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for the Preparation
of Organic Compounds

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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.

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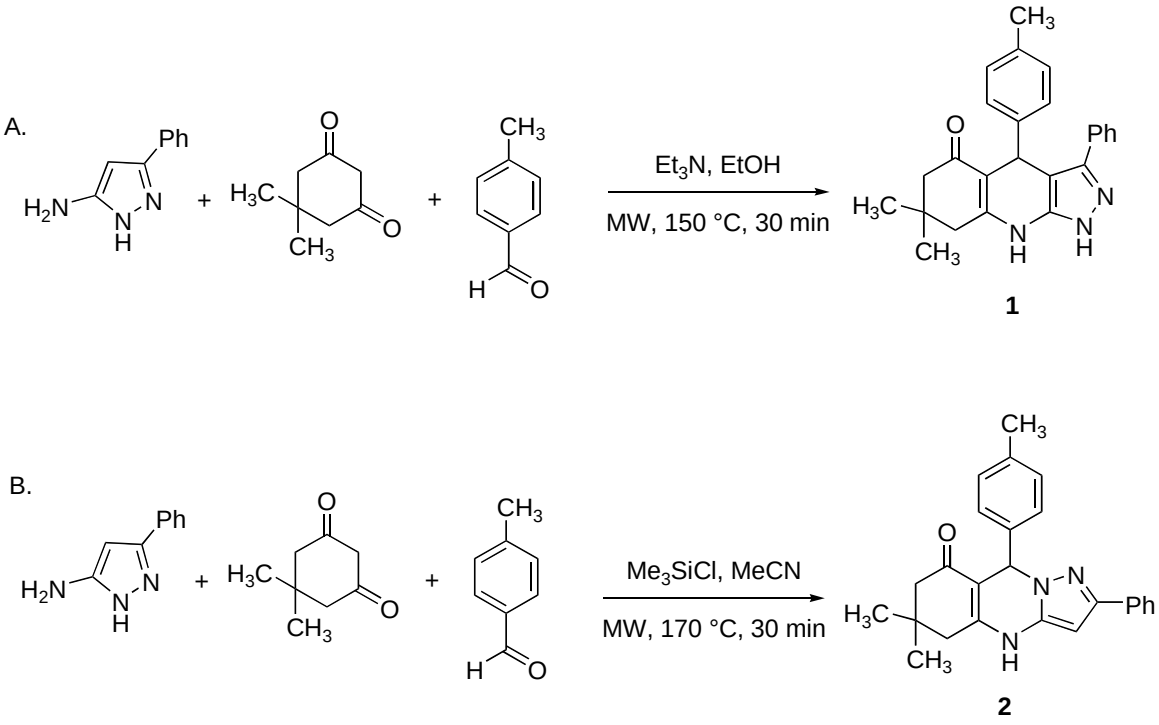
ONE-POT MULTICOMPONENT PREPARATION OF TETRAHYDROPYRAZOLOQUINOLINONES AND TETRAHYDROPYRAZOLOQUINAZOLINONES



Submitted by Toma N. Glasnov and C. Oliver Kappe.[1]
Checked by MaryAnn T. Robak and Jonathan A. Ellman.

Caution! *During microwave heating using sealed vessel technology the reaction mixtures are heated well above their boiling points generating an internal pressure of 7-15 bar. Only special microwave process vials supplied by the vendor that are designed to withhold elevated temperatures and pressures must be used. After completion of the experiment, the vessel must be allowed to cool down to a temperature well below the boiling point of the solvent (ca. 50 °C) before removal from the microwave cavity and opening to the atmosphere. A dedicated microwave reactor for organic synthesis with appropriate online temperature and pressure monitoring must be employed.*

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1. Procedure

A. 7,7-Dimethyl-3-phenyl-4-p-tolyl-6,7,8,9-tetrahydro-1H-pyrazolo [3,4-b]quinolin-5(4H)-one (**1**). Into a dedicated 20-mL one-necked Pyrex microwave process vial equipped with a magnetic stirring bar (Note 1), 10 mL of dry ethanol (Note 2), triethylamine (981 µL, 712 mg, 7.04 mmol, 1.6 equiv) (Note 3), 5-phenyl-1*H*-pyrazol-3-amine (700 mg, 4.40 mmol, 1.0 equiv) (Note 4) and 5,5-dimethyl-1,3-cyclohexanedione (617 mg, 4.40 mmol, 1.0 equiv) (Note 5) are added and stirred vigorously for 2 min at room temperature to form a slightly brownish solution. *p*-Tolualdehyde (519 µL, 529 mg, 4.40 mmol, 1.0 equiv) (Note 6) is then added. The reaction vial is tightly sealed with a Teflon septum inserted into an aluminum crimp (Note 7) and transferred to a Biotage single-mode microwave reactor for microwave processing at 150 °C for 30 min (Notes 8 and 9). After the reaction mixture has been processed, the vial is cooled down to 50 °C using the gas-jet cooling feature of the instrument (5 min) and subsequently removed from the microwave cavity by the robotic arm. After decrimping of the sealed process vial, the dark yellow reaction mixture is quickly transferred into a 250-mL Erlenmeyer flask filled with 200 mL of water at room temperature under vigorous stirring, resulting in a bright yellow turbid suspension. The pH of the reaction mixture is brought to ca. 2 by careful addition of 7 mL of 6M HCl within ca. 1 min, which leads to the formation of a yellow precipitate. After stirring for an additional 60 min at room temperature the precipitate is collected by suction filtration on a Büchner funnel with a coarse glass frit and then is triturated with water (3 × 20 mL) by turning off the vacuum, adding the solvent, crushing the solid and mixing thoroughly with a spatula, and then turning on the vacuum to remove the solvent. The product is subsequently dried overnight in a drying oven at 50 °C under vacuum. For purification the crude product is transferred to a Büchner funnel with a medium glass frit and triturated with dichloromethane (3 × 20 mL), applying gentle suction to remove the filtrate after each trituration. The solid is then dried for 1 h in a drying oven at 50 °C under vacuum to yield 1.19–1.22 g of pale yellow powdery solid. The solid is then transferred to a 50-mL Erlenmeyer flask equipped with a magnetic stirbar and the flask is heated to 90 °C, adding 25–26 mL of EtOH slowly until the solid is dissolved. The hot solution is then quickly filtered (hot filtration) by suction filtration through filter paper on a Büchner funnel (Note 10). The clear yellow solution is reheated in the 90 °C oil bath, and then the heat and

