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Novel Synthesis Of Thianinhydrin

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Abstract: The synthesis of the previously reported thianinhydrin (**12**) was achieved from 3-methylthiophene *via* the corresponding 5,6-dihydrocyclopenta[*b*]thiophen-4,6-dione (**10**). Conversion of **10** to the tricarbonyl (**12**) proceeded in good yield using dimethydioxirane oxidation of 5,6-dihydro-5-dimethyl aminomethylenecyclopenta[*b*]thiophen-4,6-dione (**14**). The fluorescence intensity of the zinc salt of the product of **12** and glycine was similar to that obtained from the product of ninhydrin and the same amino acid. © 1997 Elsevier Science Ltd.

Introduction

Since the serendipitous discovery of ninhydrin[1] and its reaction with amines and amino acids to afford the violet-colored compound known as Ruhemann's purple,[2] this reagent has earned a prominent position in analytical, peptide, and forensic chemistry. Many synthetic strategies have been designed for the formation of the strained tricarbonyl ring,[3] but few general, high-yielding routes to ninhydrin analogs have been found.

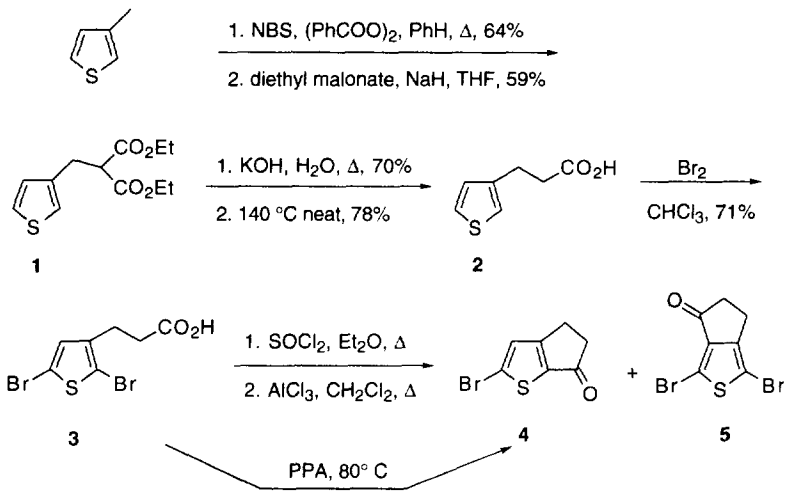
In a continuation of our synthetic efforts toward novel ninhydrin analogs which can be used as reagents for the detection of latent fingerprints,[4] we report a new approach to the previously known thianinhydrin **12** (5,5-dihydroxy-5,6-dihydrocyclopenta[*b*]thiophen-4,6-dione). This thiophene isostere of ninhydrin was prepared by Dallemagne and co-workers[5] *via* diazotization of amino cyclopenta[*b*]thiophenones and subsequent oxidation to the corresponding tricarbonyl. Since the use of this compound as a reagent for the visualization of latent fingerprints had not been investigated, we developed an efficient, large-scale synthesis of **12** in order to study its color-forming reaction with amino acids. The new approach (Scheme 3) provides **12** from the corresponding 5,6-dihydrocyclopenta[*b*]thiophen-6-one (**6**)[6,7] in four high yielding steps, utilizing simple reagents. The methodology described is applicable to the syntheses of other analogs.

Discussion and Results

We began our investigations (Scheme 1) with the radical side-chain bromination of 3-methyl thiophene,[8]

followed by the subsequent displacement of the allylic bromide with sodio diethyl malonate to prepare diester **1**.[9] Saponification of the ester proceeded in good yield by heating at reflux with aqueous hydroxide.

