional petroleum ether (70 mL) into a 500 mL round-bottomed flask and concentrated by rotary evaporation (40 °C, 3 mmHg) to give the crude product (~44 g) as a clear yellow to orange oil (Figure 3D) (Notes 37 and 38). This material is used directly in the next reaction without further purification (Note 39).



**Figure 3. (A) Reaction Assembly for Step C; (B) Dark green reaction mixture; (C) Yellow reaction mixture after acetone quench and warming; (D) Product after work-up and concentration (photos provided by submitters)**

D. *Trimethylsilyl*[ $^{13}\text{C}$ ]*methylamine hydrochloride* (**4**) (Note 40). A solution of *N*-[ $^{13}\text{C}$ ]*methyl(trimethylsilyl)-benzophenone imine* (44 g crude) in MTBE (350 mL) (Note 41) is placed in a hydrogenation apparatus containing 10 g of Pd/C (10%) (Note 42) (Figure 4A). The mixture is stirred under 20 psi of hydrogen for 24 h (Note 43), at which time LCMS show all the starting material is consumed (Note 44).

The mixture is filtered through a short pad of Celite<sup>TM</sup> 545 and rinsed with MTBE (100 mL). The colorless filtrate solution is stirred for 15 min while bubbling nitrogen slowly into the solution. A solution of 2M HCl in ether (Note 45) is added slowly over 45 min to give a fluffy white solid, and stirring is continued for 2 h (Note 46). The mixture is filtered through a sintered glass funnel (Note 47) to collect the solid trimethylsilylmethylamine hydrochloride salt. After drying under suction for 1 h, the vacuum is removed and the solid is broken up using a spatula. MTBE (50 mL) is added to the solid and stirred using the spatula for 2 min. Vacuum is applied again to remove the solvent and isolate a fluffy white solid (15.5 g) (Note 48). This product is transferred to a 250 mL round bottomed flask and suspended in isopropanol (100 mL) (Note 49). The

suspension is heated in an oil bath to 85 °C to give a slight yellow solution. The temperature of the oil bath is reduced to 40 °C and MTBE (300 mL) is added slowly via a funnel. The product begins to precipitate before all MTBE is added. The resulting suspension is allowed to cool to room temperature over 30 min and then placed in the freezer at -20 °C and left overnight.

Filtration through a sintered funnel and rinsing with MTBE (50 mL) gives shiny white fluffy crystals, which are dried under suction using an inverted funnel dispensing nitrogen (Figure 4B) for 2 h to give white crystals (10.56 g, 52%) (Notes 50 and 51) (Figure 4C), which are stored in a screw cap flask.



**Figure 4. (A) Hydrogenation apparatus used in Step D; (B)  $\text{TMS}^{13}\text{CH}_2\text{NH}_2 \cdot \text{HCl}$  drying under nitrogen; (C)  $\text{TMS}^{13}\text{CH}_2\text{NH}_2 \cdot \text{HCl}$  product in a screw cap flask (photos provided by checkers)**

E. *2,2-Diethyl-1,3-propanedinitrite* (5). A 500 mL, single-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (35 mm x 15 mm, oval) is charged with sodium nitrite (34.5 g, 99%, Fisher Scientific) and 2,2-diethyl-1,3-propanediol (26.4 g, 99%, Sigma Aldrich) followed by water (130 mL). The resulting suspension is stirred at ~500 rpm at 0–4 °C in an ice-water bath and fitted with a 250 mL pressure-equalizing funnel. The funnel is charged with 6 M aqueous hydrochloric acid (80 mL, 99%, Sigma Aldrich). This HCl solution is added dropwise (~1 drop per 2 seconds) over the course of 30 min at 0 °C, the funnel is removed and the resulting

yellow/green solution allowed to stir for a further 30 min at 0 °C (Figure 5). The reaction mixture is transferred to a 500 mL separatory funnel and NaCl (~2 g) is added to assist separation (The mixture should be swirled but not shaken). The aqueous layer is discarded and cold sat. aq. Na<sub>2</sub>CO<sub>3</sub> (50 mL)



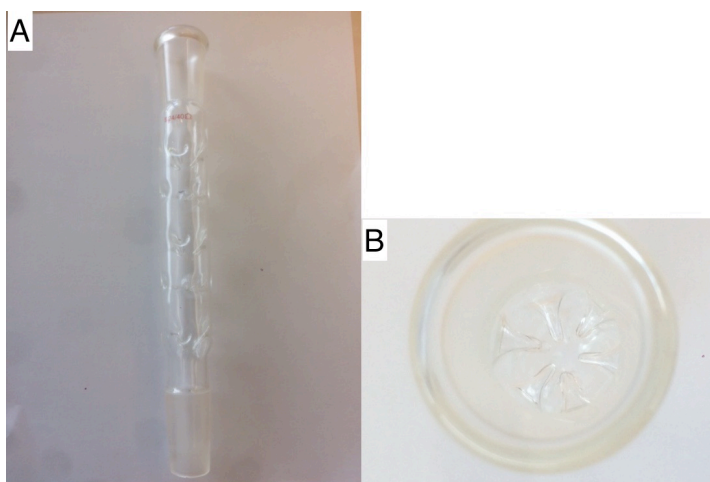
**Figure 5. Propanedinitrite reaction assembly (photos provided by checkers)**

is added followed by cold sat. aq. NaCl (100 mL) to assist separation. The product is washed with cold sat. aq. NaCl (100 mL) once more and then collected in a 100 mL beaker with Na<sub>2</sub>SO<sub>4</sub> (~20 g). The dried product is transferred to a 100 mL round-bottomed flask under suction filtration through a sintered glass funnel to give the product as a yellow oil (32 g, 84%). Sodium sulfate (5 g) is added and the solution is stored in a sealed container in a fridge (0–4 °C). This reagent is used without further purification (Note 52).

*F. Trimethylsilyldiazo*<sup>[13C]</sup>*methane* (6). Trimethylsilyl<sup>[13C]</sup>-amine hydrochloride (10 g) is transferred to a 125 mL Erlenmeyer flask. Diethyl ether (30 mL) (Note 14) is added, followed by a freshly prepared solution of 2M aq NaOH (40 mL) (Note 2). The biphasic solution is swirled until all



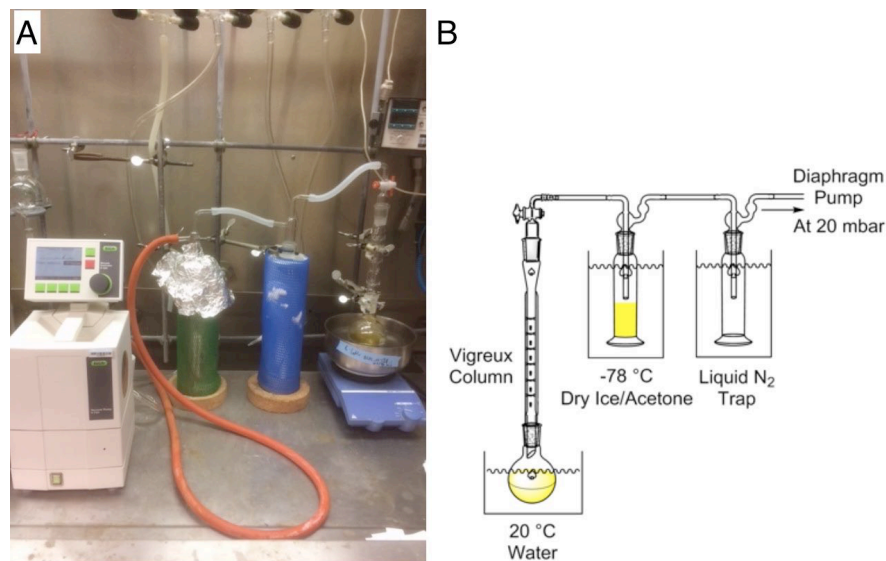
solids are dissolved, and the colorless solution is transferred to a 250 mL separatory funnel. The Erlenmeyer flask is rinsed with additional 2M NaOH solution (30 mL) and ether (10 mL), both of which are added to the separatory funnel. The aqueous layer is saturated with NaCl (15.4 g, 0.22 g per mL of 2N NaOH solution). The organic layer is removed and the aqueous layer is extracted with ether (2 x 25 mL). The combined organic extracts are dried over Na<sub>2</sub>SO<sub>4</sub> (5 g) for 10 min, then filtered through a sintered funnel to a 250 mL round-bottomed flask. The Na<sub>2</sub>SO<sub>4</sub> is rinsed with ether (10 mL). The colorless solution is stirred using a Teflon-coated magnetic stirbar (35 mm x 15 mm, oval). The flask is placed in an oil bath and fitted with a Vigreux column, short condenser and collection flask (Note 53) (Figure 6A and 6B). Diethyl ether is slowly distilled from the colorless solution at 46 °C for 4 h, then at 48 °C for another 4 h. The remaining colorless solution is stored at -10 °C overnight.



**Figure 6. (A) Vigreux column used by the checker; (B) Vigreux column showing indents (photos provided by checkers)**

Trimethylsilyl[<sup>13</sup>C]methylamine as a solution in diethyl ether in a 250 mL round-bottomed flask is placed in a water bath. Anhydrous 2-Me-THF (45 mL) (Note 54) is added followed by 3-nitrophenol (1 g) (Note 55) and 2,2-diethyl-1,3-propanedinitrite (5) (20 mL). A yellow solution is obtained. The single-necked round-bottomed flask is fitted with a nitrogen gas adapter and stirred at 25 °C for 1 h. The nitrogen gas adapter is removed and replaced with a Vigreux column (Note 53), which is topped with a gas

adapter connected to a series of two solvent traps via Tygon tubing. The second solvent trap is connected to a digitally controlled (vacuum control V-850) vacuum pump (Buchi V-700) (Note 56) (Figure 7A-B). The first trap is cooled at  $-78\text{ }^{\circ}\text{C}$  in a dry-ice/acetone bath, while the second is cooled with liquid nitrogen (Figure 7).



**Figure 7. (A) Set-up for distillation step (photo provided by checker); (B) Diagram of set-up for distillation step (diagram from submitter)**

The distillation is started at room temperature and the vacuum slowly lowered to 75 mmHg (75 mmHg/5 min) in 45 min. Gas evolution starts around 360 mmHg, and the evolution (bubbling) is rapid at about 80 mmHg. The vacuum is left at 20 mmHg for 30 min, then at 15 mmHg for another 30 min. The bright yellow distillate (Note 57) is warmed to 25 °C and transferred to a 250 mL separatory funnel and rinsed with 2 mL of 2-Me-THF. The solution is washed with sat. aq. NaCl (2 x 10 mL), dried for 10 min over MgSO<sub>4</sub> (2 g) (Note 58), gravity filtered through a sintered funnel, and rinsed with 2-MeTHF (3 mL). A total of about 50 mL of the product (Note 59) solution was obtained, and the solution is stored over molecular sieves (Note 60). The concentration of the trimethylsilyl[<sup>13</sup>C]methane is determined by Q NMR comparison to bibenzyl (Note 61) to be 0.66 M, which indicates the formation of ca.

33 mmol of the product. The reaction flask contains 37 mL of undistilled deep yellow solution (Note 62).

## 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 ( $^{13}\text{C}$ )methanol, p-toluenesulfonyl chloride, tetrahydrofuran, acetic acid, ethyl acetate, sodium carbonate, sodium sulfate, diethyl ether, n-butyllithium, benzophenone imine, petroleum ether, diisopropylamine, chlorotrimethylsilane, acetone, methyl *tert*-butyl ether, palladium on carbon, hydrogen gas, 2 M hydrogen chloride (HCl) in diethyl ether, isopropanol, sodium chloride, 2-methyltetrahydrofuran, 3-nitrophenol, sodium nitrite and 2,2-diethyl-1,3-propanediol). Step D involves the use of hydrogen gas, this is highly flammable and explosive, keep away from all sources of heat and potential sources of electrical sparks. Step D also involves the use of palladium on carbon, this can be pyrophoric, especially after use in a hydrogenation reaction. The filtration should be conducted under a flow of nitrogen and the filter cake should never be allowed to become completely dry. Once the filtration is complete, the palladium on carbon residue should be immediately moistened with water to prevent spontaneous ignition. Step E involves the preparation

of 2,2-diethyl-1,3-propanedinitrite, alkyl nitrates are known vasodilators and should not be removed from the fume hood unless stored in a well-sealed container. Step F involves the preparation of trimethylsilyldiazo[ $^{13}\text{C}$ ]methane, this should be regarded as highly toxic and must be handled with all precautions appropriate for work with highly toxic substances. Ensure fume cupboard is working correctly before commencing use/preparation of this reagent and do not remove it from the fume cupboard unless stored in a well-sealed container. An emergency quenching solution of methanol:acetic acid 10:1 should be on hand in the case of a spill.

