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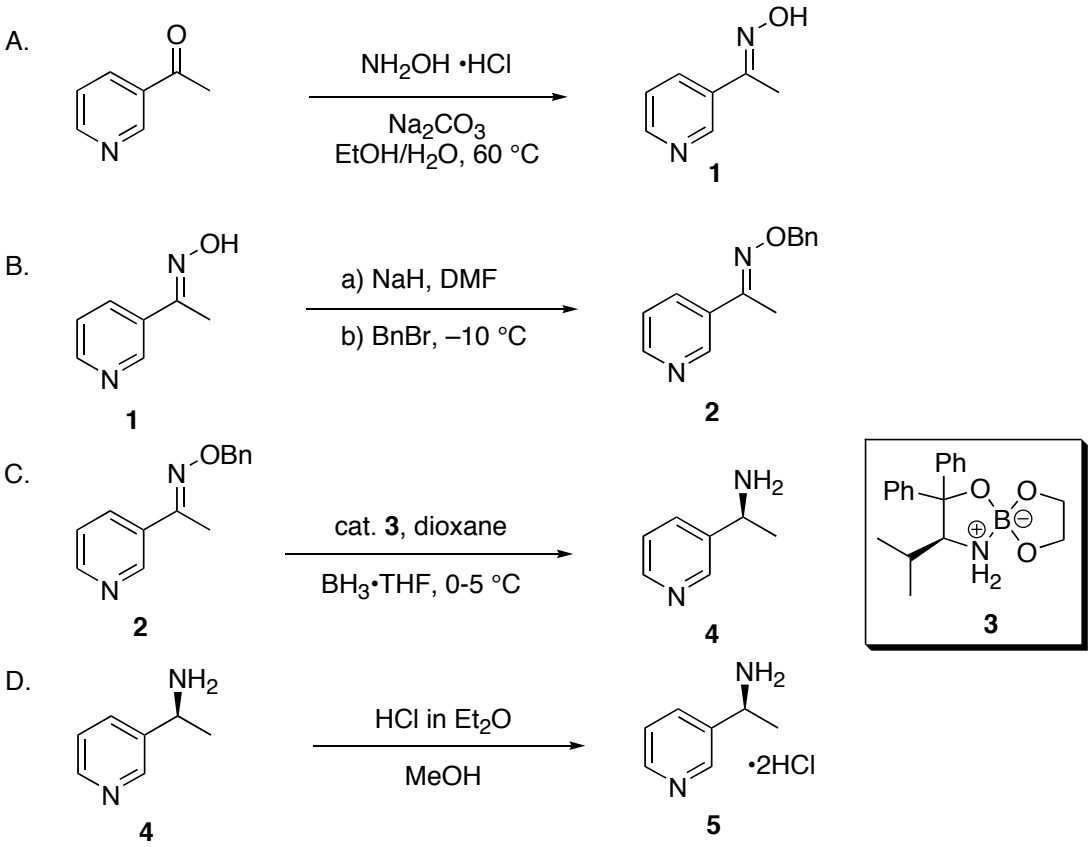
CATALYTIC ENANTIOSELECTIVE BORANE REDUCTION OF BENZYL OXIMES: PREPARATION OF (*S*)-1-PYRIDIN-3-YL-ETHYLAMINE BIS HYDROCHLORIDE



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1. Procedure

*A. (E)-1-Pyridin-3-yl-ethanone oxime (**1**).* A 250-mL, three-necked, round-bottomed flask is equipped with a 2-cm Teflon-coated magnetic stir bar, a reflux condenser, a pressure-equalizing dropping funnel and a rubber septum through which a thermocouple thermometer probe is inserted. The flask is charged with 3-acetyl pyridine (12.1 g, 100 mmol) (Note 1), EtOH (100 mL) and NH_2OH•Cl (11.85 g, 170 mmol), and the mixture is heated with a heating mantle to 55 °C. A pre-made solution of Na_2CO_3 (7.46 g, 70 mmol) in water (20 mL) is added dropwise over 10 min via the dropping funnel. At the end of the addition, the temperature has risen to 62 °C. The heterogeneous mixture is stirred at 60 °C for 2.5 h (Notes 2 and 3), then

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filtered through a 60-mL medium-porosity sintered-glass funnel to remove the inorganic salts. The solid is washed with EtOH (2 x 20 mL) and the combined filtrate is transferred to a 500-mL, round-bottomed flask and concentrated by rotary evaporation (50 °C, 20 mmHg) to afford 19 g of solid residue. Then, water (250 mL) is added along with a 2.5-cm Teflon-coated magnetic stir bar and the mixture is warmed to 70 °C (Note 4) using a heating mantle. The heat is turned off, allowing the mixture to slowly cool to ambient temperature over 3 h. The product is isolated by filtration on a 150-mL medium-porosity sintered glass funnel, washed with water (2 x 15 mL), and dried for 15 h under vacuum (60 °C, 20 mmHg) to afford (*E*)-1-pyridin-3-yl-ethanone oxime (**1**) (11.3 g, 83%) as a white crystalline solid (Notes 5, 6, 7, and 8). A second crop is obtained as follows. The filtrate from the crystallization is extracted with EtOAc (3 x 100 mL). The combined organic extracts are washed with brine (50 mL), filtered through a bed of sodium sulfate, and concentrated by rotary evaporation (40 °C, 20 mm Hg) to 1.9 g. This solid material is transferred to a single-necked 100-mL round-bottomed flask along with water (35 mL) and a 1.5-cm Teflon-coated magnetic stir bar. The mixture is warmed using a heating mantle to 80 °C with stirring to dissolve all the solids (Note 9). The heating mantle is turned off, allowing the solution to slowly cool to ambient temperature over 1 h. The mixture is held at room temperature an additional hour, then filtered through a 60-mL medium porosity sintered glass funnel, washed with water (2 x 5 mL), and dried for 15 h under vacuum (60 °C, 20 mmHg) to afford (*E*)-1-pyridin-3-yl-ethanone oxime (**1**) (1.40 g, 10%) containing 0.6% of the undesired *Z*-isomer. The first and second crops have similar purity by NMR and can be combined (12.7 g, 93%).

*B. (E)-1-Pyridin-3-yl-ethanone O-benzyl-oxime (**2**).* An oven-dried 500-mL, three-necked, round-bottomed flask is equipped with a 2.5-cm oval Teflon-coated magnetic stirrer, a pressure-equalizing dropping funnel on the middle neck, a rubber septum through which is inserted a thermocouple temperature probe, and a nitrogen inlet adapter connected to a nitrogen line and gas bubbler. Nitrogen is flowed through the flask while cooling. The flask is charged with anhydrous DMF (175 mL, dried with 3 Å 1.6 mm pelleted sieves) and cooled to –15 °C (internal temperature) using a dry-ice acetone bath at –25 °C. Sodium hydride (4.59 g, 60%, 115 mmol, 1.4 equiv) is added to the cold DMF solution. A solution of (*E*)-1-pyridin-3-yl-ethanone oxime (**1**) (10.95 g, 80.5 mmol) in anhydrous DMF (80 mL, dried with 3 Å 1.6 mm pelleted sieves is added dropwise via the dropping funnel

over 15 min, followed by a rinse of DMF (5 mL). The temperature of the yellow heterogeneous mixture rises to –10 °C during the addition of the oxime. The resulting mixture is stirred for 30 min at –12 to –10 °C, then benzyl bromide (14.45 g, 85 mmol, 1.05 equiv) is added dropwise via syringe over 10 min (Note 10). After complete addition, the mixture is stirred for 40 min at –12 to –10 °C and checked by TLC for reaction completion (Note 11). A saturated aqueous NH_4Cl solution (100 mL) is added to quench the reaction. The first 20 mL is added slowly over 10 min with hydrogen evolution, with an exotherm of +5 °C being observed during those 10 min. The remaining 80 mL is added over the next 5 min with an exotherm leading to a temperature of 23 °C. The mixture is transferred to a 2-L separatory funnel. The flask is rinsed with water (100 mL) and EtOAc (200 mL), which are also transferred to the separatory funnel. The layers are separated. The aqueous layer is extracted with EtOAc (2 x 100 mL). The organic layers are combined, washed with water (2 x 100 mL), then with brine (50 mL). The organic layer is filtered through a bed of sodium sulfate (40 g), rinsing the bed with EtOAc (100 mL). The resulting organic filtrate is concentrated by rotary evaporation (40 °C, 20 mmHg) to give a yellow oil (22 g) (Note 12). The material is purified by chromatography on SiO_2 (Note 13). The resulting oil is further vacuum dried at room temperature (20 mmHg) for 15 h to afford (*E*)-1-pyridin-3-yl-ethanone *O*-benzyl-oxime (**2**) (18.02 g, 99%) as a pale yellow oil (Note 14).