Scheme 1



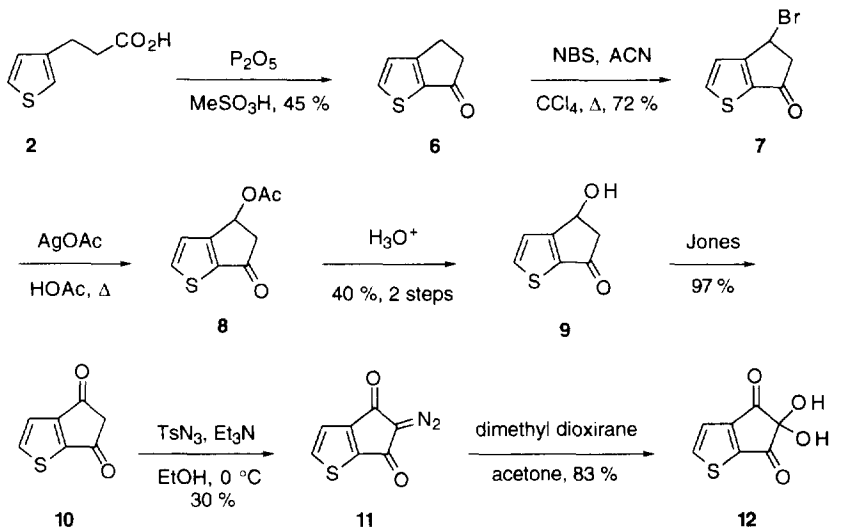
Decarboxylation of the diacid was effected by heating this compound neat. Since we had envisioned a bromination step as part of our oxidation protocol to form the trione, we brominated the two and five positions of **2** and attempted cyclization of the resulting 2,5-dibromo acid chloride. We expected formation of the 2,3-fused system (**4**) to predominate since bromine is not an effective blocking group in the reactive *alpha* positions under Friedel-Crafts conditions.[10,11] Cyclization of the acid chloride with aluminum trichloride afforded a mixture of **4** and **5** which was virtually inseparable by column chromatography. Ring-closure with PPA afforded a low yield of **4**.[11]

The thiophene unsubstituted acid **2** was then treated with different Friedel-Crafts reagents, the best conditions for this cyclization being P_2O_5 in methanesulfonic acid[12] (Scheme 2). Various methods of oxidizing 1-indanones that were successful in the synthesis of other ninhydrin analogs[3] proved too vigorous for the fused five-membered rings. Since the oxidation of 1,3-indandiones proceeds more readily than that of indanones, we decided to prepare the 1,3-dione **10**[5] *via* bromide **7**. Mono-bromination of thiaindanone **6**[6,7] under radical conditions using the reportedly more reactive initiator azobis(cyclohexanecarbonitrile) (ACN)[13] proceeded in good yield. Solvolysis of the bromide with silver acetate in acetic acid, and subsequent hydrolysis of the acetate afforded keto alcohol **9**.[5] It was determined that purification of the intermediate acetate did not affect the yield of the alcohol, so crude **8** was hydrolyzed directly after filtration and concentration of the reaction mixture. Oxidation of alcohol **9** to the diketone proceeded in nearly quantitative yield using Jones reagent.

Oxidation of dione **10**[5] was not as straightforward as imagined. Attempted α-nitrosation of the 1,3-diketone afforded only starting material, even when the more reactive *n*-butyl nitrite[14] was used in place of sodium nitrite. α-Dibromination proceeded in high yield, but subsequent Kornblum oxidation to the triketone[15] could not be effected. We then investigated the formation of diazodione **11**, followed by oxidation using

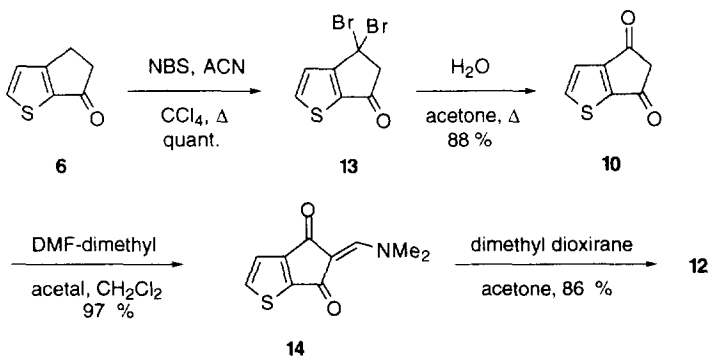
dimethydioxirane[16,17] which allowed a clean conversion to the thianinhydrin (Scheme 2). Dimethydioxirane was also used recently in the formation of tricarbonyls.[18,19]

