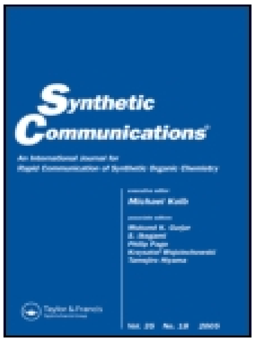

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# Synthesis of Quadruply Carbon-13 Labeled Tetramethyltetrathiaful Valene

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# SYNTHESIS OF QUADRUPLY CARBON-13 LABELED TETRAMETHYLTETRATHIAFULVALENE

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**Abstract:** A short synthesis of tetramethyltetrathiafulvalene quadruply labeled with carbon-13 is described.

Organic metals and superconductors are of great interest due to their potential use in applications requiring low density, low heat generation, flexibility and synthetically controlled properties.[1] Typically composed of charge transfer salts of tetrathiafulvalenes or tetraselenafulvalenes, they exhibit high and anisotropic conductivities. While synthetic studies continue to search for novel structures with enhanced electronic properties, physical studies are still uncovering new aspects of the electronic states which vary with anionic counterions, applied pressure, temperature, or applied magnetic fields. One probe which has proven valuable for the analysis of the physical properties of the Bechgaard salts is NMR.[2] We recently used $^1$H NMR studies to find singular behavior in the pressure-tuned competition between spin-Peierls and antiferromagnetic ground states of bis(tetramethyltetrathiafulvalene)

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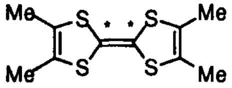
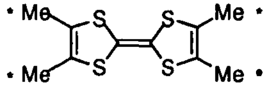
hexafluorophosphate.[3a] $^{13}C$ NMR is also a useful spectroscopic probe, but the low natural abundance of $^{13}C$ and inequivalent molecular sites can cause complications. Therefore, we have embarked on synthetic studies to prepare tetramethyltetrathiafulvalene selectively labeled with carbon-13 to facilitate physical studies employing $^{13}C$ NMR analysis.

Previously, we synthesized doubly carbon-13 labeled tetramethyltetrathiafulvalene (TMTTF) **1**, starting from carbon-13 labeled carbon disulfide, wherein the two carbons of the central double bond were labeled.[4] We then utilized **1** in solid state $^{13}C$ NMR studies which determined the high magnetic field – low temperature phase diagram of $(TMTTF)_2PF_6$.[3b] We speculated that having the $^{13}C$ spectroscopic probes of the magnetic behavior located on the methyl group carbons might provide complimentary information on the magnetic structure of the conducting salts. Therefore, we decided to prepare and test compound **2** wherein each of the four methyl groups of the tetramethyltetrathiafulvalene are carbon-13 labeled. This paper provides details on a short synthesis of $^{13}C_4$-tetramethyltetrathiafulvalene **2** starting from ethyl acetate labeled with carbon-13 at C-2.



**1**



**2**

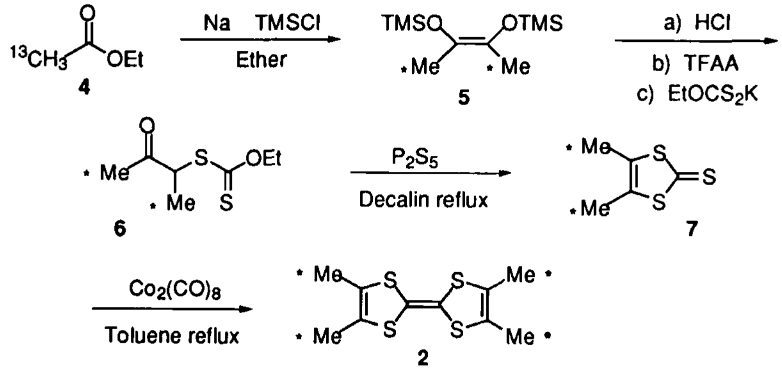
The most direct route to tetramethyltetrathiafulvalene labeled at the four methyl groups seemed to be direct deprotonation[5] of tetrathiafulvalene (**3**) followed by alkylation with methyl iodide. In fact, the tetralithio anion is known and has been reacted with electrophiles such as hexachloroethane, 1,2-dibromotetrachloroethane, or tellurium to form tetra-substituted tetrathiafulvalene derivatives.[6] Indeed, when tetrathiafulvalene was treated with 10 equivalents of LDA followed by 10 equivalents of methyl iodide in THF at rt, tetramethyltetrathiafulvalene was formed, but in only 2% yield from a complex mixture (eq 1). Therefore, we opted for a longer, more traditional synthesis despite the necessity of early introduction of the carbon-13 labels.

