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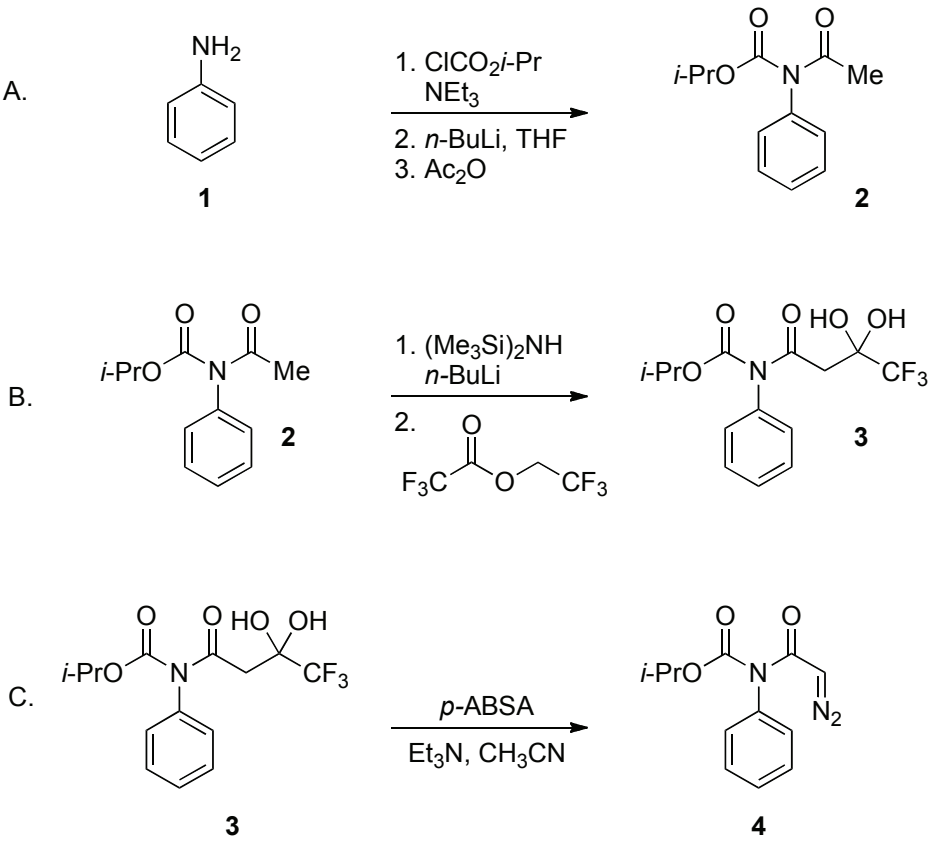
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

PREPARATION OF ISOPROPYL 2-DIAZOACETYL(PHENYL)CARBAMATE



Submitted by Hubert Muchalski, Amanda B. Doody, Timothy L. Troyer, and Jeffrey N. Johnston.[1]
Checked by John Frederick Briones and Huw M. L. Davies.

1. Procedure

Caution! Diazo compounds are presumed to be toxic and potentially explosive and therefore should be handled with caution in a fume hood. Although 4-acetamidobenzenesulfonyl azide exhibited no impact sensitivity,[2] proper caution should be exercised with all azide compounds. Although in carrying out this reaction numerous times we have never observed an explosion, we recommend that this preparation be conducted behind a safety shield.

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*A. Isopropyl acetyl(phenyl)carbamate (**2**).* A 1000-mL, 3-necked, round-bottomed flask equipped with an overhead mechanical stirrer (teflon paddle, 7 × 2 cm), thermometer (to −100 °C), and 250-mL graduated pressure-equalizing addition funnel fitted with a rubber septum and argon inlet needle (Note 1) is charged with isopropyl chloroformate (252 mL, 252 mmol, 1.09 equiv) (Notes 2 and 3) and cooled to 0–5 °C using an ice–water bath. Aniline (21.2 mL, 232 mmol) (Note 4) is added over a period of 30 min via addition funnel. The resulting suspension is vigorously stirred while triethylamine (35 mL, 252 mmol, 1.09 equiv) (Note 5) is added dropwise via addition funnel over 30 min (Note 6). The suspension is stirred vigorously and allowed to warm to room temperature using a water bath; stirring is continued for 1 h. The suspension is poured into a 1000-mL separatory funnel containing ethyl acetate (300 mL) (Note 4) and 1 N HCl (200 mL), and the aqueous phase is separated and extracted with ethyl acetate (2 x 50 mL). The combined organic layers are washed with 1 N HCl (2 x 100 mL), water (100 mL), and saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered through a fritted-glass funnel of medium porosity, and concentrated by rotary evaporation (50 °C, 40 mmHg), and then dried for 15 h (23 °C, 0.1 mmHg) to afford 40.7 g of white solid (98%) (Notes 7 and 8). The solid is used without further purification.

The product is transferred to a flame-dried, 1000-mL, 3-necked, round-bottomed flask equipped with an overhead mechanical stirrer (teflon paddle, 7 × 2 cm), thermometer, and 250-mL graduated pressure-equalizing addition funnel fitted with a rubber septum and argon inlet needle (Note 1). Anhydrous tetrahydrofuran (273 mL) (Note 9) is added, and the resulting solution is cooled to −70 °C using a dry ice–acetone bath. *n*-Butyllithium (96.3 mL, 241 mmol, 1.06 equiv) (Note 10) is added via addition funnel over a period of 20 min (Note 11). The resulting light brown solution is vigorously stirred for an additional 15 min, and acetic anhydride (24.8 mL, 261 mmol, 1.15 equiv) (Note 4) is added via syringe over a period of 5 min. The resulting suspension is vigorously stirred and warmed to room temperature using a water bath; stirring is continued for 3 h (Note 12). The yellow suspension is poured into a 1000-mL separatory funnel containing diethyl ether (250 mL) and water (250 mL), and the aqueous phase is separated and extracted with diethyl ether (2 x 100 mL). The combined organic layers are washed with saturated sodium bicarbonate solution (2 x 100 mL) and saturated NaCl solution (150 mL), dried over $MgSO_4$, filtered through a fritted-glass funnel of medium porosity, and concentrated

by rotary evaporation (50 °C, 40 mmHg), and then dried for 12 h (23 °C, 0.1 mmHg) to afford 50.8 g of yellow solid (99%) (Note 13), which is used without further purification.