Scheme 2



To make this approach more attractive for commercial production of ninhydrin analogs, we eliminated the use of silver and chromium reagents. Dione **10** was prepared beginning with the radical dibromination of **6** in quantitative yield. The crude dibromide **13** was heated in an aqueous acetone solution to provide **10** (Scheme 3). We have also improved the yield for the oxidation of **10** while avoiding the use of the potentially explosive tosyl azide. Dione **10** was treated with DMF-dimethyl acetal[20] to afford enamine **14** in nearly quantitative yield. Treatment of **14** with dimethydioxirane afforded a clean conversion to the ninhydrin.

Scheme 3



The fluorescence intensity of **12** on reaction with glycine and treatment with zinc nitrate was measured and compared to the intensities of the products from ninhydrin and one of the most efficient analogs 5-(2-thienyl)ninhydrin,[4] under the same conditions. These measurements showed that the fluorescences of the zinc complexes from ninhydrin and **12** were about equal to that of the background Whatman paper. The fluoresence of the complex of the product resulting from 5-(2-thienyl)ninhydrin and glycine was roughly three times more

intense than the background fluorescence. Therefore, at the concentrations and the excitation power used, the zinc complexes of **12** and ninhydrin do not fluoresce, but the complex from 5-(2-thienyl)ninhydrin does, as was expected since this compound is one of the most fluorescent ninhydrin analogs.

The synthesis of a sulfur analog of ninhydrin which does not exhibit significantly increased fluorescence intensity over ninhydrin on reaction with amino acids dispels the previous belief that the sulfur atom was the cause of the increased fluorescence seen with other sulfur analogs. It also reaffirms the belief that thiophene and benzene derivatives exhibit strikingly similar physical properties.

This new route to ninhydrin analogs not only provides a short synthesis of the previously reported thianinhydrin under mild conditions, but the protocol employed will allow the preparation of a variety of other heterocyclic analogs. The oxidation of 1,3-diketones using this mild and inexpensive two-step procedure should also be applicable to the synthesis of other tricarbonyl compounds.

Experimental Section

All solvents were reagent grade. Triethylamine and CH_2Cl_2 were distilled from CaH_2. Tosyl azide[21] and dimethydioxirane[16] were prepared as described in the literature. Proton (500 MHz) and carbon (125 MHz) magnetic resonance spectra were obtained on an AM 500 instrument, in $CDCl_3$ unless otherwise noted. Melting points are reported in °C and are uncorrected. High resolution mass spectra and elemental analyses were obtained at the Department of Chemistry of the University of Pennsylvania. Fluorescence intensity measurements were conducted on the zinc complexes of the products of glycine and ninhydrin, thianinhydrin and 5-(2-thienyl)ninhydrin at the Forensic Services Division of the United States Secret Service using a Hitachi F-4500 fluorescence spectrophotometer. The three reagent solutions were 1 mM, the glycine solution was 0.5 mM, and the zinc nitrate solution was 100 mM, each in a 3:1 mixture of MeOH: H_2O. The samples were prepared by sequentially placing 10 microliter each of glycine, reagent, and zinc nitrate on the same spot on Whatman paper and allowing the spot to dry between each step. Three dimensional fluorescence plots made by using a solid sample holder provided measurements of maximum intensity and the corresponding excitation/emission wavelengths. All three samples exhibited excitation maxima at 525-550 nm and emission maxima at 550-575 nm depending on the specific reagent used in the complex.

