COMMUNICATION

Studies in sulfur heterocycles. Part 13.[1] An expedient synthesis of 7-hydroxybenzo[*b*]thiophene and its 2- and 3-substituted derivatives

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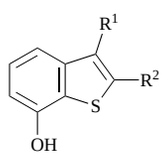
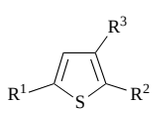
Two expedient routes to 7-hydroxybenzo[*b*]thiophene and its 2- and 3-substituted derivatives from readily available starting materials are described which constitute a vast improvement over the known methods of synthesis.

Of all the hydroxybenzo[*b*]thiophenes, which are used *inter alia* as intermediates in the synthesis of sulfur analogues of bioactive indoles[2] and in the annelation of five-,[3] six-[4–6] or seven-membered[7] oxygen heterocycles onto the benzo[*b*]thiophene core, 7-hydroxybenzo[*b*]thiophene **1** is the least exploited. This is presumably because of the lengthy and uneconomical syntheses that are known to date,[8–11] the one reported by Rahman *et al.*[11] probably constituting the only exception. This contrasts with many efficient syntheses of other hydroxybenzo[*b*]thiophenes that were developed by existing synthetic methodologies. For the continuation of our work,[1] a ready supply of **1** in a reasonable quantity was necessary, which called for a short and economic synthesis of this compound.

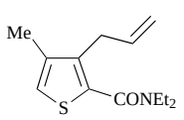
Following our earlier reported high yielding conversion of 5,6-dihydrobenzo[*b*]thiophen-7(4*H*)-one into **1**, we now report two other expedient routes to the latter.



1 $R^1 = R^2 = H$
8 $R^1 = H$, $R^2 = Me$
9 $R^1 = Me$, $R^2 = H$



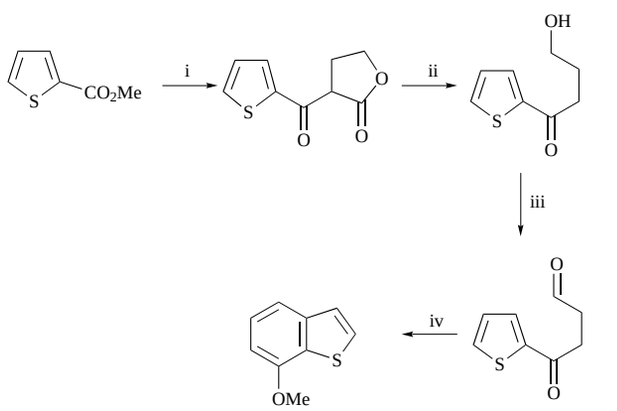
2 $R^1 = SiMe_3$, $R^2 = CONEt_2$, $R^3 = H$
3 $R^1 = SiMe_3$, $R^2 = CONEt_2$, $R^3 = Allyl$
4 $R^1 = Me$, $R^2 = CONEt_2$, $R^3 = H$
5 $R^1 = Me$, $R^2 = CONEt_2$, $R^3 = Allyl$
6 $R^1 = CONEt_2$, $R^2 = H$, $R^3 = Me$



7

The first method constitutes a four step synthetic protocol and affords **1** in excellent yield; the method can also be used to synthesize the 2- and 3-methyl derivatives with equal efficiency. The methodology, which was earlier employed by Sibi *et al.*[12] consists of $CONEt_2$ mediated directed metallation (Bu^tLi–TMEDA–THF, −78 °C)—transmetallation[13] ($CuBr{\cdot}SMe_2$), quenching with allyl bromide and LDA mediated cyclisation. Thus *N*,*N*-diethyl 5-trimethylsilylthiophene-2-carboxamide **2**, obtained from thiophene *via* sequential metallation (Bu^nLi–TMEDA–THF, −78 °C) and electrophile quenching (diethylcarbamyl chloride and chlorotrimethylsilane), smoothly allylated to afford **3** (76% yield), which on subsequent cyclisation and desilylation (Bu_4NF) afforded **1** in 82% yield. In a similar manner *N*,*N*-diethyl-5-methylthiophene-2-carboxamide **4** was allylated to **5** (65% yield) from which 2-methyl-7-hydroxybenzo[*b*]thiophene **8** was obtained in 56% yield. For the synthesis of 3-methyl-7-hydroxybenzo[*b*]thiophene **9** silyl protection at the intermediate stage was not necessary because 3-methylthiophene deprotonated (Bu^nLi–TMEDA–THF, −78 °C), as expected[14] at the 5-position. Quenching with diethylcarbamyl chloride afforded **6** (75% yield). Allylation of **6** afforded **7** in 64% yield which was cyclised to **9** (71% yield).

