Organic Syntheses

Syntheses of Substituted 2-Cyano-benzothiazoles

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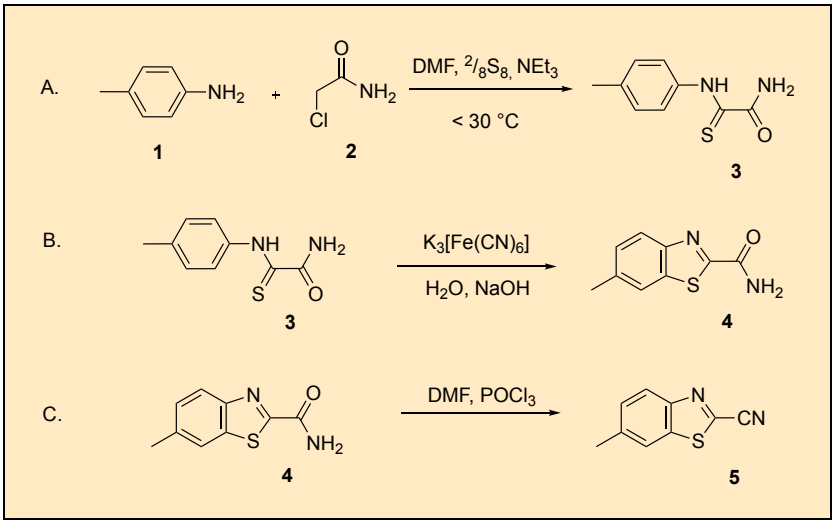

Procedure (Note 1)

A. *2-Thioxo-2-(p-tolylamino)acetamide (**3**).* A 500-mL, three-neck, round-bottomed flask is equipped with a 4-cm egg-shaped teflon-coated magnetic stir bar, a rubber septum with a thermometer inserted through it, and a stopper, leaving the central neck open (Figure 1). To the flask are added dimethylformamide (DMF) (250 mL) (Note 2), *p*-toluidine (30.3 g, 280 mmol, 1 equiv), sulfur (18.0 g, 560 mmol, 2 equiv) and triethylamine (NEt_3) (120 mL, 861 mmol, 3 equiv) (Note 3), and the contents of the flask are stirred at 700 rpm at 23 °C. Approximately 1 g portions of

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2-chloroacetamide (31.5 g, 340 mmol, 1.2 equiv) (Note 4) are added every two minutes over the course of an hour (Note 5) (Figure 2). The temperature of the reaction slowly increases upon addition of 2-chloroacetamide, and after approximately 16 min the internal temperature reaches 25 °C. The flask is then cooled using a 10 °C water bath, and the internal temperature of the reaction is maintained between 16–19 °C by occasional addition of ice to the water bath. Halfway through the addition, the stirring rate is increased to 850 rpm to account for the increasing viscosity of the reaction mixture. After complete addition, the vessel is protected against moisture with a drying tube filled with calcium chloride and is left to stir at 23 ºC for an additional 12 h (Note 6).

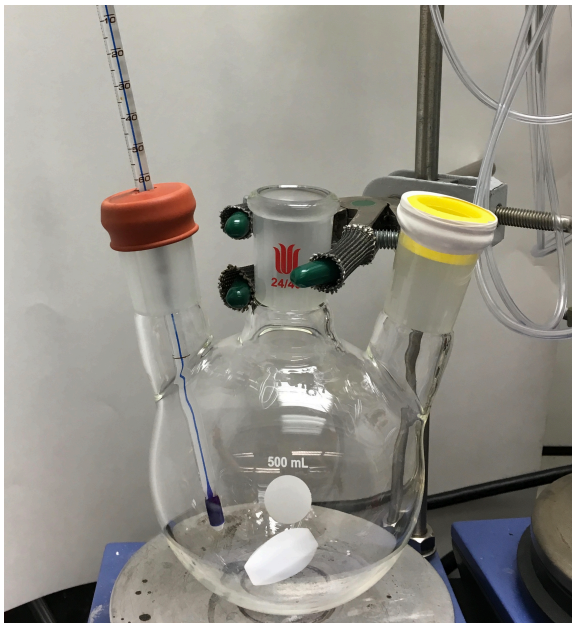


Figure 1. Reaction setup for step A

After that time, the reaction mixture is poured into 2.5 L deionized water acidified with 30 mL of concentrated HCl. The resulting precipitate is vacuum filtered using a medium-porosity 15 cm diameter glass frit. The crude material (**3**) is dissolved in 2.8 M NaOH in deionized water (150 mL) and then vacuum filtered using a 6 cm diameter Büchner funnel lined with filter paper (grade 413) to obtain a yellow solution of the thioamide (**3**). The

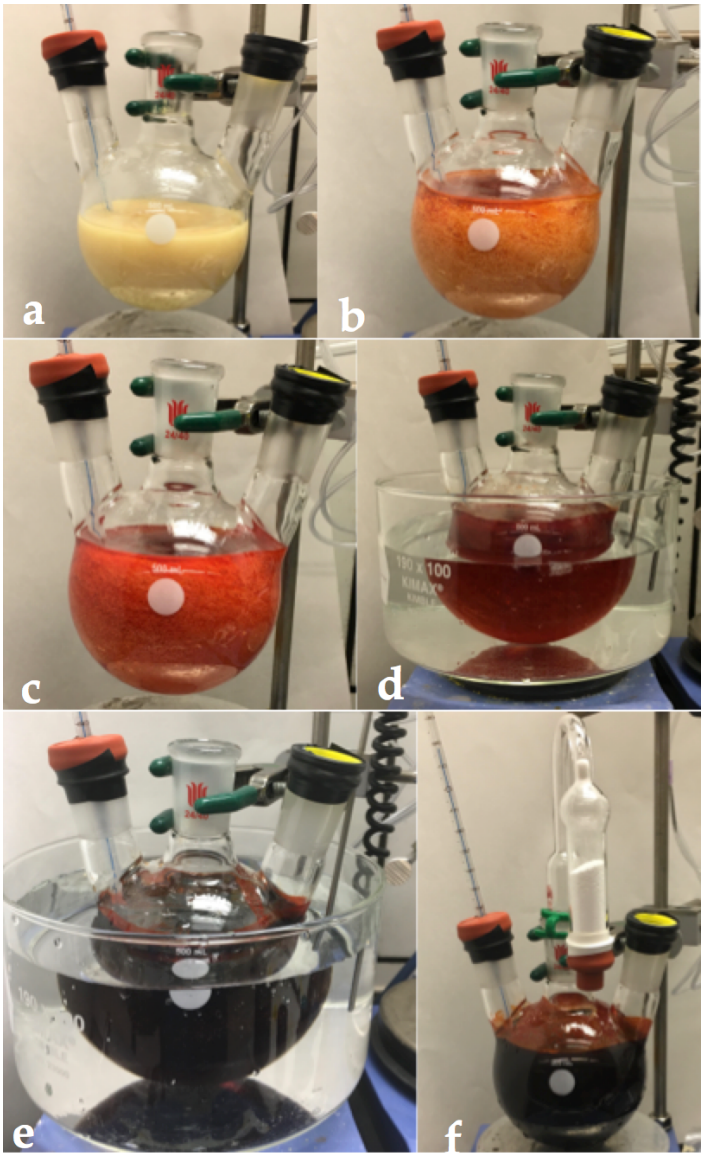


Figure 2. a: Before 2-chloroacetamide addition. b-e: Reaction darkens as 2-chloroacetamide is added. f: Drying tube attached to stir 12 h

basic solution is added dropwise to 1 L of deionized water acidified with concentrated HCl (30 mL). The product that precipitates is collected by

vacuum filtration with a medium-porosity 7 cm diameter glass frit and washed with deionized water (2 x 550 mL). The product is dissolved in 300 mL isopropyl alcohol heated to 75–80 °C using a heat gun (Note 7), then allowed to recrystallize at 23 ºC for 18 h. The resulting yellow crystals are collected via vacuum filtration through a medium-porosity 7 cm diameter glass frit and dried at 60 °C at 0.15 mmHg for 24 h to provide 17.5 g (32%) of compound **3** (Notes 8, 9, and 10) (Figure 3).