3-Thiophen-3-yl Methyl Malonic Acid Diethyl Ester (1).[9] ^{1}H NMR δ 1.22 (t, J=7.09 Hz, 6H), 3.24 (d, J=7.67 Hz, 2H), 3.63 (t, J=7.77 Hz, 1H), 4.15 (q, J=7.09 Hz, 4H), 6.93 (d, J=3.63 Hz, 1H), 7.01 (s, 1H), 7.22 (d, J=3.07 Hz, 1H); ^{13}C NMR δ 13.92, 29.10, 53.11, 61.33, 121.84, 125.54, 128.04, 137.99, 168.68; IR ($CHCl_3$) 2990, 1730, 1450, 1370, 1335, 1275, 1245, 1150, 1030, 855 cm^{-1}; HRMS *m/z* calcd for $C_{12}H_{16}O_4S$ $(M)^+$ 256.0769, found 256.0762.

3-Thiophen-3-yl-propionic Acid (2).[9] R_f 0.24 (70% EtOAc/pet. ether); ^{1}H NMR δ 2.61 (t, J=7.64 Hz, 2H), 2.90 (t, J=7.62 Hz, 2H), 6.87 (d, J=4.96 Hz, 1H), 6.91 (d, J=1.72 Hz, 1H), 7.18 (dd, J=4.88, 2.97 Hz, 1H); ^{13}C NMR δ 25.08, 34.86, 120.72, 125.72, 127.87, 140.39, 179.21; IR ($CHCl_3$) 3500, 2900 -3020, 1710, 1410, 1230 -1280, 1120, 1040, 915, 855 cm^{-1}; HRMS *m/z* calcd for $C_7H_8O_2S$ $(M)^+$ 156.0245, found 156.0246.

3-(2,5-Dibromothiophen-3-yl)propionic Acid (3).[11] A solution of bromine (3.8 mL, 0.07 mol, 2.05 equiv.) in $CHCl_3$ (50 mL) was added to **2** (5.724 g, 0.0367 mol) in $CHCl_3$ (75 mL) in an ice bath over 0.5

h. The solution was stirred 2 h at ambient temperature then poured onto ice (100 g). The $CHCl_3$ layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the dibromide which was recrystallized from hexane to afford a white solid (8.129 g) in 70 % yield. mp 87-88 °C (lit.[11] mp 89 °C); ^1H NMR δ 2.65 (t, J=7.66 Hz, 2H), 2.85 (t, J=7.68 Hz, 2H), 6.82 (s, 1H); ^{13}C NMR δ 24.16, 33.22, 108.87, 110.68, 130.53, 139.97, 177.80; IR ($CHCl_3$) 2359, 2341, 1715, 1441, 1002, 816 cm^{-1}; HRMS *m/z* calcd for $C_7H_6Br_2O_2S$ $(M)^+$ 311.8455, found 311.8482.

2-Bromo-4,5-dihydrocyclopenta[*b*]thiophen-6-one (4).[11] Dibromide **3** (2.19 g, 6.96 mmol) was dissolved in CH_2Cl_2 (15 mL) and added to PPA (60 g) heated to 80 °C with vigorous stirring. The mixture was stirred and heated for 1 h, then poured onto ice (150 g) and extracted with CH_2Cl_2 (4 × 100 mL). The combined extracts were washed with 5 % NaOH (2 × 30 mL), 1N HCl (30 mL), H_2O (3 × 30 mL), dried (Na_2SO_4), filtered, and concentrated to afford a black oil. Column chromatography using 25 % CH_2Cl_2 / pet. ether and 50 % CH_2Cl_2 / pet. ether afforded **4** (0.32 g) in 20 % yield. mp 113-114 °C (lit.[11] mp 116 °C); ^1H NMR δ 2.87 -2.92 (m, 2H), 3.00-3.04 (m, 2H), 7.10 (s, 1H); ^{13}C NMR δ 24.25, 39.63, 127.18, 129.45, 141.19, 167.41, 195.82; IR ($CHCl_3$) 3005, 2410, 1690, 1425, 1375, 1300, 1260 -1200, 1165, 1035, 990, 925, 840 cm^{-1}; HRMS *m/z* calcd for C_7H_6BrOS $(MH)^+$ 215.9244, found 215.9223.

