Fluorinated Chromenes. III. Synthesis of 3-Fluoro-2,2-dimethyl-2*H*-chromenes

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The reaction of 2-fluoro-1,1-dimethoxy-3-methylbut-2-ene (**3**) with phenols in dry pyridine leads to 3-fluoro-2,2-dimethyl-2*H*-chromenes. 3-Fluoro analogues of the natural insect antijuvenile hormones Precocene I (**1a**) and II (**1b**) have been prepared by this method.

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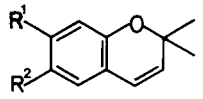
Our continuing interest in the study of structure-insect antijuvenile hormone activity relationships has recently led us to the synthesis of various fluorinated precocene analogues (1,2). In this same context, with the aim to investigate the influence of substitution of fluorine for hydrogen on the recently postulated bioactivation metabolic epoxidation of the 3,4-double bond of Precocenes I (**1a**) (3) and II (**1b**) (4), we required a procedure for the preparation of 3-fluoro-2,2-dimethyl-2*H*-chromenes.



1a: $R^1 = OCH_3$; $R^2 = H$
1b: $R^1 = R^2 = OCH_3$

Figure 1

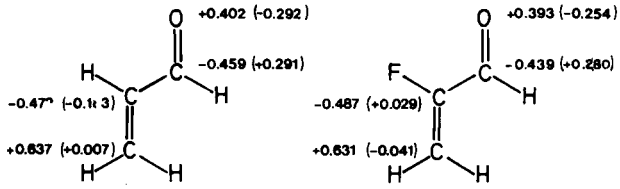
The condensation of α,β-unsaturated carbonyl compounds or masked forms thereof with phenols or phenoxides under different reaction conditions has been one of the most explored routes for the preparation of 2*H*-chromenes (5-10). The easy availability of 2-fluoro-3-methylbut-2-enal (**2**) (11) focused our attention on this synthon as our first choice for fluorine introduction at the desired site using the above procedure.

Generally, it is accepted that this condensation initially proceeds *via* *C*-alkylation on the carbonyl group at the position *ortho* to the phenolic hydroxyl group (7). Therefore, for a given phenol, according to PMO theory (12), the energy of the LUMO of the carbonyl compound as well as the coefficient of the carbonyl carbon in such orbital should determine the ease of the reaction. In order to evaluate the influence of the 2-fluoro substituent on such parameters, MNDO calculations (13-15) were performed with acrolein (14) and 2-fluoroacrolein (15) as model compounds.

The results of the calculation (see Figure) showed a very low participation of the 2-fluoro substituent in the frontier orbitals of the α,β-unsaturated carbonyl system, which was practically unaffected by the substitution of fluorine for hydrogen. Moreover, the predicted LUMO energy of 2-fluoroacrolein was somewhat lower than that of the corresponding orbital in the unsubstituted compound. On the other hand, the high value of the β-carbon coefficient in

Figure 2

LUMO and Charge Distribution of Acrolein and of 2-Fluoroacrolein



E_{LUMO} = 0.090 eV E_{LUMO} = -0.537 eV

Values in parentheses refer to net charges.

the LUMO of both compounds suggests that, if the reaction between a phenol and an α,β-unsaturated carbonyl compound really proceeds as indicated above, there should be some charge control involved in the process. In this sense, as it is shown in the Figure net charges on carbonyl carbon in acrolein and 2-fluoroacrolein are predicted to be practically equivalent.

In view of these results, the cyclocondensation of aldehyde **2** with phenols using either the procedure described by Crombie and co-workers (8) or that reported by Casiraghi and co-workers (10) was initially studied. In both cases the expected 3-fluoro-2,2-dimethyl-2*H*-chromenes (**5**) were formed but the yields were not satisfactory, probably owing to the instability of the carbonyl compound under the reaction conditions. In order to circumvent this difficulty, the aldehyde **2** was converted into the corresponding dimethyl acetal **3** by orthoformate acetalisation (86% yield) and this was used as a chromenylating agent with a series of phenols. Experimentally, mixtures of phenols **4**, acetal **3** and pyridine in a 1:2:1 molar ratio were heated at 140°, the progress of the reactions being easily monitored by glc. Relevant data for the reaction are summarized in the Table.

The reaction rate was highly influenced by the electronic effects of the substituents in the starting phenol. Electron rich phenols, such as **4a**, reacted very rapidly

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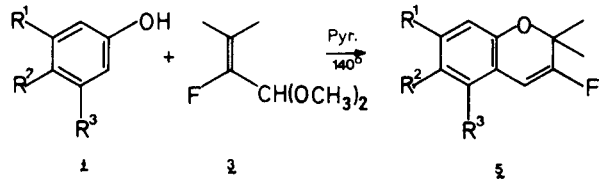

1 2 5

Figure 3

while slow reactions were observed with electron poor phenols, such as **4f**.