magnetic stirring are turned off and the solution is allowed to slowly cool to room temperature and crystallize overnight. The resulting crystals are collected by suction filtration on a Büchner funnel, washed with 2 × 1 mL of EtOH, and dried overnight in a drying oven at 50 °C under vacuum to provide 0.78–0.85 g (46-50%) of 7,7-dimethyl-3-phenyl-4-*p*-tolyl-6,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinolin-5(4*H*)-one (**1**) as yellow crystals in 99% purity (Notes 11 and 12).

B. 6,6-Dimethyl-2-phenyl-9-p-tolyl-5,6,7,9-tetrahydropyrazolo[5,1-b]quinazolin-8(4H)-one (**2**). Into a dedicated 20-mL one-necked Pyrex microwave process vial equipped with a magnetic stirring bar (Note 1), 10 mL of acetonitrile (Note 13), 5-phenyl-1*H*-pyrazol-3-amine (1.39 g, 8.74 mmol, 2.0 equiv) (Notes 4 and 14) and 5,5-dimethyl-1,3-cyclohexanedione (1.23 g, 8.74 mmol, 2.0 equiv) (Note 5) are added and stirred vigorously for 1 min at room temperature to form a yellow suspension. Chlorotrimethylsilane (222 µL, 190 mg, 1.75 mmol, 0.40 equiv) (Note 15) is added, sometimes resulting in the formation of a white precipitate that dissolves upon stirring. After an additional stirring period of 1 min at room temperature, *p*-tolualdehyde (515 µL, 525 mg, 4.37 mmol, 1.0 equiv) (Note 6) is added, whereupon the suspension turns into a yellow solution. The checkers noted that a small amount of solid sometimes remains undissolved. The formed reaction mixture is stirred for an additional 2 min and then the reaction vial is tightly sealed with a Teflon septum inserted into an aluminum crimp (Note 7) and transferred to a Biotage single-mode microwave reactor for microwave processing at 170 °C for 30 min (Notes 16 and 17). After the reaction mixture has been processed, the vial is cooled down to 50 °C using the gas-jet cooling feature of the instrument (ca. 5 min) and is subsequently removed from the microwave cavity by the robotic arm. After decrimping of the sealed process vial, the dark orange reaction mixture is quickly transferred into a 500-mL Erlenmeyer flask containing 300 mL of a vigorously stirred ethanol-water-NaOH mixture (Note 18) to adjust the pH to 8-9. The resulting suspension is stirred for an additional 2 h and is then collected by suction filtration on a Büchner funnel with a coarse glass frit and triturated with a H_2O/EtOH mixture (2:1, 3 × 20 mL) by turning off the vacuum, adding the solvent, crushing the solid and mixing thoroughly with a spatula, and then turning on the vacuum to remove the solvent. The precipitate is dried overnight in a drying oven at 50 °C under vacuum. The crude product is then transferred to a 250-mL Erlenmeyer flask containing 100 mL of acetonitrile and stirred vigorously for 10 min to break up the

solid into a fine suspension. The stirring mixture is then heated to boiling for 5 min, allowing the desired product to dissolve while leaving a side product suspended as a white solid. The hot mixture is then filtered through a medium glass-fritted Büchner funnel, applying gentle suction to assist in the filtration. The clear yellow filtrate is reheated to boiling, and 100 mL of boiling water is added. The mixture is allowed to cool to room temperature with stirring for 1 h, then the flask is placed in an ice bath and stirring is continued for an additional 1 h. During the recrystallization of product **2**, the solution becomes cloudy within 1-2 min after adding the boiling water, and crystallization proceeds as the solution begins to cool. The resulting white solid is collected by suction filtration on a Büchner funnel with a coarse glass frit, washed with 2 × 10 mL of a cold (0 °C) acetonitrile/H_2O mixture (1:1) and dried overnight in a vacuum drying oven at 50 °C to provide 1.22–1.28 g (73–76%) of 6,6-dimethyl-2-phenyl-9-*p*-tolyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]quinazolin-8(4*H*)-one (**2**) as a white fibrous solid (Notes 19 and 20).

2. Notes

1. A 20-mL microwave process vial containing the appropriate magnetic stirring bar (length 17 mm) for the Optimizer EXP microwave reactor from Biotage AB (Sweden) was used (see Figure 1).