1,3-Dibromo-5,6-dihydrocyclopenta[*c*]thiophen-4-one (5). Acid **3** (3.47 g, 10.86 mmol) was heated with thionyl chloride (3 mL) at reflux for 5 minutes, and the $SOCl_2$ was removed under reduced pressure. The resulting yellow oil was dissolved in CH_2Cl_2 (50 mL), aluminum trichloride (4.2 g, 33 mmol, 3 equiv.) was added, and the mixture was heated for 10 minutes. The reaction was poured onto an ice-HCl mixture (75 mL) and extracted with $CHCl_3$ (4 × 25 mL). The combined $CHCl_3$ layers were washed with 2N NaOH (25 mL), 2N HCl (25 mL), H_2O (25 mL), dried (Na_2SO_4), and concentrated to afford a mixture of **4** and **5** (2.42 g) which were nearly inseparable using column chromatography or recrystallization. Small amounts of **4** (0.53 g) and **5** (1.08 g) were obtained by repeated chromatography using 50% CH_2Cl_2 / pet. ether. mp 134.5-135.5 °C; ^1H NMR δ 2.87-3.05 (m); ^{13}C NMR δ 24.49, 39.29, 112.73, 127.43, 139.90, 166.26, 195.27; IR ($CHCl_3$) 3020, 2940, 1720, 1701, 1415, 1395, 1295, 1270, 1255, 1115, 1060, 990, 935, 910, 800, 750, 695 cm^{-1}; HRMS *m/z* calcd for $C_7H_4Br_2OS$ $(M)^+$ 293.8350, found 293.8341.

5,6-Dihydrocyclopenta[*b*]thiophen-6-one (6).[6,7] Finely powdered **2** (3.0 g, 19 mmol) was added to a solution of phosphorous pentoxide (15 g) in methanesulfonic acid (100 mL) and the mixture was stirred at ambient temperature for 40 min. The dark red solution was poured onto ice (150 g) and the mixture was extracted with CH_2Cl_2 (4 × 125 mL). The combined organic extracts were washed with 5 % NaOH (125 mL), 1 N HCl (125 mL), and brine (125 mL), dried (Na_2SO_4), filtered and concentrated. The solid was purified by column chromatography, eluting with 25 % Et_2O / pet. ether to provide **6** as an ivory solid (1.15 g) in 44 % yield. mp 91-92 °C (lit.[6] mp 92-93 °C); R_f 0.51 (40 % EtOAc / pet. ether); ^1H NMR δ 2.91 -2.93 (m, 2H), 2.96 -2.98 (m, 2H), 6.99 (d, J=4.83 Hz, 1H), 7.84 (d, J=4.78 Hz, 1H); ^{13}C NMR δ 23.81, 41.13, 123.87, 140.35, 140.99, 168.85, 197.07; IR ($CHCl_3$) 3000, 2920, 1695, 1425, 1300, 1370, 965 cm^{-1}; HRMS *m/z* calcd for $C_7H_{10}NOS$ $(MNH_4)^+$ 156.0483, found 156.0475; Anal. Calcd for C_7H_6OS: C, 60.84; H, 4.37. Found: C, 60.37; H, 4.44.

4-Bromo-5,6-dihydrocyclopenta[*b*]thiophen-6-one (7). To a solution of **6** (0.486 g, 3.52 mmol) in CCl_4 (40 mL) was added NBS (0.626 g, 3.52 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (catalytic amount). The mixture was heated at reflux for 5 h as the reaction was followed by TLC. The mixture

