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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.

Organic Syntheses

Synthesis of 4,5-Disubstituted 2-aminothiazoles from α,β-Unsaturated Ketones: Preparation of 5-Benzyl-4-methyl-2-aminothiazolium Hydrochloride Salt

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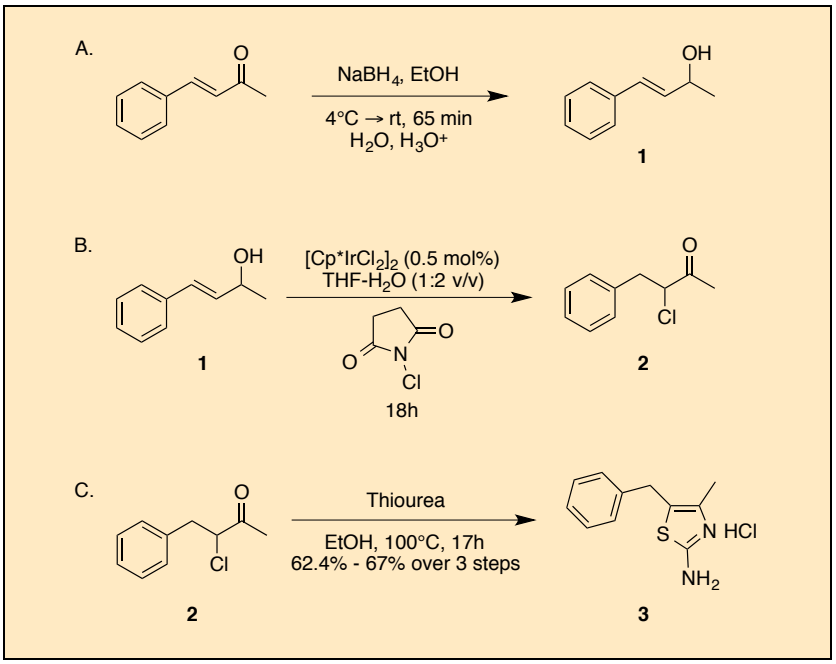

Procedure

A. *4-Phenyl-3-buten-2-ol (**1**).* A 500-mL three-necked, round-bottomed flask equipped with an octagonal Teflon-coated magnetic stir bar

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(3.5 x 1.5 cm) is flame-dried and placed under an atmosphere of nitrogen. A thermometer adapter (with a thermometer inserted) is attached to the left neck. The flask is charged with (*E*)-4-phenyl-3-buten-2-one (10.00 g, 68.4 mmol, 1.0 equiv) and absolute ethanol (100 mL) (Note 1), and stirred at room temperature for 15 min until the solid dissolves. The flask is then immersed in an ice-water bath and cooled to 4 °C. Sodium borohydride (2.59 g, 68.5 mmol, 1.0 equiv) (Note 2) is added in one portion (internal temperature during addition: 4 °C), and the reaction mixture is maintained at this temperature for 15 min. The ice-water bath is removed and the reaction is stirred for 50 min, during which time the solution warms to room temperature (Note 3). The flask is cooled in an ice-water bath to 4 °C and a 125-mL pressure-equalizing addition funnel is attached to the center neck of the flask. Deionized-water (30 mL) is added dropwise over 6 min through the addition funnel (internal temperature during addition: 4 °C – 6 °C) (Note 4). A solution of 5 mL of concentrated hydrochloric acid (Note 5) in 40 mL of deionized-water is added dropwise through the addition funnel over 15 min (internal temperature during addition: 6 °C – 20 °C) (Note 6). The ice-water bath is then removed and the reaction is stirred for 30 min, during which time the solution warmed to room temperature. The reaction mixture is transferred to a 500-mL single-necked, round-bottomed flask using 25 mL of ethyl acetate (Note 7), and then the volatile components are removed by rotary evaporation (bath temperature: 40 °C; ≈ 40 mmHg). The crude material (Note 8) is extracted in a 250-mL separation funnel with ethyl acetate (1 × 50 mL). The organic phase is washed with a saturated solution of $NaHCO_3$ (1 x 20 mL) and then a saturated solution of NaCl (1 × 20 mL). The aqueous phases are extracted with ethyl acetate (2 × 25 mL), and all the combined organics are dried in a 250-mL Erlenmeyer flask with $MgSO_4$ (2 g) (Note 9) and then filtered through a funnel with a cotton plug into a 500-mL single-necked, round-bottomed flask. The Erlenmeyer and the funnel are rinsed with ethyl acetate (20 mL). The solvent is removed using a rotary evaporator (bath temperature 40 °C; ≈ 40 mmHg), and the residue is dried under vacuum for 2 h (room temperature, 0.2 mmHg). The colorless oil (10 g) is used in the next step without further purifications (Notes 10, 11, and 12).

B. *3-Chloro-4-phenylbutan-2-one (***2***).* A 500-mL three-necked, round-bottomed flask, equipped with an octagonal Teflon coated magnetic stir bar (3.5 x 1.5 cm) and a thermometer adapter (with a thermometer inserted) in the left neck, is placed under an atmosphere of air. The flask is charged with the crude *4-phenyl-3-buten-2-ol* (**1**) **(**10 g, 67.5 mmol, 1.0 equiv) from

step A, using 14 mL of THF (Note 13) to transfer the oil into the flask. Deionized-water (28 mL) is then added to the flask to keep the solvents at a 1:2 v/v relationship. A solution of $[Cp^*IrCl_2]_2$ (273 mg, 0.342 mmol, 0.5 mol%) (Notes 14 and 15) in a mixture of THF (76 mL) and water (152 mL) (1:2 v/v) is added (Note 16), followed by the addition of *N*-chlorosuccinimide (11.2 g, 82.1 mmol, 1.2 equiv) in one portion (internal temperature during additions: 23 °C) (Note 17). The reaction mixture is stirred vigorously at room temperature for 18 h (Note 18), after which time it is transferred to a 500-mL single-necked, round-bottomed flask using 25 mL of ethyl acetate. The volatiles are then removed by rotary evaporation (bath temperature: 40 °C; ≈ 40 mmHg). To this residue (Note 19) a saturated solution of NaCl (20 mL) is added, and the mixture is extracted in a 500-mL separatory funnel with ethyl acetate (4 × 40 mL). The combined organic phases are washed with a saturated solution of NaCl (3 × 25 mL), dried in a 250-mL Erlenmeyer flask over $MgSO_4$ (3 g), and then filtered through a funnel with a cotton plug into a 500-mL single-necked, round-bottomed flask. The Erlenmeyer and the funnel are rinsed with ethyl acetate (20 mL). The solvent is removed using a rotary evaporator (bath temperature 40 °C; ≈ 40 mmHg) and the residue is dried under vacuum for 1 h (room temperature, 0.200 mmHg). The obtained red-brown oil (14.2 g) is used in the next step without further purification (Notes 20 and 21).

C. *5-Benzyl-4-methyl-2-aminothiazolium hydrochloride (**3**).* A 300-mL three-necked, round-bottomed flask equipped with an octagonal Teflon coated magnetic stir bar (3.5 × 1.5 cm), a cooling condenser in the center neck, and a thermometer adapter (with a thermometer inserted) in the left neck is flame-dried and placed under an atmosphere of nitrogen. The flask is charged with the crude of *3-chloro-4-phenylbutan-2-one (**2**)* (14.2 g) from step B and absolute ethanol (50 mL). Thiourea (5.21 g, 68.5 mmol, 1.0 equiv) (Note 22) is then added (internal temperature during addition: 23 °C) and the reaction mixture is heated at 100 °C in an oil bath for 17 h (internal temperature: 78 °C) (Note 23). The reaction is cooled down, with stirring, to room temperature and then immersed into an ice-water bath (internal temperature: 5 °C) (Note 24). The cooling condenser is removed and replaced with a 125-mL pressure-equalizing addition funnel, through which diethyl ether (60 mL) (Note 25) is added dropwise over 10 min (internal temperature: 5 °C). The reaction is then stirred for 15 min at 5 °C. The precipitated brown solid is filtered through a 150-mL fritted glass funnel (frit pore size M) and then washed with cooled (5 °C) diethyl ether (3 x 20 mL). The solid is dried under air for 30 min and vacuum-dried for

1 h (room temperature, 0.2 mmHg) to afford 5-benzyl-4-methyl-2-aminothiazolium hydrochloride (**3**) (10.29 g, 42.7 mmol, 62.4% over 3 steps) as a brown solid (Notes 26, 27, and 28).

