Lewis-acid Promoted Aromatic Cyclization of α-Chlorosulfides: Synthesis of Ethyl Isothiochroman-1-carboxylate and Related Compounds

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A variety of ethyl isothiochroman-1-carboxylates and related compounds were synthesized by treatment of 2-chloro-2-[(2-arenyl)ethylthio]acetates with stannic chloride in methylene chloride. The same procedure was applied to the synthesis of ethyl 4-chloro-4-methyltetrahydrothiopyran-2-carboxylate. Some isothiochroman-1-carboxylic acids were prepared and evaluated for antiinflammatory activity. Among the compounds tested, 7-phenoxyisothiochroman-1-carboxylic acid showed weak activity.

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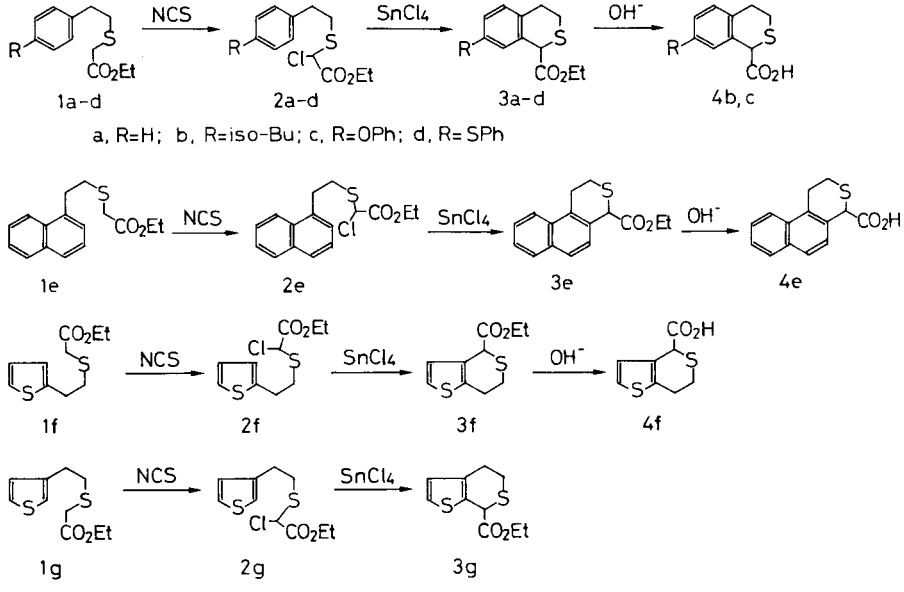
Cyclization of ethyl 2-chloro-2-(2-phenylethylthio)acetate (**2a**) to ethyl isothiochroman-1-carboxylate (ethyl 3,4-dihydro-1*H*-2-benzothiopyran-1-carboxylate) (**3a**) was reported by Böhme *et al.* [1], who obtained **3a** in 38% yield by using aluminum chloride as a catalyst. In connection with our studies directed toward the utilization of the α-chlorosulfides in organic synthesis [2-6], we reinvestigated this cyclization and found stannic chloride to be a more effective catalyst. In this paper we describe further applications of this improved procedure to the synthesis of some isothiochroman-1-carboxylates and related compounds.

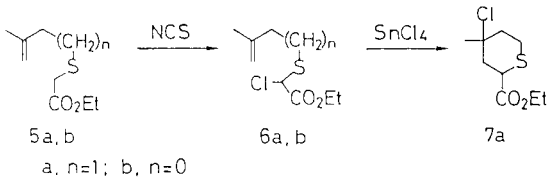
When the chloroacetate **2a** was treated with stannic chloride in methylene chloride at 0°, the isothiochroman **3a** was isolated in 87% yield [7]. Similar treatment of the chloroacetates **2b-g** gave the corresponding thiopyrans **3b-g** in the yields listed in Table 2. The structures of these compounds were assigned on the basis of the spectroscopic evidence (Table 2). The low yield of **3d** may be a result of deactivation of the benzene ring by coordination of the Lewis acid to the sulfur atom of the phenylthio group. An attempt to cyclize ethyl 2-benzylthio-2-chloroacetate (**2h**) to ethyl 1,3-dihydrobenzo[*c*]thiophene-1-carboxylate, however, was unsuccessful.

