N-Methoxy-*N*-methylcyanoformamide

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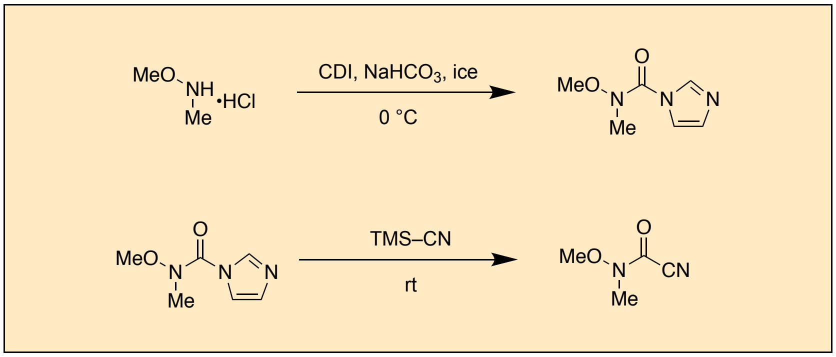
Checked by Luke E. Hanna and Sarah Reisman



Procedure (Note 1)

A. *N-Methoxy-N-methyl-1H-imidazole-1-carboxamide* (**1**). A 1-L conical flask open to the atmosphere is equipped with a large Teflon-coated, octagonal shaped stir bar (51 × 8 mm) then charged with *N*,*O*-dimethylhydroxylamine hydrochloride (20.0 g, 205 mmol, 1.0 equiv) (Note 2), ice (100 g) and sat aq $NaHCO_3$ (100 mL) (Figure 1). The reaction vessel is stirred vigorously and maintained at 0 °C in an ice-water bath, then treated with *N*,*N'* -carbonyldiimidazole (CDI) (5.4 g) in 8 portions over 15 min (43.2 g, 267 mmol, 1.3 equiv) (Notes 3 and 4). The resulting mixture

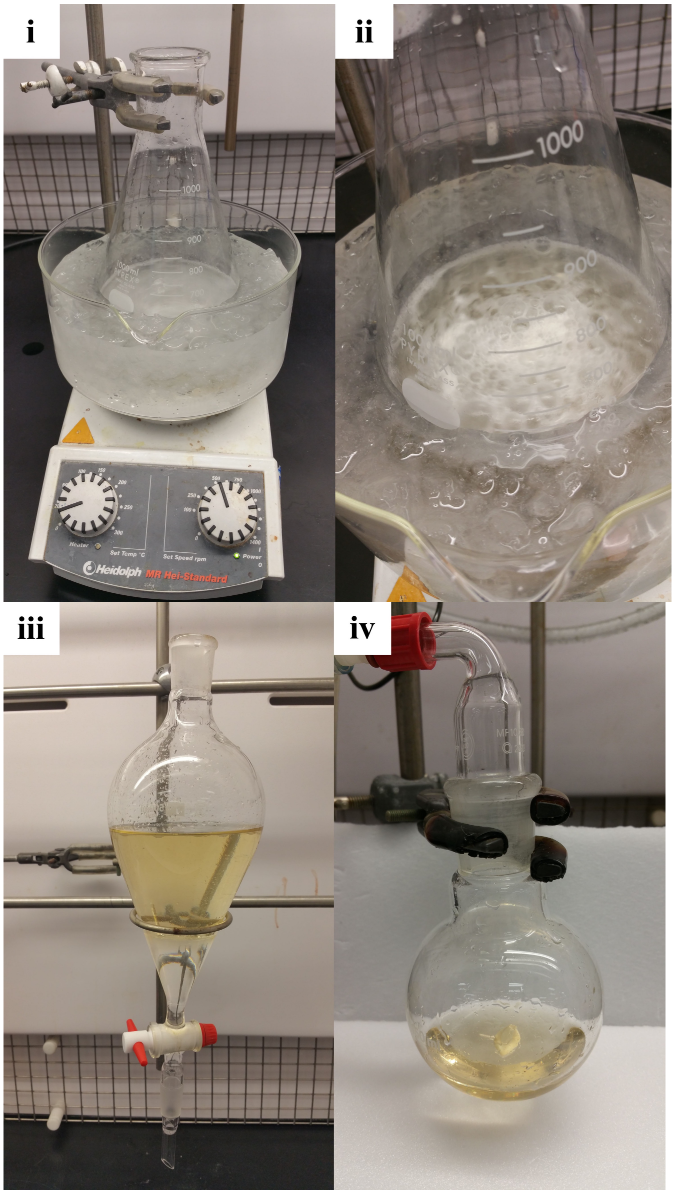


Figure 1. (i) Setup for procedure A; (ii) Release of CO_2 during final stages of addition of CDI; (iii) Separation of layers; (iv) Product 1 after rotary evaporation

is maintained at 0 °C for 1 h, then the mixture is transferred to a 500-mL separatory funnel and extracted with dichloromethane (DCM) (4 × 50 mL) (Note 5). The combined organic phases are washed with brine (1 × 50 mL), transferred to a 500-mL conical flask, and then dried over Na_2SO_4 (22 g) for 10 min. The solution is vacuum filtered, using a cotton wool plug in a glass funnel, into a tared 250-mL round-bottomed flask with a stir bar of known mass. The solution is then concentrated under reduced pressure (40 °C, 430 mmHg, rotary evaporation). The resulting pale-yellow colored oil is stirred vigorously under high vacuum (0.5 mmHg, 19 ºC, 6 h) to remove traces of DCM, which yields *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (**1**) (29.4–30.0 g, 92–94% yield at 97.5% purity) as a lemon-gold colored oil that is used without further purification (Notes 6 and 7).

B. *N-Methoxy-N-methylcyanoformamide* (**2**). A flame-dried 100-mL single-necked, round-bottomed flask equipped with a teflon-coated, egg-shaped stir bar (10 × 19 mm) is fitted with 25-mL pressure-equalizing dropping addition funnel. A glass gas inlet adapter is placed on the top of the addition funnel and connected to a nitrogen-vacuum double manifold (Figure 2). The flask is charged with *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (**1**, 15.5 g, 100 mmol), placed under vacuum (1 mmHg), and backfilled with nitrogen three times. The reaction vessel is cooled to 0 °C and the pressure-equalizing dropping addition funnel is charged with trimethylsilyl cyanide (13.1 mL, 105 mmol, 1.05 equiv) (Note 8). Trimethylsilyl cyanide is then added to the flask dropwise over 5 min. When the addition is complete the ice bath is removed, allowing the reaction vessel to warm to room temperature (19 °C), and stirring is continued at this temperature for 24 h. After 24 h, the red-orange reaction mixture is diluted with DCM (50 mL), equipped with a plastic cap, and cooled to 0 °C in a water and ice bath for 5 min. The mixture is then poured into a 500-mL separatory funnel containing sat aq $NaHCO_3$ (50 mL), ice (50 g) and brine (30 mL). The organic layer is removed after being washed with this mixture and the resulting aqueous layer is again extracted with DCM (5 × 20 mL) (Note 5). The combined organic layers are washed with brine (1 × 40 mL) and dried over anhydrous Na_2SO_4 (22 g). The solution is vacuum filtered, using a cotton wool plug in a glass funnel, into 250-mL round-bottomed flask and concentrated by rotary evaporation (415 mmHg gradually lowering to 215 mmHg, 30–35 °C).