Figure 3. 2-Thioxo-2-(*p*-tolylamino)acetamide (3) recrystallized from isopropyl alcohol

B. *6-Methylbenzo[d]thiazole-2-carboxamide (**4**).* Potassium ferricyanide (141 g, 429 mmol, 4.82 equiv) is dissolved in 1.2 L deionized water in a 2 L Erlenmeyer flask equipped with a 7.5 cm Teflon-coated stir bar and allowed to stir at 23 °C. Compound (**3**) (17.3 g, 89 mmol, 1 equiv) (Note 11) is dissolved in 3 M NaOH (100 mL, prepared with deionized water) by heating to 30–40 °C with a heat gun, and the warm solution is transferred to a 125 mL addition funnel. The solution is then added dropwise to the stirring solution of potassium ferricyanide (500 rpm) over 1 h (Note 12). The addition should be performed under a good working fume hood (Note 13). After a small amount of compound (**3**) is added the product (**4**) begins to precipitate. Over the course of the addition the reaction changes color from orange to green to yellow (Figure 4). After the complete addition of the

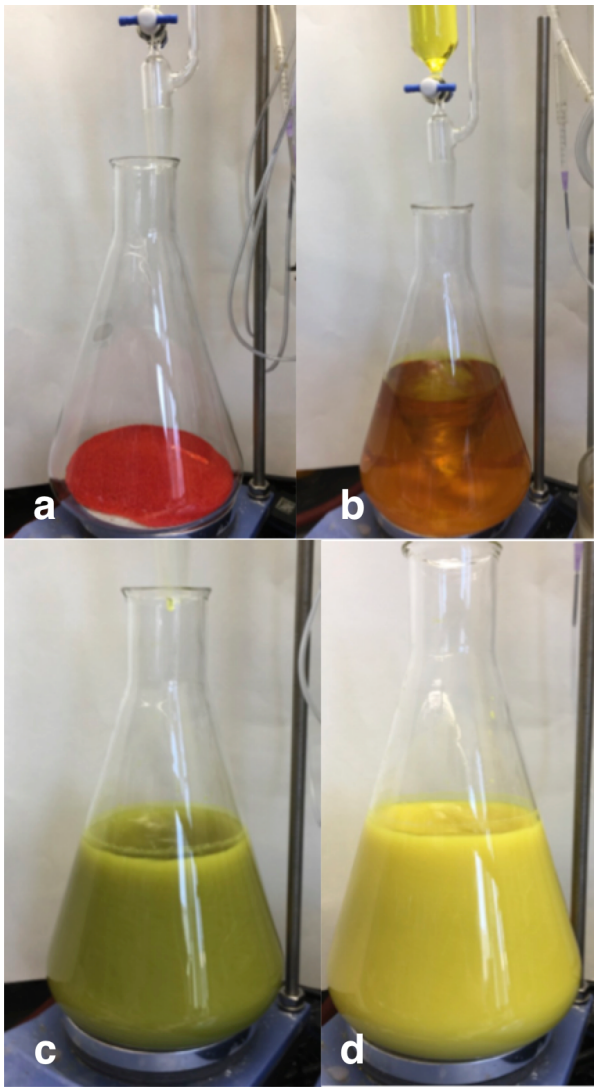


Figure 4. Reaction setup (a,b) and progress (c,d) for step B

thioamide, the stirring is continued for 30 min. The precipitate is collected by vacuum filtration on a medium-porosity 7 cm diameter glass frit, and the solid is washed with distilled water until the filtrate is clear and colorless (2 L). The product (**4**) is then dried for 24 h at 60 °C at 0.15 mmHg. The

dried material is dissolved in DMF (Note 2) (30 mL DMF per 5 g), heating to 110–120 °C with a heat gun (Note 7). After cooling to 23 °C, the flask is placed in a refrigerator (5 °C) and allowed to recrystallize for 15 h. The product is collected by vacuum filtration through a medium-porosity 2 cm diameter glass filter frit, washed with diethyl ether (3 x 20 mL), and dried for 24 h at 80 °C at 0.15 mmHg to provide 10.3 g (60 %) of a crystalline solid (Notes 14, 15, and 16) (Figure 5).

Figure 5. 6-Methylbenzo[d]thiazole-2-carboxamide recrystallized from DMF

C. *6-Methylbenzo[d]thiazole-2-carbonitrile* (**5**). In a 250-mL, three-necked, round-bottomed flask equipped with a 2-cm Teflon-coated magnetic stir bar, a septum, and a thermometer, dry DMF (100 mL) (Note 17) and compound **4** (6.0 g, 31.2 mmol, 1 equiv) are added, and the mixture is cooled to 0 °C in an ice-water bath. Over the course of 12–14 min phosphorous (V) oxychloride (4.8 mL, 51 mmol, 1.65 equiv) (Note 18) is added dropwise via syringe, while maintaining an internal temperature no greater than 5 °C. After the addition is complete, the mixture is removed from the cooling bath and allowed to warm to 23 °C (Figure 6). During this period the starting material reacts leading to a clear yellow solution from which TLC samples are taken to monitor reaction progress (Note 19). After about 1 h the reaction is complete as judged by disappearance of starting material by TLC. The reaction is poured into deionized water (500 mL). The

resulting white precipitate is filtered through a 4.5 cm diameter medium porosity fritted filter and washed with deionized water until the filtrate is neutral (500–750 mL). The product is dried in a vacuum desiccator for 24 h

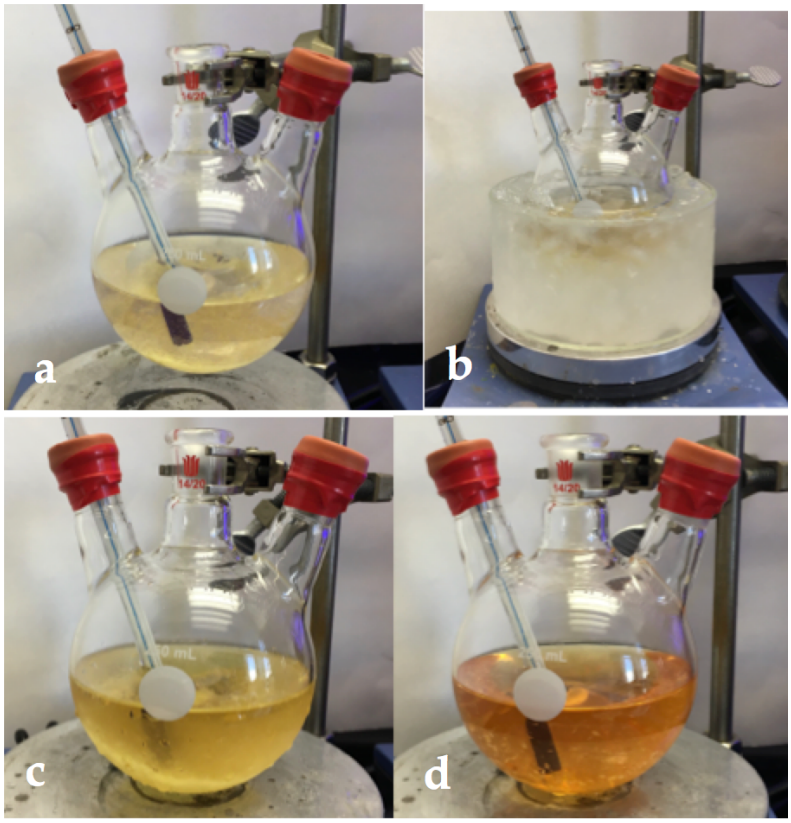


Figure 6. a: compound 4 dissolved in DMF. b: ice bath for phosphorous (V) oxychloride addition. c,d: color change as reaction progresses

at 0.15 mmHg over calcium chloride. The crude material is dissolved in *n*-heptane (80 mL) heated to 70–80 °C using a heat gun (Note 7). A small amount of brown residue remains undissolved, and is removed by vacuum filtration using a 6 cm diameter Büchner funnel lined with filter paper (grade 413). The filtrate is re-heated to dissolve any material that prematurely precipitated, and then the product is allowed to recrystallize for 18 h at 23 ºC. The product is collected via vacuum filtration through a

4.5 cm diameter medium porosity fritted filter to obtain off-white crystals (3.6 g, 66%) (Notes 20, 21, and 22). The overall yield starting from 30 g of compound **1** ranges from 13 - 15%.