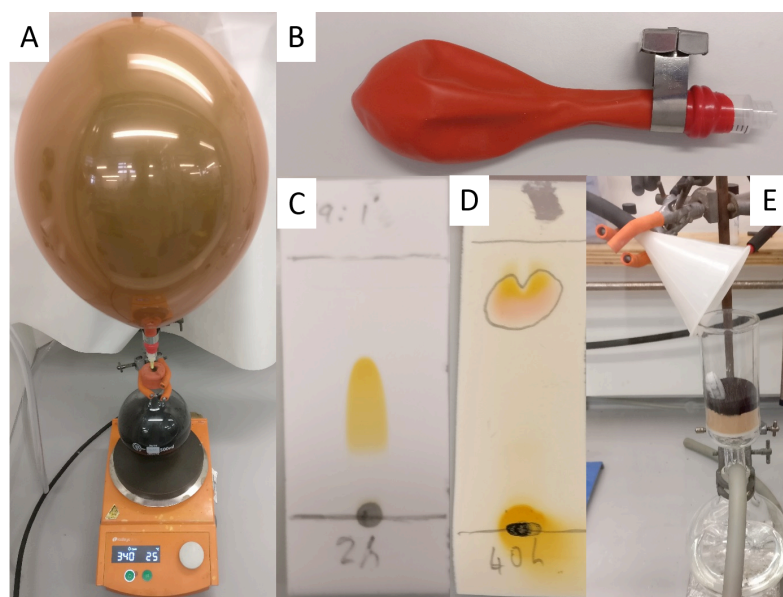
2. Sodium hydroxide (pellets, 98.9%) was purchased from Fisher Scientific and used as received.
3. Deionized water was used.
4. The checkers used [ $^{13}\text{C}$ ]methanol purchased from Sigma-Aldrich with 100% purity by GC and 99%  $^{13}\text{C}$ -labelled. [ $^{13}\text{C}$ ]Methanol was purchased by the submitters from CK-isotopes (98% purity, 99%  $^{13}\text{C}$ -labelled) and used as received.
5. The checkers used *p*-toluenesulfonyl chloride purchased from Sigma-Aldrich (99%). The submitters purchased *p*-toluenesulfonyl chloride (99%) from Acros Organics and used the material as received.
6. The checkers used tetrahydrofuran purchased from Sigma-Aldrich (>99.9% with 250 ppm BHT). Tetrahydrofuran (>99% with 250 ppm BHT) was purchased by the submitters from Fisher Scientific and used as received.
7. Vigorous stirring with a large stir bar is essential to facilitate efficient mixing. The submitters reported stirring at 800 rpm to achieve a mild vortex.
8. Acetic acid (>99.5%) was purchased from Sigma Aldrich and used as received.
9. The reaction flask may be scratched with a spatula to initiate crystallization.
10. Ethyl acetate (>99%) was purchased from Fisher Scientific and used as received.
11. Sodium carbonate (>99%) was purchased from Fisher Scientific and used as received.
12. Sodium chloride (99%) was purchased from Fisher Scientific and used as received.

13. Sodium sulfate (anhydrous, granular, 99%) was purchased from Fisher Scientific and used as received.
14. Diethyl ether (>99%) was purchased from Fisher Scientific and used as received.
15. Characterization data for [<sup>13</sup>C]Methyl *p*-toluenesulfonate (1): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ : 2.46 (s, 3H), 3.74 (d, *J* = 150 Hz, 3H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H); <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ : 21.6, 56.1, 128.1, 129.9, 132.2, 144.9.
16. The weight percent (wt%) purity was determined to be 98.4 wt% by quantitative <sup>1</sup>H NMR (Q NMR) using dimethylsulfone (99.96 wt%) purchased from Sigma Aldrich as an internal standard.
17. The checkers used THF (anhydrous, >99.9% stabilized with 250 ppm BHT) purchased from Sigma-Aldrich. Tetrahydrofuran (>99.8%, unstabilized) was purchased by the submitters from Fisher Scientific and dried by passage through an activated alumina column under argon.
18. The submitters used an insulated bucket filled with dry ice and acetone to maintain the temperature at -78 °C.
19. The checkers used *n*-butyllithium (2.5 M in hexanes) from Acros Organics. The certificate of analysis indicated 2.67 M. The *n*-butyllithium solution was used as received and was not titrated. *n*-Butyllithium (2.5 M in hexanes) was purchased by the submitters from Acros Organics and titrated before use (Note 20).
20. Freshly titrated *n*-butyllithium in hexanes (167 mL) should be used, although the volume required will depend on the concentration of the *n*-butyllithium solution. The submitters titrated *n*-butyllithium against diphenylacetic acid (2 mmol) in tetrahydrofuran (15 mL) at room temp (approx. 20 °C in a water bath) until the appearance of a consistent yellow color.<sup>3</sup> The titration was performed in duplicate.
21. The submitters stirred the reaction at 340 rpm, which resulted in a slight vortex being visible.
22. The checkers purchased benzophenone imine (98%) from Oakwood Products, Inc. Benzophenone imine (98%) was purchased by the submitters from Fluorochem and used as received. The submitters report the solution to be a dark red color.
23. The submitters stirred the reaction at 500 rpm, which resulted in a mild vortex being visible.

24. The color of the reaction at this stage can vary from red to blue to black with no noticeable effect on yield or purity after the quench and workup.
25. As the product imine is susceptible to hydrolysis the work-up should be conducted swiftly. An insoluble white precipitate may form at this stage, in such cases the workup should be followed as normal, any precipitate remaining in the organic layer after separation will be removed by filtration.
26. Petroleum ether (bp 35–60, ACS reagent) was purchased from Sigma-Aldrich.
27. The checkers used Celite™ 545 from Fisher, rinsed with petroleum ether before use. Kieselguhr washed with acid was purchased from Fisher Scientific by the submitters and used as received.
28. *N*-[<sup>13</sup>C]Methyl benzophenone imine, relevant NMR resonances in crude material: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ : 3.25 (d, *J* = 135 Hz, 3H), 7.15–7.19 (m, 2H), 7.29–7.50 (m, 6H), 7.56–7.62 (m, 2H); <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ : 41.5, 127.8, 128.0, 128.2, 128.3, 128.5, 129.8, 136.5 (d, *J* = 6.1 Hz), 139.8 (d, *J* = 7 Hz), 169.6 (d, *J* = 3.9 Hz).
29. The submitters found this compound to be sensitive to chromatographic media, undergoing hydrolysis to benzophenone, which has an identical *R*<sub>f</sub> to that of the desired product in numerous solvent systems. Distillation is difficult due to the similar boiling points of the starting material and product. If this material were required in pure form the submitters would recommend using equimolar amounts of starting materials rather than the ratios employed here.
30. The checkers used diisopropylamine (redistilled, 99.95%) from Sigma-Aldrich without further purification. Diisopropylamine (>99.5%) was purchased from Sigma Aldrich by the submitters and was purified by distillation over calcium hydride under N<sub>2</sub> before use.
31. The checkers used a dry ice/acetone bath (–78 °C), followed by a dry ice/chloroform bath (–60 °C). The submitters utilized an insulated bucket filled with ethanol and cooled with an immersion cooler. An overhead mechanical stirrer with a propeller type paddle (35mm) was used by the submitters to stir the cooling bath.
32. The checkers used TMSCl from Sigma-Aldrich (≥ 99.0% (GC)) without purification. Chlorotrimethylsilane (98%) was purchased from Sigma Aldrich by the submitters and purified by distillation over calcium hydride under N<sub>2</sub> before use.

33. At higher temperatures, such as  $-30\text{ }^{\circ}\text{C}$ , double silylation of the imine methyl group is much more prominent. As such, the reaction was examined at  $-45\text{ }^{\circ}\text{C}$  and found to provide a product ratio of 0:96:4 (starting material : product : disilylated material), demonstrating some flexibility with temperature control.
34. Acetone (>99%) was purchased from Fisher Scientific and used as received.
35. Quenching with water or an organic alcohol caused protodesilylation; therefore, acetone should be used to quench the reaction.
36. The checker used a 3 cm tall plug of Celite™ 545 filter aid (not acid-washed) powder from Fisher, and the Celite™ was rinsed with petroleum ether (50 mL) before use. The submitters used "Kieselgur washed with acid" for filtration to remove lithium chloride. Other filter aids may provide similar results; however, an aqueous workup should be avoided as protodesilylation can occur.
37. The crude material is a mixture of starting material, product and disilylated material, which contain  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) resonances at 3.26, 3.31, and 3.04 ppm, respectively. The ratio of products (based solely on these three compounds) can be determined by the following calculation;  $\text{Product \%} = (b/2) * 100 / ((a/3) + (b/2) + (c/1))$ . Where a = starting material, b = product and c = disilylated material by integration of their respective  $^1\text{H}$  NMR peaks.
38.  $N$ -[ $^{13}\text{C}$ ]Methyl(trimethylsilyl)benzophenone imine, relevant peaks in crude material:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 0.2 (d,  $J = 1.5\text{ Hz}$ , 9H), 3.27 (d,  $J = 127.5\text{ Hz}$ , 2H), 7.11 (m, 2H), 7.28–7.30 (m, 2H), 7.36–7.50 (m, 3H), 7.50–7.53 (m, 2H);  $^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  : -0.1 (d,  $J = 3.6\text{ Hz}$ ), 130.0, 130.1, 130.2, 130.5, 130.6, 131.3, 138.9 (d,  $J = 5.7\text{ Hz}$ ), 142.7 (d,  $J = 6.7\text{ Hz}$ ), 167.0 (d,  $J = 4.2\text{ Hz}$ ).
39. The submitters found this compound to be sensitive to chromatographic media, undergoing hydrolysis to benzophenone, which has an identical  $R_f$  to the desired product in numerous solvent systems. Vacuum distillation caused decomposition of the product to give a black tar.
40. The submitters performed the hydrogenolysis using the following procedure. The 500 mL, single-necked round-bottomed flask containing  $N$ -[ $^{13}\text{C}$ ]methyl(trimethylsilyl)-benzophenone imine from the previous step is equipped with a Teflon-coated magnetic stir bar (35 mm x 15 mm, oval), flushed with nitrogen gas and charged with methyl *tert*-butyl ether (200 mL). Stirring is commenced and palladium on carbon

(7.3 g, 10% wt/wt Pd on carbon, 6.8 mmol, 5 mol% Pd) (Note 42) is added followed by additional methyl *tert*-butyl ether (70 mL) (Note 41) to rinse the sides of the flask. The flask is sealed with a rubber septum and a double walled hydrogen balloon is added (Notes 63 and 64) (Figure 8A and 8B). The flask is flushed with hydrogen by piercing the rubber septum with a small needle (40 mm, gauge 20) as an outlet. After 15 min the outlet needle is removed, the hydrogen balloon is refilled and the reaction left under this pressure at room temperature (23 °C) overnight. The following morning the balloon is replaced with a freshly made hydrogen balloon. This balloon should be refilled once more in the before being left over a second night. The following morning the reaction is checked by TLC (Notes 65, 66, and 67) (Figure 8C and 8D).

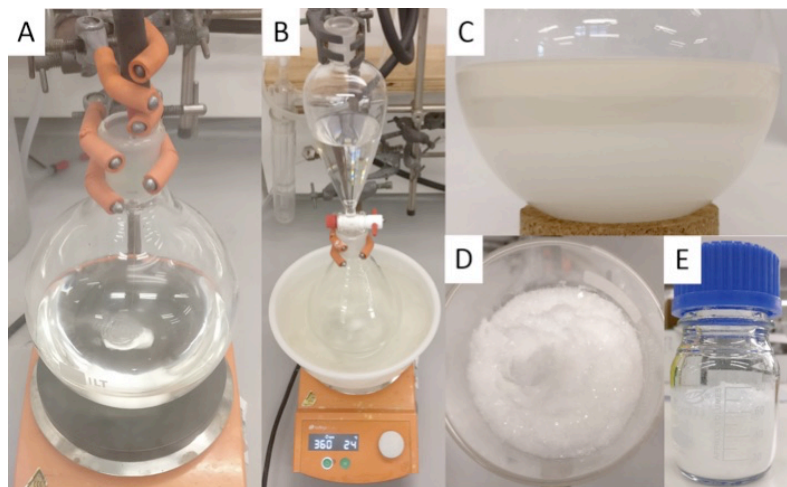


**Figure 8.** (A) Reaction Assembly for Step D; (B) Double walled hydrogen balloon; (C) TLC of starting material stained with  $I_2$ . (D) TLC at end of reaction stained with  $I_2$ ; (E) Filtration of reaction mixture under a blanket of  $N_2$  gas to give a clear solution (photos provided by the submitters)

Once complete, the remaining hydrogen gas is released slowly in the fume hood, the flask is flushed with nitrogen and the crude mixture filtered through a ~2 cm pad of kieselgur into a 1 L round-bottomed flask under an inverted funnel dispensing nitrogen gas (Figure 8E). The



kiieselgur is washed with methyl *tert*-butyl ether (MTBE) (2 x 50 mL). Water (~5 mL) is added to the used kieselgur pad, which is then disposed of as heavy metal waste. The clear, near-colorless filtrate obtained is degassed with stirring and gentle nitrogen bubbling over 10 min to remove any ammonia or methylamine side products (Figure 9A). Bubbling is suspended and the 1 L round-bottomed flask is equipped with a Teflon-coated magnetic stirbar (35 mm x 15 mm, oval) and placed in a water bath at room temperature. A 250 mL separating funnel is charged with 2 M HCl in Et<sub>2</sub>O (89 mL, 178 mmol, 1.3 equiv) (Note 45). The HCl solution is then slowly added via the 250 mL separating funnel to the reaction mixture over ~15-20 mins with slow stirring (Note 46) (Figure 9B). The resulting suspension is filtered through a sintered glass funnel (Note 47) to collect the solid trimethylsilylmethylamine hydrochloride salt. MTBE (30 mL) is added to the solid and the mixture stirred to form a slurry before removal of the solvent by further vacuum filtration and collection of the product as a fluffy white solid (15 - 17 g) (Note 48).