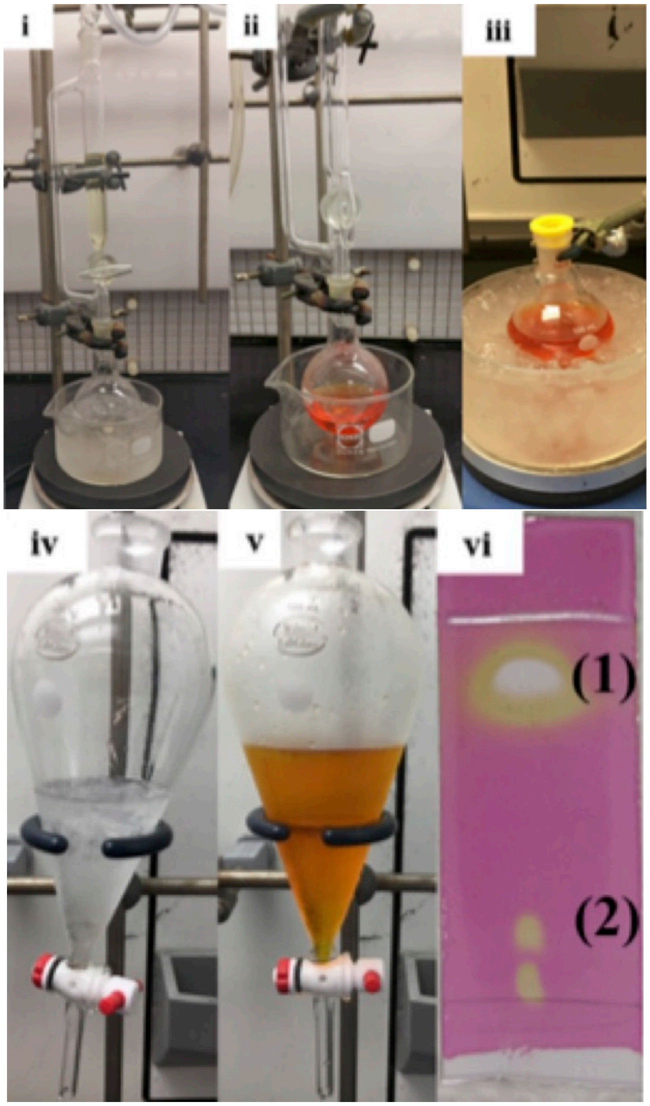


Figure 2. **(i) Setup for procedure B before addition of TMSCN; (ii) 24 h after addition of TMSCN; (iii) reaction after 24 h diluted with DCM and cooled to 0 °C; (iv) Separatory funnel prepared with $NaHCO_3$/ Ice / brine mixture; (v) Crude reaction after first wash with aqueous $NaHCO_3$/ Ice / brine mixture. (vi) TLC analysis of crude reaction mixture after 24 h (elution with diethyl ether): (1) *N*-methoxy-*N*-methylcyanoformamide (2) *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide**

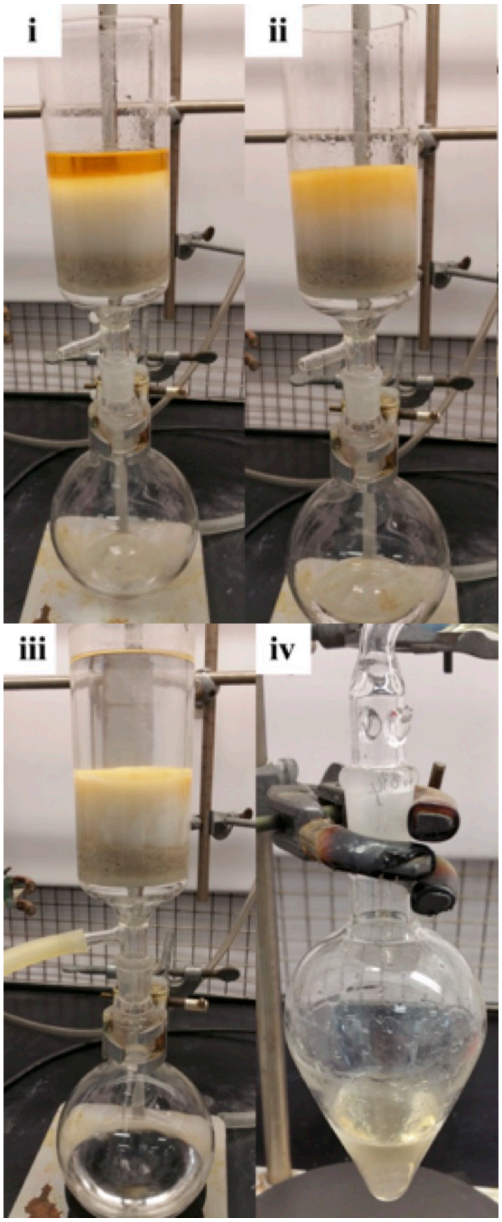


Figure 3. (i) Setup for purification of *N*-methoxy-*N*-methylcyanoformamide (2); (ii) loading; (iii) elution with diethyl ether; (iv) product after rotary evaporation

The residue is dissolved in diethyl ether (20 mL) (Note 9) and the resulting solution loaded onto a pad of silica (55 g, pre-wetted with diethyl ether on top of 10 mm of sand) (Note 10) by pipette in a sintered vacuum funnel (60 mm internal diameter, 350 mL total volume, grade 1 sinter) and eluted through with diethyl ether (400 mL) into a 500-mL round-bottomed flask by gentle vacuum suction (~400 mmHg) and monitored by TLC analysis (Note 11) (Figure 3). The ethereal solution is then concentrated by rotary evaporation (415 mmHg, 35 °C) until approximately 25 mL of the original solution remained then transferred by funnel to a 100-mL pear shaped flask (for convenience). The solution is then concentrated further by rotary evaporation and then at the pump for 4 h (10 mmHg, 18 °C) to remove traces of diethyl ether to afford *N*-methoxy-*N*-methylcyanoformamide **2** (9.5–9.8 g, 83–86% yield at 95.9 % purity) as a pale-yellow, clear, free-flowing oil that can be used without further purification (Notes 12, 13, 14 and 15).

