N-(Benzyloxy)-*N*-(pivaloyloxy)-4-(trifluoromethyl)-benzamide

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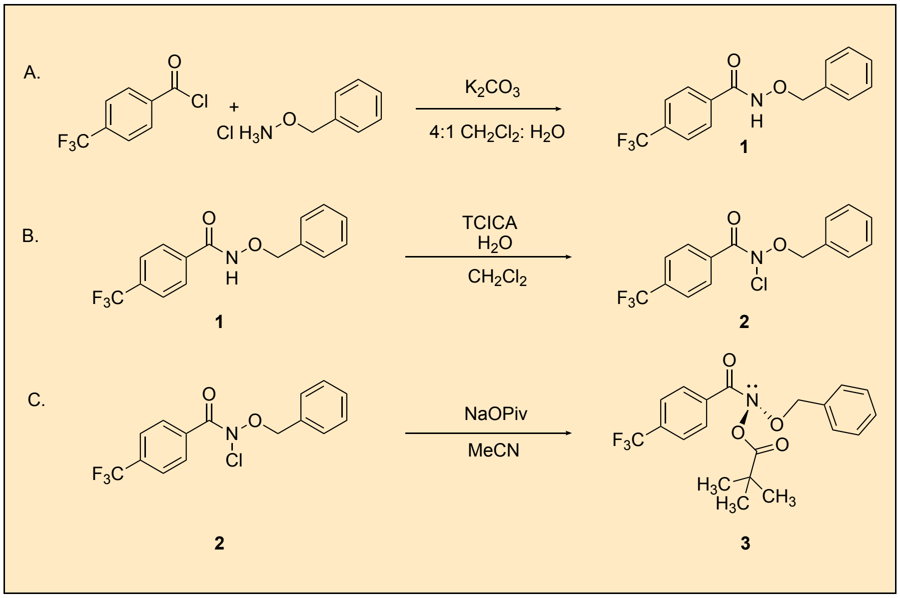
Checked by Yinuo Zheng and Pauline Chiu



Procedure (Note 1)

A. *N-(Benzyloxy)-4-(trifluoromethyl)benzamide (**1**)*. In air, an oven-dried 500 mL round-bottomed flask (24/40 joint) equipped with a 3 x 1.5 cm Teflon-

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coated egg-shaped stir bar is charged with *O*-benzyl hydroxylamine hydrochloride (9.98 g, 62.5 mmol, 1.0 equiv) (Note 2), CH_2Cl_2 (170 mL) (Note 3), and de-ionized water (50 mL). To the suspension, potassium carbonate (17.29 g, 125 mmol, 2.0 equiv) Note 4) is added in one portion, and the mixture is stirred in the open air. The flask is immersed in an ice/water bath and stirred for 15 min at 0 °C (Note 5). An oven-dried 125 mL addition funnel (24/40 joint) is attached to the flask and charged with *p*-trifluoromethyl benzoyl chloride (9.30 mL, 62.6 mmol, 1.0 equiv) (Note 6). The addition funnel is stoppered with a septum. The addition funnel is purged with argon by connecting to an argon manifold with a needle (18 G), and via another needle (18 G) to a gas outlet terminating in an oil bubbler. The neat *p*-trifluoromethyl benzoyl chloride is added dropwise over 10 min while stirring at 0 °C, and the atmosphere is maintained under a slightly positive pressure of argon for the duration of the addition (Figure 1A). A white precipitate rapidly appears. The addition funnel is rinsed with CH_2Cl_2 (3 x 10 mL), and each rinse is added to the reaction flask. Once the addition is complete, the addition funnel is removed. The flask is closed with a septum equipped with a needle to a gas outlet terminating in an oil bubbler, and the reaction is removed from the ice bath (Figure 1B). The reaction is stirred for five h at room temperature (Notes 7 and 8). The CH_2Cl_2 is removed by rotary evaporation (Notes 9 and 10) and diethyl ether (100 mL) is added (Note 11) to the resulting water suspension. The mixture is vacuum-filtered using a 250 mL (7.0 cm diameter) Büchner funnel lined with two filter paper circles moistened with deionized water; the funnel is attached to a 250 mL side-arm filter flask using a rubber filter adaptor. The white solids in the funnel are washed with diethyl ether (50 mL), followed by de-ionized water (2 x 50 mL), each time breaking the solids in the filter with a spatula and mixing thoroughly before applying the vacuum. The filter cake is washed with additional diethyl ether (50 mL) to afford a white solid (Figure 1C). The solids are transferred to a tared 125 mL round-bottomed flask using a spatula. The product is dried under vacuum (Note 12) at 70 °C overnight to yield **1** as a white powder (Figure 1D) in 89% yield (16.4 g, 55.4 mmol) (Notes 13, 14, and 15).

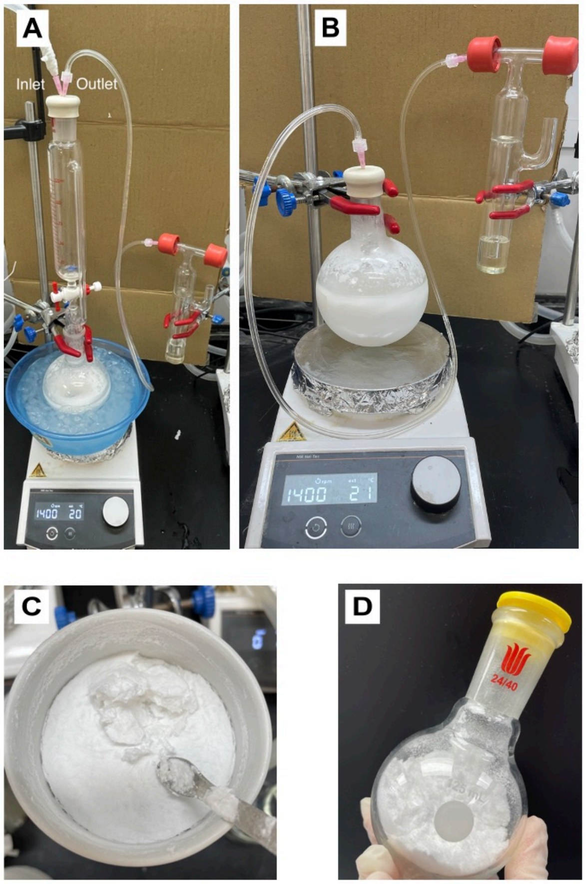


Figure 1. A) Reaction set-up, B) Reaction after addition of *p*-trifluoromethyl benzoyl chloride, C) Product after filtration, D) Final dried product (Photos provided by the checkers)

B. *N-(Benzyloxy)-N-chloro-4-(trifluoromethyl)benzamide* (**2**). In air, an oven-dried 250 mL round-bottomed flask (24/40 joint) equipped with a 3 x 1.5 cm Teflon-coated egg-shaped stir bar, is charged with **1** (5.0 g, 16.9 mmol, 1.0 equiv), CH_2Cl_2 (40 mL, 0.42 M) (Note 3) and de-ionized water (915 μl, 50.8 mmol, 3.0 equiv) (Note 16). The flask is immersed in an ice-bath and stirred for 5 min at 0 °C (Note 16) to form a white suspension. The flask is wrapped in aluminum foil (Note 17) and re-submersed in the ice-bath. Trichloroisocyanuric acid (1.97 g, 8.47 mmol, 1.5 equiv) (Note 18) is added to the flask portion-wise over 15 min (Note 19) while stirring at 0 °C. Once the addition is complete, the flask is stoppered with a septum equipped with a needle (18G) to a gas outlet terminating in an oil bubbler, and the reaction is stirred for 1.5 h at 0 °C (Notes 20 and 21) (Figure 2A). The CH_2Cl_2 is removed by rotary evaporation (Notes 9 and 22) to yield the crude product as a yellow solid. Pentane (50 mL) (Note 23) and a 3 x 1.5 cm Teflon-coated egg-shaped stir bar are added to the flask. The contents are stirred for 2 min at room temperature (Note 7) to form an even mixture of a yellow solution with white suspended solids (Note 24). The mixture is vacuum filtered using a 60 mL fritted filter funnel (24/40 joint), packed with Celite® 3 cm in height (Note 25) attached to a 250 mL round-bottomed receiver flask (Figure 2B). The white solids (excess TCICA and byproducts) are collected in the fritted filter funnel, and the reaction flask is rinsed with additional pentane (2 x 40 mL), which is subsequently passed through the fritted filter funnel. Pentane is removed from the receiver flask by rotary evaporation to dryness (Note 23). Product **2** is obtained as a pale, yellow solid (Notes 26 and 27) (Figure 2C), which is taken forward immediately to Step C (Note 28).

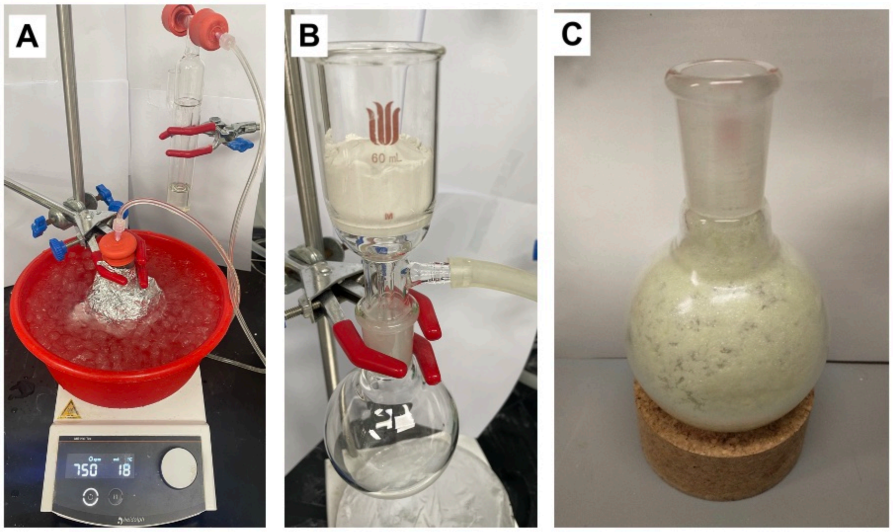


Figure 2. A) Reaction set-up after addition of TCICA, B) Filtration set-up, C) Isolation of product 2. (Photos A and B provided by the checkers, photo C provided by the submitters)