2. Anhydrous ethanol (water < 0.2 % (K.F.)) was obtained from Acros Organics and used as received.

3. Triethylamine (99% purity) was obtained from Acros Organics and used as received.

4. 5-Phenyl-1*H*-pyrazol-3-amine (97% purity) was obtained from Maybridge and used as received.

5. 5,5-Dimethyl-1,3-cyclohexanedione (>99% purity) was obtained from Fluka and used as received.

6. *p*-Tolualdehyde (97% purity) was obtained from Aldrich and used as received.

7. The aluminum crimp tops/Teflon septa are commercially available from Biotage AB (Sweden). An appropriate crimper/decapper was used for sealing and opening of the process vials.

8. The submitters employed a 300 W Biotage Optimizer Sixty EXP single-mode microwave reactor (Biotage AB, Sweden) (Figure 1). The checkers employed a 400 W Biotage Initiator EXP microwave reactor

(Biotage AB, Sweden). The instrument is programmed as follows: reaction temperature – 150 °C, reaction time – 1800 sec (30 min), hold time – on, pre-stirring – 10 sec, absorption level – high. Alternative microwave instruments may include a Discover reactor (CEM, Matthews, NC, USA).

9. An internal reaction pressure of 10–12 bars was observed.

10. Filters No 42 from Whatman were used.

11. The physical properties of 7,7-dimethyl-3-phenyl-4-*p*-tolyl-6,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]-quinolin-5(4H)-one (**1**) were as follows: yellow crystalline solid, mp 194–195 °C, R_f = 0.66 (9:1 dichloromethane/methanol, TLC on silica gel 60 F_{254} plates, UV detection); IR (film): 3631, 3139, 3056, 3016, 2955, 2904, 1585, 1569, 1539, 1504, 1486, 1419, 1376, 1257, 1214, 1141 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 0.84 (s, 3 H), 1.00 (s, 3 H), 1.95 (d, *J* = 16.1, 1 H), 2.10–2.19 (m, 4 H), 2.36 (d, *J* = 16.6, 1 H), 2.43–2.53 (m, 1 H), 5.30 (s, 1 H), 6.89 (d, *J* = 8.0, 2 H), 7.00 (d, *J* = 8.0, 2 H) 7.28 (t, *J* = 7.4, 1 H), 7.38 (apparent t, *J* = 7.5 Hz, 2 H), 7.53 (d, *J* = 7.6, 2 H), 9.90 (s, 1 H), 12.56 (s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 20.5, 26.5, 29.0, 31.9, 34.7, 40.8, 50.4, 103.4, 107.9, 125.9, 127.3, 127.8, 128.2, 128.7, 129.5, 134.2, 137.1, 144.6, 148.2, 152.0, 192.7; MS (ESI) *m/z* (relative intensity): 384 (M+H, 100). Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.03; H, 6.47; N, 10.97.

12. The submitters reported purification of the crude precipitate by crystallization from hot EtOH:H_2O (2:1) to give 0.92–1.05 g (55–63%) of product. However, elemental analysis was not provided by the submitters, and in the checkers' hands, this procedure failed to give product of satisfactory purity based on ^1H NMR and elemental analysis. The checkers found that trituration of the crude product with CH_2Cl_2 could remove most of the impurities, providing material with a single side product in approximately 10:1 ratio of desired product to side product by ^1H NMR analysis. Including this trituration step prior to recrystallization resulted in higher isolated yields under both the EtOH:H_2O recrystallization conditions provided by the submitters and the EtOH recrystallization conditions investigated by the checkers. Recrystallization from EtOH:H_2O (2:1) provides material with a 97:3 ratio of desired product to side product, while recrystallization from EtOH provides material with a 99:1 ratio of desired product to side product by ^1H NMR analysis, sufficiently pure for elemental analysis.

13. Acetonitrile (HPLC-grade, Acros Organics) was used by the submitters. The checkers used HPLC-grade acetonitrile from Fisher Scientific.

14. If equimolar ratios of the starting materials are used a different product distribution is obtained, with typically more of the Hantzsch-type product **1** being formed. In addition more side products are visible by HPLC analysis and the benzaldehyde starting material is not completely consumed. Other acidic catalysts may be applied (HCl or Lewis acids such as $LaCl_3$), however the best result is obtained when using chlorotrimethylsilane as a reaction mediator.

15. Chlorotrimethylsilane (98% purity) was obtained from Aldrich and used as received.

16. The submitters employed a 300 W Biotage Optimizer Sixty EXP single-mode microwave reactor (Biotage AB, Sweden) (Figure 1). The checkers employed a 400 W Biotage Initiator EXP microwave reactor (Biotage AB, Sweden). The instrument is programmed as follows: reaction temperature – 170 °C, reaction time – 1800 sec (30 min), hold time – on, pre-stirring – 10 sec, absorption level – high. Alternative microwave instruments may include a Discover reactor (CEM, Matthews, NC, USA).

17. An internal reaction pressure of 13–14 bars was observed.

18. The solvent mixture was prepared by mixing 200 mL of distilled water, 100 mL of ethanol and 160 mg of NaOH. Sodium hydroxide pearls (99% purity) were obtained from Acros Organics (submitters) or EMD Chemicals (checkers) and used as received.

