Organic Syntheses

Hydrodecyanation by a Sodium Hydride-Iodide Composite

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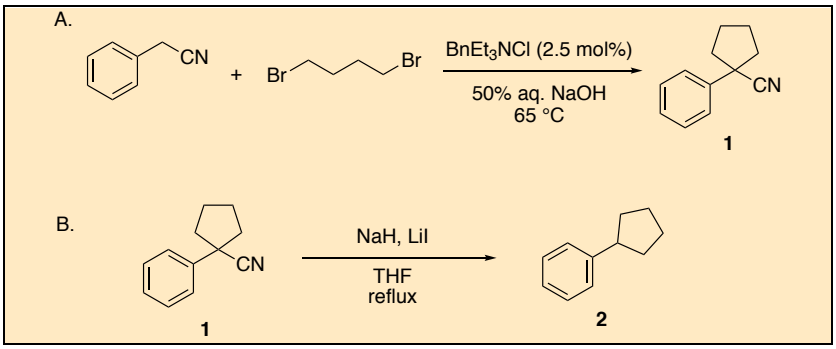
Checked by Joyce Leung and Chris Senanayake



Procedure (Note 1)

A. *1-Phenylcyclopentane-1-carbonitrile (**1**)* (Note 2). A 100 mL two-necked, round-bottomed flask is equipped with a 25 x 12 mm Teflon-coated, oval magnetic stir bar, a thermometer, rubber septum. Benzyltriethylammonium chloride (569 mg, 2.50 mmol, 0.025 equiv) (Note 3) and 50% (w/v) aqueous sodium hydroxide (25 mL) are added. The reaction vessel is placed in a water bath and benzyl cyanide (11.5 mL, 99.6 mmol, 1.0 equiv) (Note 4) is added in one portion with vigorous stirring (Note 5). 1,4-Dibromobutane (14.3 mL, 120 mmol, 1.2 equiv) (Note 6) is added portion wise (ca. 5 mL per portion) (Note 7) and the rubber septum is replaced with a Graham reflux condenser (Note 8) connected to a Schlenk line (Figure 1). The orange biphasic mixture

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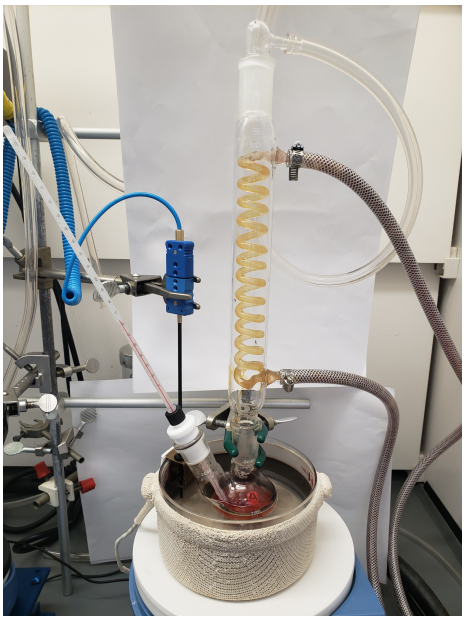

Figure 1. Reaction setup for Step A

Is heated to an internal temperature of 65 °C (Note 9) for 24 h resulting in an orange biphasic suspension (Notes 10 and 11). The reaction is cooled to 23 °C (inner temperature). Water (50 mL) is added and the layers are partitioned in a 250-mL separatory funnel. The aqueous layer is extracted twice with diethyl ether (60 mL x 2) and the combined organic layer is washed with brine (50 mL), dried over anhydrous magnesium sulfate (5 g), filtered via gravity filtration and the filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 14 mmHg) to afford an orange oil. The obtained residue is purified by column chromatography (Note 12) to afford (14.0 g, 81.9 mmol, 82%) (Note 13) of 1-phenylcyclopentane-1-carbonitrile as a pale yellow oil (Figure 2) (Notes 14 and 15).

Figure 2. Purified nitrile 1

B. *Cyclopentylbenzene (**2**)*. An oven-dried, 250 mL, three-necked round-bottomed flask equipped with a 30 x 16 mm Teflon-coated, oval magnetic stir bar, a type-T thermocouple, rubber septum and a Graham reflux condenser is connected to a Schlenk line (Notes 16 and 17). Sodium hydride (NaH) (3.75 g, 93.7 mmol, 2.0 equiv) (Note 18) and lithium iodide (LiI) (6.27 g, 46.8 mmol, 1.0 equiv) (Note 19) is charged, after which the reaction vessel is evacuated and backfilled with nitrogen three times. Dry THF (80 mL) (Note 20) is added via syringe (Note 21) and 1-phenylcyclopentane-1-carbonitrile (***1***) (8.02 g, 46.8 mmol, 1.0 equiv) is added in one portion with a THF (14 mL) rinse (Note 22). Rubber septum is quickly replaced with a 24/40 glass stopper (Note 23). The grey suspension is then refluxed (Note 24) for 5 h resulting in tan suspension (Notes 25 and 26) (Figure 3). The reaction mixture is cooled to 4 °C (inner temperature) with an ice water bath. The glass stopper is quickly replaced with a rubber septum and cold water (12 mL) is added dropwise over 5 min (Note 27) before 88 mL of cold water is added in one portion. The layers are partitioned in a 500-mL separatory funnel. The aqueous layer (Note 28) is extracted twice with diethyl ether (100 mL x 2), and the combined organic layer is washed with brine (100 mL), dried over anhydrous magnesium sulfate (10 g), and filtered via Büchner filtration. The filtrate is concentrated on a rotary evaporator under reduced pressure (30 °C, 14 mmHg) before transferring to a 50-mL round-bottomed flask to

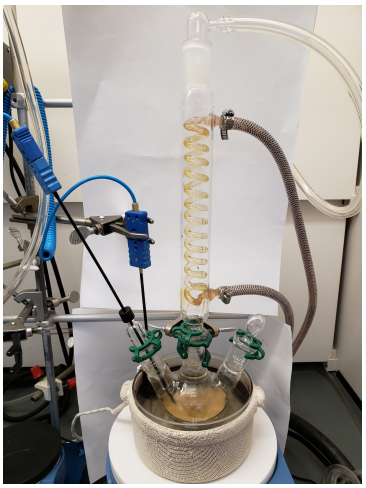

Figure 3. Reaction setup for Step B

afford a dark yellow oil. The round-bottomed flask is equipped with a 15 x 6 mm Teflon-coated, oval magnetic stir bar and attached to the short-path distillation setup (Figure 4) (Notes 29 and 30). The product is distilled under vacuum in one fraction (0.92 mmHg, 56–57 °C) (Notes 31 and 32) affording cyclopentylbenzene (**2**) (Notes 33 and 34) as a colorless liquid (6.0 g, 41.1 mmol, 88%) (Figure 5) (Note 35).