C. *N-(Benzyloxy)-N-(pivaloxy)-4-(trifluoromethyl)benzamide (**3**).* Anhydrous sodium pivalate is dried overnight in a vacuum oven (23 mmHg, 100 °C). In air, an oven-dried 200 mL pear-shaped Schlenk flask (24/40 joint; hose adaptor with PTFE stopcock) (Note 29) equipped with a 3 x 1.5 cm Teflon-coated egg-shaped stir bar is charged with the vacuum oven-dried sodium pivalate (3.15 g, 0.0254 mol, 1.5 equiv) (Note 30). The Schlenk flask is sealed with a rubber septum. The flask is attached to the Schlenk line via its hose adaptor and vacuum tubing (Note 31). The flask is evacuated and refilled with argon to obtain an inert atmosphere (Notes 32 and 33). The septum is pierced with a needle (18G) to connect to a gas outlet terminating in an oil bubbler. Dry, degassed acetonitrile (50 mL) (Note 34) is transferred to the Schlenk flask under an inert atmosphere using a 30 mL plastic syringe equipped with a needle (Note 35). The flask containing the white solids and acetonitrile is submersed in an ice-water bath and stirred vigorously (Note 5) for 30 min to form a white suspension equilibrated to 0 °C (Figure 3A). Acetonitrile (40 mL) (Note 34) is added to the 250 mL round-bottomed flask (24/40 joint) from Step B containing product **2** to form a yellow solution. The 250 mL round-bottomed flask and Schlenk flask are covered with aluminum foil (Note 36). The round-bottomed flask is sealed with a septum, which is pierced with a vent needle and an inlet needle attached to an argon line (Note 37) (Figure 3B). The solution is thoroughly sparged with argon gas for 15 min, and the vent needle is subsequently removed. Under a positive inert atmosphere, the degassed solution of **2** is added slowly to the cooled, vigorously stirred Schlenk flask over a period of 10 min via an oven-dried cannula (Note 38) to form a yellow solution with white suspended solids. The round-bottomed flask is rinsed with additional acetonitrile (2 x 5 mL) (the total volume of solvent is 100 mL, reaction concentration of 0.17 M), which is transferred to the Schlenk flask under a positive inert atmosphere using the cannula. The reaction is *vigorously* stirred (Note 5) at 0 °C under a positive flow of argon gas for 2 h (Note 39). In air, the white suspension is vacuum filtered through a plug of silica 2 cm in height (Notes 40 and 41) using a 60 mL fritted filter funnel with a 24/40 joint attached to a 500 mL round-bottomed flask (Figure 3C). White solids (sodium chloride) are collected in the frit, and the flask is rinsed with diethyl ether (100 mL) (Note 11), which is subsequently poured through the silica plug. The solvents are removed by rotary evaporation (Note 10). The residue is transferred from the 500 mL round-bottomed flask to a tared 100 mL round-bottomed flask, and the 500 mL flask is rinsed with additional diethyl ether (2 x 10 mL), which is transferred to the 100 mL flask. The solvents are removed by rotary evaporation (Note 10). The resulting oil is placed under high vacuum at room temperature (Note 7) for 2 h to yield **3** (Notes 42 and 43) as a clear oil (Figure 3D) in 93% yield (6.26 g, 15.8 mmol yield across two steps, calculated from amount of **1** used in Step B) (Note 44). Storage of **3** at 5 °C results in a waxy, off-white solid (Figure 3E) after 24 – 48 h (Note 45).

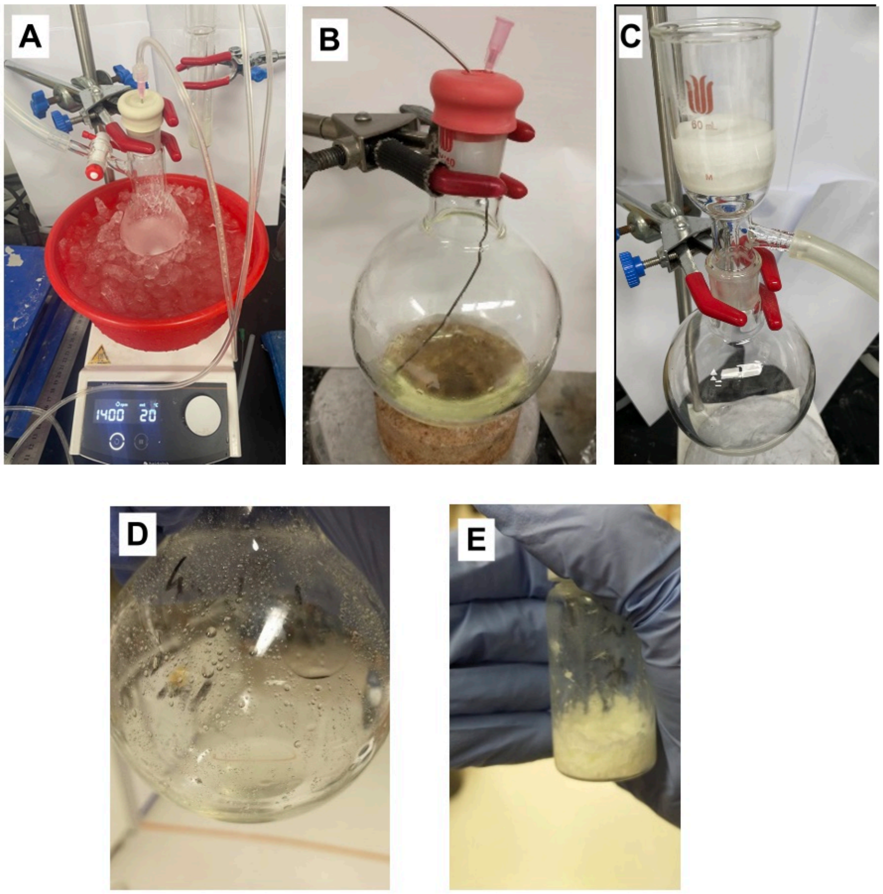


Figure 3. A) Schlenk flask set-up, B) Sparging set-up of the solution of 2, C) Filtration of product, D) Product 3 after rotary evaporation, E) Product 3 after storage at 5 °C for 48 h (Photos A and C provided by the checkers; Photos B, D, and E provided by the submitters)

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 *O*-benzyl hydroxylamine hydrochloride, *p*-trifluoromethyl benzoyl chloride, sodium carbonate, trichloroisocyanuric acid, dichloromethane, diethyl ether, pentanes, sodium pivalate and acetonitrile. Special caution should be taken with the storage and handling of **3**, as a DSC has shown that it decomposes when heated.[2] Additionally, Ames testing has demonstrated that some anomeric amide derivatives are mutagenic.[3-6] The mutagenicity of **3** was recently examined using Ames II testing. Compound **3** exhibits mutagenicity lower than other members of the anomeric amide reagent class and on par with other commonly handled laboratory reagents such as benzyl chloride.[18] Nonetheless, appropriate ventilation and personal protective equipment should be employed when handling **3**.
2. *O*-Benzyl hydroxylamine hydrochloride (97%) was purchased from Oakwood Chemical and used as received. The submitters performed the reaction on 125 mmol scale. The checkers purchased *O*-benzyl hydroxylamine hydrochloride (>98%) from Shanghai Aladdin Bio-Chem Technology Co. Ltd. which was used as received.

3. Dichloromethane ACS stabilized was purchased from Fisher and used as received. The checkers purchased GR grade dichloromethane from Duksan Pure Chemicals Co. Ltd., which was used as received.
4. Potassium carbonate (99%) was purchased from Oakwood Chemical and used as received. The checkers purchased potassium carbonate (99%) from Bide Pharmatech Ltd., which was used as received.
5. A stir rate of 1400 rpm was used.
6. *p*-Trifluoromethyl benzoyl chloride (98%) was purchased from Oakwood Chemical and used as received. The checkers purchased *p*-trifluoromethyl benzoyl chloride (>97%) from TCI (Shanghai) Development Co., Ltd. which was used as received.
7. Room temperature refers to between 20 and 25 °C throughout this manuscript.
8. The reaction can be monitored by TLC. An eluent of hexanes: ethyl acetate 5:1 was used with silica gel 60 F_{254} plates. The TLC was visualized under UV light (254 nm) to observe the consumption of *p*-trifluoromethyl benzoyl chloride (*p*-CF_3BzCl) (R_f = 0.80) and the formation of product **1** (R_f = 0.23) (Figure 4).

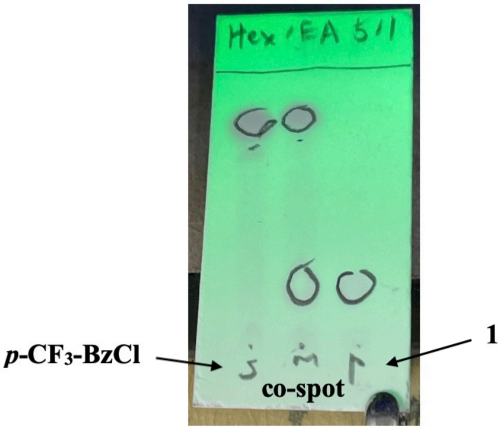


Figure 4. TLC analysis of Step A (Note 8)
(Photo provided by the checkers)

9. The magnetic stir bar is removed before rotary evaporation.
10. A Buchi rotovap R-100 was used with a bath temperature of 40 °C and vacuum at 75 - 300 mmHg.

11. Diethyl ether (BHT stabilized, certified ACS) was purchased from Fisher Chemical and used as received. The checkers purchased GR grade diethyl ether (BHT stabilized) from Duksan Pure Chemicals Co. Ltd., which was used as received.
12. The product was dried under high vacuum in a round-bottomed flask using a 24/40 joint hose adaptor. The round-bottomed flask was immersed in a heating bath with a temperature of 70 °C.
13. Product **1** is characterized as follows: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.01 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 6.6 Hz, 2H), 7.43 – 7.33 (m, 3H), 4.96 (s, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ: 162.6, 136.2, 135.9, 131.4 (q, *J* = 31.6 Hz), 129.0, 128.4, 128.0, 125.5 (d, *J* = 4.0 Hz), 123.9 (q, *J* = 272.5 Hz), 77.0 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ: –61.4 ppm. IR (diamond ATR, neat) 3177, 1646, 1327, 1163, 1121, 1110, 1066, 1039, 1015, 755, 745 cm^{-1}. HRMS-ESI (*m/z*) $[M + H]^+$calcd for $C_{15}H_{13}F_3NO_2^+$, 296.0893; found, 296.0890. mp 169–170 °C.
14. The purity of **1** is assessed as 97% using quantitative NMR (14.0 mg of 1,3,5-trimethoxybenzene internal standard, 14.1 mg of **1** dissolved in DMSO-*d6*). The checkers purchased 1,3,5-trimethoxybenzene (>99.9%, Sigma-Aldrich), which was used as received.
15. The checkers performed a duplicate run at same scale which provided 17.0 g (92 % yield) of **1** from 9.98 g of *O*-benzyl hydroxylamine hydrochloride.
16. A stir rate of 600 rpm was used.
17. The reaction should be protected from light due to the light sensitivity of TCICA and potential light sensitivity of product **2**. Aluminum foil from Reynolds wrap was employed, and the fume-hood lights were turned off.
18. Trichloroisocyanuric acid (TCICA, 95%) was purchased from Fluka and used as received. The checkers purchased TCICA from TCI (Shanghai) Development Co., Ltd., which was used as received.
19. This was performed by dividing the TCICA into 7 equal portions (~280 mg) and adding one portion every two minutes.
20. The reaction can be monitored by TLC. The reaction time reported by the submitters was 1 h, while the checkers observed some starting materials still present after 1 h; therefore, the reaction time was extended to 1.5 h. An eluent of hexanes: ethyl acetate 3:1 was used with silica gel 60 F_{254} plates. The TLC was visualized under UV light (254 nm) to observe the consumption of **1** (R_f = 0.45) and formation of product **2** (R_f = 0.8).