*C. (S)-1-Pyridin-3-yl-ethylamine (**4**).* An oven-dried, 1-L, 3-necked, round-bottomed flask, marked at the 465 mL fill prior to drying, is equipped with a 3-cm oval Teflon-coated magnetic stir bar, two rubber septa on the outer necks, and a 100-mL gas equilibrating addition funnel that is connected by a gas adapter to a nitrogen inlet and gas bubbler. A thermocouple thermometer probe is inserted through one of the septa. Nitrogen is flowed through the system as the flask is cooling. Spiroborate ester **3**[3] (5.80 g, 18 mmol) and anhydrous dioxane (230 mL, dried with 3 Å 1.6 mm pelleted sieves) are added to the flask and the heterogeneous mixture is stirred at ambient temperature. Borane-tetrahydrofuran complex (1.0 M, 235 mL, 235 mmol, 3.9 equiv) (Note 15) is added via cannula to the reaction flask over 5 min, resulting in gentle hydrogen evolution, which cools the reaction mixture by 2 °C. The resulting mixture is stirred for 0.5 h at room temperature, whereby most of the solids dissolve to give a hazy solution. This solution is cooled to 3 °C using an ice-bath, then a solution of (*E*)-1-pyridin-3-yl-ethanone *O*-benzyl-oxime (**2**) (13.54 g, 60 mmol) in anhydrous

dioxane (40 mL) is added over 1 h via the addition funnel. The addition funnel is rinsed with dioxane (5 mL). The mixture is stirred for 30 h at 0–5 °C in an ice bath (Note 16). The cold reaction is carefully quenched by the dropwise addition of methanol (100 mL) over 15 min. The flask is equipped with a reflux condenser and heated under reflux (67–69 °C) for 15 h. Then the solution is concentrated by rotary evaporation (50 °C bath, 20 mmHg) to afford 30 g of crude solid (Note 17). The residue is purified by chromatography on SiO_2 (Note 18) to provide (*S*)-1-pyridin-3-yl-ethylamine (**4**) (8.03 g) as a hazy oil that is approximately 83 wt % pure (91% yield corrected for purity) (Note 19). The enantiomeric excess is 98% by chiral HPLC of the acetyl derivative of (*S*)-1-pyridin-3-yl-ethylamine (**4**) (Notes 20 and 21).

*D. (S)-1-Pyridin-3-yl-ethylamine hydrochloride (**5**).* An oven-dried 250-mL, 3-necked, round-bottomed flask is equipped with 2-cm Teflon-coated magnetic stirrer, sealed with two rubber septa on each outer neck, through one of which is inserted a thermocouple thermometer probe, and a 100-mL gas-equilibrating addition funnel on the center neck. (*S*)-1-Pyridin-3-yl-ethylamine **4** (7.49 g, 83% pure, 50.9 mmol) is dissolved in MeOH (25 mL) and the hazy solution is filtered by syringe through a 0.45 micron Teflon syringe filter into the addition funnel. Hydrochloric acid in ether (2.0 M, 60 mL, 120 mmol, 2.4 equiv) is added to the flask via syringe and the solution is stirred vigorously (500 rpm) at ambient temperature. The amine in methanol solution is added dropwise to the HCl solution over 20 min, during which time crystallization occurs and the temperature rises to 30 °C (Note 22). The dropping funnel is rinsed with MeOH (3 mL). The mixture is stirred at ambient temperature for 2 h, then filtered through a pressure filter (Note 23), washed with diethyl ether (2 x 10 mL), and dried for 15 h (60 °C, 20 mmHg,) to afford (*S*)-1-pyridin-3-yl-ethylamine bis-hydrochloride (**5**) (8.90 g, 89% yield) as an analytically pure white solid (Note 24). Enantiomeric excess determined by chiral HPLC analysis of the acetyl derivative is 99% (Notes 25 and 26).

2. Notes

1. The following reagents and solvents used in this preparation were sourced from Sigma-Aldrich and used without further purification, including 3-acetyl pyridine (98 %), ethyl acetate (ACS reagent, >99.5%), $NH_2OH{\cdot}HCl$ (ReagentPlus 99%), NaH (60% dispersion in mineral oil),

dimethylformamide (ACS spectrophotometric grade, 99.8%), benzyl bromide (98%), hexanes (ACS reagent, >98.5%), 1,4-dioxane (ACS reagent, >99%), 1.0 M BH_3·THF stabilized with $NaBH_4$, methanol (ACS reagent, >99.8%), dichloromethane (ACS reagent, >99.5%), 2.0M HCl in diethyl ether, silica gel (200-400 mesh, 60 Å). Absolute ethanol was obtained from Pharmaco. Ammonium chloride, sodium carbonate, and sodium sulfate were sourced from Fisher. De-ionized tap water is used throughout.

2. The oxime and ketone are not separable by TLC. The reaction is followed by ^{1}H NMR as follows: A sample (0.1 mL) is added to $CDCl_3$ (1 mL) and filtered through glass wool into an NMR tube. The methyl group of 3-acetylpyridine is masked by the large OH peak of EtOH, but the aromatic protons are clearly distinguishable as markers of unreacted ketone. The reaction mixture sampled after 2 h at 60 °C contained no starting material.

3. The oxime formation at 60 °C generates a 97:3 ratio of *E*/*Z* isomers. The reaction conducted at ambient temperature results in a ratio of 88:12.

4. The mixture remains heterogeneous at 70 °C. Further product crystallization occurs upon cooling.

5. The amount of the *Z*-isomer of the isolated material ranged from 0.2 to 0.7%. The submitters analyzed the *E/Z* ratio by GC-MS using the conditions described in Note 8. The checker analyzed by 400 MHz ^{1}H NMR by integration of the *Z*-isomer (upfield from the *E*-isomer by 0.06 ppm) and comparing to the integration of both ^{13}C-^{1}H satellites (0.55% each) of the *E*-isomer. *Z*-Isomer levels could be detected and accurately integrated at the 0.2% level. An enriched sample of the *Z*-isomer (8%) was obtained by concentration of the filtrate from the crystallization. For further details on the use of ^{13}C satellites for quantitative analysis of low-level components, see Claridge, T. D. W.; Davies, S. G.; Polywka, M. E. C.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D. *Org. Lett.* **2008**, *10*, 5433-5436.

6. The submitters carried out a recrystallization from EtOAc as follows. The oxime (12.9 g) is added to ethyl acetate (70 mL) in a 250-mL single-necked flask and warmed to 75 °C with stirring to dissolve all solids. After cooling to ambient temperature, the flask is placed in a freezer at −18 °C for 5 h. The product is collected by filtration on a Büchner funnel and dried in a round-bottomed flask for 2 h at 80 °C under high vacuum (0.1 mmHg) to yield 11.2 g.

7. An analytically pure sample was prepared by recrystallization from water as follows. Oxime (2.0 g) is added to water (25 mL) in a 100-mL

round-bottomed flask containing a 1.5-cm oval Teflon-coated magnetic stir bar. The mixture is warmed to 80 °C with stirring using a heating mantle and rapidly hot filtered through a 60-mL medium-porosity sintered glass funnel that has been pre-heated to 110 °C in an oven. The resulting filtrate is re-heated to 80 °C to re-dissolve all solids, then allowed to slowly cool to ambient temperature over 1 h. After an additional 30 min at ambient temperature, the solids are collected by filtration on a 15-mL medium-porosity sintered glass funnel, washed with water (2 x 5 mL) and dried for 15 h (60 °C, 20 mmHg) to afford analytically pure product (1.5 g, 75%).

8. Physical data for (*E*)-1-pyridin-3-yl-ethanone oxime ***(1)***: mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3 H, CH_3), 7.32 (dd, 1 H, J = 4.8, 8.0 Hz, H(5)-Py), 7.98 (ddd, 1 H, J = 2.0, 1.9, 8.0 Hz, H(4)-Py), 8.61 (dd, 1 H, J = 1.5, 4.8 Hz, H(6)-Py), 8.97 (d, 1 H, J = 2.0 Hz, H(2)-Py), 10.50 (br s, 1 H, NOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.9, 123.6, 133.1, 133.8, 147.4, 149.6, 153.0; GC-MS *m/z* 136.1 ($[M]^+$); Anal. Cald. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.55; H, 5.96; N, 20.41. GC-MS analysis (1 μL sample) was carried out on a Thermo Finnigan PolarisQ, GC/MS (EI), Trace GC 2000 using a Restek RTX-5MS (5% phenylsilicon) column (30 m, 0.25 mm diameter, 0.25 μm): gas carrier He, flow 50 mL/min, split set to 0.7 mL/min; oven gradient conditions 70 °C initial Temp, 1 min, ramp of 11 °C/min until final Temp 250 °C, and hold for 10 min. Post run Temp: 300 °C for 5 min. Max Temp 350 °C, prep run timeout 10 min, equilibration time 0.5 min. MS method: source Temp 200 °C, 3 micro scans, max ion time 25 (*E*-isomer t_R 10.56 min).

9. Heating to 80 °C results in equilibration of the *E*/*Z* ratio from the original 92:8 to 97:3. The second crop material is comparable in quality to the first crop (0.5 – 0.7% *Z*-isomer).

10. Benzyl bromide is a lachrymator and should only be handled in a well vented hood.

11. A sample (0.2 mL) of the mixture is removed by syringe, quenched with water (0.5 mL) and extracted with ethyl acetate (0.5 mL). The ethyl acetate layer is analyzed by TLC, eluting with hexane/ethyl acetate (1:1 v/v) and visualized by UV: R_f 0.6 (benzyl oxime), R_f 0.3 (oxime). In both runs by the checker, the reaction was complete using the original charge of NaH. The submitters note that, if unreacted oxime is present, NaH (2.24 g, 56 mmol, 60% suspension in mineral oil) can be added to the mixture to drive the reaction to completion.

12. The crude material contains about 10 mol% EtOAc and 10 mol% DMF by ^{1}H NMR analysis.

13. The crude material is purified by chromatography on SiO_2 (150 g) in a 6-cm diameter column, wet-packed using hexanes. The column is topped with sea sand (0.5 cm). The product oil is loaded onto the column and is eluted with hexanes (400 mL) followed by 1:1 EtOAc:hexanes (1.3 L), collecting 75 mL fractions. The fractions are analyzed by TLC as described in Note 11. Fractions 7-18 are combined and concentrated by rotary evaporation (40 °C, 20 mmHg).

