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Working with Hazardous Chemicals

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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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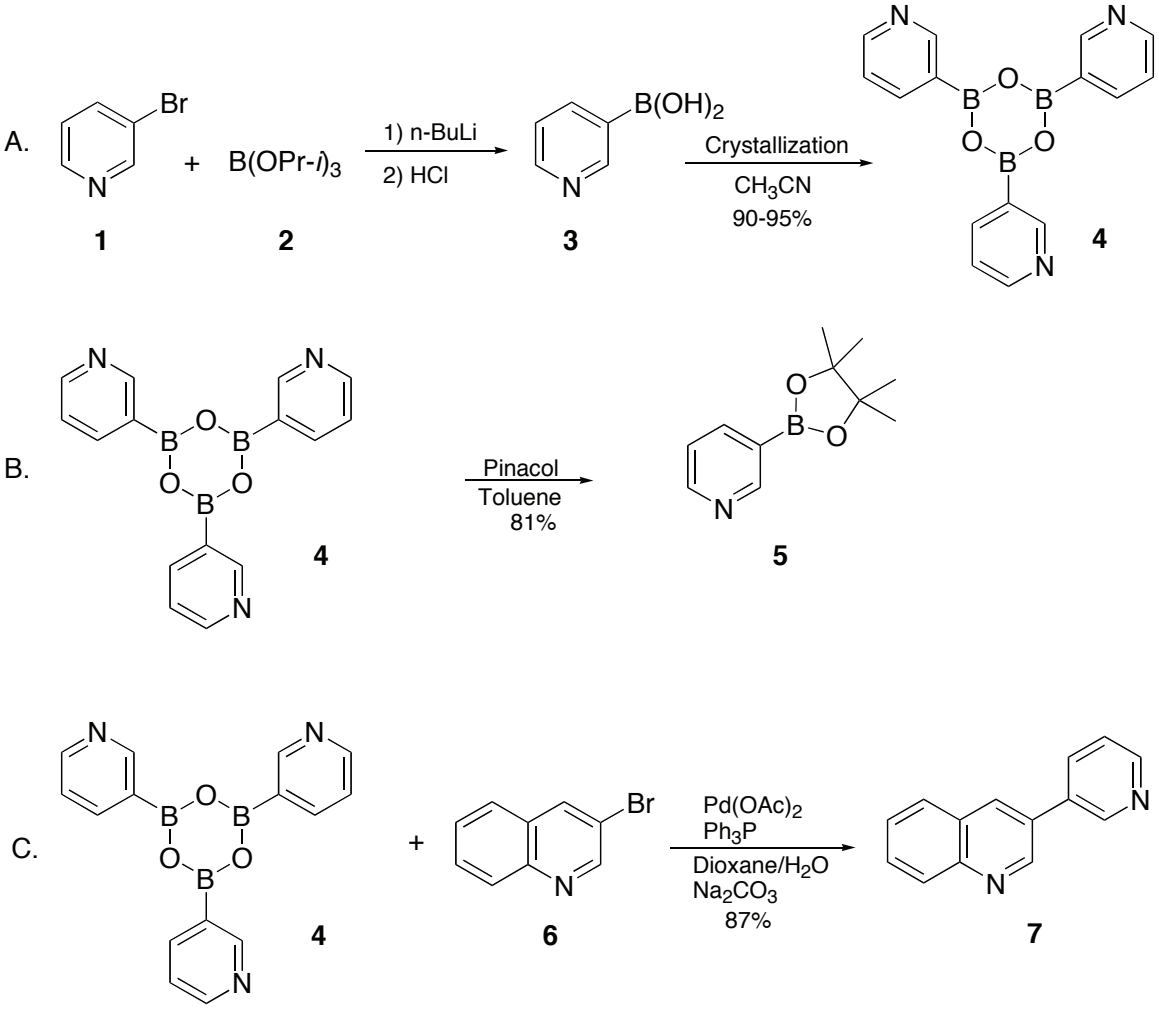
SYNTHESIS OF 3-PYRIDYLBORONIC ACID AND ITS PINACOL ESTER. APPLICATION OF 3-PYRIDYLBORONIC ACID IN SUZUKI COUPLING TO PREPARE 3-PYRIDIN-3-YLQUINOLINE [Quinoline, 3-(3-pyridinyl)-]



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Checked by Scott E. Denmark, Geoff T. Halvorsen, and Jeffrey M. Kallemeyn.