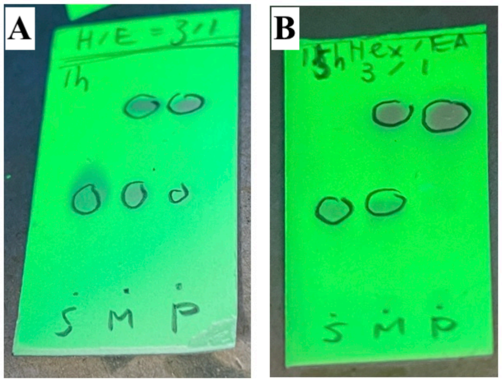


Figure 5. TLC analysis (Note 21); S is starting material (1), P is product (2), and M is a co-spot; A) TLC plate after 1 h; b) TLC plate after 1.5 h (photo provided by checkers)

21. The rate of stirring was increased to 750 rpm.
22. A rotary evaporator was used with a bath temperature of 20–25 °C and vacuum at 75 mmHg. The bath temperature was not increased further due to the potential thermal instability of **2**. The flask was wrapped in aluminum foil during rotary evaporation.
23. Pentane (ACS certified, 98%) was purchased from Fisher and used as received. The checkers purchased AR grade *n*-pentane from RCI Labscan Ltd., which was used as received.
24. The checkers used a stir rate of 400 rpm.
25. Celite® was purchased from Fisher and used as received. The checkers purchased Celite® from Alfa Aesar (Thermo Fisher Scientific Inc.), which was used as received.
26. Product **2** is characterized as follows: ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.69 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.40–7.30 (m, 3H), 7.25–7.23 (m, 2H), 5.07 (s, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 172.6, 134.8, 134.1 (q, *J* = 32.8 Hz), 133.0, 129.9, 129.7, 129.5, 128.8, 125.4 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.8 Hz), 76.8. ^{19}F NMR (376 MHz, chloroform-*d*) δ: –63.2. IR (diamond ATR, neat) 1721, 1317, 1257, 1242, 1182, 1175, 1126, 1110, 1081, 1062, 753 cm^{-1}. HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{12}ClF_3NO_2^+$, 330.0503; found, 330.0504. The characterization data for **2** was obtained immediately after preparation.
27. The purity of **2** is assessed as 97% by the checkers using quantitative NMR analysis (11.0 mg of dimethyl terephthalate internal standard,

13.2 mg of 2 dissolved in $CDCl_3$). The checkers purchased dimethyl terephthalate (>99.9%, Sigma-Aldrich), which was used as received.

28. Storage of **2** is not recommended since **2** is a heat and light-sensitive compound that was found to decompose upon storage, even at –20 °C. In order to synthesize **3** in sufficient purity, **2** should be immediately taken forward to Step C.
29. The submitters used a 200 mL pear-shaped Schlenk flask (14/20 joint; ground glass socket and hose adaptor). The socket to the hose adaptor was sealed with a ground glass key which was greased with Dow Corning high vacuum grease and secured to the flask using a metal spring and retainer clip.
30. Sodium pivalate anhydrous (98%) was purchased from Combi-blocks. When sodium pivalate hydrate (purchased from Combi-blocks) was used without drying, **3** was formed with notably decreased purity (90% relative to internal standard). The checkers purchased sodium pivalate anhydrous (≥ 97%, Alfa Aesar), which was dried in the vacuum oven before use.
31. Tygon A-60-G tubing vacuum tubing was used.
32. Vacuum was established with a vacuum pump. Five cycles of evacuating the flask to a pressure of 75 mmHg and refilling with an inert gas was performed. The submitters used nitrogen as the inert gas.
33. The reaction is sensitive to air and running the reaction under air results in a decreased yield and purity of **3**. Among multiple side products, benzaldehyde was detected in the NMR spectrum, a putative oxidation product.
34. Acetonitrile (HPLC grade, Fisher) was degassed under argon and dried by passing through a PPT Solvent Purification System. The checkers purchased Super Dry acetonitrile (water ≤ 10 ppm) from J&K Scientific, which was sparged with argon for 15 min before use.
35. An oven-dried Luer-lok 12 inch SS needle was used. The needle and the syringe should be properly purged with inert gas using standard inert gas techniques.
36. The reaction should be protected from light due to the potential light sensitivity of **2**. The fumehood light should be turned off.
37. The solution was sparged using an oven dried Luer-lok 12 inch SS needle and vented with an Exel 18G x 1 inch disposable needle. Sparging should be conducted immediately upon addition of acetonitrile to **2**. It is not recommended to leave the solution sitting in air.
38. The submitters transferred the solution of **2** using a 50 mL syringe.

39. A reaction time of 3 h was used by the submitters. The reaction can be monitored by TLC. An eluent of hexanes: diethyl ether 6:1 was used with silica gel 60 F_{254} plates. The TLC was visualized under UV light (254 nm) to observe the consumption of **2** (R_f = 0.60) and formation of product **3** (R_f = 0.52).

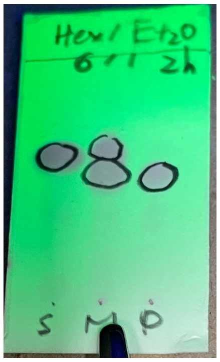


Figure 6. TLC analysis (Note 40); S is starting material (2), P is product (3), and M is a co-spot; photo provided by checkers)

40. Silica gel (40 – 63 μm, 230 – 400 mesh) was purchased from Merck Millipore and used as received.
41. The silica gel is pre-moistened with diethyl ether (Note 11).
42. Product **3** is characterized as follows: ^{1}H NMR (400 MHz, chloroform-*d*) δ: 7.76 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.40-7.34 (m, 5H), 5.14 (s, 2H), 1.09 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 175.4, 173.4, 135.6, 134.9, 133.9 (q, *J* = 32.0 Hz), 129.5, 129.4, 129.0, 128.7, 125.2 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.7 Hz), 78.0, 38.5, 26.7. ^{19}F NMR (376 MHz, chloroform-*d*) δ: –63.1. IR (diamond ATR, neat) 1770, 1733, 1324, 1267, 1165, 1124, 1066, 1017, 764, 745 cm^{-1}. HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{20}H_{20}F_3NNaO_4^+$ 418.1237; found, 418.1232. mp 36–38 °C
43. The purity of **3** is assessed as 98% by the checkers using quantitative NMR (12.8 mg of 1,3,5-trimethoxybenzene internal standard, 13.6 mg of **3** dissolved in $CDCl_3$). The checkers purchased 1,3,5-trimethoxybenzene (>99.9%, Sigma-Aldrich), which was used as received.
44. The checkers performed a duplicate run of Steps B and C at full scale, which provided 6.36 g (95 % yield) of **3** from 5.0 g of **1**.
45. The authors originally reported that long term storage is recommended at -20 °C, as **3** slowly decomposes over several months at room

temperature. However, in the course of checking the article on the application of **3** (*Org. Synth.* **2025**, *102*, 442-464), the checkers observed some decomposition even during storage of **3** at -20 °C. The authors report the storage properties depend somewhat on reagent purity and that in general storage for more than a day or two is best conducted at -78 °C.

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.

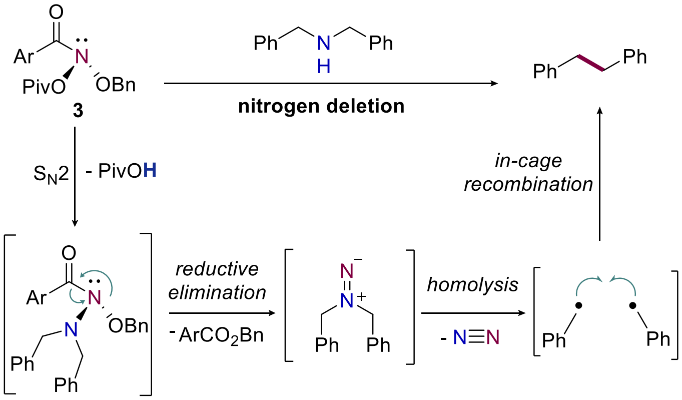
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior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

Product **3** belongs to the *N*-(alkoxy)-*N*-(acyloxy)benzamide class of anomeric amides.[3, 4, 7-9] In this class of compounds, in order to satisfy the electron demand of the two oxygen substituents, the resonance of the nitrogen lone pair with the amide carbonyl is largely diminished. This results in an *sp*^{3} configuration and pyramidalization at nitrogen.[9] Additionally, anomeric stabilization is observed between the lone pair of the alkoxy substituent and the σ* orbital of the *N*-acyloxy bond, analogous to the anomeric effect commonly observed in sugars.[3, 7, 11] These electronic effects render the amide nitrogen electrophilic in nature, and *N*-(alkoxy)-*N*-(acyloxy)benzamides have been shown to undergo substitution by an S_N2 mechanism with aniline, azide and thiol nucleophiles.[7, 8, 12, 13]

Following substitution with aniline, the resulting *N*-(amino)-*N*-(alkoxy)benzamide species can undergo a formal reductive elimination reaction, which has been shown to occur intramolecularly. This process, in which the alkoxy substituent migrates to the amide carbonyl, is also referred to as the Heteroatom Rearrangement On Nitrogen (HERON) reaction.[7, 9, 11, 14] The resulting products are an ester and a 1,1-diazene intermediate, which was observed by Glover to dimerize to a tetrazene product when derived from *N*-methylaniline.[7]

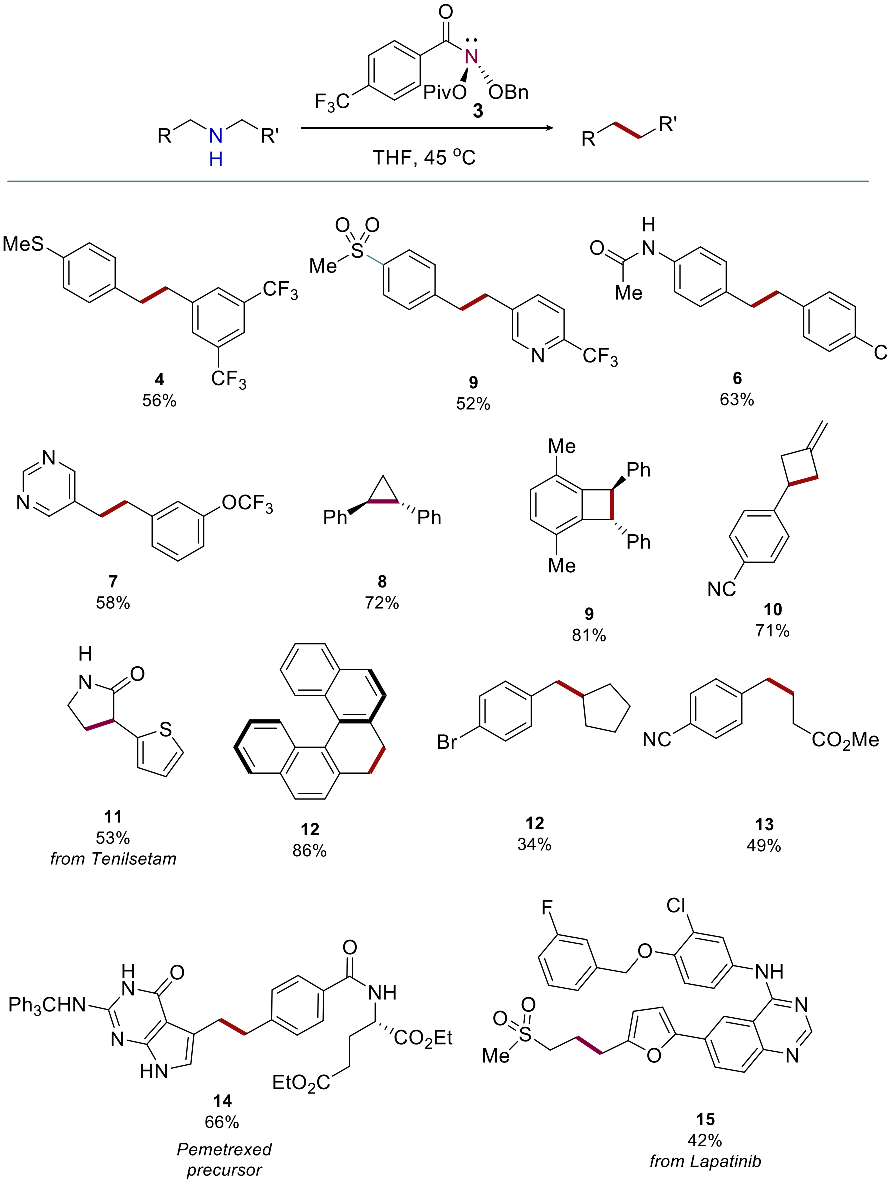


Scheme 1. *N*-(Benzyloxy)-*N*-(pivaloxy)-4-(trifluoromethyl)benzamide (3) undergoes substitution with benzylic secondary amines to yield 1,1-diazene intermediates which liberate dinitrogen to form deaminated C-C bond products