**Figure 9:** (A) Degassing of reaction mixture with N<sub>2</sub> bubbling through a needle. (B) Set-up for addition of 2 M HCl in Et<sub>2</sub>O to reaction mixture. (C) Suspension after recrystallization step. (D) Crystals collected by filtration. (E) Product in a 100 mL screw cap flask

The product is transferred to a 1 L single-necked round-bottomed flask and suspended in isopropanol (~105 mL, 6 mL/g of crude material)

- (Note 49). The suspension is heated to ~80 °C with a heat gun and swirling by hand to give a clear solution with a slight yellow coloration. This hot solution is swirled by hand while warm (~40 °C) MTBE (~313 mL, 18 mL/g of crude material) is added slowly. Material begins to precipitate before the MTBE addition is complete. The resulting suspension is allowed to cool to room temperature over 30 min, placed in a freezer (-20 °C) and left overnight (16 h). The resulting suspension is filtered with suction through a sintered glass funnel to collect the solid trimethylsilylmethylamine hydrochloride salt (Note 47) (Figure 9C-D). The resulting white crystalline solid is washed with MTBE (50 mL) then dried with suction under an inverted funnel dispensing nitrogen gas for 20 min. The white crystalline solid (13.0–14.5 g, 61–68% yield from methanol) is transferred to a 100 mL screw cap flask for storage (Figure 9E) (Notes 50 and 51).
41. The checkers used methyl *tert*-butyl ether purchased from Sigma-Aldrich (ACS reagent, > 99%). Methyl *tert*-butyl ether (99%) was purchased by the submitters from Acros Organics and used as received.
  42. Palladium on carbon (10 wt. % loading, matrix activated carbon support) was purchased from Sigma Aldrich and used as received.
  43. Hydrogen gas (>99%) was purchased from BOC gases.
  44. The checkers used Ultra Performance Liquid Chromatography-Mass Spectrometry (UPLCMS) using a medium polar method: run time 3.0 min, gradient 95% water (0.1% formic acid) and 5% MeCN to 5% water in 2.1 min, hold to 3 min at 5% water, flow 2.5 mL/min; column: BEH C18 (2.1 mm × 50 mm, 1.7 μm), *m/z* 120-1000, 0.3 μL injection. The starting material showed at 1.03 min,  $MH^+ = 269$ . A new peak was observed at 1.85 min corresponding to diphenylmethane (UV active), though no mass peak was observed.
  45. 2M HCl in diethyl ether was purchased by the checkers from Sigma-Aldrich. The submitters purchased 2M HCl in diethyl ether from VWR (Alfa Aesar brand) and used the material as received.
  46. The submitters stirred the mixture at 360 rpm until the slurry became too thick for magnetic stirring, at which point gentle swirling by hand was sufficient.
  47. A fine porosity sintered glass funnel is required to avoid the frit becoming blocked. The submitters used grade 3, (16-40 μm pore size), 65 mm diameter, 60 mm high. The filtration is slow but can be accelerated by gently stirring the product slurry with a spatula.

48. The purity of product ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) obtained at this stage varied from 90-95% by QNMR with dimethylsulfone (see Note 51 for Q NMR of purified material); therefore, further purification by a trituration/crystallization is carried out. Alternatively, the crude material can be carried through the next step with no complications, which slightly enhances the overall yield of TMSdiazomethane from methanol by eliminating loss from crystallization. Use of the crude material should only be performed if no methylamine hydrochloride ( $\delta$  2.61 in  $\text{CD}_3\text{OD}$ ) is detected in the  $^1\text{H}$  NMR spectrum of the crude material, since methylamine hydrochloride will form diazomethane in the next step.
49. Isopropanol (Chromasolv plus, 99.9%) from Sigma-Aldrich was used.
50. Characterization data for trimethylsilyl[ $^{13}\text{C}$ ]methylamine hydrochloride (4): mp 239–242 °C (*i*PrOH:MeOtBu, 1:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  : 0.22 (d,  $J$  = 2.5 Hz, 9H), 2.39 (d,  $J$  = 131 Hz, 2H).  $^{13}\text{C}$  ( $^1\text{H}$ ) NMR (101 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  : -2.8 (d,  $J$  = 4.5 Hz), 29.5. IR (ATR) 3200–2800, 2951, 1603, 1503, 1412, 1245  $\text{cm}^{-1}$ ; HRMS ESI-MS  $m/z$  calcd for  $^{13}\text{C}_1\text{C}_3\text{H}_{14}\text{NSi} [\text{M}-\text{Cl}]^+$ : 105.09236, found: 105.09180.
51. The weight percent (wt%) purity was determined to be 99.4 wt% by quantitative  $^1\text{H}$  NMR (Q NMR) using dimethylsulfone purchased from Sigma Aldrich as an internal standard (99.96 wt%).
52. Characterization data for 2,2-diethyl-1,3-propanedinitrite (5): bp 20 °C (3.5 mmHg);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 0.87 (t,  $J$  = 7.5 Hz, 6H), 1.38 (q,  $J$  = 7.5 Hz, 4H), 4.57 (s, 4H);  $^{13}\text{C}$  ( $^1\text{H}$ ) NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  : 7.2, 23.3, 40.9, 69.7.
53. The submitters used a 24 cm tall, B24 Vigreux column (16 cm of effective column, actual height 24 cm) fitted with a condenser and collection flask. The Vigreux column should have deep indents/fingers for efficient separation (Figure 6A-B). The checkers used a slightly different Vigreux column with no deep indents, see photos.
54. 2-Methyltetrahydrofuran (anhydrous, inhibitor free, >99%) was purchased from Sigma Aldrich and used as received.
55. 3-Nitrophenol (99%) was purchased from Sigma Aldrich and used as received.
56. The checker used a digitally controlled (vacuum control V-850) vacuum pump (Büchi V700). The submitters used a vacuubrand MD 4 NT VARIO diaphragm pump with a CVC 3000 vacuum controller. The

- vacuum pump exhaust should be vented into a working fume cupboard.
57. The submitters added additional 2-MeTHF (10 mL) to the crude reaction mixture and performed a second distillation prior to washing with sat. aq. NaCl solution.
  58. Magnesium sulfate (anhydrous, 99%) was purchased from Fisher Scientific and used as received.
  59. Trimethylsilyldiazo[<sup>13</sup>C]methane, relevant resonances in crude solution, both <sup>1</sup>H and <sup>13</sup>C NMR spectra are referenced to tetramethylsilane at 0.0 ppm: <sup>1</sup>H NMR (400 MHz, 2-MeTHF/Et<sub>2</sub>O) δ : 0.14 (d, *J* = 2.8 Hz, 9H), 2.71 (d, *J* = 171.6 Hz, 1H); <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, 2-MeTHF/Et<sub>2</sub>O) δ : -1.0 (d, *J* = 5.1 Hz), 21.2; HRMS ESI-MS *m/z* calcd for C<sub>3</sub><sup>13</sup>C<sub>1</sub>H<sub>10</sub>N<sub>2</sub>Si [M]<sup>+</sup> 115.16413, found: 115.06501. Slight variation in the reported chemical shifts is observed as a result of different ratios of Et<sub>2</sub>O:2-MeTHF. CHCl<sub>3</sub> may be used as an alternative reference at 7.87 ppm in the <sup>1</sup>H NMR spectrum and 79.1 ppm in the <sup>13</sup>C NMR spectrum.
  60. Molecular sieves (3Å, beads 8-12 mesh) were purchased by the checkers from Aldrich and activated before use. Molecular sieves (3Å, general purpose grade) were purchased by the submitters from Fisher Scientific and stored in an oven at 220 °C for a minimum of 5 days before use.
  61. To determine the concentration of trimethylsilyldiazo[<sup>13</sup>C]methane, bibenzyl (42.3 mg) was weighed in an amber vial, and then 0.7 mL of the trimethylsilyldiazomethane solution was added and swirled to dissolve the bibenzyl. CDCl<sub>3</sub> (Sigma-Aldrich, 99.8 atom% D) was added and <sup>1</sup>H NMR spectrum was acquired. The concentration of TMSdiazomethane was then calculated using the following calculation;  $C = (4 * m * b) / (M * V * a)$  where *M* = molecular weight of bibenzyl, *V* = volume of trimethylsilyldiazo[<sup>13</sup>C]methane solution, *m* = mass of bibenzyl, *a* = integral value of the methylene protons (δ 2.89, (s)) of bibenzyl and *b* = integral value of the methine proton (δ 2.71 (d)) of trimethylsilyldiazo[<sup>13</sup>C]methane.
  62. No attempts were made to continue the distillation and improve the yield.
  63. Thick latex balloons (0.015 inch (15 mil)) rated for 12 L gas volume were purchased from Sigma Aldrich.
  64. The submitters used two 0.015 inch (15 mil) thick latex balloons attached to a 5 mL disposable syringe barrel with electrical tape and a

- small metal hose clamp (Figure 8B). A needle (40 mm, 20 gauge) is attached and used to pierce the rubber septum.
65. Glass-backed TLC plates ( $\text{Al}_2\text{O}_3$ ) were purchased from Sigma Aldrich.
  66. Using petroleum ether: $\text{Et}_2\text{O}$  (19:1) as the eluent, the reaction is deemed complete when only diphenylmethane ( $R_f = 0.9$ ) and a baseline spot are visible. The spots can be viewed by fluorescence quenching on suitable TLC plates at 254 nm or by  $\text{I}_2$  staining. (Figure 8C-D).
  67. The time required for the hydrogenation reaction varies with scale. When the reaction is performed on smaller scales (ca. 30 mmol), the reaction was complete overnight (16 h). On full scale the reaction will theoretically consume 7.8 L of  $\text{H}_2$  gas. Replacing the balloons to ensure an excess of  $\text{H}_2$  is essential.

## 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](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.

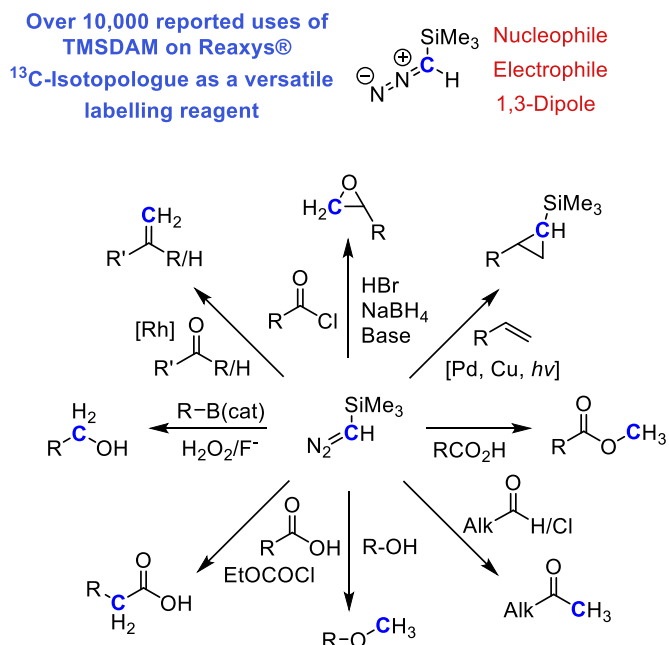
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

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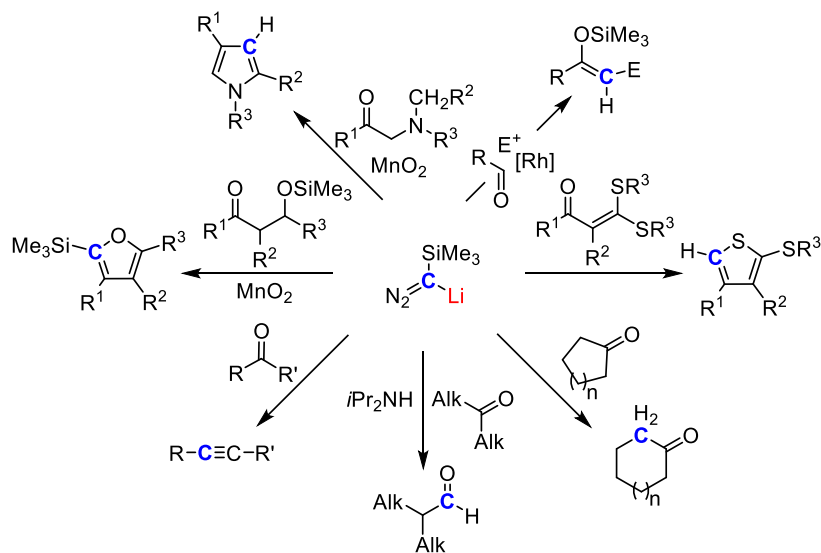
## Discussion