Figure 4. Distillation setup for purification of cyclopentylbenzene (2)

Figure 5. Purified cyclopentylbenzene (2)

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 sodium hydride, lithium iodide, benzyl cyanide, 1,4-dibromobutane, sodium cyanide, hydrogen gas, magnesium sulfate, sodium hypochlorite solution, THF, hexane, ethyl acetate and diethyl ether.
2. The procedure is slightly modified from the report by M. Makosza and A. Jonczyk.[2]

3. Benzyltriethylammonium chloride was purchased from Oakwood and was further purified by reprecipitating it through addition of ether to its saturated hot solution in acetone. The submitter purchased the reagent from Alfa Aesar.
4. Benzyl cyanide 98% was purchased from Sigma-Aldrich and used as is.
5. Submitter conducted the reaction at the stirring rate of 1400 rpm.
6. 1,4-Dibromobutane 98+% was purchased from Sigma Aldrich and used as is. Submitter purchased the reagent from Alfa Aesar.
7. One portion was added over 10 seconds by syringe, with a 30 second interval to the next addition. There was 6 °C exotherm observed after the first portion, but subsequent portions do not increase the internal temperature further. Submitter observed an initial 22 °C exotherm after the first addition.
8. Submitter used a Liebig reflux condenser.
9. The temperature controller was set to 66 °C, while the oil bath temperature fluctuated between ±2 °C during the reaction. An initial increase of internal temperature to 72–73 °C was observed for the first 20 min.
10. The reaction was monitored by TLC (EMD Millipore™ TLC Silica Gel 60 F254, glass plates) on silica gel using hexanes:EtOAc (93:7) as eluent and visualization with UV light. Benzyl cyanide had $R_f = 0.24$ and the product (***1***) has $R_f = 0.46$.
11. The time for reaction completion varies with agitation speed. Submitter reported a reaction time of 7 h.
12. Column chromatography was performed using an Chemglass Life Science chromatography column with reservoir and 4.0 mm PTFE stopcock, 1000 mL, with coarse fritted disc, top joint: ST/NS 24/40, I.D. × L 2.5 in × 8.0 in. The column was packed with 250 g of silica gel, high-purity grade, pore size 60 Å, 230-400 mesh particle size purchased from Sigma-Aldrich and was conditioned with 1 L hexanes. Residual solvent was removed before crude compound (**1**) was loaded on the column neat and hexanes (10 mL) was used to wash the flask containing compound (***1***) before loading on the column. The column was eluted with 1 L of hexanes, followed by 1 L of hexanes/EtOAc (98:2). At this point all eluent was collected, the column was eluted with 1.4 L of hexanes/EtOAc (98:2). The compound (***1***) was then concentrated on a rotary evaporator under reduced pressure (40 °C, 84 mmHg) and further dried under vacuum (room temperature, 0.92 mmHg) overnight.

13. A second reaction on identical scale provided 14.3 g (84%) of the same product. The Submitter observed potential insufficient separation between the unreacted 1,4-dibromobutane and compound (**1**).
14. 1-Phenylcyclopentane-1-carbonitrile (***1***) is bench stable. It displays the following characterization data: R_f = 0.46 (hexanes / ethyl acetate 93:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.90–1.98 (m, 2H), 2.01–2.12 (m, 4H), 2.46–2.51 (m, 2H), 7.29–7.30 (m, 1H), 7.36–7.39 (m, 2H), 7.45–7.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.3, 40.5, 47.8, 124.4, 126.0, 127.8, 128.9, 139.9. IR (film) 2964, 2876, 2232, 1600, 1465, 1448, 756, 696, 512 cm^{-1}. HRMS (DART) *m*/*z* calcd for $C_{12}H_{14}N$ $[M+H]^+$: 172.11216. Found: 172.11208.
15. Purity was determined to be 99.4% on the first run and 97.3% on the second run using qNMR and 1,3,5-trimethoxybenzene as an internal standard.
16. Submitter further flame-dried all glassware under vacuum (5 mmHg) and backfilled with nitrogen once cooled to room temperature.
17. Submitter used a Liebig reflux condenser and a thermometer instead of the thermocouple.
18. Sodium hydride in 60% dispersion mineral oil was purchased from Sigma-Aldrich. Submitter stored the reagent in an argon-filled glovebox.
19. Lithium iodide bead, (anhydrous, −10 mesh, 99.99% trace metals basis) was purchased from Sigma-Aldrich and used as received. Submitter purchased lithium iodide beads (99%) from Sigma-Aldrich and the reagent was dried over P_4O_{10} under reduced pressure (5 mmHg) at 120 °C before using.
20. Tetrahydrofuran, anhydrous, contains 250 ppm BHT as inhibitor, ≥99.9% was bought from Sigma-Aldrich and used as received. Submitter purchased tetrahydrofuran, HiPerSolv CHROMANORM® for HPLC from VWR Chemicals, which was further purified with Pure Solv MD-5 solvent purification system by Innovative Technology before use.
21. There was a 19-20 °C exotherm observed.
22. The reaction mixture was cooled to about 30 °C before compound (**1**) was added.
23. Submitter used rubber septum for the reaction. A build-up in pressure was observed during the course of the reaction; hence, a glass stopper was replaced prior to heating to reflux.
24. The temperature controller was set to 75 °C, while the oil bath temperature fluctuated between ±2 °C during the reaction.
25. The reaction was monitored by TLC (EMD Millipore™ TLC Silica Gel 60 F254, glass plates) on silica gel using hexanes:EtOAc (96:4) as eluent and

visualization with UV light. Product (***1***) had R_f = 0.33 and the product (**2**) has R_f = 0.89.

