Practical Access to Metallo-Thiophenes: Regioselective Synthesis of 2,4-Disubstituted Thiophenes

Sylvie M. Asselin, Matthew M. Bio, Neil F. Langille*, and Ka Yi Ngai*

Chemical Process R&D, Amgen, Inc., 360 Binney Street, Building 1000, Cambridge, Massachusetts 02142

Supporting Information

General Methods

All solvents and reagents were obtained from commercial suppliers and used without purification. Reactions were conducted under an atmosphere of nitrogen with a suitable outlet to accommodate modest pressure changes. Reaction temperatures were monitored by internal thermocouple. Reaction progress and compound purity were determined by HPLC analysis, using an Eclipse XDB C8, 4.6 x 150 mm, 5 μm column, with a gradient method using 0.1% (v/v) 70% $HClO_4$/water and acetonitrile as mobile phase. Assay yield and purity were assessed using HPLC comparison to high purity reference standards, and confirmed by quantitative ^{1}H NMR in DMSO-d_6 (vs. internal standards benzyl benzoate, or *N*-benzyl benzamide). ^{1}H NMR spectra were obtained using a Bruker 400 MHz spectrometer; chemical shifts are reported in ppm using the solvent internal standard ($CDCl_3$: δ 7.27, DMSO-d_6: δ 2.50, CD_3OD: δ 3.31). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling; chemical shifts are reported in ppm with the solvent as the internal reference ($CDCl_3$: δ 77.0, DMSO-d_6: δ 39.5). HRMS (ESI-TOF) spectra were obtained using Agilent 1100 systems. Liquid chromatography purification was performed on an ISCO Combiflash Companion apparatus; chromatographic purifications and isolated yields are unoptimized.

General Procedures:

Titration of isopropylmagnesium chloride:

Commercial isopropylmagnesium chloride is available as a 2 M solution in THF (Aldrich 230111). The quality of this material can be confirmed by titration[1] versus stoichiometric (±)-menthol (CAS [89-78-1]) as follows:

1. To a flask with stir bar, charge 1.000 g (6.399 mmol) of (±)-menthol, 15-20 mg of 1,10-phenanthroline, and 10.0mL (10 Vol) THF.
2. Purge the flask with nitrogen, and cool to 0 °C.
3. Charge isopropylmagnesium chloride solution in THF drop-wise, until a purple color persists for greater than one minute.
4. Calculate molarity of isopropylmagnesium chloride solution as follows:

$$\text{M (}i\text{-PrMgCl in THF)} = \frac{\textbf{weight of (±)-menthol (in grams)}}{\text{156.27 g/mol menthol}} \times \frac{\text{1000 mL /L}}{\textbf{vol } \boldsymbol{i}\textbf{-PrMgCl (in mL)}}$$

5. Acceptable molarity range for isopropylmagnesium chloride is determined to be 1.85 to 2.2 M solution, and amount used should be calculated accordingly.[2]

General method for magnesiation of heterocycles:

To a flask charge heterocycle (1.40 equiv) and THF (4 volumes, relative to heterocycle). Initiate stirring, purge the flask with nitrogen, and add 2,2,6,6-tetramethylpiperidine (0.10 equiv) in one portion at 20-25 °C. Add dropwise over ~10 min, *iso*-propylmagnesium chloride (2.00 M solution in THF, 1.00 equiv), at <30 °C. Heat the resulting clear solution to reflux (66 °C) for 18-24 h, until ^{1}H NMR analysis of a reaction aliquot quenched with CD_3OD indicates >90% deprotonation. The resulting magnesio-heterocycle is cooled to 20 °C prior to use.

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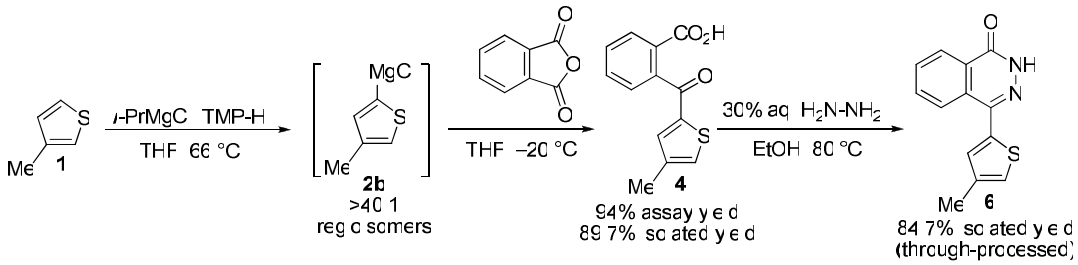
[1] Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503-2506.

[2] Commercial hexylmagnesium chloride is available as a 2 M solution in THF (Aldrich 64126). This reagent does not provide a well-defined endpoint according to the procedure in reference 1. The quality of this material can be confirmed by potentiometric titration versus stoichiometric 2-butanol. For details, see: Chen, Y.; Wang, T.; Helmy, R.; Zhou, G. X.; LoBrutto, R. *J. Pharm. Biomed. Anal.* **2002**, *29*, 393-404.

Experimental:



2-(4-Methylthiophene-2-carbonyl)benzoic acid (4).[3] 2,2,6,6-Tetramethylpiperidine (25.2 mL, 150 mmol) was charged in one portion to 3-methylthiophene **1** (147 g, 144 mL, 1500 mmol) in THF (576 mL). *iso*-Propylmagnesium chloride (2.00 M solution in THF, 633 mL, 1270 mmol) was added over 10 min at <30 °C. The resulting solution was heated to reflux at 66 °C. After 23 h, ^{1}H NMR analysis of a reaction aliquot quenched with CD_3OD indicated 98%[4] conversion to the Mg-thiophene **2b** (96.8% 2-D-4-methylthiophene, 1.2% 2-D-3-methylthiophene of theoretical 0.85 equiv). The Mg-thiophene solution was cooled to 20 °C. Phthalic anhydride **3** (170 g, 1150 mmol) in THF (720 mL) was charged to a separate flask and the resulting slurry was cooled to –20 °C. The Mg-thiophene solution (at 20 °C) was added to the phthalic anhydride slurry over 45 min, at –25 °C to –20 °C. After 20 min, the reaction was quenched with H_2O (510 mL) added over 10 min between –20 °C and 10 °C,[5] followed by 6N HCl (289 mL) to pH 2. The reaction mixture was warmed to 20 °C, and MTBE (289 mL) was added. After 10 min, the layers were separated; the upper organic layer assayed to 267 g keto acid **4** (94.1%[6]).

