A Convenient Synthesis of 2-Phenylbenzo[*b*]thiopyrylium Perchlorates

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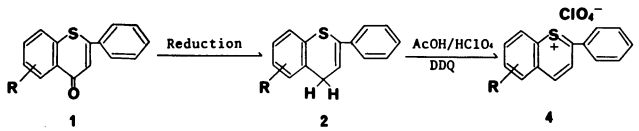
(Received August 26, 1982)

Synopsis. 2-Phenylbenzo[*b*]thiopyrylium perchlorates were conveniently prepared in good yields by reduction of 2-phenyl-4*H*-benzo[*b*]thiopyran-4-ones (thioflavones) with aluminium hydride, followed by treatment with acid in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

Flavonoid derivatives are well known to be pharmacologically active compounds. It has been reported that 2-phenylbenzo[*b*]pyrylium salts which are an important group of naturally occurring coloring matters, termed anthocyanins,[1] are significantly active in tumour-inhibiting tests.[2] 2-Phenylbenzo[*b*]thiopyrylium salts (**4a—d**) are the interesting thio analogs of anthocyanins, and a new group of pharmacologically active compounds. There are only a few known examples of synthesis of the title compounds.[3,4] For example, compound **4a** has been prepared in low yield by reduction of 2-phenylthiochroman-4-one (**3**) in a several stage process from benzenethiol.[3] In this paper, we report a convenient method for the preparation of the title compounds (**4a—d**) from 2-phenyl-4*H*-benzo-[*b*]thiopyran-4-ones (thioflavones) (**1a—d**) which can be easily prepared from benzenethiols and ethyl benzoylacetates.[5]



1a, 2a, 4a: R=H
1b, 2b, 4b: R=5-OCH_3
1c, 2c, 4c: R=6-OCH_3
1d, 2d, 4d: R=7-OCH_3 Scheme 1.

We investigated the reduction of **1a** with various reagents to prepare the title compound (**4a**). The results are summarized in Table 1. We now found that reduction of **1a** with $LiAlH_4$ and $AlCl_3$ (1/1) gave quantitatively 2-phenyl-4*H*-benzo[*b*]thiopyran **2a** which was identified by means of its NMR spectrum. The use of only $LiAlH_4$ gave compound **2a** in low yield together with other products as 2-phenylthiochroman-4-one **3** (entries 3—5, Table 1). When $NaBH_4$ is used, no reduction product was obtained (entry 6). From these results, it was shown that in the reduction of thioflavone (**1a**) with $LiAlH_4$–$AlCl_3$ a carbonyl group at the 4-position was not converted to a hydroxyl group, but to a methylene group.

Table 1. Reduction of **1** (R=H) at 25 °C

Entry	Reagent	Solvent	Reaction time/min	Yield of **2a**[a] %
1	$LiAlH_4/AlCl_3$(1/1)	THF	100	95
2	$LiAlH_4/AlCl_3$(1.5/1)	THF	100	57[b]
3	$LiAlH_4$	THF	100	2[c]
4	$LiAlH_4$	Et_2O	60	24[c]
5	$LiAlH_4$	Pyridine	200	6[d]
6	$NaBH_4$	*i*-C_3H_7OH	900	No reaction

a) Isolated Yields. b) **1a** recovered (34%). c) Structures of other products are not assigned (a number of spots on TLC were observed). d) **1a**; 29% and **3**; 22%.

Treatment of a solution of **2a** in glacial acetic acid with 60% perchloric acid for 24 h at room temperature gave 2-phenylbenzo[*b*]thiopyrylium perchlorate **4a** and 2-phenylthiochroman **5** in 45% yield, respectively. In the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), compound **4a** could be obtained selectively in 68% yield by treatment of **2a** with the same acid for 1 h at room temperature. In this reaction, it seems likely that compound **4a** is formed by elimination of a hydride ion from compound **2a**. Other new 2-phenylbenzo[*b*]-thiopyrylium salts (**4b—d**) could be obtained in high yield (81—89%) from thioflavones (**1b—d**) by the same reduction (entry 1), followed by treatment with acid in the presence of DDQ. The present method may be extended to the general synthesis of 2-phenylbenzo[*b*]-thiopyrylium perchlorates.

Thioflavones (**1a—d**) and the title compounds (**4a—d**) are currently being tested for antimicrobial activity.

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 Hitachi RMU-6E mass spectrometer operating at 80 eV.

2-Phenyl-4H-benzo[b]*thiopyran-4-ones (1a—d).* Compounds **1a** and **1c** were generally prepared by Bossert's method. **1a**: mp 125—127 °C (lit,[5] 124—127 °C), **1c**: mp 155—157 °C (lit,[5] 157 °C). Compounds **1b** (R=5-MeO) and **1d** (R=7-MeO) were obtained as follows; Reaction mixture which was prepared by Bossert's method (starting materials: *m*-methoxybenzenethiol and ethyl benzoylacetate) was chromatographed on silica gel using benzene/acetone (20/1) as an eluent to give **1b** (18%) and **1d** (33%). **1b**: mp 204—205 °C, ^{1}H-NMR($CDCl_3$): δ 3.97 (s, 3H), 6.90 (d, J=8 Hz, 1H), 7.08—7.23 (m, 2H), 7.38—7.68 (m, 6H), *m/e* (rel intensity): 268 (M^+, 100), 267 (37), 240 (29), 222 (52), 210 (26), Found: C, 71.62; H, 4.51%. Calcd for $C_{16}H_{12}O_2S$: C, 71.82; H, 4.34%. **1d**: mp 137—139 °C (lit,[5] 150 °C).

