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Synthesis of 4-Hydroxy-1-thiocoumarin Derivatives-1 : An Efficient Synthesis of Thioflocoumafen

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An efficient procedure for the preparation of 4-hydroxy-3-{1,2,3,4-tetra-hydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl}thiocoumarin (thioflocoumafen, **1a** and **1b**) is described. The key step in the synthesis involves the condensation reaction of 3-(4-methoxyphenyl)-1-tetralol (**2**) with 4-hydroxy-1-thiocoumarin (**3**).

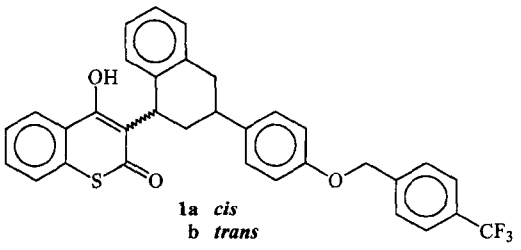
Key words : Thioflocoumafen, 4-Hydroxy-1-thiocoumarin, Anticoagulant, Rodenticide

INTRODUCTION

Rodents affect the food supply of the world and communicate several diseases to human and livestock. For their control, second-generation single-dose anticoagulant rodenticides such as brodifacoum (Dubock, 1980; Parshad, *et al.*, 1985), bromadiolone (Marsh, 1977; Meehan, 1978), difenacoum (Lund, 1981) and flocoumafen (Rowe, *et al.*, 1985; Buckle, 1986; Entwistle and Boehm, 1986; Parshad and Chopra, 1986) have been introduced. As compared to the first-generation multidose warfarin-type anticoagulants, these compounds are more susceptible by the rodents and require lesser feeding period and baits (Dubock, 1980; Lund, 1981; Parshad, *et al.*, 1985). Flocoumafen has been found to be the most effective against many species of rodents (Rowe, *et al.*, 1985; Parshad and Chopra, 1986; Johnson and Scott, 1986; Garforth and Johnson, 1987) among them. Moreover, its sulfur analog, thioflocoumafen (**1a, 1b**) showed more potent anticoagulant activity than flocoumafen with lower toxicity (Berthelon J. J., 1986). We already reported the effective synthesis of flocoumafen (Park and Jang, 1995).

The present paper describes a simple and efficient synthesis of 4-hydroxy-3-[1,2,3,4-tetrahydro-3-{4-(4-trifluoromethylbenzyloxy)phenyl}-1-naphthyl]thiocoumarin (**1**), from as starting materials, which are commercially available, anisole and phenylacetyl chloride in 19% overall yield.

The efficient synthetic route to thioflocoumafen (**1a, 1b**) is outlined in the following scheme.



1a *cis*
b *trans*

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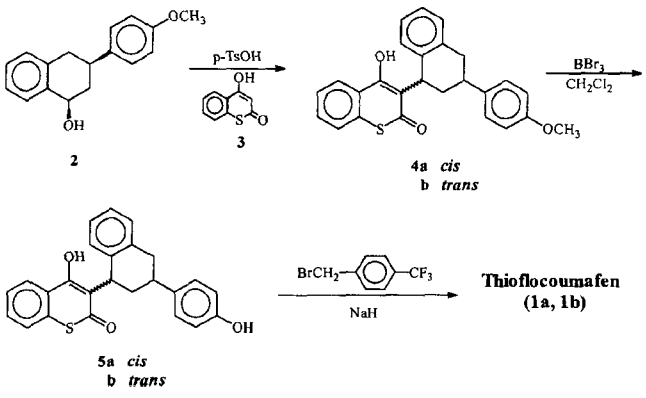
MATERIALS AND METHODS

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates from EM reagents and visualized with 254-nm UV light or ceric sulfate-ammonium molybdate-sulfuric acid spray. Flash chromatography was carried out on silica gel 60 (E. M. Merck, particle size 0.040~0.063 mm, 230~400 mesh ASTM). The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Brucker DPX 300 at 300 MHz and 75.47 MHz, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values were in Hz. The IR spectra



were obtained on a Jasco FT/IR-300E spectrometer. All melting points were uncorrected. When necessary, chemicals were purified according to the reported procedure (Perrin *et al.*, 1980).

