Fluorinated Chromenes. Synthesis of 6,7-Dimethoxy-2-methyl-2-trifluoromethyl-2*H*-chromene

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Preparation of the title compound, a trifluoromethyl analog of the natural insect antijuvenile hormone 6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (precocene II), from 3,4-dimethoxyphenol and 1,1,1-trifluoro-4,4-dimethoxy-2-methyl-2-butyl mesylate is described.

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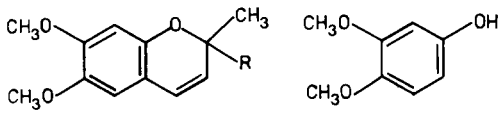
Substitution of fluorine for hydrogen to modify the bioactivity of certain molecules is a well established practice (1). We have recently reported the preparation of trifluoromethyl analogs of insect juvenile hormones to study the above effects in this field (2). In the same context, we describe in the present communication the synthesis of 6,7-dimethoxy-2-methyl-2-trifluoromethyl-2*H*-chromene (**1**), the first fluorinated analog of precocene II (**2**), a compound isolated from vegetal sources exhibiting antijuvenile hormone activity (3).

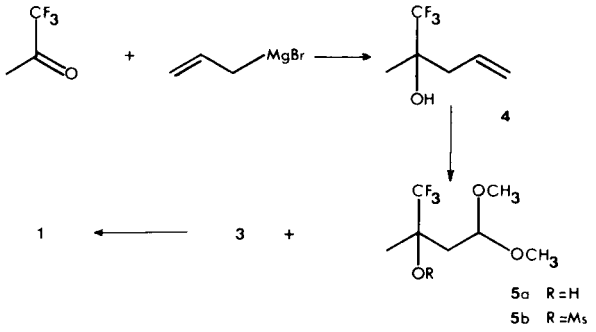


1 R = CF_3
2 R = CH_3

3

The synthetic route to **1** chosen was *via* the corresponding 4-chromanone. However, condensation of 3,4-dimethoxyphenol (**3**) and 3-trifluoromethyl-2-butenoic acid in the presence of various acid catalysts, according to described procedures (4), failed to give 6,7-dimethoxy-2-methyl-2-trifluoromethyl-4-chromanone, being in all cases the intermediate 3,4-dimethoxyphenyl ester the only product isolated from the reaction mixture.

Condensation of phenols with α,β-unsaturated aldehydes or their acetals under non-acidic conditions was contemplated as an alternative procedure (5). However, in the present case the use of the corresponding β-hydroxy derivative was thought to be more promising in order to circumvent the plausible deactivation of the carbonyl group by the trifluoromethyl substituent of the double bond. The synthon required for this purpose, 1,1,1-trifluoro-4,4-dimethoxy-2-methyl-2-butanol (**5a**) was prepared according to the sequence depicted in the Scheme.



5a R=H
5b R=Ms

Reaction of allylmagnesium bromide with 1,1,1-trifluoroacetone in diethyl ether gave the tertiary alcohol **4** in 97% yield. This alcohol was submitted to an ozonolysis and acetalization sequence (6) to afford the desired **5a** in 87% yield. However, when this compound was reacted with **3** in pyridine for 15 hours at 130° only small amounts of **1** (1-2%) were obtained. This poor result was attributed to the strength enhancement of the carbon-hydroxyl bond promoted by the presence of the trifluoromethyl substituent. This difficulty was overcome by using the corresponding mesylate derivative **5b** which under the above reaction conditions afforded a moderate yield (28%) of the desired compound **1**.

EXPERIMENTAL

The following instruments were used for the spectra described. Perkin-Elmer 257 (ir), Perkin-Elmer R 12B with tetramethylsilane as internal standard (^{1}H nmr) and trifluoroacetic acid as external standard (^{19}F nmr) and AEI MS 902S (mass spectrum).

2-Trifluoromethylpent-4-en-2-ol (**4**).

