

Synthesis of [$^2\text{H}_{13}$]Heptanoic Acid via the Desulfurization of Methyl 3-Chloro-5,6-dibromothieno[3,2,*b*]thiophene-2-carboxylate with Nickel-Aluminium Alloy in NaOD-D₂O Solution

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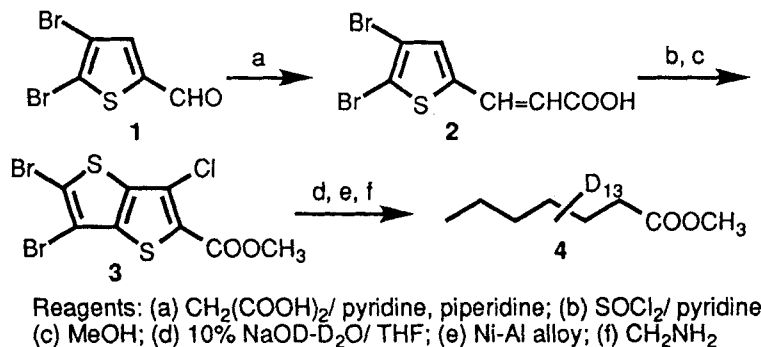
Summary

[$^2\text{H}_{13}$]Heptanoic acid was synthesized as its methyl ester (**4**) (deuterium content: 96%) with Ni-Al alloy in 10% NaOD-D₂O via the desulfurization of methyl 3-chloro-5,6-dibromothieno[3,2,*b*]thiophene-2-carboxylate (**3**), which was derived from 4,5-dibromothiophene-2-carbaldehyde (**1**) in two steps.

Key Words: Deuterium labelling, Nickel-Aluminium alloy, Desulfurization Thieno[3,2,*b*]thiophene, [$^2\text{H}_{13}$]Heptanoic acid

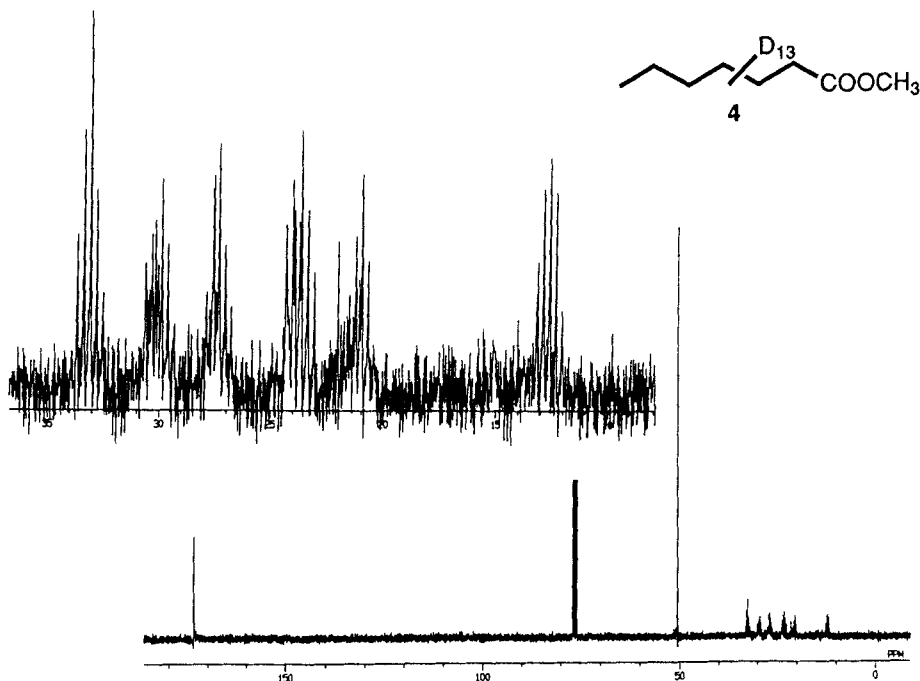
It is well known that organic sulfur compounds lose their sulfur, which is replaced by hydrogen, in the presence of Raney nickel catalyst [1]. In particular, the desulfurization of thiophene derivatives has played an important path, as many otherwise difficult compounds can be made easily accessible. During our continuing studies for synthesizing deuteriated compounds by utilizing Raney alloy in an alkaline deuterium oxide [2], we have found that brominated thiophene-2-carboxylic acids were desulfurized to deuteriated valeric acids in a one-step procedure [3]. We applied our reducing systems towards the reduction of the tri-halogenated thieno[3,2,*b*]thiophene [4], and here report the synthesis of the fully deuteriated titled acid.

