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Novel Synthesis of 2-(Trifluoromethyl)- and 2-(Perfluoroalkyl)-2-hydroxy-2*H*-chromenes and Their Regiospecific Reaction with Silyl Enol Ethers

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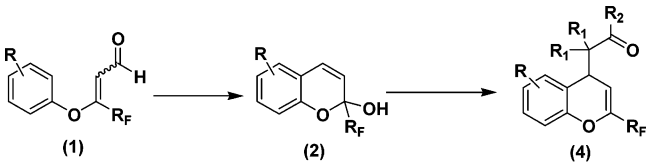
Received April 11, 2006



R = H, *p*-OMe, *m*-OMe, *m*-Me, *o*-OMe, *o*-Cl, *p*-Cl, *p*-CN, *p*-NO_2.

R_2 = H, Me, OMe, *t*-Bu; R_1 = H, Me; R_F = CF_3, C_3F_7, C_5F_{11}

The synthesis of substituted 2-(trifluoromethyl)- and 2-(perfluoroalkyl)-2-hydroxy-2*H*-chromenes **2a**−**o** was achieved in good yields by intramolecular cyclization of 3-(perfluoroalkyl)-3-phenoxypropenals **1** in the presence of aluminum chloride. Then a Lewis acid mediated nucleophilic reaction with silyl enol ethers **3** proceeded with complete regiospecificity to afford 4-functional 2-(trifluoromethyl)- and 2-(perfluoroalkyl)-4*H*-chromenes **4a**−**p** with high yields.

2-Substituted 2*H*-chromenes are an important class of oxygenated heterocyclic compounds.[1] The biological activity of many of the naturally occurring compounds which incorporate a chromene ring system[2] has resulted in several applications of substituted chromenes in synthesis,[3] and new methods of accessing these important compounds continue to be reported. These include intramolecular cyclization of Wittig intermediates,[4] micowave-assisted reaction of salicylaldehyde with enamines,[5] catalytic Petasis reaction of salicylaldehydes,[6] ring-closing olefin metathesis,[7] Baylis−Hillman reaction of 2-hydroxybenzaldehydes with methyl vinyl ketones,[8] Claisen rearrangement of propargyl phenol ethers,[9] Pd-catalyzed ring closure of 2-isoprenyl phenols,[10] and electrocyclic ring closure of vinylquinone derivatives.[11]

Despite advances in the area, methods for preparing valuable derivatives of 2-hydroxychromenes remain very limited.[12] Synthesis of 2-hydroxy-2*H*-chromenes which are cyclic allyl hemiketals is best illustrated by the preparation of benzopyrylium salts. In these reactions 2-hydroxychromenes are intermediates.[13] For example, 2-phenylbenzopyrylium salts (flavylium salts) as derivatives of naturally occurring plant pigments give on acid hydrolysis 2-hydroxychromenes which undergo a tautomeric conversion to the more stable noncyclic derivatives.[14] Earlier reports describe the hydrolysis of such benzopyrylium derivatives by treatment with large amounts of alcohols with a trace of acid. The corresponding ethers, which are rather unstable, are obtained.[12,13b]

Selective trifluoromethylation or perfluoroalkylation of organic molecules has been recognized as one of the most potentially important and efficient probes in finding and developing new biologically important compounds.[15,16] Recently, many substituted 4*H*-chromenes have displayed high antibacterial activity and powerful anticancer properties by affecting tumor vasculature progression and inducing tumor necrosis in vivo.[17] The importance of these interesting biological properties prompted us to develop a new general and efficient methodology for the preparation of trifluoromethyl- or perfluoroalkyl-containing substituted chromenes.