was cooled to ambient temperature, filtered through a fritted funnel, and washed with CCl_4 (10 mL). The filtrate was concentrated to a red oil which was purified by column chromatography, eluting with 20 % Et_2O / pet. ether. Compound **7** was obtained as an orange oil (0.541 g) in 71 % yield. R_f 0.46 (50 % Et_2O / pet. ether); ^1H NMR δ 3.27 (dd, J=19.09, 1.92 Hz, 1H), 3.62 (dd, J=19.14, 6.52 Hz, 1H), 5.43 (dd, J=1.95, 6.48 Hz, 1H), 7.14 (d, J=4.85 Hz, 1H), 7.93 (d, J=4.88 Hz, 1H); ^{13}C NMR δ 36.31, 52.81, 123.96, 141.45, 141.83, 167.13, 191.59; IR ($CHCl_3$) 1710, 1430, 1385, 825 cm^{-1}; HRMS *m/z* calcd for C_7H_6BrOS $(MH)^+$ 216.9322, found 216.9317.

4-Acetoxy-5,6-dihydrocyclopenta[*b*]thiophen-6-one (8).[5] Silver acetate (0.42 g, 2.49 mmol) was added to a solution of bromide (**7**, 0.54 g, 2.49mmol) in acetic acid (12 mL), and the mixture was heated at reflux for 24 h. The mixture was cooled to ambient temperature and filtered. The solid was washed with acetic acid (5 mL) and discarded. The filtrate was concentrated under reduced pressure to provide an orange oil which was purified by column chromatography, eluting with 20 % Et_2O/ pet. ether and 50 % Et_2O/ pet. ether to afford an orange oil (0.49 g, 98 % yield) containing traces of acetic acid. Alternatively, the crude product could be carried on directly to the next reaction with no adverse effects. R_f 0.53 (2% MeOH/CH_2Cl_2); ^1H NMR δ 2.12 (s, 3H), 2.96 (dd, J=1.97, 18.51 Hz, 1H), 3.40 (dd, J=6.45, 19.52 Hz, 1H), 6.14 (dd, J=1.93, 6.45 Hz, 1H), 7.19 (d, J=4.78 Hz, 1H), 7.94 (d, J=4.78 Hz, 1H); ^{13}C NMR δ 20.68, 47.90, 66.97, 124.25, 140.81, 143.21, 164.55, 170.55, 192.03; IR ($CHCl_3$) 3000, 1740, 1710, 1430, 1370, 1300, 1275, 1240, 1035, 970 cm^{-1}; HRMS *m/z* calcd for $C_9H_{12}NO_3S$ $(MNH_4)^+$ 214.0538, found 214.0546.

4-Hydroxy-5,6-dihydrocyclopenta[*b*]thiophen-6-one (9).[5] Compound **8** (0.49 g, 2.48 mmol) was suspended in a solution of 3 N HCl (30 mL) cooled in an ice bath. The suspension was allowed to warm slowly to ambient temperature and vigorous stirring was continued for a total of 24 h. The orange mixture was extracted with $CHCl_3$ (3 × 30 mL), and the combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography, eluting with CH_2Cl_2 and 5% MeOH/ CH_2Cl_2 to afford a golden oil (0.142 g) in 37% yield which solidified on standing. mp 67.5-68.5 °C (lit.[5] mp 70 °C); R_f 0.26 (5% MeOH/CH_2Cl_2); ^1H NMR δ 2.83 (dd, J=1.91, 18.34 Hz, 1H), 3.30 (dd, J=6.15, 18.37 Hz, 1H), 3.79 (s, 1H), 5.31 (s, 1H), 7.21 (d, J=4.78 Hz, 1H), 7.92 (d, J=4.73 Hz, 1H); ^{13}C NMR δ 51.51, 65.55, 123.39, 141.39, 141.65, 169.29, 194.22; IR ($CHCl_3$) 1710, 1600 cm^{-1}; HRMS *m/z* calcd for $C_7H_{10}NO_2S$ $(MNH_4)^+$ 172.0433, found 172.0432.