The crude keto acid **4** was concentrated by distillation (60 °C, 350 mbar) to 530-545 mL (2X vs. assay yield), and the resulting pot was maintained at 60 °C. Ethanol (1070 mL, 4X) was added, and the solution was distilled again to 530-545 mL total volume. HPLC analysis of the distillate revealed 3-

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[3] Weinmayr, V. *J. Am. Chem. Soc.* **1952**, *74*, 4352-4357.

[4] 98% conversion is calculated based on limiting reagent *i*-PrMgCl.

[5] In a power compensation calorimetry experiment conducted at 10 °C isothermal, quenching the reaction with water (4 X over 1 h, 60.6 mmol scale) resulted in a 74 kJ/mol exotherm, uncorrected for heat of mixing.

[6] Yield is based on limiting reagent phthalic anhydride.

methylthiophene as the only UV-active component. After breaking vacuum, ethanol (800 mL, 3X) was charged and the flask was cooled to 20 °C over 3 h. Water (1330 mL, 5X) was added over 2 h, and then aged for 10 h. The slurry was filtered, and the cake displacement-washed with 25% EtOH:H_2O (535 mL, 2X). The collected mother liquors and wash contained 11.6 g (4.1%) product **4**. The solid was dried on the frit at 20 °C for >24 h, under a nitrogen stream, to provide keto acid **4** as an off-white solid (261 g, 97.3 wt%, 89.7% adjusted yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.16 (br s, 1H), 7.96 (ddd, J = 0.5, 1.5, 7.5 Hz, 1H), 7.64-7.72 (m, 3H), 7.49 (ddq, J = 0.6, 1.5, 7.5 Hz, 1H), 7.09 (dq, J = 0.4, 1.5 Hz, 1H), 2.18 (dd, J = 0.4, 0.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 188.5, 166.9, 143.6, 140.7, 138.6, 136.1, 132.1, 130.7, 129.9, 129.9, 129.8, 127.4, 15.0; HRMS calculated for $C_{13}H_9O_2S_1$ [M + H – H_2O]$^+$ 229.0318, found 229.0316; IR (neat): 3050, 2970, 2920, 1690 cm^{-1}; mp: 191 °C.

4-(4-Methylthiophene-2-yl)phthalazine-1)*2H*)-one (6).[7] Crude keto acid **4** (91.9 g) was synthesized as described above. The crude MTBE/THF layer was concentrated by distillation (60 °C, 300 mbar) to 180-190 mL, and the resulting pot was maintained at 60 °C. Ethanol (367 mL, 4X) was added, and the solution was distilled again to 180-190 mL total volume. After breaking vacuum, ethanol (367 mL, 4X) was charged to the reaction and the flask was cooled to 20-30 °C. To the resulting solution was added hydrazine (35 wt % solution in H_2O, 169 mL, 1870 mmol) over 10 min, at 35 °C. The reaction was heated to 80 °C for 18 h, until HPLC assay of the resulting slurry indicated >95% conversion to product.[8]

The reaction was cooled to 20 °C over 2 h, and then aged at 20 °C for 1 h. The resulting slurry was filtered, and the cake was displacement-washed with 1:1 EtOH:H_2O (180 mL). The cake was dried

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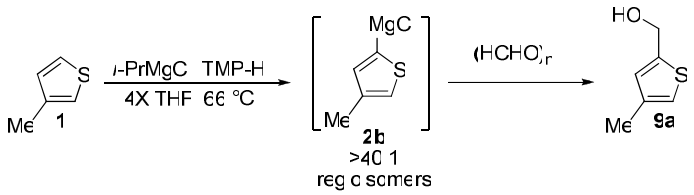
[7] Iwase, N.; Morinaka, Y.; Tamao, Y.; Kanayama, T.; Yamada, K. 3,6-Disubstituted Pyridazine Derivative Blood Platelet Aggregation Inhibitors. Eur. Pat. Appl. EP 534443 19920924, Mar. 31, 1993; *Chem. Abstr.* **1993**, *119*, 249963.

[8] This reaction proceeds below the flash point of 35% hydrazine/water (112.7 °C), and below the boiling point of a hydrazine/water azeotrope (120.3 °C). DSC and ARC scanning of the reaction components at 300 °C and 250 °C, respectively, showed no unsafe thermodynamic events.

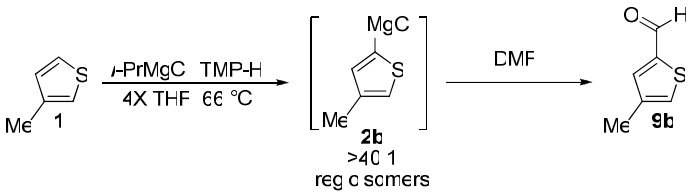
under N_2 stream at 20 °C to give 82.7 g thiophene-phthalazinone **6** as a pale yellow solid (98.6 wt %, 84.7% adjusted yield over two steps). The collected mother liquors and wash contained 1.78 g product **6** (1.9%) and 5.70 g keto acid **7** (6.1%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (d, J = 0.8, 3H), 7.09 (dq, J = 0.8, 1.1, 1H), 7.28 (d, J = 1.1, 1H), 7.86 (m, 2H), 8.17 (m, 1H), 8.53 (m, 1H), 10.31 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.83, 122.91, 126.63, 127.08, 128.22, 129.38, 130.88, 131.71, 133.70, 136.33, 138.14, 142.43, 159.72; mp: 232 °C.