The purpose of this paper is to describe the scope of a new regiospecific access to the functional 2-(perfluoroalkyl)-2*H*-chromene **2a**−**o** ring system; we also present some aspects of

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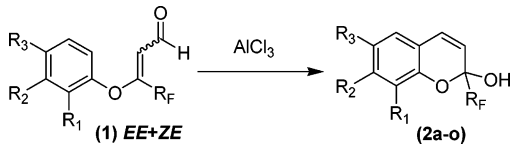
10.1021/jo060765a CCC: $33.50
Published on Web 09/28/2006

TABLE 1. Reaction Times and Yields for Compounds 2a−o

entry	compd	R_F	R_1	R_2	R_3	time (h)	temp (°C)	convn[a] (%)
1	**2a**	CF_3	H	H	OMe	4	40	90
2	**2b**	C_3F_7	H	H	OMe	4	40	92
3	**2c**	C_5F_{11}	H	H	OMe	4	40	90
4	**2d**	CF_3	H	H	H	6	40	86
5	**2e**	C_5F_{11}	H	H	H	6	40	88
6	**2f**	C_3F_7	H	Me	H	4	40	86
7	**2g**	CF_3	H	OMe	H	4	40	90
8	**2h**	C_3F_7	OMe	H	H	6	40	75
9	**2i**	C_5F_{11}	Cl	H	H	12	80	55
10	**2j**	CF_3	H	H	Cl	12	80	75
11	**2k**	C_5F_{11}	H	H	Cl	12	80	75
12	**2l**	CF_3	H	H	CN	24	80	58
13	**2m**	C_5F_{11}	H	H	CN	24	80	60
14	**2n**	C_5F_{11}	H	H	NO_2	24	80	50
15	**2o**	CF_3	H	H	NO_2	24	80	55

[a] Conversion determined by ^{19}F NMR analysis of the reaction mixtures: NMR yields based on consumed **1** and formed **2**.

SCHEME 1. Synthesis of Substituted 2-(Perfluoroalkyl)-2-hydroxy-2*H*-chromenes 2a−o



its reactivity for the preparation of 4-substituted 2-(perfloroalkyl)-4*H*-chromenes **4a**−**p**.

Synthesis of 2-(Perfluoroalkyl)-2*H*-chromen-2-ols. In a previous work[18] we reported the synthesis of β-phenoxypropenals **1** bearing a perfluoroalkyl group. These fluorinated β-phenoxypropenals **1** are synthesized with high yields in a two-step reaction that involves the formation of a perfluoroalkylated *gem*-iodoacetoxy compound,[19] which was previously developed in our group for perfluoroalkylation reactions of organic compounds.[20,21] Enals **1** appeared to be a very important synthon for the synthesis of perfluoroalkylated compounds.

In this paper, our synthetic approach is based on a Lewis acid (anhydrous $AlCl_3$) catalyzed intramolecular cyclization of a mixture of *E*,*E* and *Z*,*E* isomers of 3-(perfluoroalkyl)-3-(R_1,R_2,R_3-phenoxy)prop-2-enal **1** (Scheme 1). The method allows the preparation of a large variety of substituted 2-(perfluoroalkyl)-2-hydroxy-2*H*-chromenes **2a**−**o** (Table 1).

This procedure can tolarate a wide variety of substituents on the aromatic nucleus and could be successfully extended to highly electron-attracting groups (Table 1). We found that the use of $TiCl_4$, $SnCl_4$, or $ZnCl_2$ as Lewis acids gave low yields. $AlCl_3$ appeared to be more effective, and it was necessary to add it portionwise at 0 °C. Cyclization of **1** in the presence of aluminum trichloride required 6−24 h in refluxing dichloromethane or dichloroethane depending on the nature of the substituent on the aromatic ring. Under these conditions, complete consumption of the starting product **1** was observed, and the 2-hydroxychromenes **2a**−**o** were the major product in the crude mixture except in the case of highly electron-withdrawing substituents on the aromatic ring (R_3 = NO_2, CN, and Cl), in which small amounts of enals **1** were still present. Extension of the reaction time resulted in a decrease of the yields due to decomposition. Crude products **2a**−**o** were purified by column chromatography over silica gel. Table 1 summarizes several examples of the application of this method. In most cases, good to excellent yields are obtained.