(1)

There are a number of efficient synthetic routes for the preparation of tetramethyltetrathiafulvalene, [7,8,9] but a route was needed that would provide a convenient method of incorporating $^{13}C$ labeled atoms from commercially available carbon-13 labeled starting materials. Therefore, like our previous synthesis of doubly labeled tetramethyltetrathiafulvalene, a modified version of the synthetic route of Ferraris and coworkers[8a] was used. The overall synthetic route is shown in Scheme 1. The key intermediate is the doubly labeled acyloin condensation product **5** and its conversion to the dithiocarbonate **6**.

The synthesis began with an acyloin condensation of C-2 carbon-13 labeled (99%) ethyl acetate to convert it to 2,3-bis(trimethylsilyloxy)-2-butene (**5**) in 74% yield as reported by Rühlmann.[10] Next, we planned to convert the acyloin adduct to the α-hydroxy ketone (acetoin) and subsequently to the bromide or mesylate to allow for $S_N2$ displacement to form the desired dithiocarbonate **6**. Hydrolysis of 2,3-bis(trimethylsilyloxy)-2-butene to acetoin was reported to occur in 73% yield,[10] but due to the small scale of our trial reactions with unlabeled material, yields of only 50% were obtained. Conversion to the α-bromo or α-mesyl ketone by a variety of procedures[11] gave poor results.

Scheme 1.



(* indicates an atom of $^{13}C$)

Because of the difficulties in the stepwise-reaction path we looked for a one-pot procedure to avoid the isolation and purification of the sensitive and volatile intermediates. F. Camps et al. reported a one-pot preparation of alkyl bromides from alcohols by reacting the alcohols with an excess of trifluoroacetic anhydride (TFAA) followed by substituting the trifluoroacetate with lithium bromide in HMPT.[12] Following this procedure, treatment of acetoin with TFAA followed by potassium O-ethyl dithiocarbonate[13] in acetone gave the desired dithiocarbonate in 35-39% yields. Next, we added in the hydrolysis of the trimethylsilyl acyloin adduct in the same reaction flask. Hence, treatment of 2,3-bis(trimethylsilyloxy)-2-butene with hydrochloric acid, followed by TFAA and then potassium O-ethyl dithiocarbonate gave the product O-ethyl S-3-oxobut-2-yl dithiocarbonate (**6**) in consistent yields of 37-39%. Unfortunately, the one time this was applied to the labeled compound, the yield unexpectedly dropped to 24%.

Formation of 1,3-dithiol-2-thione **7** via ring closure of the dithiocarbonate **6** with phosphorous pentasulfide in refluxing decalin typically gave yields of 75%. The high reaction temperature is important. There are a variety of methods to dimerize related thiones to substituted tetrathiafulvalenes,[7,8] but the methyl substituted case, as opposed to substrates with electron withdrawing substituents, is more problematic. Therefore, we again chose the procedure of Le Coustumer and Mollier using dicobaltoctacarbonyl due to its convenience.[8a] Le Coustumer and Mollier reported that this coupling reaction gave tetramethyltetrathiafulvalene in only 25% yield, but as we reported previously,[4] with highly purified reactants, yields of 50% can be obtained routinely. In fact, we speculate that even greater yields might be obtained from further optimization of the reaction conditions. In the case of our $^{13}C$ labeled substrate, using sublimed thione **7** and a freshly opened bottle of dicobaltoctacarbonyl, $^{13}C_4$-tetramethyltetrathiafulvalene (**2**) was obtained in a 46% yield.

The final product, and the synthetic intermediates, provide interesting NMR spectra due to the isotopic labeling. The $^{1}J_{CH}$ is 129 Hz, while the $^{1}J_{CC}$ is 47 Hz and $^{2}J_{CC}$ is only 2 Hz. Thus, C-4 and C-5 are seen as a doublet of doublets in the $^{13}C$ NMR spectrum.

In summary, we have developed a short synthetic route for the preparation of quadruply carbon-13 labeled tetramethyltetrathiafulvalene and present detailed procedures for its synthesis.