4-Hydroxy-1-thiocoumarin (3)

Thionyl chloride (4.0 g, 33.6 mmol) was added to a well stirred solution of 2-acetylmercaptobenzoic acid (5.5 g, 28.0 mmol) and urea (30 mg) in anhydrous toluene (4.5 mL) at 10~15°C. The reaction mixture was heated in an oil bath at 100~110°C for 3 h, then cooled to room temperature to give 2-acetylmercaptobenzoyl chloride. The mixture of diethyl malonate (4.48 g, 28.0 mmol), magnesium (0.71 g, 29.2 mmol), ethanol (3.9 g, 85.3 mmol), CCl_4 (0.25 mL) and anhydrous ether (40 mL) was refluxed for 3.5 h and then cooled to 0~5°C. 2-Acetylmercaptobenzoyl chloride (6.0 g, 28.0 mmol) was added to reaction mixture with vigorously stirring and stirred at RT for 30 min. The reaction mixture was cooled to 0~5°C and 1 N HCl (20 mL) was added. The organic layer was washed with brine, dried and concentrated at reduced pressure to give diethyl 2-(2-acetylmercapto)benzoyl-malonate (9.3 g, 98.1%). The mixture of crude diethyl 2-(2-acetyl-mercapto)benzoylmalonate (2.7 g, 8.0 mmol), 3 N HCl (100 mL) and ethanol (120 mL) was refluxed for 3 h, cooled to 10°C and filtered by suction. The product was washed with water and dried in the air to afford pale yellowish crystal (1.6 g, 80.1%). The mixture of crude 3-carbethoxy-4-hydroxy-1-thiocoumarin (1.0 g, 4.0 mmol), concentrated HCl (5 mL), H_2O (5 mL) and ethanol (10 mL) was refluxed for 2 h, cooled to 10°C and filtered by suction. The product was washed with water and dried in the air to afford pale yellowish crystal (644 mg, 90.5%); m.p. 209~210°C [212~213.5°C *lit.* (Ruwet, *et al*, 1970)]; IR (KBr) 3061-2550, 1519, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.46 (br s, 1 H), 8.32 (d, *J*=7.83 Hz, 1 H), 7.83-7.63 (m, 3 H), 6.26 (s, 1 H); ^{13}C NMR ($CDCl_3$) 182.45, 166.93, 136.88, 131.48, 126.84, 126.38, 126.09, 123.79, 103.26; MS (m/e) 178 (M^+), 150, 136 (base peak), 108, 69.

***cis*-(4a) and *trans*-(4b) 4-Hydroxy-3-[1,2,3,4-tetrahydro-3-(4-methoxy-phenyl)-1-naphthyl]thiocoumarin**

Method A: *p*-TsOH (147 mg), 4-hydroxy-1-thiocoumarin (165 mg, 0.92 mmol), *cis*-3-(4-methoxyphenyl)-1-tetralol (**2**) (Park and Jang, 1995) (196 mg, 0.77 mmol) and dichloromethane (4 mL) was refluxed for 3 h, then diluted with water and extracted with dichloromethane (three times). The organic phase was extracted with diluted sodium hydroxide solution (three times) and the combined alkaline extracts were acidified and extracted with dichloromethane (three times). The dichloromethane extracts were washed with water, dried over $MgSO_4$ and then concentrated under reduced pressure to afford the crude product which gave two spots on TLC owing to the presence of two diastereoisomers. They were separated by a chromatography to give approximately equal quantities of the two isomers (242 mg, 75.8%, R_f = 0.17 and 0.27 on silica gel in hexane/ethylacetate 10 : 1). The slower-running (more polar) isomer was crystallized from ethanol, (m.p. 103~106°C). The faster-running (less polar) isomer was also crystallized from ethanol (m.p. 136.5~137.5°C).

Method B: Sulfuric acid (80%, 0.54 mL) was added dropwise with stirring to a mixture of 4-hydroxy-1-thiocoumarin (**3**, 1.69 g, 9.5 mmol), *cis*-3-(4-methoxyphenyl)-1-tetralol (**2**, 2.01 g, 7.9 mmol) and acetic acid (4 mL) at 105°C. The mixture was stirred and heated at 110 °C for 3 h, then diluted with water and extracted with dichloromethane (three times). The organic layer was treated in the same manner shown in **Method A**, to afford the desired product (230 mg, 70.4%).

The slower-running (more polar) isomer (*cis*); m.p. 103~106°C; IR (KBr) 3403, 2924, 1589, 1540, 1512, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, *J*=8.05 Hz, 1 H), 7.49-7.18 (m, 9 H), 6.89 (d, *J*=8.44 Hz, 2 H), 5.88 (br s, 1 H), 5.21 (dd, *J*=8.56, *J*=5.63 Hz, 1 H), 3.78 (s, 3 H), 3.09 (br s, 3 H), 2.35 (t, *J*=6.27 Hz, 1 H), 1.95 (t, *J*=6.07 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 185.11, 161.38, 158.61, 138.61, 137.74, 136.09, 134.42, 130.81, 130.62, 128.93, 128.40, 128.12, 128.05, 126.62, 126.52, 125.51, 124.25, 121.34, 114.39, 55.70, 40.16, 38.81, 36.54, 36.38.

