The Preparation of 3-Chlorothieno[3,2-*b*]thiophene Derivatives from Thiophene-2-acrylic Acids

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Thiophene-2-acrylic acids react with thionyl chloride in the presence of pyridine to form derivatives of 3-chlorothieno[3,2-*b*]thiophene-2-carbonyl chloride. · These compounds are easily converted to the corresponding acids and esters.

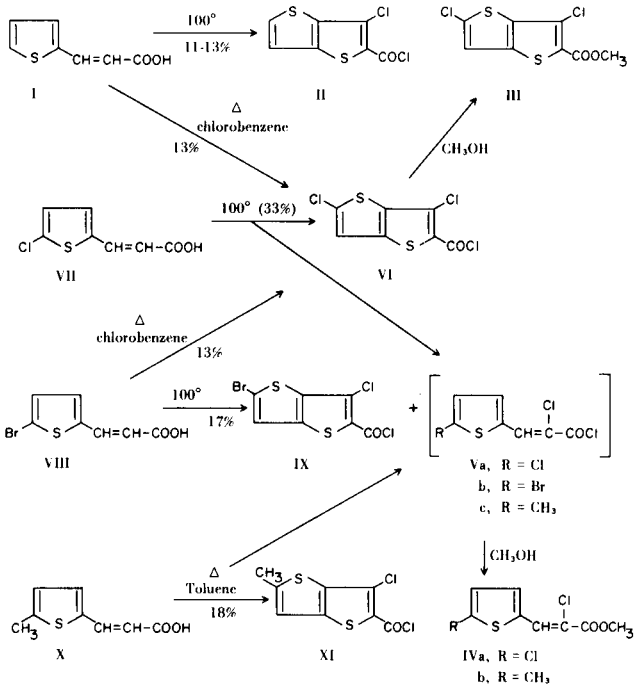
The preparation of 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride by heating cinnamic acid with thionyl chloride and pyridine was first described by Krubsack and Higa (1). This procedure has since been explored in more detail by Nakagawa *et al.* (2) and by Wright and Brabander (3) and has been shown to be a general method for the preparation of many benzo[*b*]thiophene derivatives. This reaction has now been extended to the preparation of 3-chlorothieno[3,2-*b*]thiophene-2-carbonyl chlorides by heating thiophene-2-acrylic acid derivatives with thionyl chloride and pyridine.

When thiophene-2-acrylic acid (I) was heated on the steam bath for 68-70 hours with 5 moles of thionyl chloride and 0.1 mole of pyridine, an 11-13% yield of 3-chlorothieno[3,2-*b*]thiophene-2-carbonyl chloride (II) was isolated. Variation in the ratio of thionyl chloride (2.2-5.0 moles) did not improve the yield. When the mother liquor from II was treated with methanol and chromatographed, methyl 3,5-dichlorothieno[3,2-*b*]thiophene-2-carboxylate (III) and methyl α,5-dichlorothiophene-2-acrylate (IVa) were also obtained. The structure of these chlorinated by-products was confirmed by microanalysis and nmr. α,5-Dichlorothiophene-2-acryloyl chloride (Va) is presumed to be the unisolated intermediate for the preparation of IVa. When the reaction was carried out at reflux temperature in toluene or chlorobenzene, II was not isolated and 3,5-dichlorothieno[3,2-*b*]thiophene-2-carbonyl chloride (VI) was obtained instead in 13% yield.

Compound VI was obtained in 33% yield when 5-chlorothiophene-2-acrylic acid (VII) was treated with thionyl chloride and pyridine on the steam bath, but the yield dropped to about 14% when the reaction was carried out at reflux temperature in toluene or chlorobenzene. The 3,5-dichloro compound (VI) was also obtained in 13% yield when 5-bromothiophene-2-acrylic acid (VIII) was similarly treated in refluxing chlorobenzene. The desired 5-bromo-3-chlorothieno[3,2-*b*]-

CHART I

Reaction of Thiophene-2-acrylic Acids with Thionyl Chloride and Pyridine

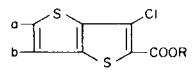


thiophene-2-carbonyl chloride (IX) was isolated in 17% yield when the experiment was repeated without solvent on the steam bath.

When 5-methylthiophene-2-acrylic acid (X) was heated with thionyl chloride and pyridine in toluene, 3-chloro-5-methylthieno[3,2-*b*]thiophene-2-carbonyl chloride (XI) was obtained in 18% yield and methyl α-chloro-5-methylthiophene-2-acrylate (IVb) was obtained from the methylated mother liquor. The desired product (XI) was not obtained when the experiment was repeated without solvent on the steam bath.