14. Physical data for *(E)*-1-pyridin-3-yl-ethanone *O*-benzyl-oxime (**2**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.28 (s, 3 H, CH_3), 5.27 (s, 2 H, OCH_2), 7.26 (ddd, 1 H, J = 0.8, 4.8, 8.0 Hz, H(5)-Py), 7.30–7.45 (m, 5 H, Ar), 7.94 (ddd, 1 H, J = 1.8, 1.8, 8.0 Hz, H(4)-Py), 8.59 (dd, 1 H, J = 1.7, 4.7 Hz, H(6)-Py), 8.88 (dd, 1 H, J = 0.6, 2.0 Hz, H(2)-Py); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.7, 76.7, 123.4, 128.1, 128.5, 128.6, 132.4, 133.4, 137.9, 147.7, 150.2, 152.7; GC-MS according to the method described in Note 8: *m/z* 226.3 ($[M]^+$) (t_R 16.44 min). Only the *E*-isomer was observed by GC/MS and ^{1}H NMR. A sample enriched in the *Z*-isomer (4:1 *E*:*Z* ratio) was prepared by reaction of 3-acetylpyridine with *O*-benzylhydroxylamine.

15. BH_3•THF (1.0 M) is added to the pre-marked line representing a 465-mL fill (dioxane (230 mL) and BH_3•THF (235 mL)). The actual amount of reagent added is determined by weighing the reagent bottle before and after addition (density 0.867 g/mL). The exact amount of borane added is not critical as comparable results are obtained with 3 to 5 equiv.

16. Completion of reaction is determined by ^{1}H NMR as follows. An aliquot (0.1 mL) is quenched into CD_3OD (0.6 mL) and 37% DCl in D_2O (0.1 mL) is added. The uncapped NMR tube is held for 1 h at ambient temperature until the hydrogen evolution ceases. The *O*-benzyl oxime resonances at 5.3 and 2.3 ppm are diagnostic of unreacted oxime. When 4 to 5 equiv of borane are used, the reaction is complete (<3% oxime) within 24 h. With 3 equiv borane, 8% oxime remained unreacted after 24 h and did not react further upon stirring an additional day.

17. The amine product can co-distill with dioxane if the temperature and vacuum are too high during concentration.

18. The amine is purified by chromatography on SiO_2 (260 g), wet packed with 10% MeOH/CH_2Cl_2 and topped with sea sand (0.5 cm). The product is dissolved with sonication in CH_2Cl_2 (40 mL), loaded, and eluted using 10% MeOH/CH_2Cl_2 (500 mL), 25% MeOH/CH_2Cl_2 (500 mL), 50%

MeOH/CH_2Cl_2 (500 mL), and 4% Et_3N/MeOH (1.5 L), collecting 250-mL fractions. The product fractions 3-8 are concentrated by rotary evaporation (40 °C, 20 mmHg) to afford 8.03 g of the product. ^{1}H NMR analysis indicated the presence of 13 wt% ethylene glycol and 4 wt% MeOH, indicating the product was approximately 83 wt % pure (91% yield corrected for purity)

19. *(S)-1-Pyridin-3-yl-ethylamine (**4**)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (d, 3 H, J = 6.6 Hz, CH_3), 2.0 (br s, 2 H, NH_2), 4.17 (q, 1 H, J = 6.6 Hz, NCH), 7.26 (dd, 1 H, J = 4.9, 8.0 H(5)-Py), 7.71 (ddd, 1 H, J = 1.6, 2.3, 7.8 Hz, H(4)-Py), 8.47 (dd, 1 H, J = 1.6, 4.8 Hz, H(6)-Py), 8.57 (d, 1 H, J = 2.2 Hz, H(2)-Py) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7, 49.3, 123.7, 133.6, 142.7, 148.2, 148.5; GC-MS conditions from Note 8) *m/z* 223.2 ($[M]^+$) (t_R 6.56 min).

20. ***Procedure for the preparation of racemic amine and acetamide:*** An oven-dried, 100-mL round-bottom flask equipped with a 1-cm Teflon-coated magnetic stirrer and a reflux condenser connected via a nitrogen adapter and a gas bubbler, is charged with benzyl oxime **2** (1.15 g, 5.1 mmol) and 1.0 M BH_3•THF (20 mL, 20 mmol). The solution is heated at reflux for 3 h, then cooled to ambient temperature and quenched by the dropwise addition of methanol (5 mL). The resulting mixture is heated at reflux for 14 h, then concentrated by rotary evaporation (40 °C bath, 20 mm Hg). The crude amine product is purified by column chromatography using 15 g silica gel wet packed with 10% MeOH/CH_2Cl_2, eluting with 50 ml MeOH/CH_2Cl_2, 50 mL MeOH, and 100 mL 5% Et_3N/MeOH, taking 10-15 mL fractions. Fractions 3-10 are combined and concentrated by rotary evaporation (40 °C bath, 20 mm Hg) to afford an oil (0.56 g, 90% yield). The acetamide is prepared by dissolution of the racemic amine (0.22 g, 1.8 mmol) in CH_2Cl_2 followed by addition of Et_3N (0.3 g, 3.0 mmol), Ac_2O (0.20 g, 2.0 mmol) and 4-dimethylyaminopyridine (DMAP) (15 mg). The mixture is stirred at ambient temperature for 30 min. The solvent is removed by rotary evaporation (40 °C bath, 20 mm Hg) and the residue is purified by chromatography on SiO_2 (15 g), eluting with 100 mL CH_2Cl_2:MeOH (97:3 v/v), collecting 10 mL fractions. Fraction 3 is concentrated by rotary evaporation (40 °C bath, 20 mm Hg) to afford the acetamide product (0.19 g, 64%). Fraction 4 is likewise concentrated to afford additional product (100 mg, approx 80% pure by NMR, 27% yield; overall yield from both fractions, 91%) TLC conditions: 10% MeOH/CH_2Cl_2, R_f 0.5.

21. The submitters developed a chiral GC assay to analyze the ee of the derivatized amine as follows: Crompack Chirasil-Dex-CB column (30 m × 0.25 mm × 0.25μm). Conditions: 90 °C, 2 °C/min to 120 °C, hold 20 min; 2 °C/min to 130 °C, hold 20 min; 2 °C/min to 140 °C, hold 20 min, gives one enantiomer t_R 70.70 min, other enantiomer t_R 73.47 min. The checkers developed a chiral HPLC assay for the derivatized amine as follows: Chiralpak AD-H column (150 x 4.6 mm, 5 micron), A: Heptane, B: 1:1 MeOH:EtOH, 5% B for 4 min, then to 40% B over 18 min, hold 3 min, then to 5% B over 3 min, 20 min post time, 1.0 mL/min, ambient temperature, 210 nm. The undesired (*R*)-enantiomer elutes at 9.5 min, the desired (*S*)-enantiomer at 12.5 min.

22. Crystallization of the bis-HCl salt begins immediately and a high stirring rate is maintained to prevent clumping.

23. The bis-hydrochloride salt is hygroscopic, especially as a solvent-wet solid, and requires isolation under a nitrogen atmosphere. The checker used a pressure filter (cf, Sigma-Aldrich Z147656 or Z422886) under nitrogen to isolate the bis-HCl salt.

24. (*S*)-1-Pyridin-3-yl-ethylamine bis-hydrochloride (**5**): mp 191–193°C; $[\alpha]^{20}_D$ +5 (*c* 1.5, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ: 1.66 (d, 3 H, *J* = 7.0 Hz, CH_3), 4.79 (q, 1 H, *J* = 7.0 Hz, NCH), 8.09 (dd, 1 H, *J* = 5.9, 8.2 Hz, Py), 8.66 (d, 1 H, *J* = 8.3 Hz, Py), 8.77 (d, 1 H, *J* = 5.8 Hz, Py), 8.87 (d, 1 H, *J* = 1.4 Hz, Py); ^{13}C NMR (100 MHz, D_2O) δ: 18.5, 48.0, 128.0, 137.7, 140.5, 142.1, 145.5. Anal. Cald. for $C_7H_{12}Cl_2N_2$: C, 43.09; H, 6.20; Cl, 36.35; N, 14.36. Found: C, 43.31; H, 6.45; Cl, 36.35; N, 14.26.

25. The ee of the bis-HCl salt was determined by the derivatization method and HPLC analysis described in Notes 20 and 21. The derivatization method using the bis-HCl salt required an additional 2 equiv of triethylamine. Formation of the hydrochloride salt does not substantially enrich the ee of the product.

26. The table below summarizes three asymmetric reduction experiments carried out by the checker at the 60-mmol scale. The data suggest slightly improved enantioselectivity using 3-4 equiv vs 5 equiv of borane. The reaction with 3 equiv of borane did proceed to completion. Crystallization as the bis-HCl salt affords little to no ee upgrade.