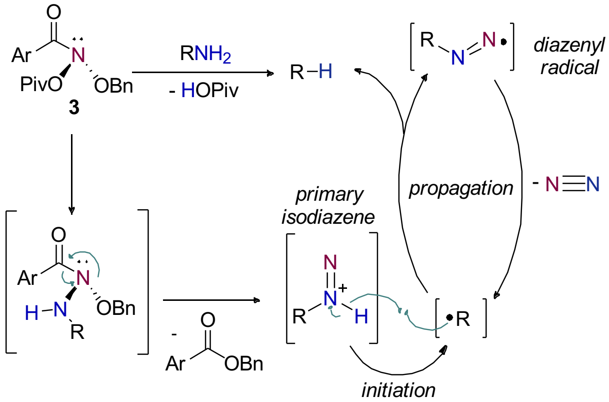
Our group has recently demonstrated that anomeric amide **3** promotes “deletion” of nitrogen from benzylic secondary amines. In this reaction, the 1,1-diazene intermediate instead undergoes a homolytic extrusion to liberate dinitrogen and produce stabilized benzylic radical fragments. These fragments recombine by an in-cage radical mechanism resulting in the net “deletion” of amines from molecular scaffolds (Scheme 1).[15] *N*-(benzyloxy)-*N*-(pivaloxy)-4-(trifluoromethyl)benzamide (**3**) was specifically optimized for this reaction, with the bulky *N*-pivaloyl substituent designed to prevent unwanted *N*-acetylation of amines and the trifluoromethyl group added to increase the rate of the initial substitution reaction.

We have used **3** to selectively edit secondary amines containing a range of functional groups and heterocycles (**4**-**15**) (Table 1). Nitrogen deletion of cyclic secondary amines results in a ring contraction, which has been applied to give substituted cyclobutene products from pyrrolidine precursors (**9**, **10**). This methodology also enabled a new synthetic route to the chemotherapeutic Pemetrexed (**14**) and enabled the late-stage editing of the kinase inhibitor Lapatinib (to afford **15**).

Table 1. Selected substrate scope of secondary amines with 3



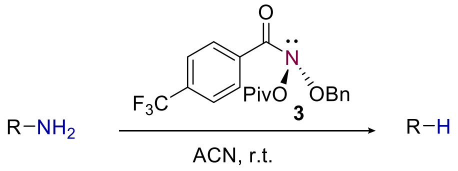
We have also recently shown that primary amines undergo nucleophilic substitution with **3**, and that following the subsequent rearrangement of the *N*-(amino)-*N*-(alkoxy)benzamide intermediate, a primary isodiazene species is liberated.[2] In contrast to the mechanism of secondary isodiazenes described above, these primary isodiazene intermediates (a previously unknown reactive species) liberate dinitrogen by a distinct free radical chain HAT mechanism, resulting in the production of alkane product (Scheme 2). The hydrogen atom incorporated in the product has been shown to originate from the amine -NH_2 and resulting isodiazene -*N-H* by computational modeling and deuterium labelling studies.

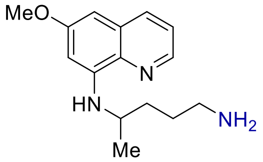


Scheme 2. Direct deamination of primary amines via primary isodiazene intermediates using *N*-(benzyloxy)-*N*-(pivaloxy)-4-(trifluoromethyl)-benzamide (3)

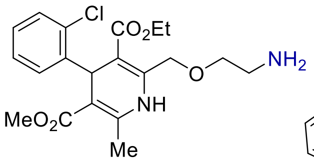
Prior to this report, deamination of aliphatic amines typically required pre-functionalization of the amino group by pyridylation or tosylation to generate a better leaving group.[16] Reports of direct deamination of primary amines to alkanes without pre-functionalization required the use of harsh reagents and conditions which severely limited the utility of these reactions.[16] In contrast, reagent **3** facilitates direct, mild deamination at room temperature and the reaction exhibits excellent functional group tolerance, enabling the 'deletion' of primary amines as a new late-stage editing tool on a variety of biomolecules (Table 2). Indeed, a range of complex pharmaceuticals (**16 – 19**) were selectively deaminated using **3**. Amino acids (**21**) were also successfully deaminated, as well as β-glucosamine (**20**) with retention of anomeric purity, resulting in a new, selective route to β-2-deoxyglucose. Anilines (**22 – 24**) were shown to undergo deamination at 45 °C.

Table 2. Selected substrate scope of primary amines with 3

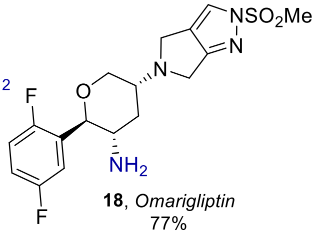




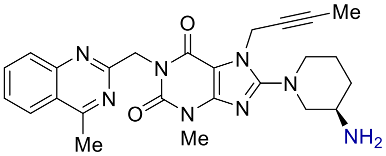
16, *Primaquine*
53%



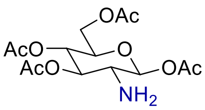
17, *Amlodipine*
71%



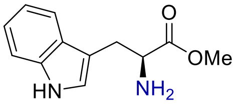
18, *Omarigliptin*
77%



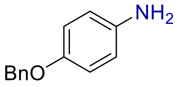
19, *Linagliptin*
65%



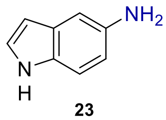
20, *-glucosamine*
78%



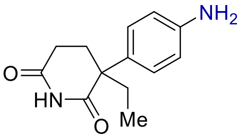
21, *tryptophan*
71%



22
53%*



23
72%*



24, *Aminoglutethimide*
64%*

* Reaction temperature 45 ^{o}C

These applications of **3** prompted us to develop the present reproducible large-scale synthesis. The synthesis of *N*-(alkoxy)-*N*-(acyloxy)benzamides was first reported by Glover and involves chlorination of the requisite *N*-(alkoxy)benzamide with *tert*-butylhypochlorite followed by substitution with a sodium acyloxy salt.[3, 5, 8, 9] Due to safety concerns associated with *tert*-butylhypochlorite, which is volatile, and sensitive to both heat and light,[17] we developed an alternative chlorination procedure using TCICA, as well as a convenient pentane filtration procedure to remove excess TCICA and its byproducts from **2**. The final substitution with sodium pivalate was initially found to be highly variable upon scale up, with formation of inseparable pivalic acid and pivalic anhydride impurities in many instances. Extensive attempts were made to purify **3**, however, this was unsuccessful due to the instability of **3** to both silica and alumina chromatography and its reticence to crystallize. The procedure reported here, with careful control of the concentration and temperature suppresses the formation of impurities and dramatically improves the reproducibility of the reagent preparation on scale.

In summary, we have developed a convenient, scalable preparation for the synthesis of *N*-(benzyloxy)-*N*-(pivaloxy)-4-(trifluoromethyl)benzamide (**3**) on a 5 g scale. Reagent **3** can be used for the late-stage of editing of primary and secondary amines from complex molecular scaffolds.

References

1. Department of Chemistry, University of Chicago, Chicago, Illinois, 60637, United States. Email: marklevin@uchicago.edu ORCID: 0000-0002-4461-363X. The University of Chicago is thanked for start-up funding. K.J.B. thanks the George Van Dyke Tiers Foundation for fellowship support. J.L.D. thanks the NSF GRFP (DGE: 1746045) for fellowship support. M.M. and A.K.T. thank the Odyssey Scholars program for funding.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

N-(Benzyloxy)-4-(trifluoromethyl)benzamide: Benzamide, 4-(trifluoromethyl)-; (1455359-81-5)
O-Benzyl hydroxylamine HCl: Hydroxylamine, *O*-benzyl-; (2687-43-6)
Potassium carbonate: potassium carbonate; (584-08-7)
p-trifluoromethylbenzoyl chloride: 4-(trifluoromethyl)benzoyl chloride; (329-15-7)
Trichloroisocyanuric acid (TCICA): 1,3,5-Trichloro-2,4,6-triazinetrione ; (87-90-1)
Acetonitrile (CH_3CN): acetonitrile; (75-05-8)
Sodium pivalate anhydrous: sodium pivalate; (1184-88-9)

Kate (Kathleen) Berger is from Medicine Hat, Alberta, Canada and attended the University of British Columbia, Vancouver where she obtained her B.Sc. Kate obtained her Ph.D. from the University of Chicago in 2022, studying anomeric amides for secondary and primary amine deletion chemistry.

Balu Dherange is from Pune, India. After completing a Masters degree from Pune University, he studied for his Ph.D at IIT Kanpur, India under the supervision of Dattatraya Dethe in the area of natural product synthesis. In 2018, he joined Prof K. C. Nicolaou's group as a post-doctoral associate at Rice University, where he worked on the design, synthesis, and biological investigation of novel anticancer compounds. In 2019, he moved to the Levin group, where his research focuses on carbon insertion and nitrogen deletion methodologies.

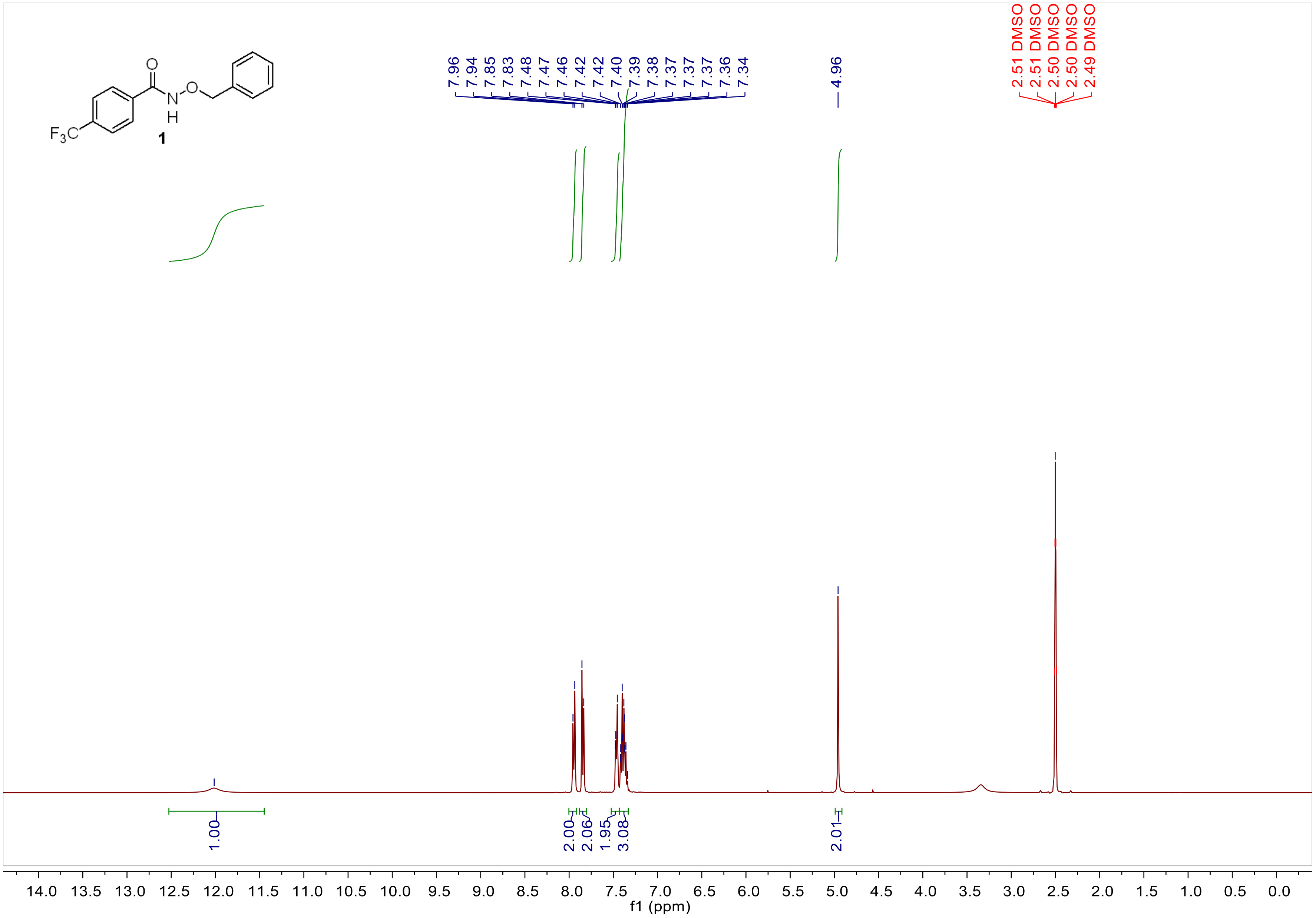
Megan Morales is originally from Miami, Florida. She currently attends the University of Chicago and is expected to receive a Bachelor's of Science in Chemistry in 2024. She joined the Levin group in 2021 where she began her research involvement with anomeric amides.