The acid chlorides were converted to the corresponding acids and methyl esters by heating with aqueous dioxane and methanol, respectively (Table II).

The nmr spectra of selected carboxylic acids and esters were measured and aromatic proton assignments made as described in the following table.



Chemical Shifts of Aromatic Protons (J Values)

R	a	b
H	8.01d (5)	7.60d (5)
H	CH_3 (a)	7.24s
H	Cl	7.67s
H	Br	7.74s
CH_3 (b)	8.05d (5)	7.59d (5)
CH_3 (b)	Cl	7.70s
CH_3 (b)	Br	7.80s

(a) Singlet, 2.11 δ. (b) Singlets, ca. 3.90 δ.

The nmr spectra of thiophene-2-acrylic acid derivatives were also measured and proton assignments were made as described below.

These assignments fit the proposed structures. The J value of 16 Hz for the a,b protons indicates that the compounds are in the *trans* configuration.

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. The nmr spectra were recorded on a Varian A-60 Spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal standard. J values are in Hz. Signals are designated as follows: s, singlet; d, doublet; dd, double doublet.

Thiophene-2-acrylic Acids (Table I).

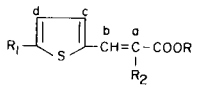
These compounds were prepared by a modification of the procedure of King and Nord (4). A mixture of 0.4 mole of the thiophene-2-carboxaldehyde, 50 g. (0.48 mole) of malonic acid, 125 ml. of pyridine and 1.8 ml. of piperidine was heated on the steam bath for 18 hours and then poured into 300 ml. of ice and water and 200 ml. of concentrated hydrochloric acid. The precipitate was filtered off, washed with water, and recrystallized from 95% ethanol. The mother liquor was concentrated for recovery.

Thieno[3,2-*b*]thiophene-2-carbonyl Chlorides. Procedure A, without Solvent.

A mixture of 0.1 mole of the thiophene-2-acrylic acid, 0.8 ml. (0.01 mole) of pyridine and 36.3 ml. (0.5 mole) of thionyl chloride was heated on the steam bath for 68-70 hours and then concentrated to remove volatile material. The residue was boiled with 100-200 ml. of hexane and decanted from the dark insoluble material. On cooling to room temperature the thieno[3,2-*b*]-thiophene-2-carbonyl chloride precipitated and was further purified by recrystallization from hexane or benzene. If the hexane solutions were allowed to stand in the cold room before filtering, unwanted thiophene-2-acryloyl chloride derivatives also separated. If the concentrated mother liquors were warmed with methanol and cooled, precipitation occurred. Partition chromatography on these precipitates resulted in methyl α-chlorothienyl-2-acrylates and a number of other unidentified products.

Procedure B, with Solvent.

A mixture of 0.1 mole of the thiophene-2-acrylic acid, 0.8 ml. (0.01 mole) of pyridine, 36.3 ml. (0.5 mole) of thionyl chloride and 100 ml. of toluene or chlorobenzene was heated at reflux temperature for 68-70 hours. The reaction mixture was filtered (or decanted) to remove insoluble material and concentrated to remove the solvent. The residue was boiled with 100-200 ml. of hexane and allowed to cool to room temperature. The crystalline product was recrystallized from hexane or benzene.



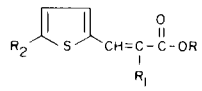
Chemical Shifts of Protons (J Values)

R	R_1	a(R_2)	b	c	d
H	CH_3 (a)	6.04d (16)	7.68d (16)	7.30d (4)	6.84d (4)
H	Cl	6.15d (16)	7.66d (16)	7.39d (16)	7.15d (4)
H	Br	6.18d (16)	7.68d (16)	7.35d (4)	7.27d (4)
CH_3 (b)	CH_3 (c)	Cl	8.22s	7.62d (4)	7.00dd (4)
CH_3 (b)	Cl	Cl	8.26s	7.72d (4)	7.40d (4)

(a) Singlet, 2.50 δ. (b) Singlet, 3.83 δ. (c) Doublet, 2.52 δ.

TABLE I

Thiophene-2-acrylic Acid Derivatives

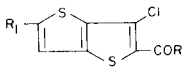


R	R_1	R_2	Yield, %	M.p., °C	Formula	Anal.	C, %	H, %	Br, %	Cl, %	S, %
H	H	Cl	70	204-207 (a)	$C_7H_5ClSO_2$	Calcd.	44.6	2.7		18.8	17.0
						Found	44.6	2.6		18.8	17.0
H	H	Br	72	212-214 (b)	$C_7H_5BrSO_2$	Calcd.	36.1	2.2	34.3		13.8
						Found	36.2	2.2	34.2		13.9
H	H	CH_3	66	164-167 (c)	$C_8H_8SO_2$	Calcd.	57.1	4.8			19.0
						Found	57.1	4.7			18.8
CH_3	Cl	Cl	(d)	98-100	$C_8H_6Cl_2SO_2$	Calcd.	40.5	2.6		29.9	13.5
						Found	40.9	2.5		30.0	13.6
CH_3	Cl	CH_3	(e)	73-75	$C_9H_9ClSO_2$	Calcd.	49.9	4.2		16.3	14.8
						Found	49.6	4.0		16.3	14.9