1. Procedure

A. 3-Pyridylboronic acid [tris(3-pyridyl)boroxin]. A 1-L, 3-necked flask equipped with a temperature probe, overhead stirrer, and a

nitrogen inlet adaptor capped with a rubber septum is charged with 320 mL of toluene, 80 mL of THF, triisopropyl borate (55.4 mL, 240 mmol), and 3-bromopyridine (19.3 mL, 200 mmol) (Notes 1, 2). The mixture is cooled to –40 °C using a dry ice/acetone bath and 96 mL of *n*-butyllithium solution (2.5M in hexanes, 240 mmol) (Note 3) is added dropwise with a syringe pump over 1 h. The reaction mixture is stirred for an additional 30 min maintaining the temperature at –40 °C. The acetone/dry ice bath is then removed, and the reaction mixture is allowed to warm to –20 °C whereupon a solution of 200 mL of 2N HCl solution is added. When the mixture reaches room temperature, it is transferred to a 1-L separatory funnel and the aqueous layer (pH ≈ 1) is drained into a 500-mL Erlenmeyer flask equipped with a magnetic stir bar. The pH of the aqueous layer is adjusted to 7.6-7.7 using 5N aqueous NaOH (ca. 30 mL) (Note 4). A white solid precipitates out as the pH approaches 7. The aqueous mixture is then saturated with solid NaCl, transferred to a 1-L separatory funnel, and extracted with three 250-mL portions of THF. The combined organic phases are concentrated on a rotary evaporator to leave a solid residue which is suspended in 80 mL of acetonitrile for crystallization. The mixture is heated to 70 °C in an oil bath, stirred for 30 min, and then allowed to cool slowly to room temperature and then to 0 °C in an ice bath. After being stirred at 0 °C for 30 min, the mixture is filtered through a fritted-glass funnel. The solid is washed with 15 mL of cold (5 °C) acetonitrile, and then dried under vacuum to afford 18.9 g of tris(3-pyridyl)boroxin·1.0 H_2O as a white solid (Note 5).

B. 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine. A 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirbar and a Dean-Stark trap fitted with a condenser capped with a nitrogen inlet adaptor is charged with tris(3-pyridyl)boroxin·0.85 H_2O (3.0 g, 9.1 mmol), pinacol (4.07 g, 34.4 mmol) (Note 6), and 120 mL of toluene. The solution is heated at reflux for 2.5 h in a 120 °C oil bath. The reaction is complete when the mixture changes from cloudy-white to clear. The solution is then concentrated under reduced pressure on a rotary evaporator to afford a solid residue. This solid is suspended in 15 mL of cyclohexane (Note 7) and the slurry is heated to 85 °C, stirred at this temperature for 30 min, and then allowed to cool slowly to room temperature. The slurry is filtered, rinsed twice using the mother liquors, washed with 3 mL of cyclohexane, and dried

under vacuum to afford 4.59 g (82%) of 3-pyridylboronic acid pinacol ester as a white solid (Note 8).

C. 3-Pyridin-3-yl-quinoline. A 100-mL, round-bottomed Schlenk flask equipped with a magnetic stir bar is charged with tris(3-pyridyl)boroxin·0.85 H_2O (3.80 g, 11.5 mmol), 3-bromoquinoline (6.24 g, 30.0 mmol) (Note 9), 30 mL of a 2M aqueous solution of Na_2CO_3, and 30 mL of 1,4-dioxane (Note 10). Palladium(II) acetate (0.336 g, 1.5 mmol) and triphenylphosphine (1.57 g, 6.0 mmol) are added (Note 10), the mixture is degassed using five vacuum/nitrogen back-fill cycles, and then is heated to 95 °C for 2.5 h with vigorous stirring (Note 11). The mixture is allowed to cool to room temperature, transferred to a 500-mL separatory funnel, and diluted with 100 mL of water and 150 mL of ethyl acetate. The aqueous layer is separated and back-extracted with 50 mL of ethyl acetate, and the combined organic layers are extracted with three 50-mL portions of 1M HCl solution. The combined acidic aqueous layers are treated with 40 mL of 5M aqueous NaOH resulting in a pH of ca. 9. The cloudy aqueous layer is then extracted with three 50-mL portions of ethyl acetate. The combined organic layers are dried over $MgSO_4$, filtered into a 500-mL, round-bottomed flask, and concentrated on a rotary evaporator under reduced pressure to afford a brown solid. Isopropyl acetate (10 mL) is added and the slurry is heated to reflux at which point 40 mL of heptane is added. The mixture is allowed to cool to room temperature over 3 h, and then is stirred at room temperature for 2 h. The solid is isolated by filtration, washed with 10 mL of 4:1 heptane/isopropyl acetate, and dried under vacuum at room temperature to give 5.36-5.40 g (87%) of 3-pyridin-3-ylquinoline as a white solid (Note 12).

