Synthesis of 3-Substituted 4*H*-1-Benzothiopyran-4-ones

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Received October 22, 1984

3-Substituted 2-phenyl-4*H*-1-benzothiopyran-4-ones (thioflavones) were prepared to test antimicrobial activity. It was found that 3-(phenyl)thiochromone derivatives (isothioflavones) were prepared by the Meerwein reaction of thiochromone with *p*-nitrobenzenediazonium ion. 3-(Formyl)thioflavone exhibits weak antimicrobial activity against *Trichophytons* and *Candida*.

J. Heterocyclic Chem., **22**, 821 (1985).

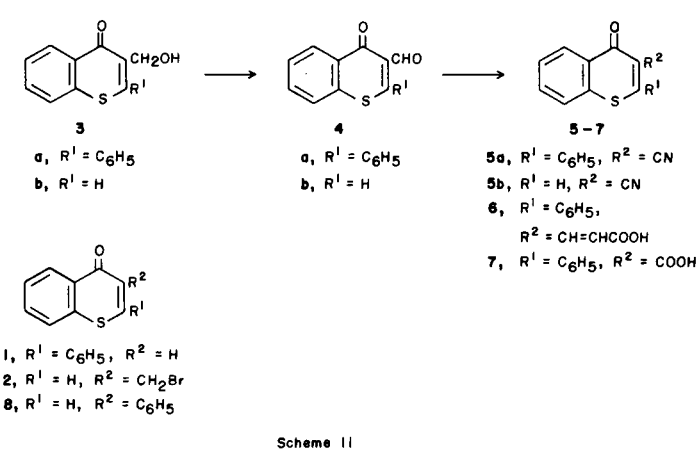
We have attempted to prepare some 2-phenyl-4*H*-1-benzothiopyran-4-ones (thioflavones) **1** which would be biologically effective compounds and reported that the introduction of a specific substituent group into the 3-position of **1** was required for antimicrobial activation [1,2]. In the field of chromone chemistry, a specific substituent group (acrylic acid or tetrazole) in the 3-position of chromone is also required for biological activation [3].

In this paper, we report the preparation of new 3-substituted thioflavones and thiochromones and also report their antimicrobial activity.

3-(Formyl)thioflavone and 3-(formyl)thiochromone were useful synthons which can be efficiently converted into pharmacologically active compounds and new heterocyclic compounds. 3-(Formyl)thioflavone **4a** was prepared by the Sarett oxidation of 3-(hydroxymethyl)thioflavone **3a** with chromium trioxide. Reaction of **4a** with hydroxylamine hydrochloride in ethanol gave the 3-cyano derivative **5a**. Condensation of **4a** with malonic acid afforded *trans*-3-(4*H*-1-benzothiopyran-4-one-3-yl)acrylic acid (**6**) in 45% yield. Oxidation of **4a** with sulfamic acid and sodium chlorite gave the 3-carboxylic acid derivative **7**. Similarly, compounds **4b** and **5b** were successively prepared from 3-(hydroxymethyl)thiochromone (**3b**) which was obtained by hydrolysis of 3-(bromomethyl)thiochromone (**2**).

As isoflavonoids have a wide range of biological activities, it was considered of interest to make the 1-thio analogues. The synthesis of 3-(phenyl)thiochromone (isothioflavone) (**8**) which was formed from atropic acid was first achieved by Katekar and Thomson [4]. Only a few substituted isothioflavones similarly have been prepared [4,5]. We now found that isothioflavone derivative **10** was ob-