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 *N*,*O*-dimethylhydroxylamine hydrochloride, *N*,*N*' -carbonyldiimidazole, sodium bicarbonate, dichloromethane, silica gel, diethyl ether, sodium sulfate, and trimethylsilyl cyanide. *Trimethylsilyl cyanide is highly toxic*

and flammable. Ensure that trimethylsilyl cyanide is used only in a well-ventilated fumehood with appropriate protective equipment.

2. *N*,*O*-Dimethylhydroxylamine hydrochloride (99%) was purchased from AK Scientific and used as received.
3. *N*,*N*′ -Carbonyldiimidazole (CDI) (98%) was purchased from AK Scientific and used as received.
4. When all *N*,*O*-dimethylhydroxylamine hydrochloride has reacted, addition of excess *N*,*N′* -carbonyldiimidazole results in carbon dioxide evolution. After all portions have been added a small amount of cold water (5 °C, 20-30 mL) is used to rinse the CDI that had stuck to the funnel and sides of the flask. Also, it is important to make sure the CDI is not delivered as large clumps but as powder. This helps insure a constant internal temperature as the reaction is exothermic.
5. Dichloromethane EMSURE, ACS, 99.8% was purchased from Merck and used as supplied.
6. The reaction has been performed three times at the scale described above by the submitters and checkers. On one of these occasions trace amounts (~4%) of imidazole was observed. Spectral data for (**1**) were consistent with reported data.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.39 (s, 3H), 3.68 (s, 3H), 7.06 (s, 1H), 7.57 (t, *J* = 1.4 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 34.7, 61.4, 118.8, 129.5, 137.9, 149.5. HRMS (ESI-TOF, *m*/*z*) calcd for $C_6H_9N_3O_2$ $[M+H]^+$: 156.0768; found; 156.1185; IR (NaCl) 3122, 2979, 2939, 2823, 1691, 1461, 1391, 1226, 734 cm^{-1}.
7. The weight percent (wt%) purity was determined to be 97.5 wt% by quantitative ^{1}H NMR (QNMR) using analytical grade dimethyl fumarate (*TraceCERT*) purchased from Sigma-Aldrich as an internal standard.
8. Trimethylsilyl cyanide (98%) was purchased from Sigma-Aldrich and used as supplied.
9. Diethyl ether was purchased from Honeywell (Burdick and Jackson 99.9%, preservative free) and used after purification through activated alumina using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al*.[4]
10. Silica (Davisil, 40-63 μm) was purchased from Grace and used as supplied. Sand (acid washed, LR) was purchased from UNILAB and used as supplied.

11. Only trace amounts of compound **2** were evident by TLC after elution with 400 mL of diethyl ether. Analysis using diethyl ether elution and staining with potassium permanganate solution, product **2** $R_f = 0.84$.
12. Product **2** after purification through silica contained approximately 2% 1,3-dimethoxy-1,3-dimethylurea.[5] Product **2** has the following physical and spectroscopic data: ^{1}H NMR 97:3 *mixture of rotamers* (400 MHz, $CDCl_3$) δ : 3.25 (s, NCH_3, *major*), 3.49 (s, NCH_3, *minor*), 3.78 (s, OCH_3, *minor*), 3.86 (s, OCH_3, *major*); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 32.4, 63.3, 110.1, 144.2; HRMS (ESI-TOF, *m/z*) calcd for $C_4H_6N_2O_2$ $[M+H]^+$: 115.0508; found; 115.0497; IR (NaCl) 2946, 2237, 1690, 1460, 1395, 1199, 987, 711 cm^{-1}.
13. The weight percent (wt%) purity was determined to be 95.9 wt% by quantitative ^{1}H NMR (QNMR) using analytical grade dimethyl fumarate (*TraceCERT*) purchased from Sigma-Aldrich as an internal standard.
14. If desired, distillation is carried out using a fractional short-path distillation bridge with a 5 cm Vigreux (see Figure 4). Distillation (9.35 g) through a short-path distillation bridge affords compound **2** as colorless free-flowing liquid (8.60 g, 92% at 94.4% purity). Vigorous magnetic stirring is employed throughout the duration of the distillation and a $CO_{2(s)}$ /ethanol trap is in place between the Schlenk line and the vacuum pump. Chilled water is circulated through the condenser and the setup is evacuated to 19 mmHg and heating of the oil bath to 110 °C is initiated. The first ~300 μL of distillate is discarded and the fraction boiling at 81-84 °C, 19 mmHg (25 mbar) is collected into a 25-mL Schlenk flask. Product **2** after distillation contained approximately 2% 1,3-dimethoxy-1,3-dimethylurea.
15. The authors recommend storage below 0 °C under inert, anhydrous conditions, preferably in a Schlenk flask. **CAUTION:** The reagent decomposes slowly[6] on exposure to moisture, presumably releasing HCN, CO_2, and *N*,*O*-dimethylhydroxylamine with potentially a build-up of pressure within the flask. The checkers found **2** to be stable when stored at –19 °C for three months; users should proceed with caution if the reagent is stored for longer periods and should always carefully open storage vessels in a well-ventilated fume hood.

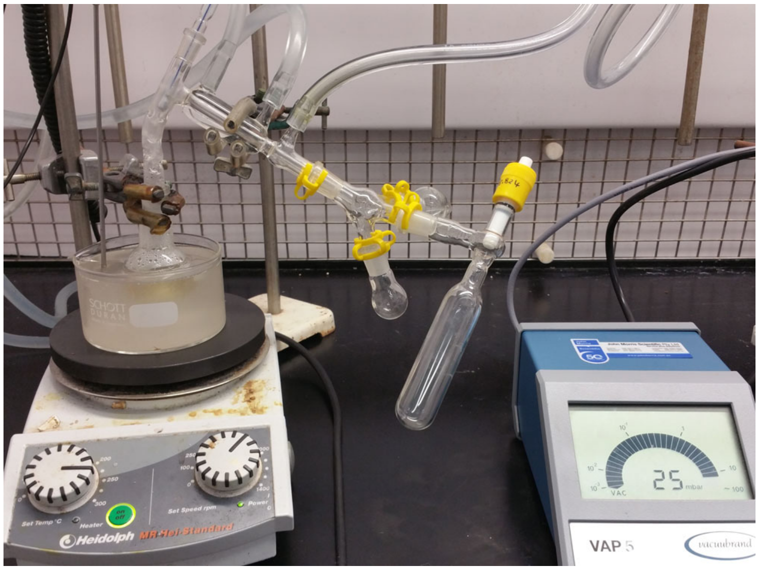


Figure 4. Setup used by submitters for the distillation of compound 2

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.