A solution of 1,1,1-trifluoroacetone (11.8 g., 0.100 mole) in dry diethyl ether (30 ml.) was added dropwise to a vigorously stirred solution of allylmagnesium bromide (0.14 mole) in dry diethyl ether (170 ml.) at 0° under a dry nitrogen atmosphere. Then, the mixture was stirred for 4 hours at room temperature. The crude was acidified with 2*N* aqueous hydrogen chloride (65 ml.), the aqueous layer was decanted and extracted with diethyl ether. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and dried (magnesium sulfate). The organic solvent was evaporated in a conventional distillation apparatus, fitted with a 30 cm × 1.4 cm Vigreux column, and the residue was distilled to give the title compound (14.9 g., 97%), b.p. 108-110°/760 torr.; ir (carbon tetrachloride): 3600, 3420, 3080, 2980, 1640, 1285, 1190, 1165, 1150, 1095, 1055, 1000, 925 cm^{-1}; ^{1}H nmr (carbon tetrachloride): δ 1.26 (s, 3H, CH_3), 2.25-2.50 (m, 2H, CH_2), 4.95-6.20 (m, 4H, COH, $CH{=}CH_2$); ^{19}F nmr (carbon tetrachloride): δ −4.7.

Anal. Calcd. for $C_6H_9F_3O$: C, 46.80; H, 5.89. Found: C, 46.87; H, 6.20.

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3-Hydroxy-3-trifluorobutyraldehyde Dimethyl Acetal (**5a**).

A solution of **4** (6.16 g., 0.040 mole) in methanol (120 ml.) was ozonized at −70° in an Ozonair, Labo 60, apparatus. After completion, a mixture of dimethyl sulfide (4.8 ml.) and methanolic hydrogen chloride (6 ml.) in methyl orthoformate (48 ml.) was added under stirring and a dry nitrogen atmosphere. The mixture was allowed to warm up to room temperature and stirring was maintained for 20 hours. The organic solvent was evaporated in a distillation apparatus as above and the residue was treated with aqueous sodium bicarbonate. The aqueous layer was decanted and extracted with diethyl ether. The combined organic extracts were dried (magnesium sulfate) and evaporated to give a residue, which was distilled at reduced pressure to afford the title compound (7.05 g., 87%), b.p. 76-78°/16 torr.; ir (carbon tetrachloride): 3470, 2990, 2830, 1180, 1165, 1120, 1095, 1060, 1040 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.31 (s, 3H, CH_3), 1.88 (d, J = 5.5 Hz, 2H, CH_2), 3.30 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 4.30 (s, 1H, OH), 4.54 (t, J = 5.5 Hz, 1H, CH); ^{19}F nmr (carbon tetrachloride): δ −4.30.

Anal. Calcd. for $C_7H_{13}F_3O_3$: C, 41.62; H, 6.48. Found: C, 41.59; H, 6.74.

6,7-Dimethoxy-2-methyl-2-trifluoromethyl-2*H*-chromene (**1**).

A solution of mesyl chloride (1.95 g., 0.017 mole) in dry diethyl ether (10 ml.) was added dropwise to a stirred mixture of sodium hydride (0.44 g., 0.018 mole) and **5a** (3.03 g., 0.015 mole) in dry diethyl ether (70 ml.). The mixture was stirred 2 hours at room temperature and then saturated aqueous sodium bicarbonate (50 ml.) was added. The aqueous layer was decanted and extracted with diethyl ether. The combined organic extracts were dried (potassium carbonate) and evaporated to give a colourless liquid mixture (3.5 g.) of **5a** (22%) and **5b** (78%) (relative intensity signals in ^{19}F nmr at δ −4.30 and −2.70). This mixture was heated at 140° for 20 hours with **3** (1.08 g., 0.007 mole) and dry pyridine (5 ml.). Then 2*N* sulfuric acid was added and the mixture was extracted with diethyl ether (70 ml.). The aqueous layer was decanted and extracted with diethyl ether. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, dried (potassium carbonate) and evaporated at reduced pressure to give a residue (1.23 g.). This residue was bulb to bulb distilled and the main fraction of this distillation (0.63 g.), b.p. 135-140°/0.3 torr, was purified by chromatography on a 15 cm × 1.5 cm aluminum oxide column (30 g., 1:1 hexane:methylene chloride) to yield the title compound (0.53 g., 28%); ir (carbon tetrachloride): 3040, 2990, 2930, 2830, 1650, 1620, 1510, 1465, 1455, 1280, 1245, 1215, 1200, 1170, 1150, 1100, 1085 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.53 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.35 (d, J = 11 Hz, 1H, =CH), 6.25-6.50 (m, 3H, =CH and ArH); ^{19}F nmr (carbon tetrachloride): δ −4.05; ms: m/e 275 ($M+1$), 274 (M^+), 259 ($M-CH_3$), 255 (M-F), 243 ($M-OCH_3$), 215, 205 ($M-CF_3$).

Anal. Calcd. for $C_{13}H_{13}F_3O_3$: C, 56.99; H, 4.78. Found: C, 57.09; H, 4.48.

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