(4-Methylthiophen-2-yl)methanol (9a).[9] Magnesiothiophene **2b** was generated according to the general magnesiation procedure (20.0 mmol scale), cooled to 20 °C, and then added over 30 min to a 0 °C solution of *p*-formaldehyde (0.840 g, 1.40 equiv) in THF (13.8 mL, 5 volumes, relative to heterocycle). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of the thiophene-Grignard (90 min). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was slightly acidic (pH 5). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 2.28 grams (88.9%) assay yield of **9a**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and careful concentration *in vacuo* provided the desired compound **9a** as a pale yellow amorphous solid (1.78 g, 82.5 wt%, 57% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.39 (s, exchangeable, 1H), 4.73 (app. s, 2H), 6.81 (s, 1H), 6.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6,

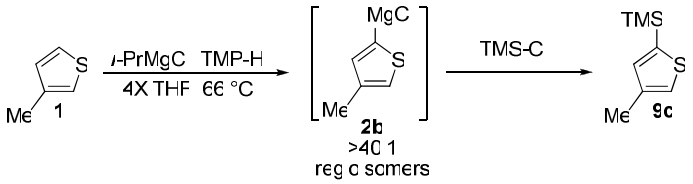
[9] (a) Lozanova, A. V.; Moiseenkov, A. M.; Semenovskii, A. V. *Izv. Akad. Nauk, Ser. Khim.* **1980**, 958-959. (b) Wang, C.-C.; Chen, H.-C.; Wang, S.-H.; Lin, M.-C.; Shieh, T.-L.; Huang, Y.-H.; Chuang, S.-C.; King, C.-H. R. Preparation of 4-oxoquinazoline derivatives as kinesin inhibitors. U.S. Pat. Appl. US 2008-125094, Nov. 27, 2008; *Chem. Abstr.* **2008**, *150*, 5760.

59.9, 120.5, 127.7, 137.4, 143.8; HRMS calculated for $C_6H_7O_1S_1Na_1$ [M+Na] 150.01153, found 150.01150; IR (neat): 3645, 2925, 1020 cm^{-1}.

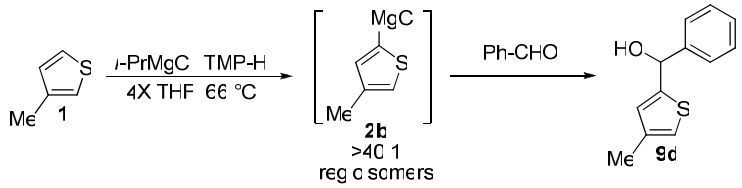


4-Methylthiophene-2-carbaldehyde (9b).[10] Magnesiothiophene **2b** was generated according to the general magnesiation procedure (20.0 mmol scale), cooled to 20 °C, and then added over 30 min to a 0 °C solution of *N,N*-dimethylformamide (1.26 mL, 1.40 equiv) in THF (13.8 mL, 5 volumes, relative to heterocycle). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of the thiophene-Grignard (15 min). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was slightly acidic (pH 4-5). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 2.20 grams (87.2%) assay yield of **9b**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and careful concentration *in vacuo* at 0 °C provided the desired compound **9b** as a volatile pale yellow oil (2.05 g, 74.0 wt%, 60.1% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (s, 3H), 7.37 (s, 1H), 7.58 (s, 1H), 9.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.9, 143.6, 139.1, 137.9, 131.0, 15.4; HRMS calculated for $C_6H_7O_1S_1$ [M+H] 127.02121, found 127.02101; IR (neat): 2925, 2865, 1765, 1386, 1020 cm^{-1}.

[10] (a) Jean, S. *J. Org. Chem.* **1954**, *19*, 70-3. (b) Smith, K.; Barrat, M. L. *J. Org. Chem.* **2007**, *72*, 1031-1034.



Trimethyl(4-methylthiophen-2-yl)silane (9c).[11] Magnesiothiophene **2b** was generated according to the general magnesiation procedure (20.0 mmol scale), cooled to 20 °C, and then added over 30 min to a 0 °C solution of chlorotrimethylsilane (3.55 mL, 1.40 equiv) in THF (13.8 mL, 5 volumes, relative to heterocycle). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of the thiophene-Grignard (1 h). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was neutral (pH 7). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 2.92 grams (85.7%) assay yield of **9c**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and careful concentration *in vacuo* at 0 °C provided the desired compound **9c** as a volatile colorless oil (2.14 g, 96.1 wt%, 60.4% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.35 (s, 9H), 2.34 (2, 3H), 7.09 (s, 1H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.3, 138.9, 136.5, 126.0, 15.0, -0.1; HRMS calculated for $C_8H_{16}S_1Si_1$ [M+H] 171.06637, found 171.06602; IR (neat): 2925, 1675, 1438, 1274 cm^{-1}.



(4-Methylthiophen-2-yl)(phenyl)methanol (9d).[12] Magnesiothiophene **2b** was generated according to the general magnesiation procedure (20.0 mmol scale), cooled to 20 °C, and then added over 30 min to a 0 °C solution of benzaldehyde (2.85 mL, 1.40 equiv) in THF (13.8 mL, 5 volumes, relative to

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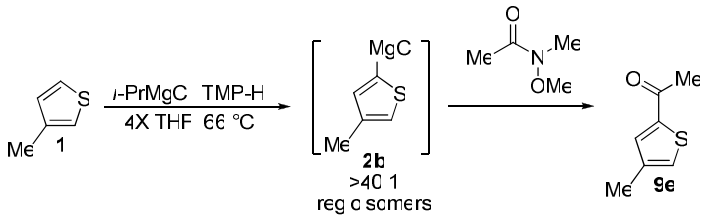
[11] Albertin, L.; Bertarelli, C.; Gallazzi, M. C.; Meille, S. V.; Capelli, S. C. *J. Chem. Soc., Perkin Trans. 2*, **2002**, 1752-1759.