Table 1. Summary of Checkers Results for the Enantioselective Reduction of Benzyl Oxime **2**, 60 mmol scale

	Equiv BH_3·THF	Unreacted oxime	Yield of amine **4**	ee of amine **4**	Yield of HCl salt **5**	ee of HCl salt **5**
Run 1	5	<3%	88%	94%	85%	94%
Run 2	4	3%	91%	98%	89%	99%
Run 3	3	8 %	86%	99%	89%	99%

Safety and 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

The catalytic enantioselective borane reduction of C=N bonds is of great interest due to the formation of nonracemic primary amines which are widely used as key intermediaries in the synthesis of a large variety of pharmaceuticals, chiral auxiliaries, catalysts and resolving agents.[4] Although the asymmetric reduction of oxime ethers with borane-based catalysts offers a facile and direct approach to obtain enantioenriched primary amines, more than a stoichiometric amount of *in situ* prepared oxazaborolidines was previously employed to obtain a high degree of enantioselectivity.[5] Fontaine, et al.[6] used 2.5 equiv of the diphenylvalinol-derived B-H oxazaborolidine to achieve complete reduction with high selectivity. Itsuno and co-workers[7] reported the first catalytic borane-based reduction of acetophenone *O*-benzyl oxime using 10 mol % of the B-H oxazaborolidine, generated *in situ* from (*S*)-diphenylvalinol, obtaining (*S*)-1-phenylethanamine in 52% ee. Thus, the development of highly enantioselective reagents for the catalytic reduction of benzyl oximes is highly desirable.

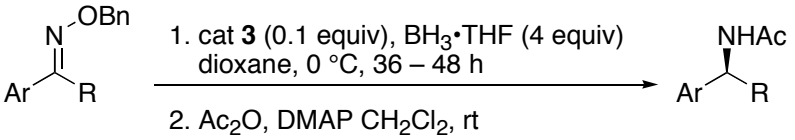
Recently, we reported the reduction of benzyl oxime ethers affording the desired primary amines in good to high yield and excellent enantioselectivities using catalytic amounts (10-30%) of the stable spiroborate ester **3**,[3] which has been previously discovered in our group as a new class of catalysts.[8,9] Optically active pyridine-derived amines have

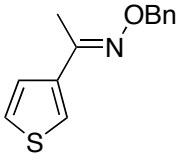
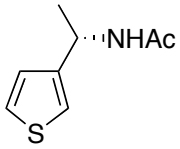
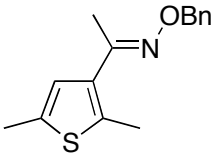
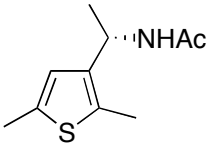
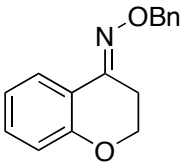
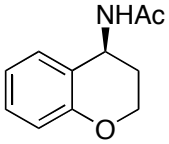
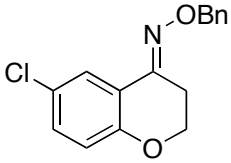
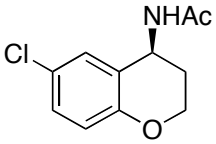
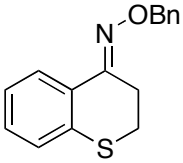
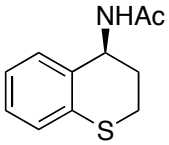
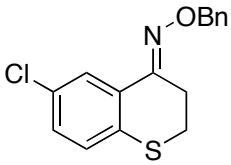
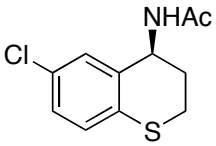
attracted a strong interest, primarily, due to their existence in naturally occurring compounds, such as tobacco alkaloids,[10] or as potential drug candidates.[11] The procedure described here presents the first catalytic asymmetric reduction of *(E)*-1-pyridin-3-yl-ethanone *O*-benzyl-oxime (**2**) to *(S)*-1-pyridin-3-yl-ethylamine (**4**), used as a representative method for the rapid access of primary amines with a high degree of enantiopurity and good yield using a simple and convenient approach. Since the enantiofacial selectivity in the reduction of C=N bonds depends not only on the chirality of the transfer agent but also on the *E*/*Z* isomeric purity,[12] the present procedure affords a high ratio of *E/Z* isomer (>95%) in the crude product, and the *E*- isomer is readily obtained by a simple recrystallization from either water or EtOAc with >99% purity as analyzed by GC/MS and ^{1}H NMR. Pure (*E*)-benzyl oxime ether is obtained in high yield (>95%) from the (*E*)-oxime by the reaction with NaH and benzyl bromide in DMF at –10 °C. In contrast, use of *O*-benzylhydroxylamine to directly access oxime ether **2** in one step from 3-acetylpyridine results in a 4:1 ratio of *E*/*Z* isomers, which are not readily separable by flash chromatography and are not crystalline.

To achieve excellent enantioselectivity and high yield in the spiroborate borane-mediated reduction of benzyl oxime ether **2**, moisture has to be rigorously excluded from the reaction medium and BH_3•THF of high purity is also required. The enantioselectivity of the primary amine is slightly affected by the reaction solvent: in dioxane a 97–99% ee was achieved, while in THF a 95% ee was observed. However, similar chemical yields were afforded after column chromatography (>80%) in both solvents. The amine from the chromatography contained up to 15% ethylene glycol as indicated by NMR analysis. Therefore, the bis-hydrochloride salt **5** was readily prepared with high purity from diethyl ether/methanol in 85–90% yield. The amine bis-hydrochloride salt is very hygroscopic as a solvent-wet solid and has to be handled under nitrogen during isolation, but the dry solid is less hygroscopic and picks up water slowly over several hours when exposed to ambient air. The bis-hydrochloride salt is more stable to decomposition by oxidation and more convenient to handle than the free amine.

An analogous procedure can be applied to other heteroaryl, heterocyclic and pyridyl alkyl *O*-benzyl oxime ethers, and the results are summarized in Tables 2 and 3.

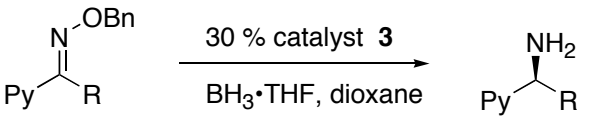
Table 2. Asymmetric Reduction of (*E*)-Heteroaryl and Heterocyclic *O*-Benzyloximes

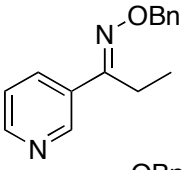
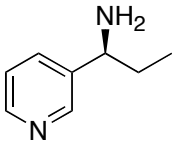
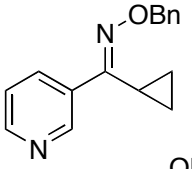
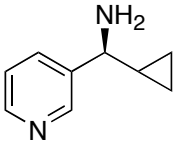
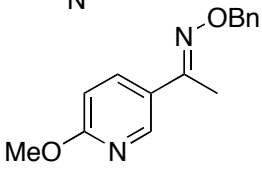
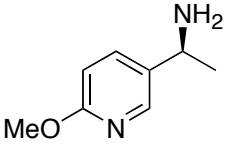
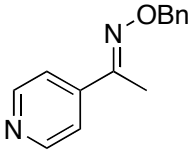
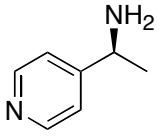
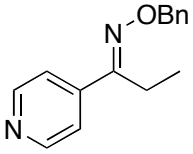
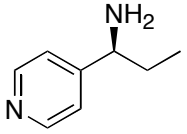
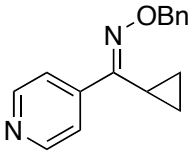
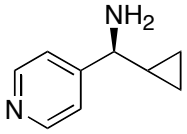
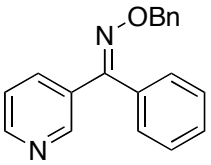
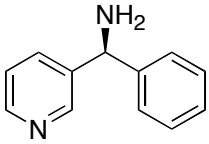
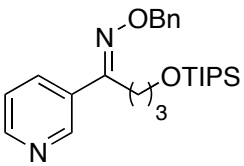
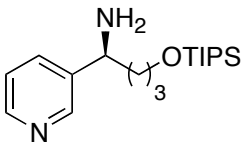


Entry	Benzyl oxime	Acetamide[a]	Yield (%)[b]	ee (%)[c]
1			85	98
2			92	96
3			76	94
4			73	95
5			71	99
6			70	94

[a] The reactions were carried out using 4 equiv of borane stabilized with $NaBH_4$.
[b] Isolated yield of amides purified by column chromatography. [c] Determined by GC of acetyl derivatives on chiral column (CP-Chirasil-DexCB).

Table 3. Preparation of other Chiral Pyridyl Amines via Borane Reduction Catalyzed by Spiroborate Ester **3**



Entry	Benzyl oxime	Amine[a]	Yield (%)[b]	ee (%)[c]
1			89	99
2			83	96[d]
3			88	98
4			84	99
5			85	96
6			91	98
7			82	95
8			95	95[e]

[a] The reactions were carried out using 1 equiv of oxime ether (1 mmol), 0.3 equiv of catalyst **3** and 5 equiv of borane stabilized with $NaBH_4$ in dioxane at 10 °C. [b] Isolated yield based on the acetyl derivative of amines. [c] Determined by GC on a chiral column (CP-Chirasil-Dex-CB). [d] Determined by chiral HPLC (Chiralcel OD-H column). [e] Determined by chiral HPLC (Chiralcel IB column).