In the case of substitutions occurring on the *meta*-position on the aromatic ring of propenals (R_2 = Me and OMe) the ^{19}F NMR spectroscopy of each of the reaction mixtures showed only one sharp singlet, which had been assigned to the CF_2 or CF_3 group of the corresponding chromenols **2f** and **2g**. The NMR coupling pattern of **2f** and **2g** showed unambiguously in all cases that the substitution was only in the 7-position. No formation of 5-substituted chromenols was observed probably due to steric hindrance. This reaction is the first example of successful regiospecific synthesis and isolation of perfluoroalkylated 2-hydroxy-2*H*-chromenes.

The structures of the final products **2a**−**o** were established by standard spectroscopic means and confirmed by HRMS and microanalysis. Moreover, chemical transformations confirmed their structure. Few reports deal with the structure of 2-hydroxychromenes.[22] Some works on 2-hydroxychromanones reported a ring−chain isomerization[23a] or ring opening[23b] of these compounds. Other authors reported a β-diketo form[24] or cyclic forms[25a] of these compounds. In contrast with the nonfluorinated analogues, Morera and Ortar reported that 2-(trifluoromethyl)-2-hydroxychromanones exist only in the cyclohemiketal form both in the solid state and in solution.[25b] These results indicate unambiguously that the ring forms are always present, due to the powerful inductive control of the polyfluoroalkyl group. In our case, we reached the same conclusion since no isomers were observed in NMR spectros-

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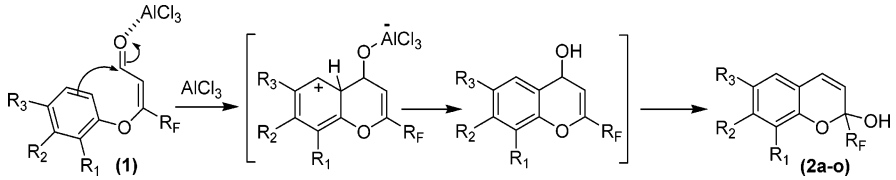
TABLE 2. Data and Yields for 4-Substituted 2-(Perfluoroalkyl)-4*H*-chromenes 4a−p

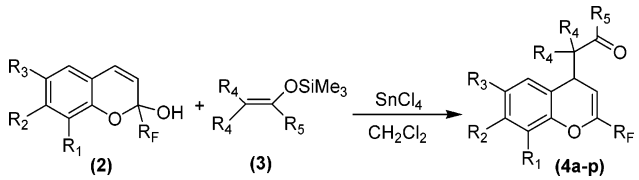
synthesized compd **4**	starting product **2**	R_F	R_1	R_2	R_3	R_4	R_5	convn[a] (%)
4a	**2c**	C_5F_{11}	H	H	OMe	H	Me	>95
4b	**2c**	C_5F_{11}	H	H	OMe	Me	H	>95
4c	**2a**	CF_3	H	H	OMe	Me	H	>95
4d	**2a**	CF_3	H	H	OMe	Me	OMe	>95
4e	**2a**	CF_3	H	H	OMe	H	*t*-Bu	>95
4f	**2g**	CF_3	H	OMe	H	Me	OMe	95
4g	**2g**	CF_3	H	OMe	H	H	*t*-Bu	96
4h	**2h**	C_3F_7	OMe	H	H	H	*t*-Bu	96
4i	**2e**	C_5F_{11}	H	H	H	H	Me	>95
4j	**2d**	CF_3	H	H	H	Me	H	96
4k	**2f**	C_3F_7	H	Me	H	H	Me	95
4l	**2i**	C_5F_{11}	Cl	H	H	H	*t*-Bu	>95
4m	**2m**	C_5F_{11}	H	H	CN	H	Me	92
4n	**2l**	CF_3	H	H	CN	H	Me	>95
4o	**2n**	C_5F_{11}	H	H	NO_2	Me	H	92
4p	**2o**	CF_3	H	H	NO_2	Me	H	>95

[a] Conversion determined by ^{19}F NMR analysis of the reaction mixtures: NMR yields based on consumed **2** and formed **4**.