Scheme I



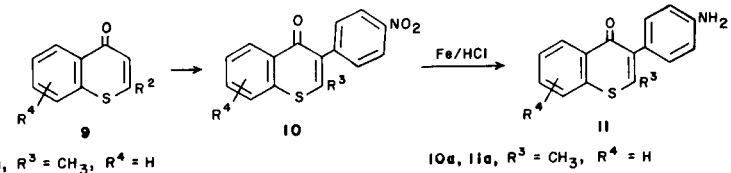
3: a, $R^1 = C_6H_5$; b, $R^1 = H$

4: a, $R^1 = C_6H_5$; b, $R^1 = H$

5–7: **5a**, $R^1 = C_6H_5$, $R^2 = CN$; **5b**, $R^1 = H$, $R^2 = CN$; **6**, $R^1 = C_6H_5$, $R^2 = CH{=}CHCOOH$; **7**, $R^1 = C_6H_5$, $R^2 = COOH$

1, $R^1 = C_6H_5$, $R^2 = H$
2, $R^1 = H$, $R^2 = CH_2Br$
8, $R^1 = H$, $R^2 = C_6H_5$

Scheme II



9: a, $R^3 = CH_3$, $R^4 = H$; b, $R^3 = CH_3$, $R^4 = 5\text{-}CH_3$; c, $R^3 = CH_3$, $R^4 = 6\text{-}CH_3$; d, $R^3 = CH_3$, $R^4 = 7\text{-}CH_3$; e, $R^3 = CH_3$, $R^4 = 8\text{-}CH_3$; f, $R^3 = H$, $R^4 = H$

10

11: **10a**, **11a**, $R^3 = CH_3$, $R^4 = H$; **10b**, **11b** $R^3 = CH_3$, $R^4 = 5\text{-}CH_3$; **10c**, **11c** $R^3 = CH_3$, $R^4 = 6\text{-}CH_3$; **10d**, **11d**, $R^3 = CH_3$, $R^4 = 7\text{-}CH_3$; **10e** **11e**, $R^3 = CH_3$, $R^4 = 8\text{-}CH_3$; **10f** $R^3 = H$, $R^4 = H$

Table I

Products from the Meerwein Reaction of Thiochromones

No.	Mp °C	Yield %	Analysis % Found C	H	N
10a	173-176	26	64.66	3.63	4.42 [a]
10b	167-170	11	65.22	4.13	4.64 [b]
10c	169-171	19	65.76	4.08	4.67 [b]
10d	192-194	12	65.30	3.94	4.17 [b]
10e	182-187	10	65.45	4.02	4.75 [b]
10f	221-224	5	63.53	2.90	4.83 [c]

[a] Calcd. for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. [b] Calcd. for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50. [c] Calcd. for $C_{15}H_5NO_3S$: C, 63.59; H, 3.20; N, 4.94.

Table II

3-(4-Aminophenyl)-2-(methyl)thiochromone Derivatives

No.	Mp °C	Yield %	Analysis % Found C	H	N
11a	145-147	15	71.61	4.79	5.50 [a]
11b	132-135	48	72.54	5.51	4.63 [b]
11c	140-142	40	73.09	5.01	5.24 [b]
11d	179-181	33	72.25	5.13	4.27 [b]
11e	168-172	50	72.25	5.34	4.95 [b]

[a] Calcd. for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. [b] Calcd. for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98.

tained by the Meerwein reaction of thiochromone. Compound **10** was obtained by the coupling of **9** with *p*-nitrobenzenediazonium ion in the presence of a catalyst and sodium acetate (Table I). When an excess of benzenediazonium ion was used in this reaction, the yield improved to 26% yield. However, the yield could not be improved by a simple modification consisting of homogeneous solution by added 18-crown-6.

Reaction product from **9f** was determined to be 3-(4-nitrophenyl)-4*H*-1-benzothiopyran-4-one (**10f**) on the basis of the ^{1}H-nmr spectrum, in which a signal for a vinyl proton (δ 6.88) in the 3-position of **9f** disappeared. Compound **10f** has a different mp and ir spectrum from those of the authentic 2-(4-nitrophenyl)thiochromone [6].

These results show that the Meerwein reaction of thiochromone as well as chromone [7] with the diazonium ion gave only the 3-phenyl derivative (isothioflavone). The 4'-amino derivative **11** was obtained by a standard reduction from **10** (Table II).

