Synthesis of Thioflavones from *t*-Butylthiobenzene Derivatives

Hiroyuki NAKAZUMI*, Tooru KITAGUCHI, Tamio UEYAMA, Teijiro KITAO

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

We have attempted to prepare some 2-phenyl-4*H*-benzo[*b*]-thiopyran-4-ones (thioflavones) which exhibit antimicrobial activity[1]. It is well known that polyphosphoric acid (PPA) promotes the cyclization of benzenethiols **(1)** with β-keto esters to 4*H*-benzo[*b*]thiopyran-4-ones (thiochromones)[2]. It has been reported that this method affords the thiochromones **(4)** free from the isomeric thiocoumarins **(5)**. However, we have now found that the reaction of 3,5-dimethoxybenzenethiol **(1d)** with ethyl benzoylacetate **(3a)** yields a mixture of the corresponding thioflavone **(4da)** and thiocoumarin **(5da)**. In this communication, we report an improved synthesis of methoxy-substituted thioflavones from *t*-butylthiobenzenes **(2)**. The results are compared with the known preparation of compounds **4** from the corresponding benzenethiols **(1)**.

Table 1. *t*-Butylthiobenzenes (**2**) prepared

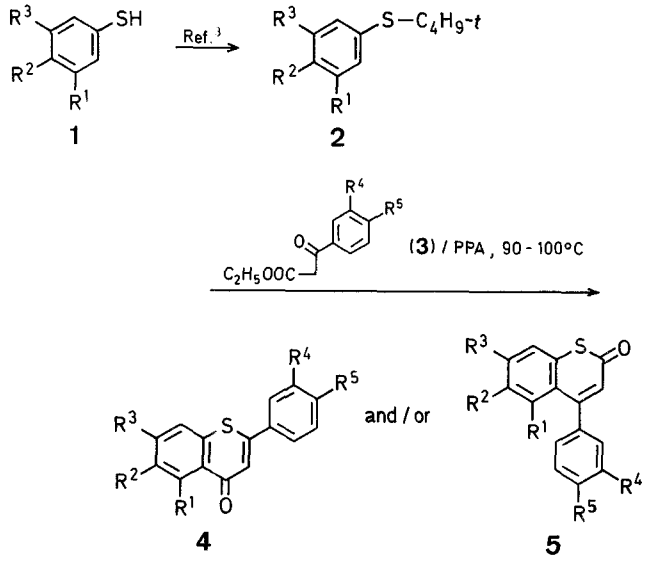
Product	Yield [%]	b.p.[a] [°C]/torr	Molecular Formula[b] or Lit. b.p. [°C]/torr	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
2a	70	60°/0.3	73°/5[3]	1.26 (s, 9H); 7.26–7.65 (m, 5H)
2b	51	75°/0.3	142°/50[4]	1.22 (s, 9H); 2.29 (s, 3H); 7.06 (d, J = 8 Hz, 2H); 7.38 (d, J = 8 Hz, 2H)
2c	71	120°/0.2	$C_{11}H_{16}OS$ (196.3)	1.25 (s, 9H); 3.77 (s, 3H); 6.80 (d, J = 9 Hz, 2H); 7.41 (d, J = 9 Hz, 2H)
2d	20	200°/0.35	$C_{12}H_{18}O_2S$ (226.3)	1.30 (s, 9H); 3.79 (s, 6H); 6.45–6.55 (m, 2H); 6.72 (d, J = 2.4 Hz, 1H)

[a] Kugelrohr distillation.
[b] The microanalyses were in satisfactory agreement with the calculated values: C ± 0.30, H ± 0.32.

Table 2. Thioflavones **4** and Thiocoumarins **5** prepared.

Educts							Product	Yield [%]		m.p. [°C]	Molecular formula[c] or Lit. m.p. [°C]
1 or **2**	R^1	R^2	R^3	**3**	R^4	R^5		A[a]	B[b]		
a	H	H	H	**a**	H	H	**4aa**	80	77[d]	123–124°	124–126°[2]
b	H	CH_3	H	**a**	H	H	**4ba**	49	71[d]	147–149°	154°[2]
c	H	OCH_3	H	**a**	H	H	**4ca**	37	50[d]	155–157°	157°[2]
c	H	OCH_3	H	**b**	H	OCH_3	**4cb**	73	12	161–162°	$C_{17}H_{14}O_3S$ (298.4)
d	OCH_3	H	OCH_3	**a**	H	H	**4da**	16	7	145–146°	$C_{17}H_{14}O_3S$ (298.4)
							5da	–	16	104–106°	$C_{17}H_{14}O_3S$ (298.4)
d	OCH_3	H	OCH_3	**c**	OCH_3	OCH_3	**5dc**	5.9	2.3	157–159°	$C_{19}H_{18}O_5S$ (358.4)

[a] Method A starting from **2**.
[b] Method B starting from **1**.
[c] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.33.
[d] Yields of 80–90% are reported in Ref.[2].