Discussion

In 1983 Mander and colleagues reported the use of methyl cyanoformate for the selective *C*-acylation of ketone enolates to form *β*-ketoesters.[7] Since this report cyanoformates have been the preferred reagent for this transformation, other reagents regularly give varying amounts of the unwanted *O*-acylation products.[8] In recent times the ethyl,[9] benzyl,[10] and allyl[11] cyanoformates have all been successfully employed for the synthesis of the corresponding *β*-ketoesters in organic synthesis. Despite the popularity and widespread use of cyanoformates the analogous cyanoformamides have never been exploited in the synthesis of *β*-ketoamides from the corresponding ketones.

Recently, our laboratory required a concise synthesis of a *β*-keto Weinreb amide from the corresponding ketone. Our investigations established that the reagents commonly used for the synthesis of Weinreb amides from organometallic reagents were unsuccessful when applied in the reaction of ketone enolates.[6] This prompted our investigation into the reactivity of *N*-methoxy-*N*-methylcyanoformamide, a compound we anticipated would exhibit similar reactivity to the related cyanoformates.

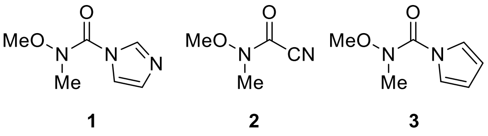
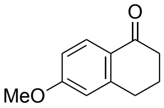
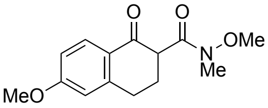
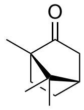
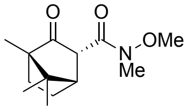
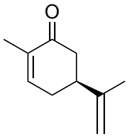
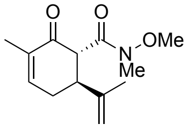
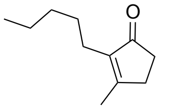
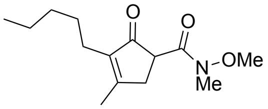
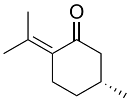
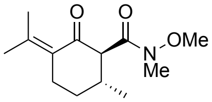
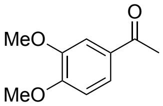
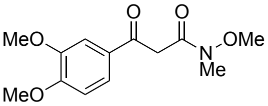
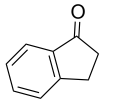
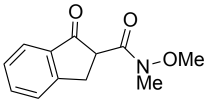
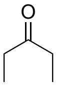
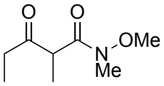
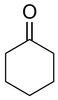
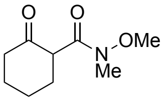


Figure 5. *N*,*O*-Dimethylcarbamoylating reagents

Table 1. ***C*-Carbamoylation of Ketones using *N*-Methoxy-*N*-methylcyanoformamide (2)**

Entry	Substrate	Product	Yield[a]
1			86%
2			87%
3			83%
4			82%
5			93%
6			67%
7			83%
8			77%
9			76%

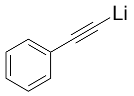
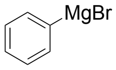
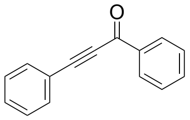
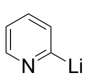
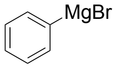
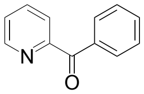
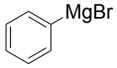
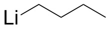
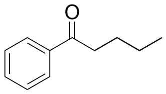
[a] ketone (1.0 mmol), LiHMDS (1.1 mmol), THF, −78 Â°C, 1 h, then **2** (1.1 mmol), −78 Â°C, 0.25 h.

A study was conducted which compared the ability of reagent **2** to react with ketone enolates alongside the imidazole reagent **1** and *N*-methoxy-*N*-methylcarbamoylpyrrole (**3**).[6,12] Although all reagents reacted with ketone enolates, only reagent **2** formed the product *β*-ketoamides rapidly in high yields.

A wide range of lithium enolates, when treated with *N*-methoxy-*N*-methylcyanoformamide, efficiently underwent selective *C*-carbamoylation to form the product *β*-ketoamides in excellent yields (Table 1). Enones, benzylic and aliphatic ketones all reacted in high yields with reagent **2** to give the desired products.

In addition, **2** could serve as a carbonyl dication synthon in the preparation of unsymmetrical ketones, and therefore we sequentially exposed **2** to various organometallic species (Table 2). Excellent yields were obtained in all cases irrespective of the type of organometallic and order of addition. In contrast with *N*-methoxy-*N*-methylcarbamoylpyrrole (**3**)[12] the selective monoaddition of reagent **2** with sp^2-hybridized Grignard reagents is also possible (Entry 3, Table 2).

Table 2. Unsymmetrical Ketone Synthesis using N-Methoxy-N-methylcyanoformamide (2)

Entry	First Nucleophile	Second Nucleophile	Product	Yield[a]
1				89%
2				86%
3				86%

[a]Organolithium reagents were added at –78 °C and organomagnesium reagents were added at 0 °C.

The procedure reported herein was derived from our original communication[6] and is both operationally simple and requires a minimal amount of purification. The ease of synthesis of **2** coupled with the efficiency, high reactivity and versatility of the reaction of compound **2** with enolates and organometallics suggests that this reagent is an excellent addition to the synthetic chemist's toolbox.

References

1. Research School of Chemistry, The Australian National University, Canberra, ACT 2601, Australia. Email: brett.schwartz@anu.edu.au. BDS is indebted to Dr Keats Nelms (Beta Therapeutics Pty Ltd), Prof. Martin Banwell (The Australian National University) and Assoc. Profs. Mark Coster and Rohan Davis (Griffith Institute for Drug Discovery). JN is grateful to the Australian Government for an APA scholarship.
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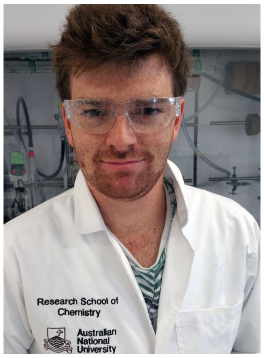
Appendix
Chemical Abstracts Nomenclature (Registry Number)

N,*O*-Dimethylhydroxylamine hydrochloride: Methanamine, *N*-methoxy-, hydrochloride; (6638-79-5)

