

Synthesis of 3-(Substituted Methyl)-2-phenyl-4*H*-1-benzothiopyran-4-ones

Hiroyuki NAKAZUMI,* Tamio UEYAMA, Hikaru SONODA, and Teiji KITAO

Department of Applied Chemistry, College of Engineering, University of Osaka Prefecture, Sakai, Osaka 591

(Received November 17, 1983)

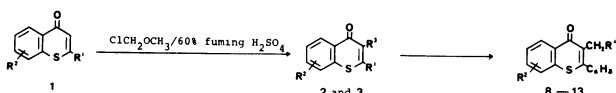
Synopsis. Reaction of 2-phenyl-4*H*-1-benzothiopyran-4-ones and related compounds with chloromethyl methyl ether and fuming sulfuric acid gave mainly 3-chloromethyl compound, whereas chloromethylation of methoxy-substituted thioflavones took place at another position or gave tris(chloromethyl) compound. 3-(Chloromethyl)thioflavone could be easily converted into various 3-(substituted methyl)-thioflavones which showed significant antimicrobial activity against *Trichophyton*s.

We have attempted to prepare some 2-phenyl-4*H*-1-benzothiopyran-4-one (thioflavone) (**1**) which would be biologically and pharmacologically effective compounds.^{1,2} We now examine the introduction of specific substituent groups (chloromethyl and acetoxymethyl) into the 3-position of **1**, because the introduction of these groups into the corresponding position of 1,4-naphthoquinones³ and 4*H*-1-benzothiopyran-4-one 1,1-dioxides⁴ is required for bioactivation. However, it is well known that no chloromethylation directly occurs at the 3-position of 4*H*-1-benzothiopyran-4-ones (thiochromones).⁴ 3-(Chloromethyl)thioflavone **2a** may be a key compound, one which can be efficiently converted into other pharmacologically active compounds. Few reports are available on the preparation of the title compounds. In this paper, we report the direct chloromethylation of various thioflavones and related compounds.

A common chloromethylation of thiochromone 1,1-dioxides with formaldehyde and hydrogen chloride is well known; however, the thiochromone⁴ and **1a** are not chloromethylated by the same method. Chloromethylation of **1a**⁵ was accomplished by use of chloromethyl methyl ether and 60% fuming sulfuric acid, which were previously applied in the chloromethylation of benzyl chloride.⁵ The chloromethyl derivative was determined to be 3-(chloromethyl)thioflavone **2a** on the basis of ¹H-NMR spectrum, in which

a signal for a chloromethyl group appeared at δ 4.52 and a signal for a vinyl proton (δ 7.20) in the 3-position of **2a** disappeared. When the chloromethylation was carried out at 75°C, compound **3a** was isolated as the main product. 2-(Methyl)thiochromone **1b** and other thioflavones **1c**—**1i** were chloromethylated under the same conditions. In the case of 6-(methoxy)thioflavone **1d**, which possesses a powerful electron-donating group, chloromethylation did not take place at the 3-position, but at the 5-position. The ¹H-NMR signal for a chloromethyl group of product **2d** was shifted downfield to δ 5.58. On the other hand, a weak electron-donating methyl group at the same position led to 3-chloromethylated product **2c**. Methyl group and methoxycarbonyl group at the 8-position also led to 3-chloromethylated products **2h** and **2f**, respectively. Compound **3f** was isolated as a by-product. Chloromethylation of the thioflavone was also influenced by a substituent group in a phenyl group at the 2-position. Methoxyl and methyl substituent in the phenyl group led to tris(chloromethyl) compound **2e**, bis(chloromethyl) compound **2i**, and **2j**, respectively. The structure of compound **2j** was determined to be 3-(chloromethyl)-3'-(hydroxymethyl) derivative by means of its ¹H-NMR signal, which was shifted upfield to δ 2.44 for a OH proton of hydroxymethyl group, while the signal of the same group at the 3-position of compounds **3a**, **3b**, and **3f** appeared at δ 3.27—3.63. An electron-withdrawing nitro group at the 4'-position led to 3-chloromethyl compound **2g**. These results show that reaction of the thioflavone with chloromethyl methyl ether and fuming sulfuric acid generally gives only a 3-chloromethylated compound. The same chloromethylation of **1b**, flavone, and 2-methylchromone gave 3-chloromethyl derivatives **2b**, **4**, and **5** in 19—76% yields, respectively. New 3-(substituted methyl)thioflavones were easily prepared by reaction of **2a** with nucleophilic reagents, as shown in Scheme 1. For examples, reaction of **2a** with an excess of aniline, morpholine, bis(2-hydroxyethyl)amine, and sodium alkoxides⁷ gave compounds **8**—**13**, respectively. The chlorine atom of a chloromethyl group of flavone derivative **4** was also converted into ethoxyl and acetoxyl group (compounds **6** and **7**) in good yields. The described method should be advantageous for direct transformation of thioflavones or flavone into their 3-(substituted methyl) derivatives.