Trimethylsilyldiazomethane (TMSDAM) is a highly versatile reagent for organic synthesis. It exhibits reactivity as a nucleophile under basic conditions, an electrophile under acidic conditions, a 1,3-dipole under neutral/basic conditions and can even function as a source of diazomethane.<sup>4-7</sup> This ambivalent reactivity allows it to participate in a plethora of different transformations, from simple S<sub>N</sub>2 reactions to cycloadditions, metal mediated insertions, carbene chemistry and a variety of rearrangements (Schemes 1-3).<sup>8-10</sup> Its reactivity is well known and has

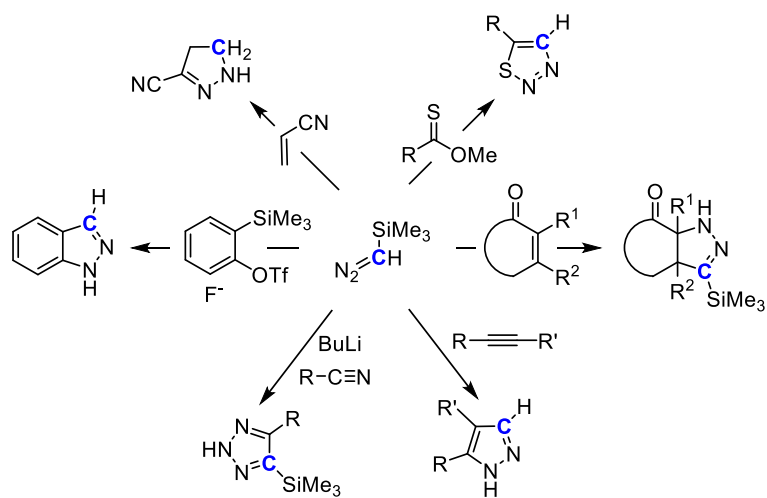


Scheme 1. Selected examples of TMSDAM as a C1 synthon<sup>8</sup>

been extensively documented (over 10,000 recorded uses on Reaxys) while the reagent itself has a reliable preparatory procedure<sup>11</sup> and is commercially available.<sup>12</sup>



Scheme 2. Selected examples of Li-TMSDAM as a C1 synthon<sup>9</sup>



Scheme 3. Selected examples of Li/TMSDAM as a CNN synthon<sup>10</sup>

Based on this, we propose a  $^{13}\text{C}$ -isotopologue of TMSDAM to be a highly valuable reagent for the predictable and facile synthesis of  $^{13}\text{C}$ -labelled compounds for both chemical and biological studies.<sup>8-10</sup> Indeed, the potential application of  $^{13}\text{C}$ -labelled-TMSDAM as a derivatization agent for mass spectrometry has recently formed part of a patent claim.<sup>13</sup> However, to date no synthesis or application of such a reagent has been published in either the academic or patent literature. Aware that a practical synthesis enhances the application opportunities of any new reagent, we have developed a high-yielding, chromatography free synthesis of  $^{13}\text{C}$ -labelled-TMSDAM starting from  $^{13}\text{CH}_3\text{OH}$  as a readily available and cheap source of  $^{13}\text{C}$ .<sup>14</sup>

The final step in this synthesis involves the diazotization of trimethylsilylmethylamine which was recently reported by Lebel and co-workers in 60-68% conversion.<sup>10f</sup> This provides an ethereal solution of TMSDAM which can be utilized without isolation for reactions which tolerate the presence of organic nitrite residues and water. A purification procedure was also reported to remove the nitrite residues and dry the solution. While we found the conversions to be reproducible the yield of TMSDAM after purification was between 40-47% in our hands. Seeking to improve this for a  $^{13}\text{C}$ -labelled synthesis we noted that the acid catalyst employed (1-adamantanecarboxylic acid, 15 mol%) consumed 15% of the TMSDAM by methylation. We also noted that the multi-step washing procedure employed before distillation was required to remove the nitrite reagent (1,3-propanedinitrite). Finally, the diazotization was conducted by addition of the nitrite reagent at reflux, causing a powerful exothermic reaction which we sought to avoid for safety reasons.

Our studies revealed that 3- $\text{NO}_2$ -phenol (10 mol%) functioned as an excellent acid catalyst. It allowed for a slightly lower catalyst loading, a homogeneous reaction mixture, a much lower reaction temperature (room temp,  $\sim 20^\circ\text{C}$ ) and the catalyst was much more resistant to methylation by TMSDAM (compared with 1-adamantane carboxylic acid). We also found that by replacing the nitrite reagent with a higher boiling analogue (2,2-diethyl-1,3-propanedinitrite) we could eliminate the nitrite washes from the purification procedure and simply carry out a vacuum distillation. Combined, this allowed for higher in-situ conversions of 80-88% (compared to 60-68%) and isolated yields of 57-67%.

The preparation of the diazotization precursor trimethylsilyl- $^{13}\text{C}$  methylamine hydrochloride was optimized with the goal of avoiding



time-consuming purification procedures. The resulting route facilitates the synthesis of pure trimethylsilyl[<sup>13</sup>C]methylamine hydrochloride in 61–68% yield from [<sup>13</sup>C]MeOH with only one purification step (trituration/recrystallization). This material can be utilized for in-situ diazotization and subsequent reactions as reported by Lebel<sup>10f</sup> or purified from the nitrite residues and dried as described in the above procedure.

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11. Shioiri, T.; Aoyama, T.; Mori, S. *Org. Synth.* **1990**, 68, 1.
12. [www.sigmaaldrich.com](http://www.sigmaaldrich.com), CAS number: 18107-18-1 checked on 21/11/2017.
13. Kurland, I. J., Int. Pat. Appl. WO 2017/079102, A1, May 11, 2017.
14. Commercially available from a range of suppliers including Sigma-Aldrich, CKisotopes and Goss Scientific. We received quotes ranging from £1.98 - £3.46 per mmol.

### Appendix

#### Chemical Abstracts Nomenclature (Registry Number)

- [<sup>13</sup>C]Methanol: Methanol-<sup>13</sup>C; (14742-26-8)
- p*-Toluenesulfonyl chloride: Benzenesulfonyl chloride, 4-methyl-; (98-59-9)
- Tetrahydrofuran: Furan, tetrahydro-; (109-99-9)
- Acetic acid: Acetic acid; (64-19-7)
- Sodium carbonate: Carbonic acid disodium salt; (497-19-8)
- Sodium sulfate: Sulfuric acid disodium salt; (7757-82-6)
- n*-Butyllithium: Lithium, butyl-; (109-72-8)
- Diphenylacetic acid: Benzeneacetic acid,  $\alpha$ -phenyl-; (117-34-0)
- Benzophenone imine: (1013-88-3)
- Diisopropylamine: 2-Propanamine, *N*-(1-methylethyl)-; (108-18-9)
- Chlorotrimethylsilane: Silane, chlorotrimethyl-; (75-77-4)

Methyl *tert*-butyl ether: Propane, 2-methoxy-2-methyl-; (1634-04-4)  
 2 M HCl in diethyl ether: Hydrochloric acid; (7647-01-0)  
 Dimethylsulfone: Methane, sulfonylbis-; (67-71-0)  
 Isopropanol: 2-Propanol; (67-63-0)  
 2-Methyltetrahydrofuran: Furan, tetrahydro-2-methyl-; (96-47-9)  
 3-Nitrophenol: Phenol, 3-nitro-; (554-84-7)  
 Sodium nitrite: Nitrous acid, sodium salt; (7632-00-0)  
 2,2-Diethyl-1,3-propanediol: (115-76-4)  
 Hydrochloric acid: Hydrochloric acid; (7647-01-0)  
 Magnesium sulfate: Sulfuric acid magnesium salt (1:1); (7487-88-9)  
 Bibenzyl: Benzene, 1,1'-(1,2-ethanediyl)bis-; (103-29-7)



Guy Lloyd-Jones FRS studied Chemical Technology at Huddersfield, obtained his doctorate at Oxford with John Brown FRS, and did postdoctoral research with Andreas Pfaltz at Basel. He began his independent career in 1996 at the University of Bristol, building a research group specializing in kinetics, NMR and isotopic labelling. In 2013 he moved to take up The Forbes Chair at the University of Edinburgh and in the same year was elected to the UK National Academy of Science (FRS).



Chris Nottingham completed a B.Sc. in Chemical and Pharmaceutical Science at the Galway-Mayo Institute of Technology in 2012 before obtaining a Ph.D. in organic chemistry under the supervision of Prof. Patrick Guiry MRIA at University College Dublin in 2016. He is currently performing postdoctoral research at the University of Edinburgh under the direction of Prof. Guy C. Lloyd-Jones FRS.



Bachir Latli obtained his Ph.D. in organic chemistry in 1991 at Stony Brook University under the supervision of Prof. Glenn Prestwich. He then joined the laboratory of the late Prof. John Casida at the University of California in Berkeley. In 1998 he moved to Boehringer Ingelheim Pharmaceuticals in Ridgefield, Connecticut, where he is a Senior Research Fellow.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

$^{13}\text{CH}_3\text{OTs}$

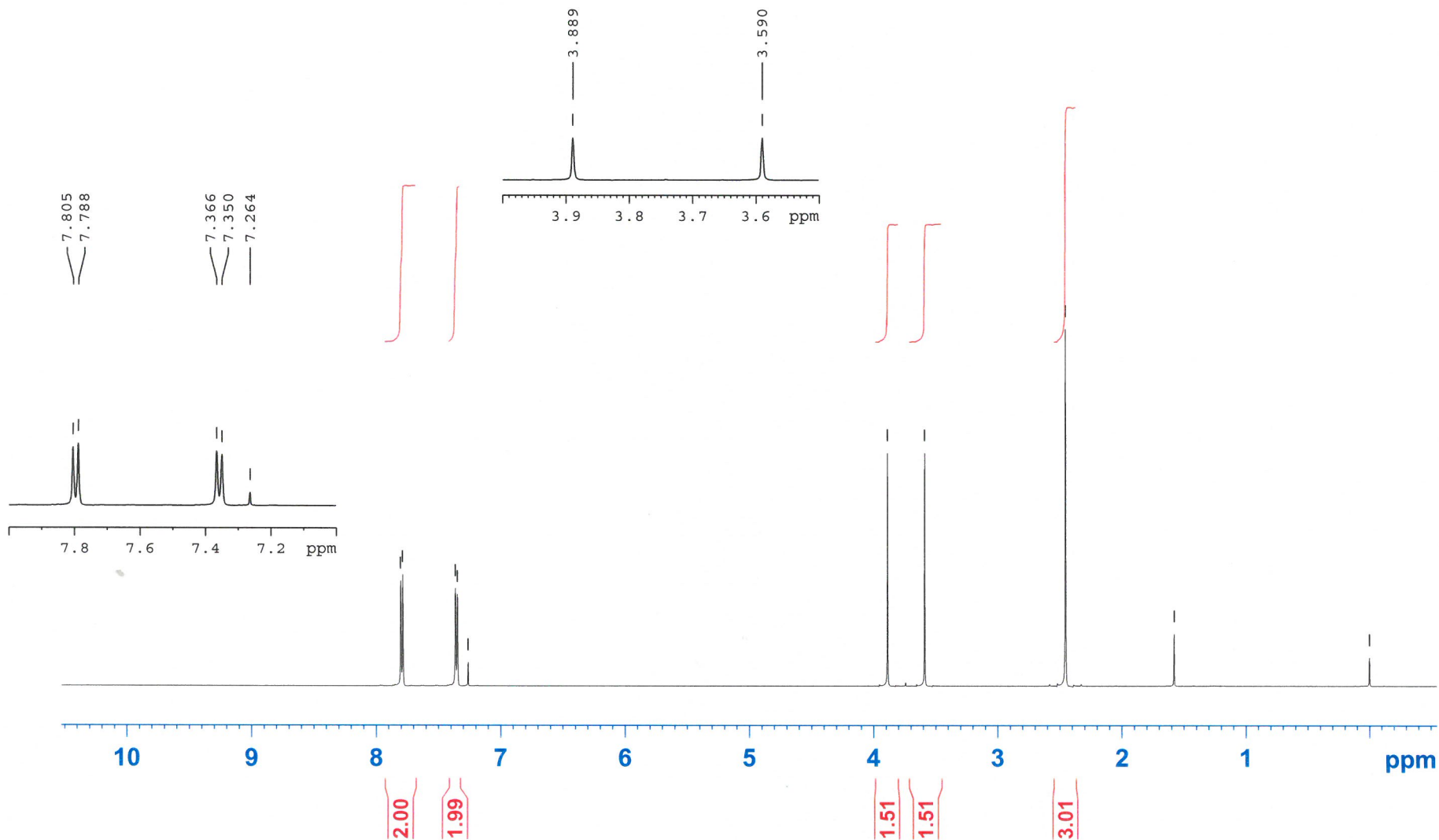
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7.37  
7.35  
7.26