19. The physical properties of 6,6-dimethyl-2-phenyl-9-*p*-tolyl-5,6,7,9-tetrahydropyrazolo[5,1-*b*]-quinazolin-8(4*H*)-one (**2**) were as follows: white solid, mp 235–238 °C; R_f = 0.74 (9:1 dichloromethane/methanol, TLC on silica gel 60 F_{254} plates, UV detection); IR (film): 2960, 2921, 2873, 1642, 1582, 1569, 1430, 1383, 1361, 1344,1250 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.93 (s, 3 H), 1.05 (s, 3 H), 2.04 (d, *J* = 16.1 Hz, 1 H), 2.16–2.26 (m, 4 H), 2.43–2.51 (m, 1 H), 2.56 (d, *J* = 16.7 Hz, 1 H), 6.16 (s, 1 H), 6.18 (s, 1 H), 7.04 (d, *J* = 8.2 Hz, 2 H), 7.07 (d, *J* = 8.2 Hz, 2 H), 7.26 (t, *J* = 7.3 Hz, 1 H), 7.34 (apparent t, 2 H), 7.71 (d, *J* = 7.7 Hz, 2 H), 10.50 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 20.6, 26.7, 28.7, 32.1, 49.8, 57.3, 85.4, 105.0, 125.0, 126.6, 127.6, 128.5, 128.6, 133.1, 136.3, 138.2, 140.2, 149.1, 150.1, 192.3; MS (ESI) *m/z* (relative intensity): 384 (M+H, 100). Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.39; H, 6.31; N, 11.00.

20. The submitters reported purification of the crude precipitate by crystallization from hot 2-propanol:H_2O (2:1). However, elemental analysis was not provided by the submitters, and in the checkers hands, this procedure failed to give product of satisfactory purity based on ^1H NMR and elemental analysis. The checkers found that the main side product which remained after crystallization from 2-propanol:H_2O exhibited low solubility in hot acetonitrile. Therefore, hot filtration of an acetonitrile solution of the crude mixture followed by crystallization from acetonitrile:H_2O (1:1) was found to provide analytically pure product (^1H NMR and elemental analysis).

Figure 1. Optimizer Sixty EXP single-mode microwave reactor with 20 mL reaction vessel (Biotage AB, Sweden).

Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Multicomponent condensation reactions (MCRs) of 5-aminopyrazoles with cyclic 1,3-diketones and aromatic aldehydes can lead to the formation of several different tricyclic reaction products due to the presence of at least three non-equivalent nucleophilic reaction centers in the aminopyrazole building block (N1, C4 and NH_2).[2,3] The resulting partially hydrogenated azoloazines belong to a class of interesting target structures owing to their specific role in several biological processes and their diverse physiological activities.[4] Therefore, these MCRs have recently attracted the interest of the synthetic community and several reports have already discussed the formation of isomeric reaction products of type **1** or **2** from these three-component condensations.[3] In general these MCRs lead to the formation of product mixtures of pyrazoloquinolinones (Hantzsch-type product **1**) or pyrazoloquinazolinones (Biginelli-type product **2**) with difficult to control selectivities.[2,3] We have recently found that by employing high-temperature microwave processing, the reaction can be effectively tuned toward the formation of either the Hantzsch or Biginelli-type condensation products using a basic (Hantzsch) or acidic (Biginelli) reaction medium.[2]

In recent years, microwave-assisted organic synthesis (MAOS) has attracted considerable attention, and has become a very popular and convenient tool for performing organic reactions at high temperatures in sealed vessels.[5,6] In particular, the use of dedicated single-mode microwave reactors that enable the rapid and safe thermal processing of reaction mixtures in sealed vessels under controlled conditions with concurrent temperature and pressure monitoring has greatly increased the general acceptance of this method in the scientific community. Microwave dielectric heating not only often enables a dramatic reduction in reaction time, but also enhances reactions in terms of yield, purity and reproducibility in comparison to conventional thermal heating.[5,6]

1. Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria. oliver.kappe@uni-graz.at

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Triethylamine: *N*,*N*-diethylethanamine; (121-44-8)
5-Phenyl-1H-pyrazol-3-amine: 1*H*-pyrazol-3-amine, 5-phenyl-; (1571-10-7)
Dimedone: 1,3-cyclohexanedione, 5,5-dimethyl-; (126-81-8)

p-Tolualdehyde: benzaldehyde, 4-Methyl-; (104-87-0)