The preparative route to methyl [$^2\text{H}_{13}$]heptanate (**4**) is outlined in Scheme 1.



Scheme 1

4,5-Dibromothiophene-2-carbaldehyde (**1**) [5], readily available from thiophene in two steps, was condensed with malonic acid in the presence of a mixture of pyridine and piperidine to furnish 3-(4,5-dibromothieryl)acrylic acid (**2**) in 65% yield. Intramolecular cyclization of this acid (**2**) by using thionyl chloride in the presence of pyridine, followed by the treatment of the resulting acid chloride with methanol, provided methyl 3-chloro-5,6-dibromothieno[3,2,*b*]thiophene-2-carboxylate (**3**) in 13% yield. Under an argon atmosphere the carboxylate (**3**) was desulfurized with Ni-Al alloy in 10% NaOD- D_2O at

Fig. 1 67.94 MHz $^{13}\text{C}\{^1\text{H}\}$ n.m.r. spectrum of methyl [^{13}C]heptanoate (**3**).

95 °C over the course of 2 h and then esterified with diazomethane; the fully deuteriated heptanoic acid was obtained as its methyl ester (**4**) in 35% yield (from **3**) and 96% deuterium content.

The 67.94 MHz $^{13}\text{C}\{^1\text{H}\}$ n.m.r. spectrum of the ester (**4**) showed septet lines ($^1J_{\text{C-D}}$ 18.6 Hz) for C-7 due to C-D coupling at δ_{C} 12.60, and quintet lines ($^1J_{\text{C-D}}$ 18.9 Hz, 19.5 Hz, 18.9 Hz, 18.9 Hz, and 19.8 Hz) for C-6, C-4, C-5, C-3, and C-2 at δ_{C} 20.97, 23.65, 27.33, 29.89, and 33.08 (Fig. 1). This spectrum indicates that the deuterium atoms are almost fully incorporated into the ester (**4**).

Experimental

General.—All of the melting points were determined in a Yanagimoto micro-apparatus and are uncorrected. Mass spectra were recorded on a Nippon Denshi JMS-OISG-2 mass spectrometer at 75 eV by using a direct inlet system. ^1H and $^{13}\text{C}\{^1\text{H}\}$ n.m.r. spectra were obtained on a JEOL EX-270 n.m.r. spectrometer at 270 MHz and at 67.94 MHz, respectively, in CDCl_3 with Me_4Si as an internal reference. I.r. spectra were recorded on a Jasco IR-700 infrared spectrometer. Elemental analysis was performed with a YANAKO MT-5 CHN-corder. Column chromatography was carried out on Sillica gel (Wako gel C-300).

Materials.— D_2O (99.9 atom %D) was obtained from Frosst Canada Inc., Division of Merk, and 40% $\text{NaOD-D}_2\text{O}$ (99.5 atom %D) from Merk & Co. Inc. Ni-Al alloy (50:50 wt%) was available from Kishida chemical Co., Ltd. 4,5-Dibromothiophene-2-carboaldehyde (**1**) was prepared according to the reported procedure [5]: colourless prisms; m.p. 83-84 °C (lit., [5] 78-79 °C).