SCHEME 2. Mechanism of Formation of 2-(Perfluoroalkyl)-2-hydroxy-2*H*-chromenes 2a−o



SCHEME 3. Formation of 2-(Trifluoromethyl)- and 2-(Perfluoroalkyl)-4*H*-chromenes 4a−p



copy even at low temperature, and there were no carbonyl bands in the IR spectra.

Formation of 2-hydroxychromenes **2a−o** could be explained by an intramolecular electrophilic aromatic cyclization induced by aluminum trichloride, giving a 4-hydroxy-4*H*-chromene as an intermediate. A further rearrangement generates the more stable 2-hydroxy-2*H*-chromenes **2**[13,22] (Scheme 2).

During our work, the synthetic scope of these new molecules **2** showed an interesting reactivity. Here we describe the reactivity of these unique and original molecules toward C-nucleophiles such as silyl enol ethers.

Reaction 2*H*-Chromenols 2 with Silyl Enol Ethers. When 2-hydroxy-2*H*-chromenes **2** were treated with trimethylsilyl enol ethers **3** in the presence of a Lewis acid such as $SnCl_4$, substituted 4*H*-chromenes **4a−p** were obtained with very high yields (Scheme 3).

2-Hydroxychromenes **2** reacted easily with trimethylsilyl derivatives **3** in a remarkably regiospecific and fast reaction with reaction times on the order of minutes. Moreover, in all cases the ^{19}F NMR spectra of the crude mixtures indicated that these reactions proceeded in high yields without side reactions. The results and yields are summarized in Table 2.

These reactions occur almost exclusively at the 4-position of the chromene. No formation of the 1,2-addition product was observed. It seems that the regiospecificity of the nucleophilic attack of the silyl ethers **3** on the chromenol ring depends on the steric effects of the C2 perfluorinated group.

These new compounds were identified by ^1H, ^{19}F, and ^{13}C NMR spectroscopy, and their structure was confirmed by mass spectrometry and microanalysis. The ^1H NMR spectra of 4*H*-chromenes **4** showed signals for the two protons of the propanonyl group in the case of chromenes **4a, 4i**, and **4k** and of the butanonyl group for chromenes **4e** and **4g**, showing a characteristic AB system for each of them (Scheme 4) ($^3J_{HH}$ = 7.8 Hz and $^2J_{HH}$ = 18.1 Hz for the first proton and $^3J_{HH}$ = 5.5 Hz and $^2J_{HH}$ = 18.1 Hz for the other proton) (see the Supporting Information, II, pp S_2, S_{13}, S_{19}, S_{26}, and S_{29}). However, for chromenes **4h** and **4l** these protons appeared as a doublet for the first proton ($^3J_{HH}$ = 2.5 Hz) and a singlet for the other one (Scheme 4) (see the Supporting Information, II, pp S_{22} and S_{32}). Finally, for chromenes **4m** and **4n** the two propanonyl protons appeared as a doublet with coupling constant $^3J_{HH}$ = 6.7 Hz (Scheme 4) (see the Supporting Information, II, pp S_{33} and S_{35}). The $^1H-^1H$ COSY spectra of **4a**, **4e, 4g−i**, and **4k−n** showed a clear cross-peak between their allylic protons and the two protons of the propanonyl or butanonyl groups.

The mechanism of formation of these perfluoroalkylated 4*H*-chromenes **4a−p** could be explained by the nucleophilic attack of the silyl enol ether **3** on a benzopyrylium, **5**, or on a trichlorostannic intermediate, **6**. Subsequent elimination of the trimethylsilyl group assisted by a chloride anion yields **4a−p**. Such processes have been studied with simple acetals and would proceed through an oxocarbonium,[26] **5**, or a stannic species, **6**.[27] (Scheme 5).