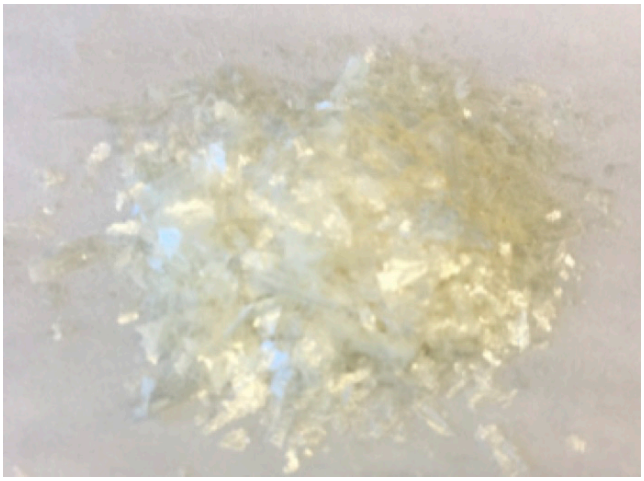


Figure 7. 6-Methylbenzo[d]thiazole-2-carbonitrile

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, as well as the proper procedures for dimethylformamide, *p*-toluidine, triethylamine, sulfur, 2-chloroacetamide, calcium chloride, concentrated hydrochloric acid, sodium hydroxide, isopropyl alcohol, potassium ferricyanide, phosphorous (V) oxychloride, and *n*-heptane.

2. Dimethylformamide (99.5 %) was obtained from TCI Deutschland GmbH and used as received. The checkers obtained 99.5% DMF from TCI America.
3. *p*-Toluidine (99 %), sulfur (99 %) and triethylamine (99 %) were obtained from ABCR-GmbH Germany and used as received. The checkers obtained *p*-toluidine (99 %) and triethylamine (99 %) from Aldrich and sulfur from Strem (≥99 %).
4. 2-Chloroacetamide (98.5 %) was purchased from Sigma Aldrich Germany and used as received. The checkers obtained 2-chloroacetamide from Aldrich (≥98 %).
5. During each addition the brown slurry becomes partially red; an exothermic reaction occurs over time. If the addition is carried out too rapidly, temperatures of > 60 °C could be observed, leading to a remarkable decrease in yield.
6. The drying tube should not produce a closed system.
7. Care should be taken to remove any extraneous flammable solvent from proximity of the heat gun.
8. Melting point: 170–173 °C (isopropyl alcohol); IR (thin film): 3385, 3229, 3166, 1700, 1548, 1532, 1403, 1386, 1299, 1176, 1104, 1045, 822, 782, 768, 738, 652 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) δ: 2.31 (s, 3H), 7.19–7.28 (m, 2H), 7.79–7.89 (m, 2H), 8.13 (d, J = 19.6 Hz, 2H), 12.04 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ: 20.8, 38.9, 39.1, 39.3, 39.5, 39.7, 39.9, 40.2, 123.2, 129.0, 136.0, 136.2, 162.4, 185.7. HRMS [M + H] calcd for $C_9H_{11}N_2OS$: 195.0592. Found: 195.0590. TLC: R_f = 0.63 in 50% *n*-heptane-ethylacetate (1:1 *n*-heptane:ethylacetate) solvent system.
9. Purity of the product was assessed as >98% by Q NMR using ethylene carbonate as the internal standard.
10. A second reaction performed on equivalent scale provided 18.0 g (33%) of the identical product.
11. Potassium hexacyanoferrate (III) (98 %) was purchased from Applichem GmbH and used without further purification. The checkers obtained potassium hexacyanoferrate (III) from Alfa Aesar (≥98 %).

12. The solution in the addition funnel cools to 23 °C over the course of the addition. Gentle heating of the joint of the addition funnel may be necessary to break up clogs.
13. During the addition, toxic vapors evolve.
14. Melting point 252–254 °C (DMF); IR (ATR): 3305, 3167, 1689, 1651, 1615, 1498, 1393, 1141, 1111, 1079, 1049, 810, 699 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) δ: 2.47 (s, 3H), 7.35–7.51 (m, 1H) 7.92–8.11 (m, 3H), 8.44 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ: 21.2, 38.9, 39.1, 39.3, 39.5, 39.7, 39.9, 40.2, 122.4, 123.6, 128.66, 136.6, 136.9, 151.0, 161.4, 163.8. [M + H] calcd for $C_9H_9N_2OS$: 193.0436. Found: 193.0427. TLC R_f = 0.54 in 50% *n*-heptane-ethyl acetate (1:1 *n*-heptane:ethyl acetate) solvent system.
15. Purity of the product was assessed as >97% by Q NMR using ethylene carbonate as the internal standard.
16. A second reaction performed on equivalent scale provided 11.5 g (67%) of the identical product. The submitters reported yields of 7.1–7.4 g (38–40%) of material with mp = 254–255 °C.
17. Dry dimethylformamide (99.8 %) extra dry over molecular sieves were purchased from Acros Organics and used as received.
18. Phosphorous (V) oxychloride (99 %) was purchased from Fisher Scientific GmbH and used as received. The checkers obtained phosphorous (V) oxychloride from Alfa Aesar (99 %).
19. The TLC is run with *n*-heptane-ethyl acetate (1:1) on silica gel 60 coated (0.2 mm) aluminum plates with fluorescence indicator UV_{254}. R_f of compound **5** = 0.78
20. Melting point: 86–88 °C (*n*-heptane); IR (thin film): 3417, 2943, 2228, 1642, 1453, 1316, 1244, 1133, 816 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52–2.59 (m, 3H), 7.46 (ddd, *J* = 8.4, 1.6, 0.5 Hz, 1H), 7.75 (dq, *J* = 1.6, 0.8 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 22.0, 76.8, 77.2, 77.5, 113.3, 121.4, 124.8, 129.9, 135.4, 135.8, 139.7, 150.6. HRMS [M + H] calcd for $C_9H_7N_2O$: 175.0330. Found: 175.0335.
21. Purity of the product was assessed as >98% by Q NMR using ethylene carbonate as the internal standard.
22. A second reaction performed on equivalent scale provided 3.6 g (66%) of the identical product.

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.

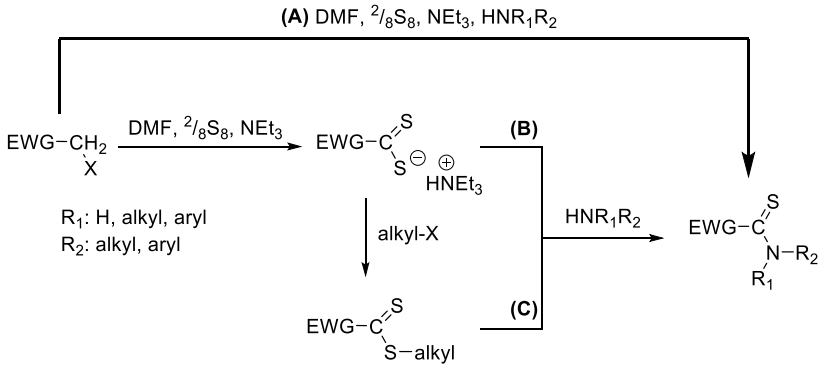
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior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

Thioamides are a very distinguished group of chemical compounds with a broad spectrum of applications,[2] including in tuberculosis medication.[3] Furthermore the compounds are used for synthesis of heterocyclic compounds – especially thiazoles and benzothiazoles[4a,b] – and have been applied as building blocks for Firefly Luciferin precursors.[5a,b]

A drawback of this compound class is its typical preparation route, which makes use of hazardous compounds such as phosphorus pentasulfide and hydrogen sulfide.[6] An efficient and selective method for the preparation of thioamides is the aminolysis of dithiocarboxylates, which can be synthesized *in situ* by oxidation of CH-acidic compounds such as 2-chloroacetamide or α-halo acetophenones at 23 °C.[7] This "mild thiolation" method utilizes elemental sulfur in an aprotic polar solvent such as DMF and a tertiary amine base, thereby avoiding harsher conditions.[8] Into a mixture of sulfur, base and solvent, the CH-acidic compound is added slowly, forming the dithiocarboxylate, which can be further transformed into dithiocarboxylic acid esters or thioamides (Scheme 1).



