4,7-Dimethoxy-1,10-Phenanthroline: An Excellent Ligand for the Cu-Catalyzed *N*-Arylation of Imidazoles

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Supporting Information

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General Considerations.

All reactions were carried out in resealable test tubes with teflon septa and run under a dry argon or nitrogen atmosphere. Copper (I) oxide (97%) was purchased from Aldrich company as a red powder. Anhydrous Cs_2CO_3 (99.9%) was purchased from Alfa Aesar; the bulk of the material was stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (~5 g) were removed from the glovebox in glass vials, stored in the air in a desiccator filled with anhydrous calcium sulfate, and weighed in the air. Poly(ethylene glycol) (M_n 3,400) was purchased from Aldrich. Generally, aryl halides and imidazoles were purchased from commercial sources and used without further purification. When necessary, aryl halides were filtered through neutral alumina, or distilled. Butyronitrile (≥ 99 %) was purchased from Aldrich and used without further purification. Anhydrous solvents were purchased from Aldrich in Sure-Seal ® bottles. Flash column chromatography was performed with EM Science silica gel 60 (230-400 mesh). In all cases, dichloromethane was used to transfer the crude reaction material onto a silica gel column. A gradient elution technique was used for column chromatography, beginning with hexane and continuing to the specified concentration of ethyl acetate in hexane.

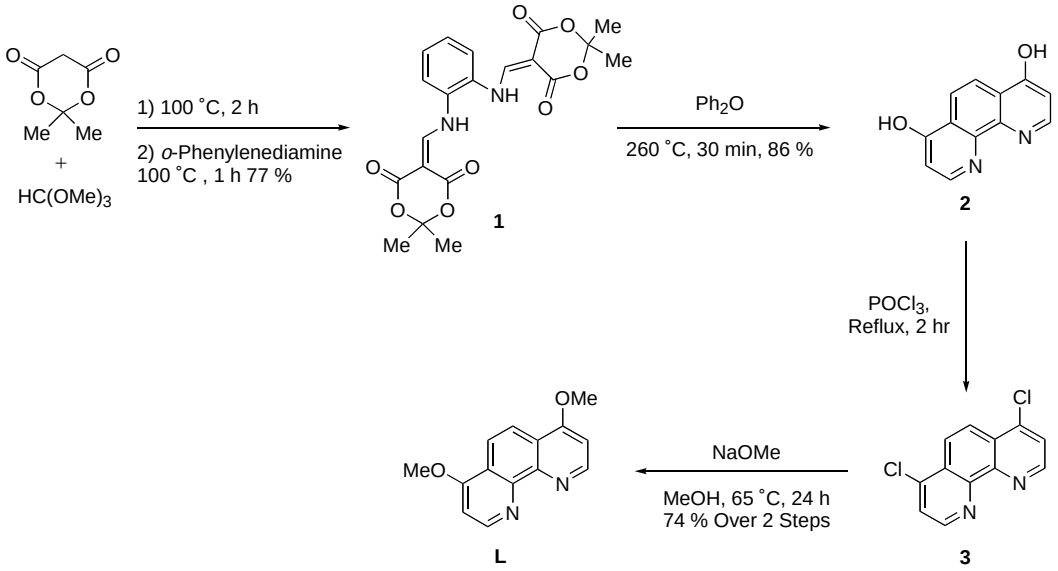
Yields reported in the publication are isolated (except where noted) and represent an average of at least two independent runs. Yields reported in the supporting information refer to a single experiment. Compounds described in the literature were characterized by comparing their ^{1}H NMR, and melting point (m.p.) to the previously reported data; their purity was confirmed by gas chromatographic analyses (GC). For known compounds prepared using the new method (conditions) described, a copy of the ^{1}H NMR spectrum, of each, is included. GC analyses were

performed on a Hewlett Packard 6890 instrument with an FID detector and a Hewlett Packard 10 m x 0.2 mm i.d. HP-1 capillary column using dodecane as an internal standard. Previously unknown compounds were synthesized, purified and analyzed from a single run and were then repeated to determine an average yield. They were characterized by ^{1}H NMR, ^{13}C NMR, m.p., and elemental analysis. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. For those compounds that did not give a satisfactory elemental analysis, a copy of their ^{1}H NMR spectrum is included. ^{1}H NMR and ^{13}C NMR were recorded on Varian 300 MHz and 500 MHz instruments with chemical shifts reported relative to the deuterated solvent or TMS. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR instrument for all previously unknown compounds (KBr disc). Melting points (uncorrected) were obtained on a Mel-Temp II capillary melting point apparatus.

Synthesis of 4,7-dimethoxy-1,10-phenanthroline (L).

The synthesis of **L** was adapted from literature precedent.[1] A larger scale preparation of **L** can be preformed as follows. Alternatively, **2** can be purchased in gram quantities from commercial sources.

Scheme 1. Synthesis of 4,7-Dimethoxy-1,10-Phenanthroline



1,2-Bis-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)amino]benzene (1).

An oven-dried 2 L 2-neck flask equipped with a mechanical stirrer was charged with trimethyl orthoformate (850 mL, 7.8 mol) and Meldrum's acid (101 g, 0.700 mmol). The flask was fitted with a reflux condenser; the contents were flushed with N_2 and brought to a gentle reflux for 2 h. The resulting red solution was cooled (~ 80 ˚C) and phenylene diamine (32.4 g, 300 mmol) was added portionwise (*exothermic reaction*) resulting in the formation of a yellow solid. The mixture was heated to reflux, stirred vigorously for an additional hour and then cooled to room temperature. The resulting solid was filtered, washed with cold acetone (slightly soluble) and dried to afforded 95 g (77%) of product as a flaky light-yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.34 (br d, 2H), 8.50 (d, 2H), 7.41 (m, 4H, all ArH), 1.74 (s, 12H, Me). m.p. 208-210, decomp. (Lit. 209, decomp.).[3a]

4,7-Dihydroxy-1,10-phenanthroline (2). A 5 L 3-neck flask equipped with a mechanical stirrer and a *large air-cooled* reflux condensor was charged with 3 L of diphenyl ether and was heated to 240 ˚C using a heating mantle. During the addition of **1**, the flask was open to atmospheric

pressure under a stream of N_2. Precursor **1** was added in small portions resulting in vigorous gas evolution (***Caution***). When the addition was complete, the mixture was brought to reflux (260 ˚C) for 30 min. The mixture was allowed to cool to 80 ˚C, and the precipitate was isolated by vacuum filtration and washed with acetone until the filtrate was colorless. The product was further washed with excess hexane and diethyl ether. Drying by vacuum filtration, then under hi-vac at 60 ˚C, afforded 41.5 g (86%) of a fine dark-brown powder. Although the title compound was essentially insoluble in common NMR solvents, a spectrum could be obtained using NaOH in D_2O. ^{1}H NMR (D_2O, NaOH, 400 MHz) δ 8.17 (d, 2H, *J* = 5.6 Hz), 7.75 (s, 2H), 6.43 (d, 2H *J* = 5.6 Hz). Anal Calc. for $C_{12}H_8N_2$: C 67.92, H 3.80. Found: C 67.60, H 3.59. m.p. stable up to 250 ˚C (Lit. 471-474, decomp.).[2]

4,7-Dichloro-1,10-phenanthroline (3). A 1 L 2-neck round bottom flask equipped with a stir bar, reflux condenser, and distillation apparatus was flame-dried and allowed to cool under an atmosphere of N_2. Phosphorous oxychloride (400 mL) and **2** (20.0 g, 94.3 mmol) were added to the flask under a N_2 purge. The apparatus was immersed in an oil bath and heated at reflux for 2 h (the condenser for the distillation apparatus was not filled with water at this time). After this period, the circulation of water for the distillation apparatus was turned on and roughly half of the excess phosphorous oxychloride was removed by gentle vacuum distillation. The solution was cooled to room temperature and crushed ice was slowly added to the reaction mixture (***Caution:*** *very exothermic!*) while keeping the temperature between 10 and 30 ˚C with an ice bath. When HCl gas evolution ceased, the acidic solution was stirred for one hour at room temperature to dissolve the black solids that formed. The resulting dark cloudy solution was filtered through activated charcoal (Darco®) to give a translucent-beige solution, which was

brought to pH 13 by the slow addition of 20% KOH solution while maintaining the temperature below 25 ºC. The white precipitate that formed was collected by suction filtration, washed with excess H_2O, and dried under vacuum overnight at 60 ºC affording **3** as a white solid. The product was used in the subsequent step without further purification. ^{1}H NMR (DMSO, 400 MHz) δ 9.09 (d, 2H, *J* = 4.8 Hz), 8.41 (s, 2H), 8.08 (d, 2H, *J* = 4.8 Hz). m.p. 245-247 (Lit. 249-250).[3c]

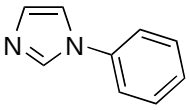
4,7-Dimethoxy-1,10-phenanthroline (L). An oven-dried 3-neck round bottom flask was cooled under a stream of nitrogen. Anhydrous methanol (1.2 L) was added, and purged with N_2 for 10 min. Sodium metal (9.20 g, 400 mmol) was slowly added in small pieces while the solution was stirred. A reflux condenser was attached, and **3** (all that was produced in the previous step) was added. The flask was heated to reflux for 24 hours under an atmosphere of N_2. Concentration of the resulting solution to ~30 mL and addition of cold water (250 mL) resulted in the precipitation of a tan solid. The flask was stored overnight in a refrigerator to allow complete precipitation of the solid. The product was collected by filtration, washed with excess water, and dried under vacuum overnight at 60 ºC affording 16.7 g (74 % over 2 steps) of a tan solid, which can be recrystallized from benzene. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.93 (d, 2H, *J* = 5.3 Hz), 8.18 (s, 2H), 7.03 (d, 2H, *J* = 5.3 Hz), 4.09 (s, 6H). m.p. 210-212 (Lit. 209-210).[3e]

General procedure for the *N*-arylation of imidazoles with aryl iodides.

An oven-dried screw-cap test tube was charged with Cu_2O (0.025 mmol), **L** (0.075 mmol), imidazole (1.2 mmol), aryl iodide (1.00 mmol, if solid), poly(ethylene glycol) (200 mg), Cs_2CO_3 (1.4 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon or nitrogen, and this sequence was repeated an

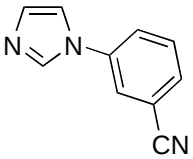
additional time. Aryl iodide (1.00 mmol, if liquid) and solvent (0.5 mL) were then added successively. The reaction tube was sealed, and stirred in a pre-heated oil bath for the designated time period. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and filtered through a plug of celite, eluting with additional dichloromethane (50 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography to provide the desired product.

Experimental procedures for the *N*-arylation of imidazole with aryl iodides.