[12] Agarwal, N.; Ravikanth, M. *Tetrahedron*, **2004**, *60*, 4739-4747. See also ref. 10b.

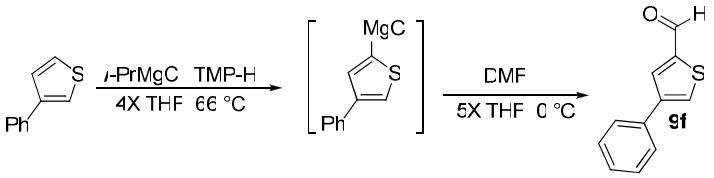
heterocycle). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of the thiophene-Grignard (18 h). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was slightly acidic (pH 4). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 3.73 grams (91.2%) assay yield of **9d**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and concentration *in vacuo* provided the desired compound **9d** as an off-white amorphous solid (2.88 g, 86.7 wt%, 61.1% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 3H), 2.46 (broad s, 1H), 5.99 (s, 1H), 6.70 (s, 1H), 6.85 (s, 1H), 7.30-7.41 (m, 3H), 7.44-7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 72.5, 120.6, 126.3, 127.0, 128.0, 128.6, 137.4, 143.2, 127.9; HRMS calculated for $C_{12}H_{12}S_1O_1Na_1$ [M+Na] 227.05011, found 227.05050; IR (neat): 3030, 2984, 1690, 1295, 1180 cm^{-1}.



1-(4-Methylthiophen-2-yl)ethanone (9e).[13] Magnesiothiophene **2b** was generated according to the general magnesiation procedure (20.0 mmol scale), cooled to 20 °C, and then added over 30 min to a 0 °C solution of *N*-methoxy-*N*-methylacetamide (2.98 mL, 1.40 equiv) in THF (13.8 mL, 5 volumes, relative to heterocycle). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of the thiophene-Grignard (18 h). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was slightly acidic (pH 4-5). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 2.45 grams (87.4%) assay yield of **9e**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and careful

[13] (a) Hartough, H. D.; Kosak, A. I. *J. Am. Chem. Soc* **1947**, *69*, 3093-3096. (b) Armstrong, A.; Pullin, R.D. C.; Jenner, C. R.; Scutt, J. N. *J. Org. Chem.* **2010**, *75*, 3499-3502.

concentration *in vacuo* at 0 °C provided the desired compound **9e** as a volatile yellow oil (2.10 g, 91.8 wt%, 68.8% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H), 2.49 (s, 3H), 4.73 (app. s, 2H), 7.19 (s, 1H), 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 26.6, 129.4, 134.3, 138.7, 143.9, 190.5; HRMS calculated for $C_7H_8O_1S_1$ [M+H] 141.03686; found 141.03690; IR (neat): 3030, 2984, 1820 cm^{-1}.



4-Phenylthiophene-2-carbaldehyde (9f).[14] Magnesiothiophene **8a** was generated according to the general magnesiation procedure (20.0 mmol scale, 18 h deprotonation), cooled to 20 °C, and then added over 30 min to a 0 °C solution of *N,N*-dimethylformamide (1.26 mL, 1.40 equiv) in THF (13.8 mL, 5 volumes). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of the thiophene-Grignard (30 min). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was slightly acidic (pH 6). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 3.32 grams (88.3%) assay yield of **9f**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and careful concentration *in vacuo* at 0 °C provided the desired compound **9f** as a white amorphous solid (2.07 g, 99.0 wt%, 54.4% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (m, 1H), 7.46 (m, 2H), 7.61 (m, 2H), 7.87 (m, 1H), 8.05 (m, 1H), 9.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 126.3, 128.0, 129.1, 129.6, 134.4, 134.7, 143.7, 144.4, 182.9; HRMS calculated for $C_{11}H_8O_1S_1$ [M+H] 189.03686, found 189.03723; HRMS calculated for $C_{11}H_7O_1S_1Na$ [M+Na] 211.01881, found 211.01881; IR (neat): 3030, 2984, 2848, 1780, 1390 cm^{-1}.

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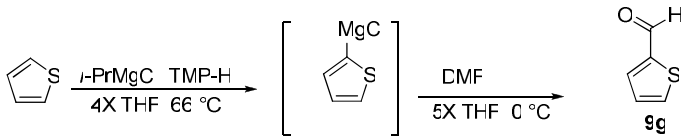
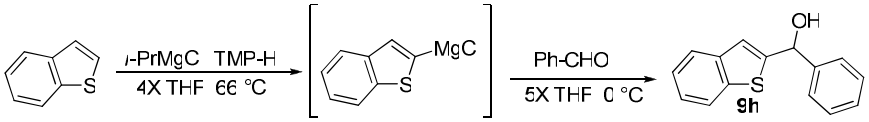
[14] Johnson, A. L. *J. Org. Chem.* **1976**, *41*, 1320-1324.



Thiophene-2-carbaldehyde (9g).[15] Magnesiothiophene **8b** was generated according to the general magnesiation procedure (20.0 mmol scale, 20 h deprotonation), cooled to 20 °C, and then added over 30 min to a 0 °C solution of *N,N*-dimethylformamide (1.26 mL, 1.40 equiv) in THF (13.8 mL, 5 volumes). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of the thiophene-Grignard (10 min). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was slightly acidic (pH 6). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 2.07 grams (92.3%) assay yield of **9g**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and careful concentration *in vacuo* at 0 °C provided the desired compound **9g** as a colorless volatile oil (1.20 g, 99.0 wt%, 53.0% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (m, 1H), 7.79 (m, 2H), 9.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6, 143.5, 136.2, 134.8, 128.0; HRMS calculated for $C_5H_5O_1S_1$ [M+H] 113.00556, found 113.00587; IR (neat): 2970, 1750, 1420 cm^{-1}.