Julia L. Driscoll is originally from Pittsburgh, Pennsylvania. She received a B.S. in Chemistry from the University of Pittsburgh where she worked on the synthesis of complex bioactive molecules with Kazunori Koide. Julia is currently a graduate student in the Levin Group working on the development of reagents and methods for single-atom deletions.

Ahit Kaan Tarhan is from Istanbul, Turkey. He currently attends the University of Chicago and is expecting to receive a combined B.S. and M.S. in Chemistry in 2022. Kaan joined the Levin Group in 2020 and has been working on computationally guided design of new anomeric amide reagents, as well as synthesis of anomeric amides.

Mark D. Levin, originally from Cleveland, Ohio, is an Associate Professor of Chemistry at the University of Chicago, where his group develops new organic reactions. Mark obtained a B.S. in chemistry from the University of Rochester studying with Alison J. Frontier, a Ph.D. in chemistry from the University of California, Berkeley studying with F. Dean Toste, and conducted postdoctoral research with Eric N. Jacobsen at Harvard University.

Yinuo Zheng is from Wenzhou, China. She graduated from Central China Normal University in 2020 with B. S. in Applied Chemistry. She is continuing her Ph.D. studies in organic chemistry at the University of Hong Kong under the supervision of Prof. Pauline Chiu. Her research interests are in the area of copper-catalyzed reactions.



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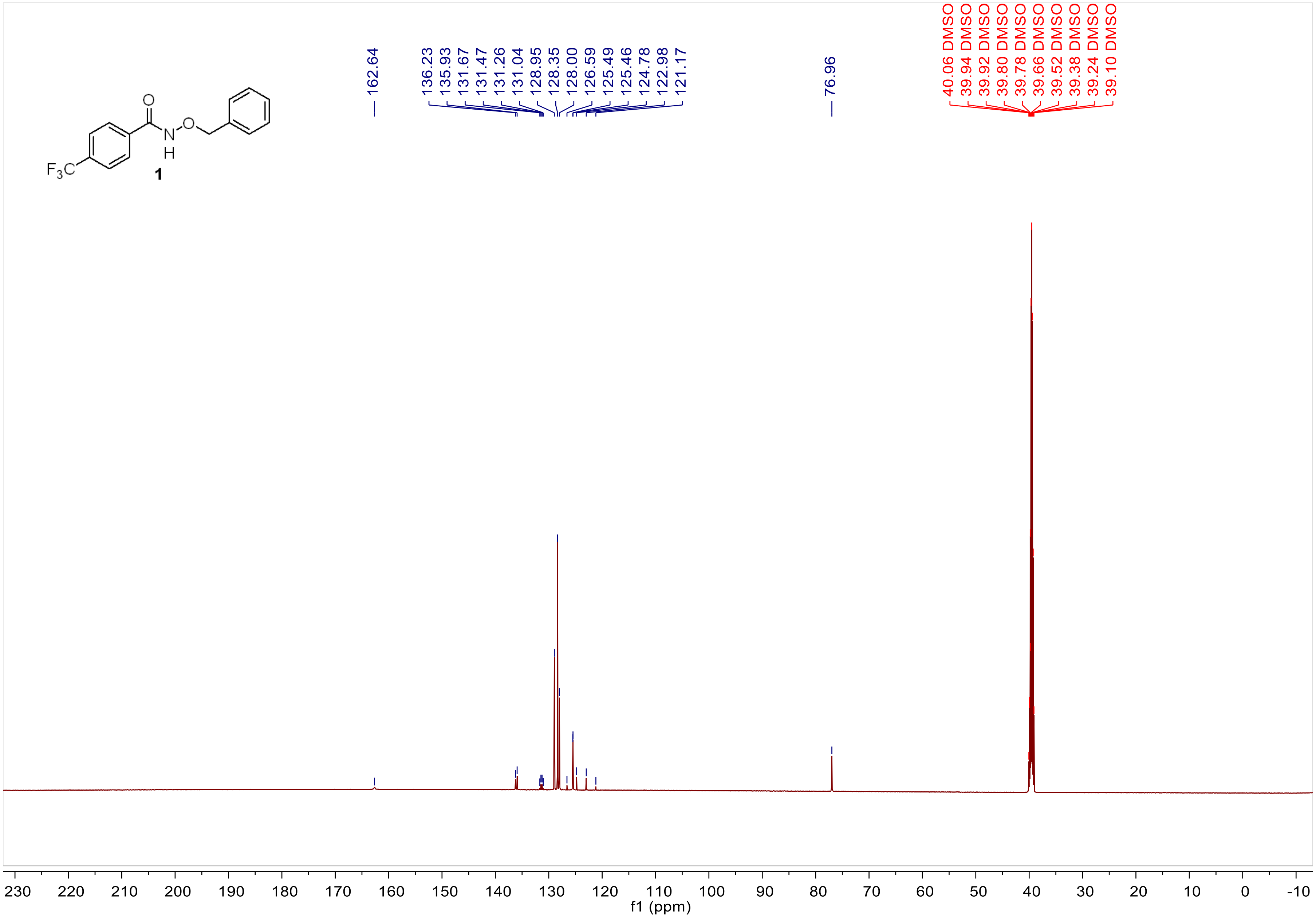
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39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
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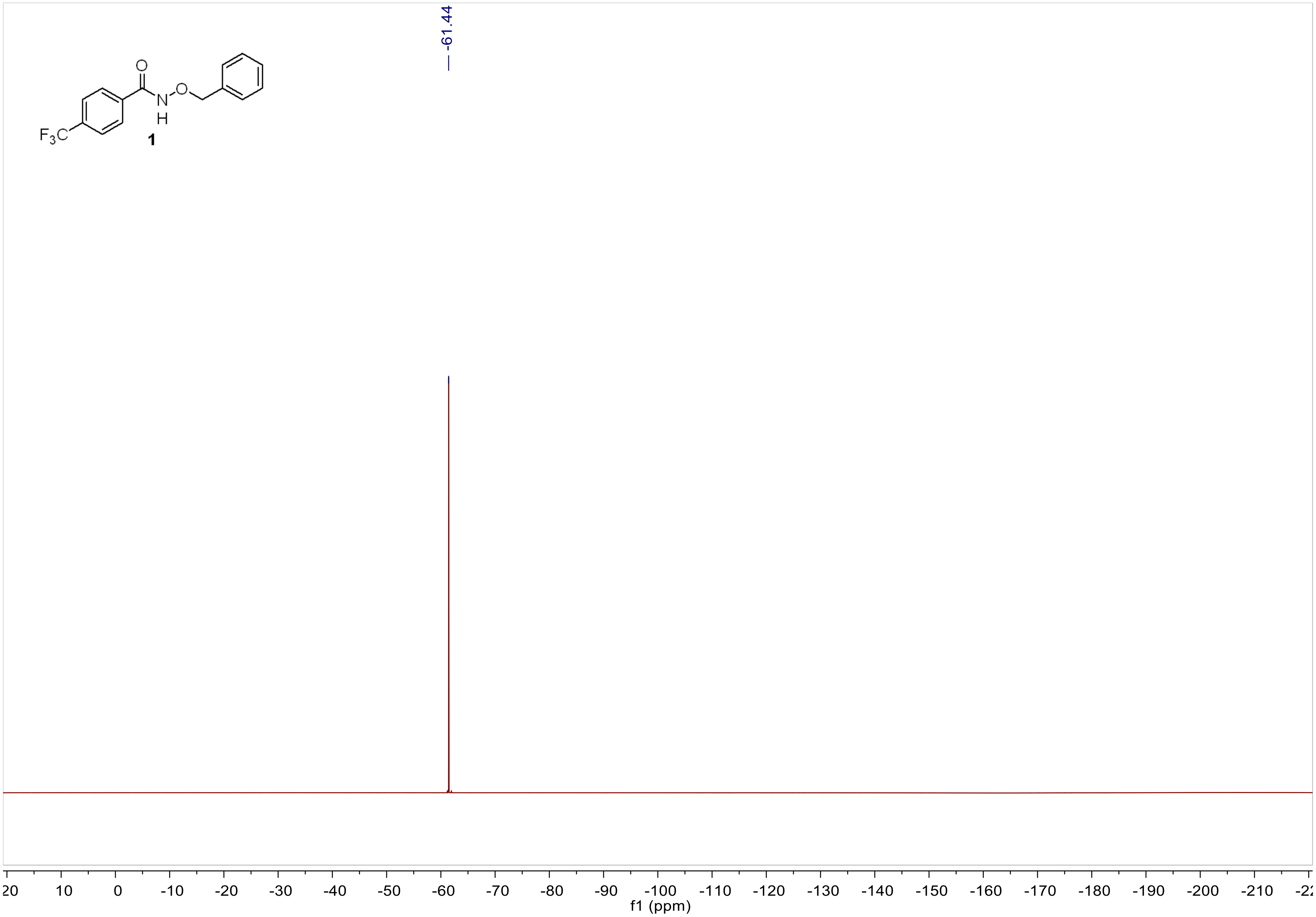