The minimum inhibitory concentrations (MIC) of isothioflavones and 3-substituted thioflavones against the seven microorganisms are compared in Table III. Isothioflavone **8** as well as thioflavone **1** is inactive against all of the microorganisms tested. Comparison of the activities of compounds **9a** and **11a** against *Trichophytons* shows that replacing the hydrogen in **9a** by the *p*-aminophenyl group in **11a** resulted in 2 to 4-fold increase in activity, but in a decrease in activity against other microorganisms. A comparison of activities of compounds **1** and **4a** against *Trichophytons* shows that replacing the hydrogen in **1** by the formyl group in **4a** resulted in an increase in activity. However, the formyl derivative **4a** was less active than the corresponding 3-(chloromethyl)thioflavone [2]. The introduction of the carboxyl or the cyano groups does not improve the antimicrobial activity. Some of 3-substituted thioflavone (**4a**, **5a**, **6**, and **7**) prepared herein did not exhibit antitumor activity against P-388 lymphocytic leukemia (T/C = 97-113%).

EXPERIMENTAL

All the melting points are uncorrected. Proton nmr spectra were taken on a JEOL JNM-MH-100 spectrometer with tetramethylsilane as an internal standard. Elemental analyses were recorded on a Yanaco CHN recorder MT-2. Mass spectra were recorded on a Hitache RMU-6E mass spectrometer operating at 80 eV. Infrared spectra were recorded on a Shimazu IR-420 spectrometer. Antitumor activity tests were done on 3PS31 by the NCI according to the protocol described in Instruction 14, Screening Data Summary Interpretation and Outline of Current Screen, Drug Evaluation Branch, Drug Research and Development Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

Table III

MIC (μg/ml) of Isothioflavones and Related Compounds

No.	*S. cerevisiae* IFO 0203	*C. utillis* OUT 6020	*P. crustosum* Thom	*R. chinensis* IFO 4745	*T. rubrum* IFO 5467	*T. mentagrophytes* IFO 6202	*C. albicans*
1, 8	[a]	[a]	[a]	[a]	[a]	[a]	[a]
4a	[a]	[a]	[a]	[a]	12.5	12.5	50.0
5a	[a]	[a]	[a]	[a]	[a]	[a]	[a]
7	[a]	400	[a]	800	800	800	[a]
9a [b]	25.0	25.0	50.0	400	200	200	200
11a	[a]	[a]	400	[a]	100	50.0	400

[a] >800 μg/ml. [b] Ref [1].

3-Bromomethyl-4*H*-1-benzothiopyran-4-one (**2**).

A mixture of 3-(methyl)thiochromone (8.0 g, 45 mmoles) [8], *N*-bromosuccinimide (8.1 g, 45 mmoles), a trace of benzoyl peroxide (0.1 g, 0.4 mmole) and benzene (400 ml) was refluxed for 25 hours. The reaction mixture was filtered and the filtrate was chromatographed on silica gel using benzene to give compound **2** (11 g) in a yield of 96%, mp 169-170°; ms: m/e 256 ($M^+ + 2$, 17), 254 (M^+, 16), 175 (100), 147 (56); ^{1}H-nmr (DMSO-d_6): δ 4.73 (s, 2H), 7.59-7.90 (m, 3H), 8.44 (m, 1H), 8.72 (s, 1H); ir: 1615 cm^{-1} (C=O).

Anal. Calcd. for $C_{10}H_7BrOS$: C, 47.08; H, 2.77. Found: C, 47.29; H, 2.69.

3-Hydroxymethyl-4*H*-1-benzothiopyran-4-one (**3b**).

A solution of **2** (8.7 g, 34 mmoles) and sodium formate (2.6 g, 39 mmoles) in formic acid (50%, 85 ml) was heated at 95° for 16 hours. After cooling, the mixture was poured into ice-water (900 ml), and the resulting solid was filtered, and was chromatographed on silica gel using chloroform to give **3b** (2.0 g) in a yield of 31%, mp 124-126° (lit [9] 123-125°).

