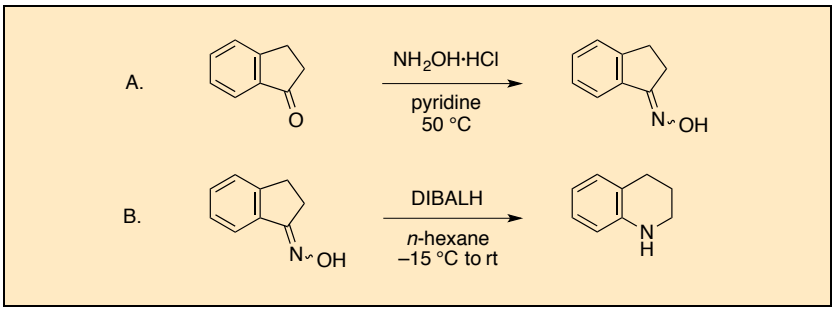
Organic Syntheses

DIBALH-Mediated Reductive Ring-Expansion Reaction of Cyclic Ketoxime

Taku Imaizumi, Kentaro Okano, and Hidetoshi Tokuyama*[1]

Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba 6-3, Aramaki, Aoba-ku, Sendai 980-8578, Japan

Checked by Lang-Tin Xu and Dawei Ma



Procedure

A. *1-Indanone oxime.* A 500-mL one-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (3.5 x 1.5 cm) is charged with 1-indanone (13.2 g, 100 mmol) (Note 1), pyridine (50 mL) (Note 2), and hydroxylamine hydrochloride (7.30 g, 105 mmol, 1.05 equiv) (Note 3). After stirring for 20 min (500 rpm) at 50 °C (Note 4), the reaction mixture is cooled to ambient temperature and concentrated on a rotary evaporator under reduced pressure (20 °C, 1 mmHg) to remove pyridine. To the residue are added ethyl acetate (300 mL) and 1 M aqueous HCl (50 mL). After the mixture is partitioned, the aqueous layer is extracted with ethyl acetate (50 mL), and the combined organic extracts are washed with 1 M aqueous HCl (2 x 100 mL) and brine (100 mL). The organic layer is dried over Na_2SO_4 (40 g) and filtered through cotton wool. The filtrate is concentrated on a

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rotary evaporator under reduced pressure (20 °C, 16 mmHg) to afford 1-indanone oxime (Notes 5, 6 and 7) as a pale yellow solid (14.5 g, 99%).

B. *Tetrahydroquinoline*. A 1-L oven-dried three-necked round-bottomed flask equipped with an overhead mechanical stirrer (paddle size: w = 8 cm, h = 1.5 cm), a 200-mL pressure-equalizing dropping funnel with a rubber septum, and a straight inlet adapter with a side arm 3-way stopcock fitted with an argon gas inlet and a thermometer (Figure 1) is charged with DIBALH (1.00 M in *n*-hexane, 199 mL, 199 mmol, 4.50 equiv) (Note 8) through the pressure-equalizing dropping funnel (Note 9). After the

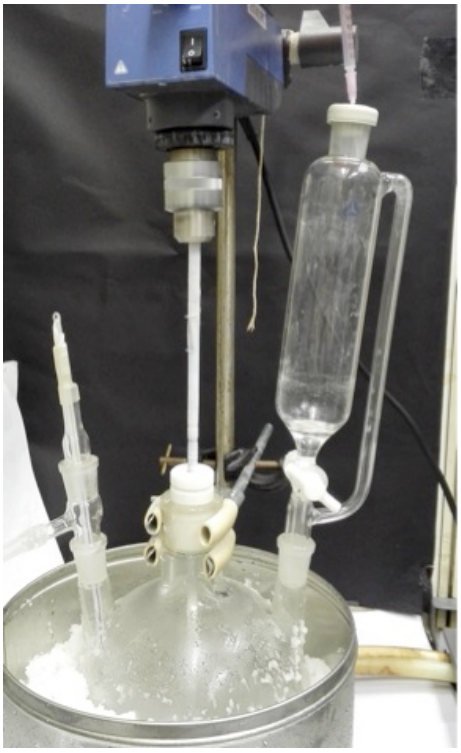

Figure 1. Reaction Assembly for Step B

dropping funnel is replaced with a rubber septum, the solution is cooled to –16 ~ –11 °C (internal temperature) using a brine/ice bath. The rubber septum is removed, and 1-indanone oxime (6.50 g, 44.2 mmol) is added portionwise over 3 min with stirring (300 rpm) *via* a powder addition funnel, while keeping the internal temperature below 22 °C. The funnel is

washed with distilled hexanes (5 mL), and the septum is fitted to the flask. After stirring for 5 min, the reaction mixture is warmed to ambient temperature and stirred for 2.5 h (Note 10). The paddle of the overhead mechanical stirrer is washed with distilled hexanes (10 mL) and removed (Note 11). The mixture is cooled to 2–3 °C (internal temperature) with an ice bath and gradually poured into saturated aqueous Rochelle salt (400 mL, precooled to 3 °C using an ice bath) (Note 12) in a 2-L three-necked round-bottomed flask with stirring (300 rpm) using an overhead mechanical stirrer (paddle size: w = 8 cm, h = 1.5 cm), while keeping the internal temperature below 30 °C. After the mixture is transferred to the flask with the aid of ethyl acetate (50 mL), the mixture is warmed to ambient temperature and stirred for 3.5 h. The resulting two-phase solution is partitioned, and the aqueous phase is extracted with ethyl acetate (2 x 100 mL). The combined organic extracts are washed with brine (200 mL), dried over Na_2SO_4 (40 g), and filtered through cotton wool. The filtrate is concentrated on a rotary evaporator under reduced pressure (20 °C, 16 mmHg), and the resulting residual oil is dried *in vacuo* for 2 h in a desiccator (20 °C) (Note 13) to afford 5.95–5.96 g of a pale yellow liquid, which is purified by silica gel column chromatography (hexanes-ethyl acetate = 13:1) (Notes 14 and 15). The fractions containing the product are collected and concentrated on a rotary evaporator under reduced pressure (40 °C, 16 mmHg), and the residual oil is dried *in vacuo* for 3.5 h in a desiccator (20 °C) to yield tetrahydroquinoline as a pale yellow oil (5.08 g, 86%) (Note 16 and 17).

Notes

1. 1-Indanone (>99%) was purchased from Sigma-Aldrich Co. and used as received without further purification.
2. Pyridine (99.5%) was purchased from J&K Scientific and used as received without further purification.
3. Hydroxylamine hydrochloride (98%) was purchased from Sigma-Aldrich Co. and used as received without further purification.
4. The reaction typically requires 20 min to consume all the 1-indanone and is monitored by TLC analysis on Merck silica gel 60 F_{254} plates developing with hexanes/ethyl acetate (3:1). The R_f values of 1-indanone and 1-indanone oxime are 0.39 and 0.33, respectively (visualized with 254 nm UV lamp and stained with an ethanol solution

of $Ce_2(SO_4)_3$ and phosphomolybdic acid (Ce-PMA). After dipping the TLC plate to the Ce-PMA solution, the chromatogram is stained by heating).