## Experimental Section

### 2,3-bis(trimethylsilyloxy)-1,4-$^{13}C_2$-2-butene

Freshly distilled[15] chlorotrimethylsilane (12.4 g, 114 mmol) was added to a suspension of sodium dust[16] (2.8 g, 122 mmol) in dry ether (40 mL). Immediately, C-2 $^{13}C$ labeled (99%) ethyl acetate (5.00 g, 55.5 mmol, 99% $^{13}C$) was added dropwise (4.1 mL/hr). The reaction started after a 5-10 min induction period and brought the ether to boiling. After 1h the addition was complete and after an additional 30 min stirring at rt, the sodium chloride was removed by filtration of the blue solution under Argon. The sodium chloride was washed with potions of dry ether (200 mL). The ether was removed in vacuo and the residue was distilled (Bp 70-73°C, 10-15 Torr) to yield 4.8 g (74 %) of a colorless liquid. (Bp reported for unlabeled compound: 69-73°C, 12-13 mm[10]) The $^1H$ NMR spectrum showed a mixture of Z and E isomers in the ratio 12:1. $^1H$ NMR (400 MHz, $C_6D_6$) Z Isomer $\delta$: 0.29 (18 H, s), 1.74 (9 H, d, $J_{CH}$ = 126 Hz); Z Isomer $\delta$: 0.21 (18 H, s), 1.93 (9 H, d, $J_{CH}$ = 126 Hz). $^{13}C$-NMR (100 MHz, $C_6D_6$) Z Isomer $\delta$: 1.32, 17.91 ($^{13}C$ labeled), 130.57 (dd, $J_{CC}$ = 53, 11 Hz); E Isomer $\delta$ (partial): 1.04, 16.65 ($^{13}C$ labeled). MS (EI): 234 ($M^+$, 100), 161 (17), 147 (86), 119 (43), 111 (30). HRMS (EI): calc for $C_8{}^{13}C_2H_{24}O_2Si_2$ ($M^+$): 234.1382; found: 234.1379.

### O-Ethyl S-1,4-$^{13}C_2$-3-oxobut-2-yl dithiocarbonate

This reaction was monitored carefully by silica gel tlc: 2,3-bis(trimethylsilyloxy)-1,4-$^{13}C_2$-2-butene Rf = 0.8; acetoin Rf = 0.2; product Rf = 0.6; hexanes / ethyl acetate 8:2; anisaldehyde stain. Water (0.38 mL, 21 mmol) and concentrated hydrochloric acid (80 µL) were added to a solution of 2,3-bistrimethylsilyloxy-1,4-$^{13}C_2$-butene (4.80 g, 20.6 mmol) in THF (35 mL). After 10 min at rt, trifluoroacetic anhydride (4.8 mL, 34 mmol) was added in one portion and the mixture was stirred 10 min in a water bath. The volatile components of the mixture were removed by pumping on an oil pump for 10 min. Acetone (dry, 60 mL) and potassium O-ethyl dithiocarbonate[13] (12.1 g, 75 mmol) were added. After stirring for 1.25 h, the yellow solution was added to water and the product was extracted with ether (3x). The organic phase was washed with saturated sodium bicarbonate solution (2x) and brine (1x). After drying with magnesium sulfate, the solvents were removed in vacuo to yield the product (0.97 g, 24%) as a yellow oil. (Typical yields were 37-39%.) (Bp reported for unlabeled compound: 66-68°/0.15 mm[14]) $^1$H NMR (500 MHz, $C_6D_6$) $\delta$: 1.41 (3 H, t, $J$ = 7.1 Hz), 1.46 (3 H, dd, $J_{CH}$ = 131 Hz, $J_{HH}$ = 7.3 Hz), 2.29 (3 H, d, $J_{CH}$ = 128 Hz), 4.42 (1 H, qd, $J_{HH}$ = 7.3, $J_{CH}$ = 4.7 Hz), 4.60 - 4.67 (2 H, m). $^{13}$C-NMR (125 MHz, $C_6D_6$) $\delta$: 13.85, 15.60 ($^{13}$C labeled), 27.66 ($^{13}$C labeled), 54.15 (dd, $J_{CC}$ = 34, 15 Hz), 70.84, 204.92 (d, $J_{CC}$ = 42 Hz), 212.72 (d, $J_{CC}$ = 2 Hz). MS (EI): 195 (M+H$^+$, 80), 194 (M$^+$, 36), 161 (100), 134 (13), 105 (15). HRMS (EI): calc for $C_5{}^{13}C_2H_{13}O_2S_2$ (M+H$^+$): 195.0424; found: 195.0426. calc for $C_5{}^{13}C_2H_{12}O_2S_2$: 194.0346; found: 194.0354.