Scheme 1. Mechanism of the thioamide formation. (A) one-pot synthesis as used in the described procedure above. (B) Step wise protocol. (C) Step wise protocol for the thioamide formation employing amines with low nucleophilicity.

The amine employed for the thioamide synthesis can already be present at the beginning of the oxidation reaction or be added later (Scheme 1, A and B). The simple isolation of the reaction product is also a benefit in the "mild thiolation" strategy. The reaction mixture is poured into an excess of water and the product is filtered off. Due to the crystalline nature of the thioamide, recrystallization provides an efficient and simple method to purify the product. The synthetic scope of this reaction procedure was reviewed earlier.[9] The second step, a Jacobsen cyclization, employs a basic aqueous solution of the thioamide and potassium hexacyanoferrate(III).[10] The resulting benzothiazole precipitates as the thioamide is added. This cyclization method can be applied for *p*-alkyl and *p*-alkoxy-substituted

thioamide derivatives; however, *p*-hydroxy or *p*-nitro aniline derivatives are incompatible substrates for this cyclization due to the single electron transfer processes involved in the cyclization step.[11] The colorless benzothiazole carboxamide can be easily dehydrated. An early method employs boiling phosphorus oxychloride as the dehydration reagent.[12] More recently, it was shown that a small excess (1.05 to 1.2 equiv.) of this reagent in DMF at low temperatures is sufficient to form the corresponding nitrile.[13] In the procedure presented here 1.65 equiv. of the dehydrating reagent had to be applied. It is believed that a Vilsmeier-Haack complex is responsible for this mild dehydration.

The "mild thiolation" concept illustrated in this paper offers an excellent synthetic route to dithiocarboxylic acid derivatives. The transformation into a benzothiazole and subsequent dehydration shows how precursor structures for Firefly luciferin derivatives can be obtained with only moderate synthetic effort.

References

1. Institute of Organic Chemistry and Macromolekular Chemistry, Friedrich-Schiller University, 07743 Jena, Germany. E-mail: hendryk.wuerfel@uni-jena.de. The authors are grateful for the financial support of Prof. Dr. Rainer Beckert and Prof. Dr. Thomas Heinze.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

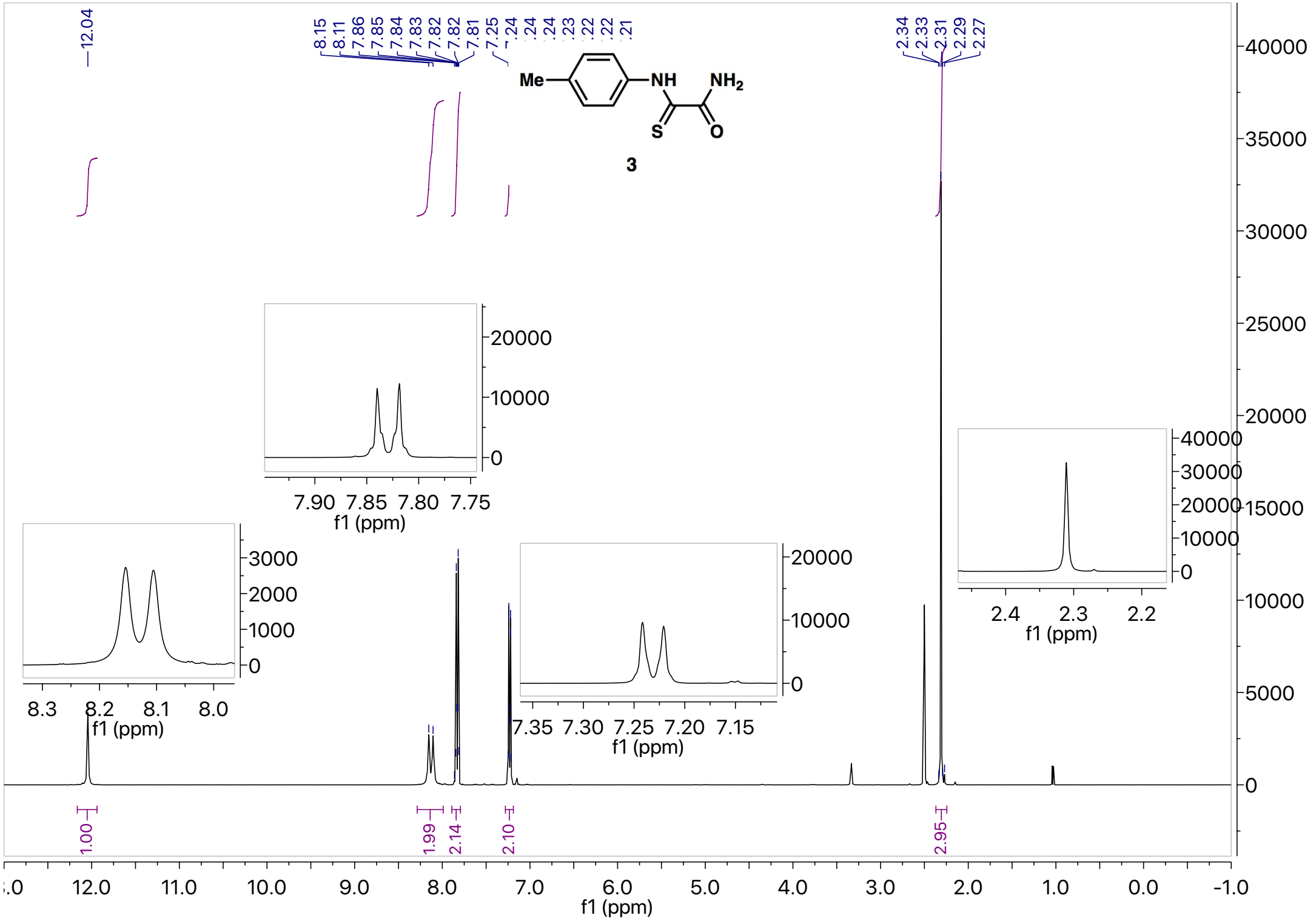
Dimethylformamide: *N*,*N*-Dimethylformamide; (68-12-2)
p-Toluidine: 4-Aminotoluene; (106-49-0)
Sulfur: sulfur (7704-34-9)
Triethylamine: triethylamine; (121-44-8)
2-Chloro Acetamide: 2-chloro acetamide; (79-07-2)
HCl: hydrochloric acid; (7647-01-0)
NaOH: sodium hydroxide; (1310-73-2)
Potassium ferricyanide: Potassium hexacyanoferrate(III); (13746-66-2)
heptane: *n*-heptane; (142-82-5)
Posphoroxychloride: Phosphor(V)-oxychloride (10025-87-3)

Hendryk Würfel recieved his diploma in organic chemistry from the Friedrich-Schiller university (FSU) Jena (Germany) in 2009. He finished his thesis in 2012 at the same institute and did a three year postdoctoral stay at the group of Prof. S. Spange in Chemnitz (Germany). He is currently employed as scientific researcher at the Friedrich-Schiller University - Jena in the group of Prof. T. Heinze and works with photoactive Polysaccharide derivatives.

Dörthe Jakobi received her diploma in organic chemistry from the Friedrich-Schiller university (FSU) Jena (Germany) in 2015. She works currently as Ph.D. student in the group of Prof. Rainer Beckert (Friedrich-Schiller University). Her research includes fluorescent nitrogen containing heterocycles.

Caitlin Lacker received her B.S. in Chemistry from Southwestern University in Georgetown, Texas in 2016. During her time there, she conducted research in the lab of Dr. Michael Gesinski on the synthesis and application of a novel, gold-cleavable protecting group for alcohols. Currently, Caitlin is a graduate student at the California Institute of Technology in the lab of Professor Sarah Reisman, focusing on the development of new, asymmetric methodologies.