3-(4,5-Dibromothieryl)acrylic Acid (2).—A vigorously stirred mixture of 4,5-dibromothiophene-2-carboaldehyde (**1**) (24.3 g, 90 mmol), malonic acid (18.7 g, 0.18 mol), dry pyridine (45.0 ml), and piperidine (0.8 ml) was heated at 95-100 °C for 2 h and at reflux for an additional 5 min. After the reaction mixture had cooled to room temperature, the content was poured into a large amount of water and acidified with conc. HCl to pH 1. The precipitate was collected by filtration and washed with a small portion of water to afford **2** (20.3 g, 65%) as colourless needles (ethanol): m.p. 236-239 °C (decomp); δ (CDCl_3) 6.27 (1H, d, J 15.8 Hz), 7.57 (1H, s), 7.64 (1H, d, J 15.8 Hz), and 12.59 (1H, brs); ν (KBr) 3078, 1674, 1621, 1406, 1310, 1263, 1195, 964, and 834 cm^{-1} ; m/z (intensity) 313 (20), 311 (44), and 309 (22) (M^+); Found: C, 26.70; H, 1.36. $\text{C}_7\text{H}_4\text{Br}_2\text{O}_2\text{S}$ requires C, 26.95; H, 1.29%.

Methyl 3-Chloro-5,6-dibromothieno[3,2,b]thiophene-2-carboxylate (3).—A vigorously stirred mixture of 3-(4,5-dibromothieryl)acrylic acid (**2**) (18.7 g, 60 mmol), thionyl chloride (21.8 ml, 0.3 ml), and dry pyridine (0.5 ml) was heated at 95-100 °C for 70 h. The reaction mixture was then concentrated *in vacuo* and the residue was leached with refluxing hexane. The solution was evaporated under reduced pressure and to the residue was added methanol (30 ml) and the whole mixture was refluxed for 1 h. After the reaction mixture had cooled to room temperature, to the resultant was added 1 l of

water and the crystalline precipitate was collected by filtration, and then chromatographed with dichloromethane as eluent to afford **3** (3.11 g, 13%) (hexane-chloroform=1:1/v:v): m.p. 202-203 °C; δ (CDCl₃) 3.95 (3H, s); ν (KBr) 2952, 1721, 1490, 1429, 1353, 1246, 1093, 809, and 754 cm⁻¹; m/z (intensity) 394 (21), 392 (75), 390 (100), and 388 (47) (M⁺); Found: C, 24.61; H, 0.77. C₈H₃Br₂ClO₂S₂ requires C, 24.17; H, 0.79%.

Methyl [²H₁₃]heptanate (4).—A mixture of methyl 3-chloro-5,6-dibromothieno[3,2,*b*]thiophene-2-carboxylate (**3**) (1.17 g, 3.0 mmol), NaOD-D₂O (10%; 15.0 ml), prepared from NaOD (40%; 3.7 ml) and D₂O (11.3 ml), and dry THF (2.0 ml) was vigorously stirred at 90 °C for 10 min. To the homogeneous solution was added Ni-Al alloy (6.3 g) in small portions over a period of 0.5 h and the mixture was heated at 90 °C for 2 h. This operation was carried out in a glove box under an argon stream. After cooling to room temperature, the reaction apparatus was removed from the box and the insoluble materials were filtered through celite and washed with a small portion of water. The filtrate and the washings, which were combined, were acidified with conc. HCl to pH 1 and extracted with dichloromethane (2 x 30 ml). After the extracts were dried (MgSO₄), to this solution was added cautiously diazomethane-ether solution [6], prepared from *N*-nitrosomethylurea (410 mg) and KOH (40%; 1.5 ml), until the generation of N₂ gas had ceased. The removal of the solvents *in vacuo* left a residue, which was distilled to afford **4** (175 mg, 35%) as a colourless liquid: b.p. 107-110 °C/ 128 Torr (lit .[7], 171-171.5 °C/ 761 Torr as for ²H₀ form); ν (NaCl) 2952, 2214, 2100, 1742, 1436, 1272, and 1084 cm⁻¹; δ (CDCl₃) 3.67 (3H, s)

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