5. The mixture of (*E*)- and (*Z*)-1-indanone oxime (*E*/*Z* = 7:1) exhibits the following physicochemical properties: R_f = 0.33 and 0.17 (hexanes/ethyl acetate = 3:1); Merck silica gel 60 F_{254} plates (visualized with 254 nm UV lamp and stained with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid (Ce-PMA). After dipping the TLC plate to the Ce-PMA solution, the chromatogram is stained by heating); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.86–2.89 (m, 0.26 H), 2.97–3.00 (m, 2 H), 3.05–3.08 (m, 2.29 H), 7.23–7.34 (m, 3.55 H), 7.69 (d, *J* = 7.6 Hz, 1.0 H), 8.46 (d, *J* = 7.6 Hz, 0.13 H), 9.05 (br s, 0.16 H), 9.45 (br s, 0.87 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.20, 28.70, 28.87, 29.04, 121.82, 125.67, 125.80, 127.02, 127.21, 129.81, 130.61, 131.27, 133.89, 136.10, 148.66, 149.64, 160.77, 164.26; Chemical shifts were given relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). IR (neat, cm^{-1}): 3157, 3124, 3096, 3064, 2849, 1654, 1479, 1458, 1432, 1411, 1334, 1070, 986, 956, 833, 818, 753; Anal. calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 72. 67; H, 6.19; N, 9.45.
6. The E and Z isomers the 1-indanone oxime can be isolated in pure form by preparative TLC (hexanes/ethyl acetate = 1:1). (*E*)-1-Indanone oxime exhibits the following physicochemical properties: R_f = 0.33 (hexanes/ethyl acetate = 3:1); mp = 146.5–150.0 °C (ethyl acetate); IR (neat, cm^{-1}): 3178, 3063, 2850, 1655, 1480, 1456, 1432, 1410, 1334, 1070, 987, 957, 833, 819, 775, 753, 580, 569, 544, 526, 514; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.96–3.00 (m, 2 H), 3.05–3.08 (m, 2 H), 7.22–7.36 (m, 3 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 8.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.13, 28.73, 121.76, 125.83, 127.22, 130.63, 136.16, 148.63, 164.26; Chemical shifts were given relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). Anal. calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.46; H, 6.16; N, 9.50. These spectral data are identical with those reported in the literature.[2] (Z)-1-Indanone oxime exhibits the following physicochemical properties: R_f = 0.17 (hexanes/ethyl acetate = 3:1); mp = 137.6–140.9 °C (ethyl acetate); IR (neat, cm^{-1}): 3200, 3075, 2884, 1662, 1462, 1442, 994, 954, 808, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.83–2.87 (m, 2 H), 3.05–3.09 (m, 2 H), 7.25–7.39 (m, 3 H), 8.35 (br s, 1H), 8.43 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.88, 29.08, 125.70, 127.02, 129.80, 131.24, 133.87, 149.60, 160.74; Chemical shifts were given relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.16 ppm for

^{13}C NMR). Anal. calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.43; H, 6.14; N, 9.43.

7. A second reaction provided 14.6 g (99%) of the mixture of E and Z isomers.
8. DIBALH (1.00 M in *n*-hexane) was purchased from J&K Scientific and used as received without further purification.
9. A pressure-equalizing dropping funnel is used to handle DIBALH safely. DIBALH is transferred via disposable syringe from the bottle into the pressure-equalizing dropping funnel. The volume of 199 mL is marked on the dropping funnel prior to oven drying.
10. The reaction process is monitored by TLC analysis on silica gel 60 F_{254} plate. The R_f values of 1,2,3,4-tetrahydroquinoline, (*E*)-1-indanone oxime, (*Z*)-1-indanone oxime, and 2-isobutyl-1,2,3,4-tetrahydroquinoline are 0.48, 0.33, 0.17, and 0.67, respectively (hexanes/ethyl acetate = 3:1) (visualized with 254 nm UV lamp and stained with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid (Ce-PMA). After dipping the TLC plate to the Ce-PMA solution, the chromatogram is stained by heating).
11. When this reaction is carried out in ca. >10 g scale, the following procedure is recommended to avoid large volume extraction: the reaction mixture is cooled to 2 °C (internal temperature). After portionwise addition of sodium fluoride (28.0 equiv) for 2 min (internal temperature should be kept below 40 °C), water (20.0 equiv) is carefully added dropwise for 8 min, causing a temperature rise to ca. 44 °C. The mixture is stirred (300 rpm) using an overhead mechanical stirrer (paddle size: w = 8 cm, h = 1.5 cm) for 30 min followed by stirring for 1 h at ambient temperature. After the paddle of the overhead mechanical stirrer is washed with ethyl acetate (30 mL), the contents of the flask are passed through a pad of Celite (40 g) fitted to a Kiriyama funnel® (diameter = 14 cm, height = 8 cm, fitted with a filter paper No. 4, diameter = 9.5 cm) with ethyl acetate (3 × 150 mL). The filtrate is concentrated on a rotary evaporator under reduced pressure (20 °C, 16 mmHg), and the residual oil is dried *in vacuo* for 2 h in a desiccator (20 °C) to afford a pale yellow liquid, which is purified by column chromatography (Note 13) and dried to give tetrahydroquinoline as a pale yellow oil.
12. Potassium sodium (+)-tartrate tetrahydrate (Rochelle salt) was purchased from Sinopharm Chemical Reagent Co., Ltd and used as received without further purification.

13. Drying *in vacuo* more than 2 h results in loss of the tetrahydroquinoline due to volatilization.
14. The crude material is dissolved in eluent (5 mL) and then charged onto a column (diameter = 10 cm, height = 40 cm) of 380-gram silica gel. The column is sequentially eluted with hexanes/ethyl acetate = 13:1 (4 L), hexanes/ethyl acetate = 6:1. During chromatography, 100-mL fractions are collected. Fractions 12 − 17 and 21 − 42 were combined and concentrated on a rotary evaporator under reduced pressure (20 °C, 16 mmHg) and dried *in vacuo* to provide undesired 2-isobutyl-1,2,3,4-tetrahydroquinoline (fractions 12−17, 128–132 mg, 2%) and desired 1,2,3,4-tetrahydroquinoline (fractions 21 − 42, 5.04–5.12 g, 86–87%), respectively.
15. 2-Isobutyl-1,2,3,4-tetrahydroquinoline would be generated through the migration of the isobutyl group of DIBALH to the imine intermediate. Physicochemical properties of 2-isobutyl-1,2,3,4-tetrahydroquinoline: pale yellow oil; R_f = 0.67 (hexanes/ethyl acetate = 3:1); Merck silica gel 60 F_{254} plates (visualized with 254-nm UV lamp and stained with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid (Ce-PMA). After dipping the TLC plate to the Ce-PMA solution, the chromatogram is stained by heating); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (d, *J* = 6.6 Hz, 6 H), 1.28–1.43 (m, 2 H), 1.52–1.62 (m, 1 H), 1.70–1.80 (m, 1 H), 1.90–1.96 (m, 1 H), 2.68–2.87 (m, 2 H), 3.28–3.34 (m, 1 H), 6.47 (d, *J* = 8.2 Hz, 1 H), 6.60 (dd, *J* = 7.3, 7.3 Hz, 1 H), 6.93–6.97 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.64, 23.36, 24.61, 26.58, 28.72, 46.05, 49.40, 114.25, 117.07, 121.51, 126.84, 129.43, 144.84; Chemical shifts were given relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). IR (neat, cm^{-1}): 3408, 3051, 3015, 2954, 2867, 2843, 1607, 1585, 1484, 1434, 1384, 1366, 1354, 1309, 1273, 1258, 1153, 745, 716; Anal. calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.20; H, 9.98; N, 7.39. These spectral data are identical with those reported in the literature.[3]
16. Physicochemical properties of 1,2,3,4-tetrahydroquinoline: pale yellow oil; R_f = 0.48 (hexanes/ethyl acetate = 3:1); Merck silica gel 60 F_{254} plates (visualized with 254-nm UV lamp and stained with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid (Ce-PMA). After dipping the TLC plate to the Ce-PMA solution, the chromatogram is stained by heating); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.91–1.97 (m, 2 H), 2.75 (t, *J* = 6.4 Hz, 2 H), 3.28 (t, *J* = 5.5 Hz, 2 H), 6.46 (d, *J* = 7.8 Hz, 1 H), 6.58 (dd, *J* = 7.4, 7.4 Hz, 1 H), 6.94–6.98 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.29, 27.10, 42.09, 114.29, 117.01, 121.51, 126.83, 129.62, 144.90; Chemical shifts

were given relative to $CDCl_3$ (7.26 ppm for ^1H NMR, 77.16 ppm for ^{13}C NMR). IR (neat, cm^{-1}): 3406, 2926, 2840, 1606, 1584, 1504, 1468, 1355, 1310, 1267, 746; Anal. calcd. for $C_9H_{11}N$: C, 81.16; H, 8.32; N, 10.52. Found: C, 80.86; H, 8.33; N, 10.53. These spectral data are identical with those reported in the literature.[4]

17. A second reaction provided 5.10 g (87%) of the product.

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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.