Notes

1. (*E*)-4-Phenyl-3-buten-2-one (*Acros Organics*, 99%) and ethanol (*Fisher Scientific*, ACS Reagent Grade, absolute, anhydrous) were used as received. The submitters used (*E*)-4-phenyl-3-buten-2-one purchased from *Sigma-Aldrich Co.* (99%) and ethanol purchased from *VWR* (GPR Rectapur, 99.5%) as received.
2. Sodium borohydride (*Sigma-Aldrich Co.*, 98%, powder) was used as received. The submitters used sodium borohydride purchased from *Fisher Scientific* (98%, granules) as received.
3. The reaction can be monitored by TLC analysis on glass-backed extra hard layer TLC plates (*Silicycle*, 60 Å, 250 μm thickness, containing F-254 indicator) using a 10:90 solution of EtOAc:pentane as eluent, and visualized with $KMnO_4$ stain. The ketone starting material has $R_f = 0.29$ (yellow spot) and the allylic alcohol product has $R_f = 0.19$ (yellow spot).
4. The stirring must be vigorous because a white solid is formed with the addition of water (boron salts).
5. Hydrochloric acid (*EMD Chemicals*, ACS Reagent Grade, 37%) was used as received. The submitters used hydrochloric acid purchased from *VWR* (AnalaR Normapur, 37%) as received.
6. It is important to add the water before the acidic solution to avoid side-reactions of the allylic alcohol (**1**) in the reaction media.
7. Ethyl acetate (*Fisher Scientific*, Analytical reagent grade) was used as received.
8. After evaporation of the solvent, the crude is a biphasic system.
9. Magnesium sulfate anhydrous (*Alfa Aesar*, 99.5%, anhydrous powder) was used as received.
10. The crude reaction mixture, which may include a small quantity of ethyl acetate, contains allylic alcohol **1**, which has the following spectroscopic properties that correspond with the data described in literature:[3] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (d, J = 6.4 Hz, 3 H), 1.57 (bs, 1 H), 4.50 (dq, J = 6.4 Hz, J = 1.2 Hz, 1 H), 6.27 (dd, J = 16 Hz, J = 6.4 Hz, 1 H), 6.58 (d, J = 16 Hz, 1 H), 7.22–7.26 (m, 1 H), 7.30–7.33 (m,

2 H), 7.38–7.39 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.4, 68.9, 126.4, 127.6, 128.6, 129.4, 133.5, 136.7.

11. The crude should be immediately used in the next step to avoid decomposition.
12. Pure 4-phenyl-3-buten-2-ol (**1**) was prepared by carrying out the reaction on half scale, and then purifying the crude product mixture by column chromatography. The crude oil is loaded onto 35.3 g silica gel (SilicaFlash® F60 (40-63 μm/230-500 mesh) purchased from Silicycle) that had been dry-packed in a 3 cm diameter chromatography column and wetted with a 5:95 solution of EtOAc:pentane. The product is eluted with 300 mL of a 5:95 solution of EtOAc:pentane, followed by 200 mL of a 10:90 solution of EtOAc:pentane, followed by 200 mL of a 20:80 solution of EtOAc:pentane, followed by 200 mL of a 30:70 solution of EtOAc:pentane, and the eluent is collected in 15 mL fractions in 16x125mm test tubes. Fractions 10-39 (R_f = 0.19 (yellow spot), visualized with $KMnO_4$, 10:90 solution of EtOAc:pentane as eluent) are combined in a 1-L round-bottomed flask and concentrated under reduced pressure (bath temperature 23 °C; ≈ 20 mmHg) to give pure 4-phenyl-3-buten-2-ol (**1**) as a colorless oil. Compound **1** has the following spectroscopic properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (d, J = 6.4 Hz, 3 H), 1.81 (bs, 1 H), 4.49 (q, J = 6.4 Hz, 1 H), 6.27 (dd, J = 16, 6.4 Hz, 1 H), 6.57 (d, J = 16 Hz, 1 H), 7.23–7.26 (m, 1 H), 7.30–7.33 (m, 2 H), 7.38–7.39 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.4, 68.9, 126.4, 127.6, 128.5, 129.3, 133.5, 136.7. IR (neat) cm^{-1}: 3346, 3026, 2972, 1494, 1449. HRMS (ESI) Exact mass calcd for $C_{10}H_{11}$ $[M–OH]^+$: 131.0855, found: 131.0856.
13. Tetrahydrofuran (non-stabilized THF purchased from Fisher Scientific and passed through a column of activated alumina.) was used. The submitters used tetrahydrofuran purchased from *Sigma-Aldrich Co.*, (ACS Reagent Grade, containing 250 ppm BHT as inhibitor) as received.
14. Dichloro(pentamethylcyclopentadienyl)iridium (III) dimer (*Strem Chemicals*, 98%) was used as received. The submitters note that the iridium dimer can be synthesized by the procedure described in the literature[4] as well, obtaining the same results.
15. A mixture containing $[Cp^*IrCl_2]_2$ (273 mg) in a THF-water mixture (1:2 v/v) (228 mL) is stirred with an octagonal Teflon coated magnetic stir bar (3.7 x 0.7 cm) in a 500-mL Erlenmeyer flask for 2 h, followed by sonication for 30 minutes. Alternatively, the solution can be prepared at the same time as step A is carried out and let stir for about 4 h with an

octagonal Teflon coated magnetic stir bar (3.7 x 0.7 cm). Both methods worked equally well.

16. When the solution of $[Cp^*IrCl_2]_2$ in the THF-water (1:2 v/v) mixture was added to the crude mixture containing the allylic alcohol **1**, the system becomes biphasic.
17. *N*-Chlorosuccinimide (*Sigma-Aldrich*, 98%) was used as received.
18. The reaction can be monitored by ^{1}H NMR spectroscopy: a drop of the organic phase (top layer) is dissolved in $CDCl_3$. Allylic alcohol consumption is confirmed by a decreased intensity of the ^{1}H NMR resonances at 6.58 (d, J = 16 Hz, 1 H) and at 6.27 (dd, J = 16 Hz, J = 6.4 Hz, 1 H). Simultaneously, formation of the α-chloroketone product (**2**), can be followed by monitoring the peak at 4.41 (dd, J = 8, 6.2 Hz, 1 H).
19. After evaporation, the crude mixture is biphasic.
20. The ^{1}H NMR spectrum of α–chloroketone (**2**, crude mixture) corresponds with the NMR data previously described in the literature:[5b] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.29 (s, 3 H), 3.08 (dd, J = 14.3 Hz, J = 8 Hz, 1 H), 3.34 (dd, J = 14.3 Hz, J = 6.2 Hz, 1 H), 4.41 (dd, J = 8 Hz, J = 6.2 Hz, 1 H), 7.18–7.34 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.8, 39.8, 63.8, 127.2, 128.6, 129.3, 136.1, 202.6.
21. Pure 3-chloro-4-phenylbutan-2-one (**2**) was prepared by carrying out the reaction on half scale using pure 4-phenyl-3-buten-2-ol (**1**), and then purifying the crude reaction mixture by column chromatography. The crude oil is loaded onto 65.3 g silica gel that had been dry-packed in a 5 cm diameter chromatography column and wetted with *n*-pentane. The product is eluted with 300 mL of *n*-pentane, followed by 200 mL of a 1:99 solution of EtOAc:pentane, followed by 1-L of a 2:98 solution of EtOAc:pentane, and the eluent is collected in 60 mL fractions in 2.5 x 20 cm test tubes. Fractions 10-17 (R_f = 0.58 (yellow spot), visualized with $KMnO_4$, 10:90 solution of EtOAc:pentane as eluent) are combined in a 1-L round-bottomed flask and concentrated under reduced pressure (bath temperature 23 °C; ≈ 20 mmHg) to give pure 3-chloro-4-phenylbutan-2-one (**2**) as a yellow oil. 3-chloro-4-phenylbutan-2-one (**2**) has the following spectroscopic properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.29 (s, 3 H), 3.08 (dd, J = 14.3, 8.1 Hz, 1 H), 3.34 (dd, J = 14.3, 6.2 Hz, 1 H), 4.41 (dd, J = 8, 6.2 Hz, 1 H), 7.21–7.33 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.8, 39.8, 63.8, 127.2, 128.6, 129.3, 136.1, 202.6. IR (neat) cm^{-1}: 3030, 2928, 1715, 1357, 1157. HRMS (ESI) Exact mass calcd for $C_{10}H_{11}ClONa$ $[M+Na]^+$: 205.0391, found: 205.0394.