Glc routine analyses of the reaction crudes revealed the appearance of by-products which were not investigated in detail, but they could presumably arise from overalkylation of performed chromenes. This problem became more serious in the attempted chromenylations of phenol, *o*-cresol, *o*-methoxyphenol and *p*-methoxyphenol, not shown in the table, where the presence of peaks with the expected retention times for the corresponding fluorinated chromenes was initially observed in the control chromatograms, but their intensities decreased even faster than those of the starting phenols as the reactions proceeded, rendering the procedure worthless for synthetic purposes in these cases. Accordingly, it can be concluded that satisfactory yields can be obtained whenever overalkylation is minimized by the absence of activated sterically unencumbered positions in the resulting chromenes.

Table

Compound No.	R^1	R^2	R^3	Reaction Time (h)	Yield (%)
5a	OCH_3	OCH_3	H	2.5	63
5b	-O-CH_2-O-		H	4	50
5c	OCH_3	H	H	3	32 (a)
5d	H	H	OCH_3		
5e	CH_3	H	CH_3	5	84
5f	H	$COCH_3$	H	6	49 (b)
5g	H	$COCH_3$	OH	5	79

(a) The reaction with 3-methoxyphenol afforded a 2.7:1 mixture of **5c** and **5d**. (b) A further addition of **3** (10 mmoles) was carried out after 3 hours. Conversion was ≅75% after 6 hours.

As far as the regioselectivity is concerned, two results deserve comment. Firstly, the formation of chromene **5g** is in agreement with the observations of Crombie and coworkers for the non-fluorinated series (8). Secondly, the reaction of 3-methoxyphenol with **3** leads to a 2.7:1 mixture of 3-fluoro-7-methoxy-2,2-dimethyl-2*H*-chromene (**5c**) and 3-fluoro-5-methoxy-2,2-dimethyl-2*H*-chromene (**5d**). Likewise, the formation of a similar mixture of regioisomers (**5c:5d**/2:1) was observed when reacting the aldehyde **2** with titanium (IV) 3-methoxyphenoxide. This procedure exhibits regiospecificity when applied to the corresponding non fluorinated aldehyde (10). Consequently, these differences in the regiochemical outcome of the reaction in the present case could be attributed to the presence of the 2-fluoro substituent in the prenyl synthon.

Work is in progress for extension of the above procedure for the preparation of other 3-funtionalized 2,2-dimethyl-2*H*-chromenes.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Boiling points (unless for **2**) refer to bulb-to-bulb distillation. ^1H and ^{19}F nmr spectra were obtained on a Perkin-Elmer R12B (TMS as internal standard and TFA as external standard). Ir spectra were obtained with a Perkin-Elmer 399B instrument. Gas-liquid chromatographic (glc) analyses were performed with a Perkin-Elmer model 990 chromatograph using a glass column packed with 3% OV-101 on silanized Gas Chrom. W.

2-Fluoro-1,1-dimethoxy-3-methylbut-2-ene (**3**).

2-Fluoro-3-methylbut-2-enal (**2**) (10.2 g., 0.1 mole), trimethyl orthoformate (11.7 g., 0.11 mole) and a trace (0.17 g., 0.001 mole) of anhydrous *p*-toluenesulphonic acid were boiled under reflux for 2 hours. The resulting solution was cooled to room temperature, solid sodium carbonate was added and the methyl formate was removed *in vacuo* at room temperature. The residue was then distilled at reduced pressure to afford the title compound (12.7 g., 86%), b.p. 54°/17 torr; ir (carbon tetrachloride): 2995, 2935, 2830, 1705, 1450, 1395, 1197, 1128, 1100, 1085, 1060, 992 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.63 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 3.27 (s, 6H, OCH_3), 4.89 (d, J = 14.5 Hz, 1H, -C*H*<); ^{19}F nmr (carbon tetrachloride): δ −47.3 (dxm, J_1 = 14.5 Hz).

Anal. High Resolution Mass Spectrometry Calcd. for $C_7H_{13}FO_2$: 148.0900. Found: 148.0901.

3-Fluoro-2,2-dimethyl-2*H*-chromenes (**5a-5g**). General Procedure.