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2. The checker would like to thank Tanja Brkovic for development of the chiral HPLC assay of the acetamide derivative of amine **4** described in Note 21.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(–)-(*S*)-1-(1,3,2-Dioxaborolan-2-yloxy)-3-methyl-1,1-diphenylbutan-2-amine; (879981-94-9)

3-Acetyl pyridine; (350-03-8)

Hydroxylamine hydrochloride; (5470-11-1)

Sodium hydride; (7646-69-7)

Benzyl bromide; (100-39-0)

Borane tetrahydrofuran complex solution, 1.0 M in tetrahydrofuran; (14044-65-6)

(*E*)-1-Pyridin-3-yl-ethanone oxime; (106881-77-0)

(*E*)-1-Pyridin-3-yl-ethanone *O*-benzyl-oxime: Ethanone, 1-(3-pyridinyl)-, *O*-(phenylmethyl)oxime, (1*E*)-; (1010079-98-7)

(*S*)-1-Pyridin-3-yl-ethylamine: 3-Pyridinemethanamine, α-methyl-, (α*S*)-**;** (27854-9)

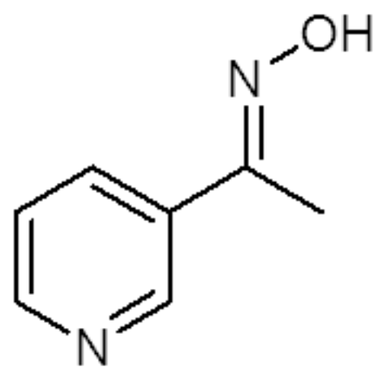
(*S*)-1-Pyridin-3-yl-ethylamine hydrochloride: 3-Pyridinemethanamine, α-methyl-, dihydrochloride, (*S*)-; (40154-84-5)

Margarita Ortiz-Marciales was born in 1943 in Bogotá, Colombia, and obtained her B. S. from "Universidad Nacional de Colombia" in 1968. She studied at Freigburg and Mainz Universities, Germany, for two years with a DAAD fellowship. She received her M. S. from the University of Alabama in Hunstsville under Prof. S. McManus supervision in 1973, and her Ph. D. in Organic Chemistry at the University of Alabama-Tuscaloosa in 1979 under the direction of Prof. Macmanus and Prof. R. Abramovitch. In 1980, she did postdoctoral studies in Prof. G. Larson's group at the University of Puerto Rico-Río Piedras. She joined the University of Puerto Rico- Humacao in 1981, where she is currently a professor. Her interests are in the development of new synthetic methodologies using boron and silicon compounds for the preparation of important organic intermediaries and biological active amino compounds.

Kun Huang received his B.S. degree in 1996 from Sichuan University China. He obtained his Ph. D. in 2006 at Nanjing University, China, working on the asymmetric epoxidation and propanation of chiral sulfonium ylides. Then, he worked as an advanced synthetic researcher in Wuxi Pharma Tech Co., Ltd, Shanghai, China until he moved to Puerto Rico University in Humacao for his postdoctoral studies with Professor Margarita Ortiz-Marciales on the asymmetric reduction of O-benzyl oximes and ketones catalyzed by spiroborate esters. Later, he held a postdoctoral research position at the chemistry department at Oregon State University where his research was focused on the total synthesis of natural products. Currently, he is a postdoctoral researcher at Peking University in China.

2009-39b
2nd crop
crystallized from water
nmr400b c-13

```
Current Data Parameters
NAME           2009-039
EXPNO                 5
PROCNO                1

F2 - Acquisition Parameters
Date_          20090529
Time              18.07
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG           zgdc
TD               65536
SOLVENT          CDCl3
NS               20480
DS                   4
SWH           26315.789 Hz
FIDRES         0.401547 Hz
AQ            1.2452340 sec
RG                8192
DW               19.000 usec
DE                7.00 usec
TE               293.8 K
D1           0.10000000 sec
d11          0.03000000 sec
TD0                 40

======== CHANNEL f1 ========
NUC1               13C
P1                3.30 usec
PL1               6.00 dB
SFO1        100.5584512 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2           100.00 usec
PL2              120.00 dB
PL12              24.00 dB
SFO2        399.8719994 MHz

F2 - Processing parameters
SI                32768
SF          100.5473741 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.40
```

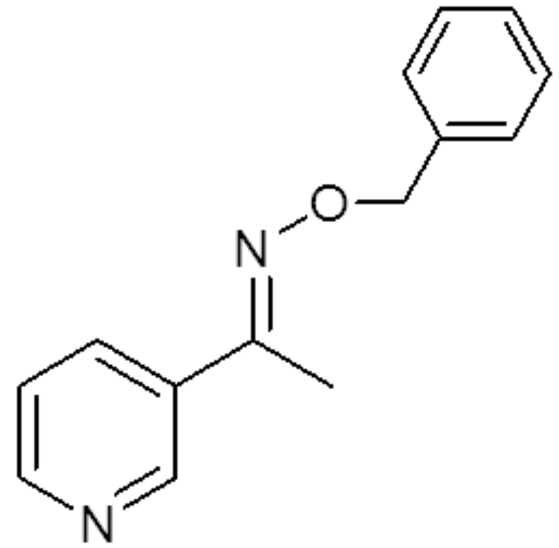


1

2009-053
after vacuum drying
nmr400b c-13

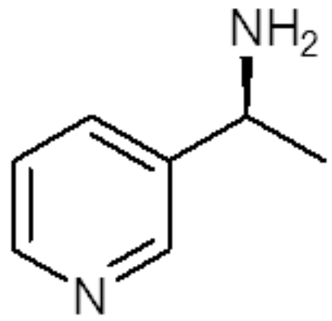
```
Current Data Parameters
NAME           2009-053
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_           20090703
Time               10.38
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG            zgdc
TD                65536
SOLVENT           CDCl3
NS                 1987
DS                    4
SWH           26315.789 Hz
FIDRES         0.401547 Hz
AQ            1.2452340 sec
RG                 8192
DW               19.000 usec
DE                7.00 usec
TE               300.0 K
D1           0.10000000 sec
d11          0.03000000 sec
TD0                  40

======== CHANNEL f1 ========
NUC1                13C
P1                 3.30 usec
PL1                6.00 dB
SFO1        100.5584512 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2            100.00 usec
PL2              120.00 dB
PL12              24.00 dB
SFO2        399.8719994 MHz

F2 - Processing parameters
SI                 32768
SF          100.5473815 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

152.59
150.12
147.63
137.90
133.33
132.38
128.53
128.37
128.03
123.27
77.55
77.24
76.92
76.63
12.61



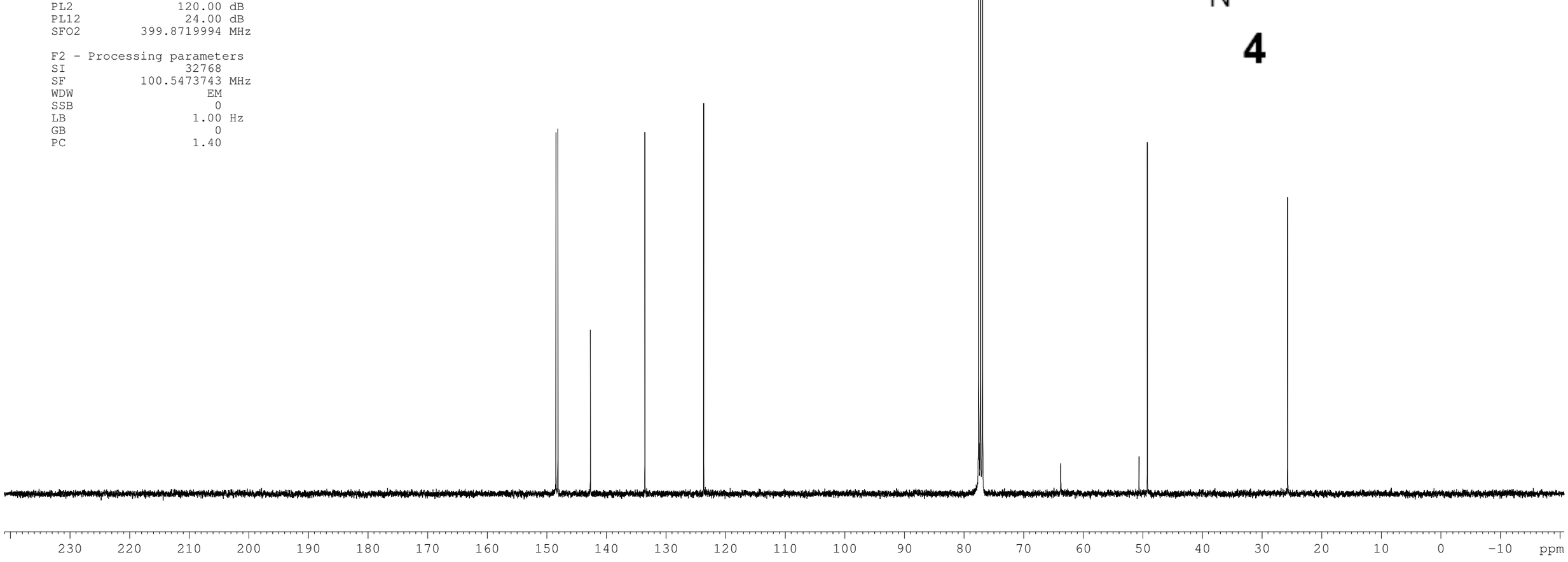
2009-051
fr 7-11
nmr400b c-13

148.50
148.16
142.71
133.57
123.70
77.55
77.43
77.23
76.91
63.78
50.66
49.26
25.71



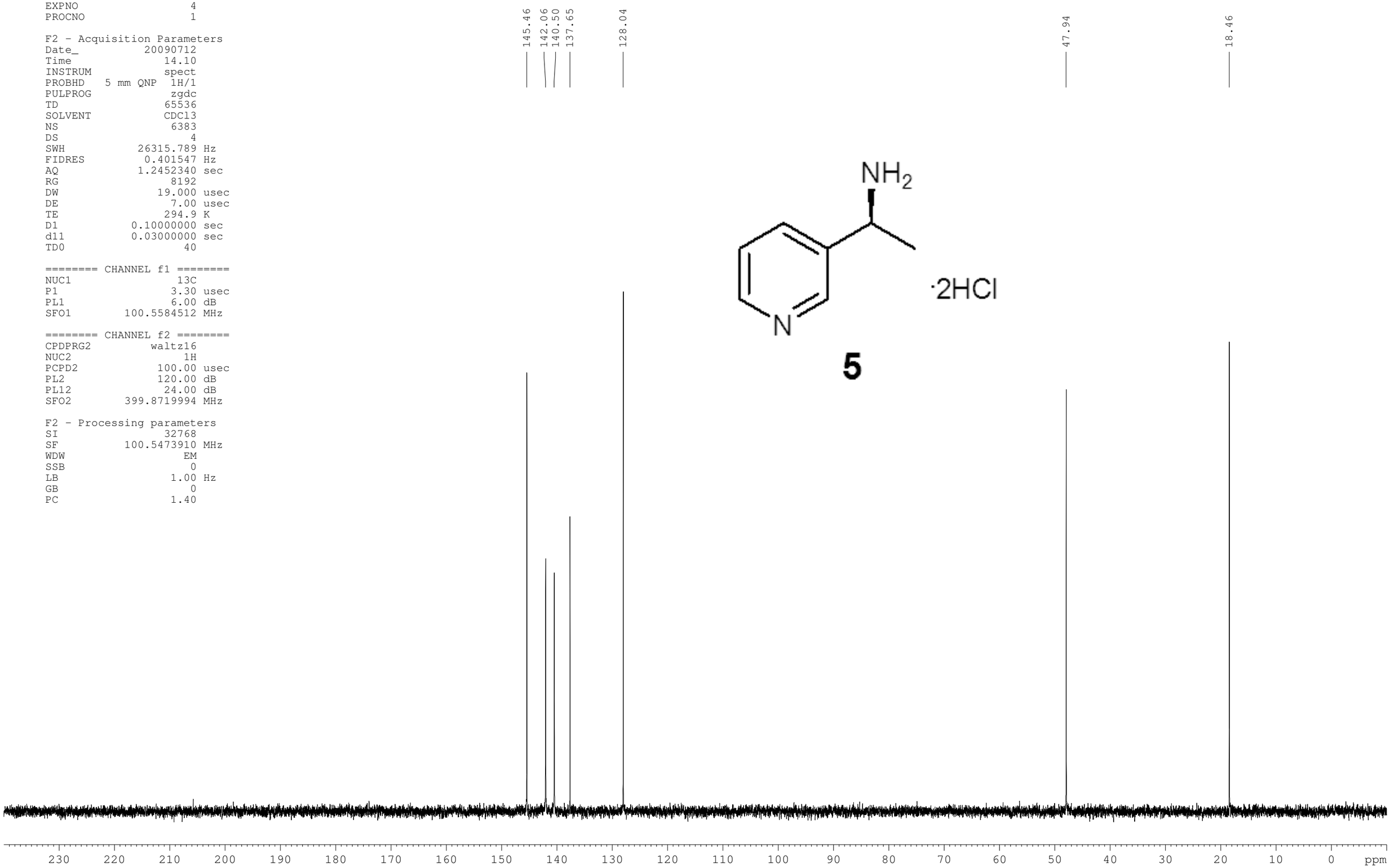
4