2. Notes

1. Toluene and THF were purchased from Fisher Scientific and dried over 4Å molecular sieves overnight prior to use. The water content of the solvents was < 50 μg/mL by Karl Fischer titration.

2. Triisopropyl borate was purchased from Aldrich Chemical Company, Inc. 3-Bromopyridine was purchased from Lancaster Synthesis. Both compounds were used without further purification.

3. *n*-Butyllithium (2.5M in hexanes) was purchased from Aldrich Chemical Company, Inc. and was titrated prior to use.

4. Measurement of pH was performed using a Metrohm model 691 pH meter equipped with a Metrohm combined LL micro pH glass electrode calibrated prior to use with pH = 2 and 9 buffers. The checkers found that adjustment to a lower pH led to product with higher amounts of inorganic impurities. The checkers also found that the use of pH paper results in different pH values as compared to the pH meter.

5. The checkers obtained trispyridylboroxin in various hydration levels (0.85 – 1.0 H_2O). A satisfactory melting point for this solid could not be obtained. ^{1}H NMR (400 MHz, CD_3OD): δ 7.66 (br s, 1H), 8.38 (d, *J* = 6.6, 1H), 8.51 (dd, *J* = 1.2, 4.4, 1H), 8.61 (br s, 1H). ^{1}H NMR spectra were complicated in other solvents such as $CDCl_3$ and DMSO-d_6. Anal Calcd. for $C_{15}H_{12}B_3O_3N_3 \bullet 1.0H_2O$: C, 54.15; H, 4.24; N, 12.63. Found: C, 53.95; H, 3.91; N, 12.35. Yield based on this formula is 85%. The submitters report obtaining the product in 91% yield.

6. Pinacol was purchased from Aldrich Chemical Company, Inc. and was used without further purification.

7. Cyclohexane was purchased from Aldrich Chemical Company, Inc. and was used without further purification.

8. The checkers obtained the product in 74-82% yield in different runs. The product exhibits the following physical properties: mp 102–105 °C; IR (KBr pellet) cm^{-1} 2994, 2968, 2932, 1609, 1572, 1476, 1410, 1361, 1209, 1154, 1063, 1017, 953, 926, 859, 833, 800, 759, 705; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 12H), 7.25 (ddd, *J* = 1.1, 4.9, 7.5, 1H), 8.03 (dt, *J* = 1.8, 7.5, 1H), 8.64 (dd, *J* = 1.9, 4.9, 1H), 8.93 (d, *J* = 1.1, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.8, 84.1, 123.0, 142.2, 152.0, 155.5; MS (EI, 70 eV): 205 (M+, 46), 204 (15), 191 (12), 190 (100), 189 (25), 162 (10), 148 (44), 147 (14), 120 (18), 119 (11), 106 (100), 105 (35), 85 (15), 59 (17), 58 (19); HRMS (EI) *m/z* 205.1280, calcd for $C_{11}H_{16}NO_2B$ 205.1274). Anal. Calcd for : $C_{11}H_{16}BO_2N$: C, 64.43; H, 7.86; N, 6.83. Found: C, 64.23; H, 7.99; N, 6.88.

9. 3-Bromoquinoline was purchased from Acros Organics and was used without further purification.

10. 1,4-Dioxane, palladium (II) acetate, and triphenylphosphine were purchased from Aldrich Chemical Company, Inc. and were used without further purification.

11. A heterogeneous mixture that is difficult to stir may be formed during the reaction. The checkers found that rapid stirring from the onset of the reaction prevented loss of stirring. Inefficient stirring was found to lower the yield of the reaction.