*B. Isopropyl phenyl(4,4,4-trifluoro-3,3-dihydroxybutanoyl)carbamate (**3**).* A 1000-mL, 3-necked, round-bottomed flask equipped with an overhead mechanical stirrer (teflon paddle, 7 × 2 cm), thermometer, and rubber septum and argon inlet needle (Note 1) is charged with hexamethyldisilazane (24.7 mL, 119 mmol, 1.05 equiv) (Note 2) in tetrahydrofuran (119 mL, 1.0 M) (Note 9) and cooled to −70 °C in a dry ice–acetone bath. *n*-Butyllithium (45.2 mL, 113 mmol, 1.00 equiv) (Note 10) is added via syringe, and the solution is stirred for 15 min. The rubber septum is then replaced with a 250-mL pressure-equalizing addition funnel fitted with a rubber septum with argon inlet needle, and isopropyl acetyl(phenyl)carbamate (25.0 g, 113 mmol, 1.00 equiv) in tetrahydrofuran (377 mL, 0.3 M) (Note 9) is added dropwise over 15 min (Note 14). The mixture is stirred at −70 °C for an additional 30 min, after which time the addition funnel is replaced with a rubber septum, and 2,2,2-trifluoroethyl trifluoroacetate (18.2 mL, 136 mmol, 1.20 equiv) (Note 2) is added in one portion via syringe (Note 15). The reaction mixture is stirred at −70 °C for 10 min, and then quenched at −70 °C with 1 N HCl (50 mL) over 1 min, and while still cold, poured into a 1000-mL separatory funnel containing 1 N HCl (250 mL) and diethyl ether (250 mL, Note 2). The phases are separated, and the organic solution is washed with 1 N HCl (200 mL) then saturated NaCl solution (200 mL). The organic solution is dried over $MgSO_4$, filtered through a fritted-glass funnel of medium porosity, and concentrated via rotary evaporation (25 °C, 40 mmHg) to afford a white sticky solid (Notes 16, 17, and 18).

*C. Isopropyl 2-diazoacetyl(phenyl)carbamate (**4**).* The hydrate is transferred to a 1000-mL, 3-necked, round-bottomed flask equipped with an overhead mechanical stirrer (teflon paddle, 7 × 2 cm), thermometer, and rubber septum and argon inlet needle (Note 1). The solid is dissolved in acetonitrile (377 mL, 0.3 M) (Note 9), then 4-acetamidobenzenesulfonyl azide (27.1 g, 113 mmol, 1.00 equiv) (Note 19) is added in one portion. The stirred reaction mixture is cooled to 0–5 °C in an ice–water bath. Once cooled, triethylamine (23.5 mL, 169 mmol, 1.50 equiv) (Note 5) is added via syringe. The reaction is stirred for 30 min, then the ice–water bath is replaced with a room-temperature bath, and the reaction mixture is stirred for an additional 3 h (Note 20). The orange suspension is then transferred to

a 1000-mL separatory funnel containing diethyl ether (350 mL) and 1 M NaOH (300 mL). The layers are separated, and the organic layer is washed with 1 M NaOH (300 mL) and then saturated NaCl solution (300 mL). The organic solution is dried over $MgSO_4$, filtered through a fritted-glass funnel of medium porosity, and concentrated via rotary evaporation (23 °C, 40 mmHg) to give a viscous red oil. The oil is dissolved in dichloromethane (10 mL) (Note 21), and the resulting solution is purified via flash chromatography (Notes 22, 23, and 24) to yield 12.0–13.2 g of yellow solid, which is then recrystallized from warm hexanes (75 mL, 60 °C) (Note 4) to give 8.6–9.2 g (34.7–37.2 mmol, 31–33% for two steps) of pure diazoimide as a yellow crystalline solid (Note 25).

2. Notes

1. The apparatus was oven-dried for 12 h and then maintained under an atmosphere of argon during the course of the reaction.

2. Isopropyl chloroformate (1.0 M solution in toluene), 2,2,2-trifluoroethyl trifluoroacetate (99%), diethyl ether (anhydrous, 99%), and 1,1,1,3,3,3-hexamethyldisilazane (>99%) were purchased from Aldrich Chemical Co. All reagents were used as received.

3. Isopropyl chloroformate is added first to the graduated pressure-equalizing addition funnel via cannula and then added to the round-bottomed flask. The addition funnel is rinsed with anhydrous toluene (2 x 10 mL) (Note 9).

4. Aniline, ethyl acetate (99.9%), hexanes (99.9%) and acetic anhydride (99%) were purchased from Fisher Scientific Company and used as received.

5. Triethylamine (99.5%) was purchased from EMD Chemicals Inc. and distilled from calcium hydride prior to use.

6. The reaction mixture is maintained at 0–5 °C during addition. After ca. 10 min, a precipitate forms. The addition funnel is rinsed with anhydrous toluene (2 x 10 mL) (Note 9).

7. The obtained solid was 99% pure by gas chromatography on an Agilent 7890A gas chromatograph equipped with flame ionization detectors. The column used was HP-5 (30 m × 0.32 mm). The following settings were used: flow = 1.0 mL/min, oven = 60 °C to 220 °C at 20 °C/min; detector = 300 °C, injector = 250 °C; t_r = 6.95 min.

8. Isopropyl phenylcarbamate displayed the following physicochemical properties: mp 82–83 °C; R_f = 0.68 (20% EtOAc/hexanes); IR (neat) 3308, 2979, 1717, 1534, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.31 (d, *J* = 6.4 Hz, 6 H), 5.05 (sept, *J* = 6.0 Hz, 1 H), 6.89 (br s, 1 H), 7.06 (t, *J* = 7.2 Hz, 1 H), 7.28–7.32 (m, 2 H), 7.41–7.43 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.3, 68.8, 118.8, 123.3, 129.1, 138.3, 153.6; HRMS (ESI): Exact mass calcd. for $C_{10}H_{13}NO_2$ 179.0946, found 180.1016 $[M+H]^+$. Anal. calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.21; H, 7.33; N, 8.01.

9. Tetrahydrofuran (THF), toluene, and acetonitrile were dried by passage through a column of activated alumina as described by Grubbs.[3] The checkers used THF that was freshly distilled from sodium benzophenone ketyl. Toluene and acetonitrile were obtained from a Glass contour solvent purifier system by SG Water USA.

10. *n*-Butyllithium (2.5 M in hexanes) was purchased from Aldrich Chemical Co. and was titrated prior to use using 2-propanol and 1,10-phenanthroline according to an established procedure.[4]

11. The reaction mixture is maintained below −60 °C during addition.

12. Reaction progress was monitored by gas chromatography on an Agilent 7890A gas chromatograph equipped with flame ionization detectors. The column used is HP-5 (30 m × 0.32 mm). The following settings were used: flow = 1.0 mL/min, oven = 60 °C to 220 °C at 20 °C/min; detector = 300 °C, injector = 250 °C; t_r = 4.90 min.

13. The obtained solid was 98% pure by gas chromatography (Note 12). An analytical sample was obtained by recrystallization from diethyl ether. Mp 85–86 °C; R_f = 0.38 (20% EtOAc/hexanes); IR (neat) 2983, 1734, 1708, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.16 (d, *J* = 6.0 Hz, 6 H), 2.62 (s, 3 H), 4.98 (sept, *J* = 6.0 Hz, 1 H), 7.09 (d, *J* = 7.0 Hz, 8 H), 7.43-7.34 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 26.5, 71.1, 128.0, 128.2, 128.9, 138.3, 153.6, 172.9; HRMS (ESI): Exact mass calcd. for $C_{12}H_{15}NO_3$ 221.1052, found 222.1246 $[M+H]^+$. Anal. calcd. for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.84; N, 6.33. Found: C, 65.08; H, 6.98; N, 6.33.