3-Formyl-2-phenyl-4*H*-1-benzothiopyran-4-one (**4a**) and 3-Formyl-4*H*-1-benzothiopyran-4-one (**4b**).

A solution of 3-(hydroxy)thioflavone **3a** (1.80 g, 6.7 mmoles) [2] in dry pyridine (30 ml) was added dropwise to a suspension of chromium trioxide (2.6 g) in dry pyridine (26 ml) at 15-20°. The mixture was stirred for 18 hours at room temperature. The reaction mixture was filtered and the residue was washed with water, and then was extracted with chloroform in a Soxhlet extractor. The extract was washed with dilute hydrochloric acid and water, dried on magnesium sulfate, and chromatographed on silica gel using chloroform to give compound **4a** (0.93 g), in a yield of 52% (benzene), mp 162-165°; ms: m/e 266 (M^+, 12), 238 (35), 237 (100); ^{1}H-nmr (deuteriochloroform): δ 7.39-7.73 (m, 8H), 8.56 (m, 1H), 10.22 (s, 1H); ir: 1695, 1615 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{10}O_2S$: C, 72.16; H, 3.79. Found: C, 72.39; H, 3.41.

Compound **4b** was similarly obtained in a yield of 72%, mp 163-166° (lit [10] 152°).

3-Cyano-2-phenyl-4*H*-1-benzothiopyran-4-one (**5a**) and 3-Cyano-4*H*-1-benzothiopyran-4-one (**5b**).

A mixture of 3-(formyl)thioflavone **4a** (0.9 g, 3.4 mmoles), hydroxylamine hydrochloride (0.245 g, 3.5 mmoles), 95% ethanol (15 ml) and a drop of concentrated hydrochloric acid was refluxed for 12 hours with stirring. After cooling, the resulting solid was filtrated and recrystallized from benzene to give compound **5a** (0.78 g), yield 87%, mp 209-211°; ms: m/e 263 (M^+, 67), 235 (21), 136 (100); ^{1}H-nmr (deuteriochloroform): δ 7.40-7.74 (m, 8H), 8.50 (m, 1H); ir: 2220 (C=N), 1630 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_9NOS$: C, 72.98; H, 3.45; N, 5.32. Found: C, 73.28; H, 3.11; N, 5.71.

Compound **5b** was similarly prepared in a yield of 97%, mp 229-230°; ms: m/e 187 (M^+, 57), 136 (100), 108 (36); ^{1}H-nmr (deuteriochloroform): δ 7.58-7.74 (m, 4H), 8.50 (m, 1H); ir: 2220 (C=N), 1640 cm^{-1} (C=O).

Anal. Calcd. for $C_{10}H_5NOS$: C, 64.16; H, 2.69; N, 7.48. Found: C, 63.98; H, 2.20; N, 7.38.

trans-3-(2-Phenyl-4*H*-1-benzothiopyran-4-one-3-yl)acrylic Acid (**6**).

A mixture of 3-(formyl)thioflavone (**4a**) (0.735 g, 2.76 mmoles), dry pyridine (16 ml), malonic acid (0.80 g, 7.69 mmoles), and piperidine (0.7 ml) was slowly heated until 110°, and then refluxed for 20 hours. The solvent was evaporated, and the resulting solid was dissolved in chloroform. The solution was extracted with 5% aqueous sodium hydrodgen carbonate. The aqueous layer was acidified with hydrochloric acid, and the resulting solid was recrystallized from methanol to give **6** (0.382 g) in a yield of 45%, mp 228-231°; ms: m/e 308 (M^+, 5), 264 (23), 263 (100), 234 (15), 202 (8); ^{1}H-nmr (DMSO-d_6): δ 6.98 (d, 15 Hz, 1H), 7.32 (d, 15 Hz, 1H), 7.51-7.98 (m, 8H), 8.44 (m, 1H), 12.26 (b, 1H); ir: 3600-2750 (OH), 1675, 1630 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{12}O_3S$: C, 70.11; H, 3.92. Found: C, 70.09; H, 3.85.