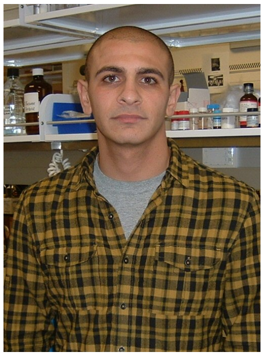
N,*N'*-Carbonyldiimidazole: 1*H*-Imidazole, 1,1'-carbonylbis-; (530-62-1)

Trimethylsilyl cyanide: Silanecarbonitrile, trimethyl-; (7677-24-9)

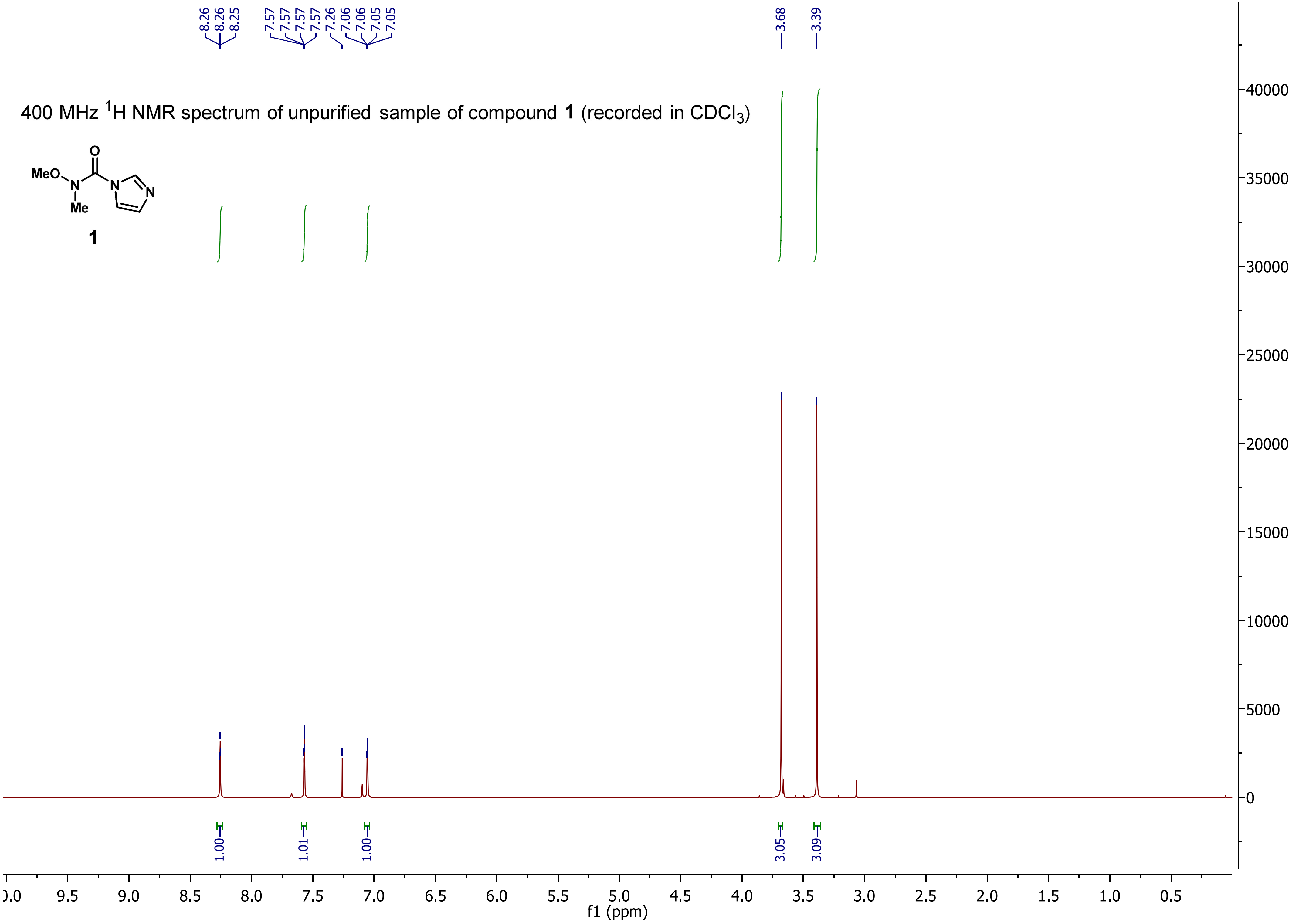


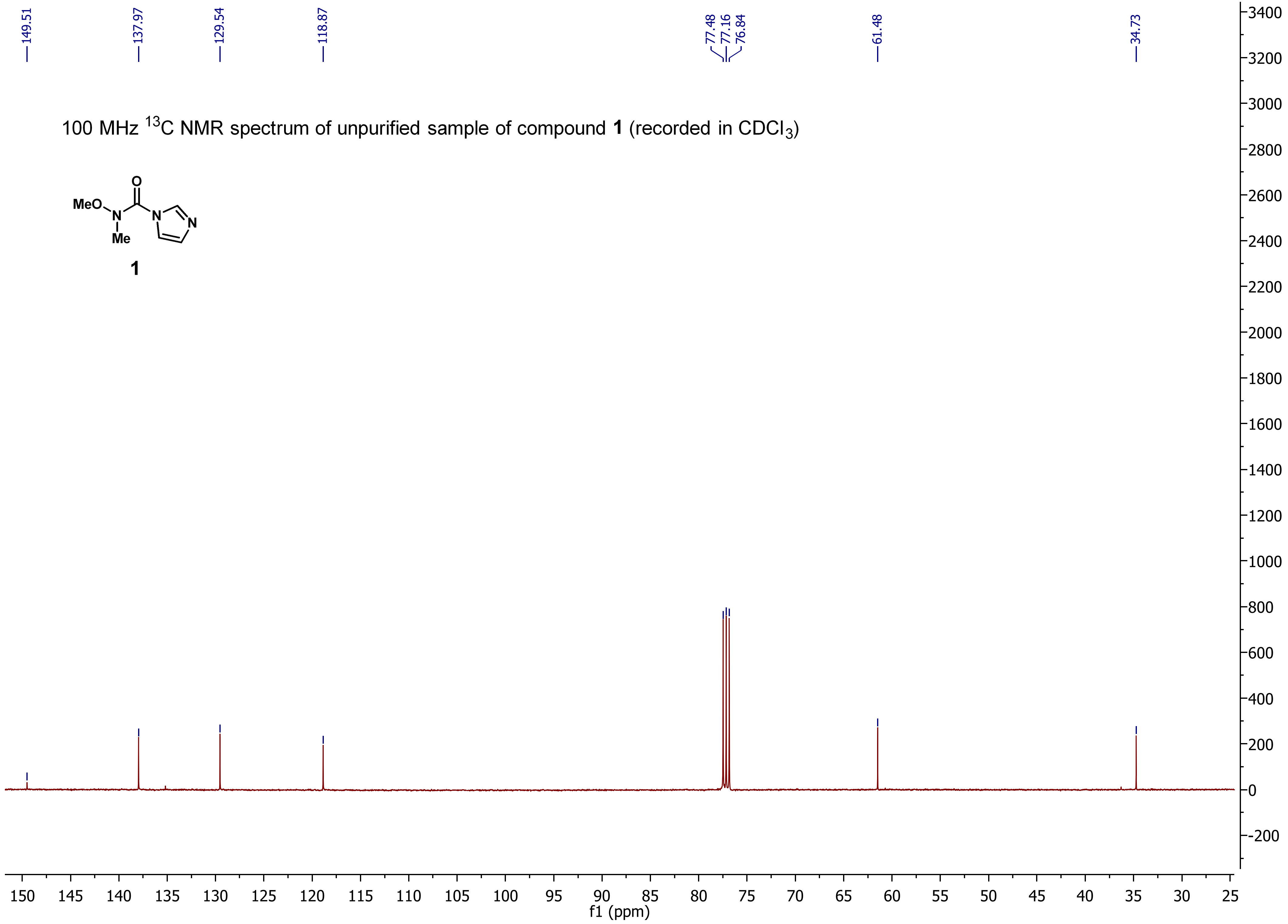
Jeremy Nugent received his undergraduate degree from The Australian National University, Canberra. He is currently undertaking his postgraduate studies in the Research School of Chemistry at The Australian National University under the direction of Professor Martin Banwell and Dr. Brett D. Schwartz. The main focus of Jeremy's current research is the development of new strategies for the synthesis of biologically active natural products.