An introduction of a chloromethyl group in the 3-position of **1a** resulted in significant antimicrobial activity against *Trichophyton*s (MIC 0.195 μ g/ml). 3-(Substituted methyl)thioflavones **3a**, **9**, and **13** (MIC 0.00488—6.25 μ g/ml), as well as 3-(alkoxymethyl)thioflavone **11**,⁷ also exhibited activity against *Trichophyton*s. On the other hand, the MIC of 3-(substituted methyl) flavones (MIC 1.56—25.0 μ g/ml) became higher (ca. 10—200-fold) than that of the corresponding thioflavones.



R ¹ , R ²	R ¹ , R ² , R ³	R ² , R ⁴
1a C ₆ H ₅ , H	2a C ₆ H ₅ , H, CH ₂ Cl	8 H, NH ₂ C ₆ H ₅
1b CH ₃ , H	2b CH ₃ , H, CH ₂ Cl	9 H, N(CH ₂ CH ₂) ₂ O
1c C ₆ H ₅ , 6-CH ₃	2c C ₆ H ₅ , 6-CH ₃ , CH ₂ Cl	10 H, N(CH ₂ CH ₂ OH) ₂
1d C ₆ H ₅ , 6-CH ₃ O	2d C ₆ H ₅ , 6-CH ₃ O-5-CH ₂ Cl, H	11 H, OR
1e 4'-CH ₃ OC ₆ H ₄ , H	2e 3'5'-(CH ₂ Cl) ₂ -4'-CH ₃ OC ₆ H ₂ , H, CH ₂ Cl	12 H, OCOCH ₂ CH ₃
1f C ₆ H ₅ , 8-CO ₂ CH ₃	2f C ₆ H ₅ , 8-CO ₂ CH ₃ , CH ₂ Cl	13 6-CH ₃ , OCH ₂ CH ₃
1g 4'-NO ₂ C ₆ H ₄ , H	2g 4'-NO ₂ C ₆ H ₄ , H, CH ₂ Cl	
1h C ₆ H ₅ , 8-CH ₃	2h C ₆ H ₅ , 8-CH ₃ , CH ₂ Cl	
1i 4'-CH ₃ C ₆ H ₄ , H	2i 4'-CH ₃ -3'-CH ₂ ClC ₆ H ₃ , H, CH ₂ Cl	
	2j 4'-CH ₃ -3'-CH ₂ OHCH ₂ C ₆ H ₃ , H, CH ₂ Cl	
	3a C ₆ H ₅ , H, CH ₂ OH	
	3b CH ₃ , H, CH ₂ OH	
	3f C ₆ H ₅ , 8-CO ₂ CH ₃ , CH ₂ OH	

Scheme 1.

TABLE 1. PHYSICAL DATA OF 3-(CHLOROMETHYL)THIOFLAVONES (2) AND 3-(HYDROXYMETHYL)THIOFLAVONES (3)