26. A pinkish hue reaction mixture with white solids was observed by the submitter after 5 hours of heating.
27. There was a 14-15 °C exotherm observed and the reaction vessel should be connected to a bubbler to vent the hydrogen gas generated.
28. The aqueous layer containing NaCN as a co-product of the reaction was treated with sodium hypochlorite solution, available chlorine 14.5 % (100 mL) purchased from Alfa Aesar overnight before discarding.
29. Vacuum was applied slowly to prevent bumping of the compound in the distillation flask.
30. The distillation set-up was evacuated and purged with nitrogen gas three times before final vacuum was applied.
31. Residual solvent was removed before heating was applied, oil bath temperature was slowly raised from 70 °C to a final temperature of 85 °C.
32. The receiver flask was submerged in an ice-bath.
33. Cyclopentylbenzene (**2**) is bench stable. It displays the following characterization data: R_f = 0.89 (hexanes/ethyl acetate 96:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.56–1.63 (m, 2H), 1.64–1.72 (m, 2H), 1.77–1.84 (m, 2H), 2.04–2.09 (m, 2H), 2.95–3.02 (m, 1H), 7.15–7.18 (m, 1H), 7.23–7.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.5, 34.6, 46.0, 125.7, 127.1, 128.2, 146.5. IR (film) 3060, 3027, 2950, 2867, 1603, 1492, 1451, 754, 696, 525 cm^{-1}. HRMS (DART) *m*/*z* calcd for $C_{11}H_{15}$ $[M+H]^+$: 147.11689. found: 147.11683.
34. Purity was determined to be ≥99.5% for both runs using qNMR and 1,3,5-trimethoxybenzene as an internal standard.
35. A yield of 90% was obtained on the second run at the same scale.

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.

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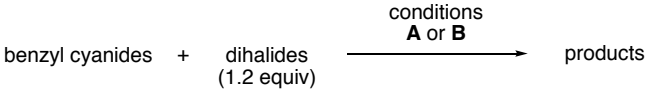
Discussion

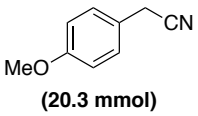
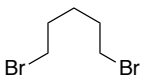
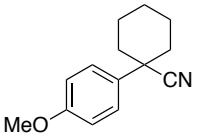
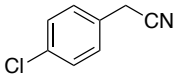
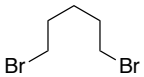
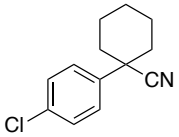
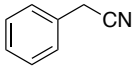
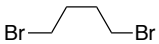
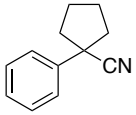
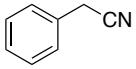
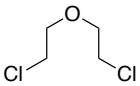
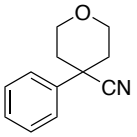
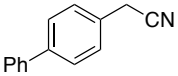
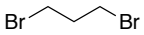
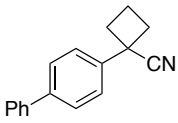
Nitriles are versatile synthons for chemical synthesis. Hydride reduction of nitriles can be performed by various covalent hydride reagents to form aldehydes or amines, depending on the choice of covalent hydride reagents.[3] Several methods for hydrodecyanation of nitriles have also been developed.[4] We recently reported the use of ionic sodium hydride (NaH) in the presence of lithium iodide (LiI) for hydrodecyanation of α-quaternary benzyl cyanides,[5] that is complementary to the existing procedures. This manuscript describes 2-step synthesis of cycloalkyl arenes from readily available benzyl cyanides.

The synthesis starts from α-dialkylation of benzyl cyanides with dihaloalkanes under phase-transfer conditions catalyzed by tetraalkylammonium salt in alkali aqueous media or under NaH-mediated reaction conditions in THF (Table 1). These processes worked smoothly to construct cyclohexane, -pentane, and -butane rings as well as a tetrahydropyran ring alpha to the cyano group.

Table 1. Synthesis of α-quaternary nitriles



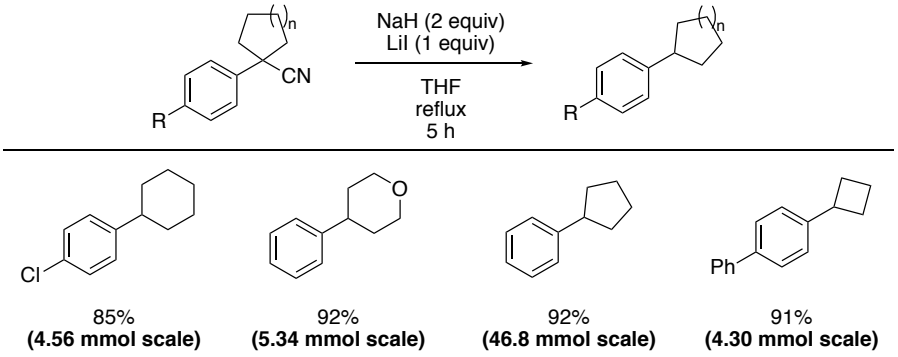
conditions **A**: Et_3BnNCl (2.5 mol%), 50% aq. NaOH, 65 °C, 7 h
conditions **B**: NaH (2.5 equiv) in THF, 0 °C to reflux, 16 h

entry	benzyl cyanides	dihalides	products	conditions	yields[a]
1	 **(20.3 mmol)**			**B**	73%
2	 **(20.0 mmol)**			**B**	71%
3	 **(99.6 mmol)**			**A**	90%
4	 **(19.9 mmol)**			**A**	64%
5	 **(8.01 mmol)**			**B**[b]	69%

[a] Isolated yields. [b] The reaction was conducted in DMSO-Et_2O (1:1) as the solvent at room temperature for 24 h.