Travis DeLano received his B.S. in Chemistry from Northeastern University in Boston, Massachusetts in 2017. While at Northeastern, Travis conducted medicinal chemistry research in the lab of Professor Michael Pollastri, and worked at both Takeda Pharmaceuticals and Vertex Pharmaceuticals. Travis is currently a graduate student in the lab of Sarah Reisman at the California Institute of Technology, where he is focused on the development of asymmetric nickel-catalyzed reductive cross coupling reactions.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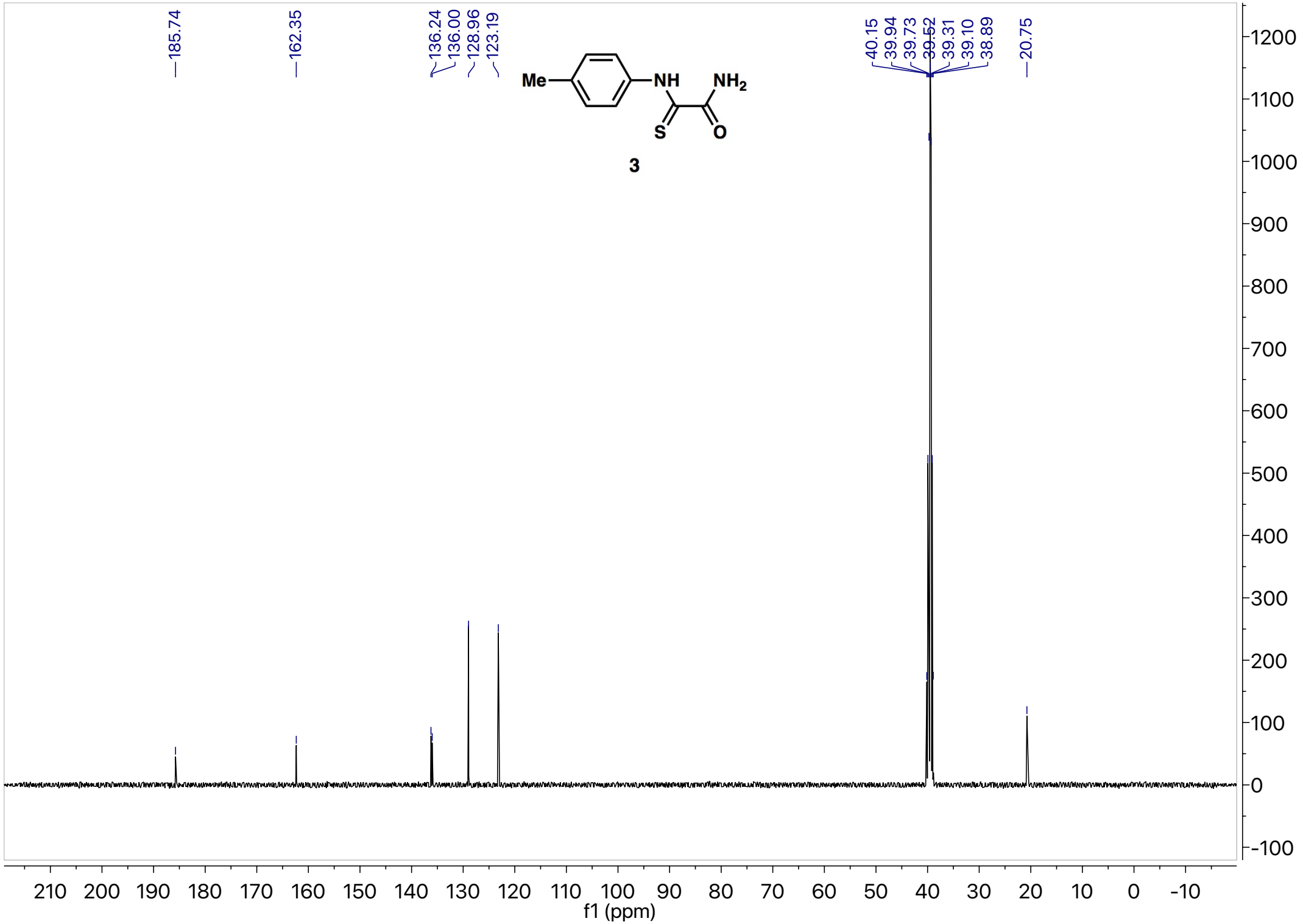
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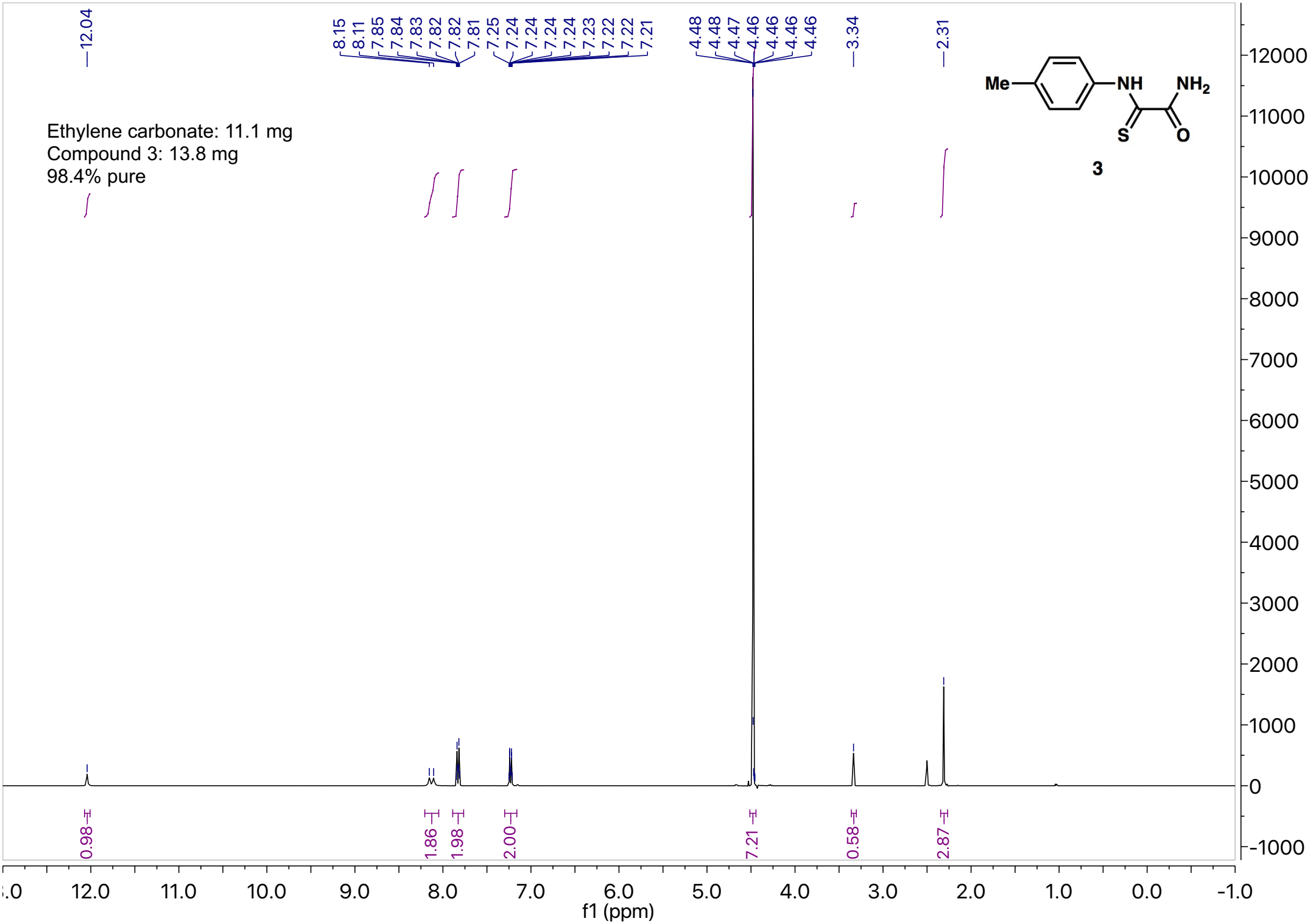
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4.46
3.34
2.31
Ethylene carbonate: 11.1 mg
Compound 3: 13.8 mg
98.4% pure
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NH