Compd	Yield ^a %	Mp °C	¹ H-NMR (δ , in CDCl ₃)	ν_{CO} /cm ⁻¹	Mass, m/z (rel intensity)	Formula	Found C	Calcd(%) H N
2a	76	130—132	4.52 (s, 2H, CH ₂) 7.46—7.61 (m, 8H) 8.60 (m, 1H, H-5)	1610	288 (M ⁺ +2, 6) 286 (M ⁺ , 13) 251 (62) 250 (100)	C ₁₈ H ₁₁ OSCl	66.87 (67.01)	3.56 (3.87)
2b	19	127—129	2.61 (s, 3H, CH ₃) 4.81 (s, 2H, CH ₂) 7.57—7.73 (m, 3H) 8.64 (m, 1H, H-5)	1610	226 (M ⁺ +2, 20) 224 (M ⁺ , 50) 189 (97) 188 (51) 161 (100)	C ₁₇ H ₉ OSCl	58.77 (58.80)	3.83 (4.04)
2c	59	154—157	2.50 (s, 3H, CH ₃) 4.43 (s, 2H, CH ₂) 7.43—7.58 (m, 7H) 8.40 (s, 1H, H-5)	1613	302 (M ⁺ +2, 7) 300 (M ⁺ , 17) 265 (91) 264 (100)	C ₁₇ H ₁₃ OSCl	68.21 (67.88)	3.96 (4.36)
2d	11	165—166	3.93 (s, 3H, OCH ₃) 5.58 (s, 2H, CH ₂) 7.22—7.66 (m, 8H)	1605	318 (M ⁺ +2, 16) 316 (M ⁺ , 37) 281 (36) 255 (76), 252 (100)	C ₁₇ H ₁₃ O ₂ SCl	64.13 (64.45)	3.98 (4.14)
2e	8.0 ^b	188—190	4.03 (s, 3H, OCH ₃) 4.51 (s, 2H, CH ₂) 4.72 (s, 4H, CH ₂) 7.65—7.71 (m, 5H) 8.65 (m, 1H, H-5)	1620	416 (M ⁺ +4, 8) 414 (M ⁺ +2, 21) 412 (M ⁺ , 20) 376 (80), 341 (73) 327 (97), 293 (100)	C ₁₈ H ₁₅ O ₂ SCl ₃	54.99 (55.16)	3.42 (3.65)
2f	77	146—148	4.02 (s, 3H, OCH ₃) 4.54 (s, 2H, CH ₂) 7.55—7.78 (m, 6H) 8.54 (d, 1H, $J=8$ Hz, H-5) 9.03 (d, 1H, $J=8$ Hz, H-7)	1715	346 (M ⁺ +2, 5) 344 (M ⁺ , 12) 309 (71) 308 (100)	C ₁₈ H ₁₃ O ₂ SCl	62.54 (62.70)	3.73 (3.80)
2g	50	220—222	4.46 (s, 2H, CH ₂) 7.20—7.88 (m, 5H) 8.30—8.62 (m, 3H)	1610	333 (M ⁺ +2, 7) 331 (M ⁺ , 21) 296 (53) 295 (57), 250 (100)	C ₁₈ H ₁₀ NO ₂ SCl	57.68 (57.92)	2.68 (3.04) (4.22)
2h	29	153—154	2.49 (s, 3H, CH ₃) 4.52 (s, 2H, CH ₂) 7.44—7.62 (m, 7H) 8.52 (m, 1H, H-5)	1615	302 (M ⁺ +2, 17) 300 (M ⁺ , 43) 265 (75) 264 (100)	C ₁₇ H ₁₃ OSCl	67.58 (67.88)	4.16 (4.36)
2i	14	164—167	2.48 (s, 3H, CH ₃) 4.50 (s, 2H, CH ₂) 4.66 (s, 2H, CH ₂) 7.35—7.71 (m, 6H) 8.60 (m, 1H, H-5)	1630	350 (M ⁺ +2, 14) 348 (M ⁺ , 20) 313 (40) 312 (61), 311 (72) 276 (100)	C ₁₈ H ₁₁ OSCl ₂	61.73 (61.90)	3.81 (4.04)
2j	39	182—183	2.44 (s, 1H, OH) 2.51 (s, 3H, CH ₃) 4.54 (s, 2H, CH ₂) 4.67 (s, 2H, CH ₂) 7.35—7.65 (m, 6H) 8.59 (m, 1H, H-5)	1605	332 (M ⁺ +2, 10) 330 (M ⁺ , 23) 312 (42) 295 (17), 277 (71) 263 (94), 262 (100)	C ₁₈ H ₁₅ O ₂ SCl	65.73 (65.35)	4.56 (4.57)
3a	38	175—177	3.60 (t, $J=7$ Hz, 1H, OH) 4.47 (d, $J=7$ Hz, 2H, CH ₂) 7.30—7.58 (m, 8H) 8.38 (m, 1H, H-5)	1605	268 (M ⁺ , 26) 250 (100) 221 (39)	C ₁₈ H ₁₂ O ₂ S	71.94 (71.62)	4.22 (4.51)
3b	9.0	147—149	2.52 (s, 3H, CH ₃) 3.63 (b, 1H, OH) 4.75 (s, 2H, CH ₂) 7.58 (m, 3H) 8.53 (m, 1H, H-5)	1605	206 (M ⁺ , 100) 191 (54) 188 (78)	C ₁₇ H ₁₀ O ₂ S	63.94 (64.05)	4.62 (4.89)
3f	6.3	149—150	3.27 (b, 1H, OH) 3.95 (s, 3H, CO ₂ CH ₃) 4.53 (s, 2H, CH ₂) 7.42—7.67 (m, 6H) 8.40 (m, 1H, H-5) 8.80 (dd, $J=8$ and 1.5 Hz, 1H, H-7)	1710	326 (M ⁺ , 21) 1608 309 (23) 308 (100) 307 (33)	C ₁₈ H ₁₁ O ₄ S	65.88 (66.24)	4.22 (4.32)