14. The carbamate is first dissolved in THF and then transferred via cannula to the addition funnel. The temperature of the reaction mixture is maintained below –60 °C during addition, and the addition time is adjusted accordingly.

15. The internal temperature is maintained below –60 °C during the addition of 2,2,2-trifluoroethyl trifluoroacetate.

16. ^{1}H NMR of the crude product is used to confirm conversion of the isopropyl acetyl(phenyl)carbamate. Integration of the resonance of the methyl group (2.60 ppm) of the isopropyl acetyl(phenyl)carbamate is calibrated to 3 hydrogens and is compared with resonances at 5.06–4.88 ppm, which correspond to the methine proton of the isopropyl group of all mixture components. In that set of resonances, only one hydrogen corresponds to isopropyl acetyl(phenyl)carbamate. In the event that acceptable conversion is not obtained (below 95%, integration of methine resonances <20), the oil can be triturated with hexanes to remove residual isopropyl acetyl(phenyl)carbamate.

17. To the obtained oil in a 1000-mL round-bottomed flask is added 200 mL of hexanes (Note 4), and the resulting solution is concentrated via rotary evaporation (23 °C, 40 mmHg). To the obtained semi-solid residue is added 200 mL of hexanes and the resulting suspension is concentrated via rotary evaporation (23 °C, 40 mmHg). The solid is filtered through a fritted-glass funnel of medium porosity to afford a white, crystalline solid that displayed the following physicochemical properties: mp 83–84 °C, IR (film) 3373, 2986, 2941, 1742, 1680, 1596, 1491, 1376, 1264 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, J = 6.3 Hz, 6 H), 3.51 (s, 2 H), 4.91 (s, 2 H), 5.00 (sept, J = 6.2 Hz, 1 H), 7.11 (dd, J = 1.7, 1.3 Hz, 1 H), 7.13 (dd, J = 2.0, 1.7 Hz, 1 H), 7.47–7.39 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 38.9, 72.6, 93.3 (q, J = 33.0 Hz), 122.3 (q, J = 284 Hz), 128.1, 128.7, 129.4, 137.1, 153.2, 174.1; ^{17}F NMR (376 MHz, $CDCl_3$) δ: −87.0 (s, 3F); HRMS (ESI): Exact mass calcd. for $C_{14}H_{16}F_3NNaO_5$ $[M+Na]^+$ 358.0878, found 358.0887. Anal. calcd. for $C_{14}H_{16}F_3NO_5$: C, 50.15; H, 4.81; N, 4.18. Found: C, 50.36; H, 4.70; N, 4.16.

18. The hydrate is not stable in solution at room temperature. If the diazo transfer cannot be performed immediately, the hydrate can be stored dry and under argon at −78 °C for up to 3 months.

19. 4-Acetamidobenzenesulfonyl azide was synthesized using the procedure of Davies.[5] *Caution! The original procedure using methylene chloride as solvent should be avoided because it could produce the highly explosive material, diazidomethane, as a side product.*[6]

20. The yellow color of the clear reaction mixture intensified while warming to room temperature. After approximately 1 h, a white solid precipitated.

21. The oily residue is too viscous to be easily transferred onto silica gel and dilution with dichloromethane is needed.

22. Flash column chromatography was performed on a silica gel column (20 cm length × 5.5 cm width, 250 g of silica gel) (Notes 23 and 24). The product was eluted with hexanes/ethyl acetate/triethylamine, 93:5:2 (ca. 700 mL of eluent are required before collecting fractions). Fractions 5-30 (50 mL each) were collected and analyzed by thin layer chromatography (TLC), eluting with hexanes/ethyl acetate, 4:1 (R_f = 0.38 for isopropyl 2-diazoacetyl (phenyl)carbamate, R_f = 0.27 for decomposition product). Visualization was accomplished with UV.

23. Silica gel was purchased from Sorbent Technologies Company with the following specifications: porosity 60 Å, particle size 40–64 mm, surface area 450–550 m^2/g.

24. Isopropyl 2-diazoacetyl(phenyl)carbamate decomposes during contact with silica gel. Silica gel deactivated with 2% triethylamine is used to avoid decomposition.

25. Isopropyl 2-diazoacetyl(phenyl)carbamate displayed the following physicochemical properties: R_f = 0.38, mp 61–62 °C; IR (neat) 3145, 2983, 2109, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.14 (d, J = 6.0 Hz, 6 H), 4.94 (sept, J = 6.0 Hz, 1 H), 6.62 (s, 1 H), 7.14–7.12 (m, 2 H), 7.42–7.33 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 51.9, 71.3, 128.1, 128.7, 129.0, 137.7, 153.5, 167.0. HRMS (ESI): Exact mass calcd. for $C_{12}H_{13}N_3O_3$ 247.0957, found 248.1030 $[M+H]^+$. Anal. calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.56; H, 5.36; N, 16.73.

Waste Disposal Information

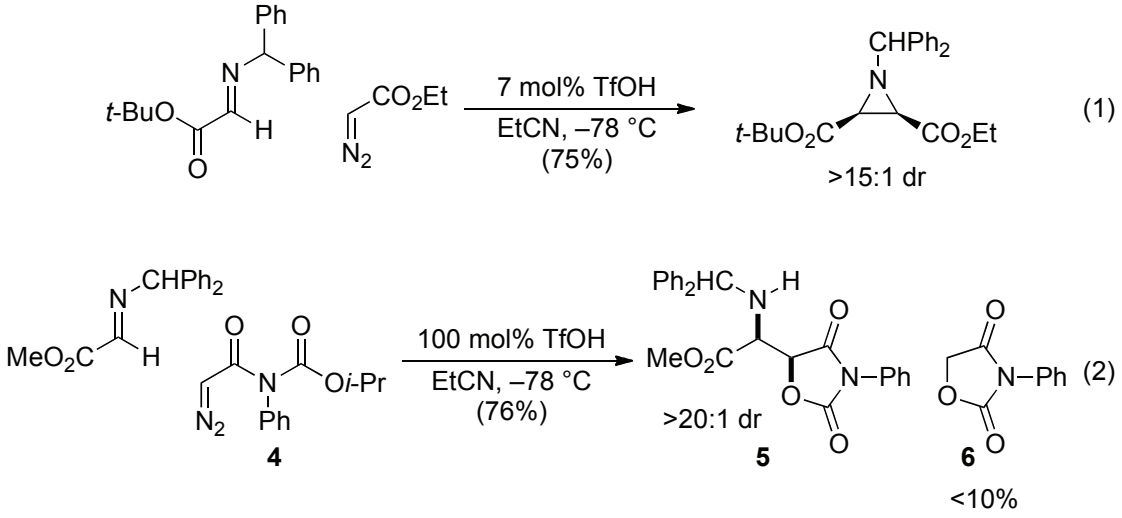
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, 1955.