The synthetic protocol employed in the second method as shown in Scheme 1 gives 7-methoxybenzo[*b*]thiophene in 40%



Scheme 1 *Reagents and conditions:* i, γ-butyrolactone, NaOMe, dry 1,4-dioxane, 110 °C, 45 h; ii, NaOH, 1,4-dioxane, 120 °C, 24 h; iii, PCC, CH_2Cl_2, room temp., 2 h; iv, BF_3–MeOH, dry MeOH, room temp., 24 h

overall yield in a four step process. This methodology was earlier used by Martin and Moody[15] in carbazole synthesis. The final product has been demethylated to **1** by Chapman *et al.*[10] in high yield.

In conclusion, we have reported two expedient methods which afford **1** in good to excellent yields *via* the two shortest routes reported to date. This should encourage its increasing exploitation as an intermediate in synthesis in which we ourselves are involved and will report on later.

Experimental

J Values are given in Hz.

Thiophene and its 2- and 3-methyl derivatives were commercially available. Methyl thiophene-2-carboxylate was obtained by esterifying commercially available thiophene-2-carboxylic acid.

2-Trimethylsilylthiophene, *N*,*N*-diethyl-5-trimethylsilylthiophene-2-carboxamide, *N*,*N*-diethyl-4-methylthiophene-2-carboxamide and *N*,*N*-diethyl-5-methylthiophene-2-carboxamide were prepared from thiophene, 2-trimethylsilylthiophene, 3-methylthiophene and 2-methylthiophene respectively by deprotonation with Bu^nLi (1.2 equiv.) at −78 °C in dry tetrahydrofuran. After 30 min at −78 °C and 4–6 h at room temp., the product was isolated by usual aqueous work up, short path distillation and/or column chromatography.

2-Trimethylsilylthiophene

Yield 84%, oil; $\delta_H(CCl_4)$ 7.59–7.13 (3H, m, aromatic protons), 0.33 (9H, s, $SiMe_3$). Sufficiently pure for carrying out subsequent steps.

N,*N*-Diethyl-5-trimethylsilylthiophene-2-carboxamide 2

Yield 80%, mp 50–52 °C (diethyl ether-light petroleum) (Found:

C, 56.90; H, 8.22; N, 5.61. $C_{12}H_{21}NOSSi$ requires C, 56.47; H, 8.23; N, 5.49%); ν_{max}/cm^{-1} 1610; $\delta_H(CCl_4)$ 7.82 (1H, d, H-3, *J* 5), 7.33 (1H, d, H-4, *J* 5), 2.36 (4H, q, CH_2CH_3), 1.65 (6H, t, CH_2CH_3), 0.39 (9H, s, $SiMe_3$).

***N*,*N*-Diethyl-4-methylthiophene-2-carboxamide 6**

Yield 67%, oil; bp 100 °C/0.5 mmHg (Found: C, 60.75; H, 7.36; N, 7.35. $C_{10}H_{15}NOS$ requires C, 60.91; H, 7.60; N, 7.10%); ν_{max}/cm^{-1} 1620; $\delta_H(CCl_4)$ 7.03 (1H, d, H-5, *J* 1.8), 6.89 (1H, d, H-3, *J* 1.8), 3.50 (4H, q, CH_2CH_3), 2.27 (3H, s, CH_3), 1.16 (6H, t, CH_2CH_3).

***N*,*N*-Diethyl-5-methylthiophene-2-carboxamide 4**

Yield 75%, oil (Found: C, 60.84; H, 7.63; N, 6.98. $C_{10}H_{15}NOS$ requires C, 60.91; H, 7.60; N, 7.10%); ν_{max}/cm^{-1} 1610; $\delta_H(CDCl_3)$ 7.14 (1H, d, H-3, *J* 3.6), 6.68 (1H, dd, H-4, *J* 3.6 and 0.9), 3.54 (4H, q, CH_2CH_3), 2.48 (3H, d, CH_3, *J* 0.9), 1.23 (6H, t, CH_2CH_3).