12. The following characterization data was obtained: mp: 122–125 °C; IR (KBr pellet): cm^{-1} 3044, 1568, 1495, 1410, 1338, 1298, 1187, 1126, 1059, 1022, 952, 932, 816, 784, 758, 709 909, 808, 786, 752, 709, 61; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (ddd, *J* = 0.9, 4.9, 7.9, 1H), 7.60 (dt, *J* = 0.9, 7.9, 1H), 7.75 (ddd, *J* = 1.2, 6.8, 8.3, 1H), 7.90 (dd, *J* = 0.9, 8.1, 1H), 8.00 (dt, *J* = 2.2, 7.8, 1H), 8.15 (d, *J* = 8.4, 1H), 8.32 (d, *J* = 2.3, 1H), 8.68 (dd, *J* = 1.5, 4.9, 1H), 8.97 (d, *J* = 2.1, 1H), 9.15 (d, *J* = 2.1, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.8, 127.3, 127.8, 128.0, 129.3, 129.9, 130.6, 133.57, 133.63, 134.6, 147.7, 148.5, 149.27, 149.29; MS (EI, 70 eV): 207 (16), 206 (M+, 100), 205 (40); HRMS (EI) *m/z* 206.0847, calcd for $C_{14}H_{10}N_2$ 206.0944). Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.43; H, 4.86; N, 13.40.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

3-Pyridylboronic acid is a useful compound for the introdution of a 3-pyridyl moiety into a molecule by the Suzuki reaction.[2-3] It is commercially available only in small quantities at high cost. Typical preparation of this class of compounds involves reaction between boronic esters and an organometallic reagent (Li or Mg)[4-7] usually prepared by magnesium insertion[4] or lithium-halogen exchange[5-7] of 3-bromopyridine. The literature protocols, however, require conditions that are not suitable for large scale, including using dibromoethane as the solvent, running the reaction at very low temperature (–78 °C), and affording poor to modest yields. Recently, we reported a revised procedure for the preparation of 3-pyridylboronic acid via lithium-halogen exchange and *in situ* quench with triisopropyl borate.[8] In this protocol, *n*-butyllithium is added to a solution of 3-bromopyridine and triisopropyl borate in THF/toluene based on the reasoning that lithium-halogen exchange is much faster than the reaction between *n*-butyllithium and triisopropyl borate. The 3-lithiopyridine intermediate thus generated, reacts rapidly with the borate in the reaction mixture, thereby minimizing the chance for 3-lithiopyridine to undergo side reactions.[9] The new procedure allows the reaction to be run at much higher temperatures, giving the best yields (90–95%) at –40 °C and a respectable 80% yield even at 0 °C. The reaction can be carried out at kilogram scale. The product is isolated by crystallization from acetonitrile in the form of boroxin **4**. The characterization of **4** is difficult, however, due to the presence of varying amounts of water. Therefore, boroxin **4** is converted to its pinacol ester **5,** which is fully characterized by spectroscopic data and elemental analysis. The utility of **4** in palladium-catalyzed cross-coupling reaction is demonstrated in a Suzuki reaction with 3-bromoquinoline.[10]

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

3-Bromopyridine: Pyridine, 3-bromo-; (626-55-1)

Triisopropyl borate: Boric acid (H_3BO_3), tris(1-methylethyl) ester; (5419-55-6)

n-Butyllithium: Lithium, butyl-; (109-72-8)

3-Pyridylboronic acid: Boronic acid, 3-pyridinyl-; (1692-25-7)

Tris(3-pyridyl)boroxin: Pyridine, 3,3',3''-(2,4,6-boroxintriyl)tris-; (160688-99-3)

Pinacol: 2,3-Butanediol, 2,3-dimethyl-; (76-09-5)

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine: Pyridine, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-; (329214-79-1)