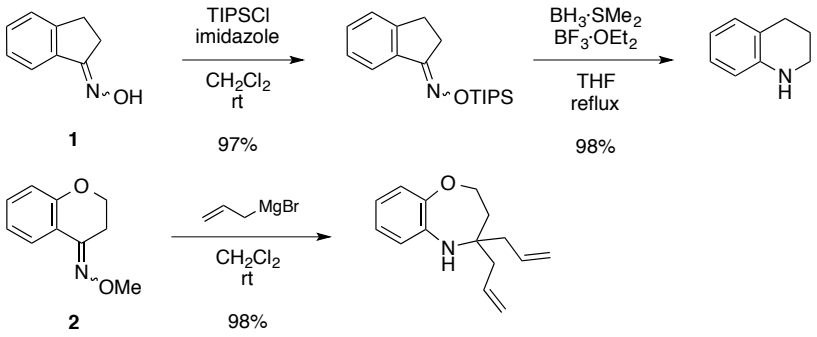
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior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

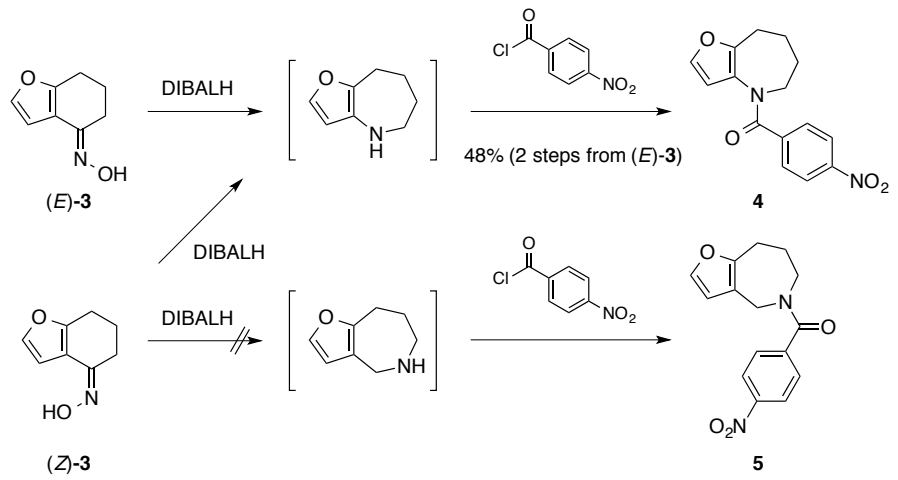
Discussion

Since benzene ring-fused nitrogen heterocycles are often found in pharmaceuticals and other bioactive compounds, considerable efforts have been devoted toward the development of effective synthetic methodologies for these compounds. In addition to the classical Beckmann rearrangement, ring-expansion reactions of oxime derivatives have also been investigated so far,[5] owing to the wide availability of the corresponding ketones (Scheme 1). The silylation of oxime **1** and subsequent treatment with $BH_3{\cdot}SMe_2/BF_3{\cdot}OEt_2$ gives tetrahydroquinoline in excellent yields.[4] Oxime ether **2** can also undergo a similar reaction.[6] Unlike the reactions that utilize *O*-functionalized oximes, the presented method provides a more facile and economical access to the cyclic amines because the hydroxyl group does not require protection.

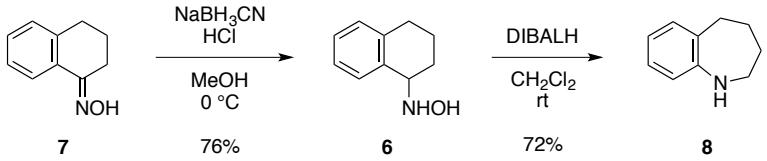
In contrast to the Beckmann rearrangement, the two possible geometries of the oxime C–N double bond can give exclusively an aromatic secondary amine in the presented method (Scheme 2).[7] Cho and co-workers reported that the separated (*E*)-oxime **3** was converted to the N-benzoyl-furo[3,2-*b*]azepine **4** in 48% yield over 2 steps. (*Z*)-Oxime **3** was also converted to the same compound, and its regioisomer **5** was not detected. The reaction is known to proceed via a hydroxylamine intermediate.[5a,5f] This was further supported by control experiments, where the synthesis of hydroxylamine **6** from a 1,2-reduction of oxime **7** gave the corresponding aromatic secondary amine **8** under the same reaction conditions (Scheme 3).[8a]



Scheme 1. Ring-expansion reaction of protected O-silyl or O-alkyloxime substrates

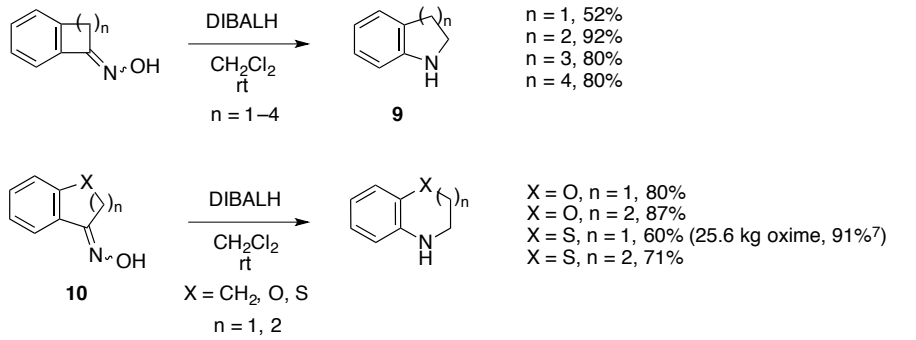


Scheme 2. Selective migration of the aryl group



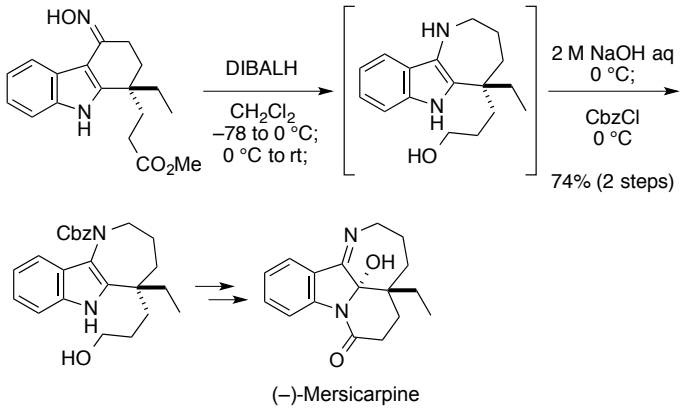
Scheme 3. Control experiments using hydroxylamine as a substrate