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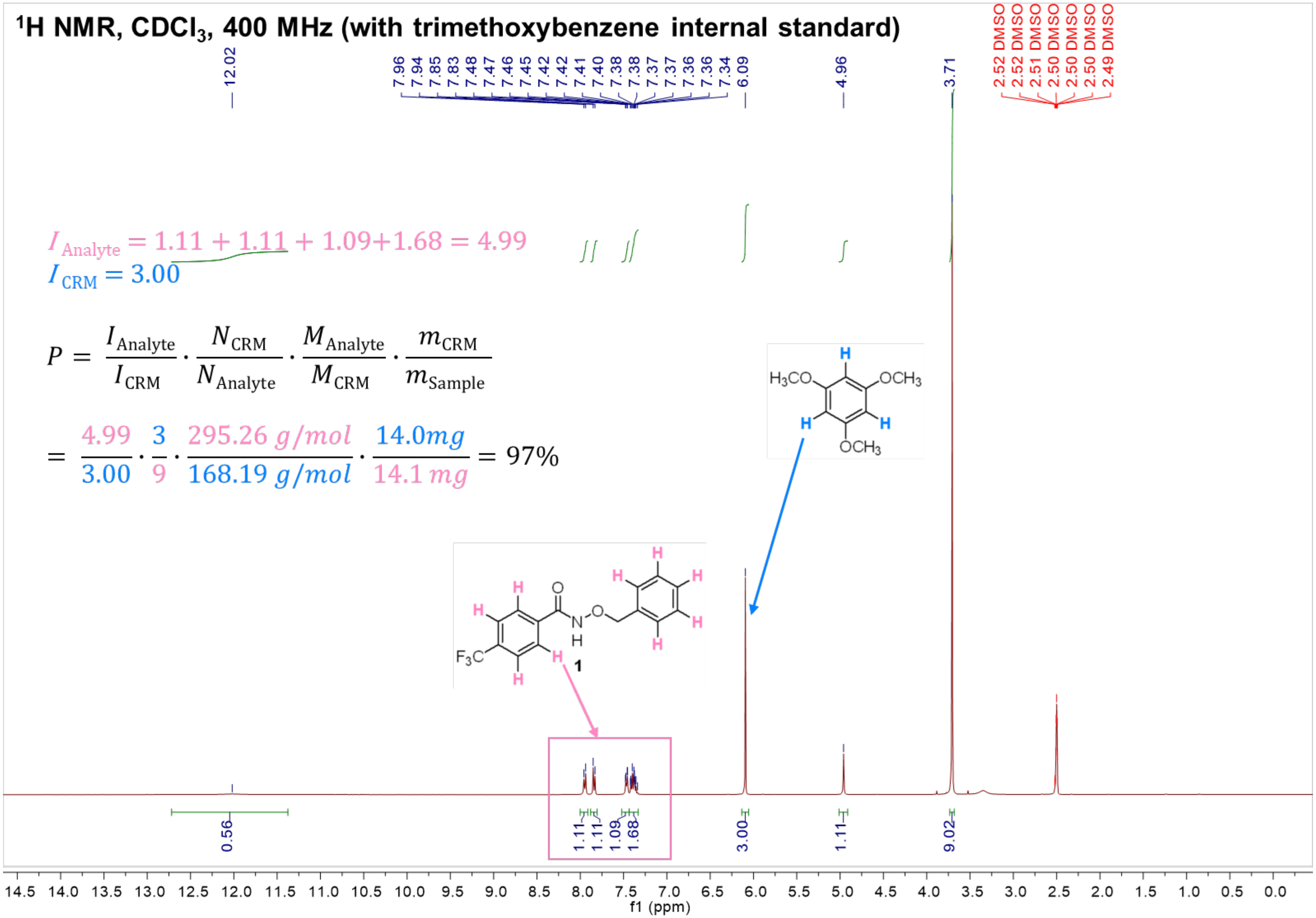
f1 (ppm)

^{1}H NMR, CDCl$_3$, 400 MHz (with trimethoxybenzene internal standard)



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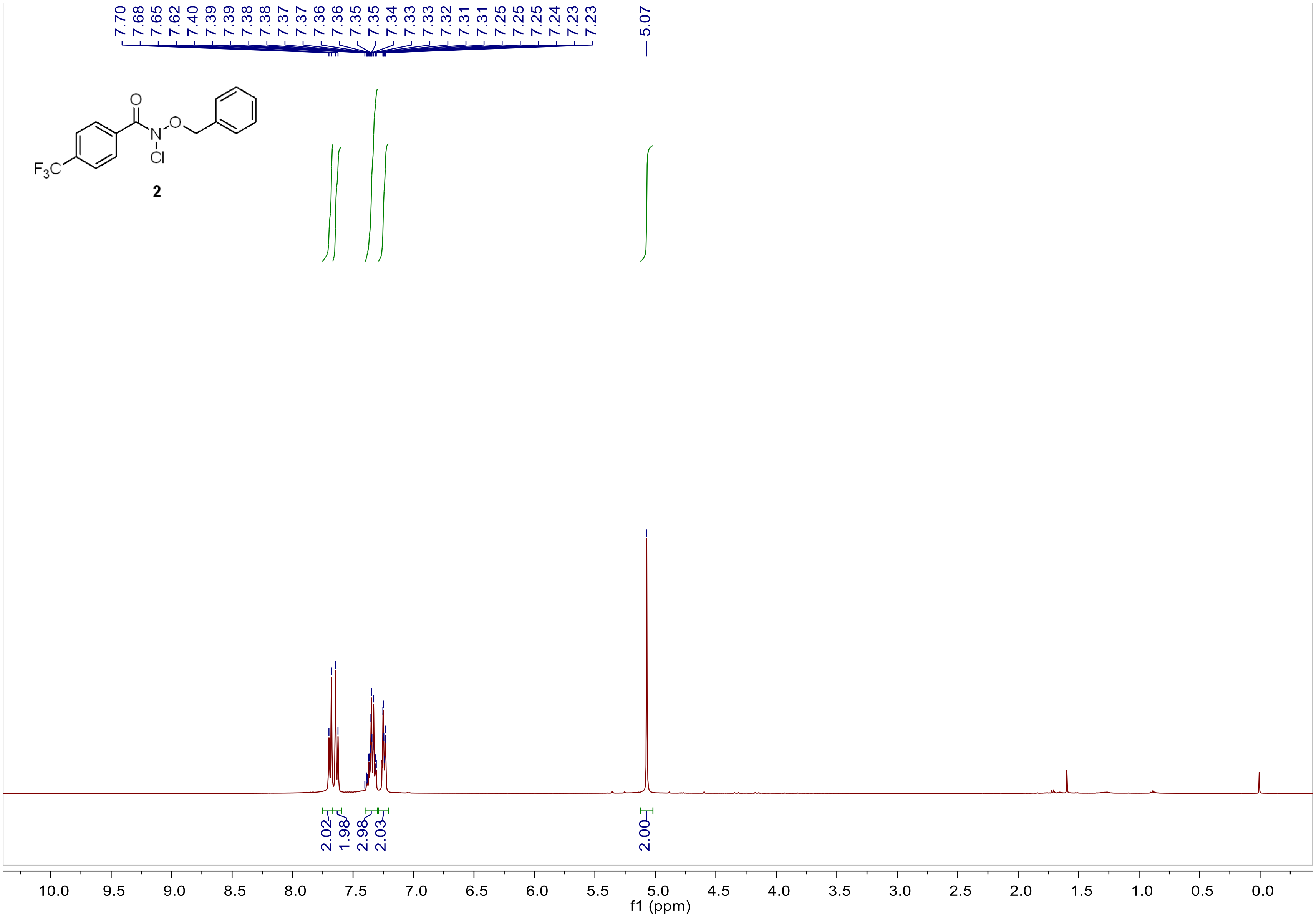
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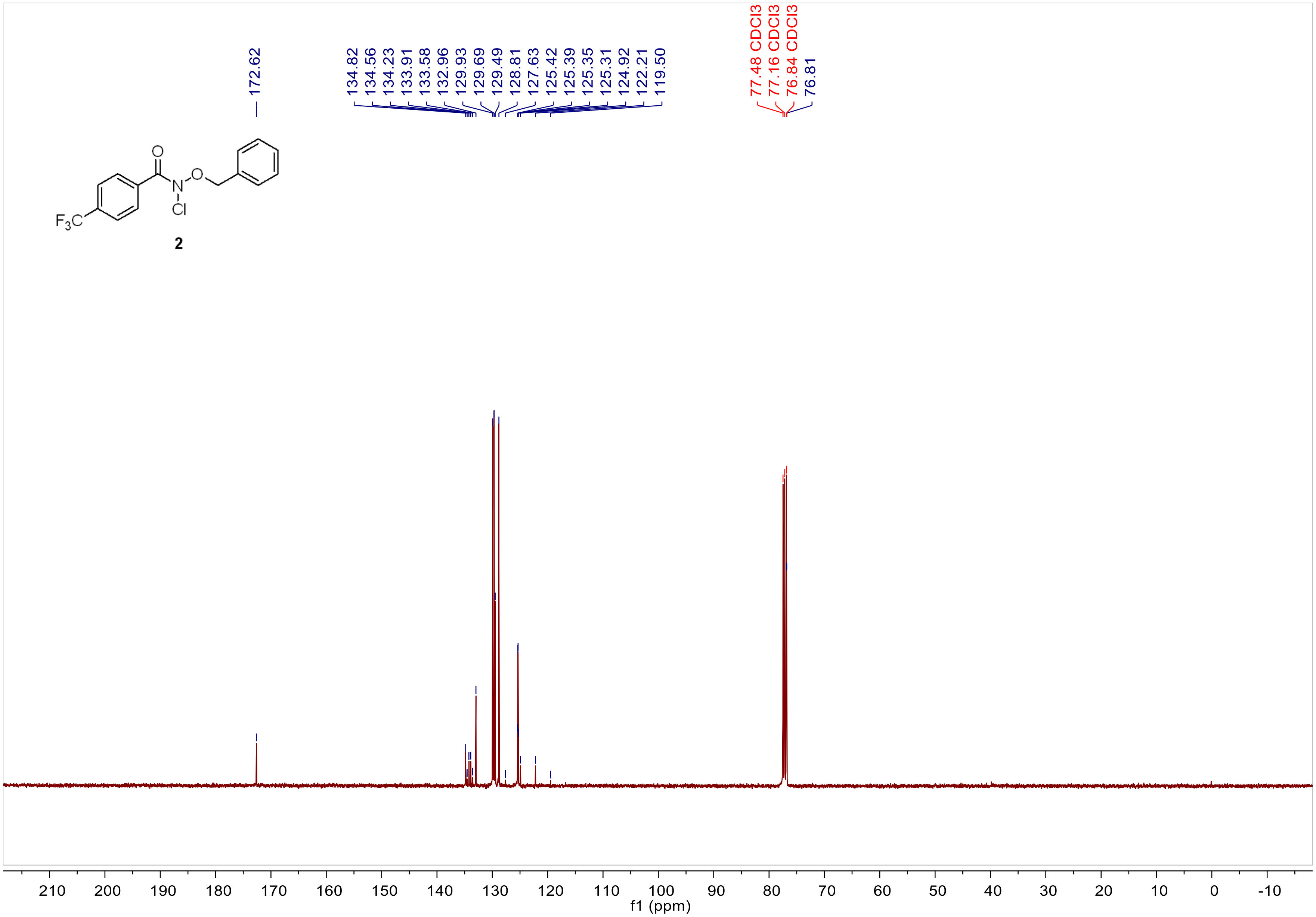
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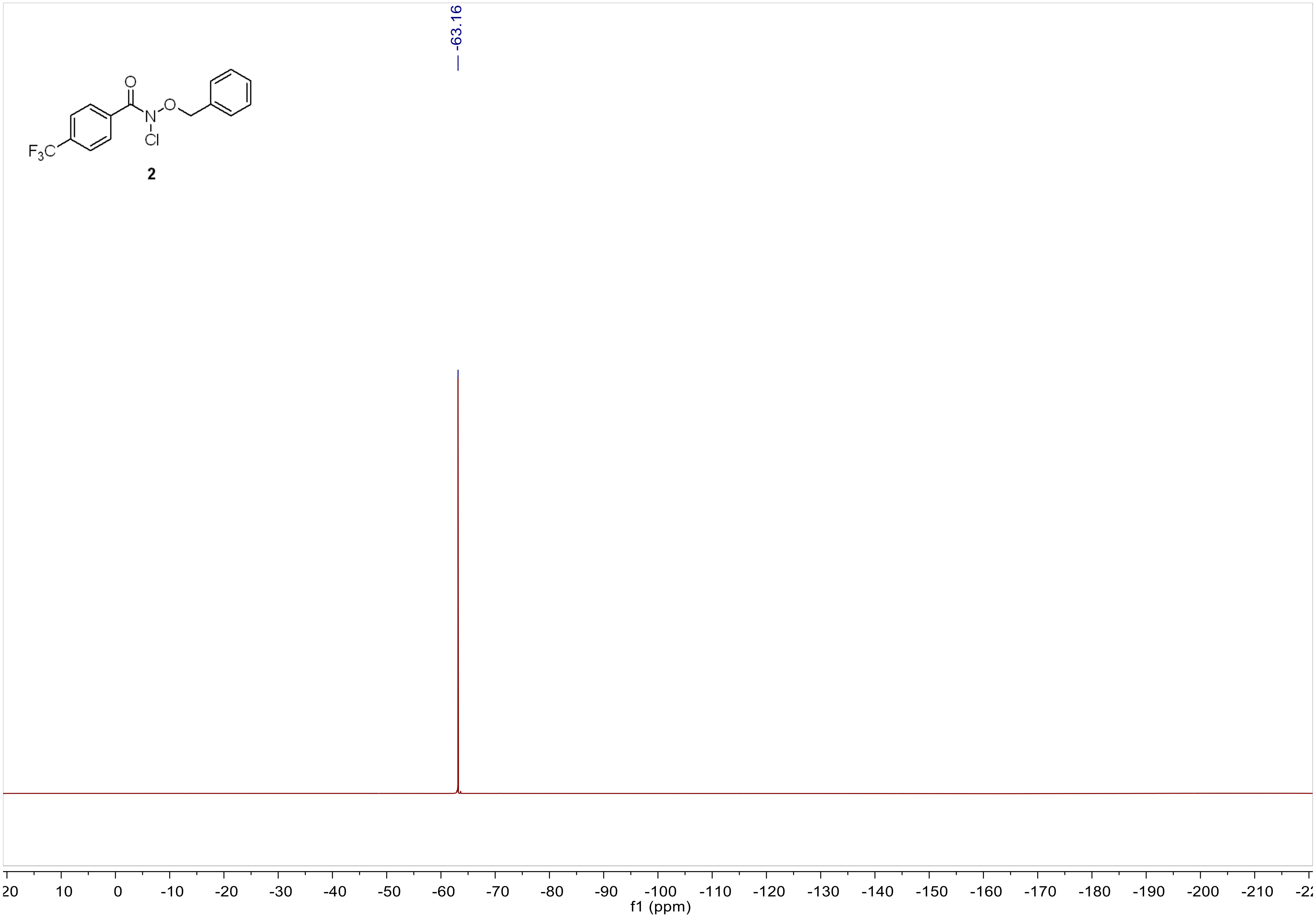
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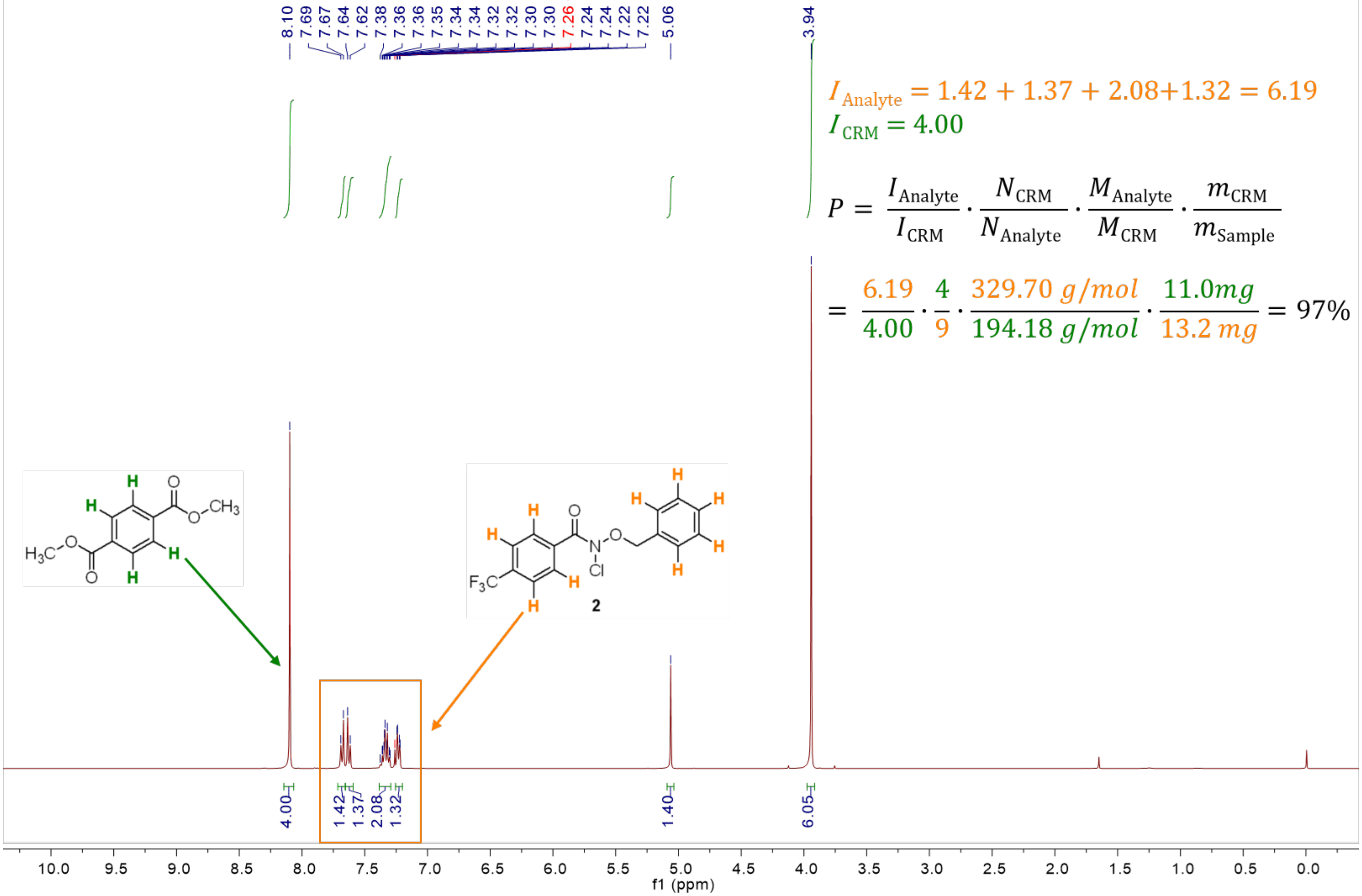
f1 (ppm)