22. Thiourea (*Sigma-Aldrich*, 99%) was used as received.
23. The reaction can be monitored by ^{1}H NMR spectroscopy: a drop of the hot mixture is dissolved in DMSO-d_6. The reaction is finished when the peak at 4.41 (dd, J = 8, 6.2 Hz, 1 H) from α-chloroketone **2** has disappeared.
24. A brown solid starts to precipitate when the reaction is cooled to room temperature and/or 5 °C. Vigorous stirring must be maintained to avoid agglomeration of the solid.
25. Diethyl ether (*Fisher Scientific*, anhydrous, BHT Stabilized, ACS Reagent Grade) was used as received. The submitters used diethyl ether purchased from *VWR* (GPR Rectapur, >99) as received.
26. 5-Benzyl-4-methyl-2-aminothiazolium hydrochloride (**3**) has the following physical and spectroscopic properties: mp = 219–221 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.20 (s, 3 H), 3.44 (bs) (water), 3.93 (s, 2 H), 7.23–7.26 (m, 3 H), 7.33 (t, J = 7.4 Hz, 2 H), 9.24 (s, 2 H),[6] 13.37 (bs, 1 H).[6] ^{13}C NMR (125 MHz, DMSO-d_6) δ: 11.5, 30.4, 116.8, 126.8, 128.3, 128.7, 131.0, 138.8, 167.8. IR (neat) cm^{-1}: 3242, 3192, 3058, 2919, 2652, 1623, 1573, 1453, 1075, 830, 760, 698. HRMS (ESI) Exact mass calcd for $C_{11}H_{13}N_2S$ $[M+H]^+$: 205.0794, found: 205.0798; Anal. Calcd for $C_{11}H_{13}N_2SCl$: C, 54.88; H, 5.44; N, 11.64; S, 13.32; Cl, 14.73; Found: C, 54.72; H, 5.63; N, 11.57; S, 13.28; Cl, 14.58 (these elemental analysis values were obtained from a sample that had been prepared by running the reaction with pure 3-chloro-4-phenylbutan-2-one (**2**); when a sample that had been prepared by running the reaction with crude 3-chloro-4-phenylbutan-2-one (**2**) was used, the CHN results were not in agreement with the calculated values despite identical ^{1}H, ^{13}C, IR, and HRMS data for both samples).
27. When the three-step sequence was run on half scale, 5.50 g (22.9 mmol) of 5-benzyl-4-methyl-2-aminothiazolium hydrochloride (**3**) was isolated as a brown solid (67% yield over three steps).
28. The submitters report a 76% yield over the three steps. The submitters also report a crystal structure of **3** that was solved from single crystal X-Ray diffraction data, confirming the substitution pattern as well as the protonation of the imidazolic nitrogen (this data was not attempted to be reproduced by the checkers).[7]

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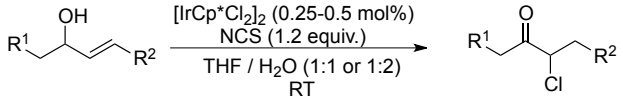
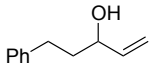
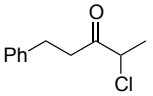
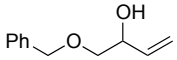
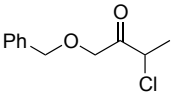
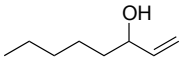
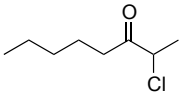
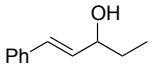
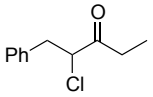
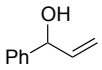
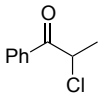
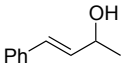
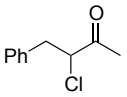
Discussion

2-Aminothiazoles are privileged structures that are found in numerous biologically active compounds, with applications as antibiotics, anti-inflammatory and psychotropic agents, among others.[8] These heterocycles can be synthesized in a straightforward manner *via* condensation of α-chlorocarbonyls with thiourea. A challenge usually encountered is, however, the selective synthesis of 4,5-disubstituted 2-aminothiazoles. This is due to the unavailability and/or tedious methods to prepare the α-chlorocarbonyls precursors in high yields and with complete selectivity.

Recently, we reported a method to synthesize selectively α-halogenated ketones from allylic alcohols. The transformation is catalyzed by $[Cp^*IrCl_2]_2$, which in the presence of a fluorinating (Selectfluor®)[9] or a chlorinating (*N*-chlorosuccinimide, **Table 1**)[5] reagent affords α-halocarbonyls (halogen = F, Cl) as single constitutional isomers in good to excellent yields.

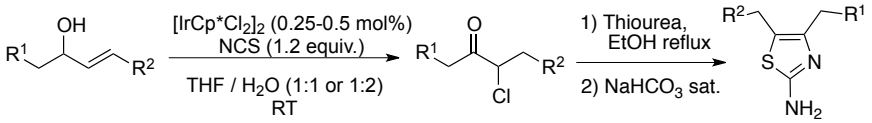
Table 1. Examples of iridium-catalyzed tandem isomerization/C–Cl bond formation of allylic alcohols.

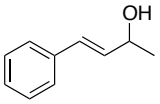
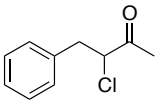
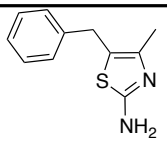
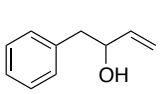
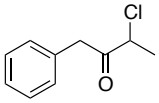
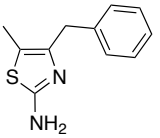
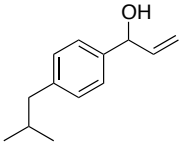
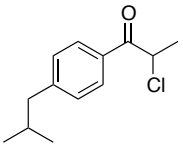
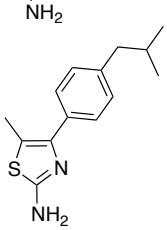
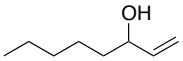
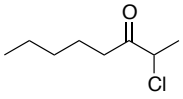
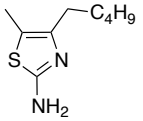


Allylic alcohol	α-Chloroketone	Isolated Yield (%)
		88
		89
		91
		89
		80
		91

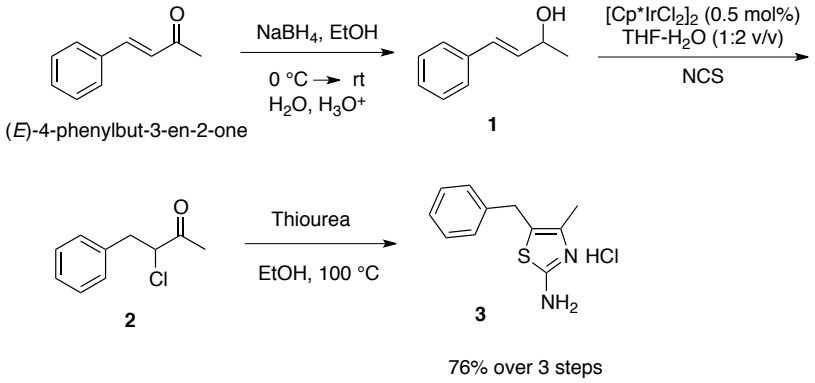
The chlorination reaction (**Table 1**) was used to synthesize a variety of 4,5-disubtituted 2-aminothiazoles from allylic alcohols. Thus, condensation of selected α–chlorocarbonyls with thiourea followed by neutralization of the thiazolium salt with sodium bicarbonate afforded the corresponding 2-aminothiazole in excellent yield after two steps (**Table 2**).[5]

Table 2. Synthesis of 4,5-disubtituted 2-aminothiazoles from allylic alcohols.



Allylic alcohol	α-Chloroketone	2-Amino thiazole	Isolated Yield (%) (two steps)
			86
			90
			82
			95

Here, we describe the large-scale synthesis of 5-benzyl-4-methyl-2-aminothiazolium hydrochloride (**3**) from enone (*E*)-4-phenyl-3-buten-2-one in 3 steps without purifications by column chromatography. In the first step, allylic alcohol **1** was synthesized from (*E*)-4-phenyl-3-buten-2-one by reduction with $NaBH_4$. The crude of **1** was directly used in the iridium-catalyzed tandem isomerization/C–Cl bond formation, yielding α-chloroketone **2**. In the last step, the crude reaction mixture containing **2** was treated with thiourea affording 2-aminothiazolium hydrochloride salt **3** (**Scheme 1**). The final product (**3**) was isolated by precipitation from the reaction mixture.