3. Discussion

Diazo compounds and their chemistry have a long history, and the unique diazo functionality translates into their versatile reactivity. Diazoalkanes have been successfully used as carbene precursors in various useful applications such as cyclopropanation and X–H (X=C, Si, O, S, N) insertion reactions.[7,8] They can also be involved in rearrangement reactions,[9] give rise to ylides,[10] or serve as 1,3-dipoles in [3+2] cycloaddition

reactions.[11] Additionally, they can be used as nucleophiles in addition reactions with carbonyl and azomethine electrophiles.[12]

Scheme 1.



The recent finding that diazo compounds can be effective substrates in carbon-carbon and carbon-heteroatom bond forming reactions when strong Brønsted acids are used as the activating agent (Scheme 1, eq 1)[13] has been followed by the development of a range of new reactions.[14] Moreover, a growing number of examples have revealed that chiral Brønsted acids can promote enantioselective carbon-carbon bond formation using diazoalkane substrates.[15,16] These successes have led to an interest in diazoalkane donors that exhibit reactivity similar to α-diazo esters, but provide new opportunities in product diversity and reaction stereocontrol. We hypothesized that the title diazoalkane (**2**) might provide a new avenue in the reaction map of diazoalkane chemistry. Indeed, we have developed a highly diastereoselective, Brønsted acid promoted *syn*-glycolate Mannich reaction using diazoimide **2** as a donor (Scheme 1, eq 2).[17]

The procedure described here is an optimized synthesis of this reagent on preparative scale. Diazoimide **2** is an acyclic variation of Doyle's oxazolidinone; the conformational mobility of the carbamate allows it to function as an oxygen donor in the *syn*-glycolate Mannich reaction.

Among the plethora of methods reported for obtaining diazo compounds, diazo transfer is one of the most reliable and efficient ways for the synthesis of diazocarbonyl compounds from the corresponding carbonyl compound. This report is an adaptation of the successful procedure reported by Doyle[18] with modifications based on the synthesis of (*E*)-1-diazo-4-phenyl-3-buten-2-one reported by Danheiser.[19]

One challenge that was overcome in the development of this preparation is the avoidance of acid-promoted decomposition of the diazoimide to oxazolidine dione **6**. When isopropyl 2-diazoacetyl(phenyl)carbamate (**2**) alone is subjected to triflic acid at room temperature, oxazolidine dione **4** is exclusively formed. A second development challenge was the preparation of fluorinated intermediate **3**. Near complete conversion of precursor **2** must be achieved for the subsequent step to be successful. If unreacted **2** is present in the diazo transfer step, it is impossible to separate it from diazoimide **4**. Straightforward trituration with a nonpolar organic solvent, such as hexanes, effects the removal of **2** should incomplete conversion occur in this step. Careful temperature control in this step normally provides for full conversion to **3**. Additionally, we obtained spectroscopic data for intermediate **3**, in agreement with the hydrate of the trifluoromethyl ketone[20] and not the enol form observed by Doyle.[18]

Although the yield of the diazo transfer (Step C) is lower than reported examples,[18,19] the desired diazoimide can be prepared as a pure crystalline solid, as determined by combustion analysis.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Isopropyl chloroformate; (108-23-6)
Aniline: benzeneamine; (62-53-3)
Triethylamine: (121-44-8)
n-Butyllithium: lithium, butyl-; (109-72-8)
Acetic anhydride: acetic acid, anhydride; (108-24-7)
1,1,1,3,3,3-Hexamethyldisilazane: silanamine, 1,1,1-trimethyl-*N*-(trimethylsilyl)-; (999-97-3)
Isopropyl acetyl(phenyl)carbamate; Carbamic acid, *N*-acetyl-*N*-phenyl-, 1-methylethyl ester; (5833-25-0)
2,2,2-Trifluoroethyl trifluoroacetate (407-38-5)
4-Acetamidobenzenesulfonyl azide; (2158-14-7)
Carbamic acid, *N*-(2-diazoacetyl)-*N*-phenyl-, 1-methylethyl ester; (1198356-59-0)

1. Department of Chemistry & Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, TN 37235-1822. E-mail: jeffrey.n.johnston@vanderbilt.edu. This work was supported by the NSF (CHE-0848856). H. M. is grateful for support by a Warren Fellowship (2009).

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Jeffrey N. Johnston completed his B.S. Chemistry degree at Xavier University in 1992 and a Ph.D. in organic chemistry at The Ohio State University in 1997 with Prof. Leo A. Paquette. He then worked as an NIH postdoctoral fellow with Prof. David A. Evans at Harvard University. He began his independent career at Indiana University, where he was promoted to Professor of Chemistry in 2005. In 2006, his research program moved to Vanderbilt University. His group has developed a range of new reactions and reagents that are used to streamline the total synthesis of complex alkaloid natural products. The development of new Brønsted acid-catalyzed reactions, as well as chiral proton catalysts, are ongoing investigational themes.