It was also of interest to see if this procedure might be applied to the ethyl 2-alkenylthio-2-chloroacetates **6**. Treatment of ethyl 2-chloro-2-(3-methyl-3-butenylthio)acetate (**6a**) with stannic chloride gave ethyl 4-chloro-4-methyltetrahydrothiopyran-2-carboxylate (**7a**) in 74% yield, while a similar treatment of ethyl 2-chloro-2-(2-methyl-2-propenylthio)acetate (**6b**) afforded only a complex mixture. The failure of the cyclization of **6b** is explained in terms of Baldwin's rule for ring-closure [8].

In view of the fact that a number of arenylacetic acids show antiinflammatory activity and are clinically used, we prepared four carboxylic acids **4b,c,e,f** by alkaline hydrolysis of the corresponding esters **3b,c,e,f** and evaluated



Scheme 1



Scheme 2

for antiinflammatory activity using carrageenin-induced rat paw edema method. Among the compounds tested, only **4c** showed weak activity.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a JASCO-IRA-1 spectrophotometer. The ^{1}H nmr spectra were determined on a JEOL JNM-PMX 60 spectrometer using solutions in deuteriochloroform and tetramethylsilane as an internal standard.

Materials.

2-(1-Naphthalene)ethanol and 2-(3-thiophene)ethanol were obtained from the Aldrich Chemical Company, Inc., and 2-(2-thiophene)ethanol and 3-methyl-3-buten-1-ol were obtained from the Tokyo Kasei Kogyo Co. Ltd. 2-(4-Isobutylphenyl)ethanol was prepared according to the reported method [9]. 2-(4-Phenoxyphenyl)ethanol was prepared from ethyl (4-phenoxyphenyl)acetate [10] by reduction with lithium aluminum hydride in 93% yield as an oil; nmr: δ 1.60 (broad s, 1H), 2.77 (t, 2H, J = 7 Hz), 3.80 (t, 2H, J = 7 Hz), 6.75-7.50 (m, 9H).

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.17; H, 6.41.

2-[4-(Phenylthio)phenyl]ethanol was prepared from ethyl [4-(phenylthio)phenyl]acetate [10] by reduction with lithium aluminum hydride in 79% yield as an oil; nmr: δ 1.77 (broad s, 1H), 2.80 (t, 2H, J = 7 Hz), 3.82 (t, 2H, J = 7 Hz), 7.20 (broad s, 9H).

Anal. Calcd. for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found: C, 72.72; H, 6.15.

The sulfide **1a** was prepared according to the reported method [1].

General Procedure for the Preparation of the Sulfides **1b-g** and **5a,b**.

An appropriate alcohol (7.8 mmoles) was sulfonylated by the usual method with *p*-toluenesulfonyl chloride (1.64 g, 8.6 mmoles) and pyridine (3 ml), and the resulting *p*-toluenesulfonate, without purification, was added to a solution of the sodium salt of ethyl thioglycolate (7.8 mmoles) in anhydrous ethanol (6 ml), and then the mixture was refluxed for 1 hour. After removal of the precipitates, the reaction mixture was concentrated and poured into water, then extracted with benzene. The extract was washed with brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (benzene) to give the product **1b-g** or **5a,b**. Yields, spectroscopic data, and analytical data are collected in Table 1.

