

The Preparation of 3-Chlorobenzo[*b*]thiophene Derivatives from Cinnamic Acids

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The reaction of cinnamic acid derivatives with thionyl chloride and pyridine is a general procedure for the preparation of derivatives of 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride from readily accessible starting materials. These compounds are easily converted to the corresponding acids, esters and amines.

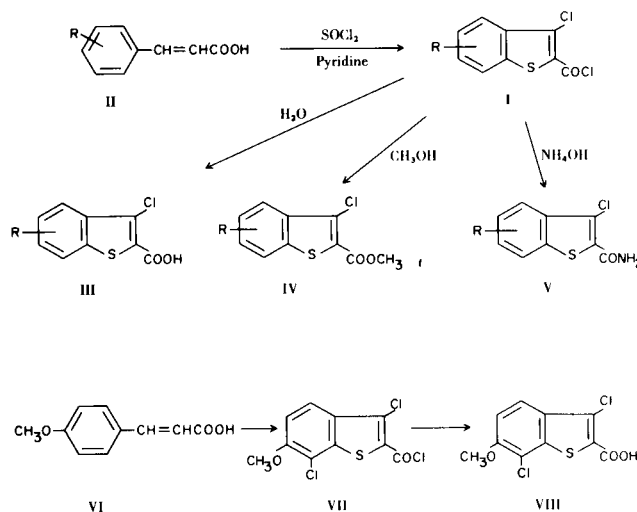
The preparation of 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride (I) by heating cinnamic acid (II) with thionyl chloride and pyridine has been described by Krubsack and Higa (1) and by Nakagawa *et al.* (2), but neither of these authors recorded the experimental details for this interesting reaction. We have studied this procedure in more detail and have applied it to substituted cinnamic acids with satisfactory results.

When cinnamic acid (II) was heated on the steam bath for 26 hours with 5 moles of thionyl chloride and 0.1 mole of pyridine, the yield of 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride (I) was less than 24% (impure product). When this mixture was heated on the steam bath for 6 days, the yield was increased to 48%. Other experiments showed that the yield could be increased to 69% by heating the same reagents for 6 days in toluene or 3 days in chlorobenzene. Compound I was not isolated when cinnamic acid and thionyl chloride were heated for 3 days in toluene in the absence of pyridine.

Similarly, *p*-substituted cinnamic acids yielded 6-substituted-3-chlorobenzo[*b*]thiophene-2-carbonyl chlorides and *o*-substituted cinnamic acids yielded 4-substituted-3-chlorobenzo[*b*]thiophene-2-carbonyl chlorides. The use of *m*-fluorocinnamic acid resulted in both the 5- and 7-fluoro derivatives.

These could be separated by recrystallization from hexane and by partition chromatography. *p*-Methoxycinnamic acid (VI) was cyclized and an additional chlorine was introduced into the benzene ring. 3,7-Dichloro-6-methoxybenzo[*b*]thiophene-2-carbonyl chloride (VII) was isolated in 40% yield. Dimethoxycinnamic acids gave complex tarry mixtures.

The acid chlorides were easily converted to the acids (III, VIII, Table II), methyl esters (IV, Table III) and amides (V, Table IV).



The nmr spectra of selected carboxylic acids were measured and aromatic proton assignments made as described in the following Table:

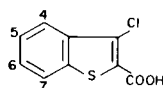
The structure of 3,7-dichloro-6-methoxybenzo[*b*]thiophene-2-carboxylic acid (VIII) was assigned based on the above nmr data. The spectrum indicated *ortho* coupling (doublet, *J* = 9) for the protons in the benzene ring, which requires that the chlorine be in the 7-position.

EXPERIMENTAL

The preparation of the compounds is described below using general procedures. Analyses, physical properties and important variations from these procedures are recorded in the Tables. Melting points are uncorrected.

Benzo[*b*]thiophene-2-carbonyl Chlorides (Table I). Procedure A, Without Solvent.