This reaction has a broad scope for the synthesis of cyclic secondary anilines **9**.[8] It should be noted that seven and eight-membered structures, which have previously been difficult to construct through the palladium- or copper-catalyzed intramolecular aryl amination, are easily accessible with this reaction (Scheme 4). In addition, heterocyclic ketoximes **10** containing an oxygen or a sulfur atom are also compatible. In addition, the reaction is applicable to the industrial-scale synthesis of 2,3,4,5-tetrahydrobenzo[*b*][1,4] oxazepine (25.6 kg oxime, 91%).[9]



Scheme 4. Scope of this reductive ring-expansion reaction

Tokuyama and co-workers applied this ring-expansion reaction to construct an azepinoindole skeleton and accomplished a total synthesis of (–)-mersicarpine (Scheme 5).[10]



Scheme 5. Application to total synthesis of (–)-mersicarpine

Unlike the previous protocol that uses DIBALH in a dichloromethane solution, this modified protocol allows us to an environment-friendly alternative of DIBALH in *n*-hexane solution.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

1-Indanone: 1*H*-Inden-1-one, 2,3-dihydro-; (83-33-0)
Hydroxylamine, hydrochloride: Hydroxylamine, hydrochloride (1:1); (5470-11-1)
Pyridine: Pyridine; (110-86-1)
Aluminum, hydrodiisobutyl-: Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7)

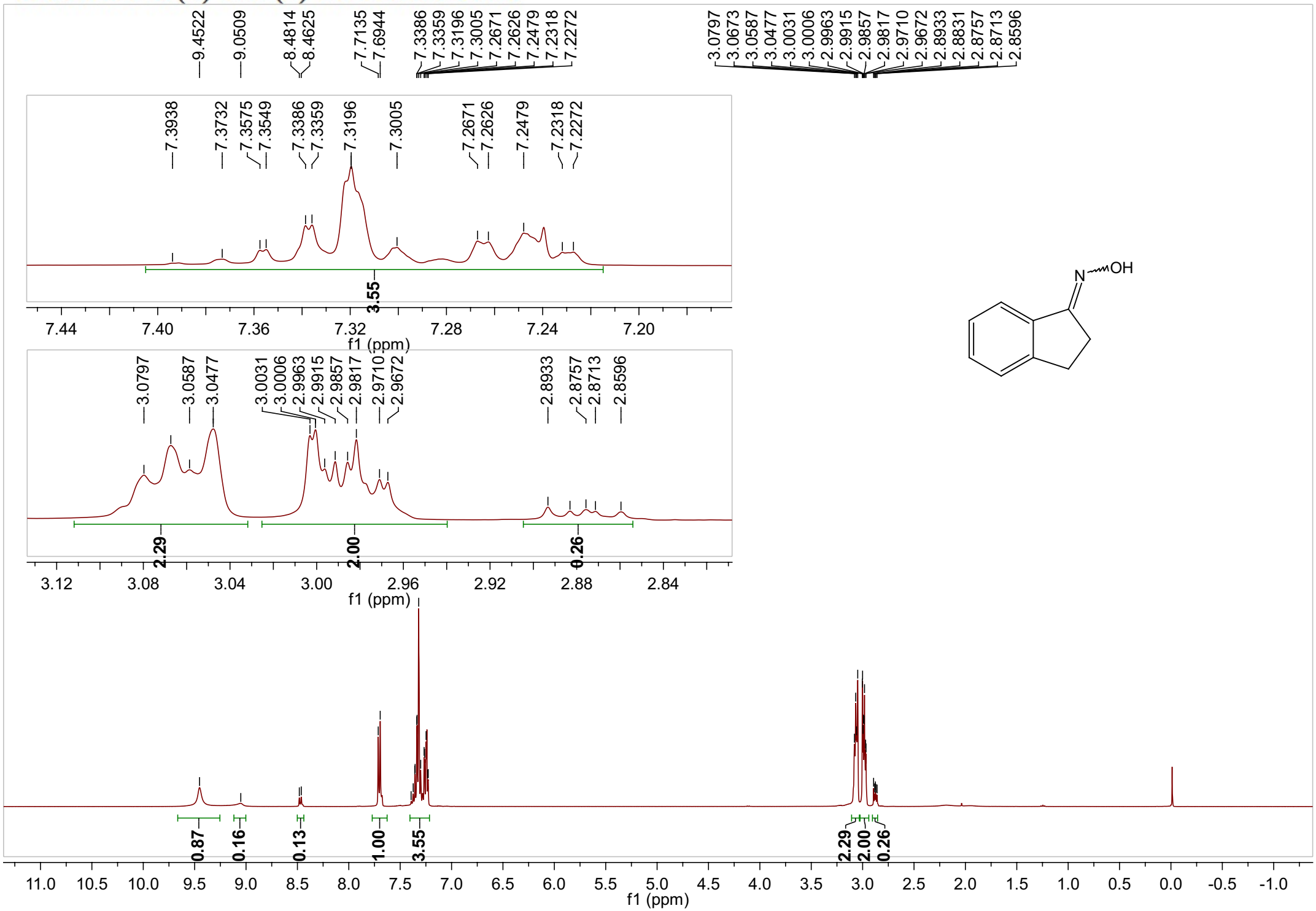
Hidetoshi Tokuyama was born in Yokohama in 1967. He received his Ph.D. in 1994 from Tokyo Institute of Technology under the direction of Professor Ei-ichi Nakamura. He spent one year (1994-1995) at the University of Pennsylvania as a postdoc with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed Associate Professor in 2003. In 2006, he was move to Tohoku University, where he is currently Professor of Pharmaceutical Sciences His research interest is on the development of synthetic methodologies and total synthesis of natural products.

Kentaro Okano was born in Tokyo in 1979. He received his B.S. in 2003 from Kyoto University under the supervision of Professor Tamejiro Hiyama. He then moved to the laboratories of Professor Tohru Fukuyama at the University of Tokyo. In 2007, he joined the faculty at Tohoku University, where he is currently an assistant professor in Professor Hidetoshi Tokuyama's group. In 2014, he visited Professor Amir Hoveyda's laboratories at Boston College as a visiting researcher. His current research interest is natural product synthesis based on the development of new synthetic methodologies.