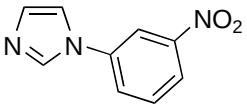
1-Phenyl-1*H*-imidazole

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), iodobenzene (112 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol), with NMP (0.5 mL) as solvent for 3 h at 110 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 3) afforded 1-phenyl-1*H*-imidazole (slightly yellow oil, 131 mg, 92 %). The low catalyst loading experiment was preformed using the general procedure with Cu_2O (0.4 mg, 0.0025 mmol), **L** (1.8 mg, 0.0075 mmol), PEG (2.0 g), Cs_2CO_3 (4.50 g, 14 mmol), iodobenzene (1.12 mL, 10 mmol), and imidazole (820 mg, 12 mmol), in butyronitrile (2.0 mL) as solvent for 48 h at 110 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 3) provided 1-phenyl-1*H*-imidazole (slightly yellow oil, 1.34 g, 93 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.47-7.41 (m, 2H), 7.36-7.29 (m, 3H), 7.25 (bs, 1H), 7.18 (bs, 1H).[3] A copy of the ^{1}H NMR spectrum is provided.



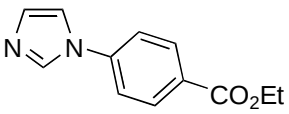
3-Imidazol-1-yl-benzonitrile

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 3-iodobenzonitrile (229 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol), with butyronitrile (0.5 mL) as solvent for 24 h at 90 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 3) 3-imidazol-1-yl-benzonitrile (white needles, 158 mg, 94 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.71-7.60 (m, 4H), 7.30 (bs, 1H), 7.25 (bs, 1H). m.p. 151-154 ˚C (Lit. 156-157 ˚C).[4] A copy of the ^{1}H NMR spectrum is provided.



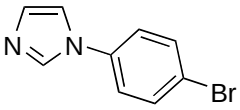
1-(3-Nitro-phenyl)-1*H*-imidazole

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 3-nitroiodobenzene (249 mg, 1.00 mmol), and imidazole (83 mg, 1.2 mmol) with acetonitrile (0.5 mL) as solvent for 29 h at 80 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 3) 1-(3-nitro-phenyl)-1*H*-imidazole (white solid, 177 mg, 93 %). ^{1}H NMR (500 MHz, CDCl3) δ 8.25 (t, 1H, *J* = 1.9), 8.19 (ddd, 1H, *J* = 1.1, 1.9, 7.9 Hz), 7.94 (s, 1H), 7.75 (ddd, 1H, *J* = 1.4, 2.2, 8.1 Hz), 7.69 (t, 1H, *J* = 8.0 Hz), 7.36 (s, 1H), 7.23 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 138.3, 125.5, 131.5, 131.2, 126.9, 122.1, 118.0, 116.2. m.p. 109-110 ˚C (Lit. 109-110 ˚C).[5] A copy of the ^{1}H NMR spectrum is provided.



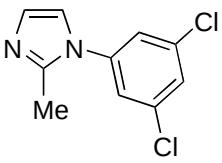
4-Imidazol-1-yl-benzoic acid ethyl ester

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), ethyl-4-iodobenzoate (168 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol), 3 Å molecular sieves (200 mg, powdered, flame activated) with acetonitrile (0.5 mL) as solvent for 23 h at 80 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 3) 4-imidazol-1-yl-benzoic acid ethyl ester (white crystals, 184 mg, 84 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (td, 2H, *J* = 1.8, 8.5 Hz), 7.96 (s, 1H), 7.48 (td, 2H, *J* = 1.8, 8.8), 7.37 (s, 1H), 7.26 (s, 1H), 4.43 (q, 2H, *J* = 7.1 Hz), 1.44 (t, 3H, *J* = 7.0 Hz). m.p. 101-103 ˚C (Lit. 100-102 ˚C).[6] A copy of the ^{1}H NMR spectrum is provided.



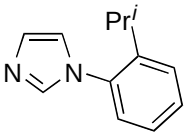
1-(4-Bromo-phenyl)-1*H*-imidazole[7]

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1-bromo-4-iodobenzene (340 mg, 1.20 mmol), and imidazole (68 mg, 1.0 mmol) with butyronitrile (0.5 mL) as solvent for 24 h at 90 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided 1-(4-bromo-phenyl)-1*H*-imidazole (white crystals, 171 mg, 78 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (bs, 1H), 7.63 (m, 2H), 7.32-7.20 (m, 4H). m.p. 120-122 ˚C. GC/MS of the crude material showed an 6.1 : 1 mixture of 1-(4-bromo-phenyl)-1*H*-imidazole to 1-(4-iodo-phenyl)-1*H*-imidazole. A copy of the ^{1}H NMR spectrum is provided.



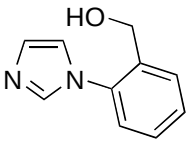
1-(3,5-Dichloro-phenyl)-2-methyl-1*H*-imidazole

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1,3-dichloro-5-iodobenzene (273 mg, 1.00 mmol), 2-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (0.5 mL) as solvent for 24 h at 110 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 3) provided 1-(3,5-dichloro-phenyl)-2-methyl-1*H*-imidazole (white needles, 194 mg, 86 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, 1H, *J* = 1.8), 7.23 (d, 2H, *J* = 1.9), 7.05 (d, 1H, *J* = 1.2), 6.99, (d, 1H, *J* = 1.2), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 135.8, 128.5, 128.4, 124.1, 14.0. IR (KBr disc, cm^{-1}) 1534, 1501, 1463, 1451, 1405, 1305, 1176, 1143, 1115, 1099, 985, 850, 781. Anal. Calc. for $C_{10}H_8N_2Cl_2$: C 52.89, H 3.55. Found: C 52.95, H 3.44. m.p. 122-125 ˚C.



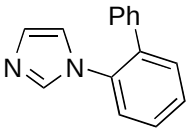
1-(2-Isopropyl-phenyl)-1*H*-imidazole

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-isopropyl iodobenzene (246 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.5 mL) as solvent for 48 h at 110 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided 1-(2-isopropyl-phenyl)-1*H*-imidazole (white crystals, 171 mg, 92 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (bs, 1H), 7.46-7.42 (m, 2H), 7.31-7.11 (m, 3H), 7.05 (m, bs), 2.74 (heptet, 1H, *J* = 6.9 Hz), 1.16 (d, 6H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 135.1, 129.4, 129.2, 127.0, 126.7, 126.4, 121.1, 27.4, 24.0. m.p. 76-77 ˚C (Lit. 67-68 ˚C).[8] Anal. Calc. for $C_{12}H_{14}N_2$: C 77.38, H 7.58. Found: C 77.42, H 7.78. A copy of the ^{1}H NMR spectrum is provided.



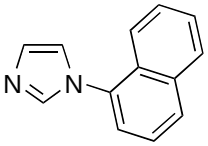
(2-Imidazol-1-yl-phenyl)-methanol

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodobenzylalcohol (234 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 24 h at 110 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided (2-imidazol-1-yl-phenyl)-methanol (clear crystals, 165 mg, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, 2H, *J* = 1.7, 7.6 Hz), 7.45 (td, 1H, *J* = 1.4, 7.5 Hz), 7.38 (td, 1H, *J* = 1.4, 7.4 Hz), 7.23 (dd, 1H, *J* = 1.1, 7.7 Hz), 7.13 (s, 1H), 7.08 (s, 1H), 4.90 (bs, 1H), 4.46 (s, 1H). m.p. 102-104 ˚C (Lit. 100.5-102.5 ˚C).[9] A copy of the ^{1}H NMR spectrum is provided.



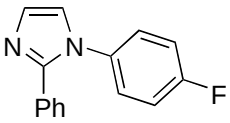
1-Biphenyl-2-yl-1*H*-imidazole

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodobiphenyl (176 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.6 mL) as solvent for 72 h at 120 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided 1-biphenyl-2-yl-1*H*-imidazole (slighly yellow crystals, 179 mg, 81 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.33 (m, 5H), 7.30-7.24 (m, 3H), 7.02 (bs, 1H), 6.82 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 137.5, 135.2, 131.5, 128.7, 128.7, 128.6, 128.3, 127.8, 126.3. Anal. Calc. for $C_{15}H_{12}N_2$: C 81.79, H 5.49. Found: C 81.50, H 5.46. m.p. 93-95 ˚C.



1-Naphthalen-1-yl-1*H*-imidazole

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1-iodonaphthalene (146 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with NMP (0.3 mL) as solvent for 24 h at 110 ˚C. The crude reaction mixture was dissolved in 20 mL of water, and extracted with dichloromethane (5 x 30 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was removed *in vacuo*. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided 1-naphthalen-1-yl-1*H*-imidazole (yellow-white solid, 179 mg, 92 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.76, (bs, 1H), 7.61-7.48 (m, 4 H), 7.43 (d, 1H, *J* = 7.0 Hz), 7.30 (bs, 1H), 7.25 (bs, 1H). m.p. 63-64 ˚C (Lit. 62 ˚C).[10] A copy of the ^{1}H NMR spectrum is provided.



1-(4-Fluoro-phenyl)-2-phenyl-1*H*-imidazole

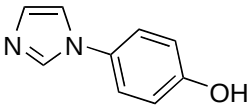
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-fluoroiodobenzene (222 mg, 1.00 mmol), 2-phenylimidazole (173 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 24 h at 110 ˚C. Chromatographic purification (hexane / ethyl acetate 3 : 1) provided 1-(4-fluoro-phenyl)-2-phenyl-1*H*-imidazole (white solid, 211 mg, 89 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 2H), 7.24-7.16 (m, 4H), 7.15-7.09 (m, 2H), 7.06 (s, 1H), 7.03-6.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 160.2, 134.5, 129.0, 128.5, 128.4, 128.2, 127.6, 127.5, 116.5, 116.2. IR (KBr disc, cm^{-1}) 1509, 1501, 1466, 1414, 1303, 1285, 1233, 1212, 1151, 1128, 1091, 1068, 970, 915, 840, 775,

747, 715, 697. Anal. Calc. for $C_{15}H_{11}N_2F$: C 75.62, H 4.65. Found: C 75.39, H 4.62. m.p. 111-114 ˚C.

General procedure for the *N*-arylation of imidazoles with aryl bromides.

An oven-dried screw-cap test tube was charged with Cu_2O (0.05 mmol), **L** (0.15 mmol), imidazole (1.2 mmol), aryl bromide (1.00 mmol, if solid), poly(ethylene glycol) (200 mg), Cs_2CO_3 (1.4 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon or nitrogen, and this sequence was repeated an additional time. Aryl bromide (1.00 mmol, if liquid), and solvent (0.5 mL) were then added successively. The reaction tube was sealed, immersed, and stirred in a preheated oil bath for the designated time period. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), filtered through a plug of celite, and eluted with additional dichloromethane (50 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography to provide the desired product.