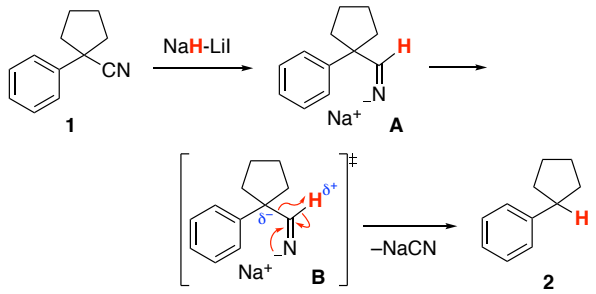
We recently discovered that unique hydride donor reactivity is conferred to sodium hydride (NaH) by its solvothermal treatment with NaI or LiI in THF and the resulting NaH-iodide composites could be used for a series of hydride reduction.[6,7] Treatment of α-quaternary benzyl cyanides with NaH

and LiI in THF under reflux conditions[8] enables hydrodecyanation to give cycloalkylarenes in good yields (Scheme 1).



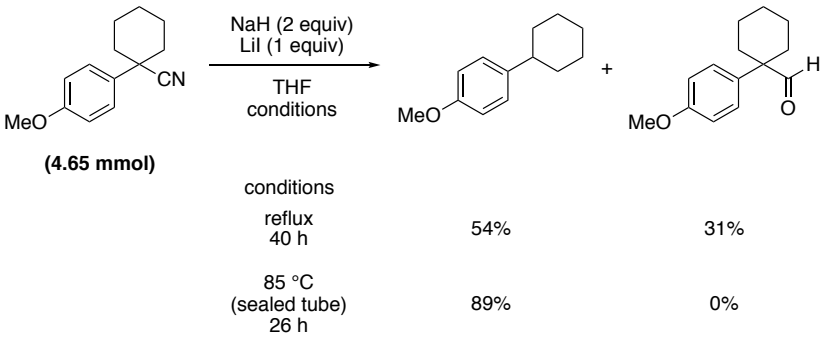
Scheme 1. Cycloalkyl arenes synthesized by hydrodecyanation

The process is initiated by hydride attack of the nitrile moiety of **1** from NaH to afford iminyl sodium intermediate **A**, which subsequently undergoes concerted C-C bond cleavage-1,2-proton shift to give hydrodecyanated product **2** and sodium cyanide (NaCN). In the transition state **B** for this C-C bond cleavage, the imine hydrogen atom has partial positive charge (δ+) and the benzylic carbon possesses partial negative charge (δ–), and thus the hydrogen rearranges to the adjacent carbon (δ–) via 1,2-proton transfer.[9] This result demonstrates the unique *umpolung* nature of the decyanation, where the nucleophilic hydride originated from NaH is changed to the electrophilic proton in the later stage.



Scheme 2. Proposed reaction mechanism of hydrodecyanation

It is observed that an electron-rich 4-methoxyphenyl group renders the rate of the C-C bond cleavage slower (Scheme 2). The reaction under reflux conditions afforded not only 4-cyclohexylanisole in 54% yield but also provides the corresponding aldehyde in 31% yield even after running for 40 h. Higher reaction temperature (85 °C) in sealed conditions (Figure 6) allowed for completion of the process within 26 h, to give 4-cyclohexylanisole as a sole product in 89% yield. It should be noted that the present protocol is thus far proven unsuccessful for non-benzylic cyanides.



Scheme 3. Reactions of 1-(4-methoxyphenyl)cyclohexane-1-carbonitrile

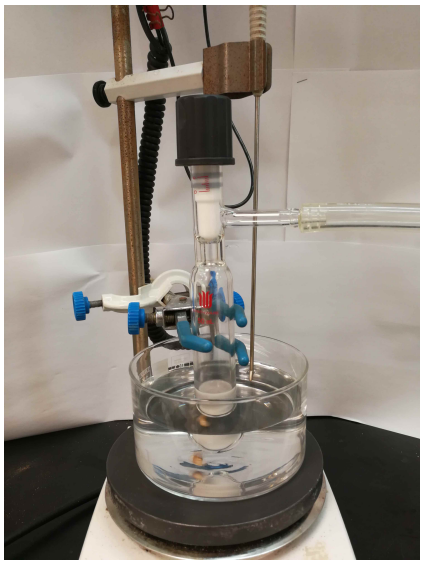


Figure 6. Reaction setup in sealed conditions (photo provided by submitter)

References

1. Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. shunsuke@ntu.edu.sg; this work was supported by Nanyang Technological University, the Singapore Ministry of Education (Academic Research Fund Tier 1: RG10/17), Singapore Economic Development Board (EDB), and Pfizer Asia Pacific Pte. Ltd. GHC thanks to EDB-Industrial Postgraduate Program (IPP) for the scholarship support.
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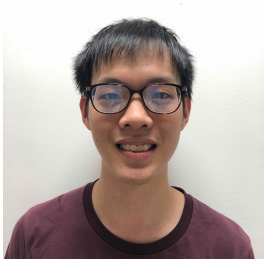
6. (a) Ong, D. Y.; Tejo, C.; Xu, K.; Hirao, H.; Chiba, S. *Angew. Chem. Int. Ed*. **2017**, *56*, 1840–1844. (b) Hong, Z.; Ong, D. Y.; Muduli, S. K.; Too, P. C.; Chan, G. H.; Tnay, Y. L.; Chiba, S.; Nishiyama, Y.; Hirao, H.; Soo, H. S. *Chem. Eur. J*. **2016**, *22*, 7108–7114.
7. For use of NaH-iodide composites as the unprecedented Brønsted bases, see: (a) Kaga, A.; Hayashi, H.; Hakamata, H.; Oi, M.; Uchiyama, M.; Takita, R.; Chiba, S.; *Angew. Chem. Int. Ed*. **2017**, *56*, 11807–11811. (b) Huang, Y.; Chan, G. H.; Chiba, S. *Angew. Chem. Int. Ed*. **2017**, *56*, 6544–6547.
8. In our original communication (ref. 4), all the reactions for hydrodecyanation were examined under sealed conditions at 85 °C in THF, while in the present procedure, we conducted hydrodecyanation under reflux conditions in THF and found it reproducible and scalable (except for the substrate in Scheme 3).
9. A stepwise pathway including fragmentation of **A** to benzylic carbanion and hydrogen cyanide followed by deprotonation cannot be ruled out as a possibility of the reaction mechanism.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