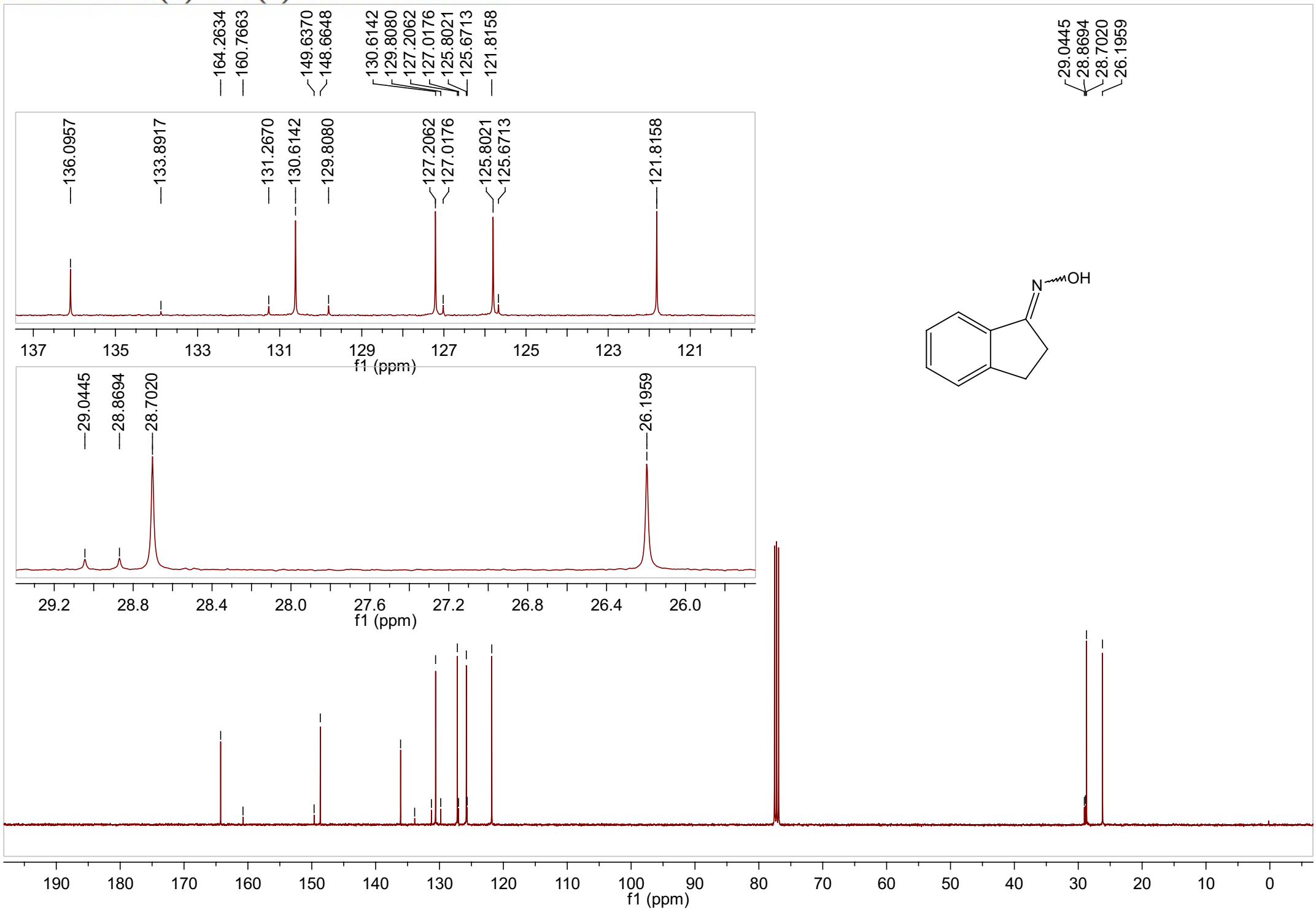
Taku Imaizumi was born in Ibaraki in 1992. He is an undergraduate student in the laboratories of Professor Tokuyama at the Faculty of Pharmaceutical Sciences, Tohoku University. His current research interest is synthesis of indole via novel rearrangement reaction.

Dr. Lan-Ting Xu received her B.S. degree from West China School of Pharmacy, Sichuan University in 2008, and her Ph.D. degree from Fudan University in 2013, under the supervision of Dawei Ma. She is now a MSD China R&D Postdoc Research Fellow in Shanghai Institute of Organic Chemistry. Her research interests include copper-catalyzed coupling reactions, metal-catalyzed direct C-H functionalization and heterocycle synthesis.

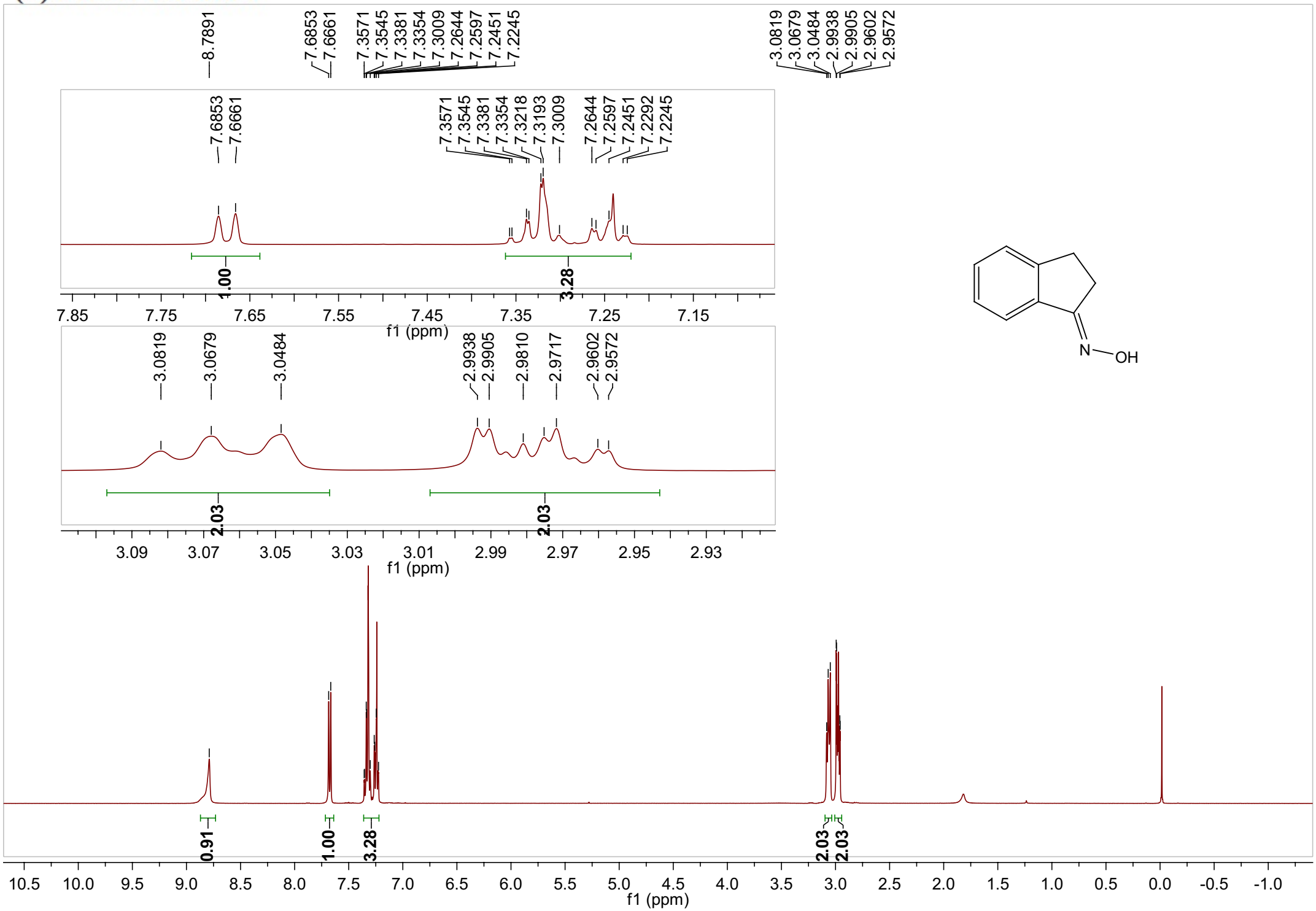
The mixtur of (*E*)- and (*Z*)-1-Indanone oxime