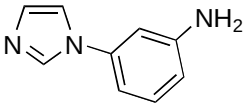
Experimental procedures for the *N*-arylation of imidazole with aryl bromides.



4-Imidazol-1-yl-phenol

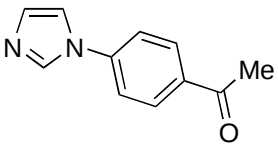
The general procedure was followed using Cu_2O (7.2 mg, 0. 05 mmol), **L** (36 mg, 0.15 mmol), PEG (400 mg), Cs_2CO_3 (1.0 g, 3.0 mmol), 4-bromophenol (172 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.5 mL) as solvent for 15 h at 110 ˚C. After cooling to ambient temperature, the crude reaction mixture was dissolved in 20 mL 2M $HCl_{(aq)}$, and washed once with diethyl ether. The aqueous layer was brought to pH 8 with Na_2CO_3, and extracted repeatedly with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated.

Chromatographic purification (1 % ethanol in ethyl acetate, dry pack) afforded 4-imidazol-1-yl-phenol (white crystals, 198 mg, 90 %). ^{1}H NMR (300 MHz, CD_3OD) δ 7.95 (bs, 1H), 7.41 (bs, 1H), 7.35-7.30 (m, 2H), 7.01 (bs, 1H), 6.92-6.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 130.8, 129.8, 124.3, 117.4, 24.0. m.p. 196-198 ˚C (Lit. 188-190˚C [203-205 ˚C MeOH, H_2O]).[11] A copy of the ^{1}H NMR spectrum is provided.



3-Imidazol-1-yl-phenylamine

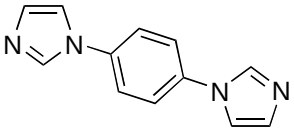
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 3-bromoaniline (109 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.25 mL) as solvent for 20 h at 110 ˚C. Chromatographic purification (ethyl acetate) afforded 3-imidazol-1-yl-phenylamine (white powder, 141 mg, 88 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (bs, 1H), 7.21-7.15 (m, 3H), 6.72-6.68 (m, 1H), 6.64-6.60 (m, 2H). 4.01 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.4, 135.6, 130.7, 130.1, 118.4, 114.0, 111.1, 107.7. m.p. 112-114 ˚C (Lit. 111-113 ˚C).[12] A copy of the ^{1}H NMR spectrum is provided.



1-(4-Imidazol-1-yl-phenyl)-ethanone

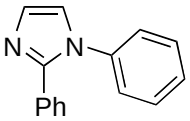
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-bromoacetophenone (199 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.4 mL) as solvent for 48 h at 110 ˚C. Chromatographic

purification (hexane / ethyl acetate 1 : 3) afforded 1-(4-imidazol-1-yl-phenyl)-ethanone (white solid, 159 mg, 86 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04, (m, 2H), 7.92 (bs, 1H), 7.46 (m, 2H), 7.33 (bs, 1H), 7.19 (bs, 1H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 140.7, 135.7, 135.4, 131.2, 130.4, 120.7, 117.8, 26.7. m.p. 112-114 ˚C (Lit. 110-112 ˚C).[13] A copy of the ^{1}H NMR spectrum is provided.



1,4-*bis*(Imidazol-1-yl)-benzene[14]

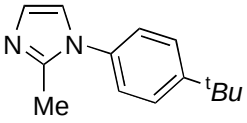
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L** (36 mg, 0.15 mmol), Cs_2CO_3 (0.90 g, 2.8 mmol), 1,4-dibromobenzene (236 mg, 1.00 mmol), and imidazole (164 mg, 2.4 mmol) with NMP (0.5 mL) as solvent for 30 h at 110 ˚C. The crude reaction mixture was diluted in excess CH_2Cl_2, and filtered through a celite plug. After removal of the solvent *in vacuo*, the product was crystallized from EtOAc and stored in a freezer overnight, to afford 1,4-*bis*(imidazol-1-yl)-benzene (white solid, 200 mg, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (bs, 2H), 7.54 (s, 4H), 7.32 (bs, 1H), 7.26 (bs, 1H). m.p. 190 ˚C (decomp.). IR (KBr disc, cm^{-1}) 1534, 1485, 1304, 1248, 1105, 1059. Anal Calc. for $C_{12}H_{10}N_4$: C 68.56, H 4.79. Found C 68.49, H 4.90.



1,2-Diphenyl-1*H*-imidazole

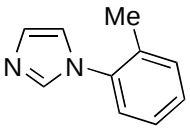
The general procedure was followed using Cu_2O (14.4 mg, 0.10 mmol), **L** (72 mg, 0.30 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-t-butylbromobenzene (173 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.6 mL) as solvent for 72 h at 120 ˚C.

Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1,2-diphenyl-1*H*-imidazole (white crystals, 198 mg, 90 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.32 (m, 5H), 7.28-7.16 (m, 6H), 7.14 (d, 1H, *J* = 1.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 130.4, 129.5, 129.1, 128.6, 128.4, 128.2, 128.2, 125.9, 123.0. m.p. 88-89 ˚C (Lit. 90 ˚C).[15] A copy of the ^{1}H NMR spectrum is provided.



1-(4-*tert*-Butyl-phenyl)-2-methyl-1*H*-imidazole

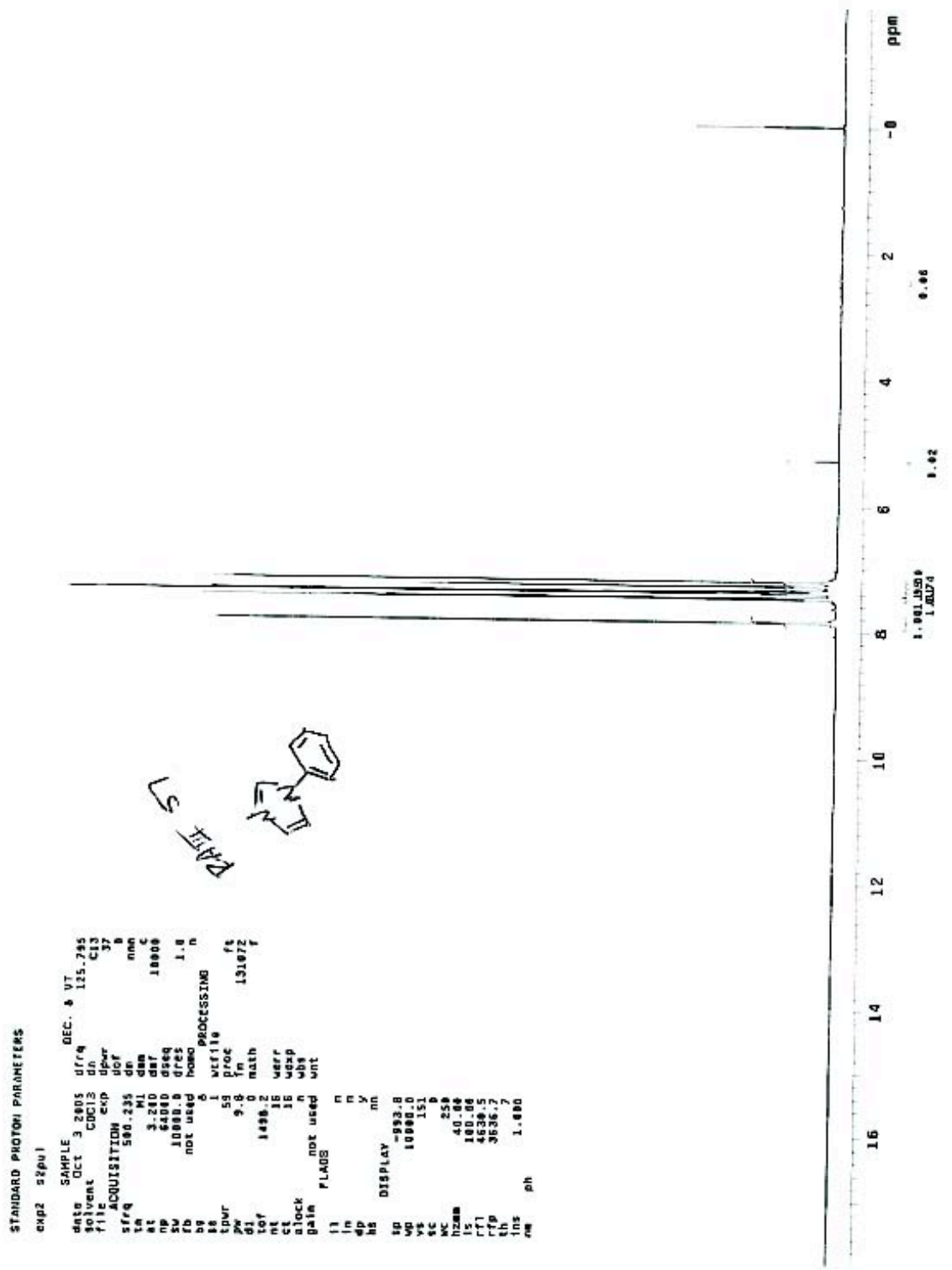
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-t-butylbromobenzene (173 μL, 1.00 mmol), 2-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (0.25 mL) as solvent for 48 h at 110 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 3) afforded 1-(4-*tert*-butyl-phenyl)-2-methyl-1*H*-imidazole (yellow oil, 207 mg, 97 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.12 (m, 1H), 6.94 (bs, 1H), 6.91 (bs, 1H), 2.28 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 135.3, 127.5, 126.3, 124.9, 12.7, 34.6, 31.3, 13.8. IR (KBr Disc, cm $^{-1}$) 2962, 2870, 1608, 1579, 1513, 1463, 1419, 1365, 1302, 1269, 1178, 1139, 1114, 996, 986, 842, 730, 674, 571. A copy of the ^{1}H NMR spectrum is provided.