Scheme 1. Synthesis of 5-benzyl-4-methyl-2-aminothiazolium hydrochloride (3) from (*E*)-4-phenyl-3-buten-2-one.

The structure of **3** was unambiguously confirmed by NMR spectroscopy, HRMS, elemental analysis and single crystal X-Ray diffraction. Single crystals were obtained by recrystallization from hot ethanol. The analysis also indicates that protonation occurred on the nitrogen of the thiazole ring.

Compound **3** crystallizes in the monoclinic crystal system (*P*2$_1$/*c* space group). The cell parameters determined for this structure are: *a* = 11.7869(5) Å, b = 7.5852(3) Å, c = 13.5158(5) Å, β = 92.805(4) °, V = 1206.95(8) Å^3.[7] The ORTEP representation of its asymmetric unit is shown in **Figure 1**. The imidazolic and amino H atoms were located in a difference Fourier map and refined without any constraint. The remaining Ar-H and CH_2-group hydrogen atoms were positioned geometrically and were constrained to ride on their parent atoms, with C—H = 0.95 Å (for Ar-H) and C—H = 0.97 Å (for CH_2-) and Uiso(H) = 1.2Ueq(C). The methyl group (C4) is disordered. The corresponding methyl hydrogen atoms were positioned geometrically and were constrained to ride on their parent atom, with C—H = 0.93 Å; and Uiso(H) = 1.5Ueq(C). The refined model describes a 30-70% disorder of methyl groups.

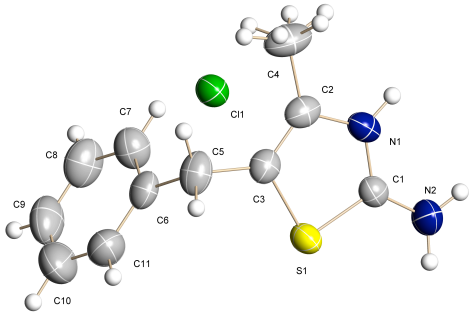


Figure 1. ORTEP representation of the asymmetric unit of 2-aminothiazole **3**. Ellipsoids are displayed at the 50% probability level. Hydrogen labels were omitted for clarity.

The supramolecular interactions in compound **3** are governed by weak hydrogen bonding-type interactions among chlorides and the protonated imidazolic and amino nitrogen atoms (**Figure 2**). Three different weak hydrogen bonds are determined, the strongest being the one corresponding to the protonated imidazole group. The distances and angles of these weak hydrogen bonds are presented in **Table 3**.

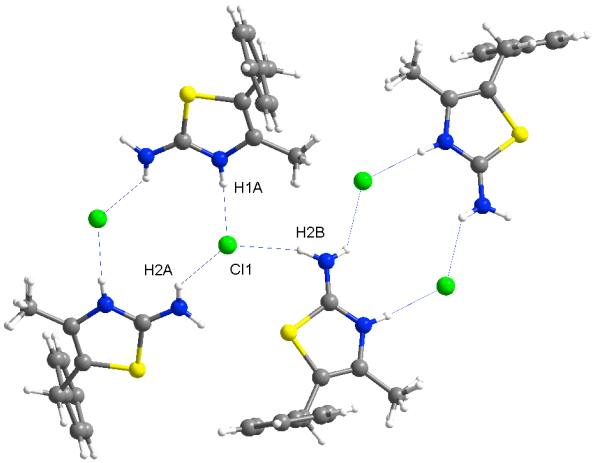


Figure 2. Hydrogen bonding-type interactions described in **3**. As it is depicted in the figure, each molecule interacts with other three neighbors through the described supramolecular interactions.

Table 3. Distances and angles of hydrogen bonds found in compound 3.

D-H•••A[1]	D-H[2] (Å)	H•••A[3] (Å)	D•••A[4] (Å)	<D-H•••A[5] (°)
N(1)i-H(1A)i..Cl(1)[1]	0.86(2)	2.19(3)	3.052(2)	175(2)
N(2)a-H(2A)a..Cl(1)[2]	0.84(2)	2.50(2)	3.182(2)	139(2)
N(2)a-H(2B)a..Cl(1)[3]	0.89(2)	2.34(2)	3.187(2)	1.60(2)
symmetry operator codes				
[1] x, y+1, z	[2] -x+1, -y+1, -z+1		[3] x, -y+3/2, z+1/2	

D: donor atom, A: acceptor atom. [1] Names of donor, hydrogen and acceptor atoms involved in the hydrogen bond. [2] Distance D – A. [3]Distances H – A. [4]Distance D – A. [5] Angle D – H – A. Ni: nitrogen atom coming from the imidazole group. Na: nitrogen atom coming from the amino group.

We have presented here a straightforward and easy procedure for the synthesis of 4,5-disubstitued 2-aminothiazolium hydrochloride salts. The method is exemplified in the synthesis of 2-aminothiazole **3** from a readily available enone. High yields of **3** are obtained in 3 steps, avoiding difficult or expensive purifications. The key step of this process is the tandem allylic alcohol isomerization/C–Cl bond formation catalyzed by iridium, which is a highly efficient method to synthesize α-(mono)chloroketones selectively.

References

1. Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden. E-mail: belen@organ.su.se. ‡These authors (A.B.G. and N.A.) contributed equally. Financial support from the Swedish Research Council (Vetenskapsrådet), the Knut and Alice Wallenberg Foundation, and the Berzelii Center EXSELENT is gratefully acknowledged.
2. Department of Materials and Environmental Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden. Financial support from the Knut and Alice Wallenberg Foundation is gratefully acknowledged.

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6. These two signals could appear at different shifts, and depend on the concentration of the sample.
7. The crystallographic data of **3** can be obtained free of charge from the Cambridge Crystallographic Data Center. For atomic coordinates, equivalent isotropic displacements parameters, bond length, angles and anisotropic displacement parameters check the CIF file (CCDC 935780).
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*E*)-4-Phenyl-3-buten-2-one; (1896-62-4)
Sodium borohydride; Sodium tetrahydridoborate; (16940-66-2)
4-Phenylbut-3-en-2-ol; (17488-65-2)
Dichloro(pentamethylcyclopentadienyl)iridium (III) dimer; (12354-84-6)
N-Chlorosuccinimide; (128-09-6)
3-Chloro-4-phenylbutan-2-one; (20849-77-8)
Thiourea; Sulfourea; Thiocarbamide; (62-56-6)
5-Benzyl-4-methyl-1,3-thiazol-2-amine hydrochloride; (95767-21-8)