2-Phenyl-4*H*-1-benzothiopyran-4-one-3-carboxylic Acid (**7**).

To a solution of 3-(fromyl)thioflavone **4a** (0.16 g, 0.60 mole) in chloroform (8 ml) a solution of sulfamic acid (0.23 g) in water (4 ml) was added. A solution of sodium chlorite (0.14 g, 1.5 mmoles) in water (2 ml) was added dropwise to the mixture at room temperature. The mixture was stirred for 4 hours, and then chloroform was added to dissolve the resulting solid. The chloroform layer was extracted with 5% aqueous sodium hydrogen carbonate and then the extract was acidified until *p*H 2. This solution was extracted with chloroform and the extract was dried on magnesium sulfate. The solvent was evaporated, and the resulting solid was recrystallized from acetone to give **7** (0.1 g) in a yield of 59%, mp 207-209°; ms: m/e 282 (M^+, 29), 281 (20), 238 (52), 237 (100); ^{1}H-nmr (DMSO-d_6): δ 7.35-7.92 (m, 8H), 8.35 (m, 1H), 13.08 (b, 1H); ir: 3250-2300 (OH), 1730, 1600 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{10}O_3S$: C, 68.07; H, 3.57. Found: C, 67.86; H, 3.21.

3-Phenyl-4*H*-1-benzothiopyran-4-one (**8**).

Compound **8** was prepared as reported [4].

Meerwein Reaction of Thiochromones.

A solution of *p*-nitrobenzenediazonium salt (*p*-nitroaniline, 36 mmoles: sodium nitrite, 36 mmoles: 20% hydrochloric acid, 38 ml) was added to a solution of thiochromone **9** (12 mmoles) [6,11] in acetone (50 ml) at 0-5°. The catalyst (copper(II) chloride hydrate, 2.3 mmoles) and sodium acetate were added to the solution until *p*H 3-4. The mixture was stirred for 1 hour at room temperature and then refluxed for 2 hours. After acetone was removed, the residue was extracted with benzene. The extract was washed with 5% aqueous sodium carbonate, and chromatographed on silica gel using benzene to give compound **10**. Recrystallization from ethanol gave an analytically pure compound with typical spectral data.

3-(4-Nitrophenyl)-2-methyl-4*H*-1-benzothiopyran-4-one (**10a**).

Compound **10a** was obtained in a yield of 26%, mp 173-176°; ms: m/e 297 (M^+, 81), 296 (100); ^{1}H-nmr (deuteriochloroform): δ 2.32 (s, 3H, CH_3), 7.47-7.80 (m, 5H, ArH), 8.50-8.78 (m, 3H, ArH); ir: 1615 cm^{-1} (C=O).

Reduction of Compound **10**.

A mixture of compound **10** (0.30 g, 1.0 mmole), ethanol (50%, 20 ml), reductive iron (0.2 g) and concentrated hydrochloric acid (2 drops) was refluxed for 2 hours. The reaction mixture was filtrated and the residue was extracted with acetone. The solvent was removed and the residue was extracted with benzene. After removing benzene, the resulting solid was recrystallized from ethanol to give a pure compound **11**.

Determination of *in vitro* Antimicrobial Activity.

The MIC was determined by a standard two-fold serial dilution method using broth media for *B. subtilis, S. aureus, E. coli, P. aeruginosa, S. cerevisiae, C. utillis, P. crustosum* and *R. chinensis* or agar media for *T. rubrum, T. mentagrophytes,* and *C. albicans.* All compounds tested herein were inactive against Gram-negative bacteria (*E. coli* IFO 3545 and *P. aeruginosa* IAM 1007) and Gram-positive bacteria (*B. substilis* K49 and *S. aureus* NCTC 8530).

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