3.89  
3.59

2.46

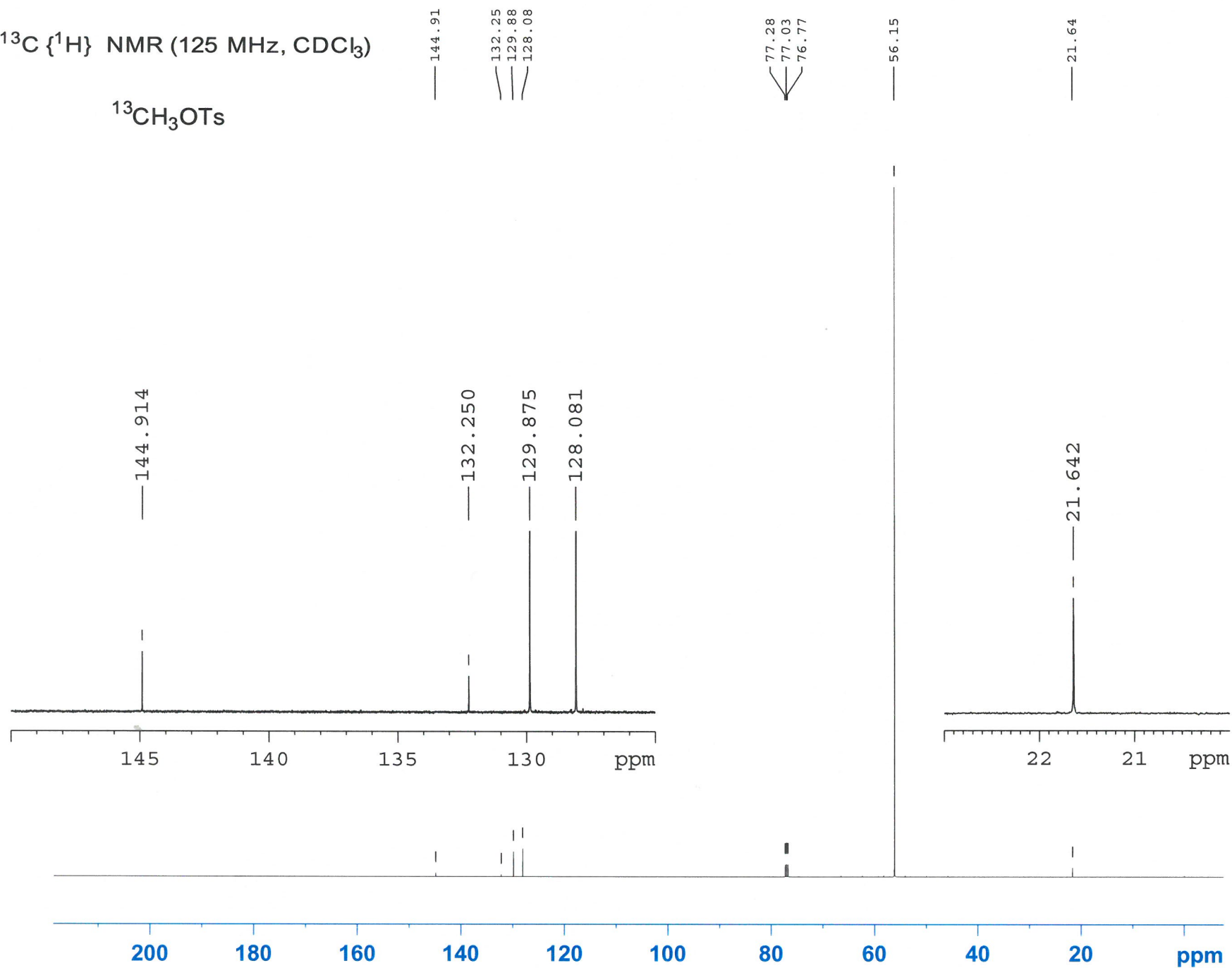
1.58

0.00

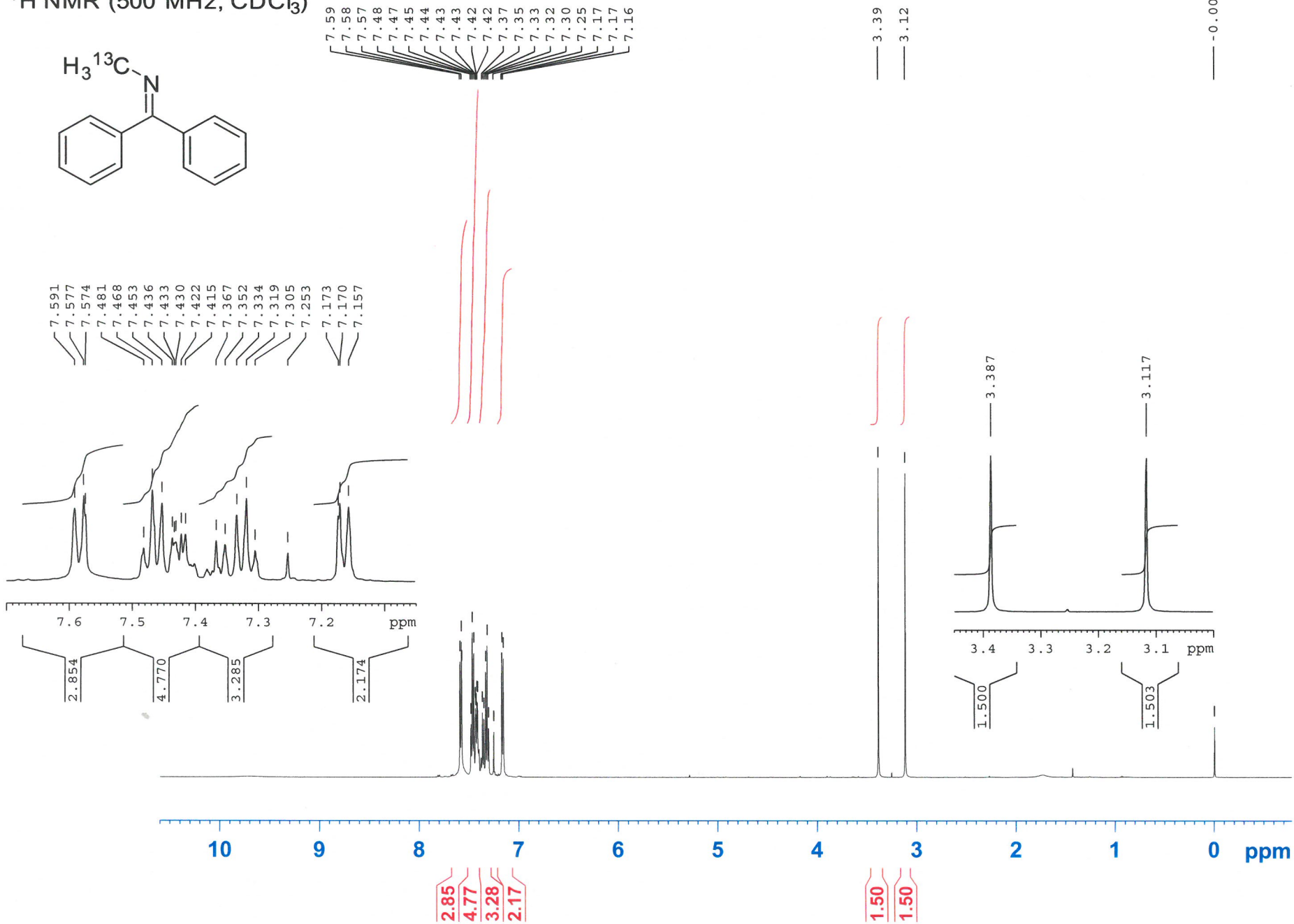
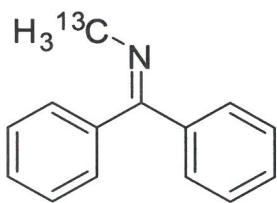


$^{13}\text{C} \{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )

$^{13}\text{CH}_3\text{OTs}$

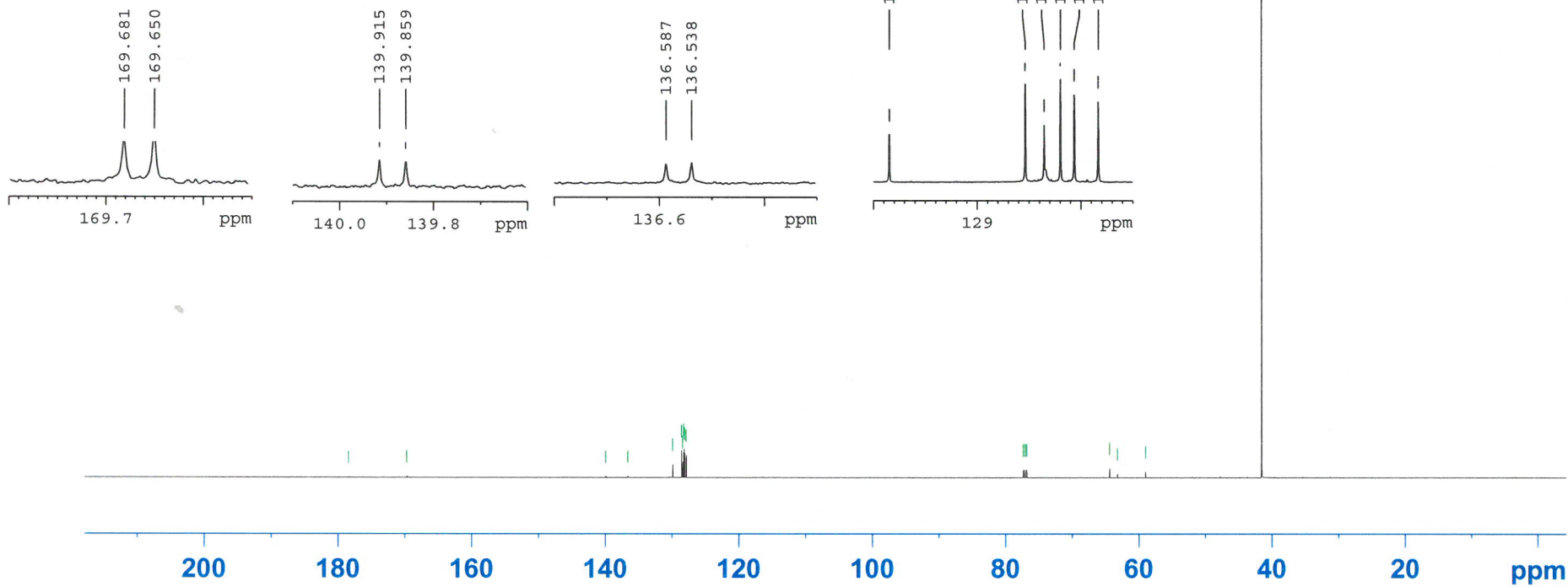
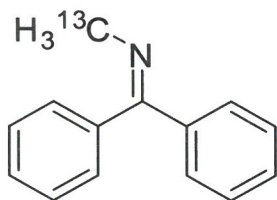