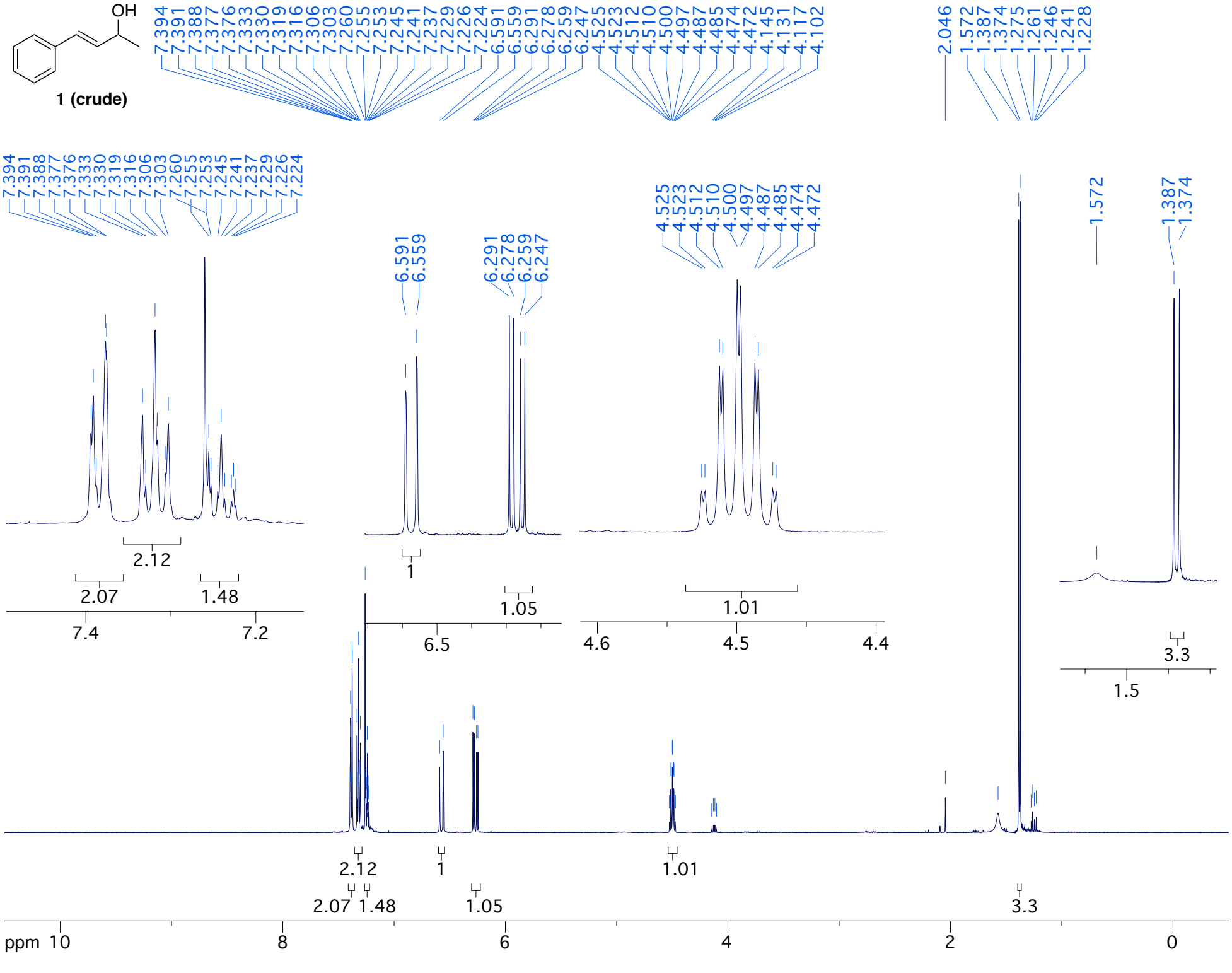
Belén Martín-Matute was born in Madrid (Spain) and obtained her Ph.D. at the Universidad Autónoma de Madrid (UAM 2002) with Prof. A. M. Echavarren. After a postdoctoral stay at Stockholm University (Sweden) with Prof. J.-E. Bäckvall working on dynamic kinetic resolutions, she joined the UAM as an Assistant Professor (2005–2007). She returned to Stockholm in 2007 and in 2014 became Full Professor. She received the Sigma-Aldrich Young Chemist Award from the Spanish Royal Society of Chemistry in 2007, and the Lindbomska Award by the Swedish Royal Academy of Sciences in 2013. Her research is focused on homogeneous and heterogeneous transition metal catalysis, as well as enzymatic transformations and mechanistic investigations.

Antonio Bermejo Gómez was born in Sevilla (Spain) in 1982. He obtained his Ph.D at the Universidad de Sevilla (US 2011) with Prof. R. Fernández and Prof. J. M. Lassaletta in the field of asymmetric catalysis using chiral hydrazones as ligands. He started his postdoctoral research work at Stockholm University (Sweden) with Prof. B. Martín-Matute in 2011. His ongoing research is focused on different transformations of allylic alcohols and synthesis of biological active compounds (collaborations with the companies *Cambrex KA* and *AstraZeneca*).

Nanna Ahlsten obtained her Ph.D in 2013 with Prof. Belén Martín-Matute at the Department of Organic Chemistry at Stockholm University. Her Ph.D studies were focused on the development of transition metal catalyzed isomerization and tandem isomerization/ halogenation reactions of allylic alcohols. She is currently a postdoctoral research assistant in the group of Dr Igor Larrosa at Queen Mary University of London (UK).

Ana E. Platero Prats was born in Barcelona (Spain) in 1984. She obtained her Ph.D at the Instituto de Ciencia de Materiales de Madrid (ICMM-CSIC) in 2011 with Prof. E. Gutiérrez Puebla and Dr N. Snejko in the field of green metal-organic frameworks for catalytic and adsorption applications. She started her postdoctoral research work at Stockholm University (Sweden) within a collaboration between Prof. X. Zou and Prof. B. Martín-Matute in 2012. Her ongoing research is focused on the functionalization and characterization of metal-organic frameworks, as well as the application of modern crystallographic tools to study these complex materials.