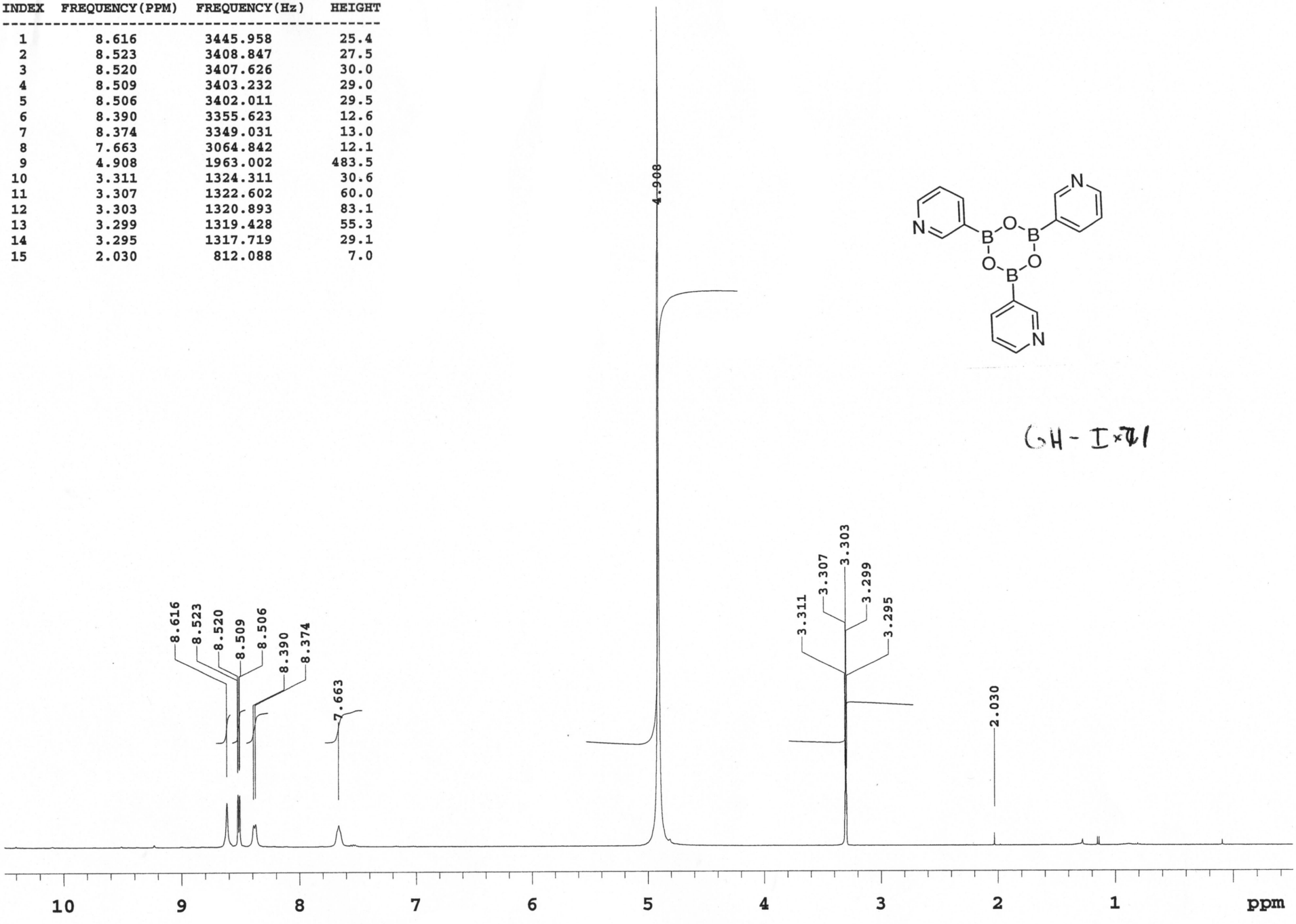
3-Bromoquinoline: Quinoline, 3-bromo-; (5332-24-1)

Palladium (II) acetate: Acetic acid, palladium(2+) salt; (3375-31-3)

Triphenylphosphine: Phosphine, triphenyl-; (603-35-0)

3-Pyridin-3-ylquinoline: Quinoline, 3-(3-pyridinyl)-; (96546-80-4)

INDEX	FREQUENCY(PPM)	FREQUENCY(Hz)	HEIGHT
1	8.616	3445.958	25.4
2	8.523	3408.847	27.5
3	8.520	3407.626	30.0
4	8.509	3403.232	29.0
5	8.506	3402.011	29.5
6	8.390	3355.623	12.6
7	8.374	3349.031	13.0
8	7.663	3064.842	12.1
9	4.908	1963.002	483.5
10	3.311	1324.311	30.6
11	3.307	1322.602	60.0
12	3.303	1320.893	83.1
13	3.299	1319.428	55.3
14	3.295	1317.719	29.1
15	2.030	812.088	7.0



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bs	4	dpwr2	1
tpwr	63	dof2	0
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ct	4	dres2	1.0
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