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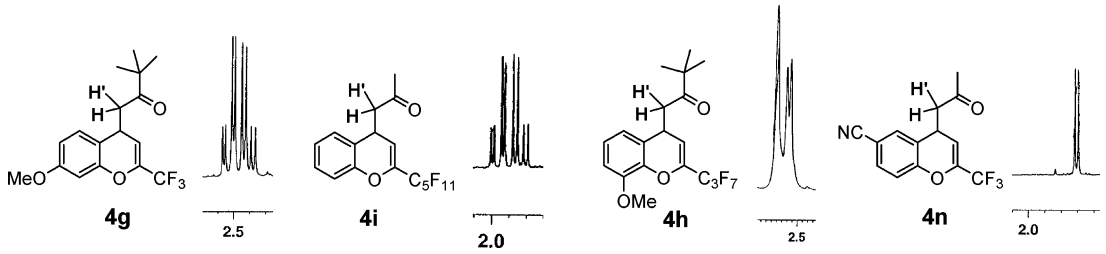
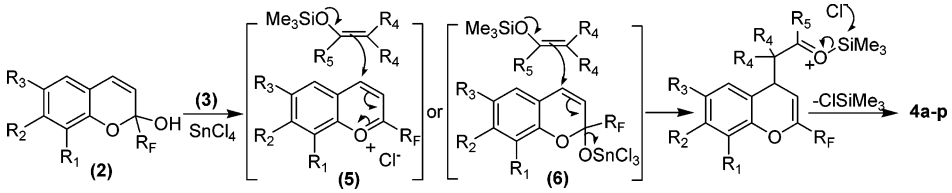
SCHEME 4. ^{1}H NMR Spectra (300 MHz) Showing Signals of Protons H and H′ of Compounds 4g, 4i, 4h, and 4n



SCHEME 5. Mechanism of Formation of 2-(Trifluoromethyl)- and 2-(Perfluoroalkyl)-4*H*-chromenes 4a−p



Since many synthetic chromenes found therapeutic applications[28,29] as antihypertensive[28a,b] or anti-ischemic agents,[28b] while other analogues are candidates in the field of potassium channel openers,[29] we developed these synthetic methods, which are practical and experimentally convenient and proceed with very high regiospecificity to afford substituted 2-hydroxy-2*H*-chromenes **2** and 4-functional 4*H*-chromenes **4**. By comparison, no similar syntheses have been reported in the literature to provide regiospecifically functionalized trifluoromethylated or perfluoroalkylated chromenes, and this is the first example of this kind of reaction for the application of Mukaiyama reagents.

Experimental Section

General Procedure for the Preparation of 2-(Perfluoroalkyl)-2*H*-chromen-2-ols 2a−o. In a round-bottom flask cooled in an ice bath, to a mixture of compounds **1** (1 equiv) in dichloromethane or dichloroethane (5 mL/g of **1**) (Table 1) was added 1.2 equiv of anhydrous aluminum trichloride portionwise. The mixture was stirred at 0 °C for 30 min, then warmed to room temperature, and put under reflux. At the end of the reaction as judged by ^{19}F NMR spectroscopy and TLC, the mixture was diluted in water, quenched carefully with a solution of sodium hydrogen carbonate, and then extracted six times with dichloromethane or dichloroethane. The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo, and a dark brown oil was obtained. The crude products were chromatographed through silica gel using an eluent gradient of ethyl acetate/petroleum ether from 10/90 to 30/70 to afford the desired chromenols **2a−o** as bright yellow oils.

2-(Trifluoromethyl)-6-methoxy-2*H*-chromen-2-ol (2a). Starting with **1** (R = *p*-OMe, $R_F = CF_3$) (10 g, 40 mmol) and aluminum chloride (6.5 g; 48 mmol) in 50 mL of dichloromethane under reflux for 4 h, 8.8 g of the title chromenol was obtained in a total yield of 88%. ^{1}H NMR (300.13 MHz, C_6D_6): δ 3.4 (s, 3H, OCH_3), 4 (br s, 1H, OH), 5.7 (d, J = 9.8 Hz, 1H, C═CH), 6.3 (d, J = 9.8 Hz, 1H, CH═C), 6.5 (d, J = 3 Hz, 1H), 6.6 (dd, J = 8.8 and 3 Hz, 1H), 6.9 (d, J = 8.8 Hz, 1H). ^{13}C NMR (75.4 MHz, C_6D_6): δ 52.9, 91.6 (q, CCF_3, $^2J_{CF}$ = 33.9 Hz), 109.8, 113.9, 114.1, 114.7, 116.7, 120.2 (q, CF_3, $^1J_{CF}$ = 285.4 Hz), 126.8, 141.8, 152.4. ^{19}F NMR (282.3 MHz, C_6D_6): δ −84.2 (s, 3F). MS (*m*/*z*): 247 (M^+, 100). IR (cm^{-1}, KBr): 3500−3200 (OH). HRMS (*m*/*z*): calcd for $C_{11}H_{10}F_3O_3$, 247.0582; found, 247.0581. Anal. Calcd for $C_{11}H_9F_3O_3$: C, 53.67; H, 3.68; O, 19.50. Found: C, 53.65; H, 3.68; O, 19.51.