Michael T. Tudesco obtained his B.S. degree in Chemistry at the University of North Carolina at Chapel Hill in 2012, performing undergraduate research under the supervision of Professor Michel R. Gagné. He is currently pursuing his Ph.D. at Baylor University under the guidance of Professor John L. Wood.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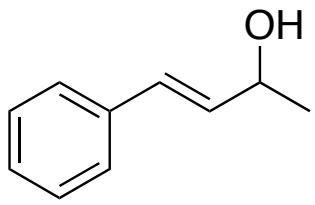
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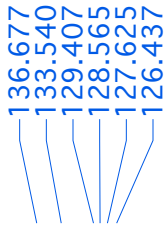
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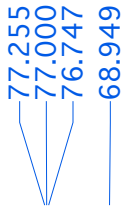
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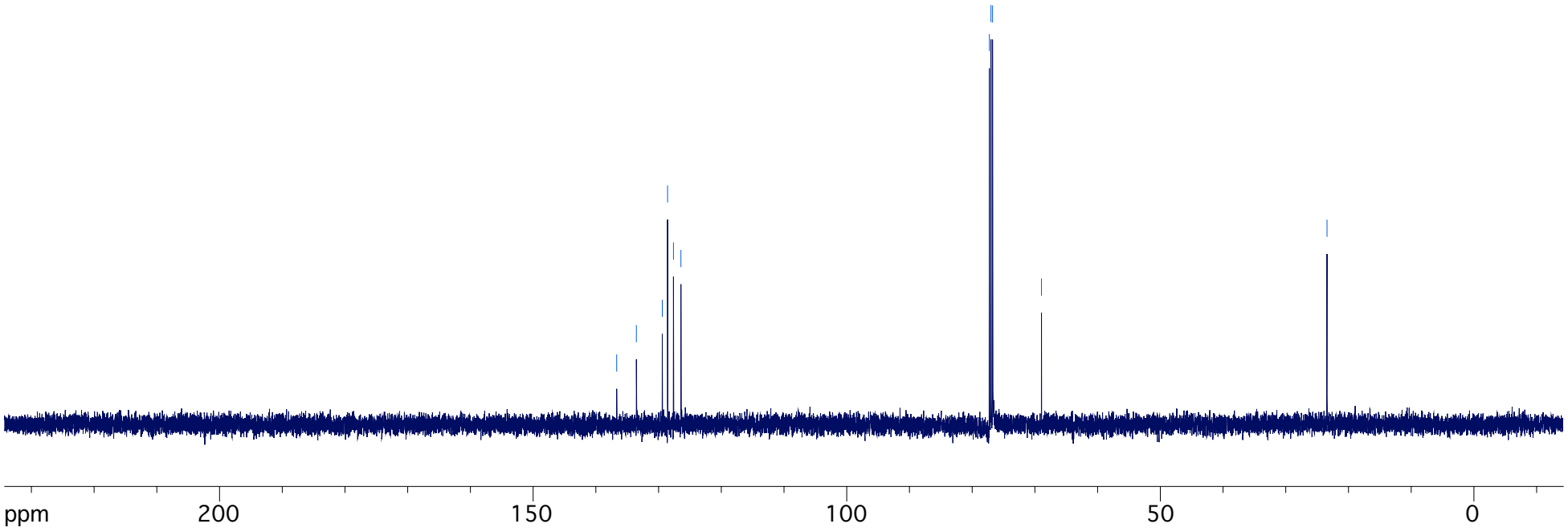
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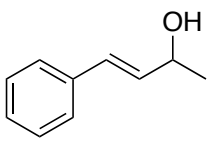
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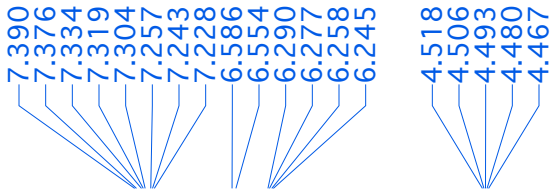
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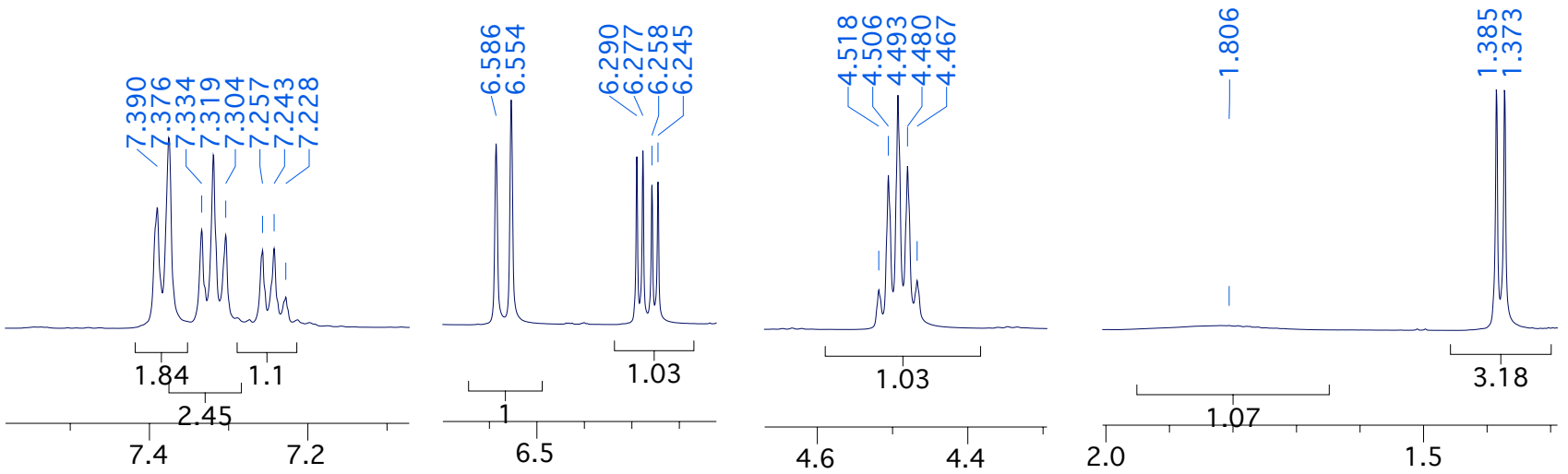
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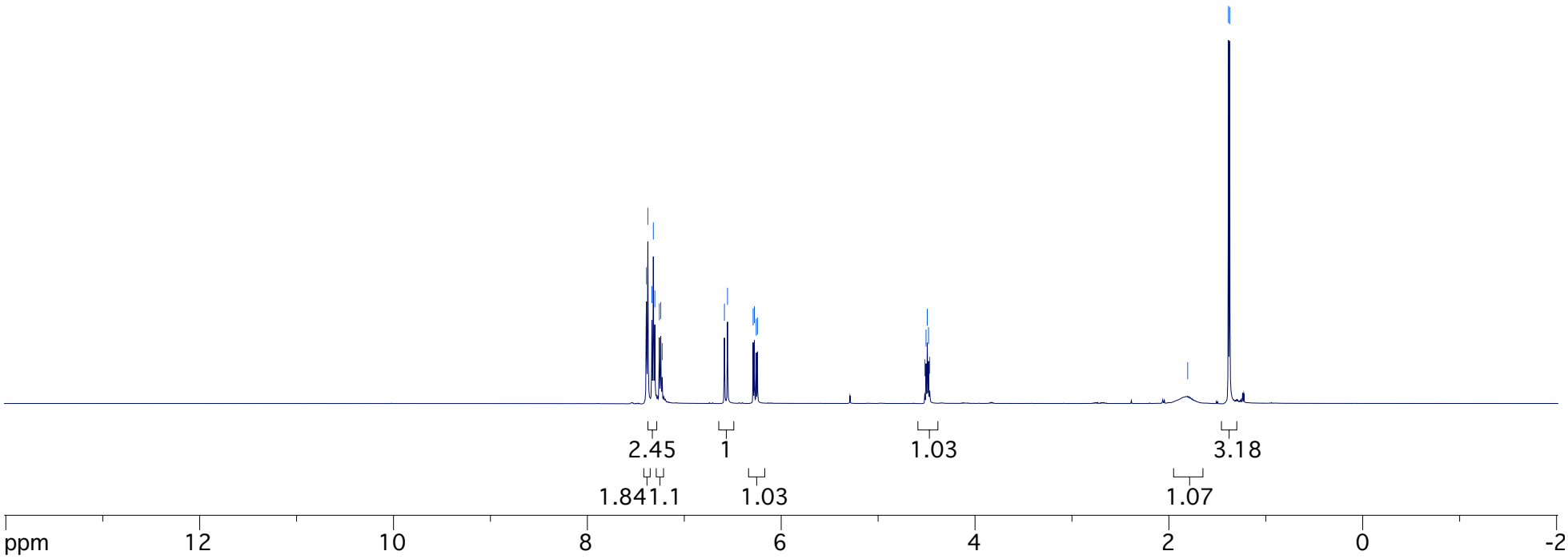
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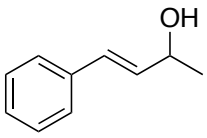

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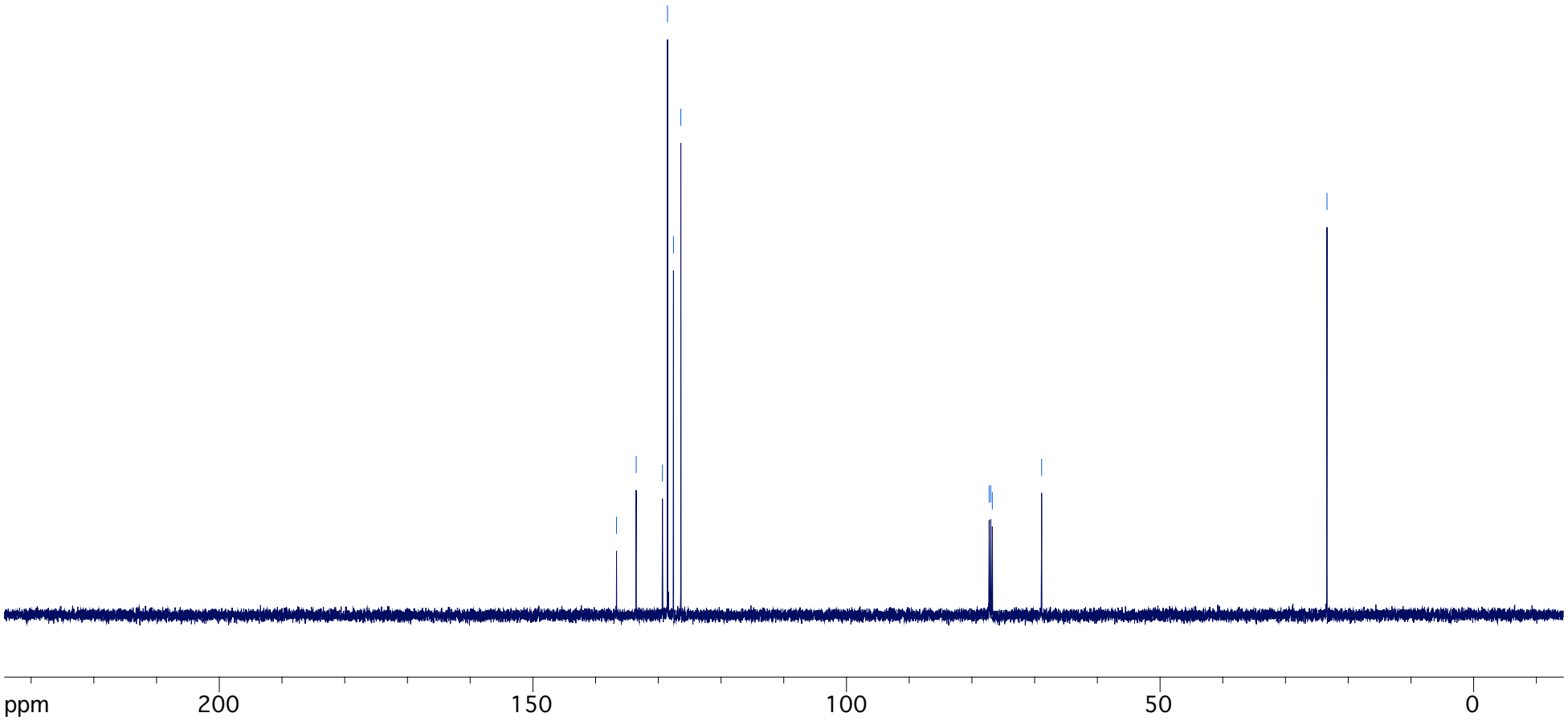