Benzo[b]thiophen-2-yl(phenyl)methanol (9h).[16] Magnesiothiophene **8c** was generated according to the general magnesiation procedure (20.0 mmol scale, 24 h deprotonation), cooled to 20 °C, and then added over 30 min to a 0 °C solution of benzaldehyde (2.85 mL, 1.40 equiv) in THF (13.8 mL, 5 volumes). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of

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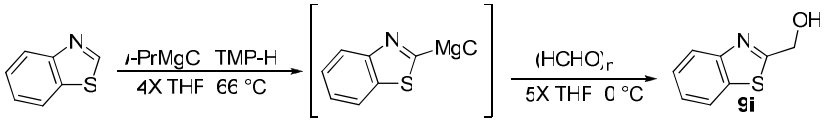
[15] CAS No [98-03-3]

[16] (a) Shirley, D. A.; Cameron, M. D. *J. Am. Chem. Soc.* **1952**, *74*, 664-665. (b) Rohbogner, C. J.; Wunderlich, S. H.; Clososki, G. C.; Knochel, P. *Eur. J. Org. Chem.* **2009**, 1781-1795.

the thiophene-Grignard (16 h). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was slightly acidic (pH 6). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 3.90 grams (81.1%) assay yield of **9h**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and concentration *in vacuo* provided the desired compound **9g** as a white solid (3.30 g, 93.8 wt%, 64.4% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.73 (s, exchangeable, 1H), 6.11 (m, 1H), 7.13 (m, 1H), 7.29-7.44 (m, 5H), 7.51 (m, 2H), 7.71 (m, 1H), 7.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.7, 142.6, 139.8, 139.5, 128.7, 128.6, 126.5, 124.3, 124.2, 123.7, 122.7, 121.3, 73.1; HRMS calculated for $C_{15}H_{12}O_1S_1Na$ [M+Na] 263.05011, found 263.05045; IR (neat): 3020, 2984, 2640, 1690, 1270, 1100 cm^{-1}.



Benzo[d]thiazol-2-ylmethanol (9i).[17] Magnesiothiophene **8c** was generated according to the general magnesiation procedure (20.0 mmol scale, 30 h deprotonation), cooled to 20 °C, and then added over 30 min to a 0 °C solution of benzaldehyde (2.85 mL, 1.40 equiv) in THF (13.8 mL, 5 volumes). The resulting mixture was stirred at 0 °C, until HPLC analysis indicated >95% conversion of the thiazole-Grignard (24 h). The reaction mixture was quenched with water, and then 6N HCl was added until the reaction mixture was acidic (pH 4). MTBE was added to provide a clean phase cut. The layers were separated, and the aqueous layer was washed once with MTBE. HPLC analysis of the combined crude organic layers revealed 2.36 grams (71.4%) assay yield of **9i**. Purification by flash chromatography (ISCO Companion, MTBE/hexanes gradient) and concentration *in vacuo* provided the desired compound **9i** as a yellow oil (2.27 g, 82.5 wt%, 56.6% adjusted isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.10 (t, J = 6.1 Hz, 1H), 5.04 (d, J= 6.1 Hz, 2H), 7.35 (m, 2H), 7.84 (m, 2H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 170.2, 153.0, 136.4, 124.6, 124.5, 123.4, 122.4, 59.9. HRMS calculated for $C_8H_7N_1O_1S_1Na$ [M+Na] 188.01460. Found 188.01400; mp 102 °C; IR (neat): 3190, 3065, 2988, 2940, 2340, 1050 cm^{-1}.

[17] (a) Courtot, C.; Tchelitcheff, S. *Compt. Rend.* **1943**, *217*, 201-3. (b) Jeffreys, R. A. *J. Chem. Soc.* **1954**, 503-505.

Acquisition Time (sec)	10.2239	*Comment*	neill	*Date*	14 Jan 2010 16:44:16		
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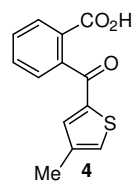
Temperature (degree C)	28.560						



4

Acquisition Time (sec)	2.3069	*Comment*	neill	*Date*	14 Jan 2010 17:00:07		
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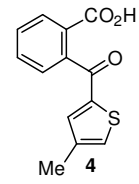
Nucleus	13C	*Number of Transients*	256	*Origin*	Bruker BioSpin GmbH		
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	28408.66	*Solvent*	DMSO-d6	*Spectrum Offset (Hz)*	12015.6895	*Sweep Width (Hz)*	28408.22
Temperature (degree C)	28.760						