1-*ortho*-Tolyl-1*H*-imidazole

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-bromotoluene (120 μL, 1.00 mmol), and imidazole (82

mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 28 h at 110 ˚C. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1-*ortho*-tolyl-1*H*-imidazole (yellow oil, 140 mg, 89 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (bs, 1H), 7.37-7.28 (m, 3H), 7.23-7.20 (m, 2H), 7.06 (bs, 1H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.4, 135.6, 130.7, 130.1, 118.4, 114.0, 111.1, 107.7.[16] A copy of the ^{1}H NMR spectrum is provided.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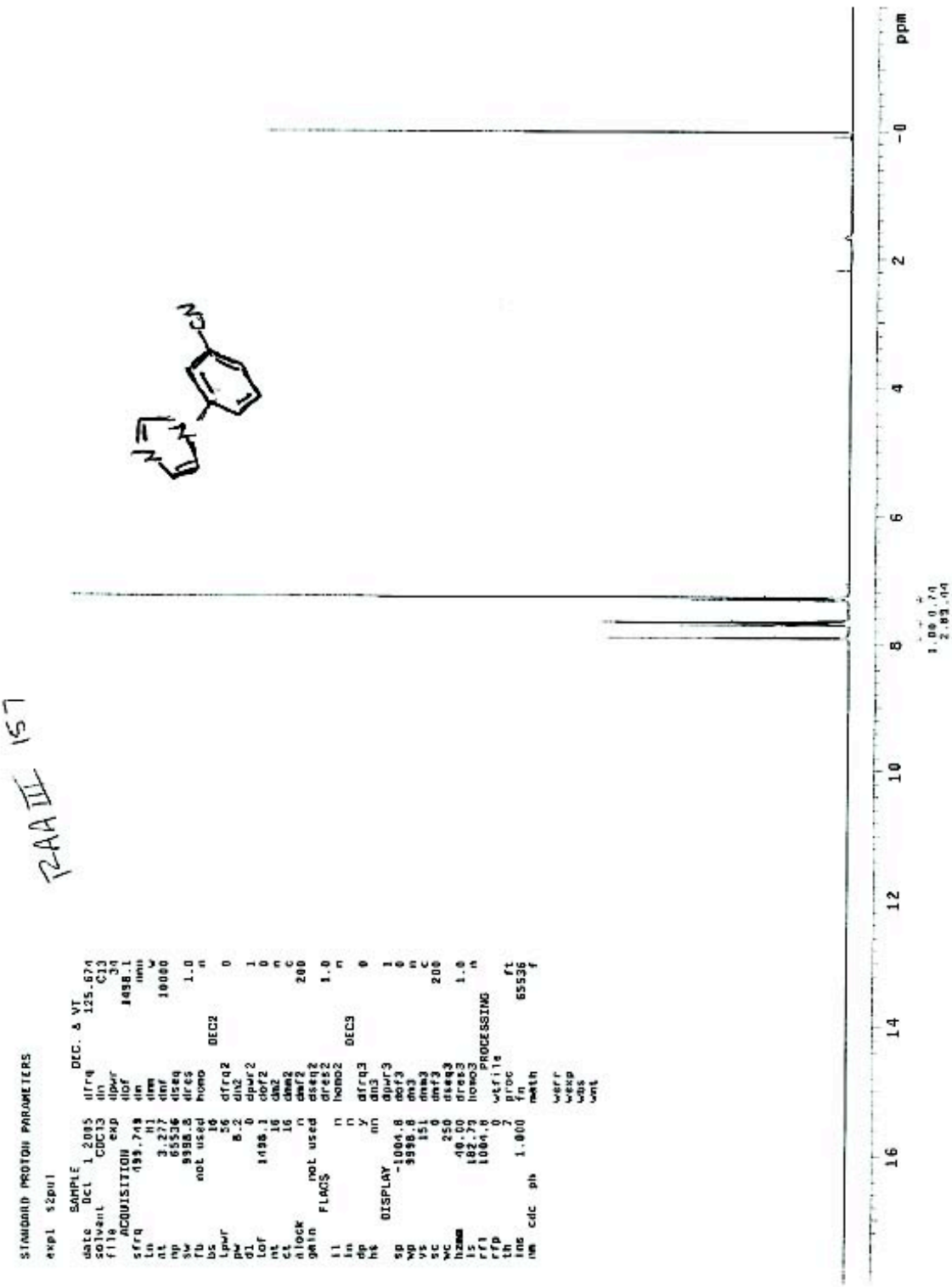
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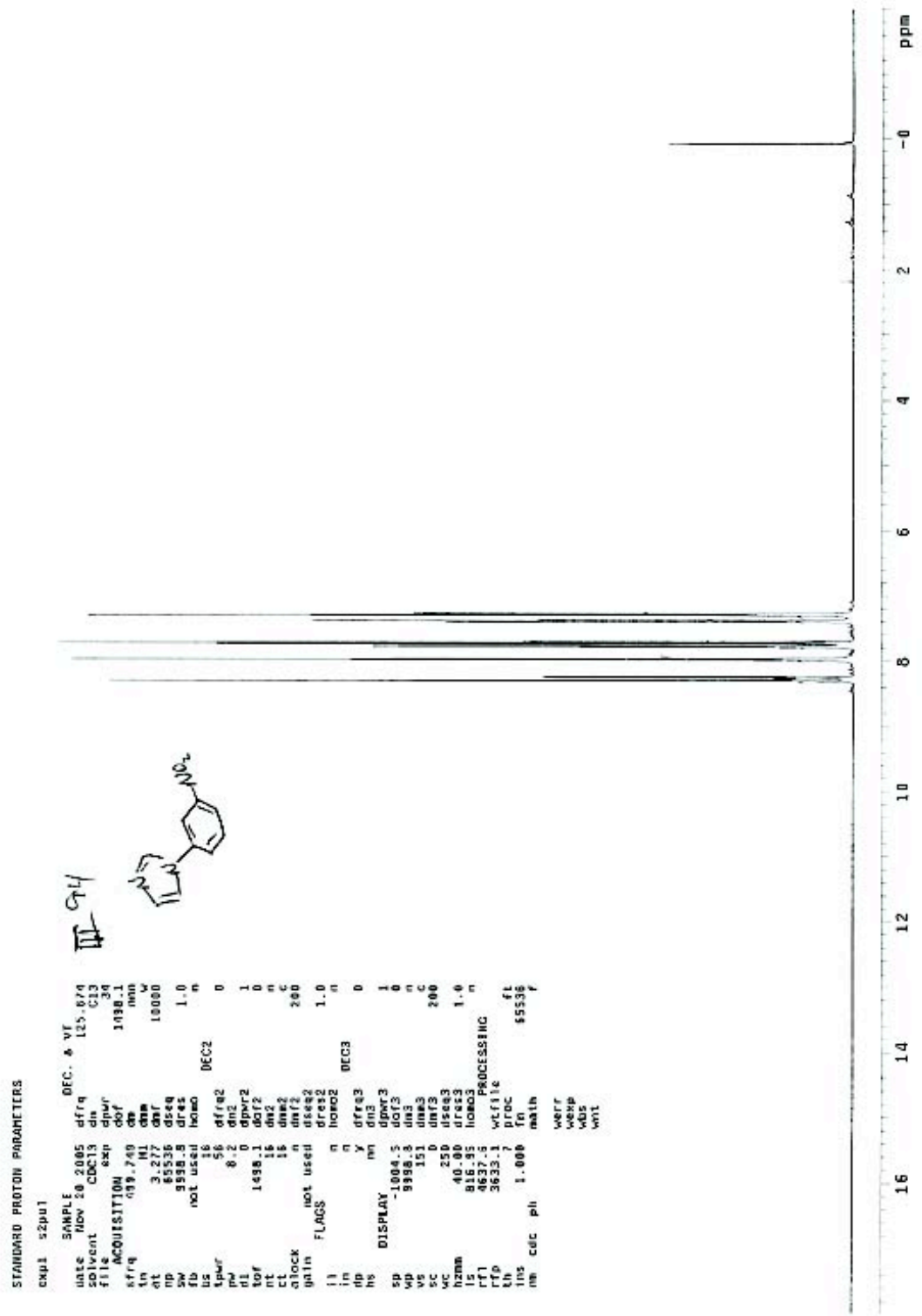
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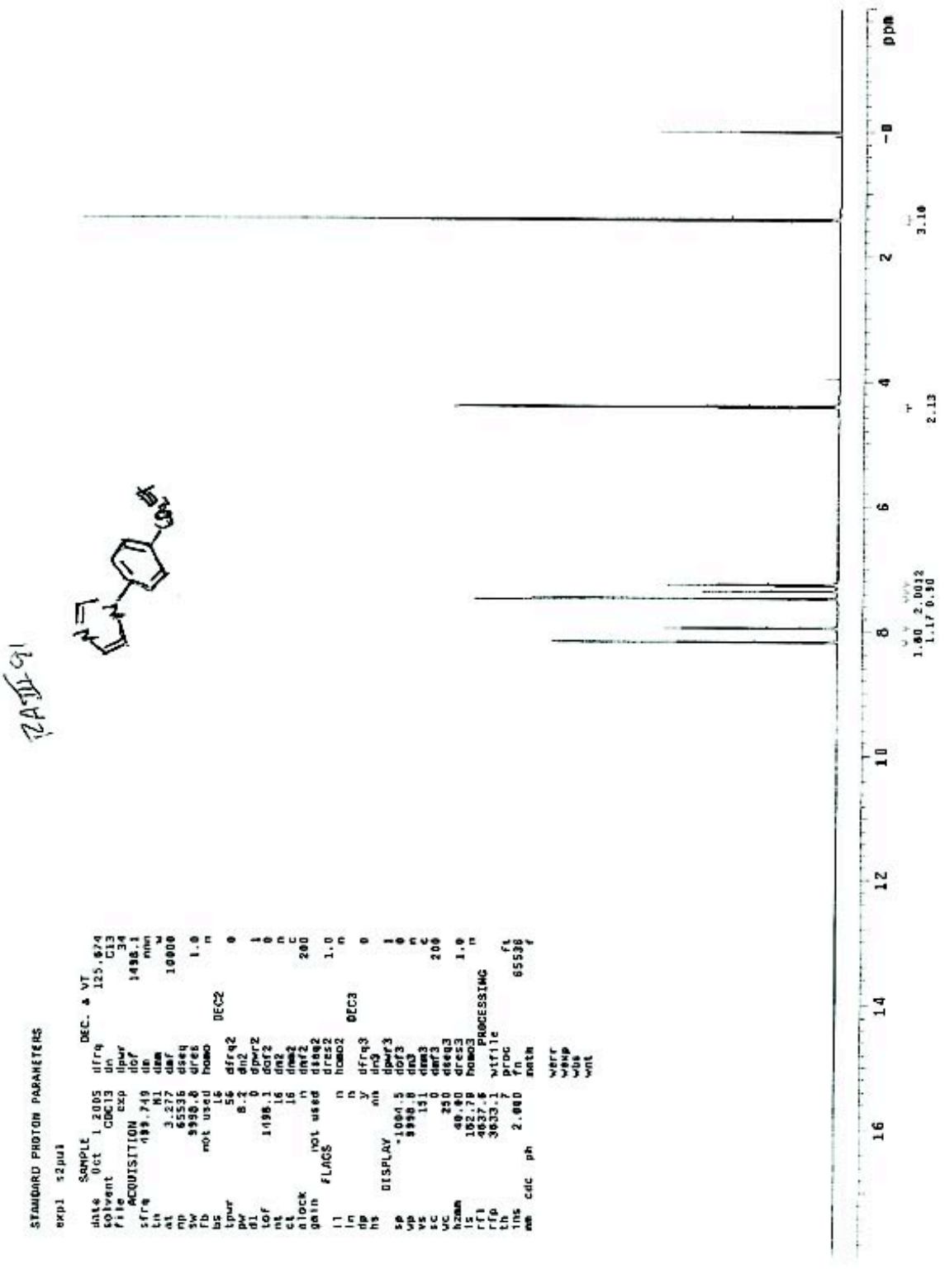
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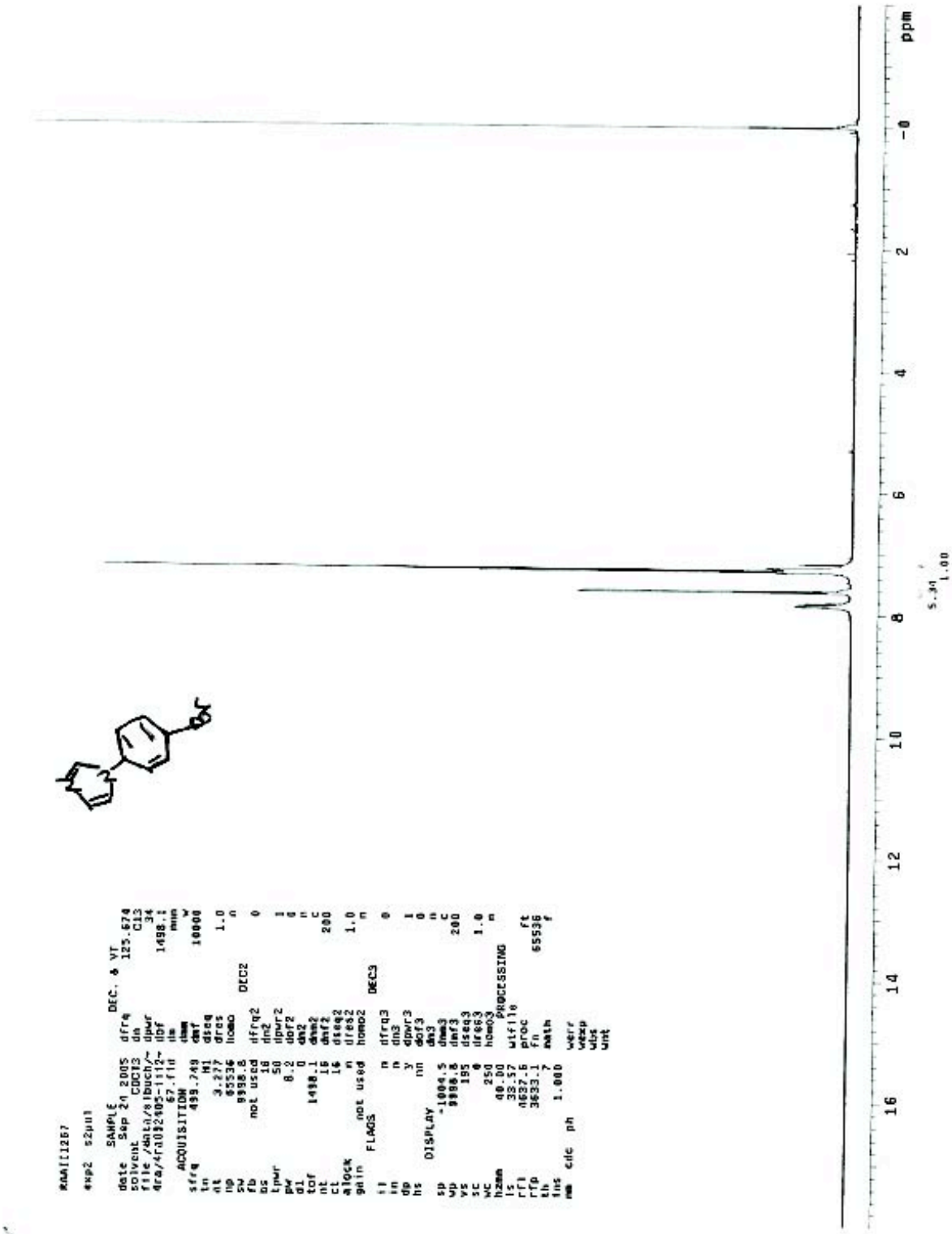
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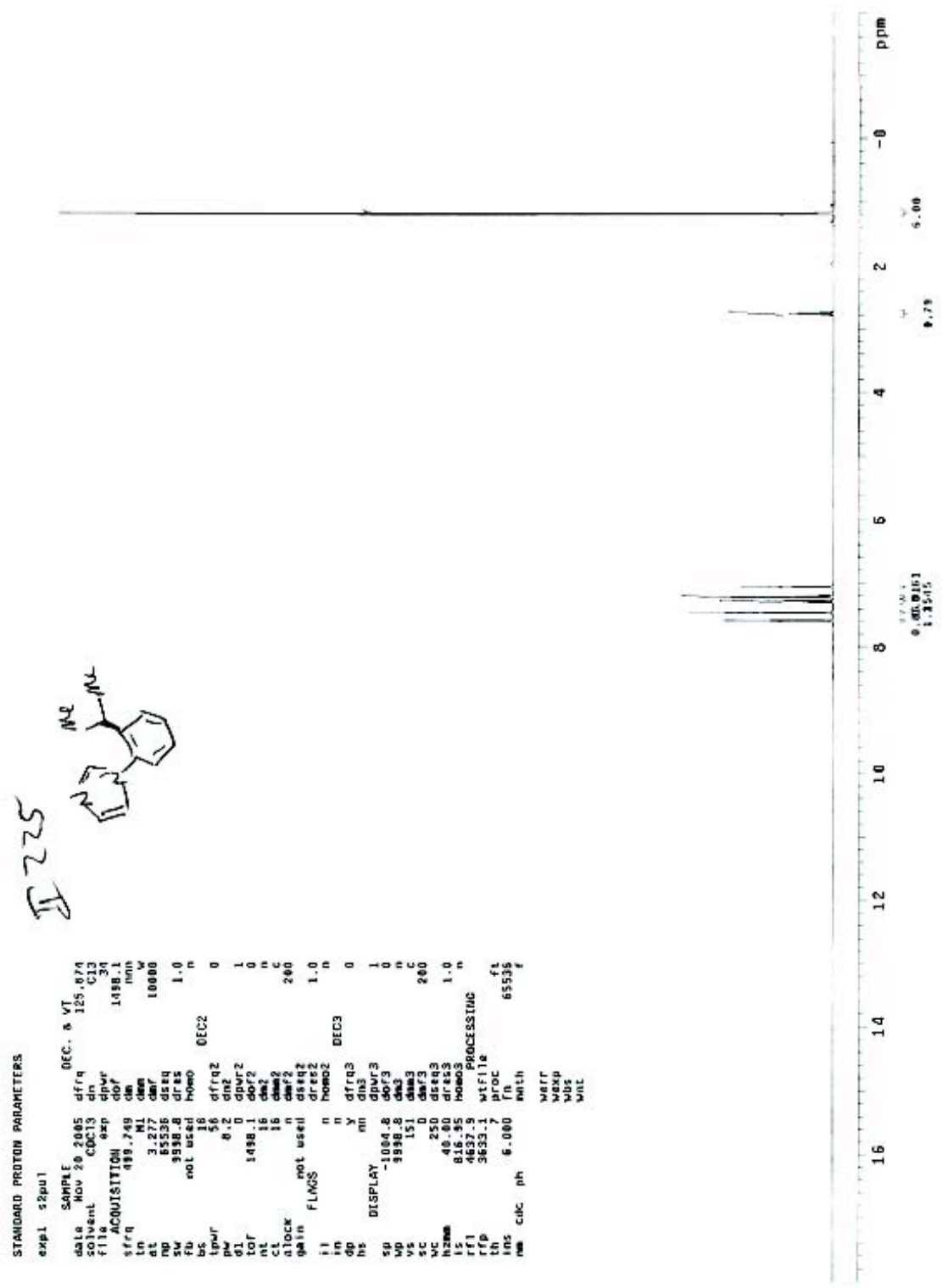