A mixture of the starting phenol (**4a-4g**) (5 mmoles), anhydrous pyridine (5 mmoles) and **3** (10 mmoles) was heated at 140° for a variable period of time, until the starting phenol reacted almost completely (glc monitoring). The reaction mixture was then cooled, pyridine and remaining **2** were removed under reduced pressure and the residue submitted to column chromatography (silica gel, hexane:ether mixtures), the 3-fluoro-2,2-dimethyl-2*H*-chromenes **5** being isolated as the less polar components.

3-Fluoro-6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (3-Fluoroprecocene II) (**5a**).

This compound had m.p. 58-59° (63% yield); ir (carbon tetrachloride): 3075, 3000, 2945, 2840, 1682, 1620, 1508, 1470, 1457, 1447, 1420, 1367, 1320, 1295, 1252, 1220, 1205, 1162, 1140, 1122, 1022, 870 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.45 (s, 6H, CH_3), 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 5.75 (d, J = 12.5 Hz, 1H, -HC=), 6.30 (s, 1H, ArH), 6.36 (s, 1H, ArH); ^{19}F nmr (carbon tetrachloride): δ −48.4 (d, J = 12.5 Hz).

Anal. Calcd. for $C_{13}H_{15}FO_3$: C, 65.54; H, 6.35. Found: C, 65.51; H, 6.50.

3-Fluoro-2,2-dimethyl-6,7-methylenedioxy-2*H*-chromene (**5b**).

This compound had m.p. 53-54°; (50% yield); ir (carbon tetrachloride): 2990, 2890, 2775, 1687, 1625, 1510, 1490, 1455, 1285, 1250, 1188, 1170, 1125, 1050, 950, 871 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.46 (s, 6H, CH_3), 5.73 (d, J = 12.5 Hz, 1H, -CH=), 5.80 (s, 2H, -O-CH_2-O-), 6.31 (s, 2H, ArH); ^{19}F nmr (carbon tetrachloride): δ −48.6 (d, J = 12.5 Hz).

Anal. Calcd. for $C_{12}H_{11}FO_3$: C, 64.86; H, 4.99. Found: C, 64.97; H, 5.26.

3-Fluoro-7-methoxy-2,2-dimethyl-2*H*-chromene (3-Fluoroprecocene I) (**5c**) and 3-Fluoro-5-methoxy-2,2-dimethyl-2*H*-chromene (**5d**).

This product was obtained in 32% yield as a 2.7:1 mixture of **5c** and **5d**. Separation was achieved by column chromatography on silica gel eluting with hexane (less polar compound **5d**) and, subsequently with 10:1 mixture of hexane:ether (**5c**), **5c** had b.p. 81-82°/0.17 torr; ir (carbon tetrachloride): 2990, 2955, 2840, 1685, 1620, 1578, 1505, 1465, 1445, 1362, 1320, 1278, 1250, 1203, 1194, 1165, 1147, 1110, 1100, 1038, 990, 855, 840 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.49 (s, 6H, CH_3), 3.70 (s, 3H, OCH_3), 5.80 (d, J = 12.5 Hz, 1H, -CH=), 6.20-6.40 (m, 2H, Ar-H), 6.60-6.80 (m, 1H, ArH); ^{19}F nmr (carbon tetrachloride): δ −48.9 (d, 12.5 Hz).

Anal. Calcd. for $C_{12}H_{13}FO_2$: C, 69.22; H, 6.29. Found: C, 69.38; H, 6.15.

Compound **5d** had b.p. 77-78°/0.17 torr; ir (carbon tetrachloride): 2990, 2952, 2935, 2835, 1680, 1602, 1587, 1480, 1470, 1440, 1320, 1278, 1260, 1210, 1170, 1138, 1083, 862, 720 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.46 (s, 6H, CH_3), 3.74 (s, 3H, OCH_3), 6.05-6.40 (m, 3H, -CH= and ArH), 6.70-7.00 (m, 1H, ArH); ^{19}F nmr (carbon tetrachloride): δ −46.2 (d, J = 13 Hz).

Anal. Calcd. for $C_{12}H_{13}FO_2$: C, 69.22; H, 6.29. Found: C, 69.51; H, 6.50.

3-Fluoro-2,2,5,7-tetramethyl-2*H*-chromene (**5e**).

This compound had b.p. 82°/0.2 torr (84% yield); ir (carbon tetrachloride): 2980, 2920, 2860, 1680, 1612, 1570, 1490, 1462, 1362, 1350, 1312, 1262, 1235, 1158, 850 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.45 (s, 6H, O-C(CH_3)$_2$), 2.17 (s, 6H, Ar-CH_3), 5.95 (d, J = 13 Hz, 1H, -CH=), 6.3-6.5 (m, 2H, ArH); ^{19}F nmr (carbon tetrachloride): δ −45.5 (d, J = 13 Hz).