^1H NMR, $CDCl_3$, 400 MHz (with dimethyl terephthalate internal standard)



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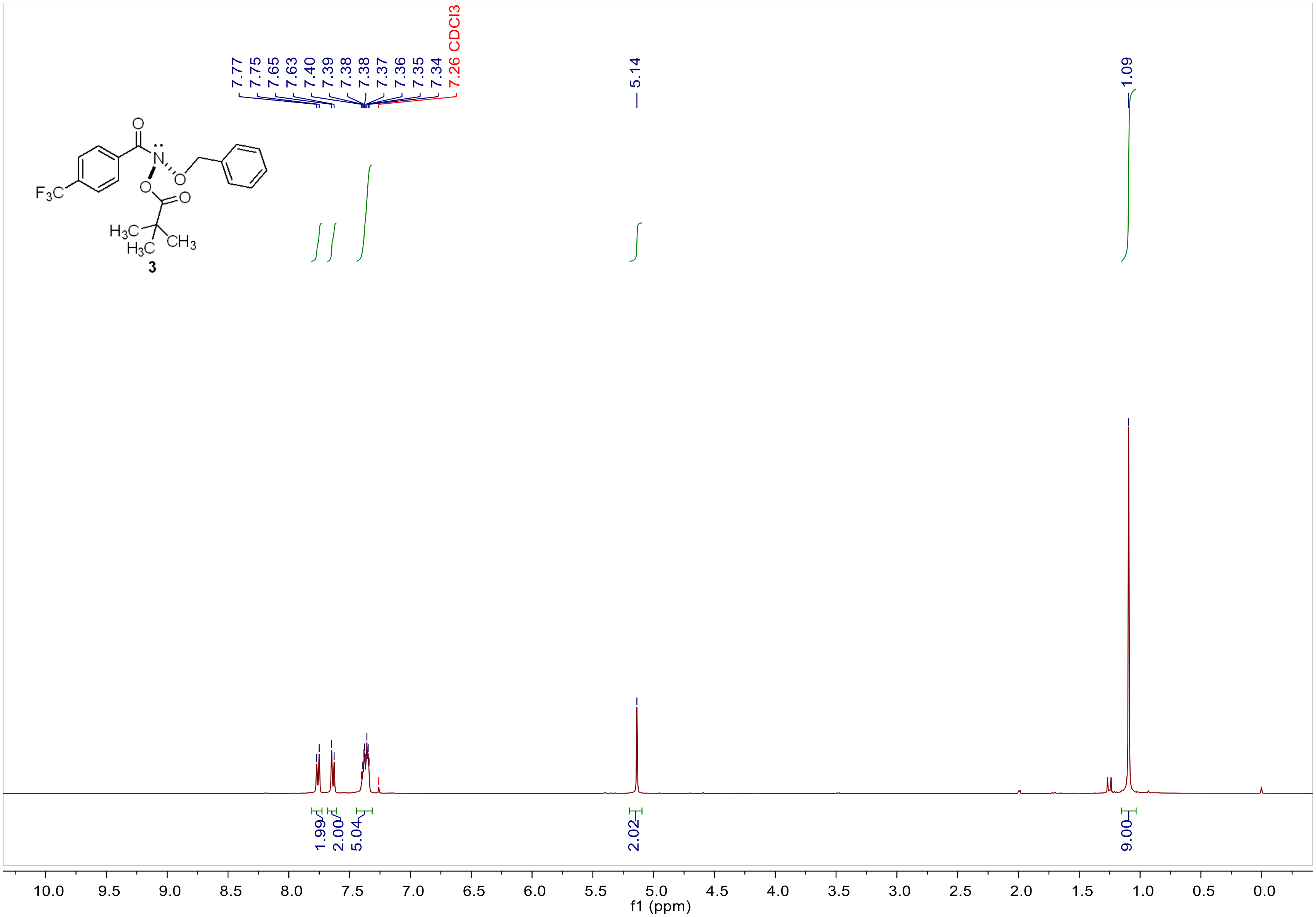
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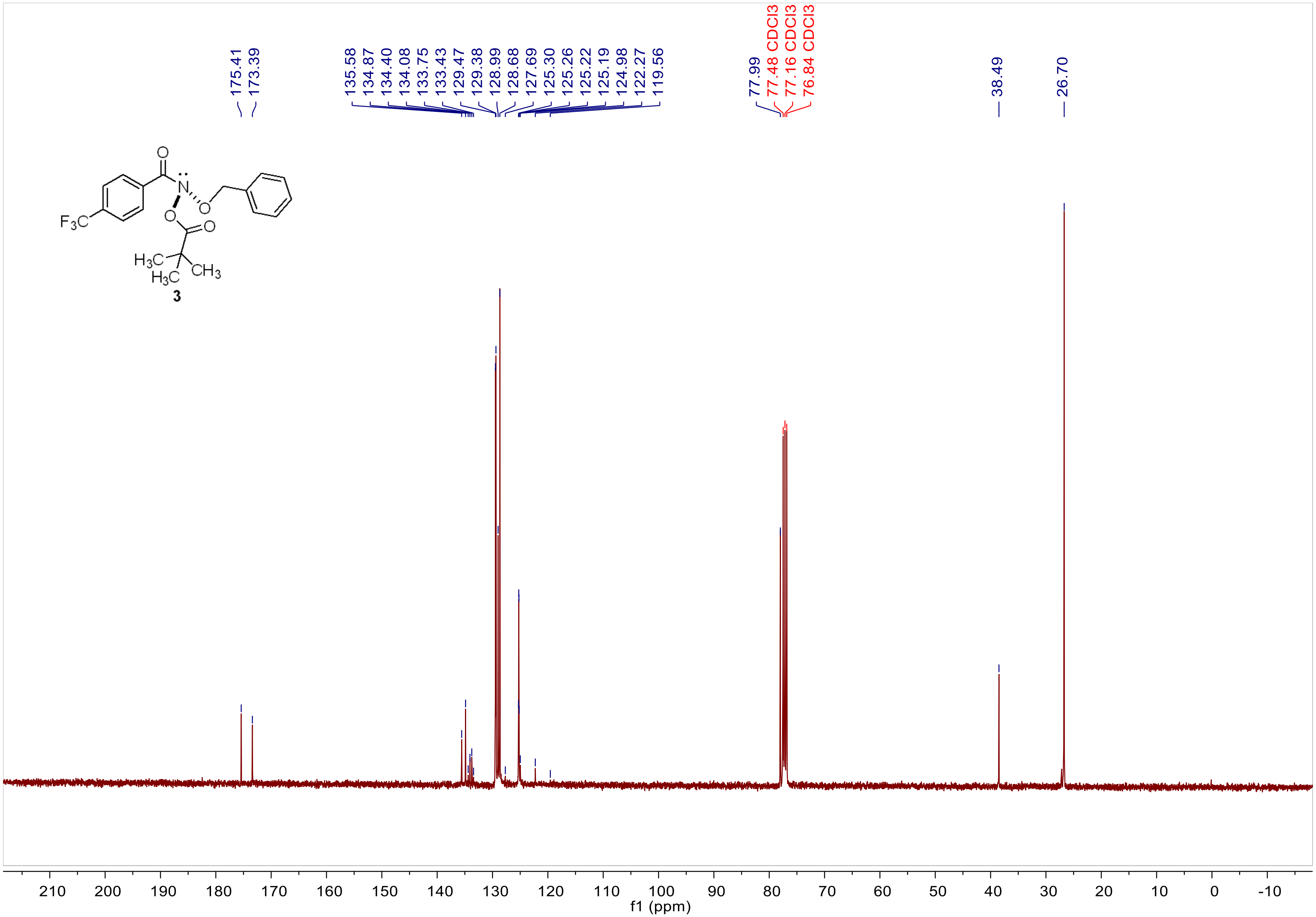
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f1 (ppm)