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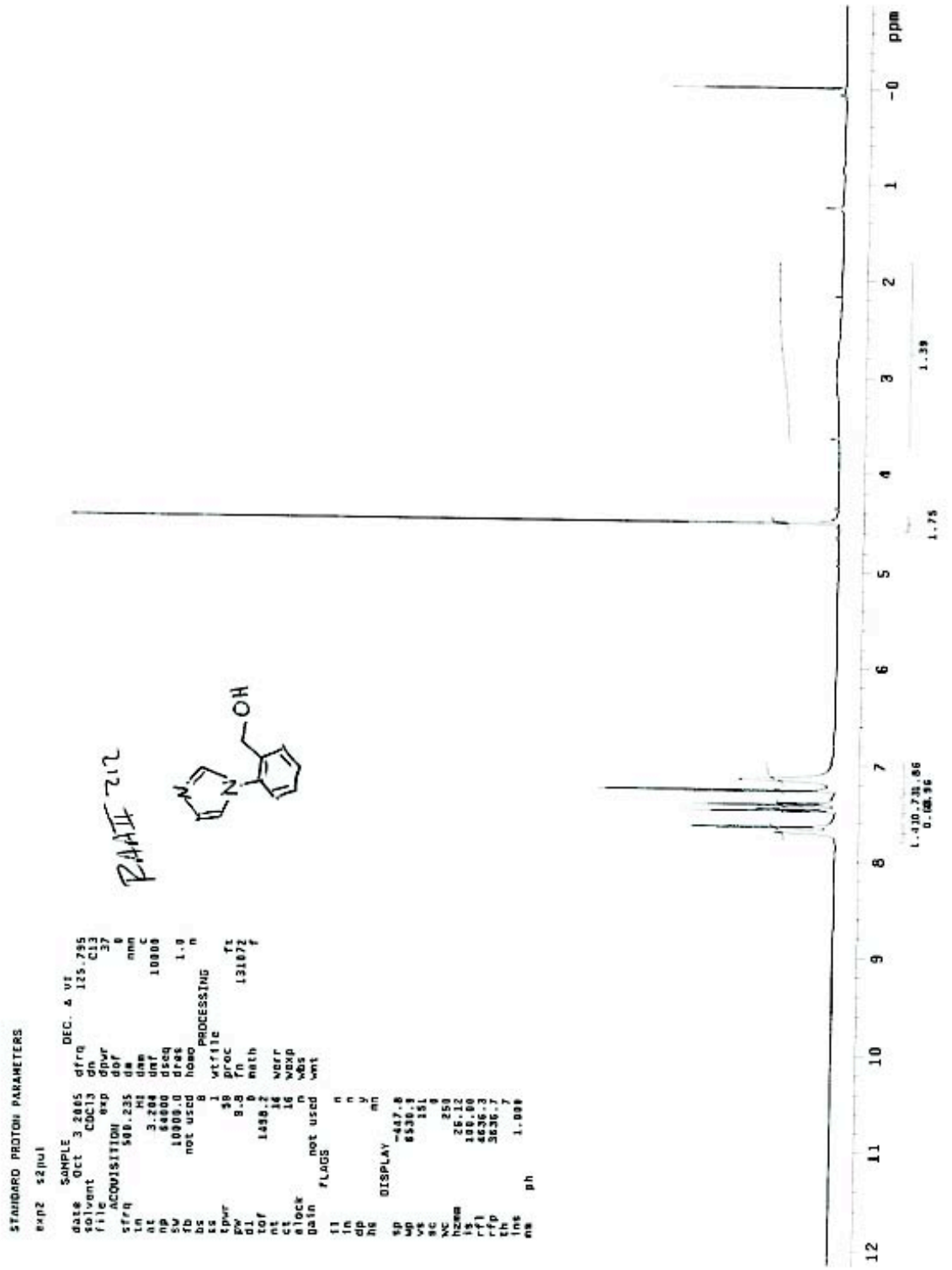
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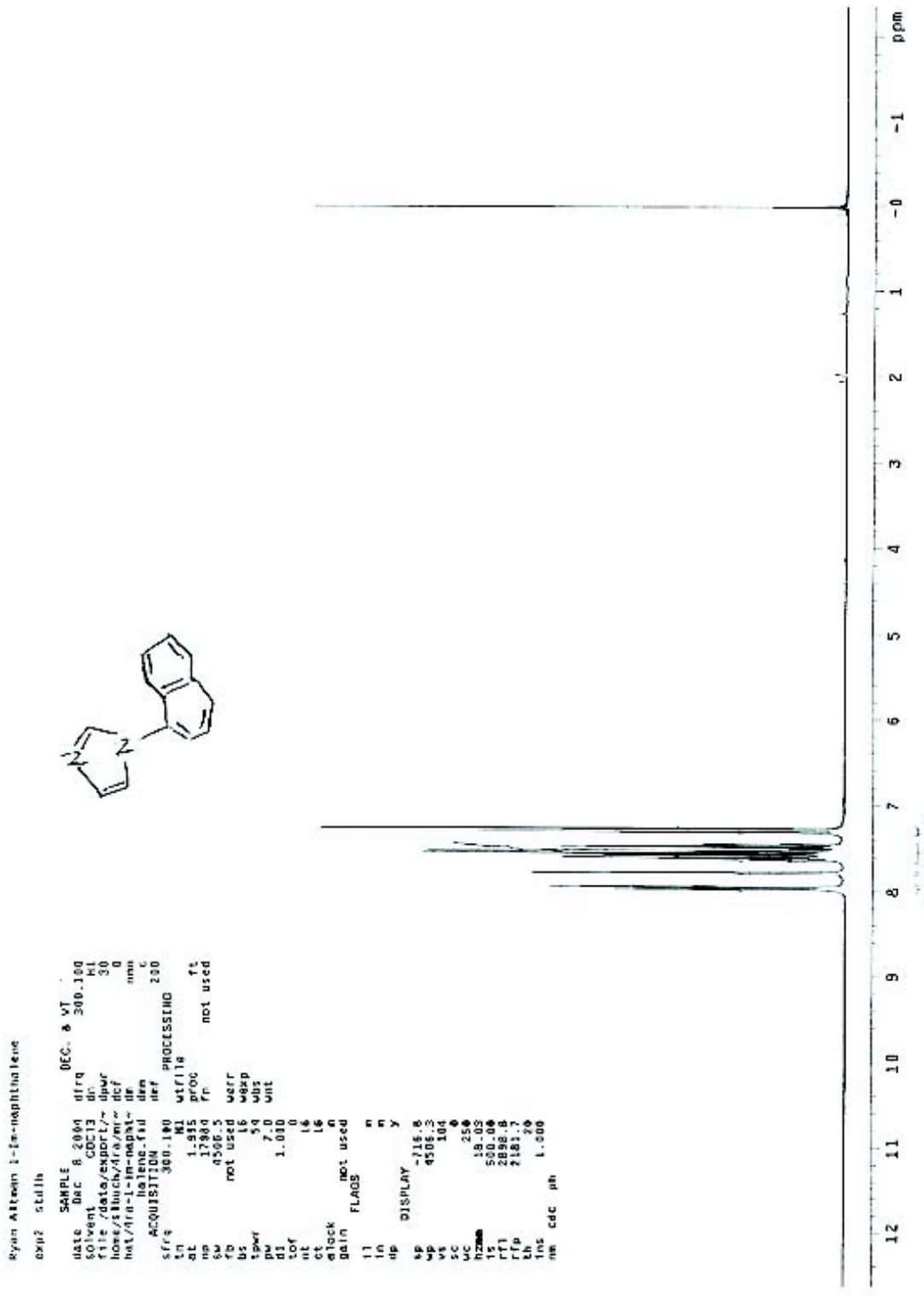
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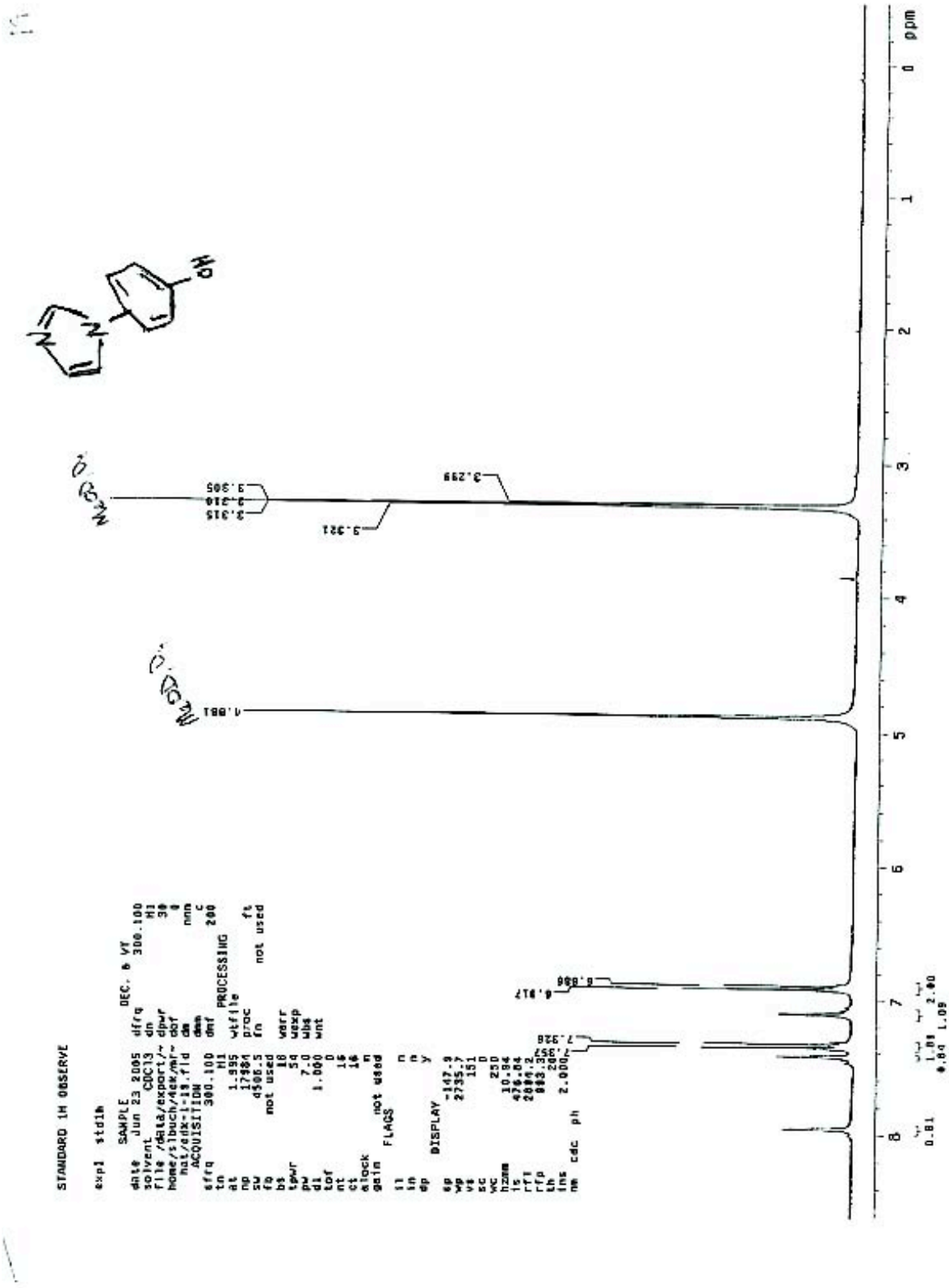
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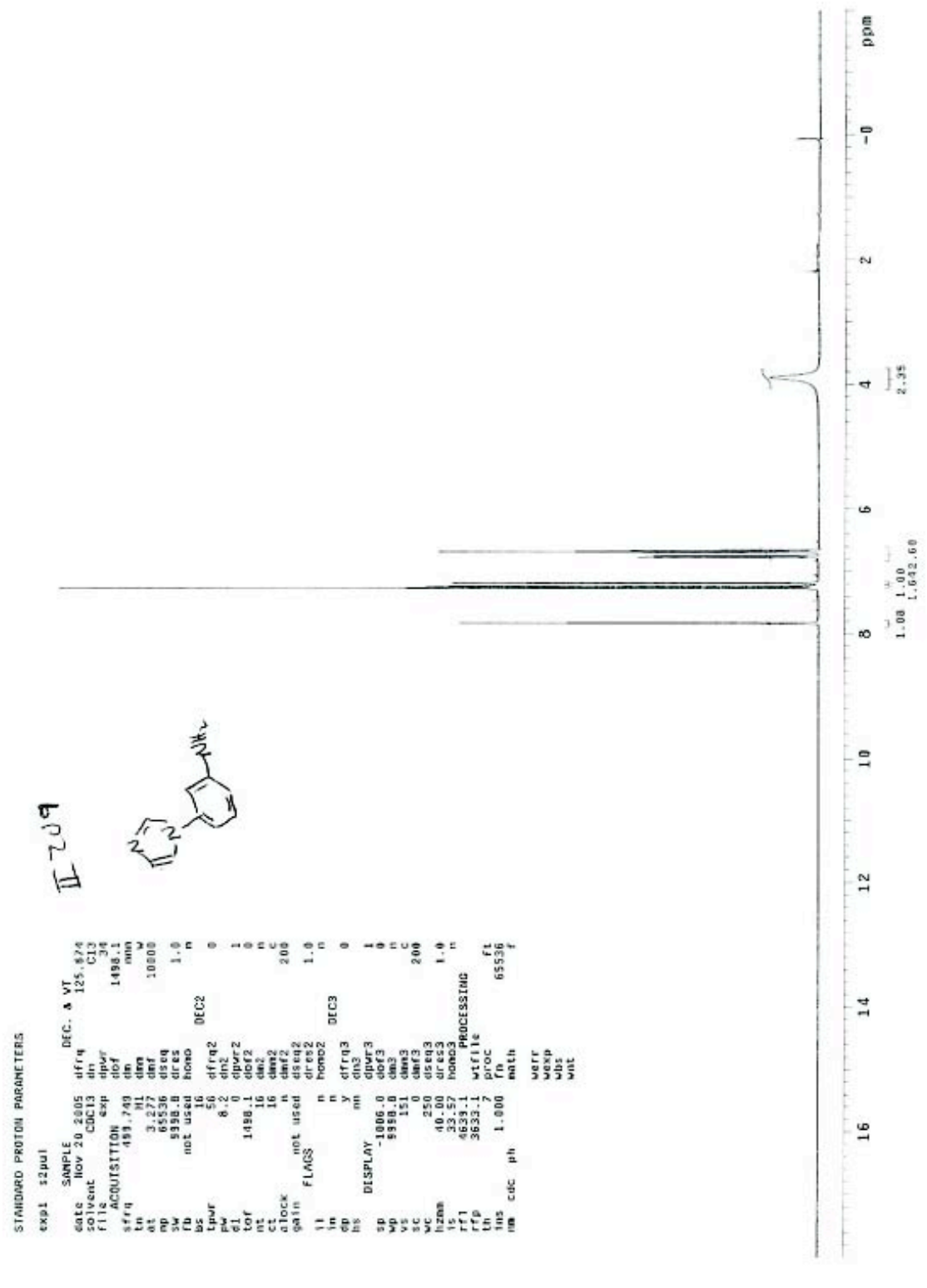
STANDARD PROTON PARAMETERS
exp1 s2pul
SAMPLE
date Nov 20 2005
solvent CDCl3
file ACQUISITION
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at 3.277
np 65536
sw 5998.8
fb
bs 16
tpwr 56
pw 8.2
d1 1.000
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -1006.0
wp 5998.0
vs 151
sc 0
wc 250
hzmm 40.00
is 33.57
rfl 4634.1
rfp 3633.1
th 7
ins
nm cdc ph 1.000
DEC. & VT
dfrq 125.824
dn C13
dpwr 34
dof 1498.1
dm nnn
dmm w
dmf 10000
dseq
dres 1.0
homo n
DEC2
dfrq2
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dseq3
dres3 1.0
homo3 n
PROCESSING
wtfile
proc f1
fn 65536
math f
werr
wexp
wbs
wnt
E209
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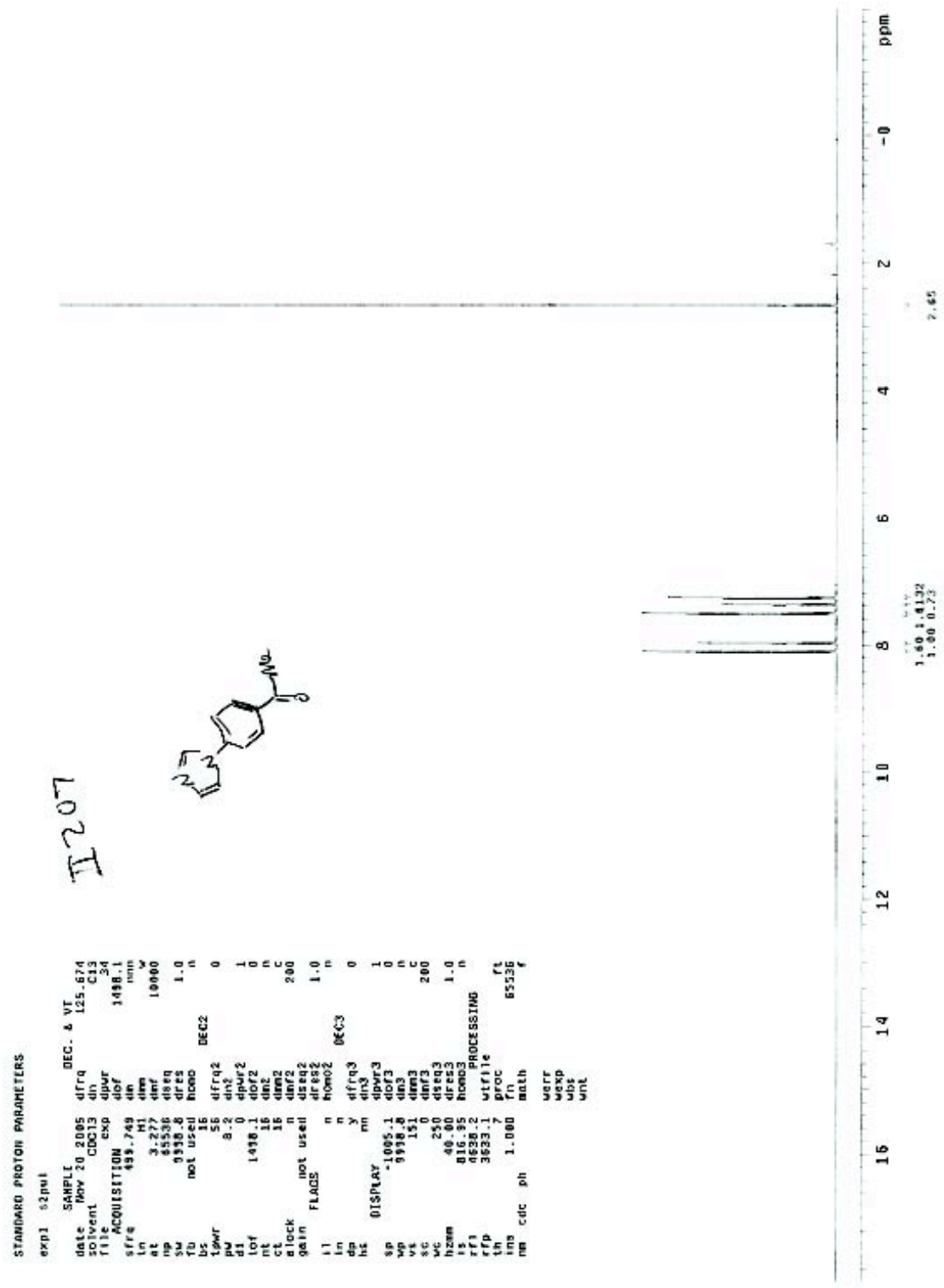
1.642.60
2.35
16
14
12
10
8
6
4
2
-0
ppm