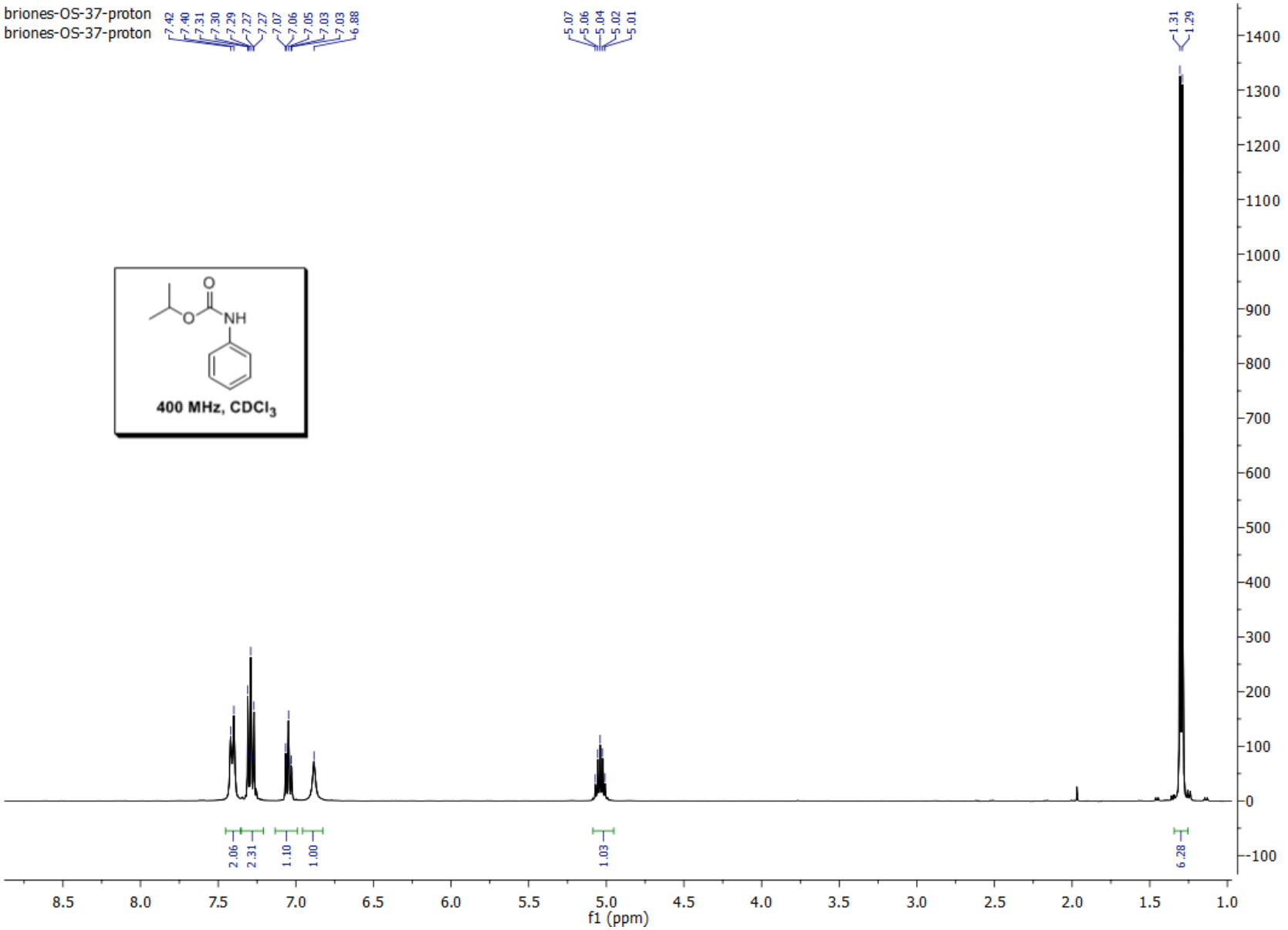
Hubert Muchalski, a native of Poland, received his B.S./M.S. degree in chemistry from Wrocław University of Technology in 2006. He is currently a graduate student with Prof. Johnston at Vanderbilt University, where he has broadened the scope of the Brønsted acid catalyzed aza-Darzens and syn-glycolate Mannich reactions while exploring new reactions based on diazoimides.

Amanda Doody was raised in Martin, Georgia, and completed her B.S. Chemistry degree (summa cum laude) from Wofford College in South Carolina in 2008. During the summer of 2007, she was an NSF-REU student at Columbia University working with Gerard Parkin. She matriculated at Vanderbilt in 2008. Under the mentorship of Prof. Johnston, Amanda's graduate research is focused on the development of Brønsted acid catalyzed additions of diazo-ylides to electrophiles and their applications in alkaloid total synthesis.

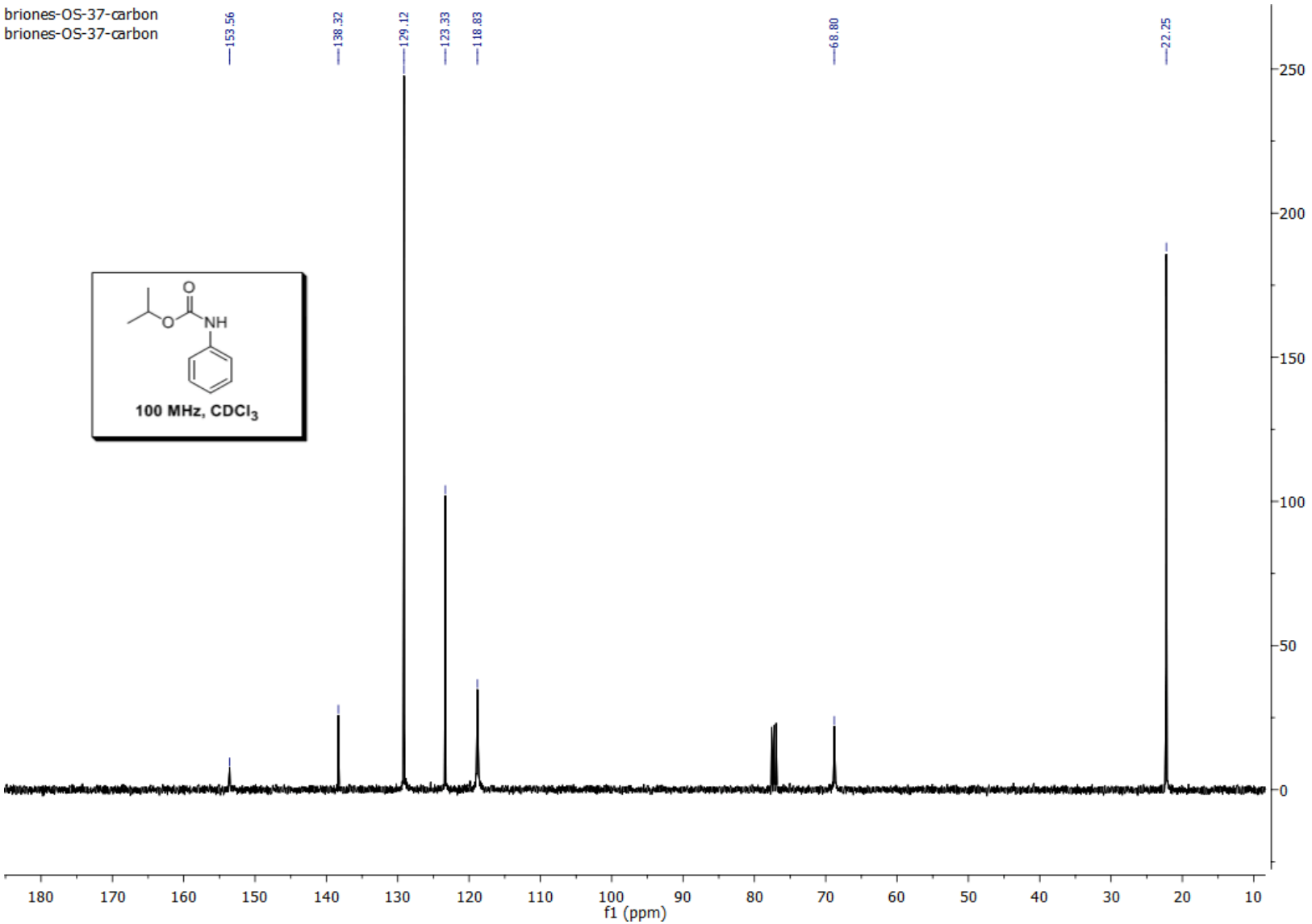
Timothy L. Troyer received his B.S. degree in chemistry from Goshen College in 1996. Following a stint in medicinal chemistry at Bristol Myers Squibb (CT), he began graduate studies with Prof. Johnston where he investigated the mechanism of the aza-Darzens reaction and developed a new Brønsted acid catalyzed syn-glycolate Mannich reaction. This work led to a Ph.D. in Chemistry in 2008 from Vanderbilt University. He is currently an Assistant Professor of Chemistry at West Virginia Wesleyan College with interests in new organocarbenes and the isolation of bioactive natural products.