4

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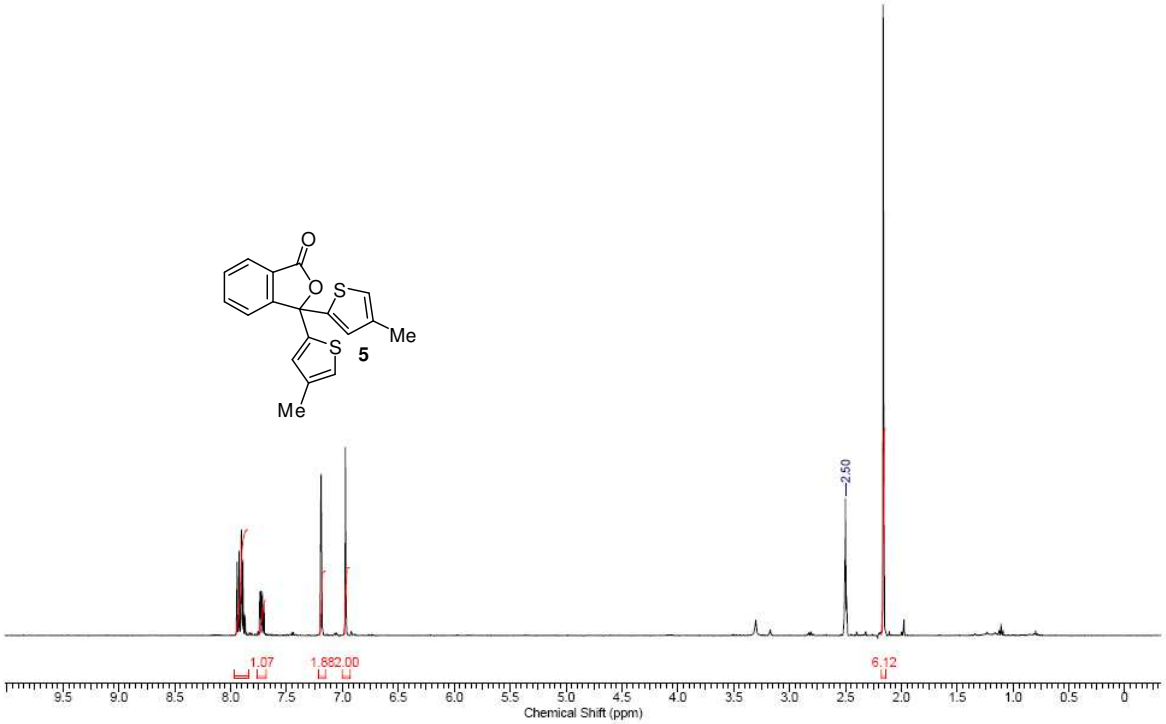
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	6410.16	*Solvent*	DMSO-d6	*Spectrum Offset (Hz)*	2495.3164	*Sweep Width (Hz)*	6410.06
Temperature (degree C)	27.000						



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Original Points Count	65536	*Owner*	smallmolecules	*Points Count*	65536	*SW(cyclical) (Hz)*	6410.16
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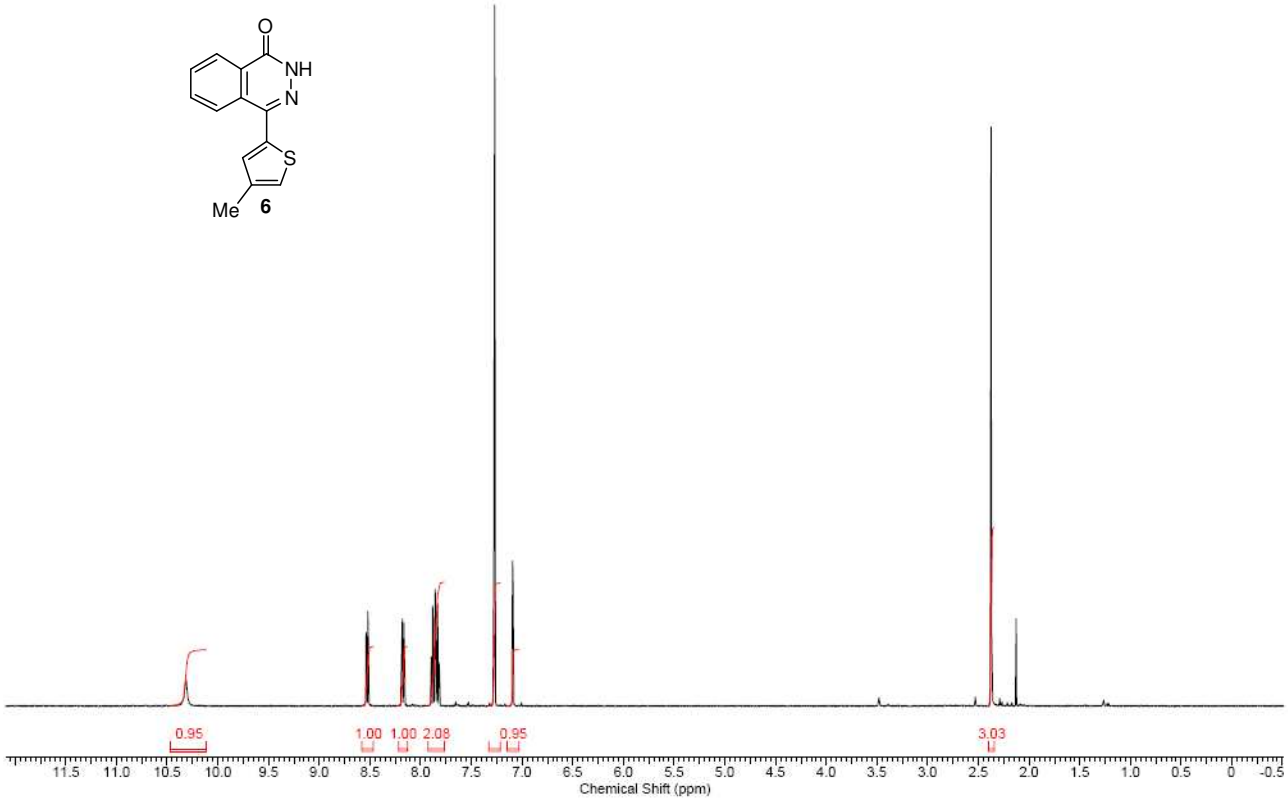
Temperature (degree C)	27.000						



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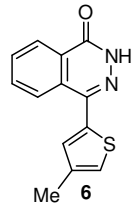
Temperature (degree C)	27.000						



6

Acquisition Time (sec)	10.2239	*Comment*	kngai	*Date*	20 Aug 2008 13:59:29		
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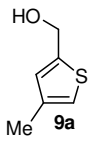
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2493.1318
Sweep Width (Hz)	6410.06	*Temperature (degree C)*	27.000				