The faster-running (less polar) isomer (*trans*); m.p. 136.5~137.5°C; IR (KBr) 3413, 2911, 1589, 1543, 1510, 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, *J*=8.15 Hz, 1 H), 7.48-7.22 (m, 7 H), 7.13 (d, *J*=8.63 Hz, 2 H), 6.82 (d, *J*=8.56 Hz, 2 H), 6.41 (br s, 1 H), 4.95 (t, *J*=5.34 Hz, 1 H), 3.77 (s, 3 H), 3.28 (dd, *J*=15.94 Hz, *J*=3.85 Hz, 1 H), 3.22-3.01 (m, 2 H), 2.39-2.29 (m, 1 H), 2.23-2.19 (m, 1 H); ^{13}C NMR ($CDCl_3$) 185.04, 162.12, 158.48, 138.28, 137.16, 136.08, 134.77, 130.93, 130.45, 128.78, 128.22, 126.62, 126.49, 125.36, 124.38, 120.98, 114.29, 55.63, 37.61, 36.72, 36.38, 35.09

***cis*-(5a) and *trans*-(5b) 4-Hydroxy-3-[1,2,3,4-tetrahydro-3-(4-hydroxy-phenyl)-1-naphthyl]thiocoumarin**

To a solution of *cis*-coumarin derivative **4a** (257 mg, 0.62 mmol) in dichloromethane (6.5 mL) was added boron tribromide (2.86 mL of 1 M solution in dichloromethane) at -20°C under nitrogen. The reaction mixture was stirred at the RT for 12 h and added a 10% $NaHCO_3$ solution (5 mL). The organic layer washed with water, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to afford the crude product. Chromatography of the crude product on silica gel (hexane/ethyl acetate 12 : 5) gave the *cis*-isomer **5a** (223 mg, 89.9%). Similarly, the *trans*-coumarin derivative **4b** (180 mg, 0.43 mmol) was converted into the *trans*-isomer **5b** (150 mg, 87.1%).

The slower-running (more polar) isomer (*cis*); m.p. 202~

204°C; IR (KBr) 3411, 2920, 1590, 1540, 1512, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, *J*=8.05 Hz, 1 H), 7.51-7.40 (m, 2 H), 7.38-7.33 (m, 1 H), 7.24-7.19 (m, 4 H), 7.09 (d, *J*=8.43 Hz, 2 H), 6.79 (d, *J*=8.44 Hz, 2 H), 5.88 (br s, 1 H), 5.69 (br s, 1 H), 5.22 (dd, *J*=8.56 *J*=5.63 Hz, 1 H), 3.06 (s, 3 H), 2.31 (t, *J*=6.27 Hz, 1 H), 1.91 (t, *J*=6.07 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 185.28, 161.27, 154.43, 138.26, 137.08, 135.60, 133.83, 130.44, 130.28, 128.48, 128.03, 127.76, 126.30, 126.15, 125.10, 123.78, 120.90, 115.40, 39.70, 38.32, 36.19, 36.05

The faster-running (less polar) isomer (*trans*); m.p. 119~122°C; IR (KBr) 3378, 1587, 1539, 1514, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99 (dd, *J*=8.15 Hz, *J*=0.95 Hz, 1 H), 7.48-7.20 (m, 7 H), 7.03 (d, *J*=8.63 Hz, 2 H), 6.75 (d, *J*=8.56 Hz, 2 H), 6.45 (br s, 1 H), 6.33 (br s, 1 H), 4.95 (t, *J*=5.34 Hz, 1 H), 3.25 (dd, *J*=15.94 Hz, *J*=3.85 Hz, 1 H), 3.17-2.97 (m, 2H), 2.37-2.27 (m, 1 H), 2.21-2.14 (m, 1 H); ^{13}C NMR ($CDCl_3$) 185.47, 162.16, 154.54, 137.96, 136.26, 135.53, 134.16, 130.57, 130.16, 130.09, 128.42, 127.86, 127.77, 126.27, 126.22, 125.87, 124.98, 123.90, 120.62, 115.41, 37.20, 36.24, 36.00, 34.72

cis-(1a) and *trans*-(1b) 4-Hydroxy-3-{1,2,3,4-tetrahydro-3-[4-(4-tri-fluoromethylbenzyloxy)phenyl]-1-naphthyl}thiocoumarin

To a suspension of sodium hydride (17 mg, 0.72 mmol) in tetrahydrofuran (1 mL) was added *cis*-coumarin derivative **5a** (240 mg, 0.60 mmol) in tertahydrofuran (1 mL). The reaction mixture was refluxed with 4-trifluoromethylbenzyl bromide (172 mg, 0.72 mmol) for 8 h and the solvent was removed under reduced pressure. The residue was treated with water and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the crude product. Chromatography of the crude product on silica gel (hexane/ethyl acetate 10 : 3) gave *cis*-isomer **1a** (182 mg, 54.3%). Similarly, the *trans*-coumarin derivative **5b** (268 mg) was converted into the *trans*-isomer **1b** (200 mg, 54.2 %).