A mixture of 0.1 mole of cinnamic acid, 0.8 ml. (0.01 mole)

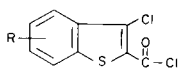


Chemical Shifts of Aromatic Protons (a)

4	5	6	7
Cl	7.57 (b)	7.57 (b)	8.08 (b)
7.67 (m, 1, 2, 9)	F	7.57 (m, 2, 9, 9)	8.16 (m, 1, 5, 9)
8.00 (d, 9)	7.66 (dd, 2, 9)	Cl	8.32 (d, 2)
7.98 (dd, 5, 9)	7.49 (m, 2, 9, 9)	F	8.03 (dd, 2, 9)
8.06 (d, 9)	8.25 (dd, 2, 9)	NO ₂	9.10 (d, 2)
Cl	7.58 (d, 2)	Cl	8.22 (d, 2)
7.83 (d, 9)	7.50 (d, 9)	CH ₃ O	Cl

(a) Nmr spectra were determined in d₆-DMSO on a Varian A-60 instrument. Chemical shifts (δ) are reported relative to tetramethylsilane ($\delta = 0.00$) internal standard. J values are in cps. Signals are designated as follows: d, doublet; dd, double doublet; m, multiplet. (b) Complex multiplet.

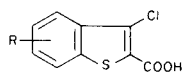
TABLE I

Benzo[*b*]thiophene-2-carbonyl Chlorides

R	Procedure A Yield, %	Procedure B Yield, %	M.p., °C	Formula	Anal.	C, %	H, %	Cl, %	S, %
H	48	69	114-116 (a)	C ₉ H ₄ Cl ₂ OS	Calcd. Found	46.8 46.7	1.7 1.7	30.7 31.1	13.9 13.8
6-CH ₃	48	43	125-127	C ₁₀ H ₆ Cl ₂ OS	Calcd. Found	49.0 49.1	2.5 2.5	28.9 28.8	13.1 13.1
4-Cl	27	--	144-146	C ₉ H ₃ Cl ₃ OS	Calcd. Found	40.7 40.5	1.1 1.1	40.1 39.9	12.1 12.2
6-Cl	41	45	136-138	C ₉ H ₃ Cl ₃ OS	Calcd. Found	40.7 40.7	1.1 1.1	40.1 39.7	12.1 12.0
5-F	--	26 (b)	108-110	C ₉ H ₃ Cl ₂ FOS	Calcd. (c) Found	43.4 43.4	1.2 1.2	28.5 28.4	12.9 12.8
6-F	--	46	109-111	C ₉ H ₃ Cl ₂ FOS	Calcd. (d) Found	43.4 43.1	1.2 1.2	28.5 28.4	12.9 12.8
6-NO ₂	18	42 (e)	186-189	C ₉ H ₃ Cl ₂ NO ₃ S	Calcd. (f) Found	39.1 39.1	1.1 1.1	25.7 25.9	11.6 11.7
4,6-diCl	--	31	135-137	C ₉ H ₂ Cl ₄ OS	Calcd. Found	36.0 36.2	0.7 0.7	47.3 47.2	10.7 10.8
6-CH ₃ O-7-Cl	40 (e,g)	--	175-177	C ₁₀ H ₅ Cl ₃ O ₂ S	Calcd. Found	40.6 40.6	1.7 1.7	36.0 35.7	10.8 10.9

(a) Ref. 1 reports m.p. 114.4-115.1°. (b) From *m*-fluorocinnamic acid. 3-Chloro-7-fluorobenzo[*b*]thiophene-2-carbonyl chloride remains in the hexane mother liquor. (c) F, Calcd: 7.6. Found: 7.8. (d) F, Calcd: 7.6. Found: 7.9. (e) Recrystallized from benzene. (f) N, Calcd: 5.1. Found: 4.8. (g) Prepared from *p*-methoxycinnamic acid.