Brett D. Schwartz received his Ph. D. in organic chemistry in 2005 under the supervision of Professor James J. De Voss at The University of Queensland. After more than a decade of post-doctoral research he now resides as a Senior Fellow at The Australian National University in Canberra.



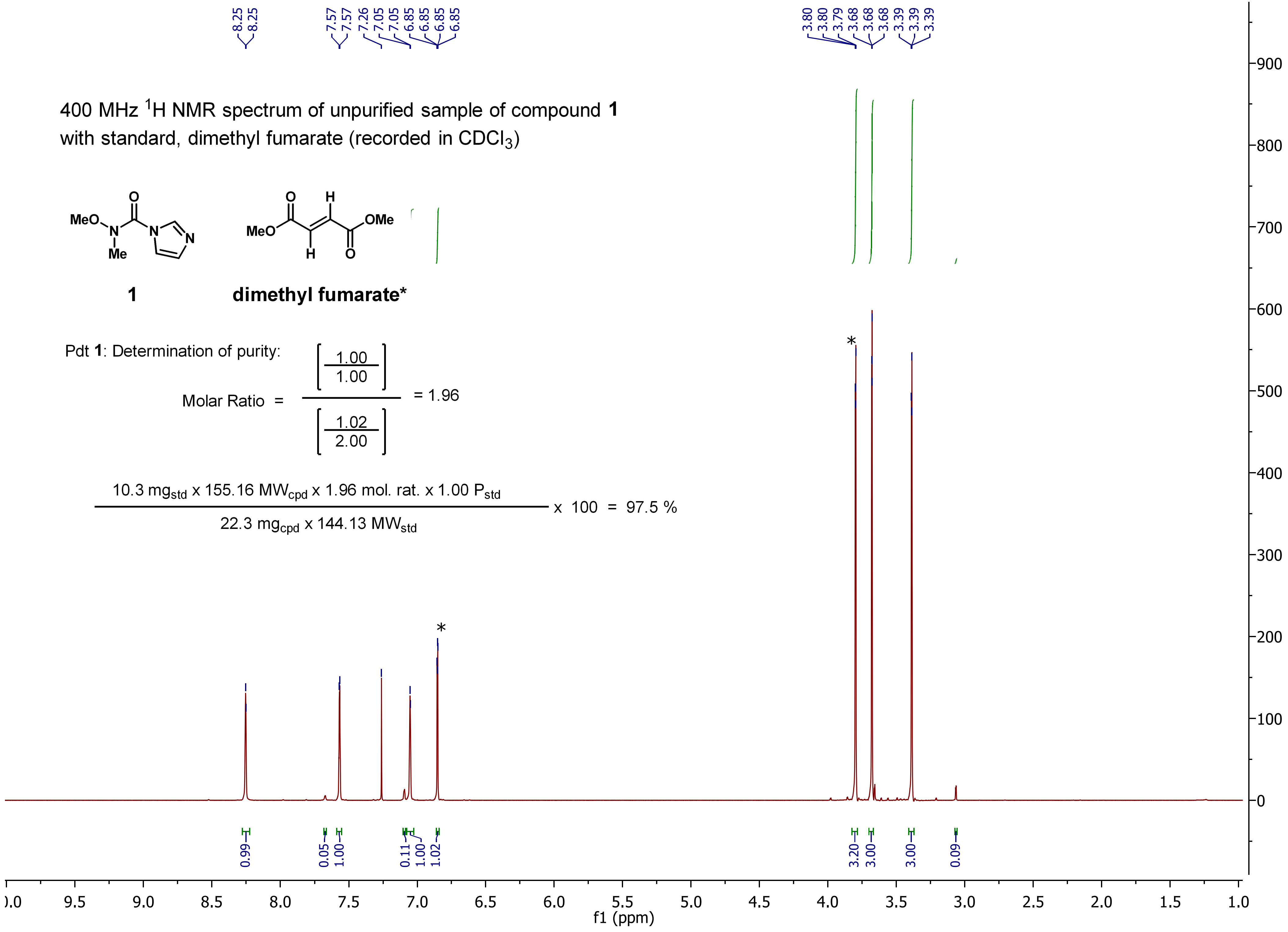
Luke E. Hanna received Ph.D. in organic chemistry in 2016 under the supervision Elizabeth R. Jarvo at the University of California, Irvine. He is currently carrying out postdoctoral studies at the California Institute of Technology studying the total synthesis of natural products in the research group of Professor Sarah E. Reisman.