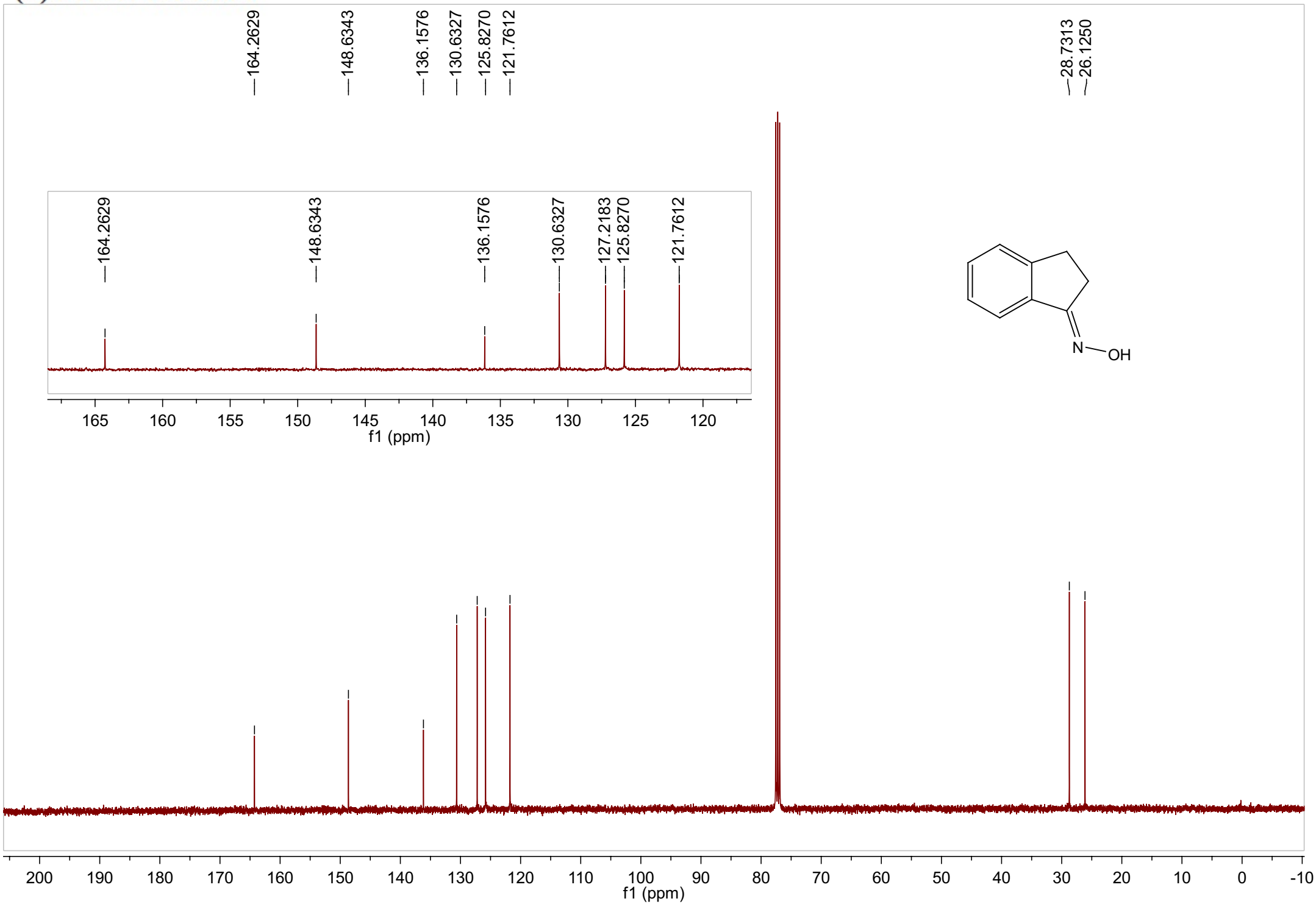
The mixtur of (*E*)- and (*Z*)-1-Indanone oxime