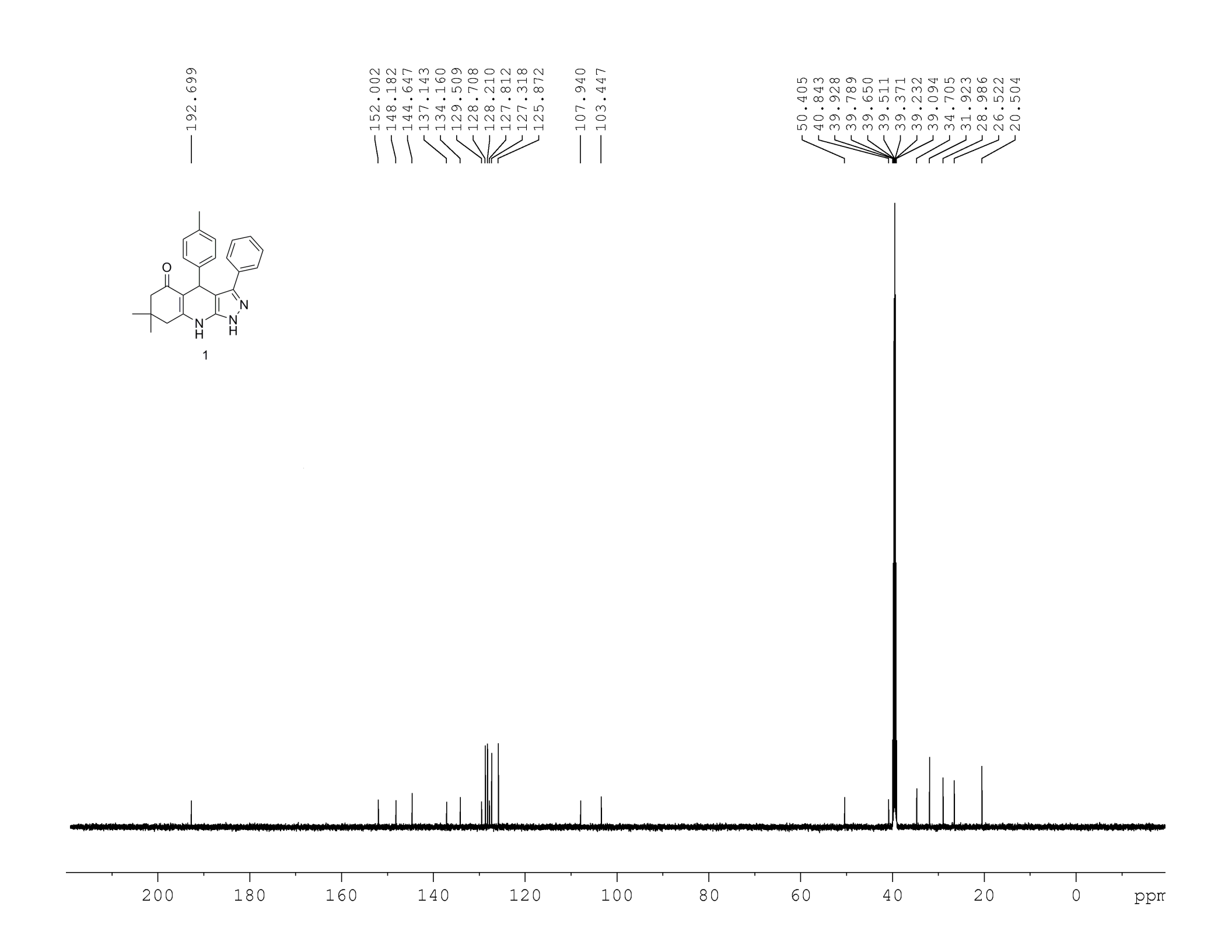
7,7-Dimethyl-3-phenyl-4-*p*-tolyl-6,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]-quinolin-5(4*H*)-one: 5*H*-Pyrazolo[3,4-*b*]quinolin-5-one, 1,4,6,7,8,9-hexahydro-7,7-dimethyl-4-(4-methylphenyl)-3-phenyl-; (904812-68-6)

Chlorotrimethylsilane: Silane, Cholorotrimethyl-; (75-77-4)

C. Oliver Kappe received his undergraduate and graduate education at the Universiy of Graz, Austria under Professor Gert Kollenz (1992). After periods of postdoctoral research work with Professor Curt Wentrup at the University of Queensland (1993-1994) and with Professor Albert Padwa at Emory University (1994-1996), he moved back to the University of Graz in 1996 to start his independent academic career. In 1999 he became Associate Professor and in 2006 was appointed Director of the Christian Doppler Laboratory for Microwave Chemistry at the University of Graz. His research interests include the development of new synthetic methods, combinatorial and high-throughput organic synthesis and heterocyclic chemistry.

Toma Glasnov was born in 1977 in Bjala Slatina, Bulgaria, and studied pharmacy at the Medical University of Sofia, Bulgaria. After obtaining his master degree in pharmacy in 2002 and work experience at Sopharma AD, he started his doctoral studies under the supervision of Professor Ivo C. Ivanov at the Pharmaceutical Faculty, Medical University of Sofia. In 2003 he moved to the University of Graz, Austria, with an Ernst-Mach grant from the Austrian Academic Exchange Service to perform research in the field of microwave-assisted organic synthesis. In 2007 he received his Ph.D. under the supervision of Professor C. Oliver Kappe.