John Frederick Briones was born in 1982 in Laguna, Philippines. He earned his B.S. degree in Chemistry from the University of the Philippines, Los Banos in 2003 and later on pursued his Master's degree at the University of the Philippines, Diliman. He joined the research lab of Prof. Huw Davies in 2007, and currently his research project focuses on Rh(II) catalyzed enantioselective transformations of alkynes.

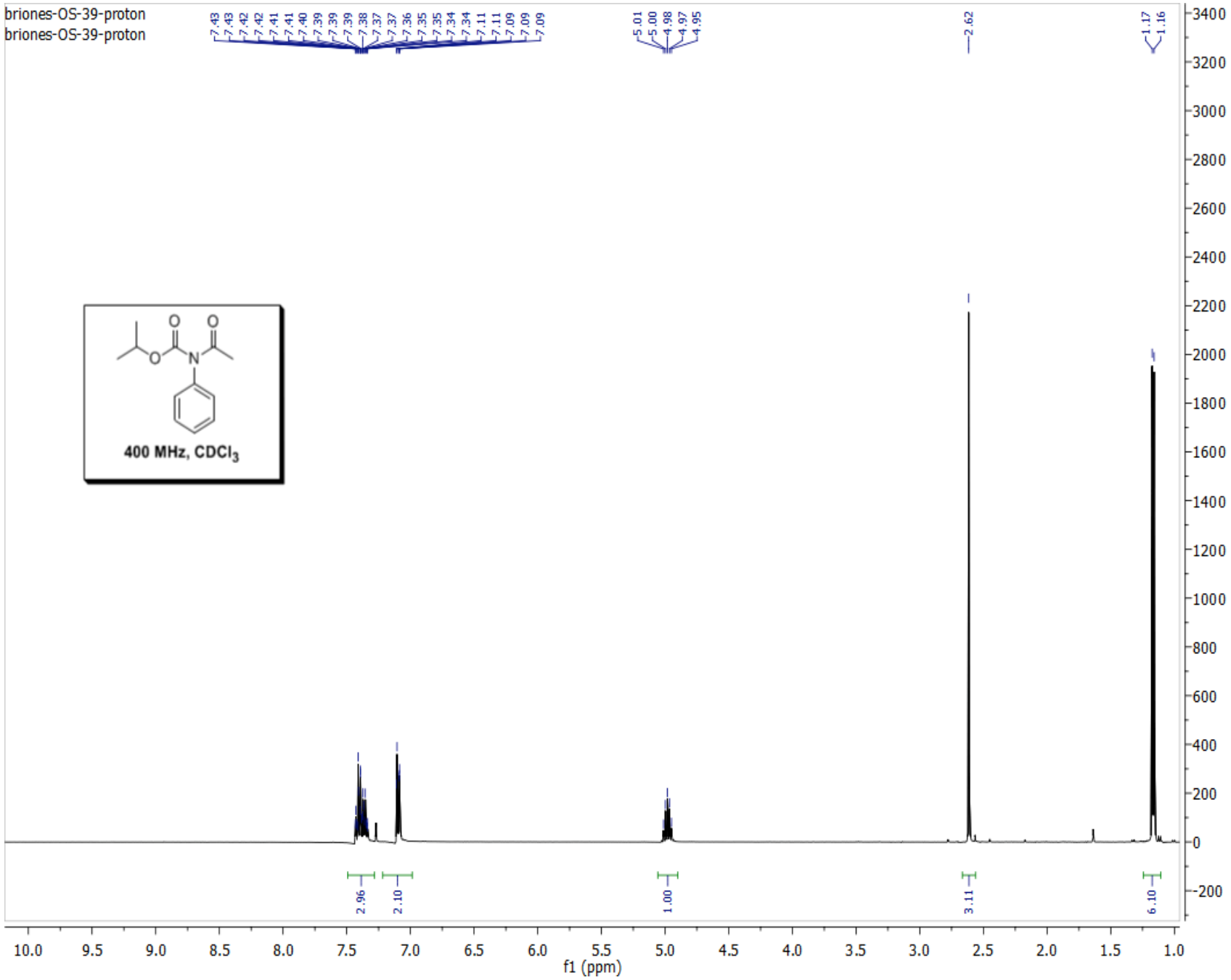
^{1}H NMR of Isopropyl phenylcarbamate



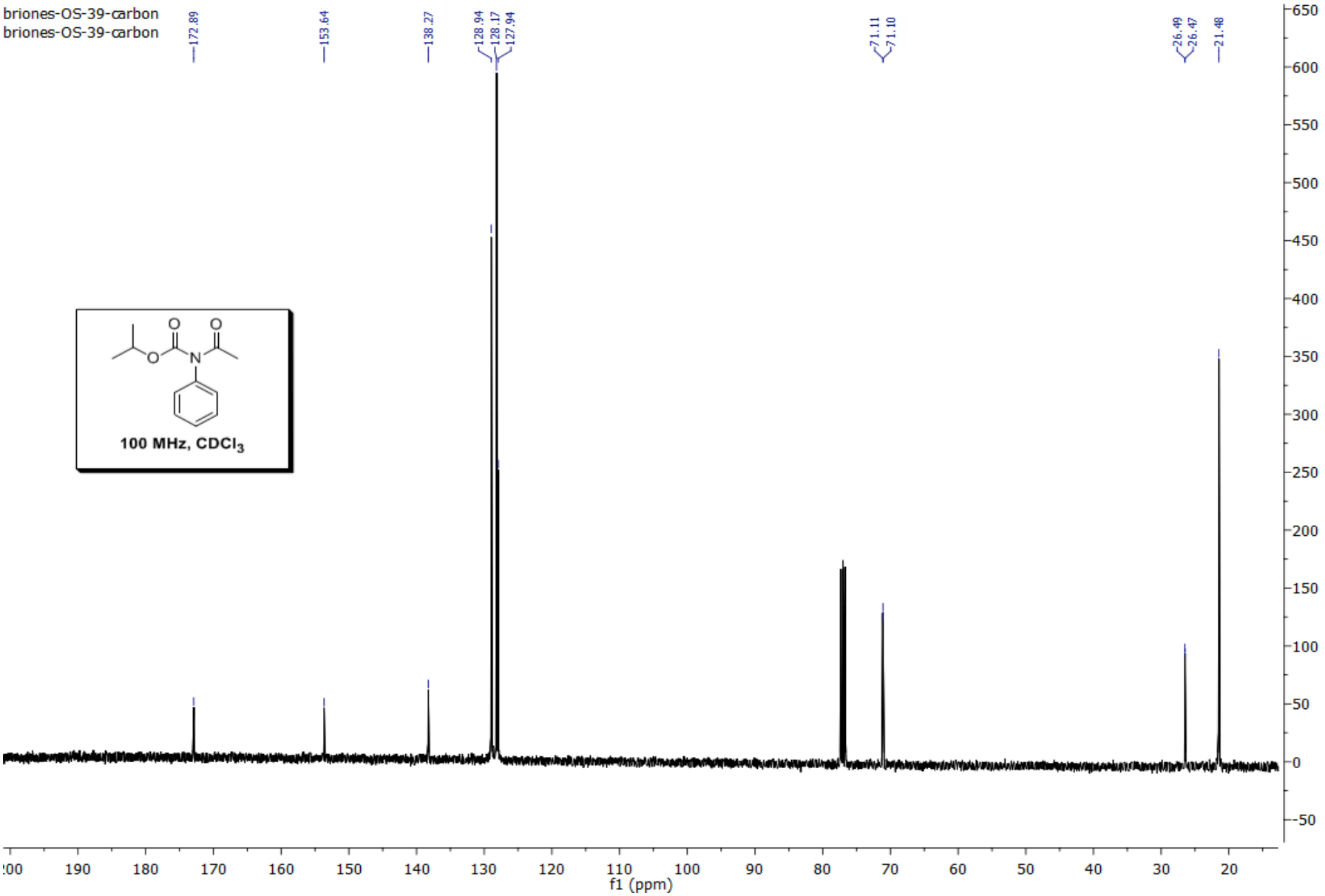
^{13}C NMR of Isopropyl phenylcarbamate



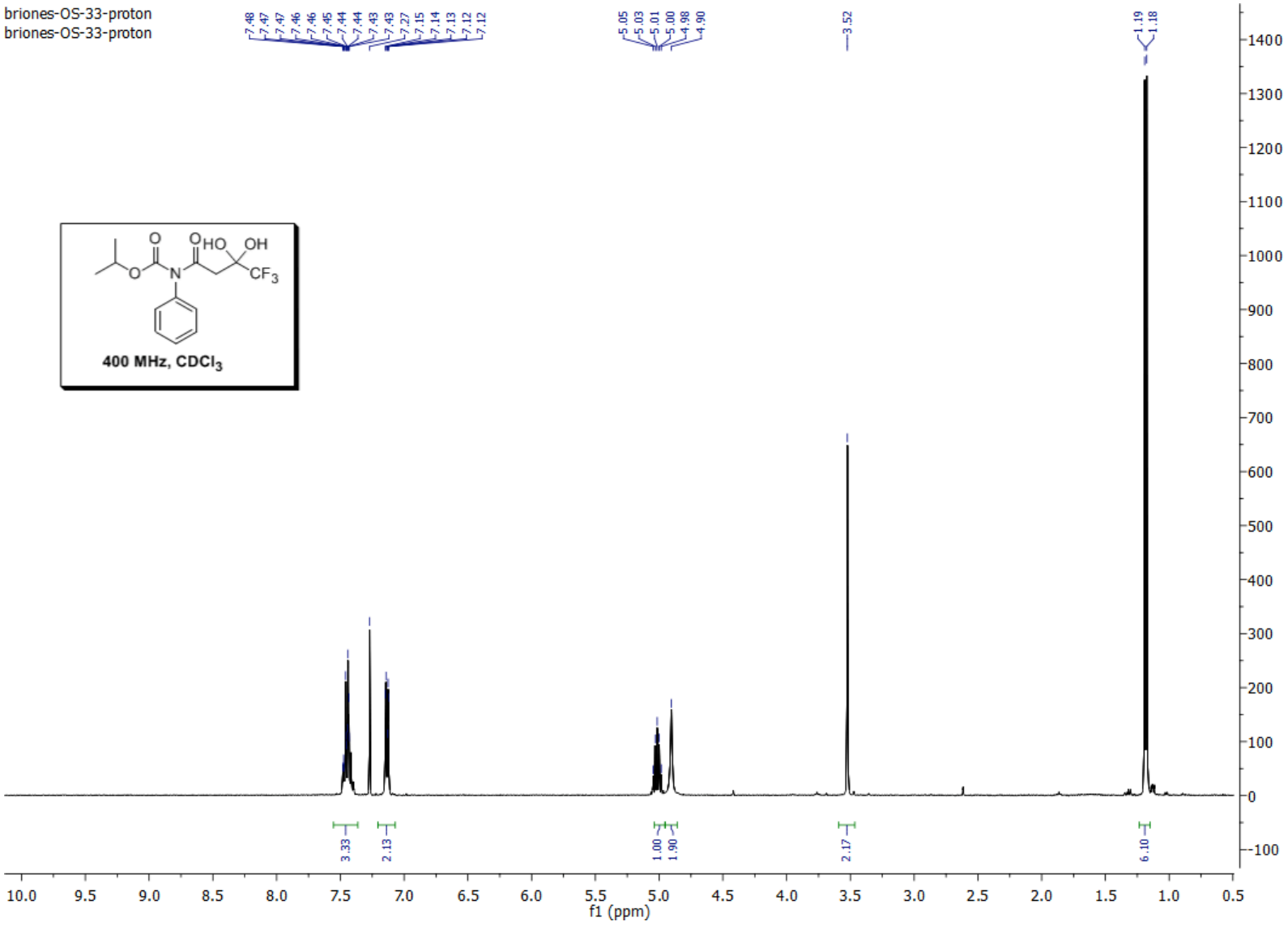
^{1}H NMR of Isopropyl acetyl(phenyl)carbamate (**2**)