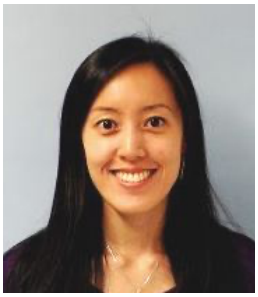
Sodium Hydroxide (1310-73-2)
Benzyltriethylammonium chloride (56-37-1)
Sodium hydride (7646-69-7)
Lithium iodide (10377-51-2)
Tetrahydrofuran (109-99-9)
Benzyl cyanide (140-29-4)
1,4-Dibromobutane (110-52-1)
1-Phenylcyclopentane-1-carbonitrile (77-57-6)
Cyclopentylbenzene (700-88-9)



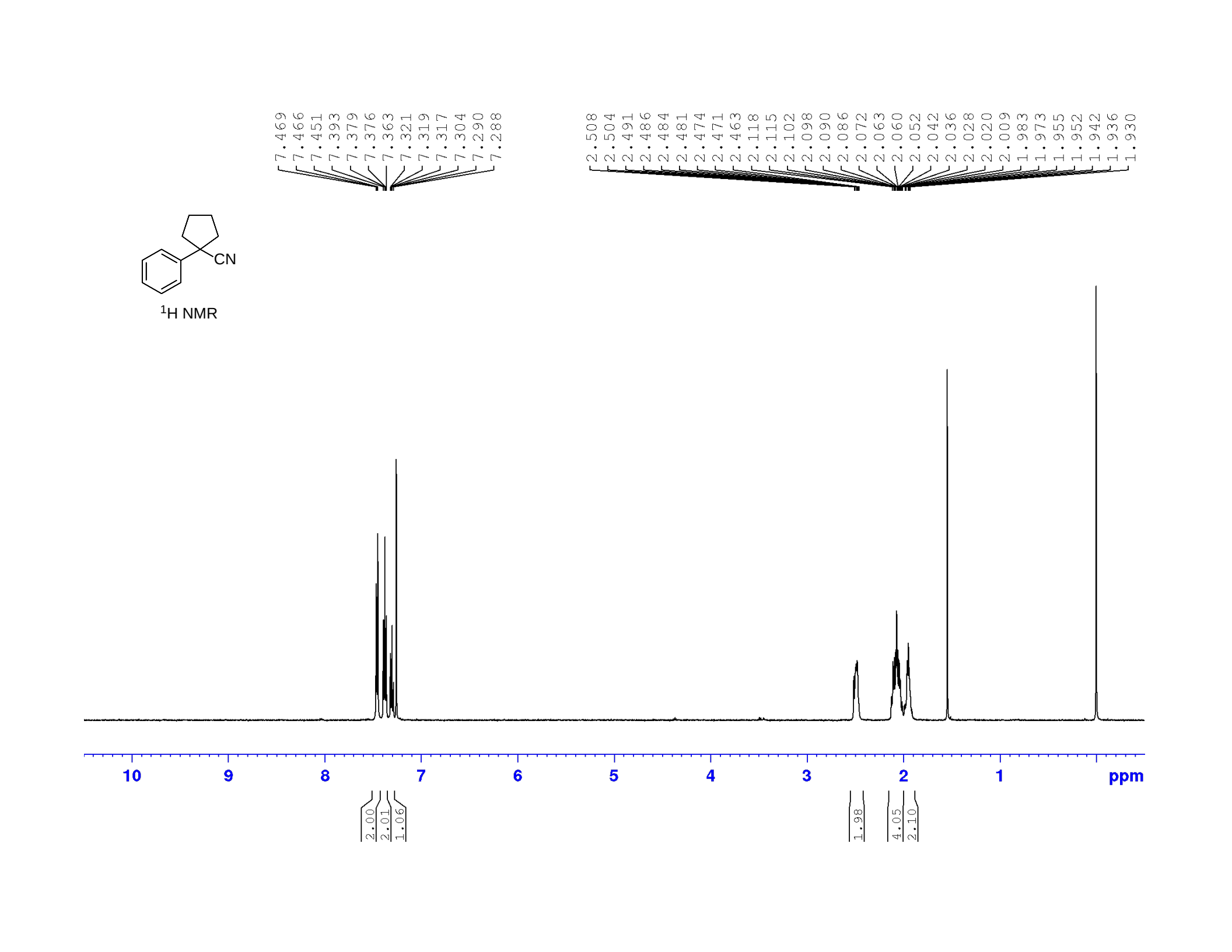
Guo Hao Chan was born and raised in Singapore. He completed his undergraduate studies at Nanyang Technological University (NTU, Singapore) in 2014 before beginning his Ph.D. work in the lab of Shunsuke Chiba at the same university under EDB-Industrial Postgraduate Program (IPP) with Pfizer Asia Pacific Pte. Ltd. He is currently focussing on methodology development using sodium hydride-iodide composites.

Derek Yiren Ong was born and raised in Singapore. He completed his undergraduate studies at Nanyang Technological University (NTU, Singapore) in 2013. He started his Ph.D. work in the lab of Shunsuke Chiba at the same university in 2016. He is currently focussing on methodology development using sodium hydride-iodide composites.