400 MHz ^{1}H NMR spectrum of unpurified sample of compound **1** (recorded in $CDCl_3$)



100 MHz ^{13}C NMR spectrum of unpurified sample of compound **1** (recorded in $CDCl_3$)

400 MHz ^{1}H NMR spectrum of unpurified sample of compound **1** with standard, dimethyl fumarate (recorded in $CDCl_3$)



1

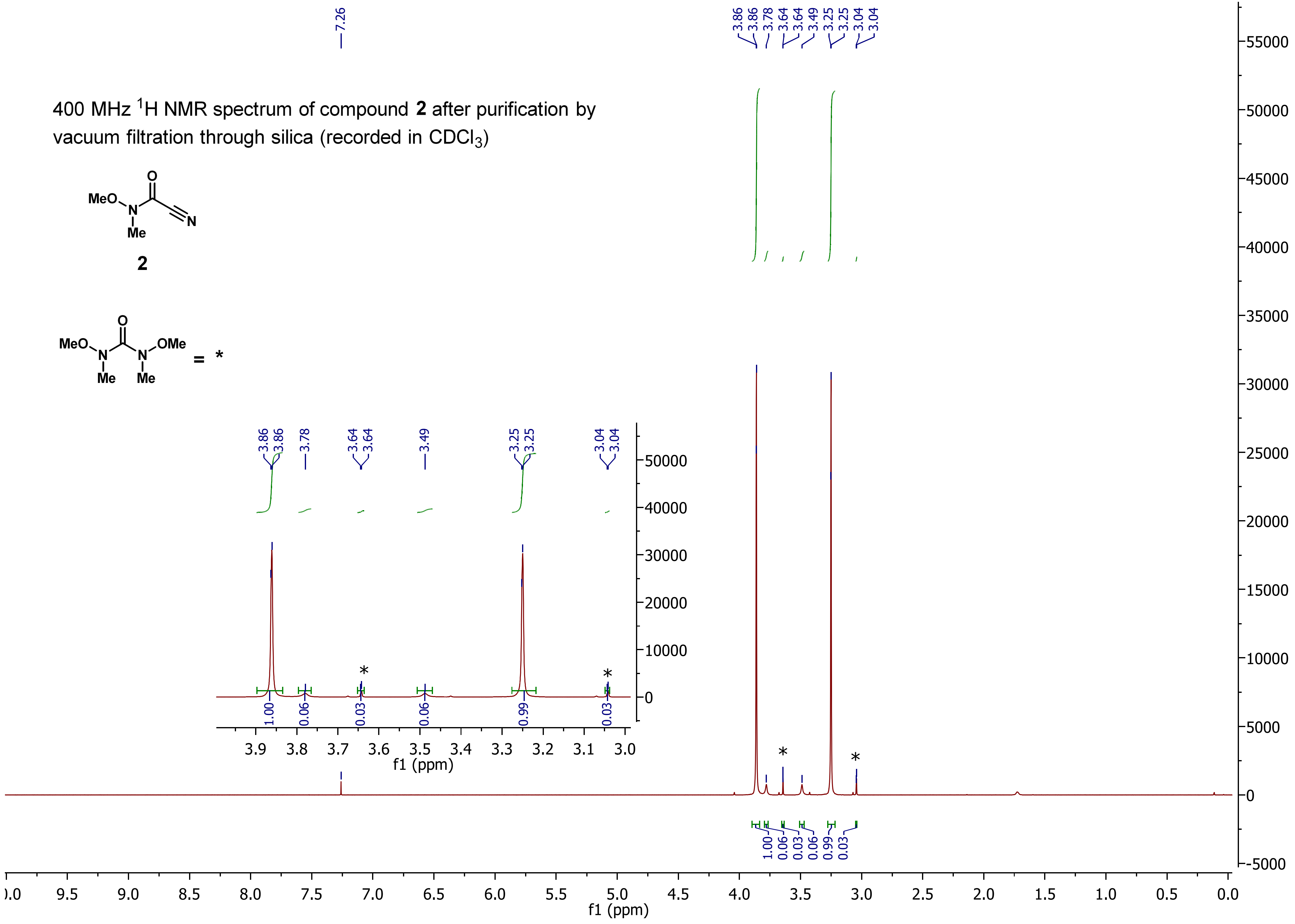
dimethyl fumarate*

Pdt **1**: Determination of purity:

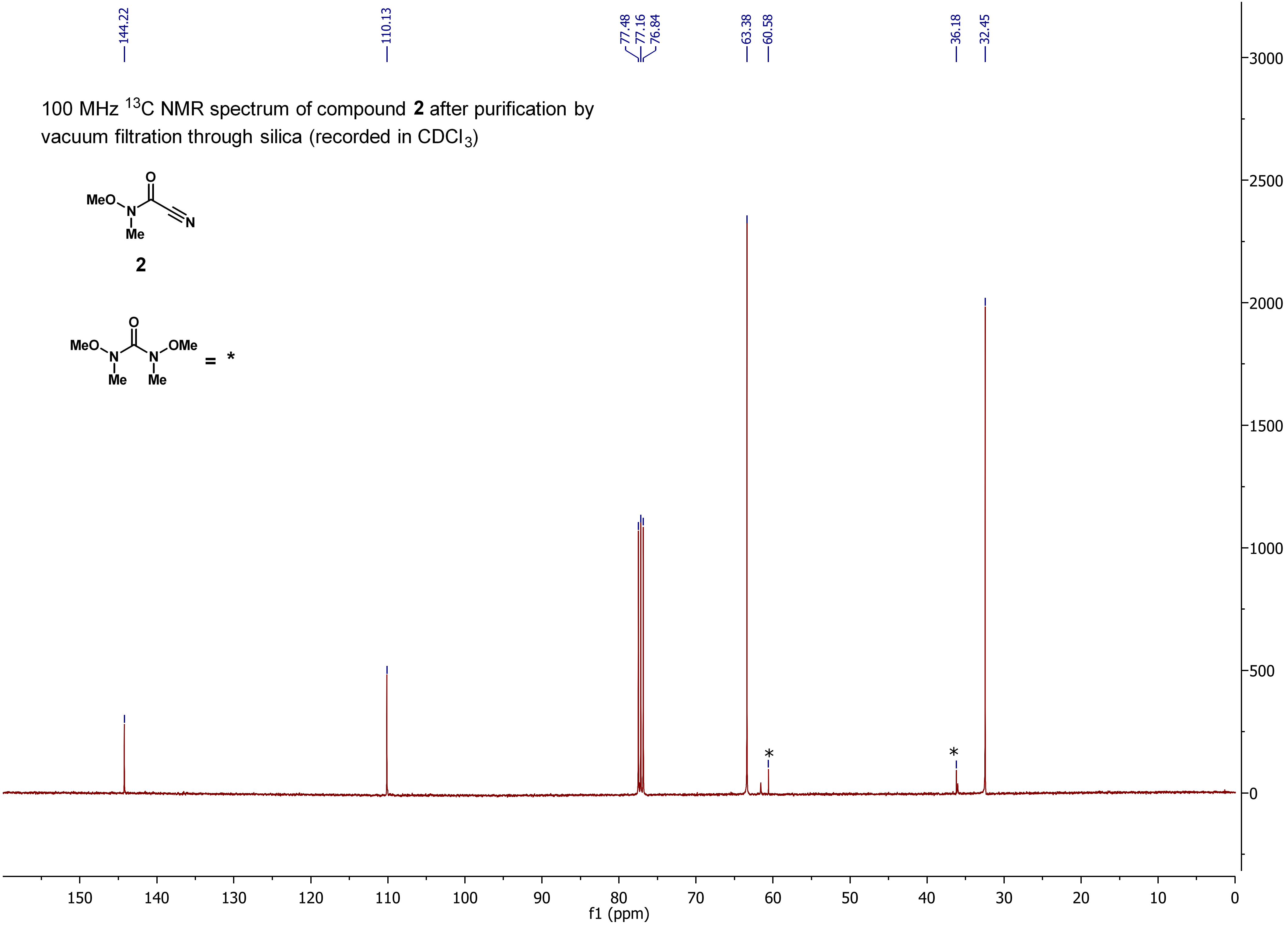
$$\text{Molar Ratio} = \frac{\left[\dfrac{1.00}{1.00}\right]}{\left[\dfrac{1.02}{2.00}\right]} = 1.96$$