2-Phenyl-4H-benzo[b]*thiopyrans (2a—d).* To a stirred suspension at 25 °C of $LiAlH_4$ (0.19 g, 5 mmol) and $AlCl_3$ (0.66 g, 5 mmol) in THF (30 ml) was added dropwise **1a** (1.2 g, 5 mmol) in THF (15 ml). The reaction mixture was stirred for 100 min at 25 °C, and then water (1.0 ml) and concd H_2SO_4 (2.5 ml) were added. After filtration, the filtrate was extracted with ether to give compound **2a** in 95% yield; mp 61—63 °C (lit,[3] 63—65 °C). Other compounds (**2b—d**) were similarly prepared and recrystallized from methanol. The mp, NMR, mass spectra, and results of elemental analysis of these compounds are summarized in Table 2.

Table 2. 2-Phenyl-4*H*-benzo[*b*]thiopyrans

Compd	Mp θ_m/°C	^{1}H-NMR in $CDCl_3$ δ	*m/e* (rel intensity)	Calcd (Found)(%) C	H
2b	58—59	3.89 (s, OCH_3), 3.65 (d, J=5 Hz, 2H) 6.32 (t, J=5 Hz, 1H), 6.86 (d, J=8 Hz, 1H) 7.10—7.81 (m, 7H)	254 (100), 253 (60) 239 (28), 223 (21) 221 (9), 177 (47)	75.56 (75.90)	5.55 (5.24)
2c	105—107	3.89 (s, OCH_3), 3.61 (d, J=5 Hz, 2H) 6.41 (t, J=5 Hz, 1H), 6.92—7.04 (m, 2H) 7.46—7.89 (m, 6H)	254 (100), 253 (75) 239 (12), 221 (11) 210 (18), 177 (45)	(75.80)	(5.37)
2d	83—84	3.90 (s, OCH_3), 3.59 (d, J=5 Hz, 2H) 6.44 (t, J=5 Hz, 1H), 6.95 (d, d, J=2 and 8 Hz, 1H), 7.15 (d, J=2 Hz, 1H), 7.31 (d, J=8 Hz, 1H), 7.49—7.90 (m, 5H)	254 (100), 253 (73) 239 (10), 221 (9) 210 (9), 177 (29)	(75.37)	(5.47)

Table 3. 2-Phenylbenzo[*b*]thiopyrylium perchlorates

Compd	Mp θ_m/°C	Yield %	^{1}H-NMR in CF_3COOH δ	Calcd (Found) (%) C	H
4b	190—192	81	4.22 (s, OCH_3), 7.50—8.25 (m, 8H) 8.67 (d, J=10 Hz, 1H), (d, J=10 Hz, 1H)	54.47 (54.10)	3.71 (3.69)
4c	231—233	82	4.27 (s, OCH_3), 7.81—8.35 (m, 7H) 8.68 (d, J=10 Hz, 1H), 9.01 (d, J=10 Hz, 1H) 9.49 (d, J=10 Hz, 1H)	(54.18)	(3.62)
4d	180—182	89	4.32 (s, OCH_3), 7.78—8.22 (m, 7H) 8.56 (d, J=9 Hz, 1H), 8.71 (d, J=9 Hz, 1H) 9.25 (d, J=9 Hz, 1H)	(54.63)	(3.67)

2-Phenylthiochroman-4-one (3). A solution of $LiAlH_4$ (0.2 g) in dry pyridine (20 ml) was added to a solution of **1a** (1.0 g) in pyridine (15 ml) at 25 °C. The mixture was stirred for 200 min at 25 °C, and then methanol (2.0 ml) and dilute hydrochloric acid (50 ml) were added. After extraction with ether, the extracts were washed with dilute HCl and evaporated. The residue was chromatographed on silica gel using benzene as an eluent to give **3** (22%), **1a** (29%) and **2a** (6%).

2-Phenylbenzo[b]*thiopyrylium Perchlorates (4a—d).* *Method A*: Compound **2a** (1.1 g) was dissolved in glacial acetic acid (6 ml), and then 60% perchloric acid (3.3 g) was added. After 1 d at room temperature, ether was added, and the resulting solid was separated and recrystallized from glacial acetic acid containing a small amount of perchloric acid to give **4a** (0.72 g). Compound **5** was isolated in 45% yield when the filtrate was extracted with ether, and recrystallized from methanol. **5**: mp 52—54 °C; *m/e* 226 (M^+, 86), 135 (100), 92 (52), 91 (42); ^{1}H-NMR ($CDCl_3$): δ 2.25—2.40 (m, 2H), 2.84—3.04 (m, 2H), 4.46 (d, d, J=9 and 3 Hz, 1H), 7.01—7.54 (m, 9H). Found: C, 79.15; H, 6.09%. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.23%.

Method B: A solution of DDQ (1.37 g) in glacial acetic acid (20 ml) was added to a solution of **2a** (1.07 g) in glacial acetic acid (6 ml) under the stirring. After 30 min, 60% perchloric acid (3.3 g) was added, and the mixture was stirred for 30 min. The resulting solid was separated, and ether was added to the filtrate. The resulting solid was again separated. The collected solid was recrystallized from glacial acetic acid to give **4a** (1.0 g) in 65% yield. The other compounds **4b—d** were similarly prepared. The yields, mp's, NMR spectra, and results of elemental analysis of these compounds are summarized in Table 3.

References

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