Shunsuke Chiba earned his Ph.D. in March 2006 from the University of Tokyo under the supervision of Prof. Koichi Narasaka. He was appointed as a Research Associate at the University of Tokyo in May 2005. In April 2007, he joined Nanyang Technological University as an Assistant Professor. In March 2012, he was granted tenure and promoted to Associate Professor in the same university. In September 2016, he was promoted to full Professor. His research focuses on methodology development in the area of synthetic organic chemistry.



Joyce Leung received her B.S. in Chemical Biology from University of California, Berkeley in 2007. After working at Nanosyn, Inc. as a Research Associate for a year, she began her graduate studies at The University of Texas at Austin, where she received her Ph.D. in organic chemistry under the supervision of Professor Michael Krische in 2013. Then she conducted postdoctoral research in the lab of Professor John Wood at Baylor University. In 2017, she joined Boehringer Ingelheim Pharm. Inc. in Ridgefield, CT, where she is currently a Senior Scientist. Her research focuses on the development of efficient and practical synthetic methods for drug candidates.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2.486
2.484
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2.471
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2.118
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2.102
2.098
2.090
2.086
2.072
2.063
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2.052
2.042
2.036
2.028
2.020
2.009
1.983
1.973
1.955
1.952
1.942
1.936
1.930
CN
1H NMR
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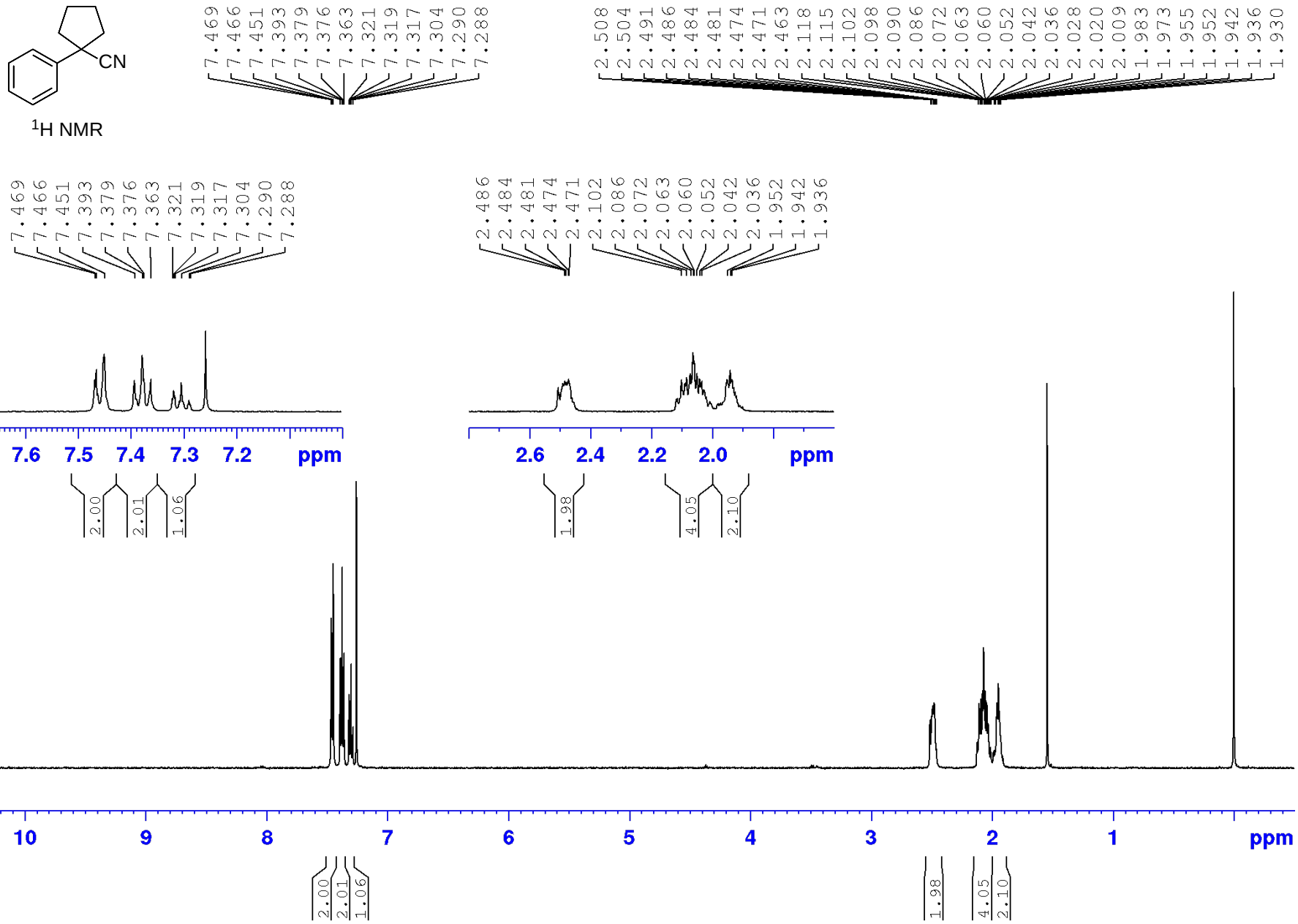
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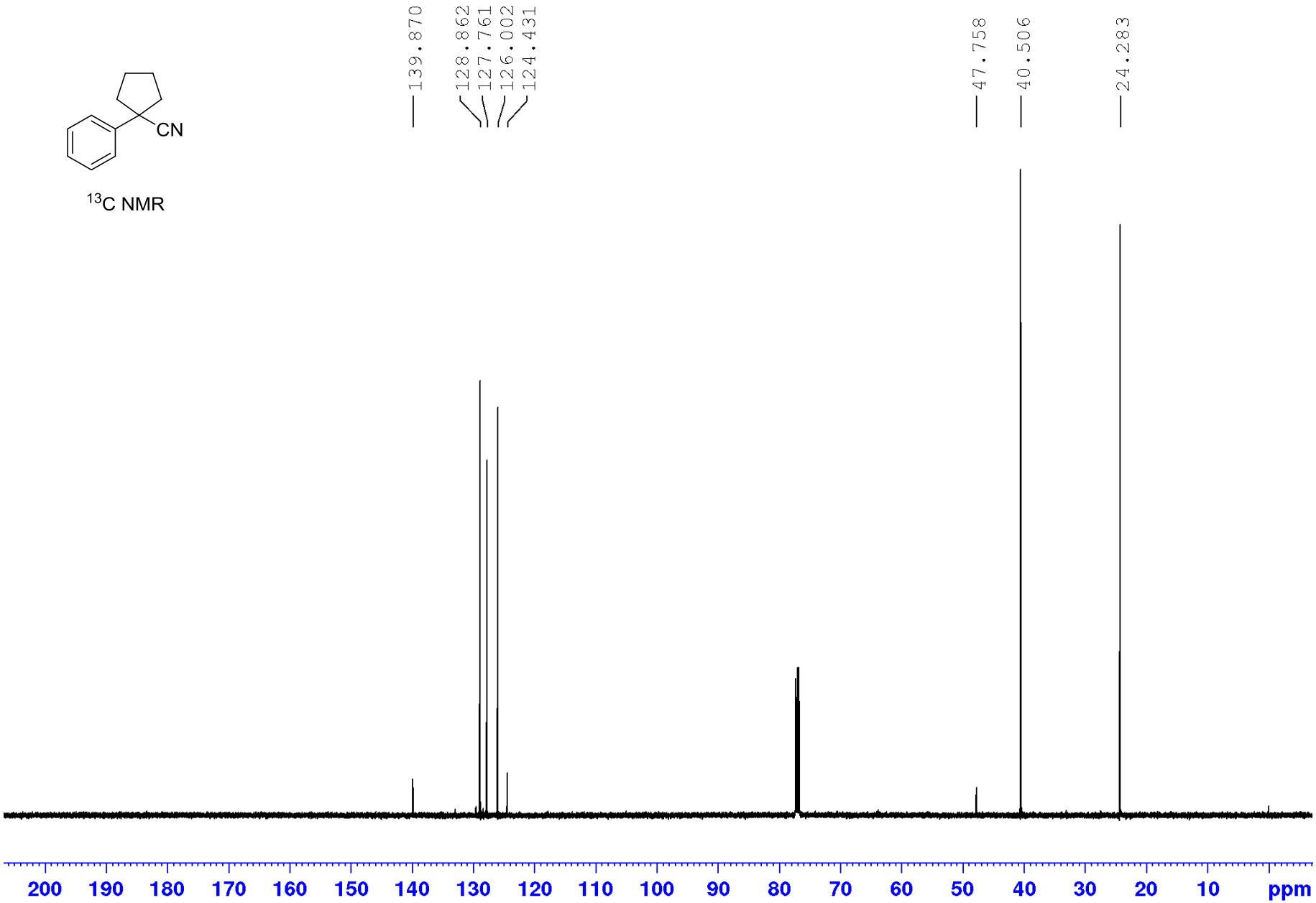
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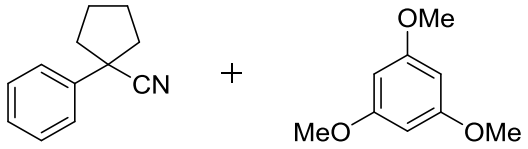