a) Yield based on the converted substrate (1a—1i). b) Isolated yield.

Experimental

All the melting points are uncorrected. ¹H-NMR spectra were taken on a JEOL JNM-MH-100 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a Shimadzu IR-420 spectrometer using KBr pellets. Elemental analyses were recorded on a Yanaco CHN recorder MT-2. Mass spectra were recorded on a Hitachi RMU-6E mass spectrometer operating at 80 eV.

2-Phenyl-4H-1-benzothiopyran-4-ones and 2-Methyl-4H-1-benzothiopyran-4-one (1a—1i). Thioflavones and 2-methylthiochromone were generally prepared by Bossert's method.⁶ The physical data of new derivative 1i are as follows. 1i; mp 120—121°C; 1608 cm⁻¹ (C=O); ¹H-NMR (CDCl₃) δ =2.42 (s, 3H, CH₃), 7.20—7.36 (m, 3H), 7.48—7.70 (m, 5H), and 8.57 (m, 1H, H-5); MS m/z (rel intensity) 252 (M⁺, 100), 224 (96), and 223 (26). Anal. (C₁₆H₁₂OS) C, H.

General Procedure for Chloromethylation. Fuming sulfuric acid (60%; 14 ml) was added dropwise to a solution of appropriate thioflavone 1 (35 mmol) in chloromethyl methyl ether (56 ml) with stirring. The reaction mixture was stirred at 60°C for 24 h, and then poured into cold water. The oily precipitate soon solidified, and the resulting solid was collected and washed with water. The crude product was chromatographed on silica gel, using benzene as an eluent, to give 2. Recrystallization from benzene/hexane (10:1) gave a pure chloromethyl derivative 2. The yields, mp's and spectral data of 2a—2j and 3a, b, f are summarized in Table 1.

TABLE 2. PHYSICAL DATA OF 3-(SUBSTITUTED METHYL)THIOFLAVONES

Compd	Yield ^a %	Mp °C	¹ H-NMR (δ , in CDCl ₃)	ν_{CO} /cm ⁻¹	Mass, m/z (rel intensity)	Formula	Found C	Calcd(%) H N
8	46	116—118	4.18 (s, 2H, CH ₂) 6.21—7.05 (m, 5H) 7.35—7.50 (m, 8H) 8.43 (m, 1H, H-5)	1610	343 (M ⁺ , 14) 252 (100)	C ₂₂ H ₁₇ NOS	76.58 (76.94)	4.57 (4.99) (4.08)
9	65	164—166	2.25—2.41 (m, 4H) 3.46—3.64 (m, 5H) 7.35—7.57 (m, 8H) 8.55 (m, 1H, H-5)	1610	337 (M ⁺ , 15) 251 (100)	C ₂₀ H ₁₅ NO ₂ S	70.91 (71.19)	5.36 (5.68) (4.15)
10	36	98—101	2.45 (t, $J=6$ Hz, 4H, N-CH ₂), 3.25 (b, 2H, OH), 3.53 (t, $J=6$ Hz, 4H, -CH ₂ -O), 3.73 (s, 2H, -CH ₂ -N), 7.49—7.70 (m, 8H), 8.65 (m, 1H, H-5)	1608	337 (17) 324 (20) 310 (23) 251 (100)	C ₂₀ H ₂₁ NO ₂ S	67.60 (67.58)	5.95 (5.96) (3.94)
12	77	120—122	1.12 (t, $J=7$ Hz, 3H, CH ₃), 2.27 (q, $J=7$ Hz, 2H, CH ₂ -CH ₃) 4.93 (s, 2H, CH ₂ O) 7.37—7.53 (m, 8H) 8.49 (m, 1H, H-5)	1730 1615	—	C ₁₉ H ₁₈ O ₂ S	70.10 (70.35)	4.64 (4.97)
13	66	99—101	1.15 (t, $J=6$ Hz, 3H, CH ₃), 2.49 (s, 3H, CH ₃), 3.52 (q, $J=6$ Hz, 2H, CH ₂ -CH ₃), 4.37 (s, 2H, CH ₂ -O), 7.47—7.75 (m, 7H) 8.47 (s, 1H, H-5)	1618	—	C ₁₉ H ₁₈ O ₂ S	73.55 (73.52)	5.79 (5.85)