### 4,5-di($^{13}$C-methyl)-1,3-dithiol-2-thione

A mixture of O-ethyl S-1,4-$^{13}C_2$-3-oxobut-2-yl dithiocarbonate (0.97 g, 5 mmol) and phosphorous pentasulfide (3.4 g, 16 mmol, freshly opened bottle) in anhydrous decalin (20 mL) under argon was heated at reflux for 90 min. During this time the mixture turned dark purple and a purple solid precipitated. The slurry was cooled to rt and decanted into a separatory funnel containing dry ether (30 mL) and the residue in the flask was washed with ether until the washings were colorless. The combined ether fractions were filtered, washed with water (3 x 25 mL), 10 % aqueous sodium hydroxide solution (3 x 25 mL), and water (3 x 25 mL), and were dried over magnesium sulfate. A saturated solution of mercury (II) chloride in methanol (9 mL) was added to the orange-red ethereal solution. The precipitated yellow-green powder was collected and washed with ether. After drying in vacuo, the powder was treated with saturated aqueous sodium sulfide and the resulting olive-green solid was filtered, washed again with saturated aqueous sodium sulfide until the washings were colorless and then washed with water. The solid was extracted into hot acetone. The acetone solution was dried with magnesium sulfate and the solvent was removed in vacuo to yield 490 mg (60%) of the product as a brown solid. Further purification by sublimation (90-115°C, 1 Torr) yielded 460 mg (56%) of bright yellow crystals. (Typical yields were about 75%.) Mp 87-91°C. (Literature value reported for unlabeled compound: 86-91°C[8a].) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 2.16 (6 H, d, $J_{CH}$ = 130 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 13.59 ($^{13}$C labeled), 134.92 (d, $J_{CC}$ = 48 Hz), 211.85. MS (EI): 164 ($M^+$, 100), 151 (23), 137 (34), 120 (16), 113 (39). HRMS (EI): calc for $C_3{}^{13}C_2H_6S_3$: 163.9699; found: 163.9701.

### $^{13}C_4$-Tetramethyltetrathiafulvalene (4,4',5,5'-Tetra($^{13}$C-methyl)[2,2']bi[1,3]dithiolylidene)

A freshly prepared solution of dicobalt octacarbonyl (freshly opened bottle) in toluene (0.21 M, 17 mL, 3.57 mmol) was added to 4,5-di($^{13}$C-methyl)-1,3-dithiole-2-thione (460 mg, 2.8 mmol) in toluene (8 mL) while sparging with carbon monoxide. Evolution of gas was observed and the dark brown solution was stirred at rt with continued CO sparging. After 3.5 h total, the mixture was heated to reflux. There was further evolution of gas and the solution turned black. After refluxing for 5-10 min, the mixture was allowed to cool to rt and filtered through a plug of silica gel with methylene chloride. The yellow-brown filtrate was collected and the solvent was removed in vacuo. The orange-black residue was rinsed with acetonitrile to remove a black oil. The orange solid was dissolved in hot acetonitrile and filtered. The acetonitrile solution was concentrated to 5 mL and the product was filtered and washed with acetonitrile to yield 170 mg (46%) of the product as orange needles. Mp 242.5-243.5°C. (Literature values reported for unlabeled compound: 244.5-245°C,[8a] 240.5-241.3°C[8c]) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 1.93 (12 H, d, $J_{CH}$ = 129 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 13.93 ($^{13}$C labeled), 109.61, 123.02 (dd, $J_{CC}$ = 47, 2 Hz). MS (EI): 266 ($M+2^+$, 51), 264 ($M^+$, 100), 204 (73), 132 (79), 119 (14). HRMS (EI): calc for $C_6{}^{13}C_4H_{12}S_4$: 263.9956; found: 263.9960.

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15. Chlorotrimethylsilane (250 mL) was heated with water (1 mL) to reflux until the evaporation of HCl stopped. After addition of calcium hydride, the mixture was heated to reflux for one hour and then distilled.
16. Sodium dispersion (Aldrich, 40 wt % in mineral spirits) was washed in a Schlenk flask with dry hexanes (3 x 60 mL) and dry ether (2 x 60 mL), dried in vacuo and stored in a drybox.

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