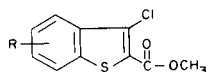
TABLE II
Benzo[*b*]thiophene-2-carboxylic Acids



R	Yield, %	M.p., °C	Formula	Anal.	C, %	H, %	Cl, %	S, %
H	98 (a)	269-271 (b)	C ₉ H ₅ ClO ₂ S	Calcd. Found	50.8 50.8	2.4 2.3	16.7 17.1	15.1 15.2
6-CH ₃	78 (c)	272-274	C ₁₀ H ₇ ClO ₂ S	Calcd. Found	53.0 53.1	3.1 3.1	15.7 15.7	14.1 14.0
4-Cl	76 (c)	278-280	C ₉ H ₄ Cl ₂ O ₂ S	Calcd. Found	43.7 44.2	1.6 1.6	28.7 28.9	13.0 13.9
6-Cl	94 (c)	286-288	C ₉ H ₄ Cl ₂ O ₂ S	Calcd. Found	43.7 43.6	1.6 1.6	28.7 28.4	13.0 12.9
5-F	97 (a)	292-294	C ₉ H ₄ ClFO ₂ S	Calcd. Found	46.9 47.0	1.8 1.6	15.4 15.6	13.9 14.0
6-F	100 (a)	293-295	C ₉ H ₄ ClFO ₂ S	Calcd. Found	46.9 47.0	1.8 1.6	15.4 15.4	13.9 14.1
6-NO ₂	98 (c)	256-258	C ₉ H ₄ ClNO ₄ S	Calcd. Found	42.0 41.6	1.6 1.6	13.8 13.5	12.4 12.5
4,6-diCl	96 (c)	301-303	C ₉ H ₃ Cl ₃ SO ₂	Calcd. Found	38.4 38.6	1.1 1.1	37.8 37.5	11.4 11.5
6-CH ₃ O-7-Cl	99 (a)	302-304	C ₁₀ H ₆ Cl ₂ O ₃ S	Calcd. Found	43.3 43.2	2.2 2.2	25.6 25.9	11.6 11.5

(a) Procedure C. (b) Ref. 2 reports m.p. 281°, Ref. 3 reports m.p. 260°. (c) Procedure D. (d) F, Calcd: 8.2. Found: 8.2. (e) F, Calcd: 8.2. Found: 8.6. (f) N, Calcd: 5.4. Found: 5.2.

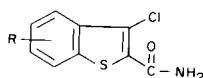
TABLE III
Methyl 3-Chlorobenzo[*b*]thiophene-2-carboxylates



R	Yield, %	M.p., °C	Formula	Anal.	C, %	H, %	Cl, %	F, %	S, %
H	92	81-82 (a)	C ₁₀ H ₇ ClO ₂ S	Calcd. Found	53.0 53.0	3.1 3.0	15.6 15.7	-- --	14.2 14.2
6-Cl	(b)	131-133 (c)	C ₁₀ H ₆ Cl ₂ O ₂ S	Calcd. Found	46.0 46.2	2.3 2.3	27.2 27.1	-- --	12.3 12.2
5-F	(bd)	142-144 (e)	C ₁₀ H ₆ ClFO ₂ S	Calcd. Found	49.1 49.3	2.5 2.4	14.5 14.4	7.8 8.2	13.1 13.4
6-F	(bd)	119-121 (f)	C ₁₀ H ₆ ClFO ₂ S	Calcd. Found	49.1 48.7	2.5 2.4	14.5 14.8	7.8 8.1	13.1 13.2
7-F	(bd)	108-110	C ₁₀ H ₆ ClFO ₂ S	Calcd. Found	49.1 49.1	2.5 2.4	14.5 14.1	7.8 7.7	13.1 13.1

(a) Ref. 3 reports m.p. 82°. (b) Prepared from a mother liquor, yield unknown. (c) Ref. 3 reports m.p. 132°. (d) Purified by partition chromatography (heptane, acetonitrile, celite). (e) Recrystallized from ethyl acetate. (f) Ref. 3 reports m.p. 120°.