a) Isolated yield.

Compounds 4 and 5 were similarly prepared from flavone⁸ and 2-methylchromone,⁹ respectively. Compound 4: yield 47%; mp 155—156°C (lit.¹⁰ 156°C). Compound 5: yield 76%; mp 103—104°C (lit.¹⁰ 103—108°C).

3-(Substituted Methyl)-2-phenyl-4H-1-benzothiopyran-4-ones and 3-(Substituted Methyl)-2-phenyl-4H-1-benzopyran-4-ones (6—13). A mixture of compound 2a and appropriate amine, sodium alkoxide or sodium propionate was heated at reflux for 2—5 h in dioxane, alcohol or propionic acid. The mixture was worked up as described above to give pure compounds 8—13. The physical data of these compounds are listed in Table 2.

Compounds 6 and 7 were similarly prepared. 3-(Ethoxymethyl)flavone 6: yield 75%; mp 102—114°C; 1640 cm⁻¹ (C=O); ¹H-NMR (CDCl₃) δ =1.31 (t, $J=7$ Hz, 3H, -CH₂CH₃), 3.73 (q, $J=7$ Hz, 2H, -CH₂CH₃), 4.48 (s, 2H, -CH₂O), 7.52—7.84 (m, 6H), 7.99—8.13 (m, 2H), and 8.45 (d, $J=7.5$ Hz, 1H, H-5). Anal. (C₁₈H₁₆O₃) C, H. 3-(Acetoxymethyl)flavone 7: yield 80%; mp 118—119°C (lit.¹¹ 115—118°C).

Determination of in Vitro Antimicrobial Activity. The minimal inhibitory concentrations (MIC) were determined by a standard two-fold serial dilution method using agar media for *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Candida albicans*.

References

- 1) H. Nakazumi, T. Ueyama, T. Endo, and T. Kitao, *Bull. Chem. Soc. Jpn.*, **56**, 1251 (1983).
- 2) H. Nakazumi, T. Ueyama, and T. Kitao, *J. Heterocycl. Chem.*, **21**, 193 (1984).
- 3) A. J. Lin, B. J. Lillis, and A. C. Sartorelli, *J. Med. Chem.*, **18**, 917 (1975).
- 4) M. H. Holshouser, L. J. Loeffler, and I. H. Hall, *J. Med. Chem.*, **24**, 853 (1981).
- 5) H. Suzuki, *Bull. Chem. Soc. Jpn.*, **43**, 3299 (1970).
- 6) F. Bossert, *Justus Liebig's Ann. Chem.*, **680**, 40 (1964).
- 7) H. Nakazumi, T. Ueyama, and T. Kitao, *J. Med. Chem.*, to be published.
- 8) T. S. Wheeler, *Org. Synth.*, **32**, 72 (1952).
- 9) S. Binecki and E. Kesler, *Acta. Polon. Pharm.*, **13**, 503 (1965).
- 10) M. V. Shah and S. Sethna, *J. Indian Chem. Soc.*, **39**, 507 (1962).
- 11) H. Hofmann, G. Salbeck, and B. Meyer, *Ber.*, **103**, 2084 (1970).