q ^{1}H NMR

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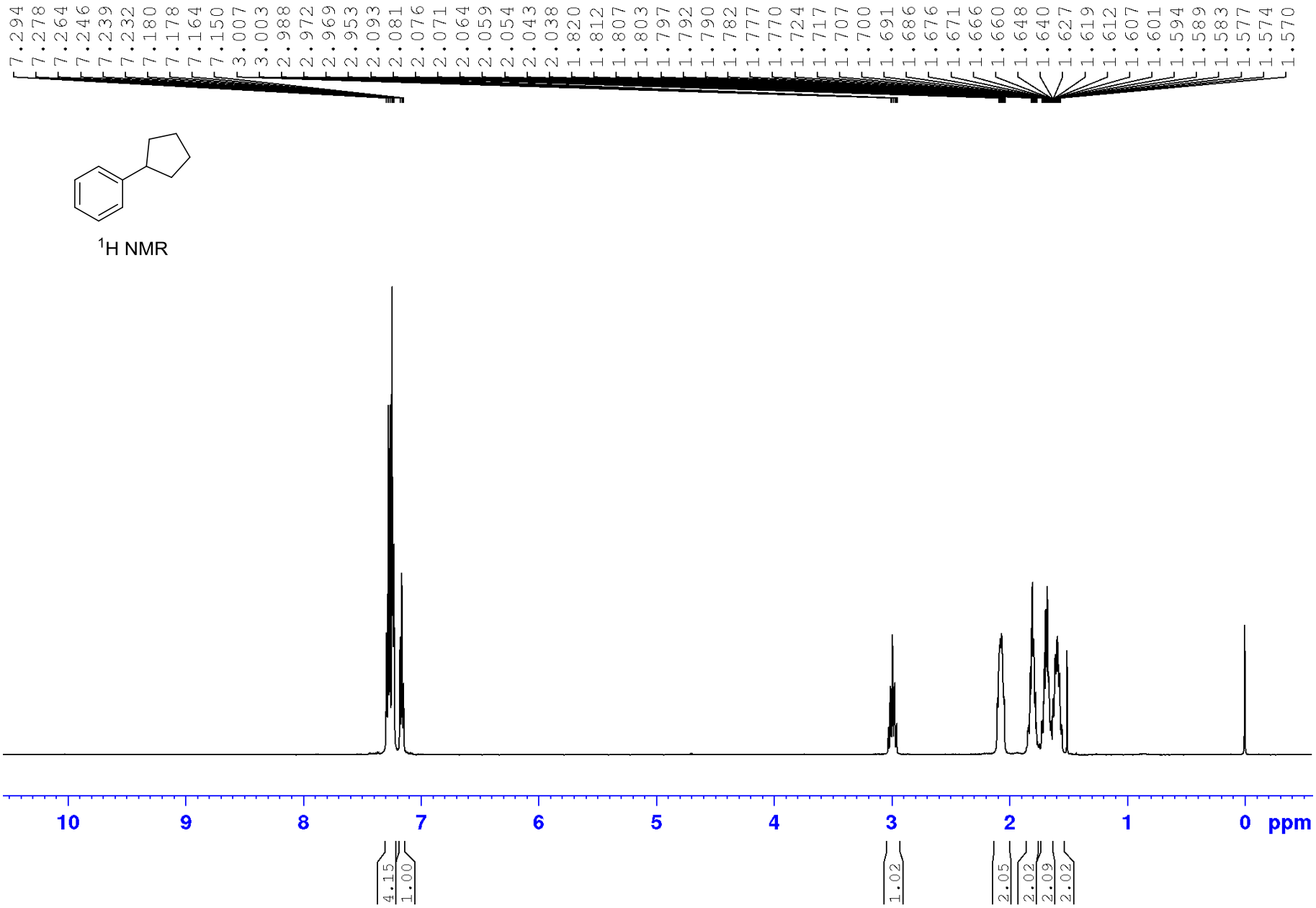
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1.577
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1H NMR
10
9
8
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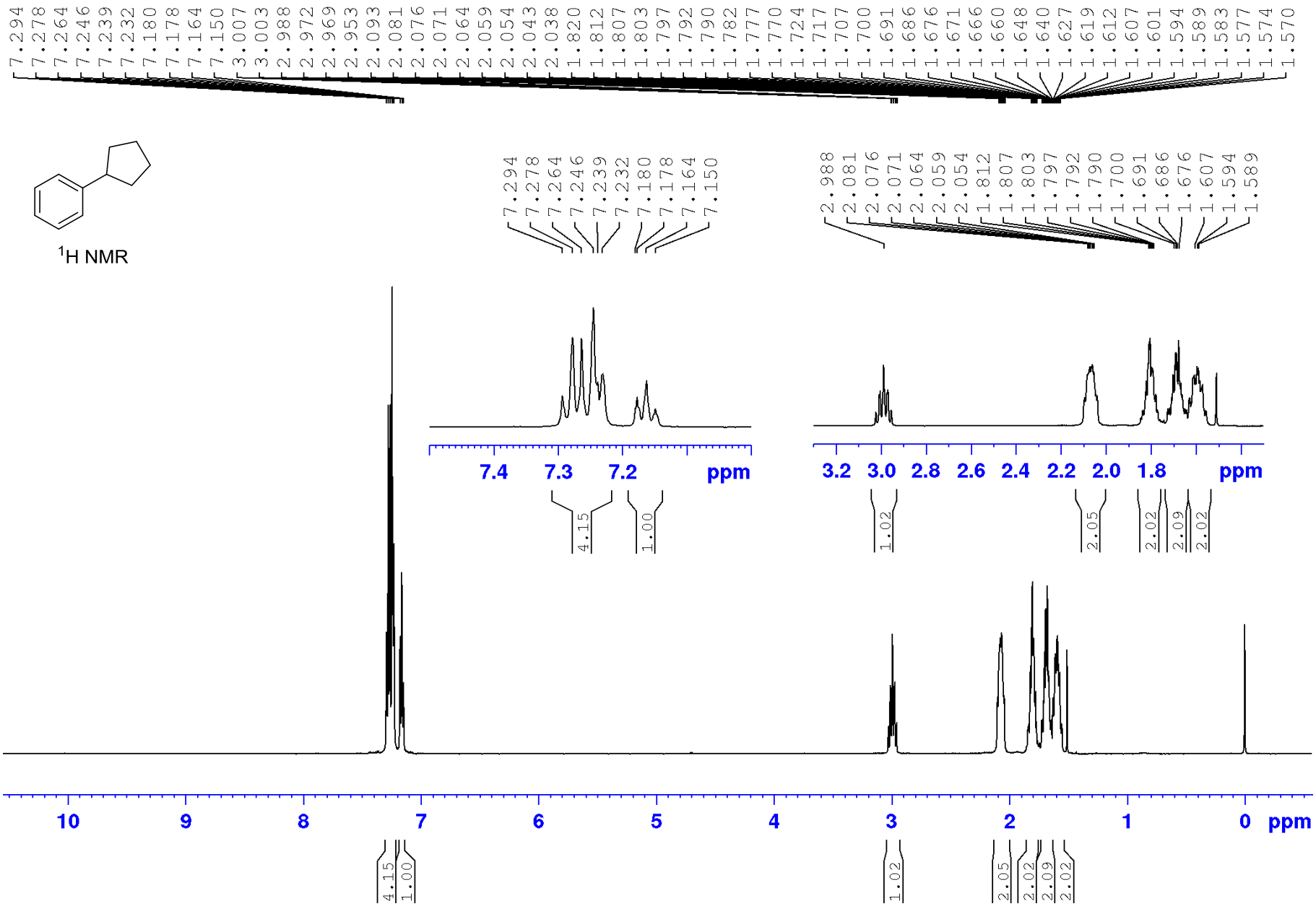
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1H NMR
7.294 7.278 7.264 7.246 7.239 7.232 7.180 7.178 7.164 7.150
2.988 2.081 2.076 2.071 2.064 2.059 2.054 1.812 1.807 1.803 1.797 1.792 1.790 1.700 1.691 1.686 1.676 1.607 1.594 1.589
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4.15 1.00
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10 9 8 7 6 5 4 3 2 1 0 ppm
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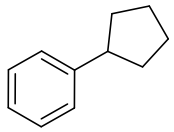

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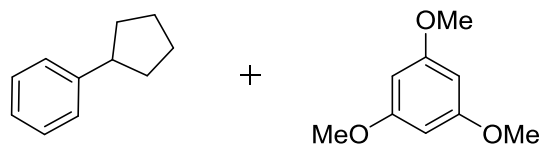
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



q ^{1}H NMR

12.3 mg product + 12.3 mg 99% TMB