$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

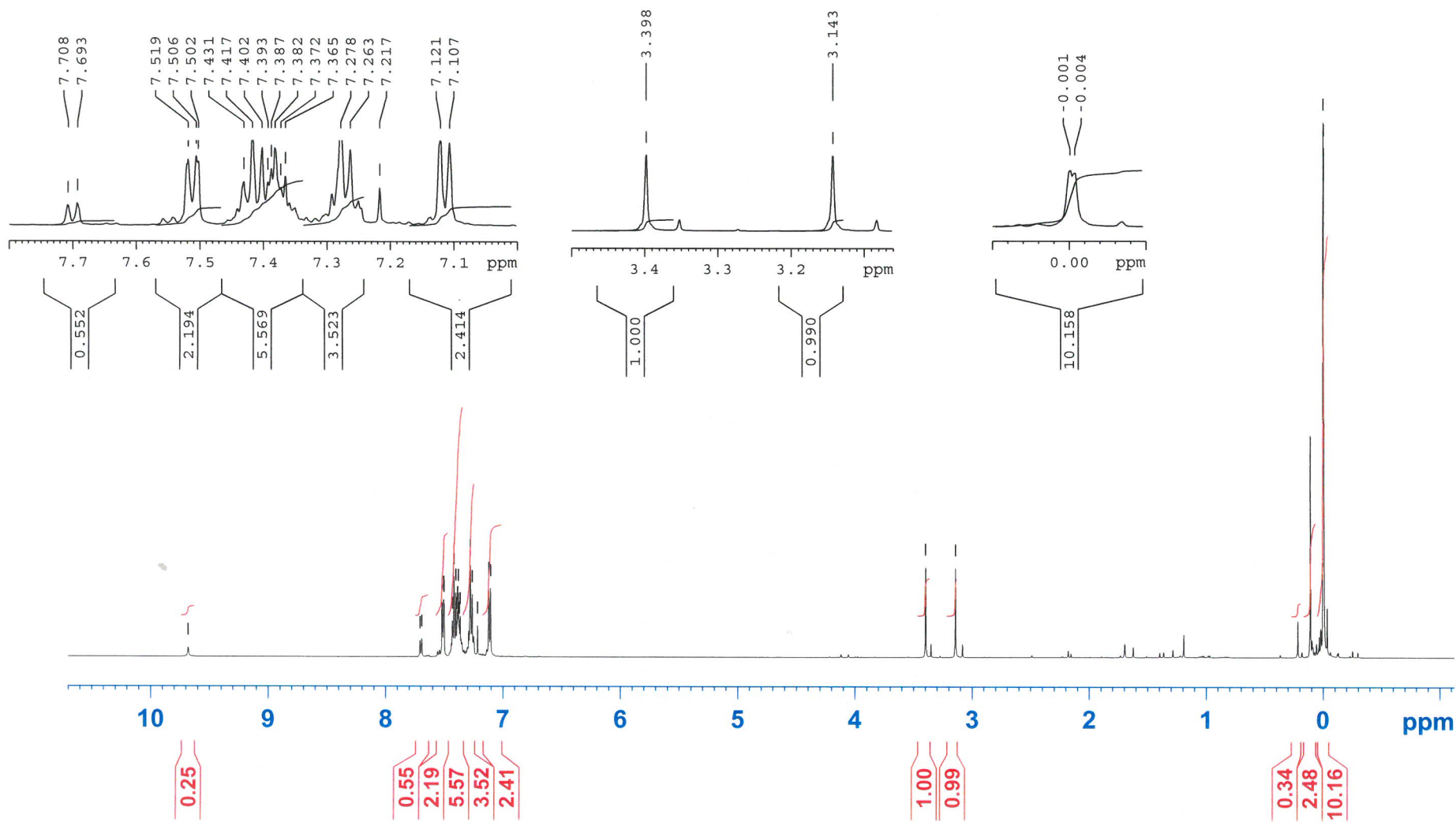
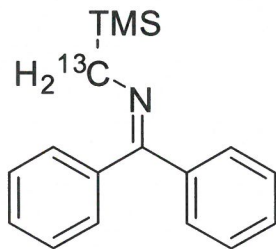




$^{13}\text{C} \{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )



$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



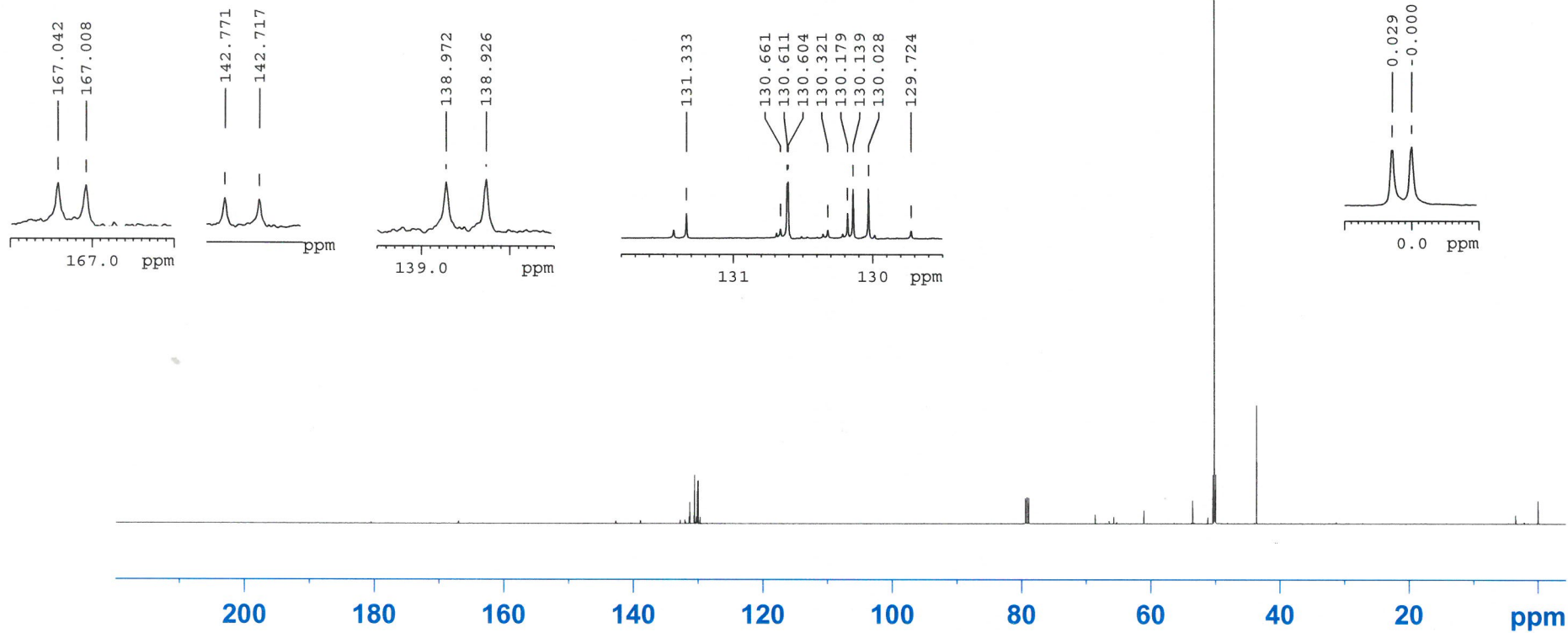
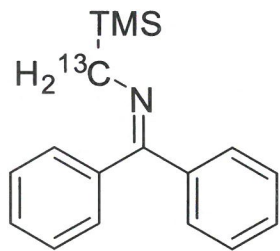
9.68

7.71, 7.69, 7.52, 7.51, 7.50, 7.43, 7.42, 7.40, 7.39, 7.39, 7.38, 7.37, 7.37, 7.28, 7.26, 7.22, 7.12, 7.11

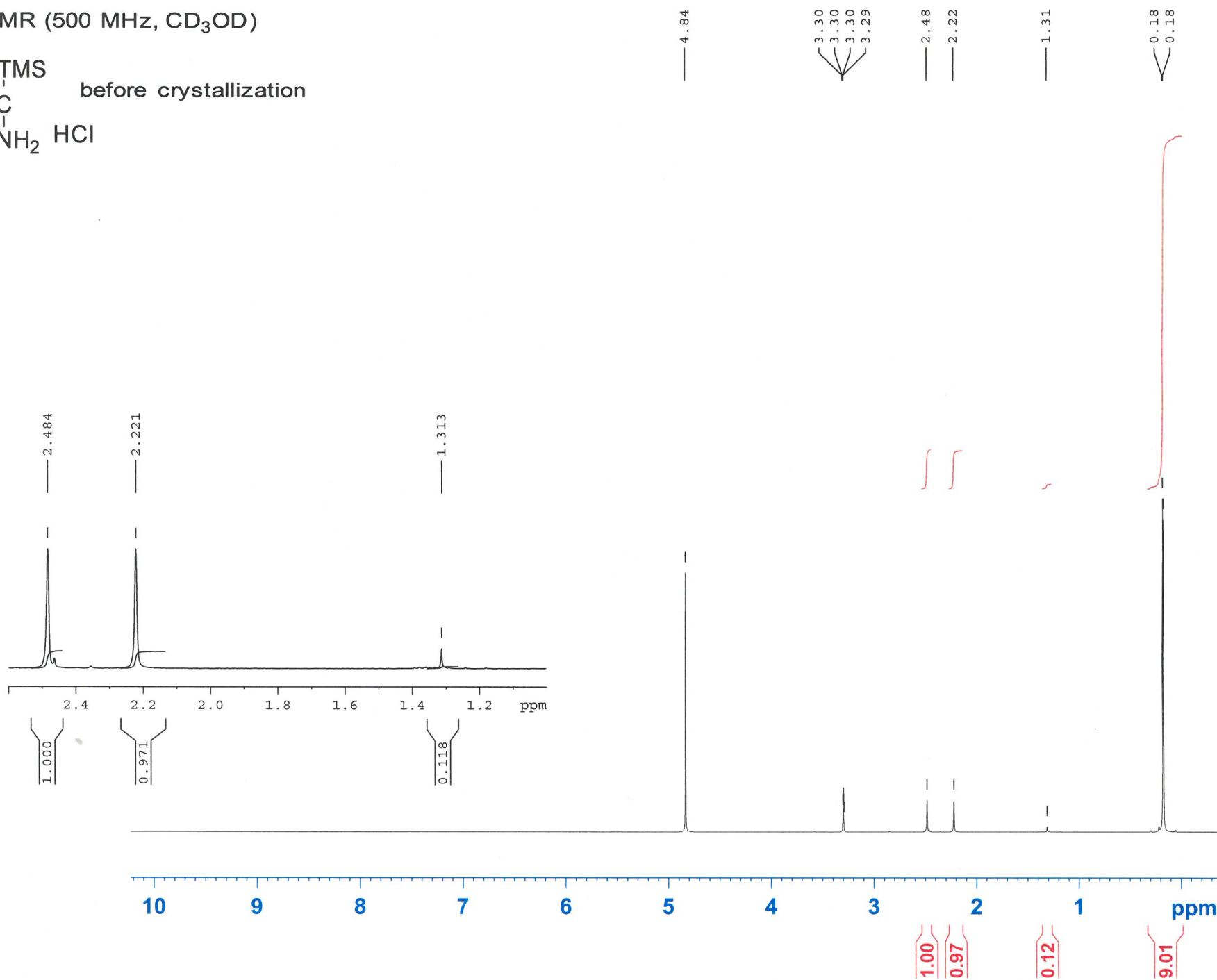
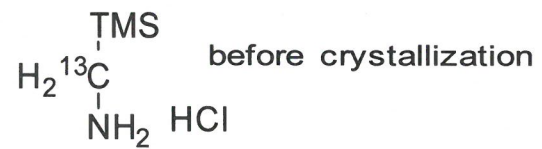
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-0.00, -0.00

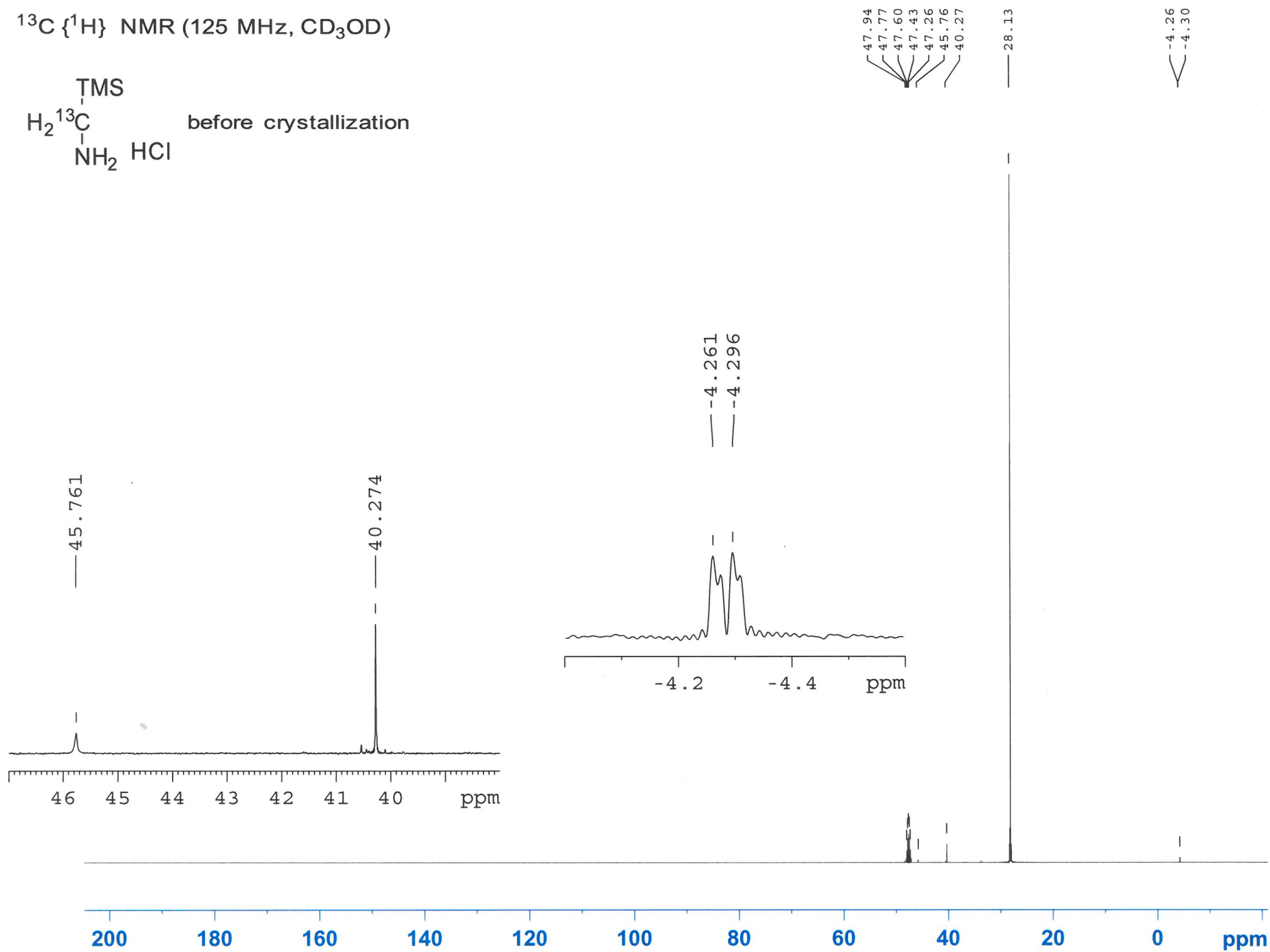
$^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )



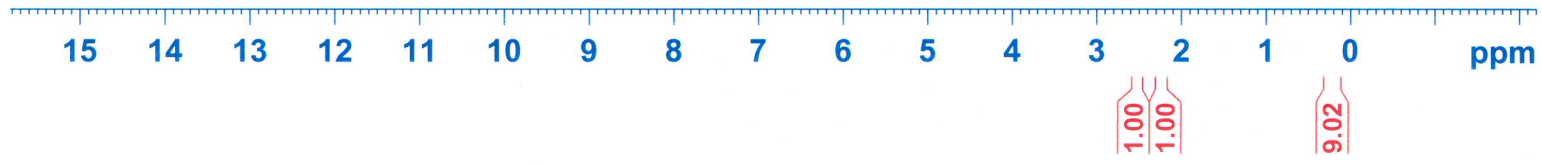
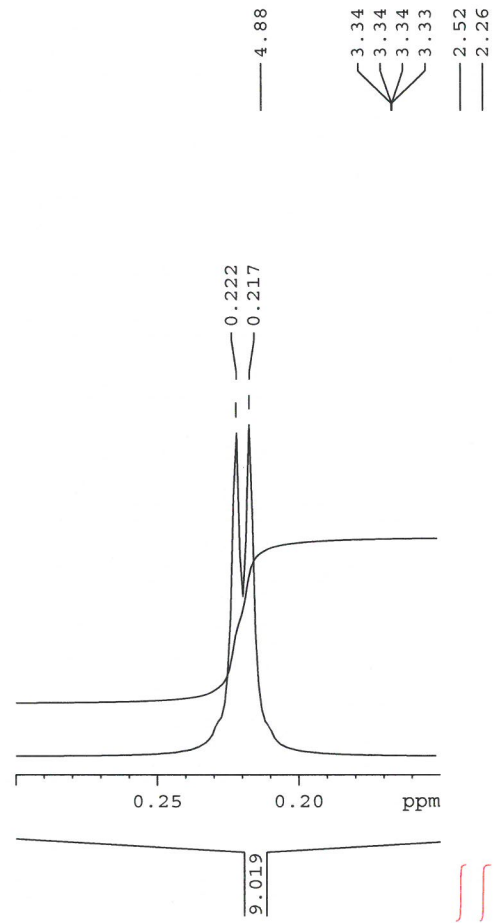
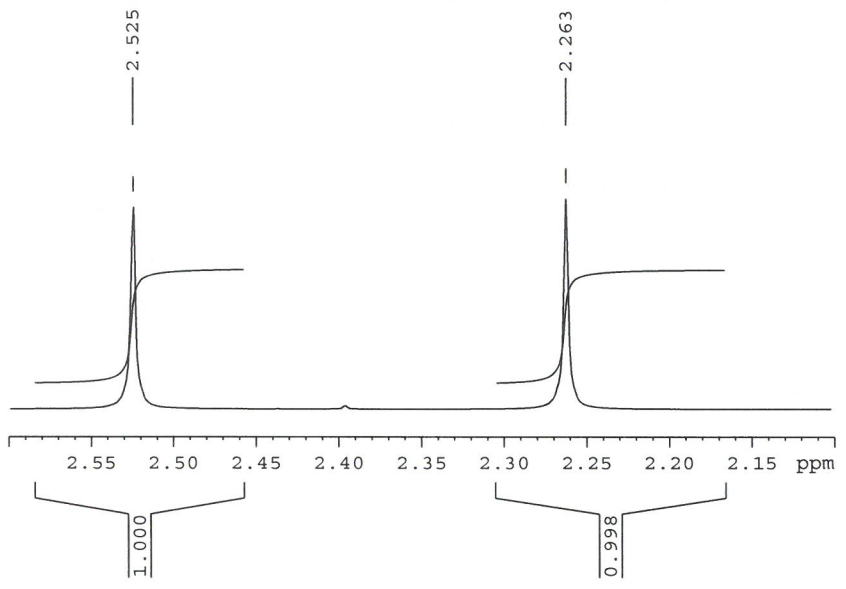
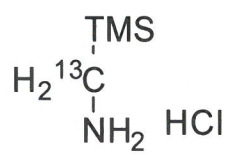
$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )



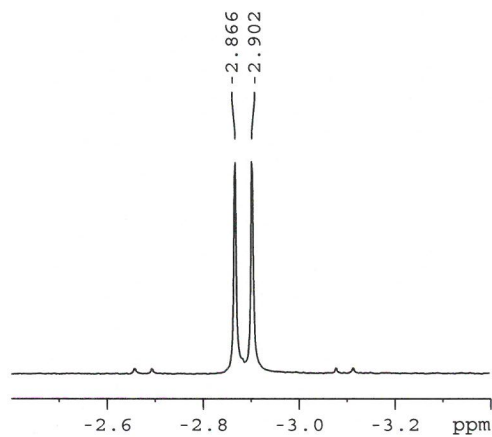
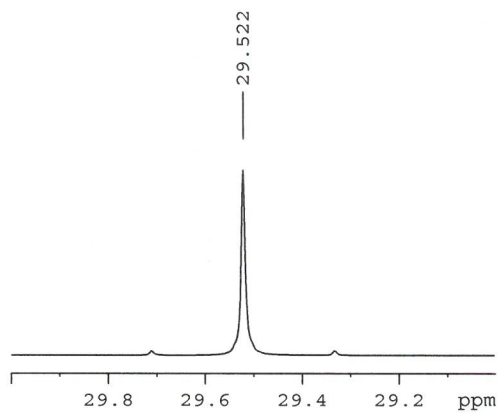
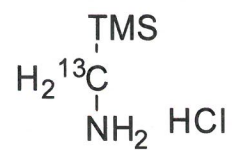
$^{13}\text{C} \{^1\text{H}\}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )



<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)



$^{13}\text{C} \{^1\text{H}\}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )



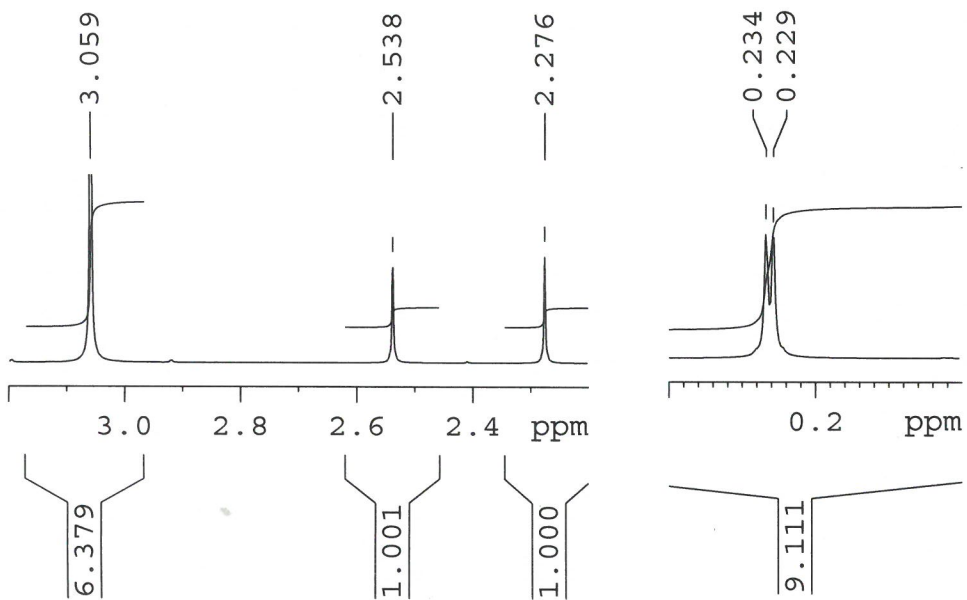
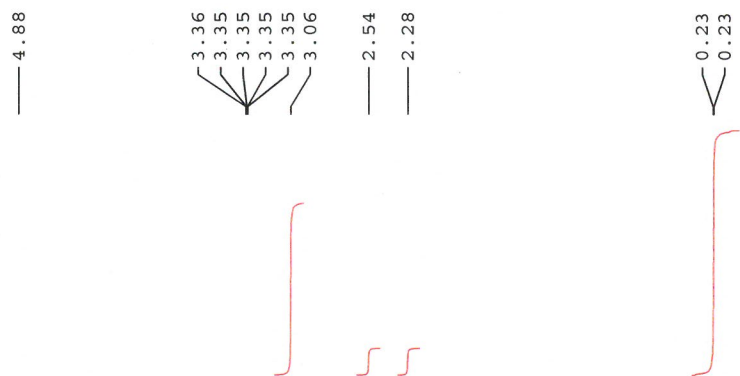
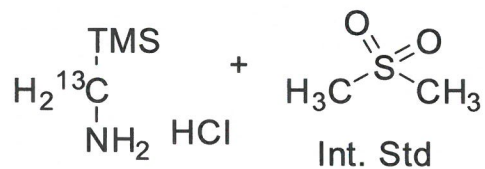
49.50  
49.33  
49.16  
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48.82  
48.65  
48.47

29.52

-2.87  
-2.90



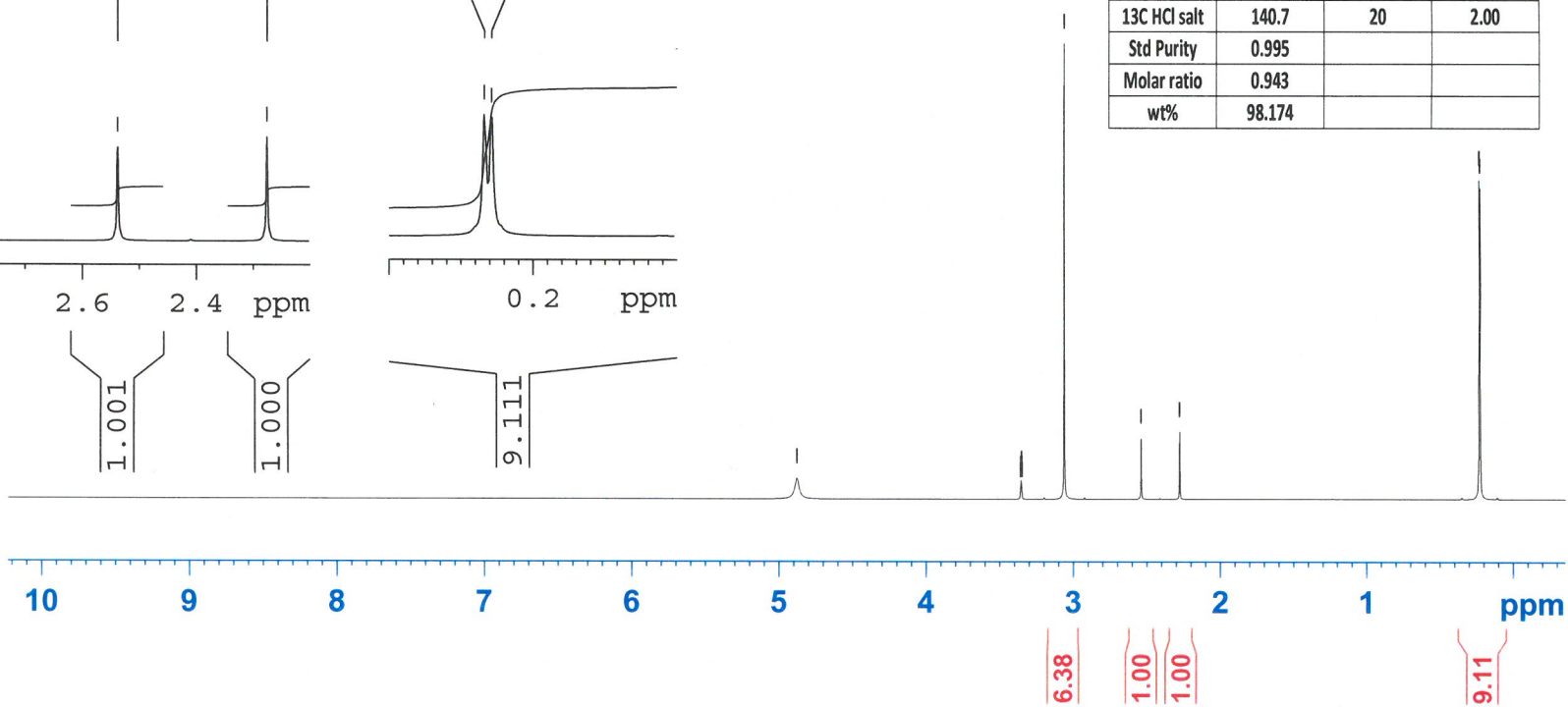
<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)



$$\text{Molar ratio} = \frac{I_{\text{cpd}}/nH_{\text{cpd}}}{I_{\text{std}}/nH_{\text{std}}}$$

$$\text{wt\%} = \frac{[mg_{\text{std}} \times MW_{\text{cpd}} \times \text{molar ratio} \times P_{\text{std}}]}{mg_{\text{cpd}} \times MW_{\text{std}}} \times 100$$