NH2
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O
3
0.98
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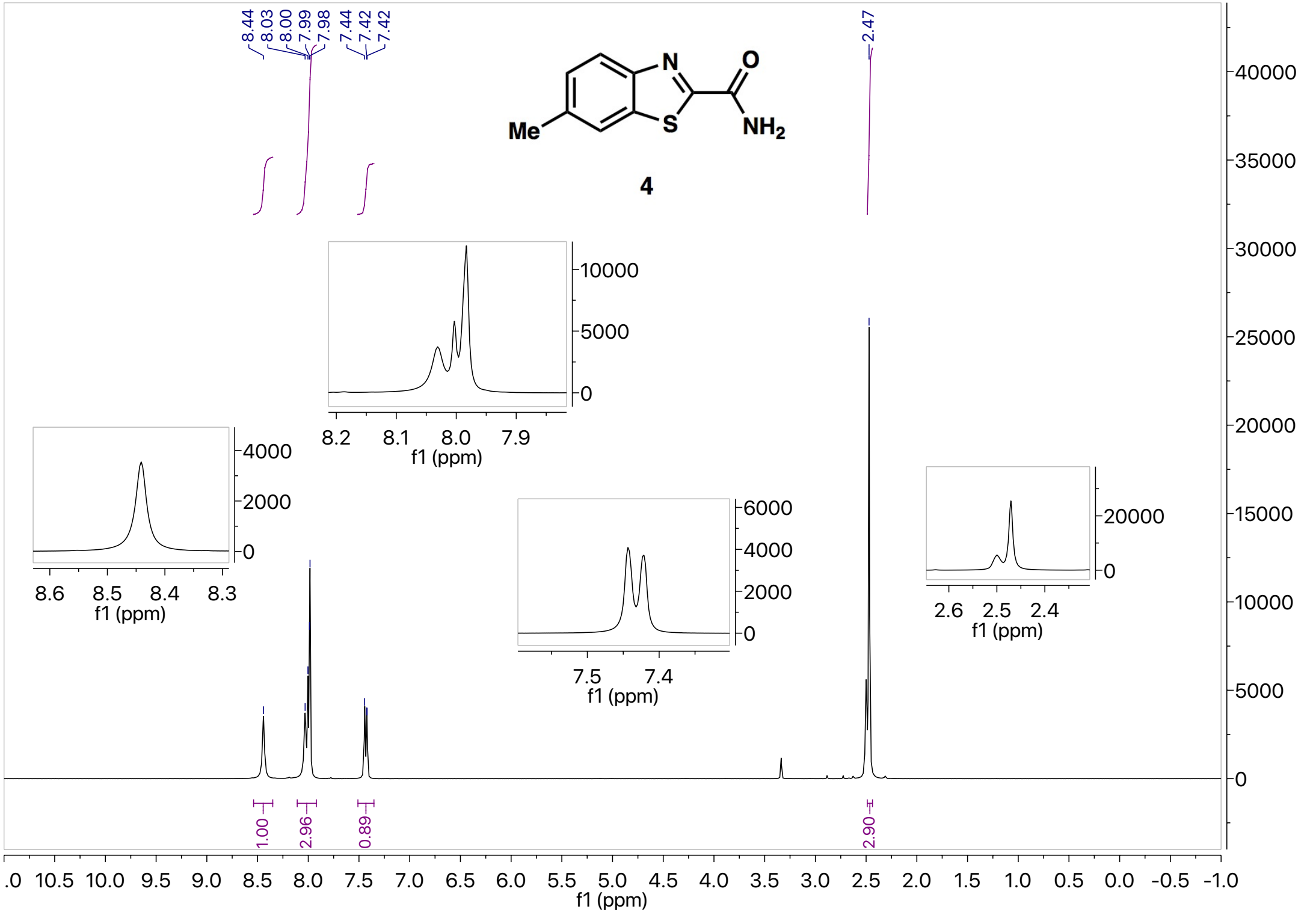
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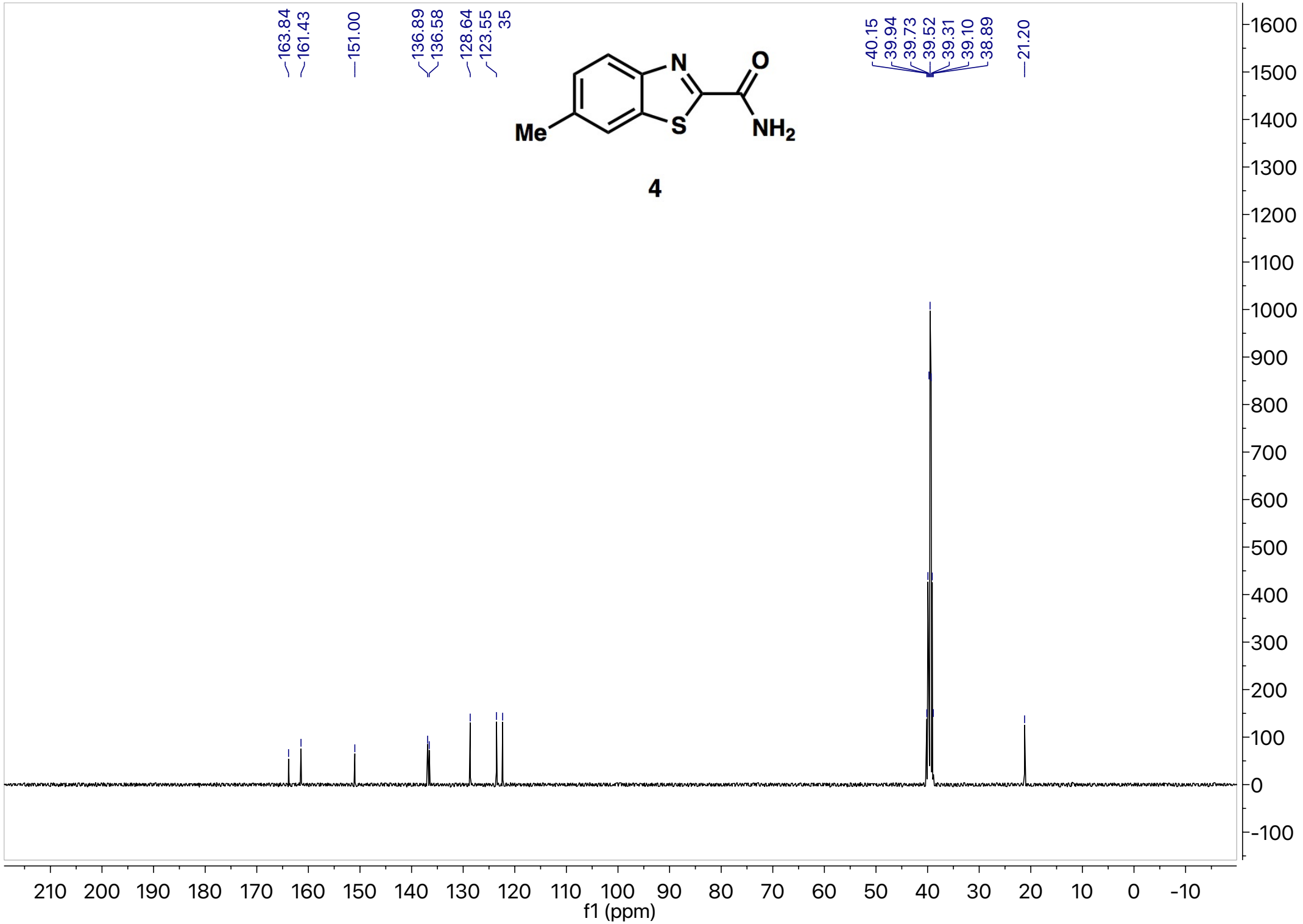
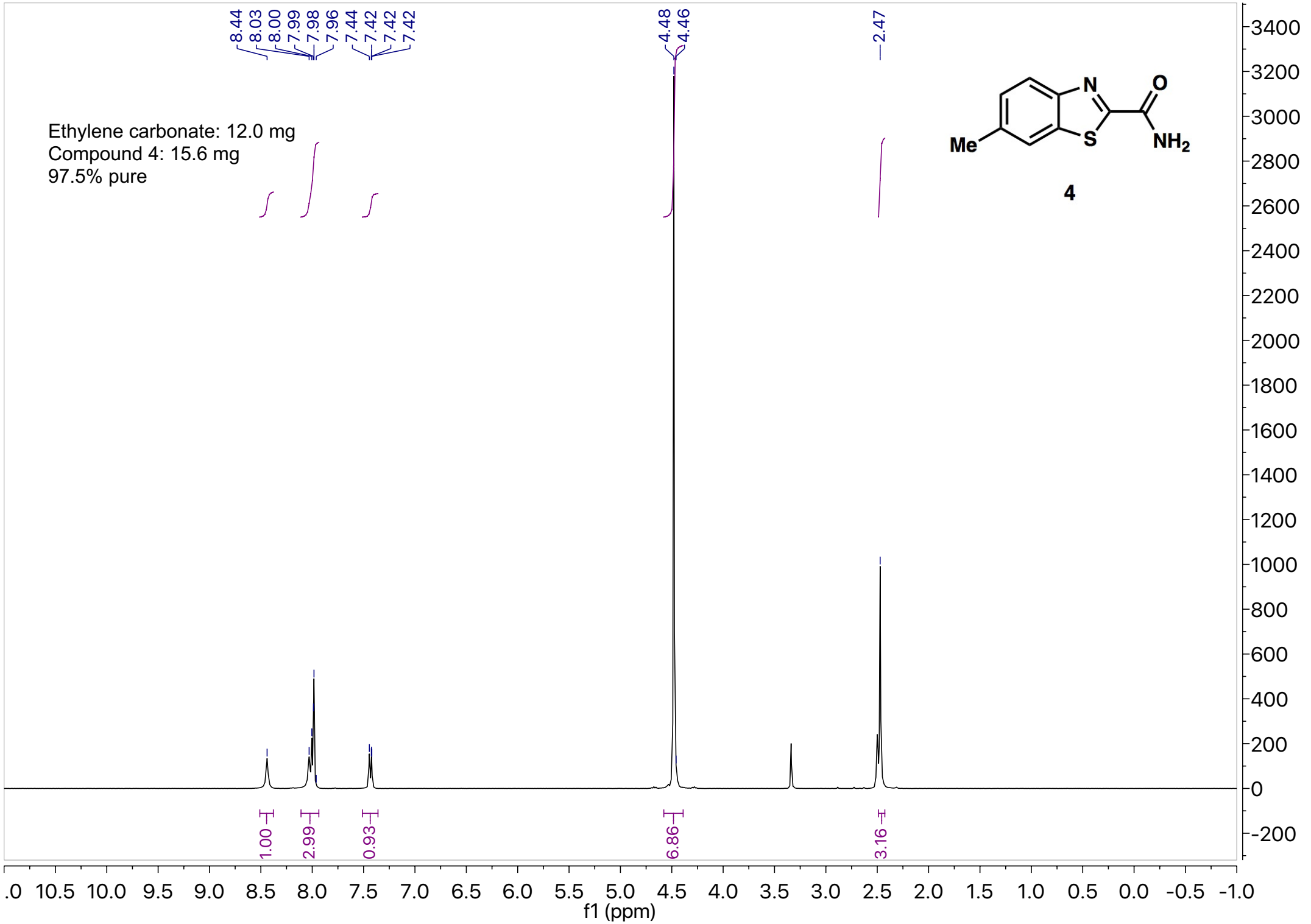
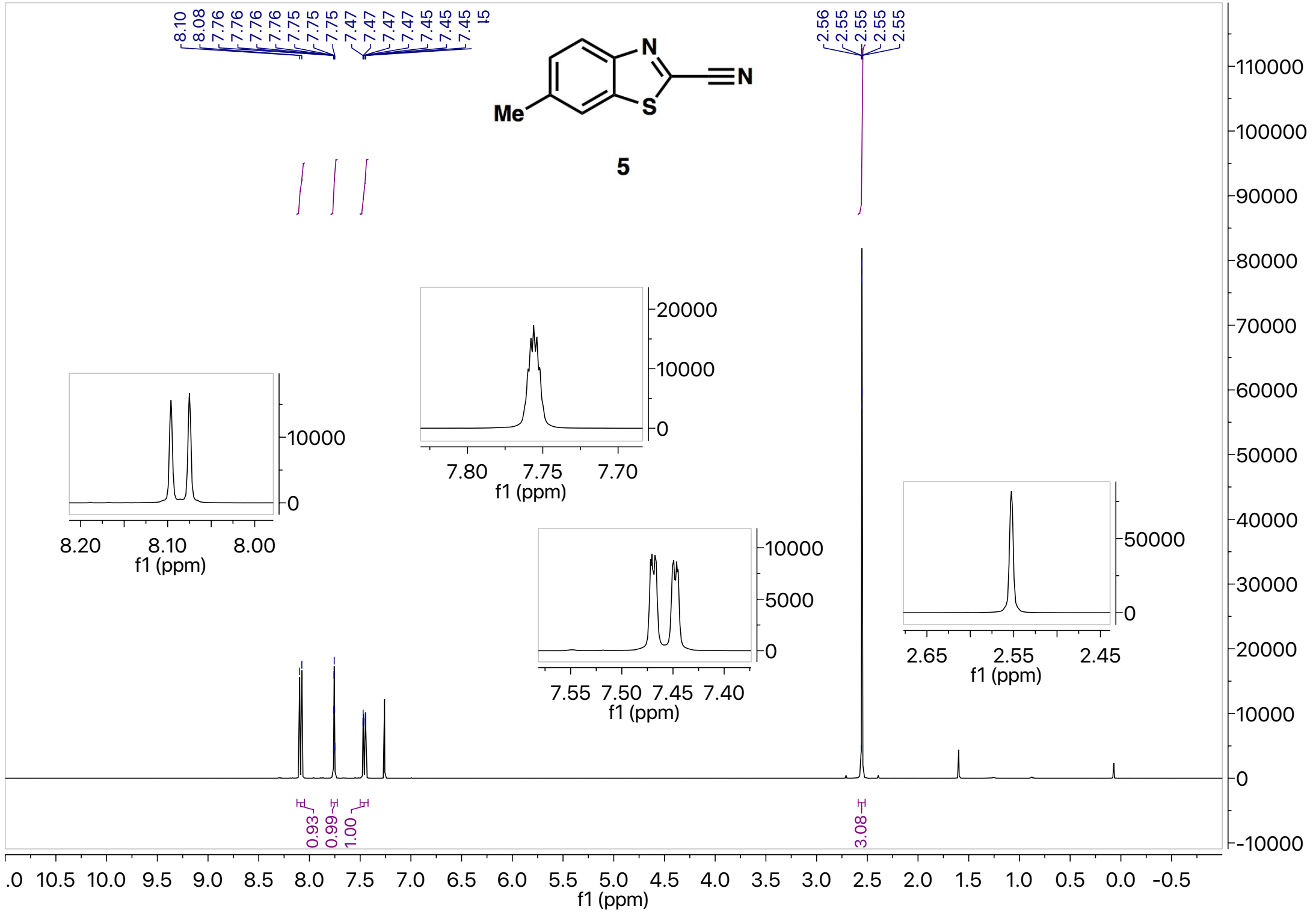
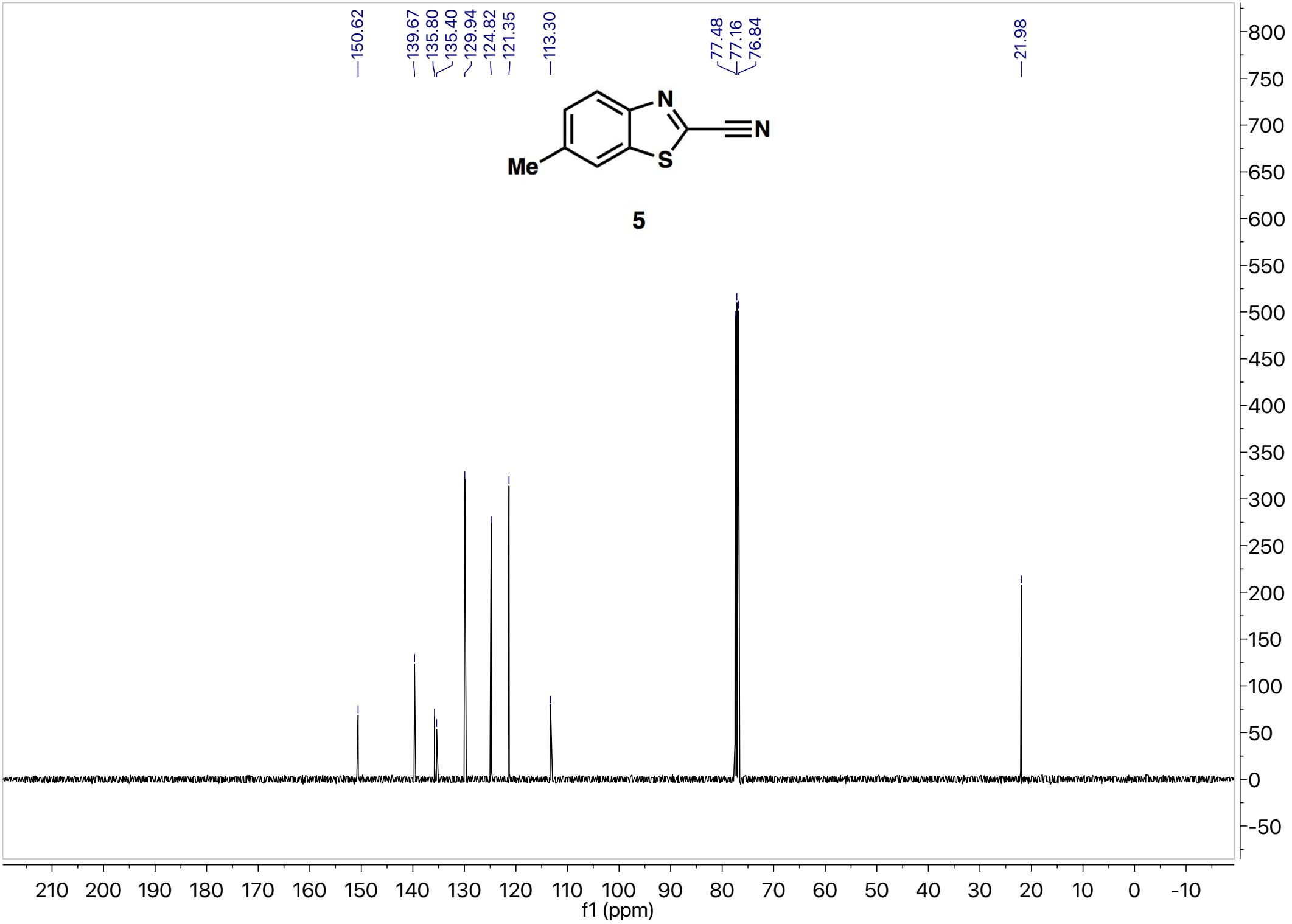
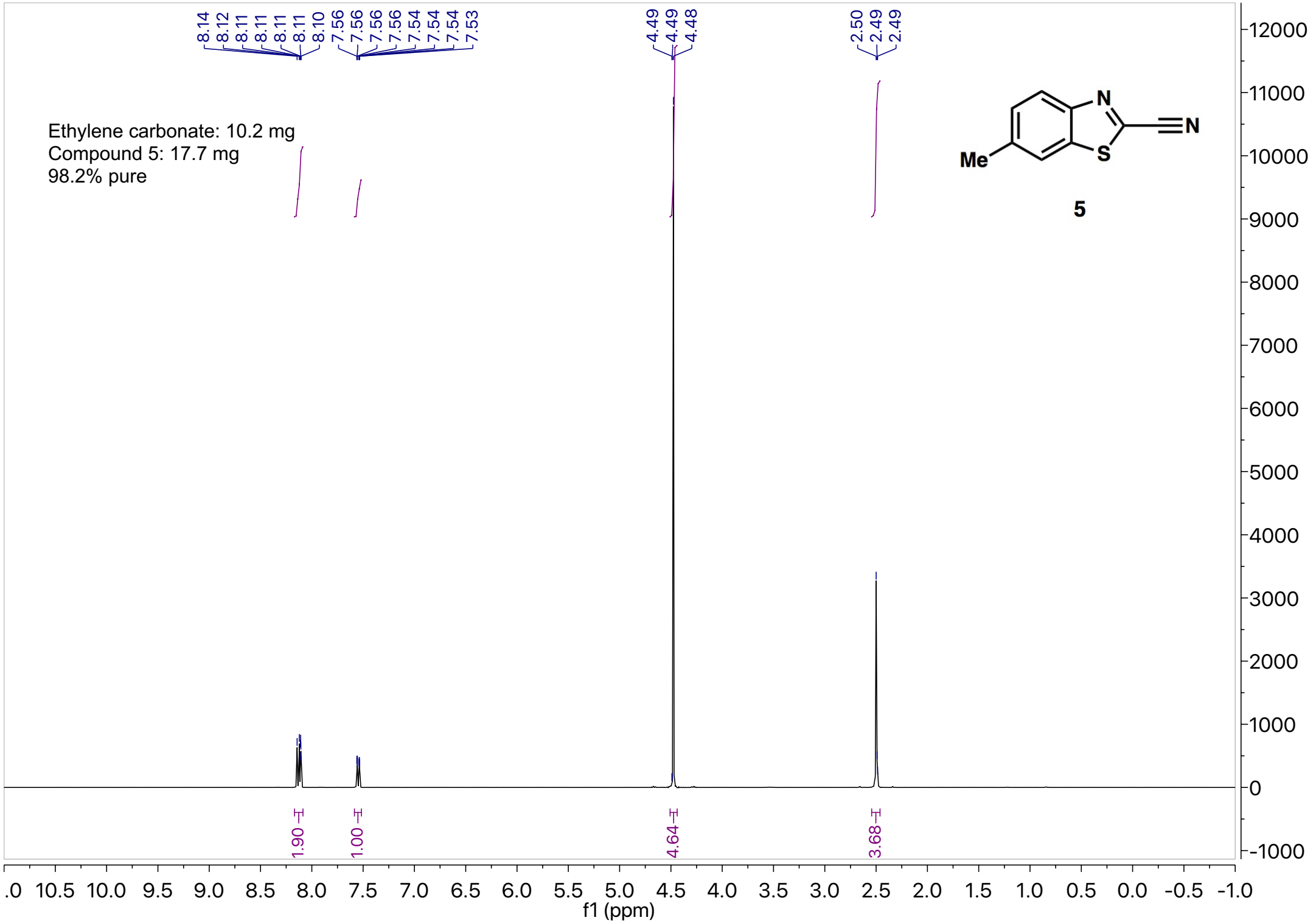
1.00
2.96
0.89
2.90