Table 1

Preparation of the Sulfides **1b-g** and **5a,b**

Compound No.	Yield %	IR, cm^{-1} (film)	Molecular Formula	Analyses (%) Calcd./Found C	H
1b	74	1730	$C_{16}H_{18}O_2S$	68.53	8.63
				68.46	8.54
1c	64	1730	$C_{18}H_{20}O_3S$	68.33	6.37
				68.60	6.08
1d	72	1730	$C_{18}H_{20}O_2S_2$	65.02	6.02
				64.85	6.14
1e	68	1730	$C_{16}H_{18}O_2S$	70.04	6.61
				70.24	6.40
1f	88	1730	$C_{10}H_{14}O_2S$	52.14	6.13
				52.01	6.13
1g	62	1730	$C_{10}H_{14}O_2S$	52.14	6.13
				52.40	6.03
5a	70	1735	$C_9H_{16}O_2S$	57.41	8.57
				57.21	8.59
5b	75	1735	$C_8H_{14}O_2S$	55.14	8.10
				55.09	8.05

General Procedure for the Preparation of the Chlorides **2a-h** and **6a,b**.

N-Chlorosuccinimide (NCS) (119 mg, 0.89 mmole) was added by portion to a stirred solution of the sulfide **1a-g**, ethyl benzylthioacetate [11] (for **2h**), or **5a,b** (0.89 mmoles) in carbon tetrachloride (2.5 ml) at 0°, and the mixture was stirred at room temperature overnight. The precipitated succinimide was filtered off and the filtrate was concentrated *in vacuo*. The crude product (**2a-h**) or (**6a,b**) was used for the next step without further purification.

Ethyl Isothiochroman-1-carboxylate (**3a**). Typical Procedure.

Stannic chloride (208 mg, 0.80 mmole) was added dropwise to a stirred solution of **2a** (206 mg, 0.80 mmole) in anhydrous methylene chloride (2 ml) at 0° and the mixture was stirred at the same temperature for 1 hour. The reaction was quenched with water and the organic layer was separated. The aqueous layer was further extracted with methylene chloride and the combined organic layers were dried over magnesium, sulfate. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene) to give 155 mg (87%) of **3a** [1] as an oil; ir (film): ν 1730 cm^{-1}; nmr (deuteriochloroform): δ 1.26 (t, CH_3, 3H, J = 7 Hz), 2.5-3.6 (m,

Table 2

Preparationof Ethyl Isothiochroman-1-carboxylates and Related Compounds **2b-g**

Compound No.	Yield %	Mp °C	IR, cm^{-1} (film)	^{1}H NMR, δ [a]	Molecular Formula	Analyses (%) Calcd. C	H	Found C	H
3b	94	oil	1730	4.41	$C_{15}H_{22}O_2S$	69.02	7.96	68.82	7.73
3c	67	oil	1730	4.38	$C_{18}H_{18}O_3S$	68.76	5.77	68.56	5.81
3d	39	oil	1730	4.37	$C_{18}H_{18}O_2S_2$	65.42	5.49	65.68	5.44
3e	85	54-55 [b]	1730 [c]	4.53	$C_{16}H_{16}O_2S$	70.56	5.92	70.41	5.98
3f	62	oil	1730	4.43	$C_{10}H_{12}O_2S_2$	52.60	5.30	52.88	5.17
3g	64	oil	1730	4.51	$C_{10}H_{12}O_2S_2$	52.60	5.30	52.39	5.27

[a] In deuteriochloroform; the signals due to C*H*-$COOC_2H_5$ only. [b] Recrystallized from methanol. [c] In potassium bromide.

Table 3

Preparation of Isothiochroman-1-carboxylic Acids and Related Compounds **4b,c,e,f**

Compound No.	Yield %	Mp °C	IR, cm^{-1} [a]	Molecular Formula	Analyses (%) Calcd./Found C	H
4b	77	127-128 [b]	1690	$C_{14}H_{18}O_2S$	67.16	7.25
					67.34	7.10
4c	72	147-148 [b]	1690	$C_{16}H_{14}O_3S$	67.11	4.93
					67.33	5.00
4e	74	218-219 [c]	1695	$C_{14}H_{12}O_2S$	68.83	4.95
					68.97	4.69
4f	92	140-141 [c]	1695	$C_8H_8O_2S_2$	47.98	4.03
					48.21	4.06

[a] In potassium bromide. [b] From ethyl acetate/*n*-hexane. [c] From methanol.