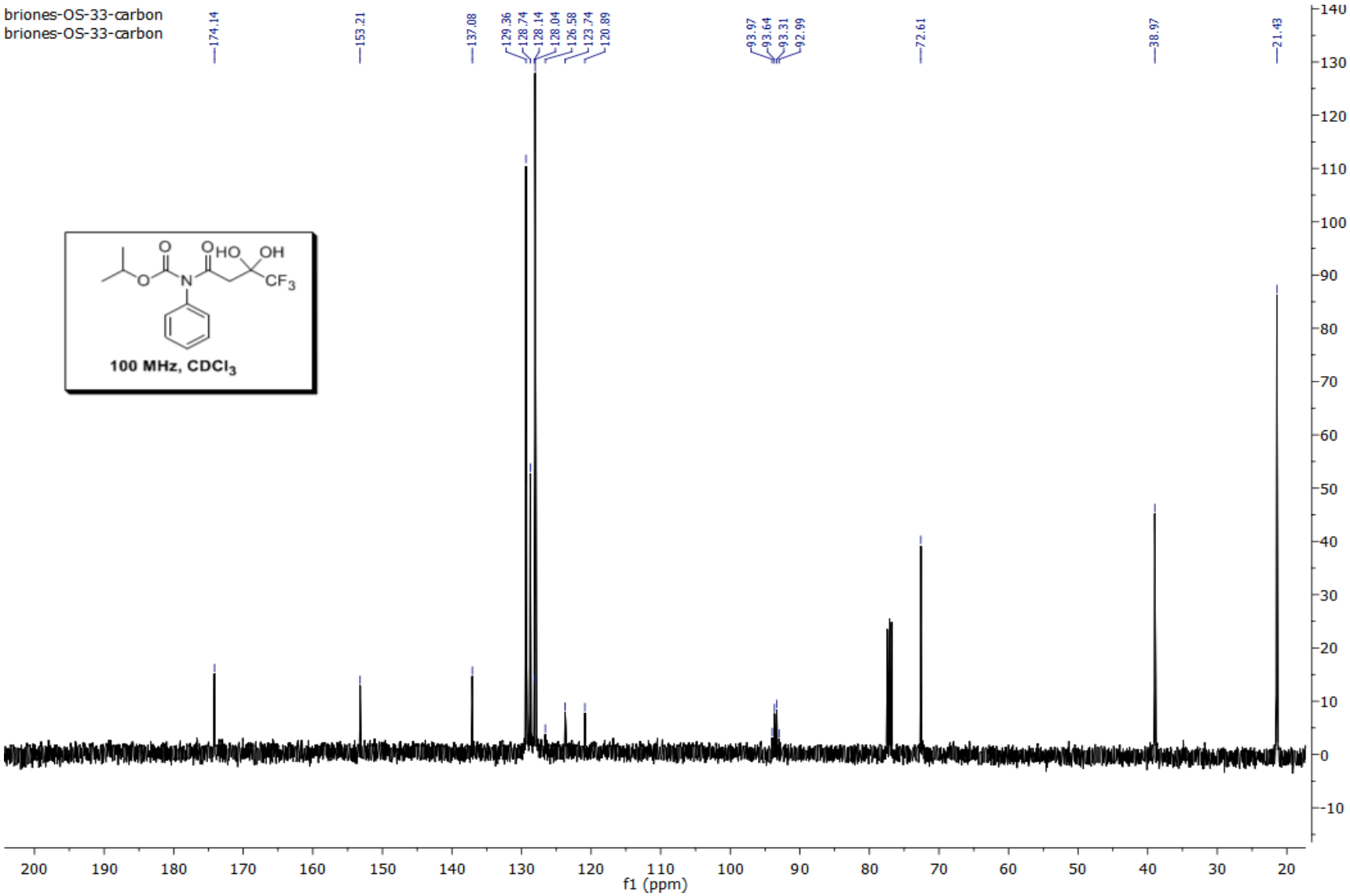
^{13}C NMR of Isopropyl acetyl(phenyl) carbamate (**2**)



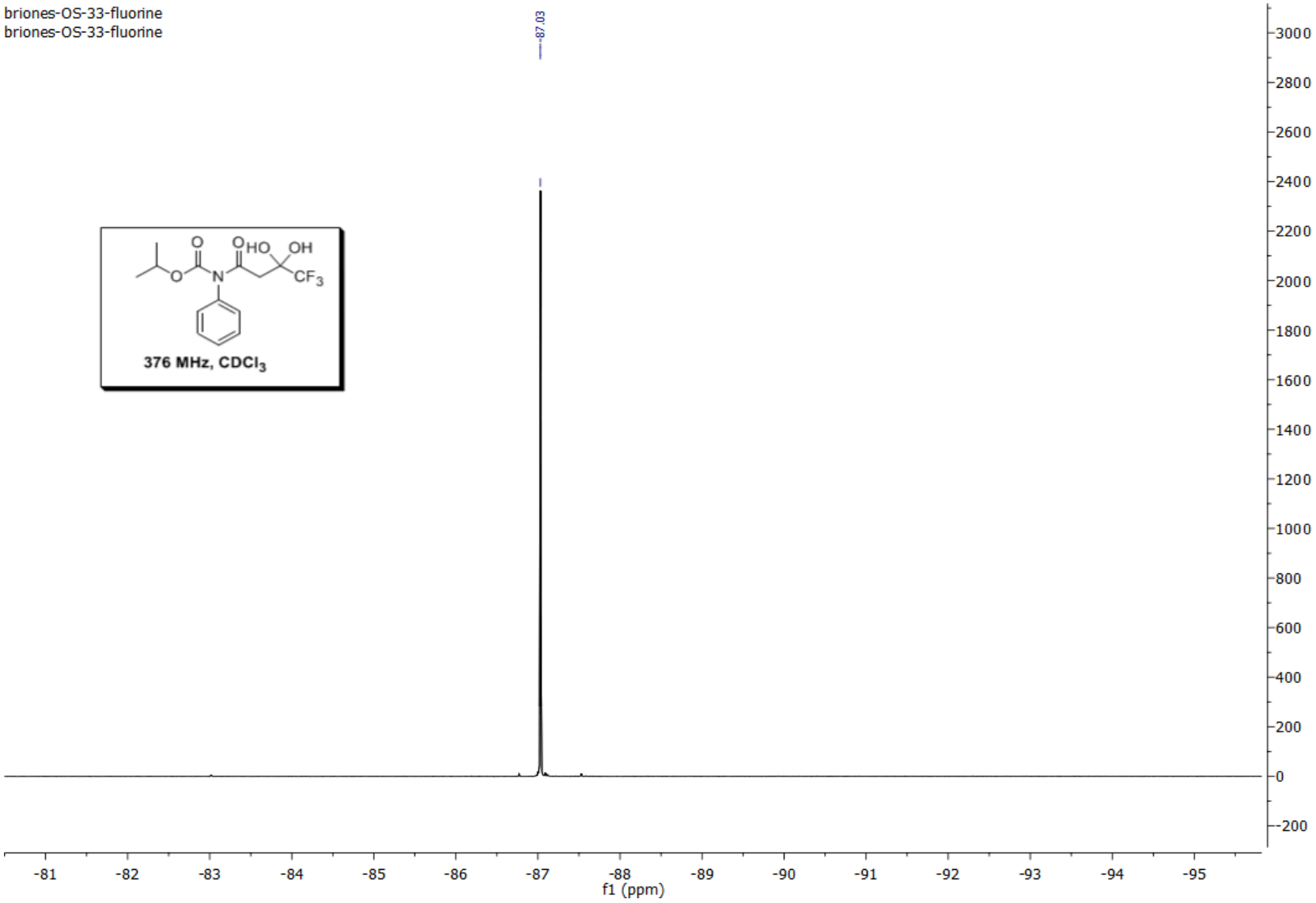
^{1}H NMR of Isopropyl phenyl(4,4,4-trifluoro-3,3-dihydroxybutanoyl)carbamate (**3**)



^{13}C NMR of Isopropyl phenyl(4,4,4-trifluoro-3,3-dihydroxybutanoyl)carbamate (**3**)



^{19}F NMR of Isopropyl phenyl(4,4,4-trifluoro-3,3-dihydroxybutanoyl)carbamate (**3**)



^{1}H NMR of Isopropyl 2-diazoacetyl(phenyl)carbamate (**4**)