9a

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Nucleus	13C	*Number of Transients*	128	*Origin*	Bruker BioSpin GmbH		
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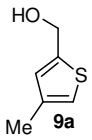

9a

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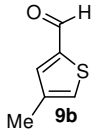
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2492.8384
Sweep Width (Hz)	6410.06	*Temperature (degree C)*	27.000				



9b

Acquisition Time (sec)	2.3069	*Comment*	kngai	*Date*	18 Aug 2008 15:28:50		
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Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	28408.66	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	12070.8818
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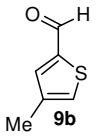
93279-22-6_20.DX



9b

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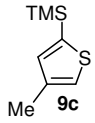
SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2493.0339
Sweep Width (Hz)	6410.06	*Temperature (degree C)*	27.000				



9c

Acquisition Time (sec)	2.3069	*Comment*	kngai	*Date*	18 Aug 2008 14:27:04		
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Frequency (MHz)	100.57	*Nucleus*	13C	*Number of Transients*	512	*Origin*	Bruker BioSpin GmbH
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	28408.66	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	12064.1025
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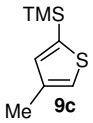
93279-27-4_20.DX



9c

Acquisition Time (sec)	10.2239	*Comment*	kngai	*Date*	09 Jun 2008 21:14:42		
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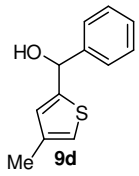
SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2795.1621
Sweep Width (Hz)	6410.06	*Temperature (degree C)*	27.000				



9d

Acquisition Time (sec)	2.3069	*Comment*	kngai	*Date*	20 Aug 2008 10:31:38		
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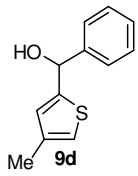
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	28408.66	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	12061.5010
Sweep Width (Hz)	28408.22	*Temperature (degree C)*	27.000				

93279-8-6_50.DX



9d

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SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2795.6511
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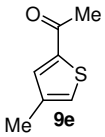

9e

Acquisition Time (sec)	2.3069	*Comment*	kngai	*Date*	18 Aug 2008 20:30:25		
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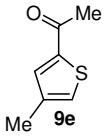
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	28408.66	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	12053.2646
Sweep Width (Hz)	28408.22	*Temperature (degree C)*	27.000				

93279-19-2_10.DX



9e

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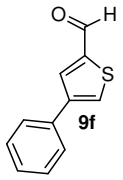
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2492.8384
Sweep Width (Hz)	6410.06	*Temperature (degree C)*	27.000				



9f

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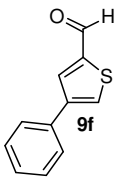
SW(cyclical) (Hz)	28408.66	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	12064.9688
Sweep Width (Hz)	28408.22	*Temperature (degree C)*	27.000				



9f

Acquisition Time (sec)	10.2239	*Comment*	kngai	*Date*	05 Aug 2008 19:30:12		
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SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2492.8381
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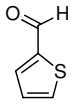

9g

Acquisition Time (sec)	2.3069	*Comment*	kngai	*Date*	18 Aug 2008 18:00:57		
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SW(cyclical) (Hz)	28408.66	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	12028.1230
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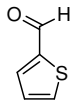

9g

Acquisition Time (sec)	10.2238	*Comment*	kngai	*Date*	27 Aug 2008 10:03:25		
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SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2795.3579
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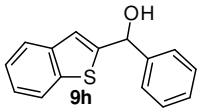
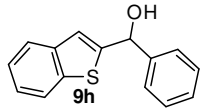
94406-27-10_10.DX



9h

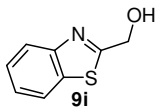
Acquisition Time (sec)	2.3069	*Comment*	kngai	*Date*	27 Aug 2008 10:47:05		
Date Stamp	27 Aug 2008 10:47:05			*File Name*	\\CHOWDER\TEAMS\NMR\JCAMP\KNGAI\2008\93279-73-11_10.DX		
Frequency (MHz)	100.62	*Nucleus*	13C	*Number of Transients*	512	*Origin*	Bruker BioSpin GmbH
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	28408.66	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	12061.0391
Sweep Width (Hz)	28408.22	*Temperature (degree C)*	27.000				

93279-73-11_10.DX



9h

Acquisition Time (sec)	10.2239	*Comment*	kngai	*Date*	21 Jul 2008 16:14:25		
File Name	\\CHOWDER\TEAMS\NMR\JCAMP\KNGAI\2008\93279-73-01_10.DX					*Frequency (MHz)*	399.93
Nucleus	1H	*Number of Transients*	16	*Origin*	Bruker BioSpin GmbH		
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	6410.16	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	2492.8381
Sweep Width (Hz)	6410.06	*Temperature (degree C)*	27.000				