Anal. Calcd. for $C_{13}H_{15}FO$: C, 75.70; H, 7.33. Found: C, 75.66; H, 7.34.

6-Acetyl-3-fluoro-2,2-dimethyl-2*H*-chromene (**5f**).

This compound had b.p. 87-88°/0.15 torr (49% yield); ir (carbon tetrachloride): 2990, 1690, 1610, 1578, 1495, 1470, 1435, 1363, 1350, 1294, 1277, 1255, 1240, 1180, 1153, 1145, 1120, 970, 895, 840, 827 cm^{-1}; ^1H nmr carbon tetrachloride): δ 1.53 (s, 6H, CH_3), 2.42 (s, 3H, CH_3CO), 5.94 (d, J = 12 Hz, 1H, -CH=), 6.72 (d, J = 8.5 Hz, 1H, ArH), 7.35-7.75 (m, 2H, ArH); ^{19}F nmr (carbon tetrachloride): δ −43.2 (d, J = 12 Hz).

Anal. Calcd. for $C_{13}H_{13}FO_2$: C, 70.89; H, 5.95. Found: C, 71.08; H, 6.22.

6-Acetyl-3-fluoro-5-hydroxy-2,2-dimethyl-2*H*-chromene (**5g**).

This compound had m.p. 87-88° (79% yield); ir (carbon tetrachloride): 2995, 2945, 1690, 1638, 1587, 1493, 1470, 1435, 1375, 1335, 1280, 1255, 1162, 1142, 1130, 1070, 895, 865 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.52 (s, 6H, CH_3), 2.46 (s, 3H, CH_3CO), 6.20 (d, J = 9 Hz, 1H, ArH), 6.23 (d, J = 12.5 Hz, 1H, -CH=), 7.36 (d, J = 9 Hz, 1H, ArH), 12.75 (s, 1H, OH); ^{19}F nmr (carbon tetrachloride): δ −45.6 (d, J = 12.5 Hz).

Anal. Calcd. for $C_{13}H_{13}FO_3$: C, 66.09; H, 5.55. Found: C, 66.21; H, 5.61.

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REFERENCES AND NOTES

(1) F. Camps, J. Coll, A. Messeguer and M. A. Pericás, *J. Heterocyclic Chem.*, **17**, 207 (1980).

(2) F. Camps, J. Coll, A. Messeguer and M. A. Pericás, *Tetrahedron Letters*, 2361 (1980).

(3) G. T. Brooks, G. E. Pratt and R. C. Jennings, *Nature*, **281**, 570 (1979).

(4) D. M. Soderlund, A. Messeguer and W. S. Bowers, *J. Agric. Food Chem.*, in press.

(5) J. O. Asgill, L. Crombie and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 59 (1978); and references cited therein.

(6) G. Casiraghi, G. Casnati and G. Salerno, *J. Chem. Soc. C*, 2546 (1971).

(7) D. G. Clarke, L. Crombie and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1007 (1974).

(8) W. M. Bandaranayake, L. Crombie and D. A. Whiting, *J. Chem. Soc. C*, 811 (1971).

(9) O. P. Malik, R. S. Kapil and N. Anand, *Indian J. Chem.*, **14**, 449 (1976).

(10) G. Sartori, G. Casiraghi, L. Bolzoni and G. Casnati, *J. Org. Chem.*, **44**, 803 (1979).

(11) Y. Bessière, D. N. H. Savary and M. Schlosser, *Helv. Chim. Acta*, **60**, 1739 (1977).

(12) For an account of PMO theory, see I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", John Wiley and Sons, London, 1976.

(13) M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 (1977).

(14) M. J. S. Dewar and W. Thiel, *ibid.*, **99**, 4907 (1977).

(15) M. J. S. Dewar and H. S. Rzepa, *ibid.*, **100**, 58 (1978).

(16) Other relevant data of 2-fluoroacrolein as predicted by MNDO calculation: equilibrium geometry C_1O: 1.218 Å; C_2C_1: 1.512 Å; FC_2: 1.328 Å; C_3C_2: 1.359 Å; H_1C_1: 1.109 Å; $H_3(ZF)C_3$: 1.088 Å; $H_3(EF)C_3$: 1.088 Å; OC_1C_2: 124.3°; FC_2C_3: 120.5°; $C_2C_3H_3(ZF)$: 123.6°; $C_2C_3H_3(EF)$: 122.3°; $C_1C_2C_3$: 123.4°; $H_1C_1C_2$: 113.8°; heat of formation: −62.7 Kcal./mole; 1st ionization potential: 10.60 eV; dipole moment 3.69 D.