```
Current Data Parameters
NAME           2009-051
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20090620
Time              12.15
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG           zgdc
TD               65536
SOLVENT          CDCl3
NS                6701
DS                   4
SWH           26315.789 Hz
FIDRES         0.401547 Hz
AQ            1.2452340 sec
RG                8192
DW               19.000 usec
DE                7.00 usec
TE               300.0 K
D1           0.10000000 sec
d11          0.03000000 sec
TD0                 40

======== CHANNEL f1 ========
NUC1               13C
P1                3.30 usec
PL1               6.00 dB
SFO1        100.5584512 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2           100.00 usec
PL2             120.00 dB
PL12             24.00 dB
SFO2        399.8719994 MHz

F2 - Processing parameters
SI                32768
SF          100.5473743 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.40
```



2009-060
Bis HCl salt
nmr400b c-13

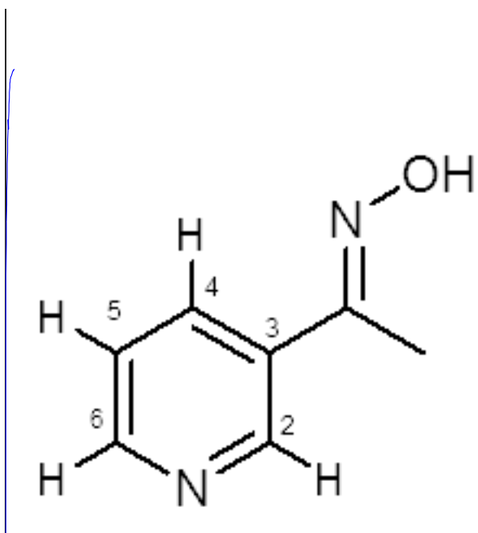
```
Current Data Parameters
NAME           2009-060
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20090712
Time              14.10
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG           zgdc
TD               65536
SOLVENT          CDCl3
NS                6383
DS                   4
SWH           26315.789 Hz
FIDRES         0.401547 Hz
AQ            1.2452340 sec
RG                8192
DW               19.000 usec
DE                7.00 usec
TE               294.9 K
D1           0.10000000 sec
d11          0.03000000 sec
TD0                 40

======== CHANNEL f1 ========
NUC1               13C
P1                3.30 usec
PL1               6.00 dB
SFO1        100.5584512 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2           100.00 usec
PL2              120.00 dB
PL12              24.00 dB
SFO2        399.8719994 MHz

F2 - Processing parameters
SI                32768
SF          100.5473910 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



oxime 2009-038B
crystallized from water
nmr400b h-1

```
Current Data Parameters
NAME            2009-038
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090525
Time               13.07
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    32
DS                     2
SWH             6578.947 Hz
FIDRES          0.200774 Hz
AQ              2.4904180 sec
RG                   256
DW                76.000 usec
DE                 7.00 usec
TE                300.0 K
D1             0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 11.50 usec
PL1                 6.00 dB
SFO1         399.8724694 MHz

F2 - Processing parameters
SI                 16384
SF           399.8700087 MHz
WDW                   no
SSB                    0
LB                 0.00 Hz
GB                     0
PC                  1.00
```

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	10.5096	4202.4738	1.13
2	8.9706	3587.0739	1.76
3	8.9657	3585.1145	1.87
4	8.6223	3447.7992	1.22
5	8.6187	3446.3596	1.32
6	8.6102	3442.9607	1.37
7	8.6066	3441.5212	1.36
8	7.9940	3196.5608	0.78
9	7.9892	3194.6415	1.39
10	7.9845	3192.7621	0.93
11	7.9740	3188.5634	0.91
12	7.9691	3186.6041	1.48
13	7.9644	3184.7247	0.97
14	7.3465	2937.6450	1.13
15	7.3344	2932.8066	1.20
16	7.3265	2929.6476	1.14
17	7.3144	2924.8092	1.11
18	7.2705	2907.2549	1.09
19	2.3159	926.0590	20.00
20	2.3058	922.0203	0.82



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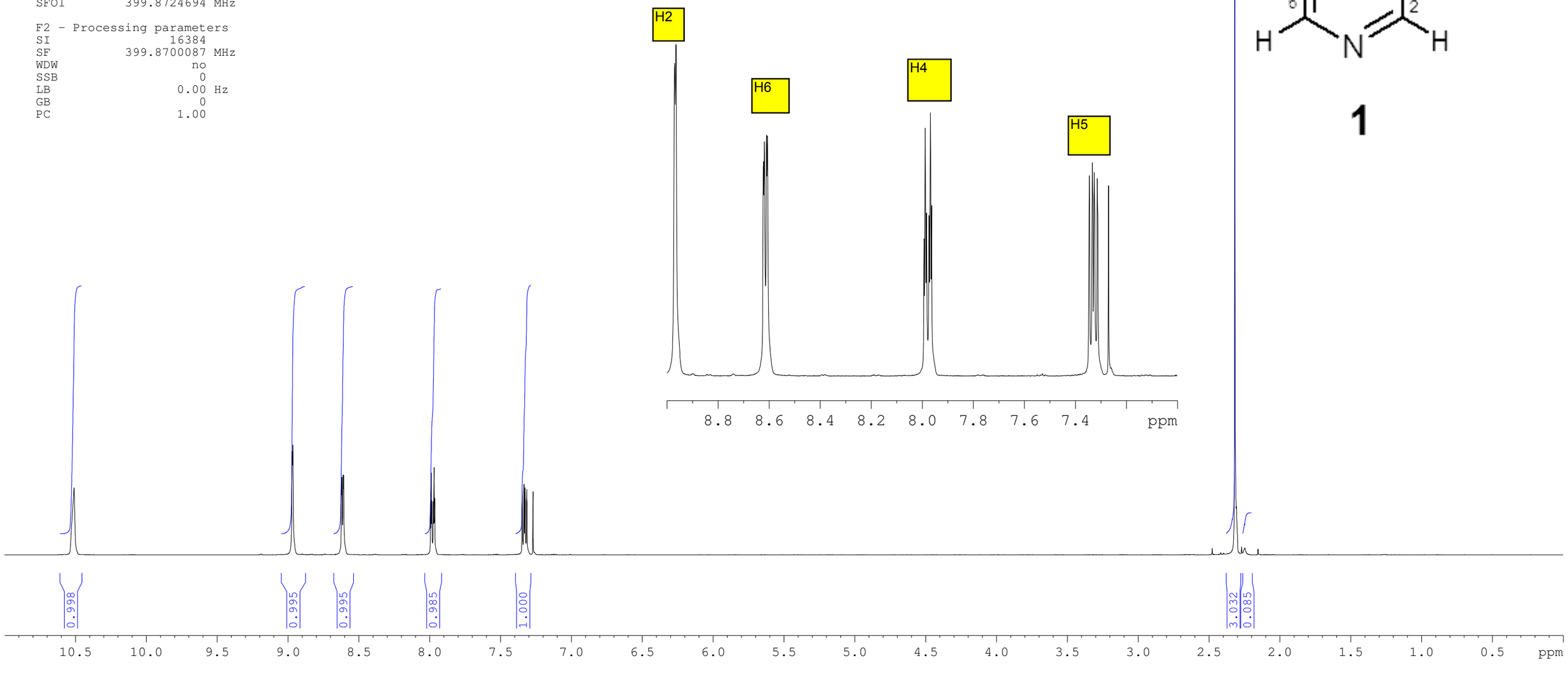