Notes: (a) Ref. 4 reports m.p. 201-203° dec. (b) Ref. 5 reports m.p. 213-215°. (c) Ref. 4 reports m.p. 165-166°. (d) Isolated by partition chromatography (heptane/methyl cellosolve) of methylated mother liquors. (e) Isolated by partition chromatography (heptane/methanol) of methylated mother liquors.

TABLE II

Derivatives of Thieno[3,2-b]thiophene-2-carboxylic Acids



R	R_1	Yield, %	M.p., °D	Formula	Anal.	C, %	H, %	Cl, %	S, %
Cl	H	11-13 (a,b)	131-134 (c)	$C_7H_2Cl_2OS_2$	Calcd.	35.5	0.8	29.9	27.1
					Found	35.4	0.8	29.8	27.2
Cl	CH_3	18 (d)	135-137 (e)	$C_8H_4Cl_2OS_2$	Calcd.	38.3	1.6	28.2	25.5
					Found	38.2	1.5	28.6	25.7
Cl	Cl	33 (a,f)	122-124 (c)	$C_7HCl_3OS_2$	Calcd.	31.0	0.4	39.2	23.6
					Found	31.1	0.4	39.4	23.7
Cl	Br	17 (a,g)	141-143 (e)	$C_7HBrCl_2OS_2$	Calcd. (i)	26.6	0.3	22.4	20.3
					Found	26.8	0.3	22.5	20.6
OH	H	90	261-263	$C_7H_3ClO_2S_2$	Calcd.	38.5	1.4	16.2	29.3
					Found	38.4	1.5	16.6	29.1
OH	CH_3	86	291-293	$C_8H_5ClO_2S_2$	Calcd.	41.3	2.2	15.2	27.6
					Found	41.4	2.2	15.5	27.2
OH	Cl	100	287-289	$C_7H_2Cl_2O_2S_2$	Calcd.	33.2	0.8	28.0	25.3
					Found	33.5	0.8	27.9	25.5
OH	Br	84	293-295	$C_7H_2BrClO_2S_2$	Calcd. (j)	28.2	0.7	11.9	21.6
					Found	28.5	0.7	11.9	21.7
OCH_3	H	75	93-95	$C_8H_5ClO_2S_2$	Calcd.	41.3	2.2	15.2	27.6
					Found	41.1	2.1	15.2	27.7

TABLE II (Continued)

R	R_1	Yield, %	M.p., °D	Formula	Anal.	C, %	H, %	Cl, %	S, %
OCH_3	Cl	(h)	134-136	$C_8H_4Cl_2O_2S_2$	Calcd.	36.0	1.5	26.5	24.0
					Found	36.0	1.4	26.8	23.6
OCH_3	Br	79	149-151	$C_8H_4BrClO_2S_2$	Calcd. (k)	30.8	1.3	11.4	20.6
					Found	31.1	1.3	12.1	21.0

Notes: (a) Procedure A. (b) The 3,5-dichloro analog is obtained as a by-product from the mother liquor as the methyl ester. (c) Recrystallized from hexane. (d) Procedure B, 68 hours in toluene. (e) Recrystallized from benzene. (f) 13.2% and 6.7% respectively in toluene and chlorobenzene from thiophene-2-acrylic acid. (g) Procedure B in chlorobenzene gave 13% 3,5-dichloro derivative instead of the expected product. (h) Isolated from a methylated mother liquor. (i) Br, Calcd: 25.3. Found: 25.2. (j) Br, Calcd: 26.9. Found: 26.7. (k) Br, Calcd: 25.6. Found: 25.3.

Methyl Thieno[3,2-*b*]thiophene-2-carboxylates.

A mixture of the acid chloride (generally an impure mother liquor) and an excess of methanol was heated at reflux temperature for about one hour and cooled. The product was filtered off and recrystallized from methanol, or was isolated by partition chromatography.

Thieno[3,2-*b*]thiophene-2-carboxylic Acids.

A mixture of 2.0 g. of the acid chloride, 4 ml. of water and 30 ml. of dioxane was heated on the steam bath overnight and then concentrated to remove the solvent. Water was added and the product was filtered off and recrystallized from dilute ethanol.

Acknowledgment.

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