TABLE IV

Benzo[*b*]thiophene-2-carboxamides

R	Yield, %	M.p., °C	Formula	Anal.	C, %	H, %	Cl, %	N, %	S, %
H	89	235-237 (a)	C ₉ H ₆ ClNOS	Calcd. Found	51.1 50.7	2.9 2.9	16.8 16.8	6.6 6.4	15.2 15.3
6-CH ₃	88	202-204 (b)	C ₁₀ H ₈ ClNOS	Calcd. Found	53.2 53.6	3.6 3.5	15.7 15.7	6.2 6.3	14.2 14.0
4-Cl	87	233-235	C ₉ H ₅ Cl ₂ NOS	Calcd. Found	43.9 44.3	2.1 2.0	28.8 29.2	5.7 5.6	13.0 13.1
6-Cl	95	271-273	C ₉ H ₅ Cl ₂ NOS	Calcd. Found	43.9 44.0	2.1 2.0	28.8 28.9	5.7 5.6	13.0 12.9
6-F	(c)	266-268	C ₉ H ₅ ClFNOS (d)	Calcd. Found	47.1 47.4	2.2 2.2	15.4 15.7	6.1 6.1	14.0 14.1
6-NO ₂	(c)	309-312	C ₉ H ₅ ClN ₂ O ₃ S	Calcd. Found	42.1 42.2	2.0 1.9	13.8 13.9	10.9 10.9	12.5 12.7
4,6-diCl	(c)	306-308	C ₉ H ₄ Cl ₃ NOS	Calcd. Found	38.5 38.6	1.4 1.3	37.9 38.2	5.0 4.7	11.4 11.5
6-CH ₃ O-7-Cl	90	271-274 (b)	C ₁₀ H ₇ Cl ₂ NO ₂ S	Calcd. Found	43.5 43.7	2.6 2.6	25.7 25.6	5.1 5.0	11.6 12.0

(a) Ref. 3 reports m.p. 227-228°. (b) Recrystallized from dilute ethanol, others from dioxane. (c) Prepared from a mother liquor, yield unknown. (d) F, Calcd: 8.3. Found: 8.8.

of pyridine and 36.3 ml. (0.5 mole) of thionyl chloride was heated on the steam bath for 6 days and concentrated to remove volatile materials. The residue was triturated with 100 ml. of petroleum ether and the precipitate was filtered. The product was boiled with hexane and filtered to remove some insoluble material. The benzo[*b*]thiophene-2-carbonyl chloride precipitated on cooling and was filtered, washed with a little hexane and dried in a vacuum oven at 50°.

Procedure B. With Solvent.

A mixture of 0.1 mole of the cinnamic acid, 0.8 ml. (0.01 mole) of pyridine, 36.3 ml. (0.5 mole) of thionyl chloride and 100 ml. of chlorobenzene was heated at reflux temperature for 3 days (68-72 hours) and filtered to remove insoluble material. The filtrate was concentrated to remove the solvent. The residue was triturated with 50 ml. of hexane and filtered. The product was generally analytically pure after one recrystallization from hexane.

Benzo[*b*]thiophene-2-carboxylic Acids (Table II). Procedure C.

A mixture of 4.0 g. of the acid chloride, 8 ml. of water and 50 ml. of dioxane was heated on the steam bath for 20 hours, and concentrated to remove the solvent. The residue was diluted with water and filtered. A nearly quantitative yield was obtained. Recrystallization was from 90% ethanol.

Procedure D.

A mixture of 0.01 mole of the acid chloride, 0.04 mole of 5*N* sodium hydroxide, 200 ml. of benzene and 50 ml. of water was stirred at room temperature for 3 days. The precipitate, if present, was filtered, boiled with dilute aqueous ethanolic hydrochloric acid and the acid recovered. If no precipitate was present, the mixture was acidified, and the acid was filtered. The product was then recrystallized from ethanol or dilute ethanol.

Methyl 3-Chlorobenzo[*b*]thiophene-2-carboxylates (Table III).

A mixture of a benzo[*b*]thiophene-2-carbonyl chloride and methanol was heated at reflux temperature for 1 hour, cooled and filtered. The precipitate was recrystallized from methanol for analysis. In some experiments, mother liquors containing the acid chloride were used and the product was purified by partition chromatography (heptane, acetonitrile).

Benzo[*b*]thiophene-2-carboxamides (Table IV).

A solution or suspension of 2.0 g. of the benzo[*b*]thiophene-2-carbonyl chloride in 75 ml. of benzene was added to a stirred mixture of 10 ml. of concentrated ammonium hydroxide and 50 ml. of benzene. After 30 minutes, the precipitate was filtered and recrystallized from dioxane or dilute ethanol.

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