The required *t*-butylthiobenzenes **2a–d** are prepared by a known procedure[3] (Table 1). The cyclization of compounds **2** with **3a, b** in PPA at 90–100°C for 1 h gives the corresponding thioflavones **4** (Table 2). In the case of the dimethoxy compound **4cb**, the yield of the modified procedure (Method A) is 73% compared to 12% obtained in the original synthesis (Method B). Furthermore, the thiochromone **4da** is the only product isolated from the reaction of **2d** with **3a** (Method A), whereas in the reaction starting from **1d** (Method B) a mixture of **4da** and of the isomeric thiocoumarin **5da** results.

In order to investigate the scope of the Method A, we have subjected some further simple *t*-butylthiobenzene such as **2a–c** to the cyclization reaction. The corresponding thioflavones **4** are obtained in 37–80% yield. From the reaction of **2d** as well as **1d** with **3c** possessing two methoxy groups, no thioflavone derivative can be isolated. However, the thiocoumarin **5dc** is found in low yield.

The structures of thiocoumarins **5da** and **5dc** have been confirmed on the basis of characterized mass spectra in which the base peak is due to the [M – 28] fragment ion[5,6]. The thioflavones **4** have been characterized by spectral data and by direct comparison with authentic samples prepared by Method B.

***t*-Butylthiobenzenes 2; General Procedure:**

Compounds **2** are prepared by a procedure adapted from Ref.[3]. Isobutene (0.086 mol) is bubbled through stirred 75% sulfuric acid (43 g) kept in an ice-bath. Then the appropriate benzenethiol[5] (**1**; 0.043 mol) is added dropwise with stirring. The mixture is kept at room temperature or 30°C for 1 h. Crushed ice (80 g) is added to the mixture, after which it is extracted with ether (3 × 100 ml). The extract is washed with water (3 × 80 ml), then dried with magnesium sulfate, and concentrated. The residual oil is purified by Kugelrohr distillation under reduced pressure or by column chromatography on silica gel using benzene as eluent.

2-Aryl-4*H*-benzo[*b*]thiopyran-4-ones(4); General Procedure:

Method A: A mixture of *t*-butylthiobenzene (**2**; 0.014 mol) and ethyl benzoylacetate[8] (**3**; 0.021 mol) is added to PPA (30 g) at 80°C with stirring and kept for 1 h at 90–100°C. The reaction mixture is poured into ice-water (100 ml) and then the resulting solid is filtered and washed with water (5 × 100 ml). The curde product is purified by column chromatography on silica gel using benzene/acetone (10/1) as eluent or by recrystallization from ethanol.

Method B: The method of preparation from benzenethiols **1** follows the procedure of Bossert[2]. A mixture of benzenethiol (**1**; 0.029 mol) and ethyl benzoylacetate[8] (**3**; 0.036 mol) is added to PPA (62 g) and then stirred for 1 h at 90–100°C. The mixture is worked up as described above to afford compounds **4** and/or **5**.

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* Address for correspondence.

[1] H. Nakazumi, T. Ueyama, T. Kitao, *J. Heterocyclic Chem.* **21**, 193 (1984).
[2] F. Bossert, *Liebigs Ann. Chem.* **680**, 40 (1964).
[3] V. N. Ipatieff, H. Pines, B. S. Friedman, *J. Am. Chem. Soc.* **60**, 2731 (1938).
[4] W. Hahn, *German Patent* 1110631 (1961), Bayer A.G.; *C. A.* **56**, 3416 (1962).
[5] H. Nakazumi, T. Kitao, *Bull. Chem. Soc. Jpn.* **50**, 939 (1977).
[6] Thiochromone derivatives[5] are characterized by an abundant molecular ion as the base peak, while the base peak of thiocoumarin derivatives[7] are due to [M – 28] fragment ion. This method is useful for the differentiation of thioflavones **(4)** and thiocoumarins **(5)**.
[7] H. Nakazumi, A. Asada, T. Kitao, *Bull. Chem. Soc. Jpn.* **53**, 2046 (1980).
[8] R. L. Shriner, A. G. Schmidt, L. J. Roll, *Org. Synth. Coll. Vol.* II, 266 (1964).