5,6-Dihydrocyclopenta[*b*]thiophen-4,6-dione (10).[5] **Method A**: A solution of chromium trioxide (0.092 g, 0.92 mmol) in sulfuric acid (0.08 mL) and H_2O (0.6 mL) was added to **9** (0.142 g, 0.920 mmol) in acetone (5 mL) at ambient temperature. The reaction was allowed to stir for 1 h, and was filtered to remove a green precipitate. The filtrate was concentrated under reduced pressure, redissolved in CH_2Cl_2 (20 mL), washed with H_2O (5 mL) and brine (5 mL), and dried (Na_2SO_4). The solution was concentrated to afford the diketone as a pale yellow solid (0.140 g) in quantitative yield.

Method B: Crude dibromide **13** (0.235 g, 0.795 mmol) was heated in a solution of acetone (15 mL) and H_2O (25 mL) at reflux for 3 h. The acetone was removed under reduced pressure and the aqueous mixture was extracted with $CHCl_3$ (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The solid residue was purified by column chromatography, eluting with CH_2Cl_2 and 1% MeOH / CH_2Cl_2 to afford **10** (0.106 g) in 88% yield. mp 130-131 °C (lit.[5] mp 132 °C); R_f 0.26 (100% CH_2Cl_2); ^1H NMR δ 3.48 (s, 2H), 7.39 (d, J=4.84 Hz, 1H), 7.99 (d, J=4.85 Hz, 1H); ^{13}C NMR δ 49.64, 120.81, 141.25, 156.39, 158.51,

188.15, 189.94; IR ($CHCl_3$) 1745, 1710, 1440, 1385, 1270, 1240 cm^{-1}; HRMS *m/z* calcd for $C_7H_8NO_2S$ $(MNH_4)^+$ 170.0296, found 170.0294.

A different method[22] using the electrophilic acylation of the acid chloride of 2-thiophenecarboxylic acid was also attempted but did not afford the same product as the two previous methods. The melting point reported for this dione[22] is also inconsistent with the one reported by Dallemagne *et al*[5] and that observed for our product.

5-Diazo-5,6-dihydrocyclopenta[*b*]thiophen-4,6-dione (11). Dione **10** (0.821 g, 5.39 mmol) was suspended in absolute ethanol (5 mL) and cooled in an ice bath. Triethylamine (0.9 mL, 7.0 mmol, 1.3 equiv.) was added all at once and the solution was allowed to stir for 5 minutes and cooled again in an ice bath. Tosyl azide[21] (1.49 g, 7.56 mmol, 1.4 equiv.) was added dropwise and the mixture was allowed to stir for 1 h. A golden solid was collected by filtration and washed with cold ethanol. The crude solid was recrystallized from ethanol with hot filtration. The diazo dione (0.289 g) was obtained as golden needles in 30% yield. mp 121-122 °C; R_f 0.37 (2% MeOH/CH_2Cl_2); ^1H NMR (CD_3OD) δ 7.33 (d, J=4.80 Hz, 1H), 8.16 (d, J=4.80 Hz, 1H); ^{13}C NMR (CD_3OD) δ 122.03, 141.61, 147.78, 150.56, 176.53, 178.26; IR ($CHCl_3$) 2120, 1715, 1690, 1375, 1350, 1235 cm^{-1}; HRMS *m/z* calcd for $C_7H_3O_2S$ $(M)^+ - N_2$ 150.9854, found 150.9858.