Ar-CH_2CH_2, 4H), 4.18 (q, OCH_2, 2H, J = 7 Hz), 4.48 (s, SCH, 1H), 7.16 (s, aromatic, 4H). Yields, spectroscopic data, and analytical data of **3b-g** are recorded in Table 2.

General Procedure for the Preparation of the Isothiochroman-1-carboxylic Acids (**4b,c,e,f**).

A mixture of the ester **3b,c,e**, or **f** (4.3 mmoles) in an aqueous 6*N* sodium hydroxide solution (2.9 ml) was refluxed for 30 minutes. After cooling, the mixture was acidified to *p*H 1 with 10% hydrochloric acid, and the precipitate was collected and recrystallized to give the corresponding product **4b,c,e**, or **f**. Yields, physical data and analytical data are reported in Table 3.

Ethyl 4-Chloro-4-methyltetrahydrothiopyran-2-carboxylate (**7a**).

By means of the same procedure as that described for the cyclization of the chloride **2** the crude chloride **6a** (423 mg, 1.9 mmoles) was treated with stannic chloride (495 mg, 1.9 mmoles) in methylene chloride (5 ml). The usual work-up gave **7a** (341 mg, 74%) as an oil; ir (chloroform): ν 1735 m^{-1}; nmr: δ 1.28 (t, 3H, J = 7 Hz), 1.4-2.7 (m, 6H), 1.66 (s, 3H), 3.15 (ddd, 1H, J = 14, 12, 2 Hz), 3.98 (dd, 1H, J = 12, 2 Hz), 4.17 (q, 2H, J = 7 Hz).

Anal. Calcd. for $C_9H_{15}ClO_2S$: C, 48.53; H, 6.79. Found: C, 48.80; H, 6.69.

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REFERENCES AND NOTES

[1] H. Böhme, L. Tils and B. Unterhalt, *Arch. Pharm.*, **297**, 325 (1964).

[2] Y. Tamura, H.-D. Choi, M. Mizutani, Y. Ueda and H. Ishibashi, *Chem. Pharm. Bull.*, **30**, 3574 (1982).

[3] H. Ishibashi, S. Akai, H.-D. Choi, H. Nakagawa and Y. Tamura, *Tetrahedron Letters*, **24**, 3877 (1983).

[4] Y. Tamura, T. Tsugoshi, H. Annoura and H. Ishibashi, *Synthesis*, 326 (1984).

[5] H. Ishibashi, Y. Kitano, H. Nakatani, M. Okada, M. Ikeda, M. Okura and Y. Tamura, *Tetrahedron Letters*, **25**, 4231 (1984).

[6] H. Ishibashi, M. Okada, K. Sato, M. Ikeda, K. Ishiyama and Y. Tamura, *Chem. Pharm. Bull.*, **33**, 90 (1985).

[7] The same ester **3a** was also obtained in 78% yield by treatment of ethyl [(2-phenyl)ethylsulfinyl]acetate with *p*-toluenesulfonic acid in boiling benzene, see Y. Tamura, H.-D. Choi, H. Shindo, J. Uenishi and H. Ishibashi, *Tetrahedron Letters*, **22**, 81 (1981).

[8] J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 736 (1976).

[9] Boots Pure Drug Co. Ltd., British Patent 971,700 (1964); *Chem. Abstr.*, **61**, 14591d (1964).

[10] J. W. Corse, R. G. Jones, Q. F. Soper, C. W. Whitehead and O. K. Behrens, *J. Am. Chem. Soc.*, **70**, 2837 (1948).

[11] A. J. H. Labuschagne, J. S. Malherbe, C. J. Meyer and D. F. Schneider, *J. Chem. Soc., Perkin Trans. I*, 955 (1978).