STANDARD PROTON PARAMETERS
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SAMPLE
date Nov 20 2005
solvent CDCl3
file exp
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tn H1
at 3.277
np 65536
sw 9930.8
fb not used
bs 16
tdwr 56
pw 8.2
d1 0
iof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -1005.1
wp 9938.8
vs 151
sc 0
wc 250
hzmm 40.00
is 816.95
rfl 4638.2
rfp 3633.7
th 7
ins 1.000
nm cdc ph
DEC. & VT
dfrq 125.674
dn C13
dpwr 34
dof 1498.1
dm nnn
dmf 10000
dmm w
dseq 1.0
dres n
homo DEC2
dfrq2
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dres3
homo3 1.0
PROCESSING
wtfile n
proc
ft 65536
math f
werr
wexp
wbs
wnt
T1207
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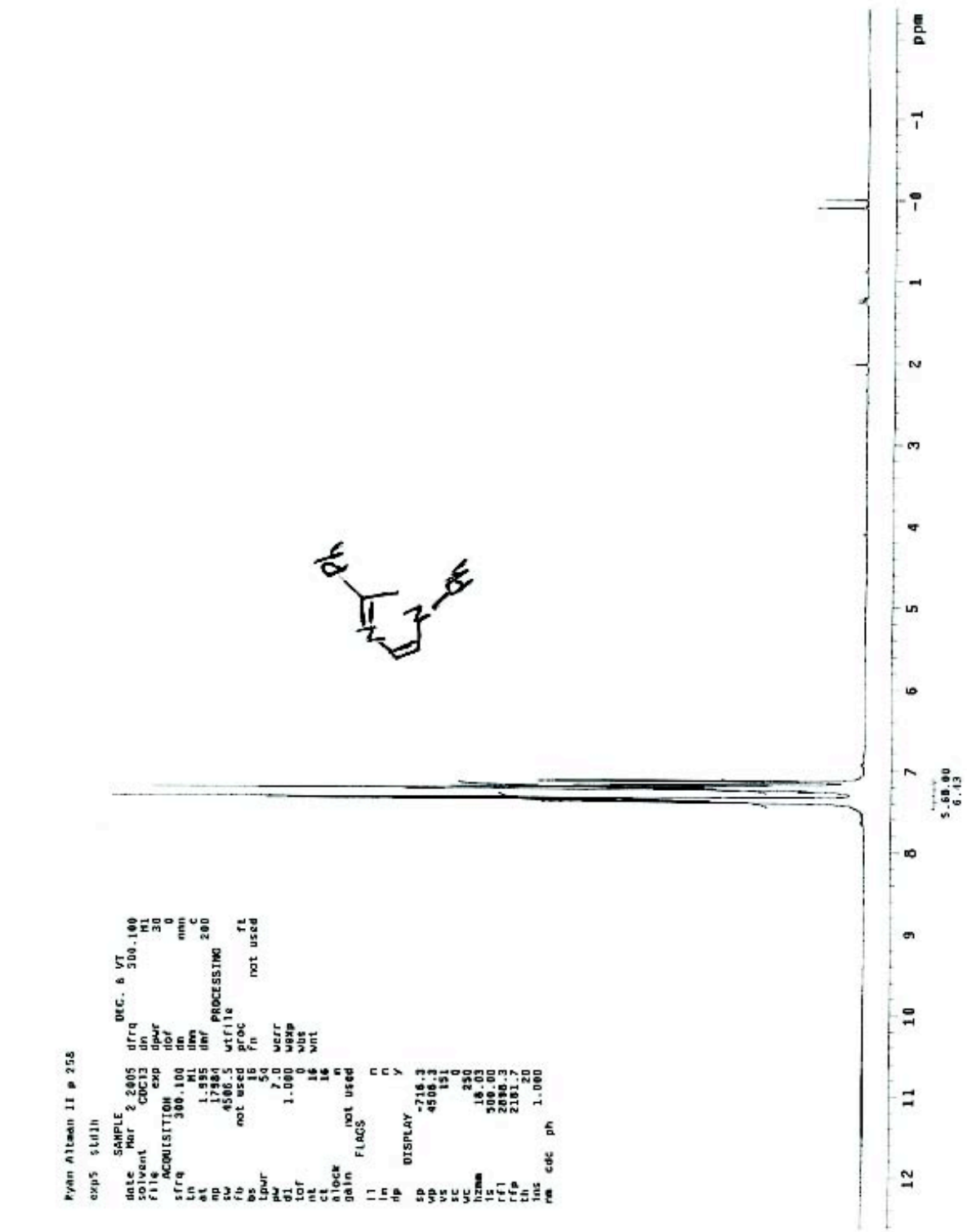
1.00 0.73
7.65
16
14
12
10
8
6
4
2
-0
ppm