$$\frac{10.3\ \text{mg}_{\text{std}} \times 155.16\ \text{MW}_{\text{cpd}} \times 1.96\ \text{mol. rat.} \times 1.00\ \text{P}_{\text{std}}}{22.3\ \text{mg}_{\text{cpd}} \times 144.13\ \text{MW}_{\text{std}}} \times 100 = 97.5\ \%$$

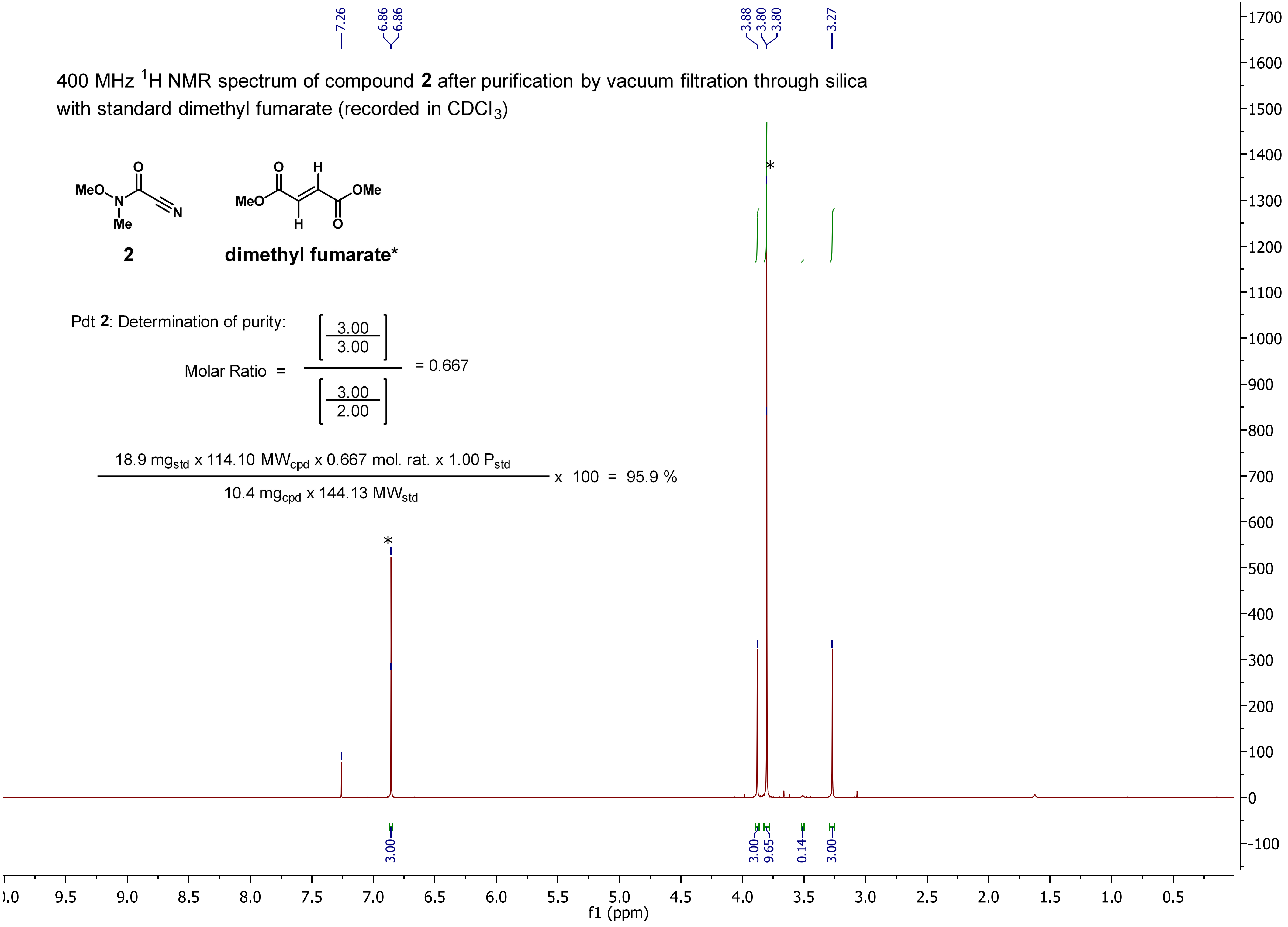
400 MHz ^{1}H NMR spectrum of compound **2** after purification by vacuum filtration through silica (recorded in $CDCl_3$)



100 MHz ^{13}C NMR spectrum of compound **2** after purification by vacuum filtration through silica (recorded in $CDCl_3$)



400 MHz ^{1}H NMR spectrum of compound **2** after purification by vacuum filtration through silica with standard dimethyl fumarate (recorded in $CDCl_3$)



2

dimethyl fumarate*

Pdt **2**: Determination of purity:

$$\text{Molar Ratio} = \frac{\left[\dfrac{3.00}{3.00}\right]}{\left[\dfrac{3.00}{2.00}\right]} = 0.667$$

$$\frac{18.9\ \text{mg}_{std} \times 114.10\ \text{MW}_{cpd} \times 0.667\ \text{mol. rat.} \times 1.00\ \text{P}_{std}}{10.4\ \text{mg}_{cpd} \times 144.13\ \text{MW}_{std}} \times 100 = 95.9\ \%$$