163.84
161.43
151.00
136.89
136.58
128.64
123.55
35
40.15
39.94
39.73
39.52
39.31
39.10
38.89
21.20
N
O
S
Me
NH2
4
f1 (ppm)


8.44
8.03
8.00
7.99
7.98
7.96
7.44
7.42
7.42
7.42
4.48
4.46
2.47
Ethylene carbonate: 12.0 mg
Compound 4: 15.6 mg
97.5% pure
N
O
S
Me
NH2
4
1.00
2.99
0.93
6.86
3.16
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


8.10
8.08
7.76
7.76
7.76
7.76
7.75
7.75
7.75
7.47
7.47
7.47
7.47
7.45
7.45
7.45
2.56
2.55
2.55
2.55
2.55
N
N
S
Me
5
0.93
0.99
1.00
3.08
f1 (ppm)


150.62
139.67
135.80
135.40
129.94
124.82
121.35
113.30
77.48
77.16
76.84
21.98
N
N
S
Me
5
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.14
8.12
8.11
8.11
8.11
8.11
8.10
7.56
7.56
7.56
7.56
7.54
7.54
7.54
7.53
4.49
4.49
4.48
2.50
2.49
2.49
Ethylene carbonate: 10.2 mg
Compound 5: 17.7 mg
98.2% pure
N
N
Me
S
5
1.90
1.00
4.64
3.68
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)