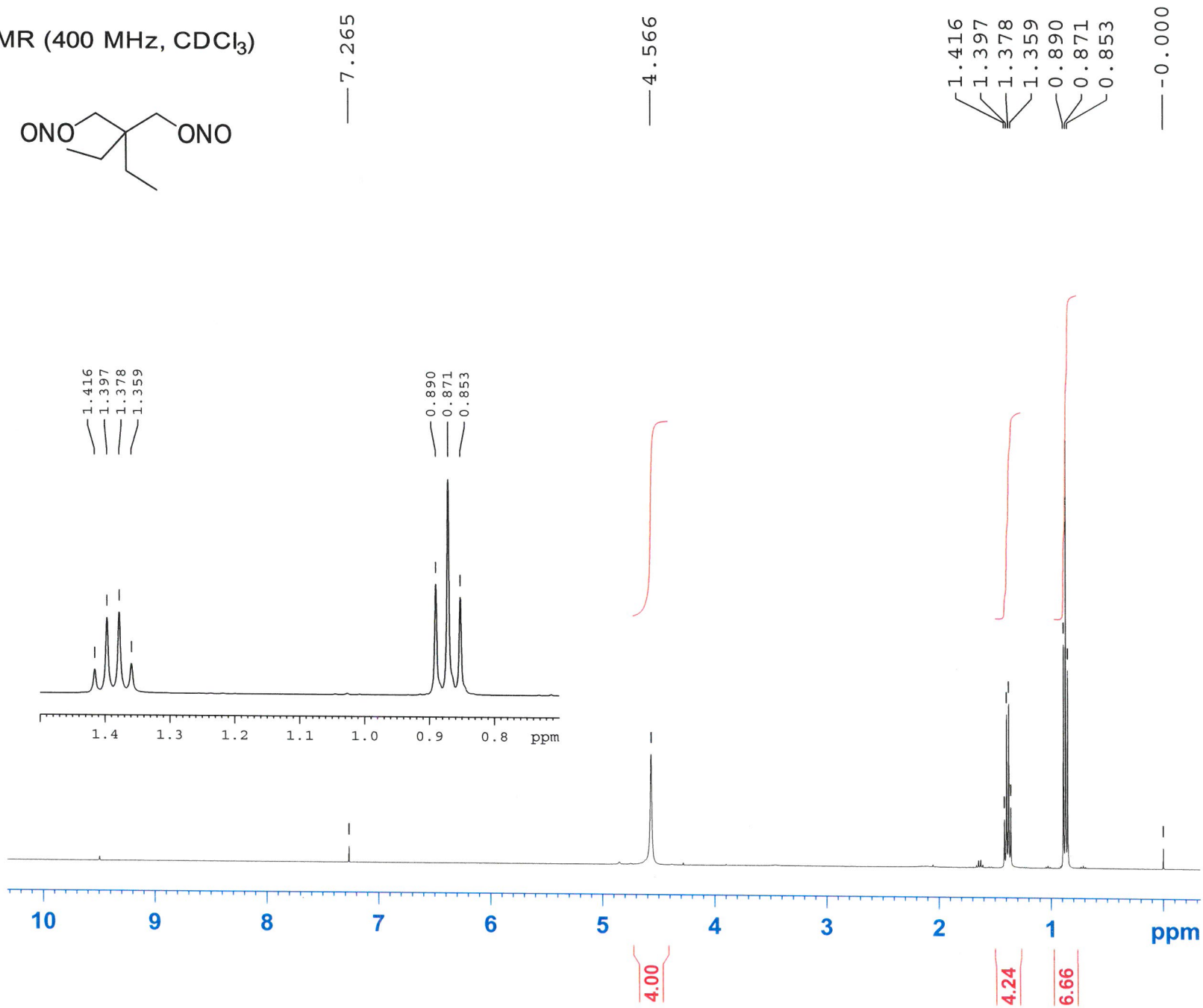
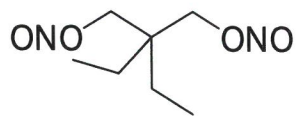
	MW	mg	integral
Me <sub>2</sub> SO <sub>4</sub>	94.13	14	6.38
<sup>13</sup> C HCl salt	140.7	20	2.00
Std Purity	0.995		
Molar ratio	0.943		
wt%	98.174		



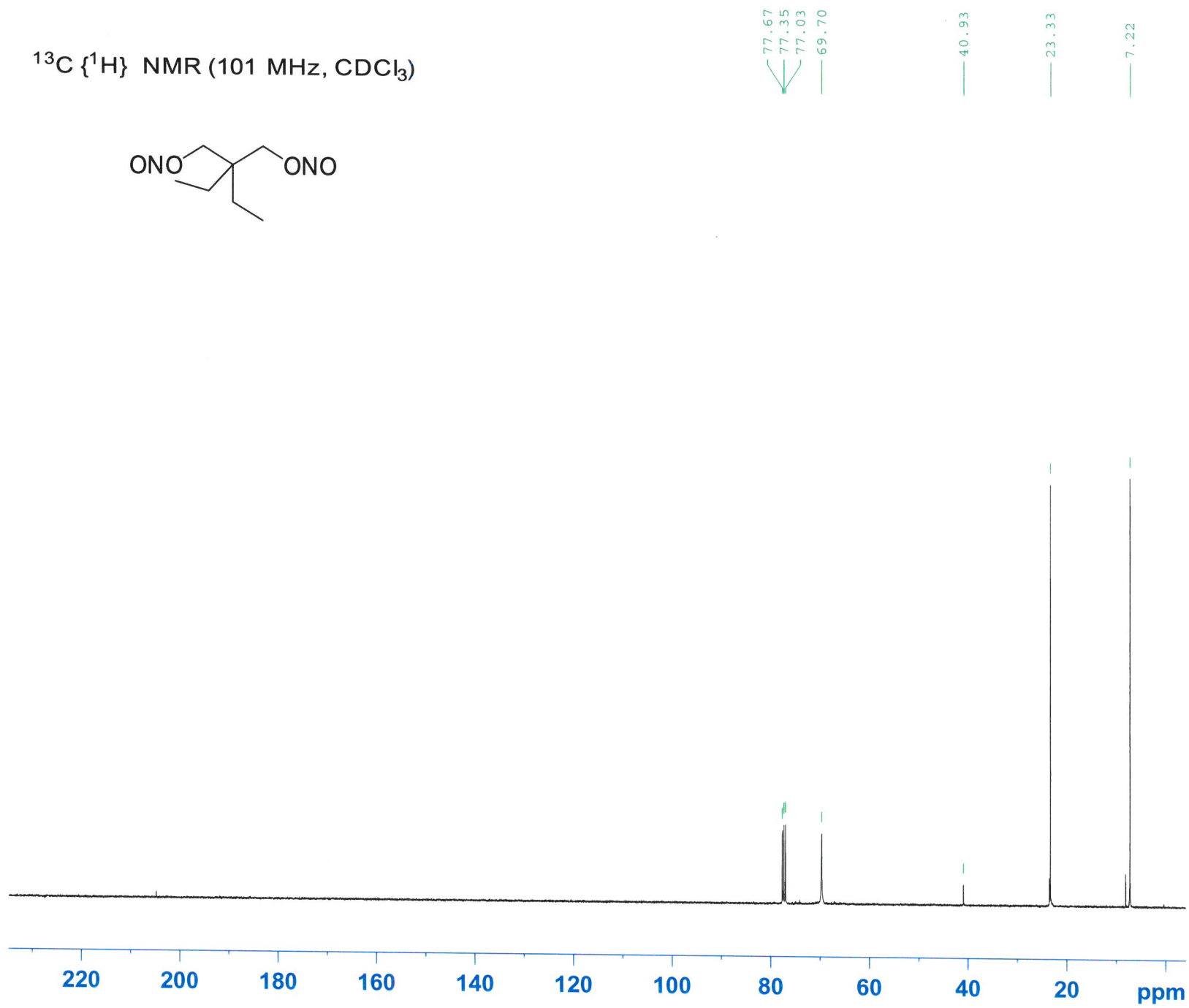
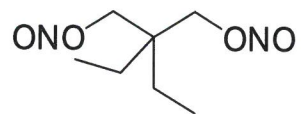
10 9 8 7 6 5 4 3 2 1 ppm



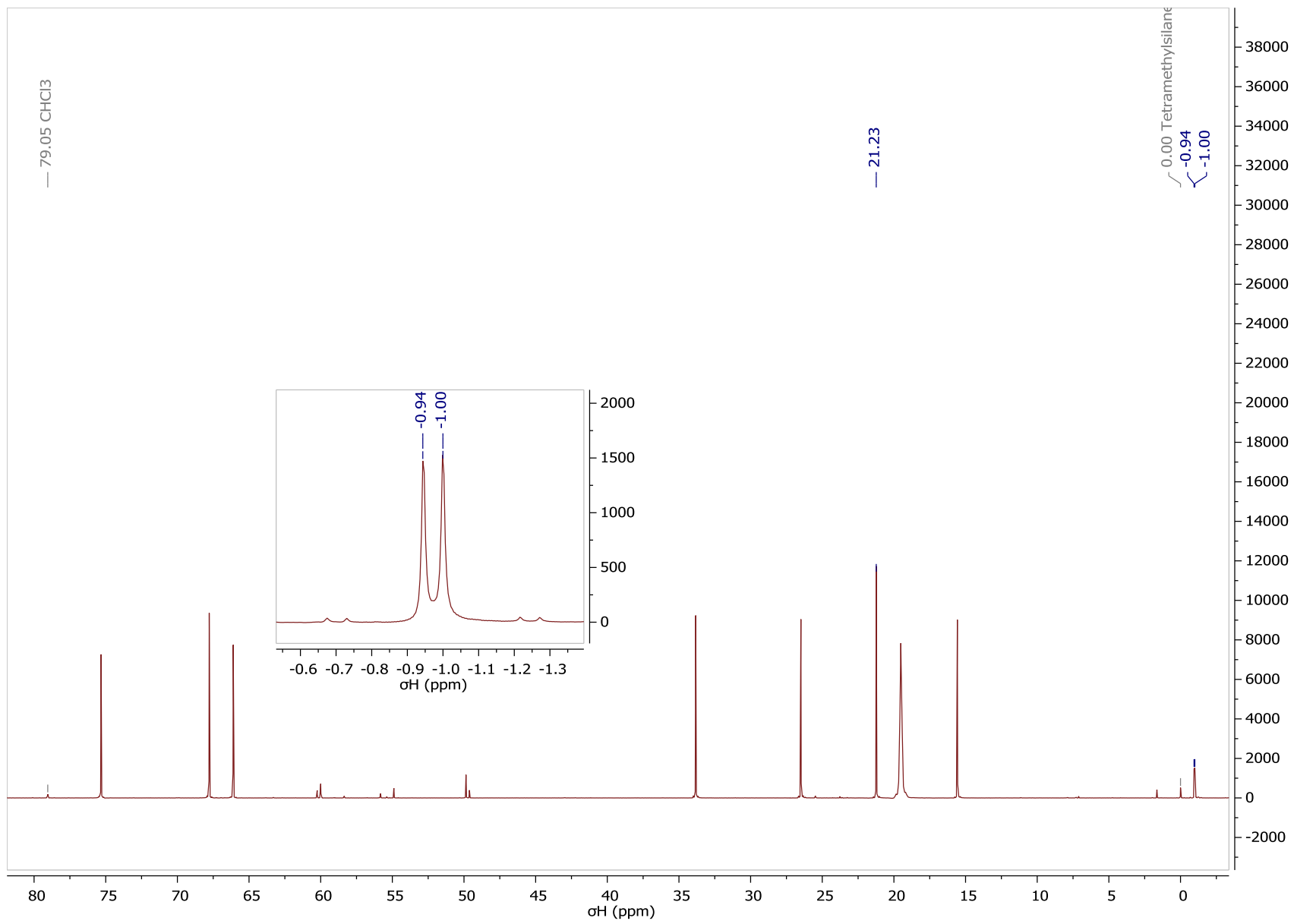
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C} \{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )







$^1\text{H}$  NMR (400 MHz, 2MeTHF/Et<sub>2</sub>O/CDCl<sub>3</sub>)