MaryAnn Robak was born in 1982 in Binghamton, NY. She studied as an undergraduate at the University at Buffalo, State University of New York, where she completed B.S. degrees in Chemistry and Medicinal Chemistry, working on undergraduate research in the labs of Dr. Joseph A. Gardella Jr. and Dr. Michael R. Detty. Currently, she is a fourth year graduate student at University of California, Berkeley, working under the direction of Dr. Jonathan A. Ellman. Her research is on the development of sulfinyl-based hydrogen-bonding organocatalysts.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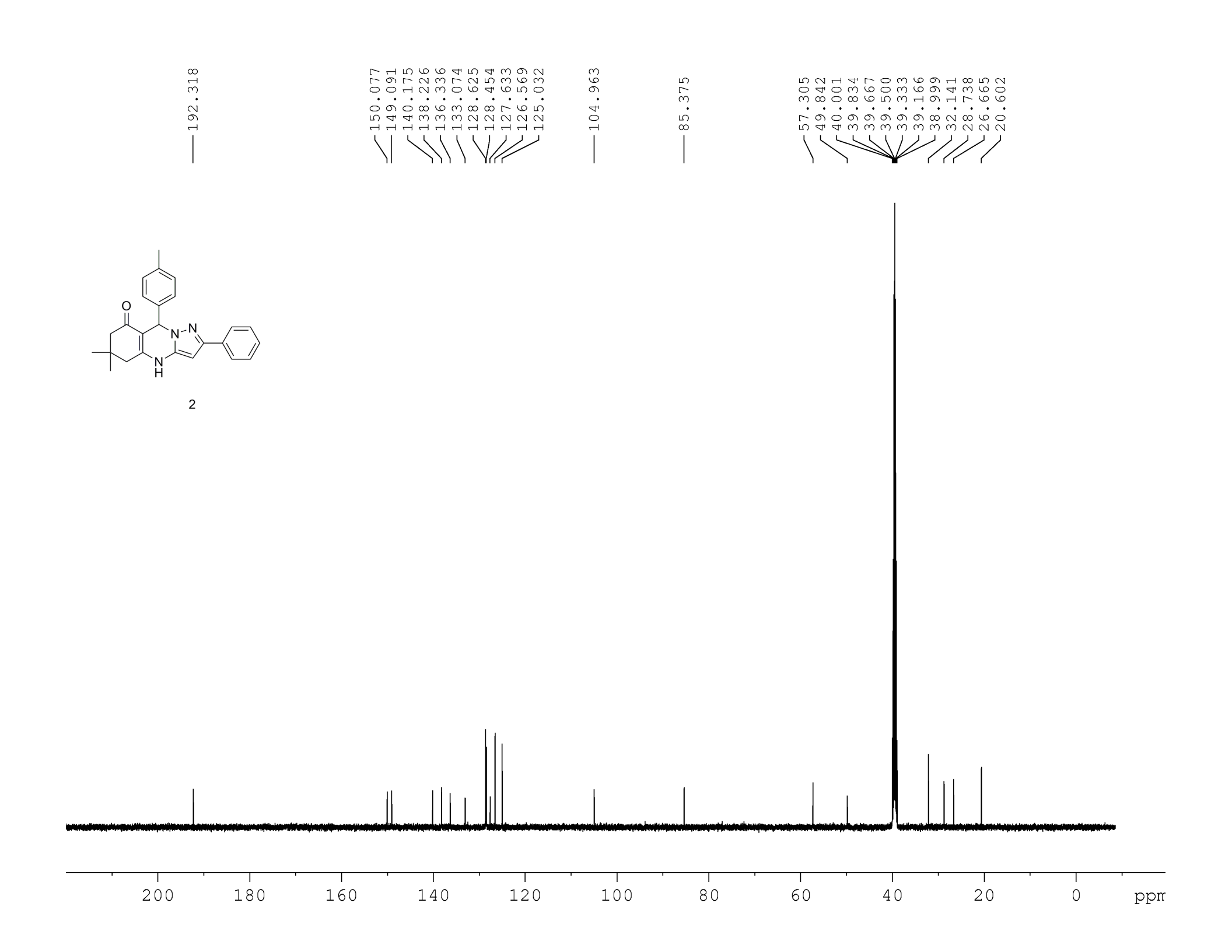
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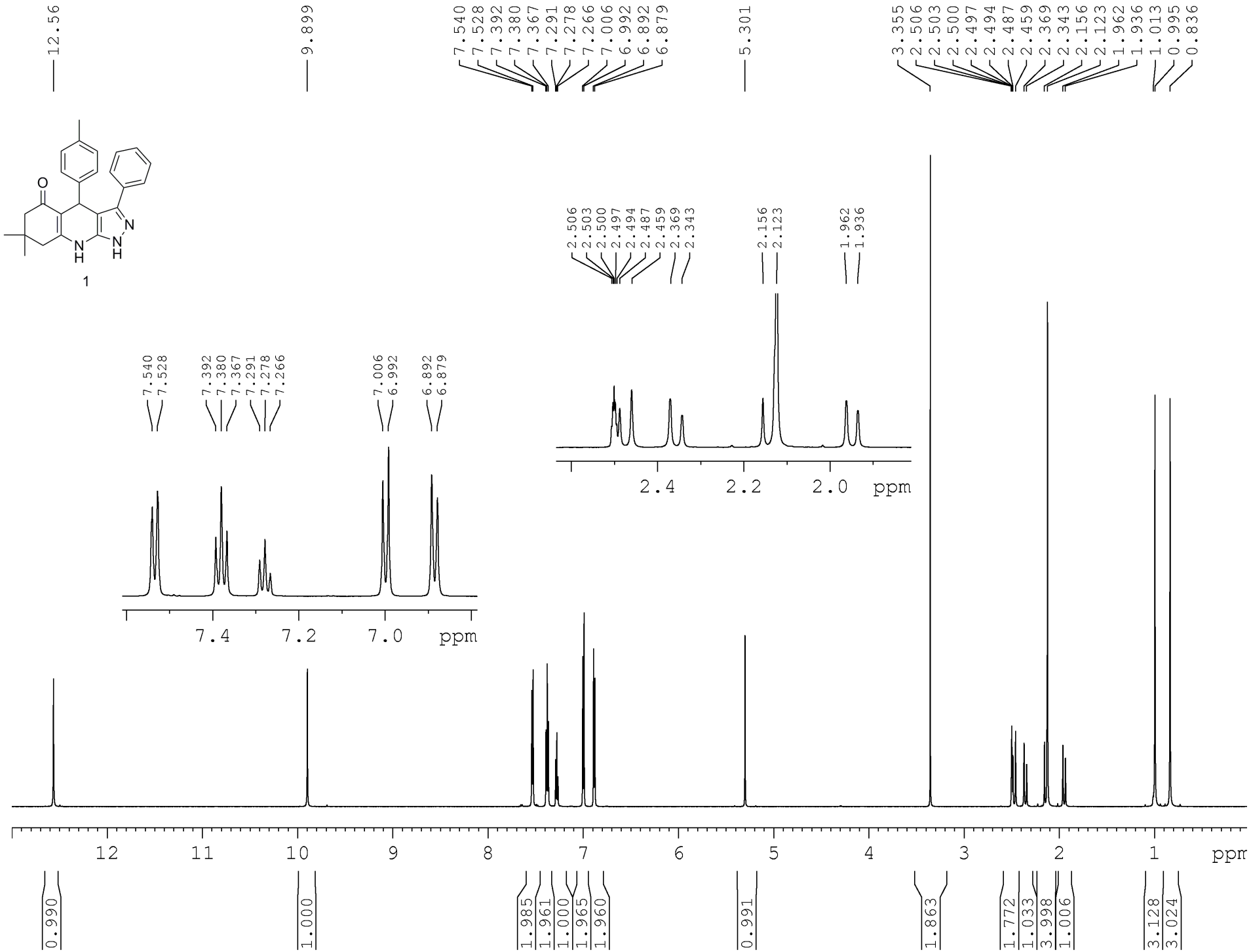
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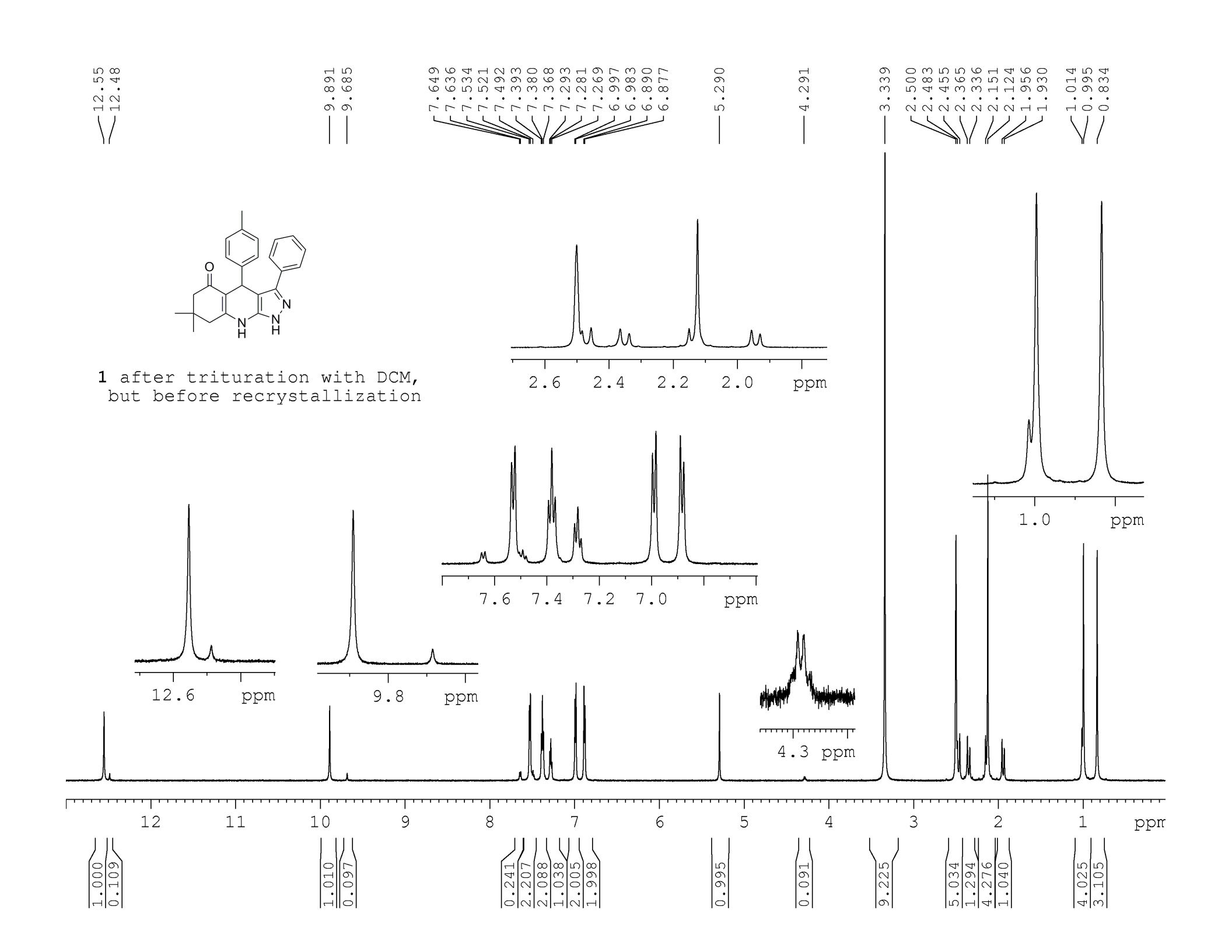
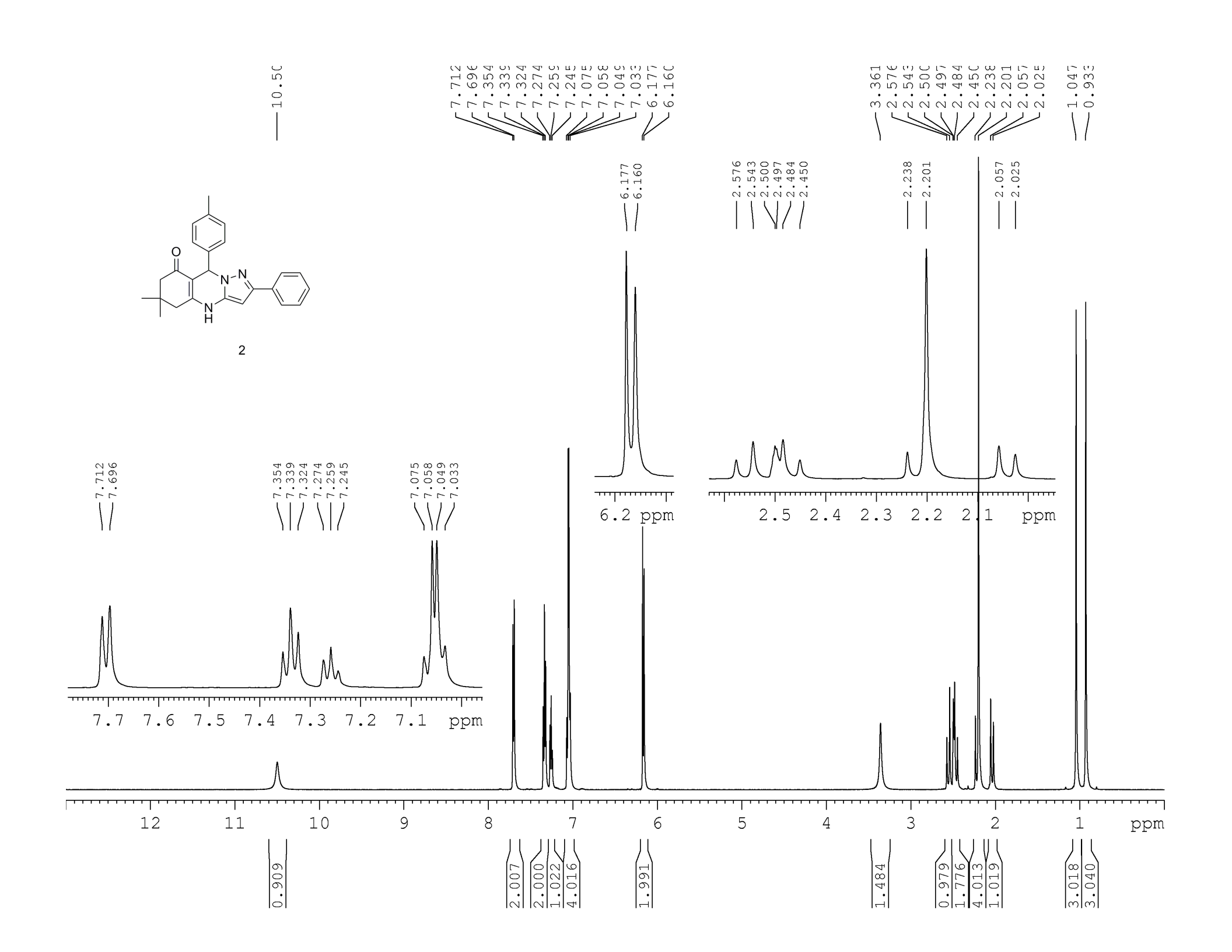
3.024