Directed metallation–allylation sequences. General procedure

Directed metallation–allylation sequences were carried out according to the following general procedure. Bu^{t}Li (1.2 equiv.) was added in small portions by syringe to a solution of the substrate in dry tetrahydrofuran at −78 °C followed by $CuBr{\cdot}SMe_2$ after 1 h. The temperature of the reaction mixture was allowed to rise to −10 °C to −15 °C and kept at that temperature for 30 min. The reaction mixture was cooled to −78 °C and allyl bromide (3 equiv.) was added. After 1 h at −78 °C the reaction mixture was allowed to attain room temperature. After filtering through a pad of silica gel and usual aqueous work up, the product was isolated and purified by column chromatography.

***N*,*N*-Diethyl-3-allyl-5-trimethylsilylthiophene-2-carboxamide 3.** Yield 76%, oil (Found: C, 60.47; H, 8.76; N, 4.95. $C_{15}H_{25}NOSSi$ requires C, 60.37; H, 8.38; N, 4.69%); ν_{max}/cm^{-1} 1635 (CO); $\delta_H(CCl_4)$ 6.92 (1H, s, H-4), 6.16–5.53 (1H, m, $CHHCH{=}CH_2$), 5.13 (1H, m, $CHH{=}CHCH_2$), 4.89 (1H, m, $CH_2CH{=}CHH$), 3.39 (4H, q, CH_2CH_3), 3.30 (1H, dd, $CHHCH{=}CH_2$, *J* 5.7, 2.1), 3.28 (1H, dd, $CHHCH{=}CH_2$, *J* 5.7, 2.1), 1.20 (6H, t, CH_3), 0.30 (9H, s, TMS).

***N*,*N*-Diethyl 3-allyl-4-methylthiophene-2-carboxamide 7.** Yield 64%, oil; bp 110 °C/0.02 mmHg (Found: C, 65.98; H, 7.76; N, 6.16. $C_{13}H_{19}NOS$ requires C, 66.36; H, 8.08; N, 5.95%); ν_{max}/cm^{-1} 1630 (CO); $\delta_H(CDCl_3)$ 6.86 (1H, d, H-5, *J* 0.9), 5.86–5.75 (1H, m, $CH_2CH{=}CH_2$), 4.98 (1H, m, $CH{=}CHCH_2$), 4.90 (1H, m, $CHH{=}CHCH_2$), 3.38 (4H, q, CH_2CH_3), 3.31 (1H, dd, $CHHCH{=}CH_2$, *J* 6, 3), 3.29 (1H, dd, $CHHCH{=}CH_2$, *J* 6, 3), 2.13 (3H, s, CH_3), 1.15 (6H, t, CH_2CH_3).

***N*,*N*-Diethyl 3-allyl-5-methylthiophene-2-carboxamide 5.** Yield 65%, oil (Found: C, 65.4; H, 7.88; N, 5.93. $C_{13}H_{19}NOS$ requires C, 65.78; H, 8.01; N, 5.90%); ν_{max}/cm^{-1} 1630 (CO); $\delta_H(CDCl_3)$ 6.52 (1H, d, H-4, *J* 0.9), 5.92–5.83 (1H, m, $CH_2CH{=}CH_2$), 5.07 (1H, m, $CH_2CH{=}CHH$), 4.98 (1H, m, $CH_2CH{=}CHH$), 3.29 (1H, dd, $CH_2{=}CHCHH$, *J* 6.6, 2.7), 3.26 (1H, dd, $CH_2{=}CHCHH$, *J* 6.6, 2.4), 3.42 (4H, q, CH_2CH_3), 3.28 (2H, m, $CH_2CH{=}CH_2$), 2.41 (3H, d, CH_3, *J* 0.9), 1.16 (6H, t, CH_2CH_3).

General procedure for cyclisation to 7-hydroxybenzo[*b*]thiophene and its 2- and 3-methyl derivatives

To a solution of LDA (prepared from 1.2 equiv. *n*-butyllithium and diisopropylamine) in dry tetrahydrofuran was added, at −78 °C, a solution of the substrate in the same solvent. After stirring for 1 h at that temperature and for 6 h at room temperature, saturated aqueous ammonium chloride was added. Usual work up and column chromatography and/or short path distillation afforded the final compounds. 7-Hydroxybenzo[*b*]thiophene[11] and 3-methyl-7-hydroxybenzo[*b*]thiophene[10] had physical characteristics and spectral data that corresponded with those that were reported by earlier workers.