Ryan Altman II p 258
exp5 stuih
SAMPLE
date Mar 2 2005
solvent CDCl3
file
ACQUISITION
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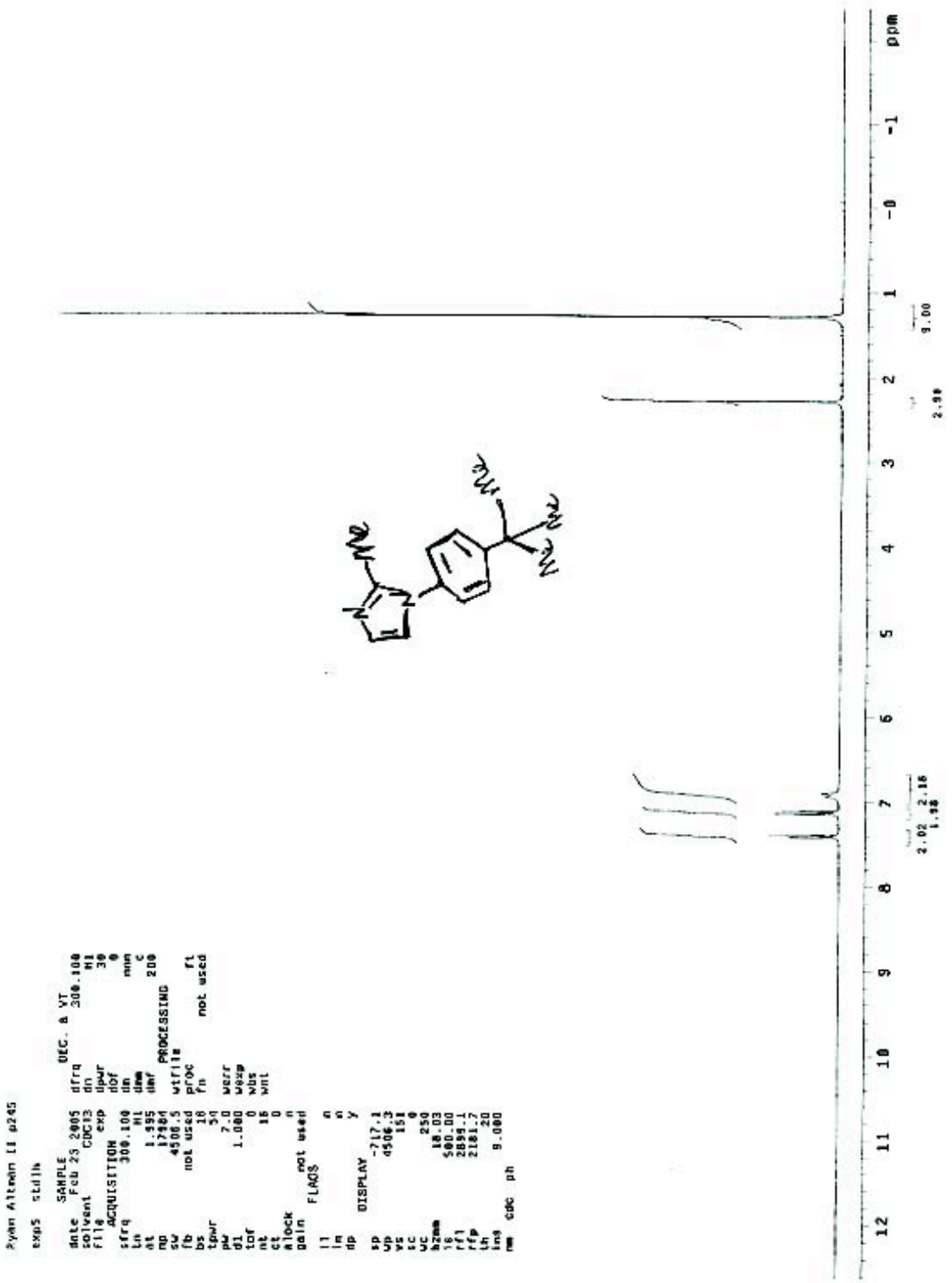
tn H1
at 1.995
np 17984
sw 4500.5
fb not used
bs 16
tpwr 52
pw 7.0
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
FLACS
ll n
lm n
dp y
DISPLAY
sp -716.3
wp 4500.3
vs 151
sc 0
wc 250
hzmm 18.03
is 500.00
rfl 2698.3
rfp 2181.7
th 20
ins 1.000
ra 68 ph
DEC. 6 VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
5.68.00
6.13
ppm