12.55
12.48
9.891
9.685
7.649
7.636
7.534
7.521
7.492
7.393
7.380
7.368
7.293
7.281
7.269
6.997
6.983
6.890
6.877
5.290
4.291
3.339
2.500
2.483
2.455
2.365
2.336
2.151
2.124
1.956
1.930
1.014
0.995
0.834
O
N
N
H
N
H
1 after trituration with DCM,
but before recrystallization
2.6 2.4 2.2 2.0 ppm
1.0 ppm
7.6 7.4 7.2 7.0 ppm
12.6 ppm
9.8 ppm
4.3 ppm
12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.000
0.109
1.010
0.097
0.241
2.207
2.088
1.038
2.005
1.998
0.995
0.091
9.225
5.034
1.294
4.276
1.040
4.025
3.105


10.50
7.712
7.696
7.354
7.339
7.324
7.274
7.259
7.245
7.075
7.058
7.049
7.033
6.177
6.160
3.361
2.576
2.543
2.500
2.497
2.484
2.450
2.238
2.201
2.057
2.025
1.047
0.933
O
N
N
H
2
6.2 ppm
2.5 2.4 2.3 2.2 2.1 ppm
7.7 7.6 7.5 7.4 7.3 7.2 7.1 ppm
12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.909
2.007
2.000
1.022
4.016
1.991
1.484
0.979
1.776
4.013
1.019
3.018
3.040