2-Methyl-7-hydroxybenzo[*b*]thiophene 8. Yield 56%, mp 65–67 °C (sublimed at 80 °C/0.5 mmHg) (Found: C, 65.84; H, 5.06. C_9H_8OS requires C, 65.82; H, 4.90%); ν_{max}/cm^{-1} 3300 (OH); $\delta_H(CDCl_3)$ 7.28 (1H, dd, H-4), 7.18 (1H, dd, H-5, *J* 6.5 and 0.4), 6.98 (1H, d, H-3, *J* 0.9), 6.67 (1H, dd, H-6, *J* 6.5 and 0.6), 2.6 (3H, d, CH_3, *J* 1.2).

2-Trimethylsilyl-7-hydroxybenzo[*b*]thiophene. Yield 74%; mp 69–70 °C (Found: C, 59.71; H, 6.49. $C_{11}H_{14}OSSi$ requires C, 59.46; H, 6.3%); ν_{max}/cm^{-1} 3320 (OH); $\delta_H(CCl_4)$ 7.40 (1H, s, H-4), 7.33–7.0 (2H, m, H-5 and H-3), 6.69–6.56 (1H, dd, H-6, *J* 8.75, 2), 5.53 (1H, br s, OH), 0.36 (9H, s, TMS).

3-(2-Thienylcarbonyl)tetrahydrofuran-2-one

Equimolar quantities of methyl thiophene-2-carboxylate and sodium methoxide were heated with 4 equiv. of γ-butyrolactone in dry 1,4-dioxane under nitrogen at 110 °C for 45 h. After addition of ice water, the pH was adjusted to 4. Extraction with chloroform, drying and column chromatography afforded the compound in 60% yield as a pale oil, ν_{max}/cm^{-1} 1760 and 1660; $\delta_H(CDCl_3)$ 8.0 (1H, dd, H-3, *J* 3.9, 0.9), 7.82 (1H, dd, H-5, *J* 5.1, 0.9), 7.26 (1H, m, H-4), 4.59 (1H, t, $CHCO$), 4.49 (2H, m, CH_2O), 3.06–2.03 (2H, m, CH_2CH_2O).

4-Hydroxy-1-(2-thienyl)butan-1-one

The previous compound was hydrolysed by heating a solution in 1,4-dioxane with aqueous sodium hydroxide for 24 h. Usual work up and column chromatography afforded the keto alcohol as a pale oil. Yield 41% (Found: C, 56.87; H, 6.28. $C_8H_{10}O_2S$ requires C, 56.44; H, 5.92%); ν_{max}/cm^{-1} 3400, 1660; $\delta_H(CCl_4)$ 7.74 (1H, dd, H-3, *J* 3.9, 0.9), 7.63 (1H, dd, H-5, *J* 5.1, 0.9), 7.12 (1H, m, H-4), 3.72 (2H, t, CH_2CO), 3.08 (2H, m, CH_2OH), 2.04 (2H, m, CH_2CH_2OH).

4-(2-Thienyl)-4-oxobutanal

The previous keto alcohol was oxidised by PCC (1.5 equiv.) by stirring under nitrogen at room temp. in dichloromethane for 48 h. Addition of diethyl ether, filtration, evaporation of the filtrate and column chromatography afforded the keto aldehyde as a brown oil in 82% yield (Found: C, 56.84; H, 4.98. $C_8H_8O_2S$ requires C, 57.11; H, 4.79%); ν_{max}/cm^{-1} 1720, 1660; $\delta_H(CCl_4)$ 9.97 (1H, s, CHO), 7.79 (1H, dd, H-3, *J* 3.9, 0.9), 7.66 (1H, dd, H-5, *J* 5.1, 0.9), 7.16 (1H, m, H-4), 3.33–2.79 (4H, m, aliphatic protons).

7-Methoxybenzo[*b*]thiophene

The previous keto aldehyde was cyclised by stirring with $BF_3{\cdot}MeOH$ (15 equiv.) under nitrogen in dry methanol for 24 h. Addition of a small quantity of diethyl ether, washing with water, drying and evaporation of the solvent followed by short path distillation afforded 7-methoxybenzo[*b*]thiophene whose spectral data agreed with those reported by previous workers.

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