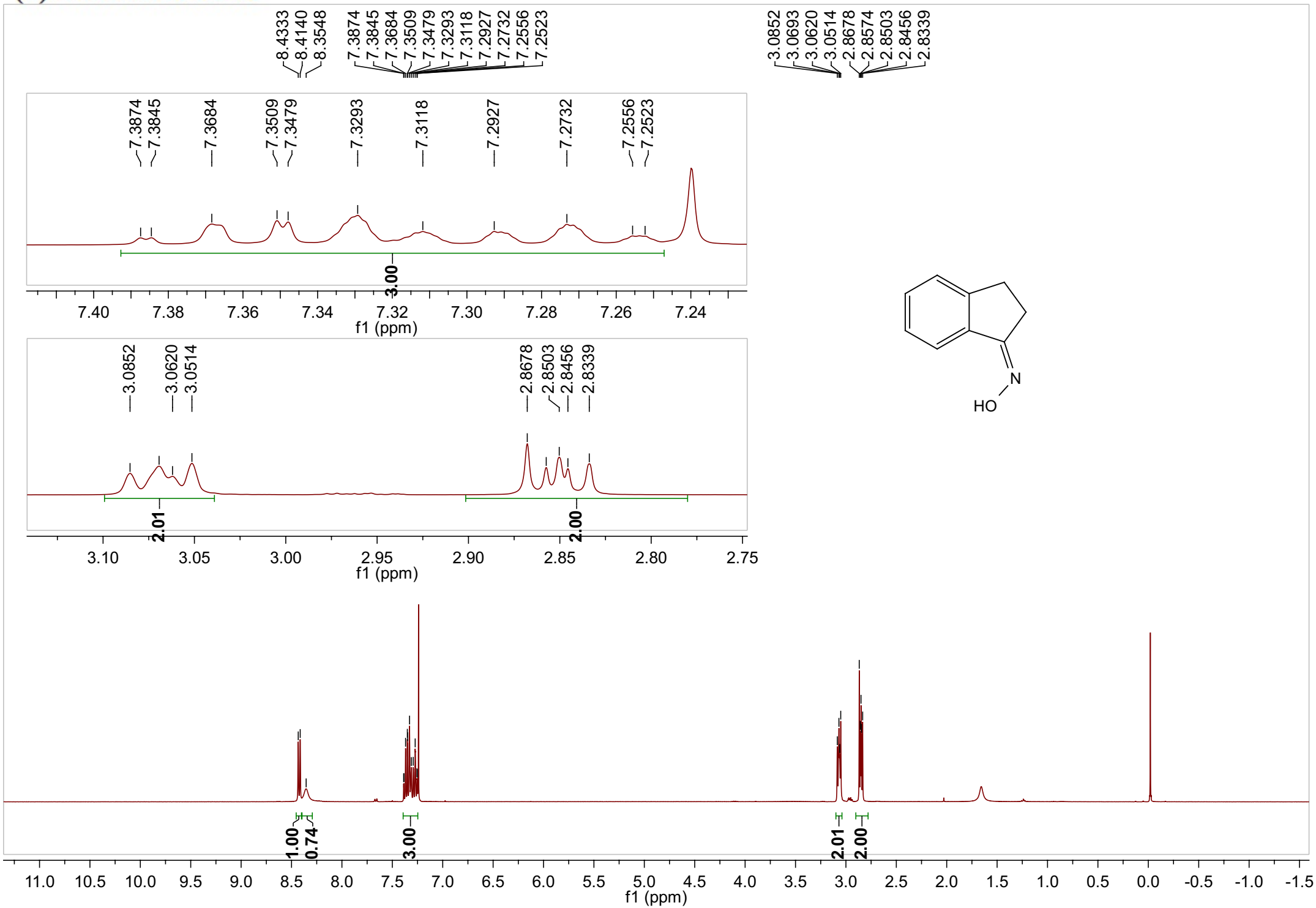
(*E*)-1-Indanone oxime



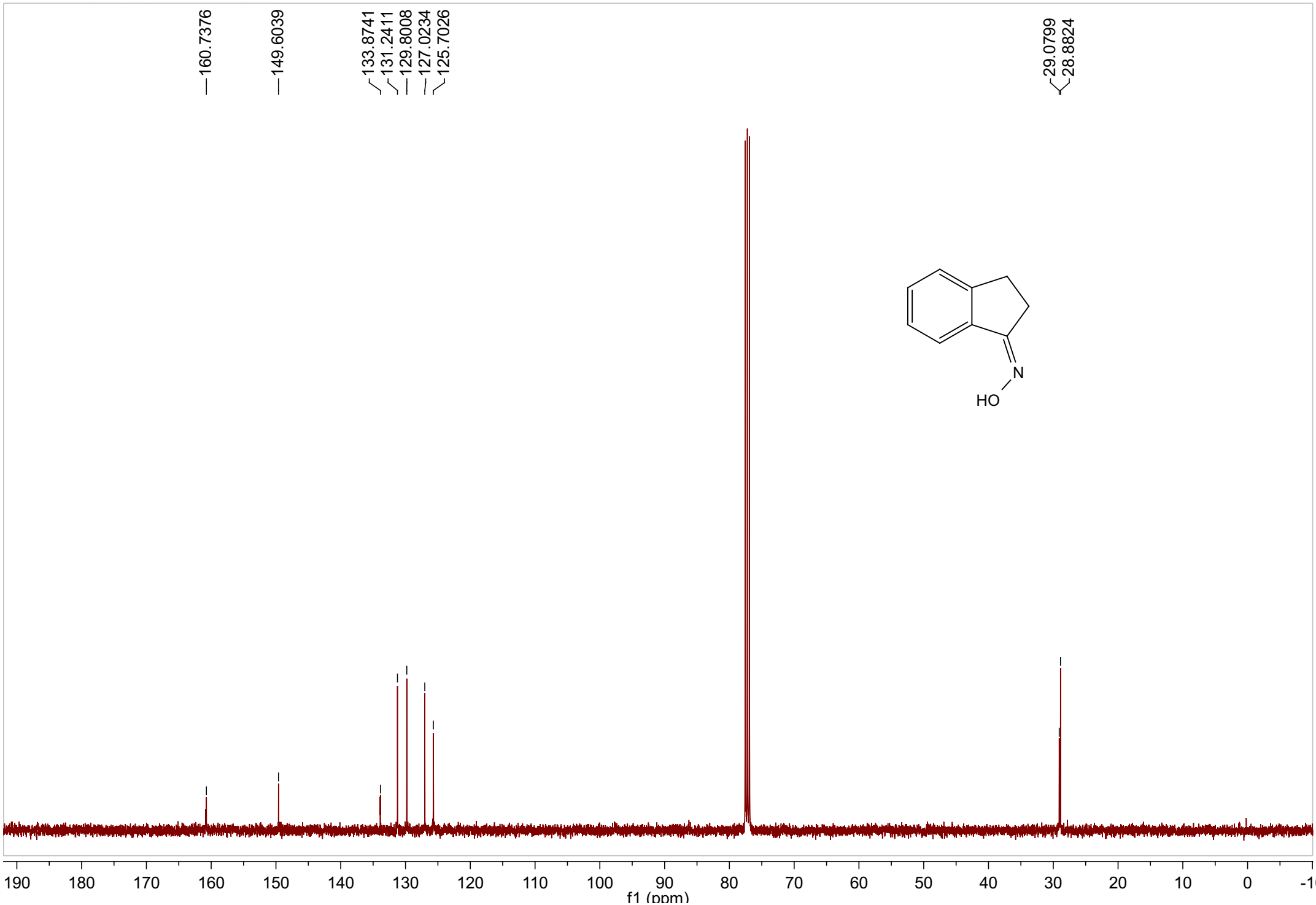
(*E*)-1-Indanone oxime



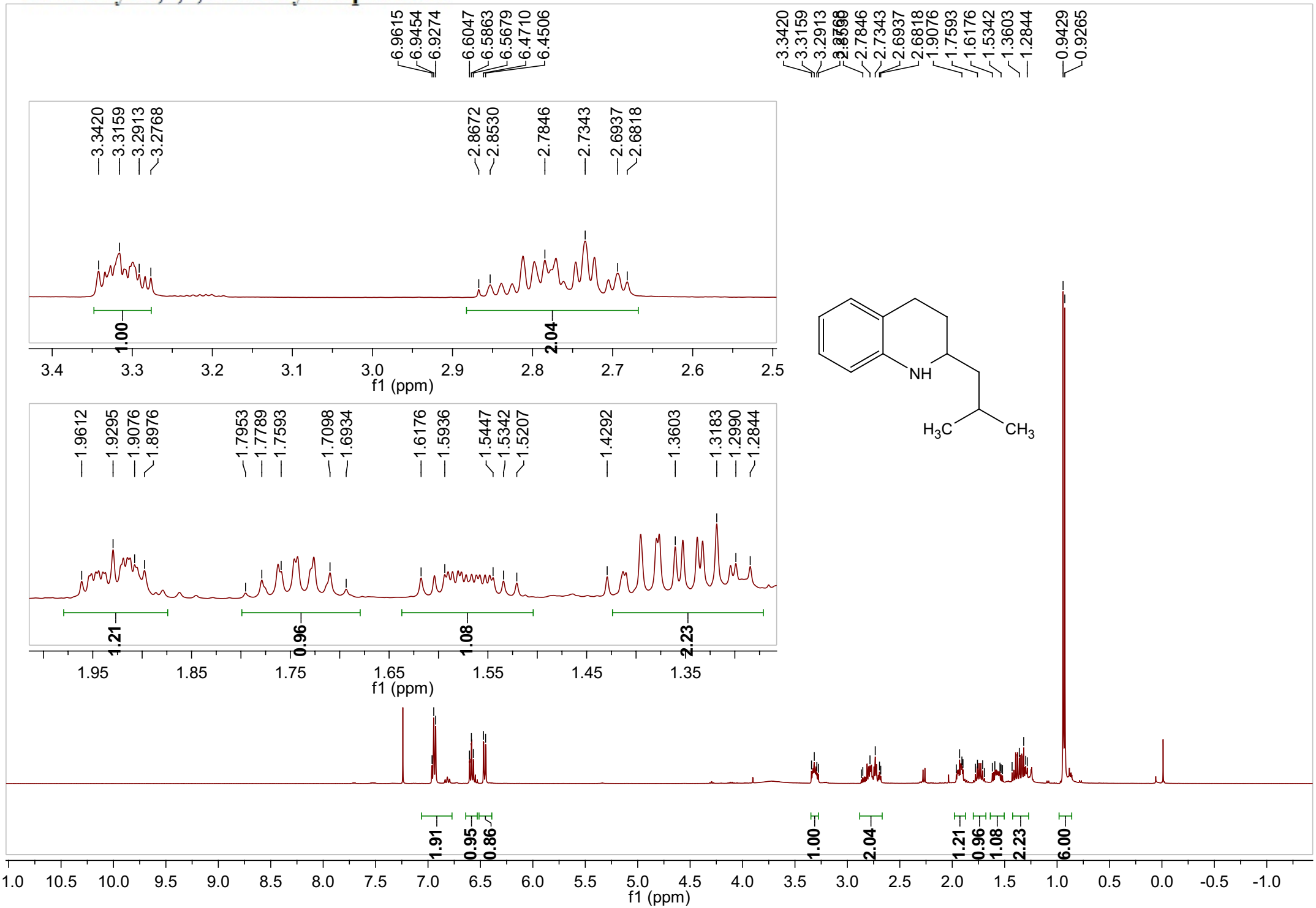
(Z)-1-Indanone oxime



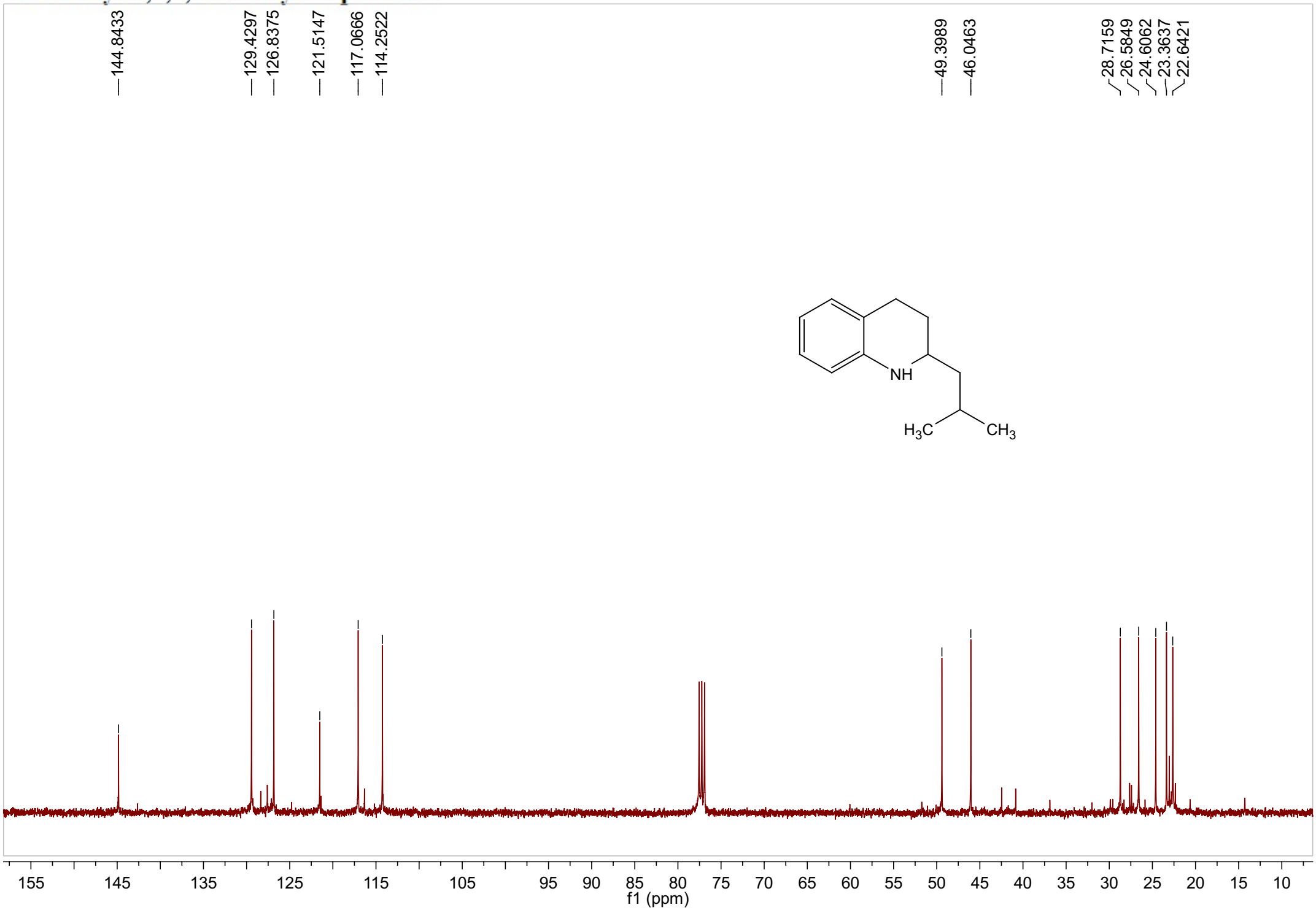