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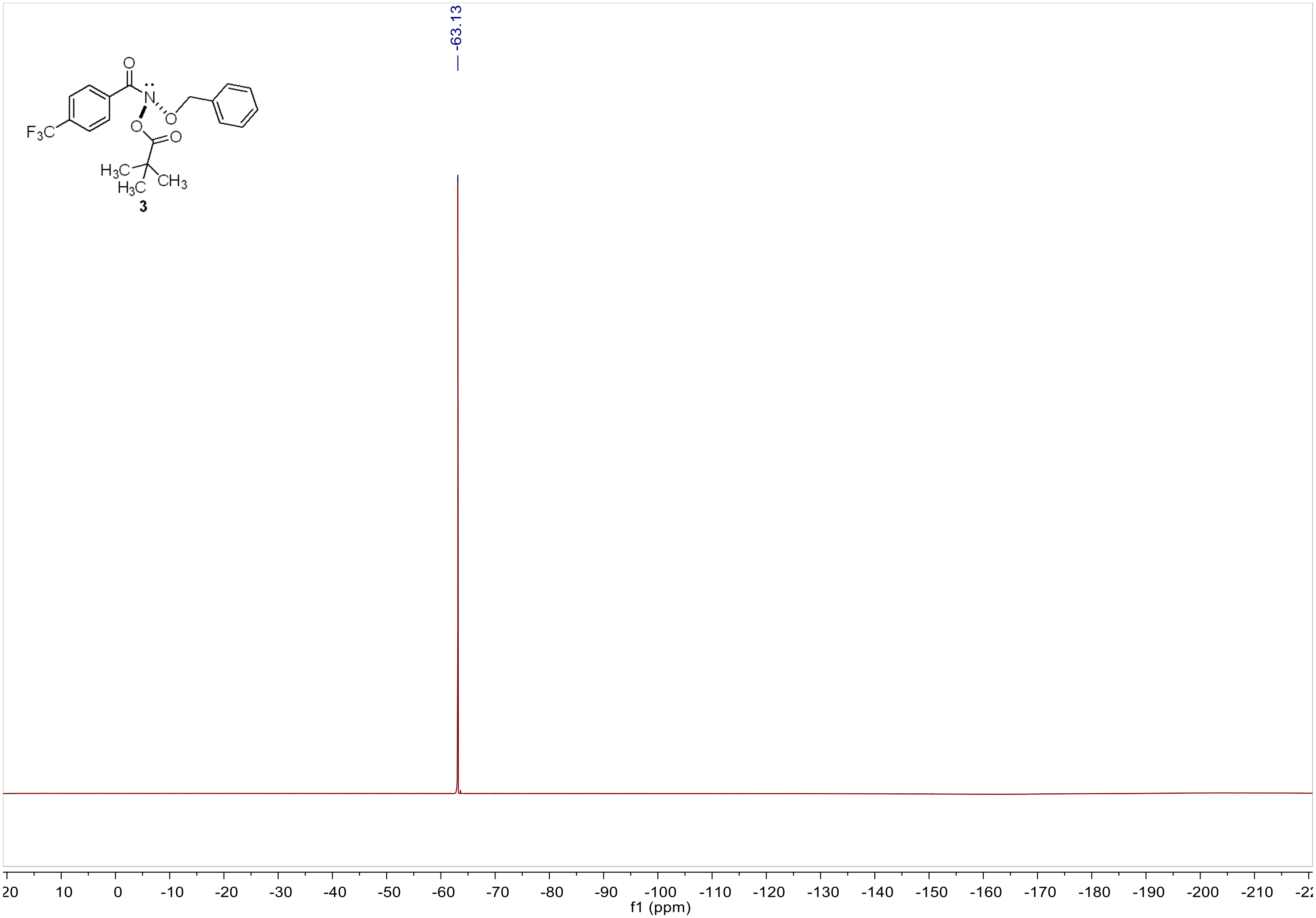
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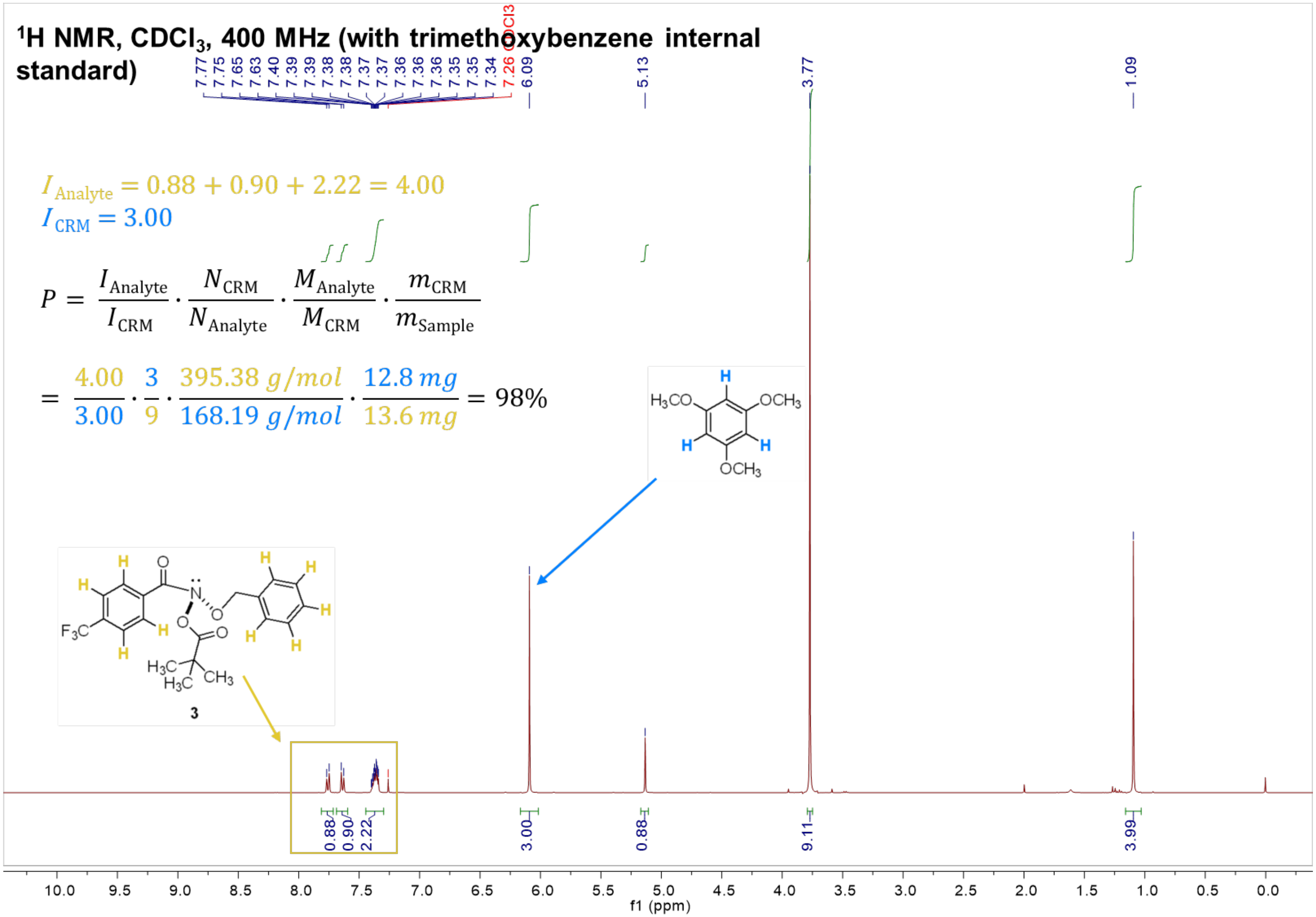

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$$I_{\text{Analyte}} = 0.88 + 0.90 + 2.22 = 4.00$$

$$I_{\text{CRM}} = 3.00$$

$$P = \frac{I_{\text{Analyte}}}{I_{\text{CRM}}} \cdot \frac{N_{\text{CRM}}}{N_{\text{Analyte}}} \cdot \frac{M_{\text{Analyte}}}{M_{\text{CRM}}} \cdot \frac{m_{\text{CRM}}}{m_{\text{Sample}}}$$

$$= \frac{4.00}{3.00} \cdot \frac{3}{9} \cdot \frac{395.38\ g/mol}{168.19\ g/mol} \cdot \frac{12.8\ mg}{13.6\ mg} = 98\%$$