Ryan Altman LI p245
exps stdlh
SAMPLE
date Feb 23 2005
solvent CDCl3
file
ACQUISITION
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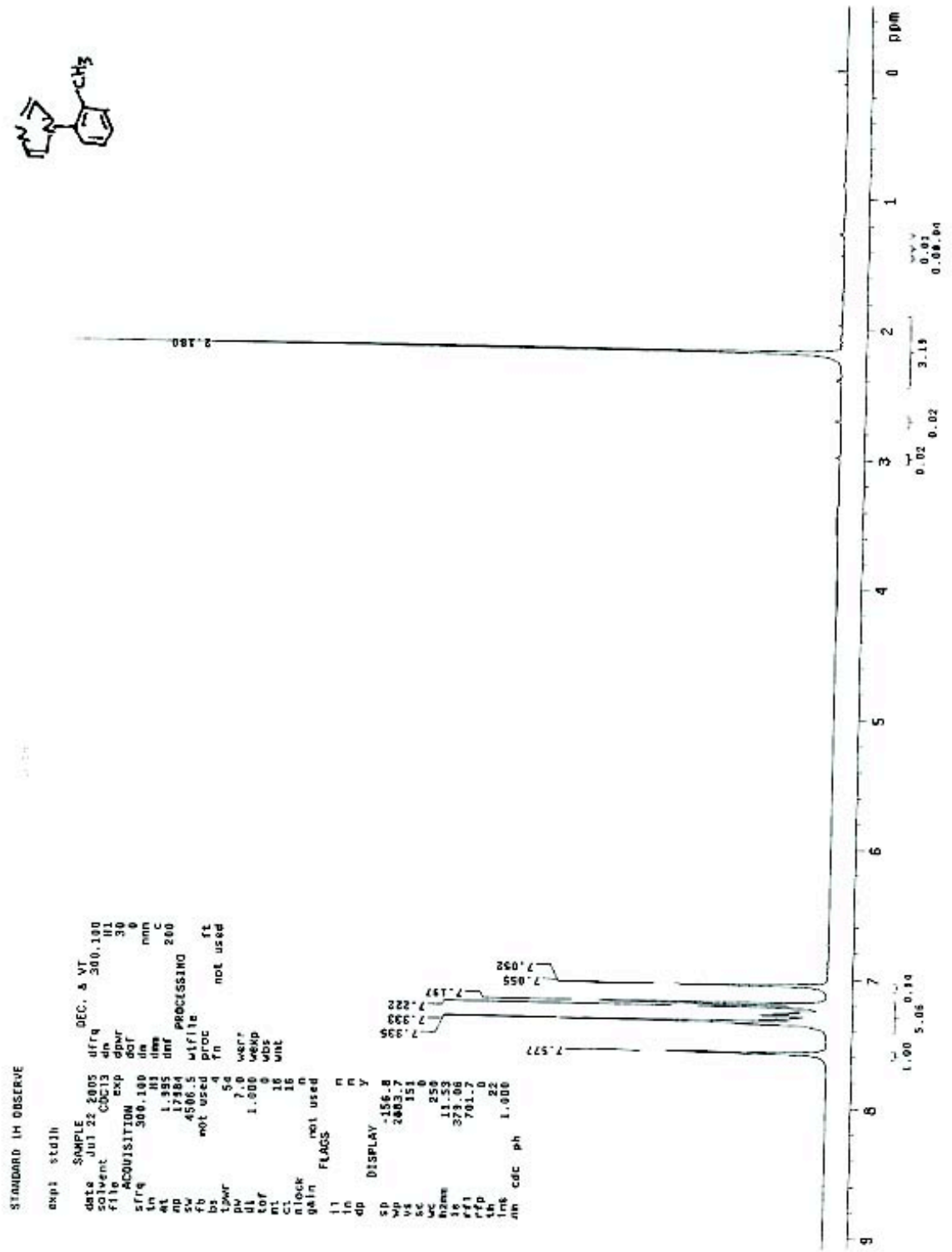
tn H1
at 1.595
np 17384
sw 4508.5
fb not used
bs
tpwr 50
pw 7.0
d1 1.000
tof 15
nt 0
ct 0
alock n
gain not used
FLAGS
DISPLAY
sp -717.1
wp 4506.3
vs 151
sc 0
wc 250
hzmm 18.03
rfl 2899.1
rfp 2181.7
th 20
ins 9.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc f1
fn not used
werr
wexp
wbs
wnt
n
n
y
2.02
2.16
1.00
2.39
9.00
ppm


STANDARD 1H OBSERVE
2.180
7.577
7.395
7.333
7.222
7.197
7.055
7.042
ppm

[1] The synthesis of **1**, **2**, **3** and **L** were performed according to a combination of the following procedures. (a) Graf, I. G.; Jastreiter, D.; da Silva, L. E.; Rebelo, R. A.; Montalban, A. G.; McKillop, A. *Tetrahedron* **2002**, *58*, 9095. (b) Schmittel, M.; Ammon, H. *Eur. J. Org. Chem.* **1998**, 785. (c) Snyder, H. R.; Freier, H. E. *J. Am. Chem. Soc.* **1946**, *68*, 1320. d) Wehman, P.; Kaasjager, de Lange, W. G.; Jartl, F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3751. (e) Zacharias, D. E.; Case, F. H. *J. Am. Chem. Soc.* **1962**, *27*, 3878-3882

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