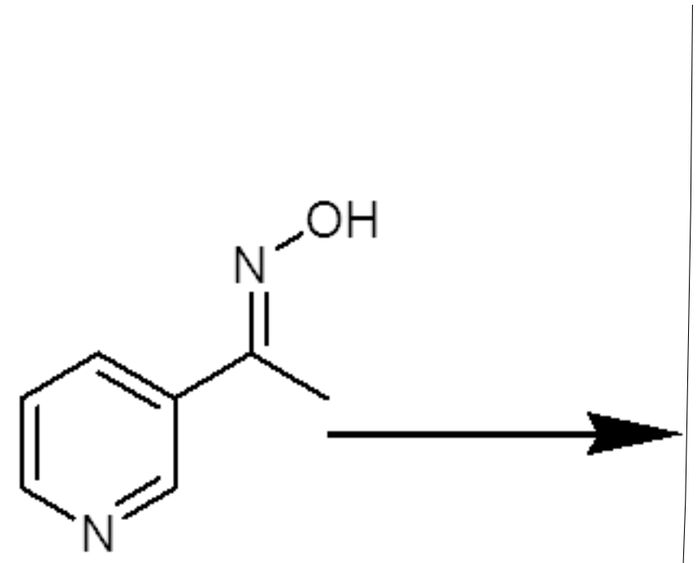
2009-037
oxime crystallized from water
nmr400b h-1

```
Current Data Parameters
NAME           2009-037
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20090525
Time               7.57
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   32
DS                    2
SWH            6578.947 Hz
FIDRES         0.200774 Hz
AQ            2.4904180 sec
RG                228.1
DW               76.000 usec
DE                7.00 usec
TE                300.0 K
D1           0.10000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                  1H
P1                 11.50 usec
PL1                 6.00 dB
SFO1        399.8724694 MHz

F2 - Processing parameters
SI                16384
SF          399.8700000 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```



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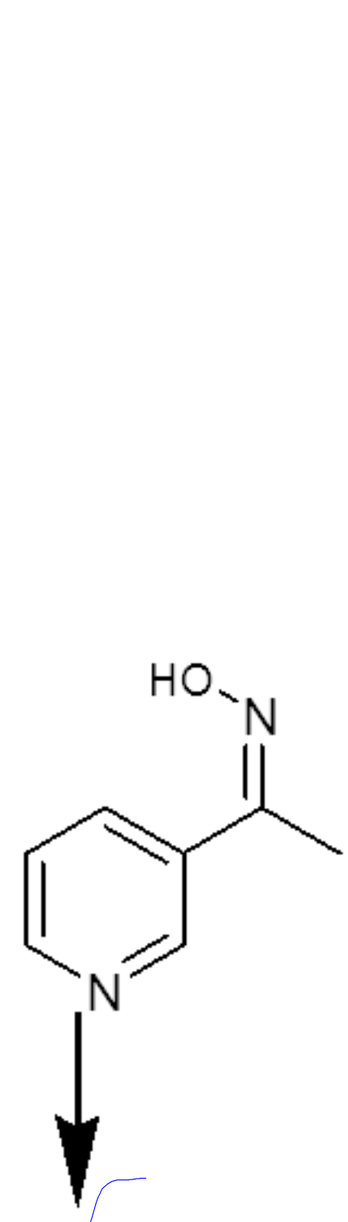
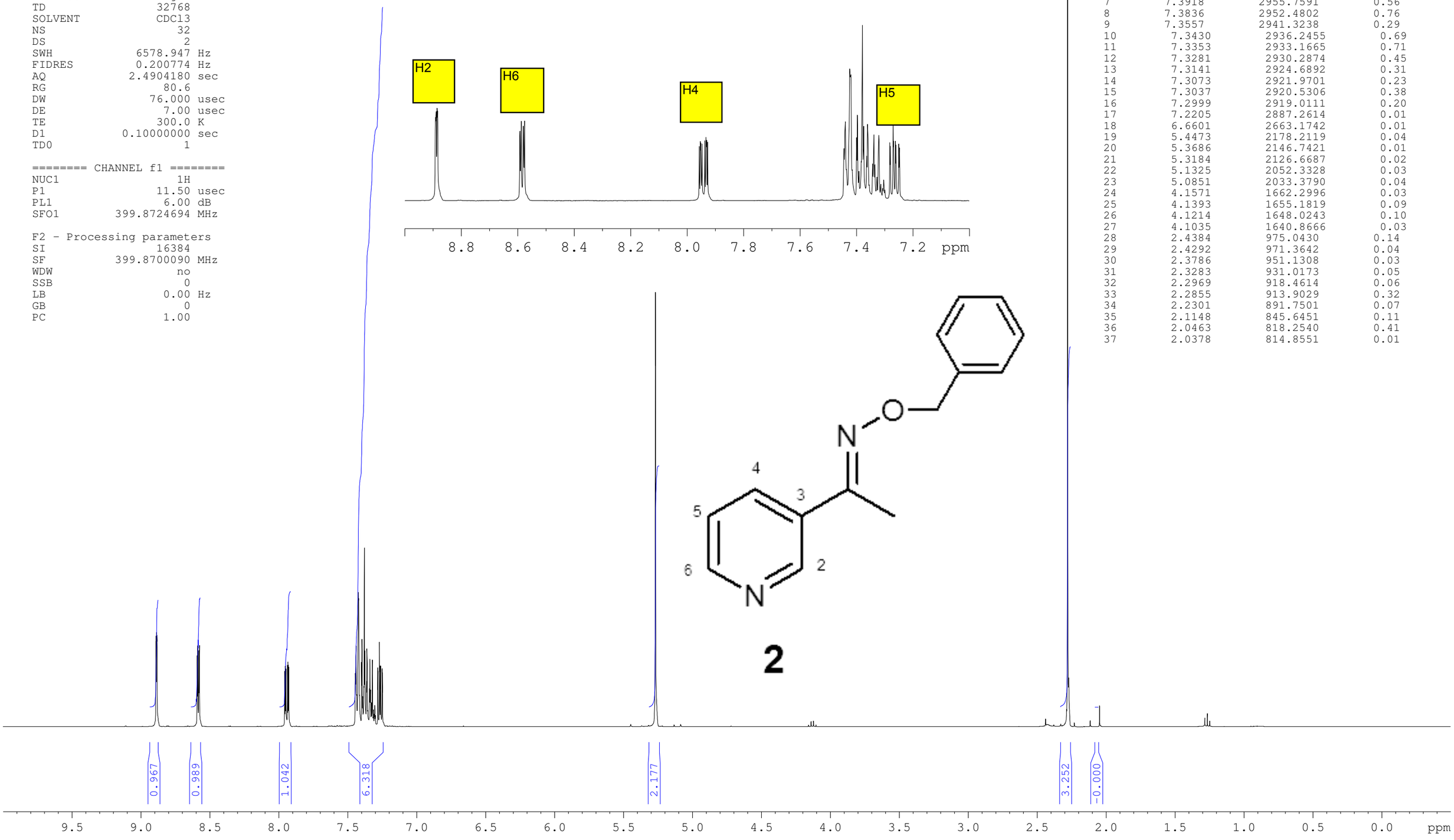


2009-053
after vacuum drying
nmr400b h-1

```
Current Data Parameters
NAME            2009-053
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090703
Time               10.26
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    32
DS                     2
SWH             6578.947 Hz
FIDRES          0.200774 Hz
AQ              2.4904180 sec
RG                  80.6
DW                 76.000 usec
DE                  7.00 usec
TE                 300.0 K
D1            0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 11.50 usec
PL1                 6.00 dB
SFO1         399.8724694 MHz