9i

Acquisition Time (sec)	2.3069	*Comment*	kngai	*Date*	27 Aug 2008 14:47:05		
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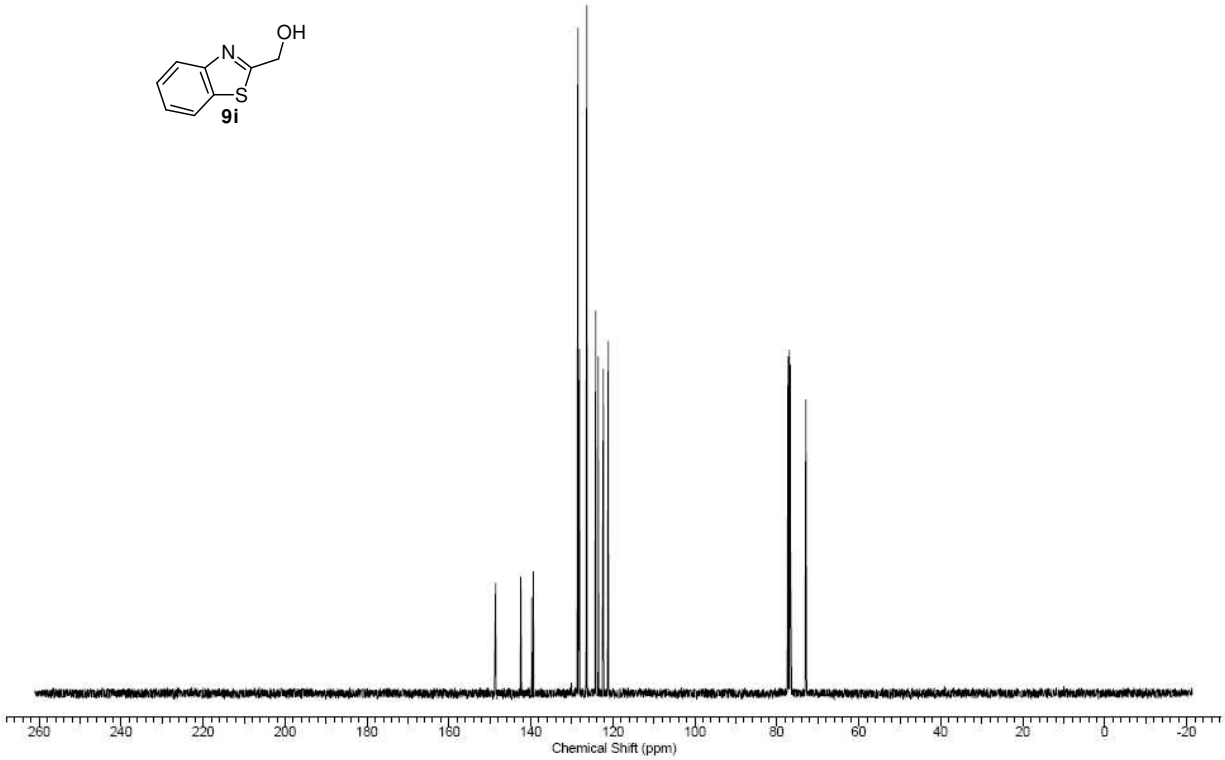
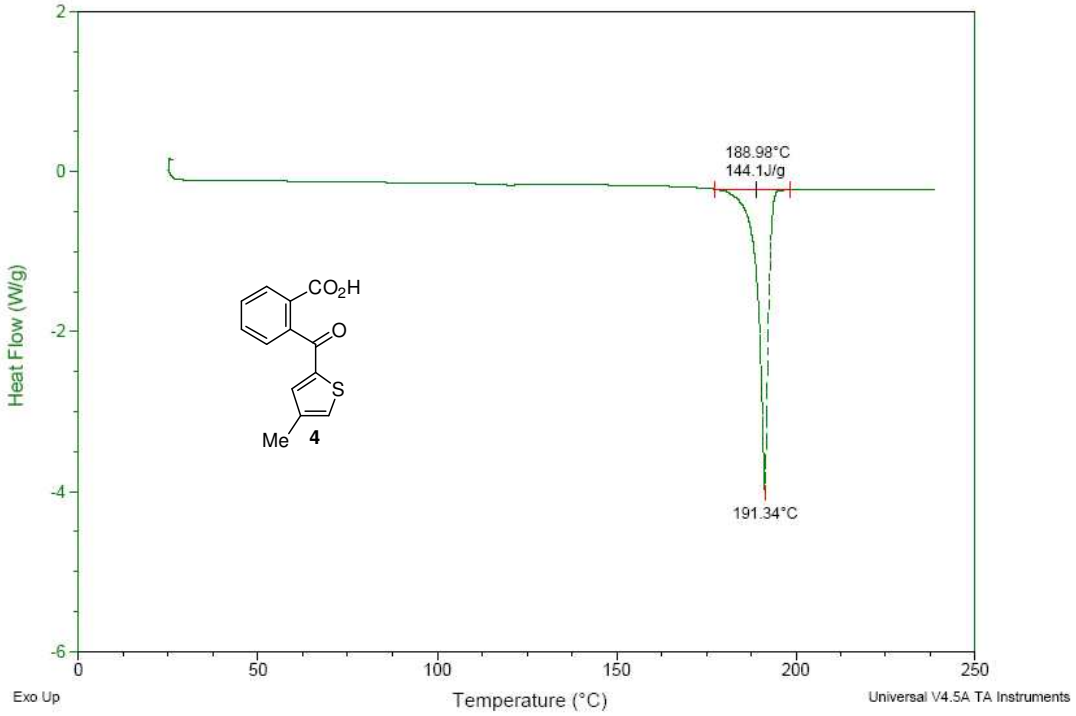
Nucleus	13C	*Number of Transients*	512	*Origin*	Bruker BioSpin GmbH		
Original Points Count	65536	*Owner*	shr-usam-cc10046			*Points Count*	65536
SW(cyclical) (Hz)	28408.66	*Solvent*	CHLOROFORM-d			*Spectrum Offset (Hz)*	12061.0391
Sweep Width (Hz)	28408.22	*Temperature (degree C)*	27.000				



Sample: 111129-03-8
Size: 5.5300 mg
Method: 25C to 240C at 5C/min
Comment: keto-acid product

DSC

File: E:\DSC\2010\March\NFL\111129-03-8.007
Operator: NFL
Run Date: 29-Mar-2010 23:03
Instrument: DSC Q200 V24.3 Build 115



Sample: 110999-49-10
Size: 3.0900 mg
Method: 25C to 240C at 10C/min
Comment: Final solid

DSC

File: E:\DSC\2010\March\Steve\110999-49-10.001
Operator: SMM
Run Date: 09-Mar-2010 16:49
Instrument: DSC Q200 V24.3 Build 115