The slower-running (more polar) isomer (*cis*); m.p. 112~115°C; IR (KBr) 3414, 2922, 1592, 1540, 1511, 1326 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, *J*=8.05 Hz, 1 H), 7.64-7.19 (m, 13 H), 6.89 (d, *J*=8.44 Hz, 2 H), 5.88 (br s, 1 H), 5.21 (dd, *J*=8.56 *J*=5.63 Hz, 1 H), 5.10 (s, 2 H), 3.09 (br s, 3 H), 2.35 (t, *J*=6.27 Hz, 1 H), 1.95 (t, *J*=6.07 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 184.25, 160.53, 156.57, 140.81, 137.66, 137.58, 135.22, 133.51, 129.95, 129.77, 128.07, 127.57, 127.34, 126.91, 125.76, 125.47, 125.08, 125.04, 124.65, 123.37, 120.42, 114.46, 68.71, 39.31, 37.87, 35.66, 35.51

The faster-running (less polar) isomer (*trans*); m.p. 7981; IR (KBr) 3393, 1590, 1548, 1511, 1326 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (d, *J*=8.15 Hz, 1 H), 7.63-7.20 (m, 11 H), 7.13 (d, *J*=8.63 Hz, 2 H), 6.87 (d, *J*=8.56 Hz, 2 H), 6.36 (br s, 1 H), 5.07 (s, 2 H), 4.95 (t, *J*=5.34 Hz, 1 H), 3.30-3.14 (m, 2 H), 3.09-3.00 (m, 1 H), 2.39-2.27 (m, 1 H), 2.23-2.18 (m, 1 H); ^{13}C NMR ($CDCl_3$) 184.69, 161.75, 156.95 141.27, 137.82, 137.45, 135.71, 134.32, 130.56, 130.13, 130.09, 128.45, 127.99, 127.84, 127.36, 126.24, 126.12, 125.54, 125.49, 124.99, 123.98, 120.56, 114.87, 69.15, 37.12, 36.36, 35.97, 34.65.

RESULTS AND DISCUSSION

For the preparation of thioflocoumafen (**1**), we required substantial quantities of 4-hydroxy-1-thiocoumarin (**3**). Several syntheses of this compound **3** have been reported in the literature (Jamkhandi and Rajagopal, 1967; Ruwet, *et al.*, 1970; Rath and Rajagopal, 1971). Most of these methods have been based on the Friedel Crafts acylation of thiophenol in which Lewis acids such as $ZnCl_2$, $AlCl_3$ or $POCl_3$ are used. These Lewis acids form an intractable solid mass during the reaction which makes the stirring of the reaction mixture and the product isolation considerably difficult. As a consequence, they suffer from drawbacks such as use of expensive reagents, tedious work-up and low yield. This led us to develop a better method for preparation for 4-hydroxy-1-thiocoumarin (**3**).

Treatment of compound **2** with 4-hydroxy-1-thiocoumarin in the presence of a catalytic amount of *p*-TsOH or 80% sulfuric acid, produced compound **4** as a ca. 1 : 1 and 2 : 1 mixture of two components believed to be *cis* and *trans* isomers, respectively (R_f=0.17 and 0.27 on silica gel in hexane/ethyl acetate 10 : 1).

The ^1H NMR spectrum of the more polar isomer **4a** (R_f=0.17) in $CDCl_3$ showed the 1-H signal as a double of doublet centered at 5.2. The coupling constants of this proton are 8.6 and 5.6 Hz, respectively, hence the 1-H is axial. This isomer was therefore assigned the *cis*-configuration. The spectrum of the less polar isomer **4b** (R_f=0.27) in $CDCl_3$ showed the 1-H signal as a triplet centered at 4.95 with coupling constant of *ca.* 5.3 Hz. This indicates that the 1-H is equatorial and hence the isomer has the *trans*-configuration.

The major by-product from the reaction of 3-(4-methoxyphenyl)-1-tetralol (**2**) with 4-hydroxy-1-thiocoumarin in the presence of catalytic amount of *p*-TsOH or 80% sulfuric acid, was identified as 2-(4-methoxy-phenyl)-1,2-dihydronaphthalene, resulting from dehydration.

The compound **4a** and **4b** were demethylated with BBr_3 in dichloro-methane (Niwa, *et al.*, 1973; McOmie and West, 1981) to afford the corresponding phenols **5a** and **5b**, respectively. The compound **5a** and **5b** were treated with sodium hydride in THF and reacted with 4-trifluoromethylbenzyl bromide to afford the final product **1a** and **1b** in 54.2% and 54.3% yield.

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