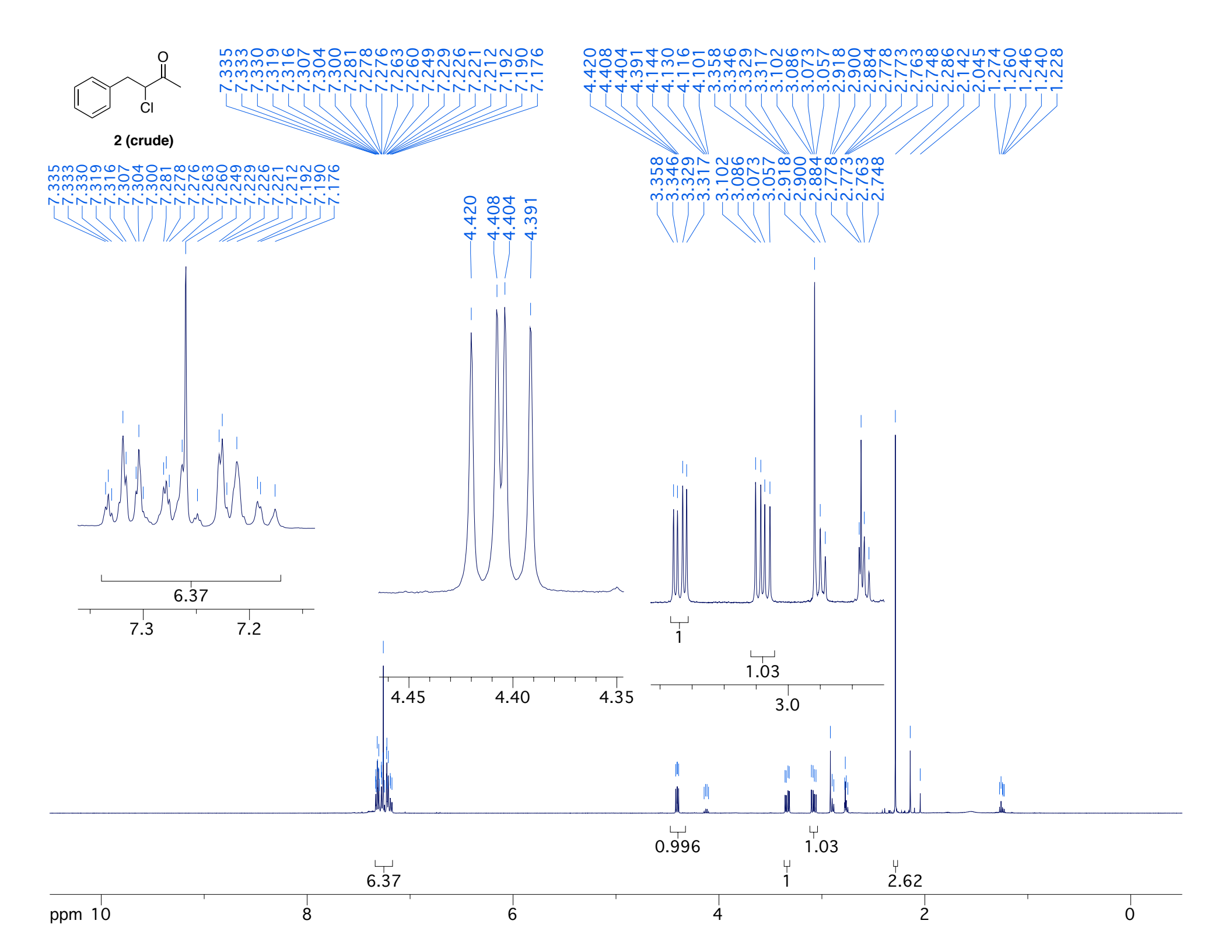
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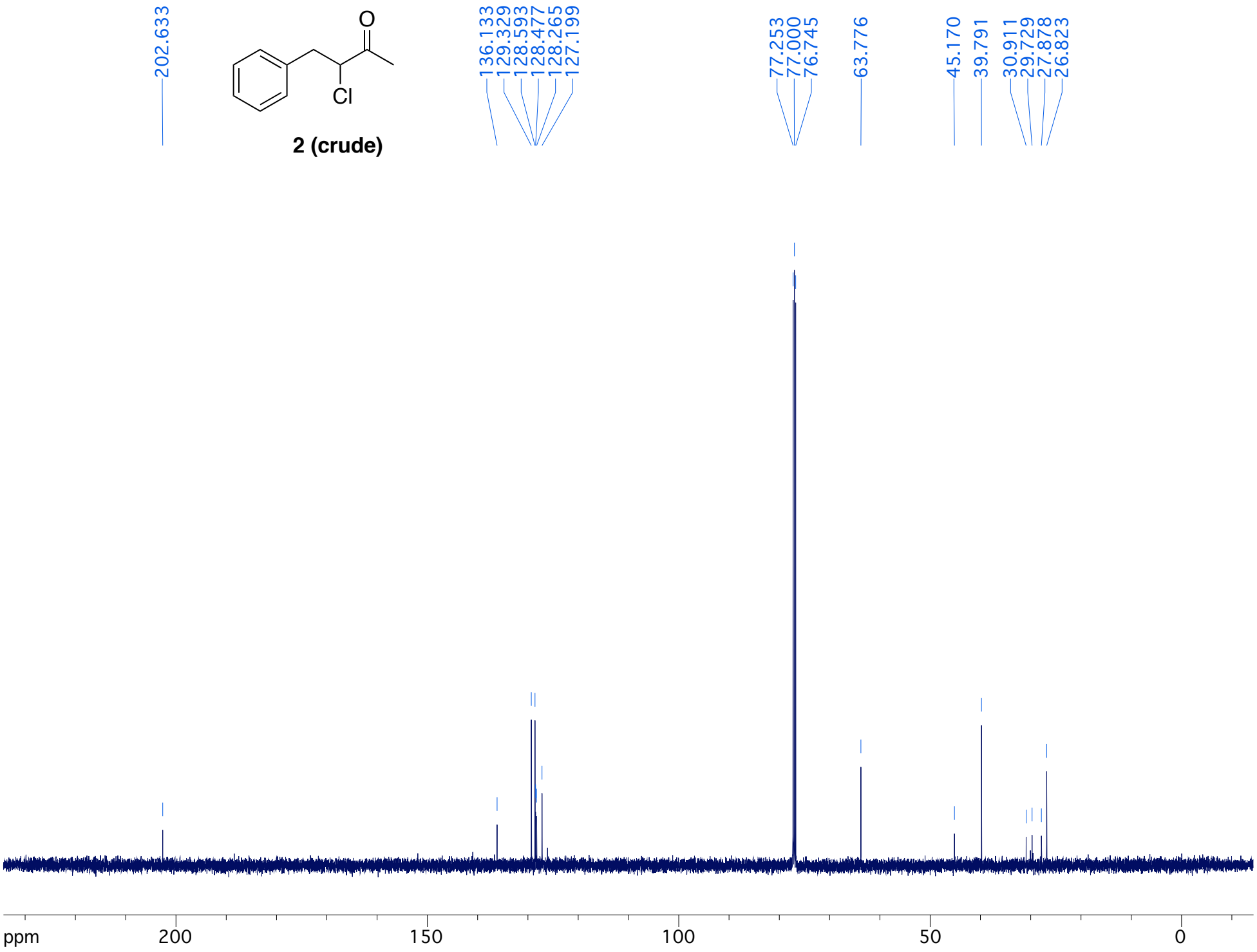
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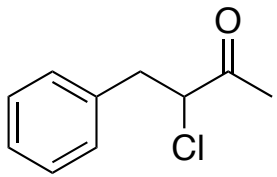
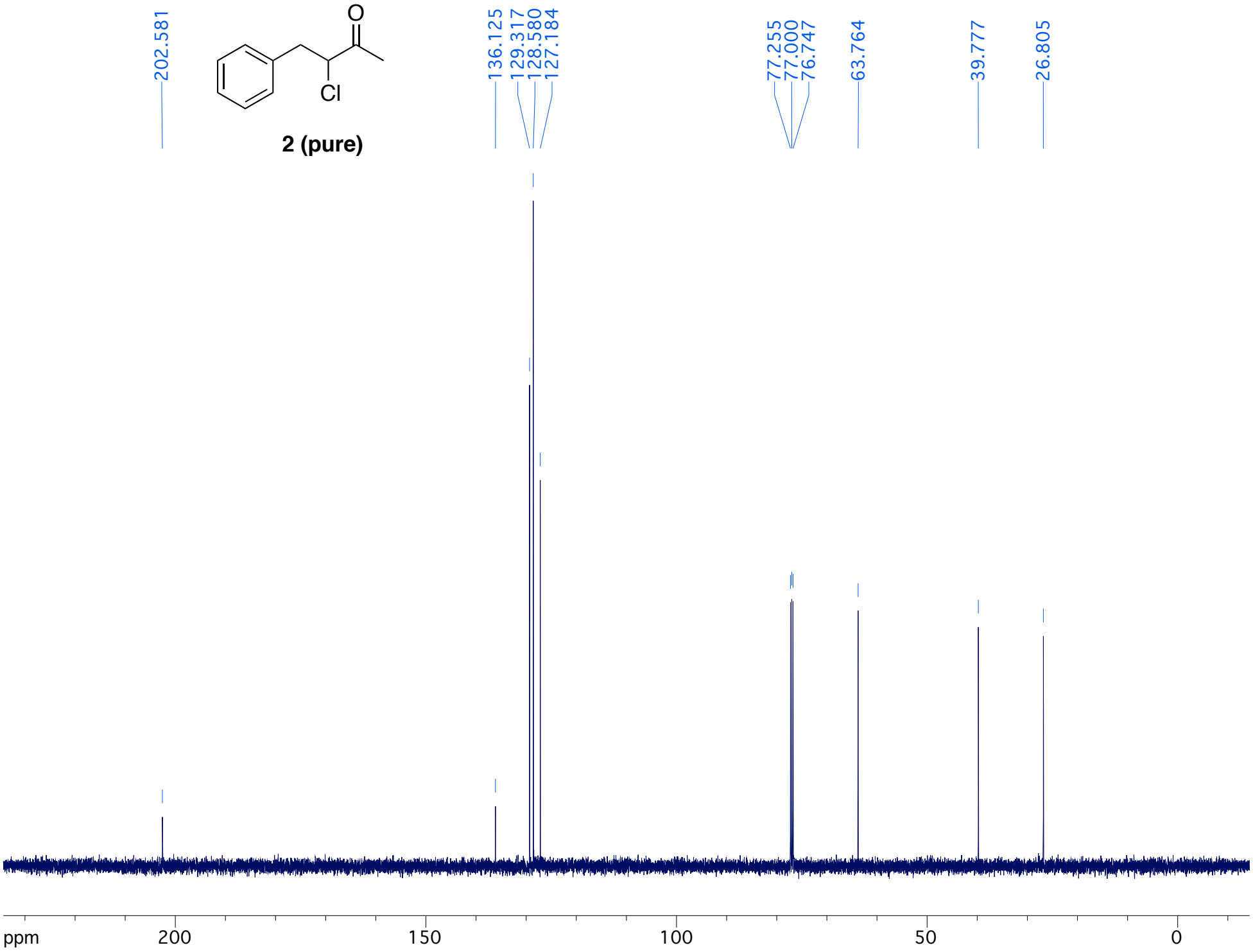
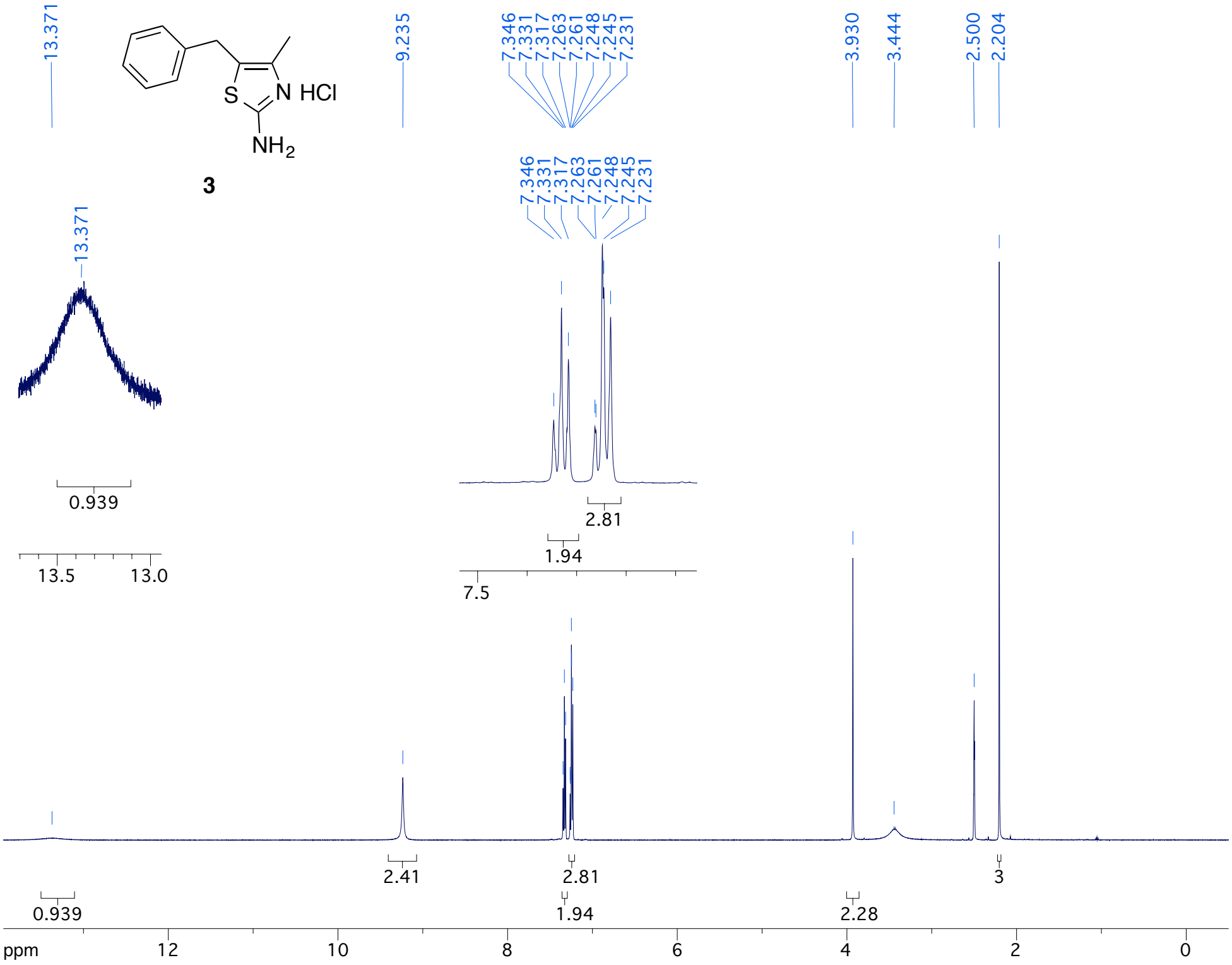
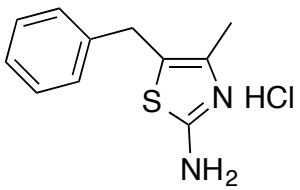

O
Cl

2 (pure)

7.334
7.320
7.305
7.279
7.265
7.259
7.250
7.228
7.214
4.423
4.411
4.407
4.395
3.359
3.347
3.331
3.318
3.103
3.087
3.075
3.058
2.285
5.15
1
1.16
1.19
3.07
7.4
7.2
4.5
4.4
4.3
3.4
3.2
3.0
ppm
10
8
6
4
2
0


202.581
O
Cl
2 (pure)
136.125
129.317
128.580
127.184
77.255
77.000
76.747
63.764
39.777
26.805
ppm
200
150
100
50
0


13.371
9.235
7.346
7.331
7.317
7.263
7.261
7.248
7.245
7.231
3.930
3.444
2.500
2.204
S
N HCl
NH2
3
0.939
2.81
1.94
2.41
2.81
3
0.939
1.94
2.28
ppm
12
10
8
6
4
2
0
13.5
13.0
7.5


S
N HCl
NH2

3

167.758
138.793
131.030
128.694
128.253
126.796
116.760
40.021
39.854
39.687
39.520
39.353
39.186
39.020
30.388
11.463
ppm
200
150
100
50
0