(*Z*)-1-Indanone oxime



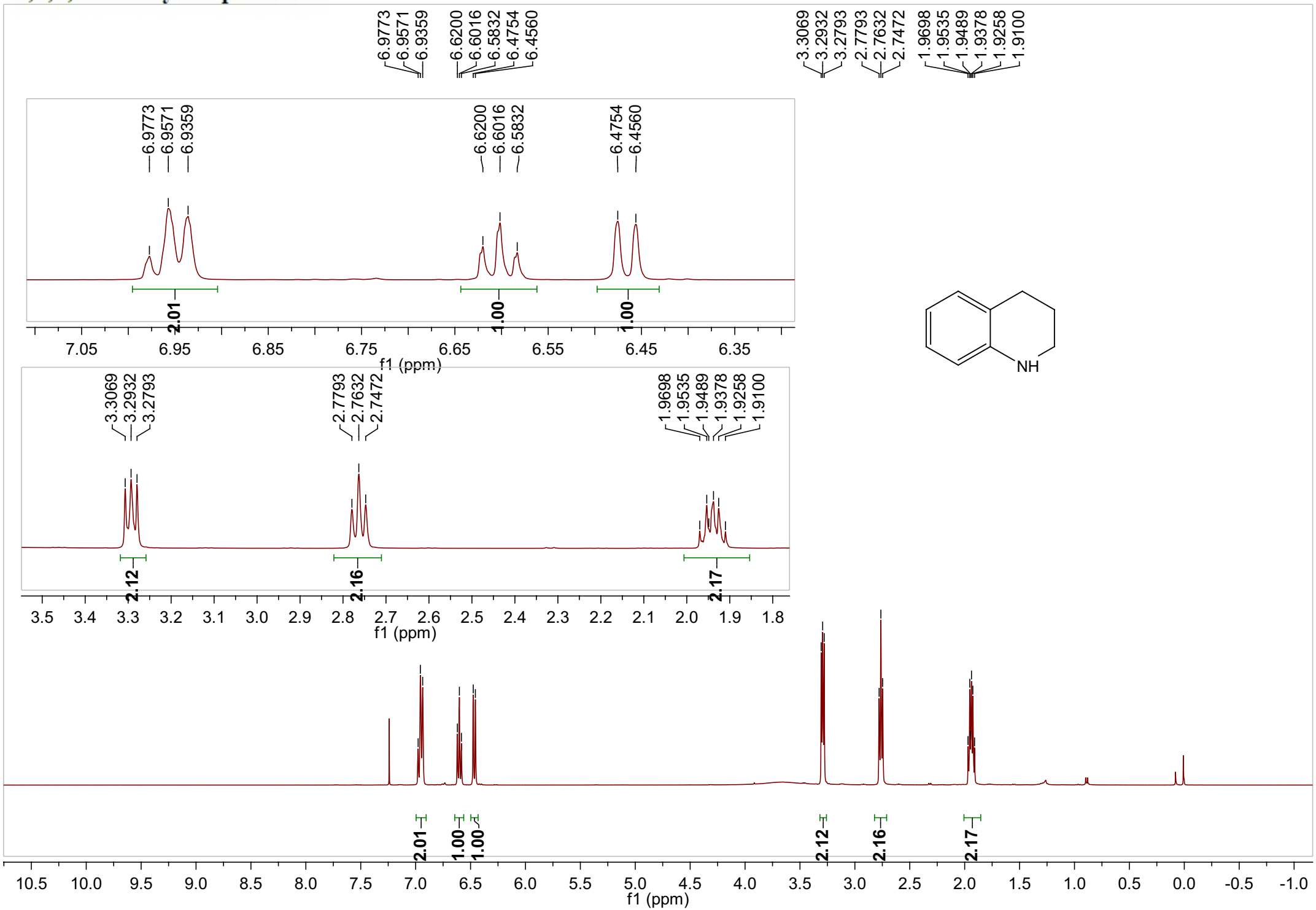
2-Isobutyl-1,2,3,4-tetrahydroquinoline



2-Isobutyl-1,2,3,4-tetrahydroquinoline



1,2,3,4-tetrahydroquinoline



1,2,3,4-tetrahydroquinoline