General Procedure for the Preparation of Substituted 2-(Perfluoroalkyl)-4*H*-chromenes 4a−p. To a stirred solution of chromenols **2** (1 equiv) and the corresponding silyl enol ether (Table 2) in anhydrous dichloromethane (5 mL/g of **2**) under argon was added at −78 °C 1 equiv of $SnCl_4$. The mixture was stirred at this temperature for 1 h and then warmed to room temperature. At the end of the reaction (2 h) as judged by ^{19}F NMR spectroscopy and TLC, the mixture was diluted in water, quenched carefully with a solution of sodium hydrogen carbonate, and then extracted with dichloromethane. The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude 4*H*-chromenes **4** were obtained in very high yields (>90%) as white solids.

1-(2-(Perfluoropentyl)-6-methoxy-4*H*-chromen-4-yl)propan-2-one (4a). To a solution of **2c** (R = 6-OMe, $R_F = C_5F_{11}$) (3 g, 6.72 mmol) and 2-[(trimethylsilyl)oxy]propene **3** (R_1 = H, R_2 = Me) (1.11 mL or 0.87 g, 6.72 mmol) in 15 mL of anhydrous dichloromethane was added 0.78 mL (6.72 mmol) of $SnCl_4$ at −78 °C. After 1.30 h, 3.2 g of title chromene **4a** was obtained in a total yield of 98%. ^{1}H NMR (250.13 MHz, C_6D_6): δ 1.4 (s, CH_3, 3H), 2 (dd, $^2J_{HH}$ = 18.1 Hz and $^3J_{HH}$ = 7.7 Hz, $CHCH_2$, 1H), 2.2 (dd, $^2J_{HH}$ = 18.1 Hz and $^3J_{HH}$ = 5.6 Hz, $CHCH_2$, 1H), 3.3 (s, OCH_3, 3H), 3.9 (m, $CHCH_2$, 1H), 5.7 (d, J = 5 Hz, ═CHCH, 1H), 6.4−6.6 (m, 2H), 6.8 (d, J = 8.7 Hz, 1H). ^{13}C NMR (75.4 Hz, C_6D_6): δ 27.4, 27.5, 50.1, 55.1, 108.1, 115.2, 120.5, 123.2, 126.8, 139.1, 148.8, 201.8. ^{19}F NMR (235.36 MHz, C_6D_6): δ −81.2 (s, 3F), −117.6 (t, $^3J_{FF}$ = 12.5 Hz, 2F), −123 (m, 4F), −126.5 (m, 2F). MS (*m*/*z*): 487 (M^+, 100). HRMS (*m*/*z*): calcd for $C_{18}H_{14}F_{11}O_3$, 487.0767; found, 487.0762. Anal. Calcd for $C_{18}H_{13}F_{11}O_3$: C, 44.46; H, 2.69; O, 9.87. Found: C, 44.44; H, 2.70; O, 9.85.

Acknowledgment. We thank Dr. Maryse Bejaud for NMR analyses and interesting discussions.

Supporting Information Available: Experimental procedures and analytical data for compounds **2b−o** and **4b−p** and ^{1}H, ^{13}C, COSY ^{1}H−^{1}H, ^{13}C−^{1}H, and ^{19}F NMR spectra for **2a−n** and **4a−p**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060765A

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