F2 - Processing parameters
SI                 16384
SF           399.8700090 MHz
WDW                   no
SSB                    0
LB                 0.00 Hz
GB                     0
PC                  1.00
```

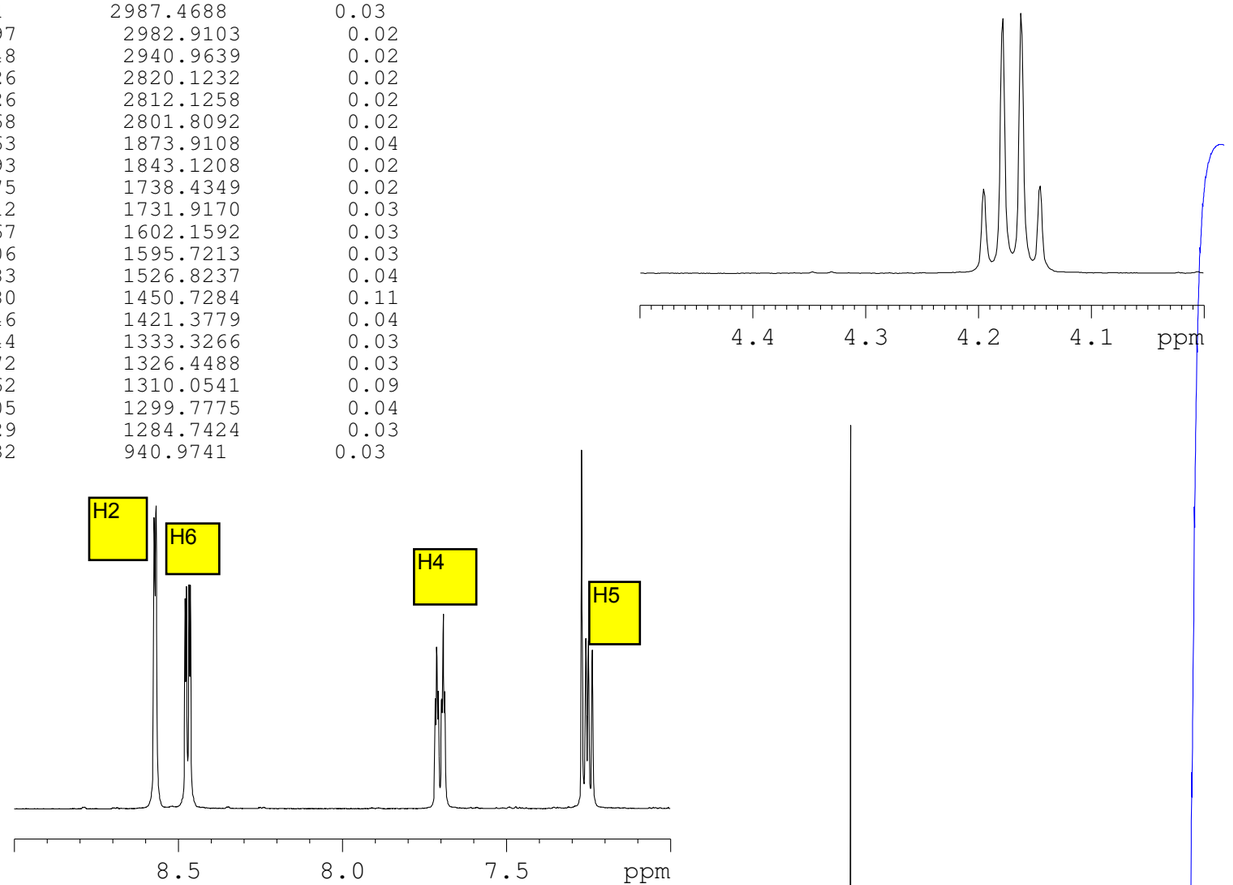
Peak	?(F1) [ppm]	?(F1) [Hz]	Inten
1	7.5768	3029.7351	0.02
2	7.5557	3021.2978	0.01
3	7.5235	3008.4220	0.01
4	7.4713	2987.5488	0.02
5	7.4357	2973.3134	0.59
6	7.4156	2965.2760	0.59
7	7.3918	2955.7591	0.56
8	7.3836	2952.4802	0.76
9	7.3557	2941.3238	0.29
10	7.3430	2936.2455	0.69
11	7.3353	2933.1665	0.71
12	7.3281	2930.2874	0.45
13	7.3141	2924.6892	0.31
14	7.3073	2921.9701	0.23
15	7.3037	2920.5306	0.38
16	7.2999	2919.0111	0.20
17	7.2205	2887.2614	0.01
18	6.6601	2663.1742	0.01
19	5.4473	2178.2119	0.04
20	5.3686	2146.7421	0.01
21	5.3184	2126.6687	0.02
22	5.1325	2052.3328	0.03
23	5.0851	2033.3790	0.04
24	4.1571	1662.2996	0.03
25	4.1393	1655.1819	0.09
26	4.1214	1648.0243	0.10
27	4.1035	1640.8666	0.03
28	2.4384	975.0430	0.14
29	2.4292	971.3642	0.04
30	2.3786	951.1308	0.03
31	2.3283	931.0173	0.05
32	2.2969	918.4614	0.06
33	2.2855	913.9029	0.32
34	2.2301	891.7501	0.07
35	2.1148	845.6451	0.11
36	2.0463	818.2540	0.41
37	2.0378	814.8551	0.01

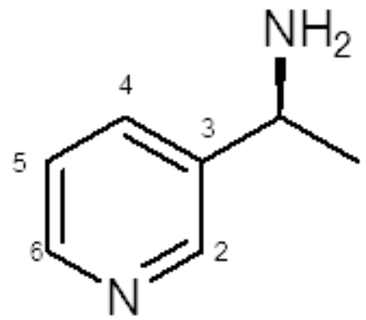


2009-051
fr 7-11
nmr400b h-1

```
Current Data Parameters
NAME            2009-051
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090620
Time               12.08
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    32
DS                     2
SWH             6578.947 Hz
FIDRES          0.200774 Hz
AQ             2.4904180 sec
RG                 287.4
DW                76.000 usec
DE                 7.00 usec
TE                300.0 K
D1            0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 11.50 usec
PL1                 6.00 dB
SFO1         399.8724694 MHz

F2 - Processing parameters
SI                 16384
SF           399.8700085 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	8.7859	3513.2179	0.03
2	8.5177	3405.9728	0.05
3	8.3470	3337.7150	0.03
4	8.2500	3298.9276	0.02
5	8.2380	3294.1291	0.02
6	7.6081	3042.2510	0.02
7	7.5901	3035.0534	0.02
8	7.4908	2995.3463	0.03
9	7.4711	2987.4688	0.03
10	7.4597	2982.9103	0.02
11	7.3548	2940.9639	0.02
12	7.0526	2820.1232	0.02
13	7.0326	2812.1258	0.02
14	7.0068	2801.8092	0.02
15	4.6863	1873.9108	0.04
16	4.6093	1843.1208	0.02
17	4.3475	1738.4349	0.02
18	4.3312	1731.9170	0.03
19	4.0067	1602.1592	0.03
20	3.9906	1595.7213	0.03
21	3.8183	1526.8237	0.04
22	3.6280	1450.7284	0.11
23	3.5546	1421.3779	0.04
24	3.3344	1333.3266	0.03
25	3.3172	1326.4488	0.03
26	3.2762	1310.0541	0.09
27	3.2505	1299.7775	0.04
28	3.2129	1284.7424	0.03
29	2.3532	940.9741	0.03

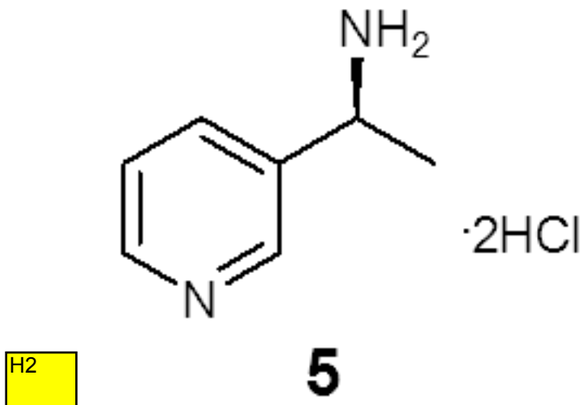




4

2009-060
crystallized bis-HCl salt
nmr500d h-1

```
Current Data Parameters
NAME            2009-060
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090711
Time               13.50
INSTRUM             spect
PROBHD   5 mm PABBI 1H-
PULPROG             zg30
TD                 65536
SOLVENT              D2O
NS                    32
DS                     4
SWH            13020.833 Hz
FIDRES          0.198682 Hz
AQ             2.5166707 sec
RG                  1024
DW                38.400 usec
DE                 6.50 usec
TE                295.0 K
D1            0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  8.60 usec
PL1                -1.00 dB
SFO1         500.3330895 MHz

F2 - Processing parameters
SI                 32768
SF            500.3300000 MHz
WDW                   no
SSB                    0
LB                 0.00 Hz
GB                     0
PC                  1.00
```



5

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity	Annotation
1	8.8716	4438.7276	4.30	
2	8.8689	4437.3767	4.32	
3	8.7846	4395.1989	2.97	
4	8.7731	4389.4451	3.04	
5	8.6728	4339.2620	2.32	
6	8.6563	4331.0066	2.43	
7	8.1023	4053.8238	2.16	
8	8.0905	4047.9199	2.25	
9	8.0859	4045.6183	2.16	
10	8.0742	4039.7645	1.94	
11	4.8148	2408.9889	0.94	
12	4.8009	2402.0343	2.94	
13	4.7870	2395.0797	2.97	
14	4.7730	2388.0751	0.97	
15	4.7003	2351.7011	40.00	
16	1.6693	835.2009	13.28	
17	1.6553	828.1962	13.15