5,5-Dihydroxy-5,6-dihydrocyclopenta[*b*]thiophen-4,6-dione (12).[5] From 11. To a solution of diazo dione **11** (0.239 g, 1.341 mmol) in acetone (15 mL) at ambient temperature was added dimethydioxirane[16] in acetone (excess, 5 mL) and the golden solution was allowed to stir for 1 h. The solution was concentrated under reduced pressure, and the solid which formed was dissolved in hot H_2O (40 mL). Decolorizing carbon was added and the suspension was heated and filtered hot. The filtrate was concentrated to 6 mL and refrigerated. The beige needles were collected by filtration to afford the thianinhydrin (0.205 g) in 83 % yield. **From 14.** To a solution of **14** (0.019g, 0.096 mmol) in acetone (5 mL) was added dimethydioxirane in acetone (excess, 3 mL) and the golden solution turned pale yellow within two minutes. After stirring for 15 minutes, the solution was concentrated under reduced pressure. The crude solid was dissolved in hot H_2O (25 mL). Decolorizing carbon was added and the suspension was filtered hot. The filtrate was concentrated to 2 mL and refrigerated overnight. Thianinhydrin (0.015 g) was collected as beige needles in 86 % yield by filtration. mp 255-257 °C (red at 135°) [lit.[5] mp 257 °C (reddens at 80 °C)]; R_f 0.64 (10% MeOH/CH_2Cl_2); ^1H NMR (acetone-d_6) δ 6.56 (s, 2H, D_2O exchangeable), 7.55 (d, J=4.83 Hz, 1H), 8.49 (d, J=4.83 Hz, 1H) [lit. (DMSO-d_6) δ 7.61 (d), 8.59 (d)]; ^{13}C NMR (acetone-d_6) δ 94.15, 122.40, 144.31, 153.84, 154.88, 189.02, 190.16 [lit. (DMSO-d_6) δ 93.03, 121.64, 144.59, 152.36, 153.35, 189.33, 190.55] ; IR (KBr) 3419, 3100, 1748, 1726, 1694 cm^{-1} [lit. (KBr) 3400, 1745, 1715, 1685]; HRMS *m/z* calcd for $C_7H_3O_3S$ $(M)^+$ – OH 183.9830, found 183.9831; Anal. Calcd for $C_7H_4O_4S$: C, 45.65; H, 2.19. Found: C, 45.44; H, 2.20.

4,4-Dibromo-5,6-dihydrocyclopenta[*b*]thiophen-6-one (13). Ketone **6** (0.109 g, 0.795 mmol) was heated at reflux with NBS (0.304 g, 1.708 mmol) and azobis(cyclohexanecarbonitrile) (catalytic) in CCl_4 (25 mL) for 4h while monitoring the reaction by TLC. The solution was cooled to ambient temperature, filtered through a fritted funnel and washed with CCl_4 (10 mL). The filtrate was concentrated under reduced pressure to provide the dibromide (0.235 g) as a golden solid in quantitative yield. Recrystallization from hexane provides pure **13.** mp 85-87 °C; R_f 0.64 (50% Et_2O/pet. ether); ^1H NMR δ 4.15 (s, 2H), 7.35 (d, J=4.92 Hz, 1H), 7.98 (d, J=4.94 Hz, 1H); ^{13}C NMR δ 42.36, 67.26, 123.60, 138.44, 142.16, 169.98, 187.11; IR

($CHCl_3$) 1721, 1522, 1435, 1280, 1260, 940 cm^{-1}; HRMS *m/z* calcd for $C_7H_5Br_2OS$ $(MH)^+$ 294.8427, found 294.8436.

5,6-Dihydro-5-dimethylaminomethylenecyclopenta[*b*]thiophen-4,6-dione (14). To a solution of **10** (0.0569 g, 0.374 mmol) in CH_2Cl_2 (4 mL) was added DMF-dimethyl acetal[20] (0.09 mL, 0.75 mmol) and the solution was stirred at ambient temperature for 24 h. The crude material was purified directly by column chromatography, eluting with 1 % MeOH / CH_2Cl_2 to afford an isomeric mixture of **14** (0.075 g) as a yellow solid in 97 % yield. mp 131-132 °C; ^1H NMR δ 3.22 (s, 3H), 3.59 (s, 3H), 7.17 -7.20 (m, 2H), 7.57 (dd, J=4.70, 13.56 Hz, 1H); ^{13}C NMR δ 43.22, 47.58, 104.70, 120.56, 135.88, 150.22, 151.39, 153.65, 183.43, 187.07; IR (neat) 3098, 2927, 1702, 1654, 1613, 1435, 1385, 1260, 1252, 1144, 1106, 997, 920, 761 cm^{-1}; HRMS *m/z* calcd for $C_{10}H_{10}NO_2S$ $(MH)^+$ 208.0698, found 208.0696.

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