Synthesis of 2-polyfluoroalkylated thiochromones and chromones

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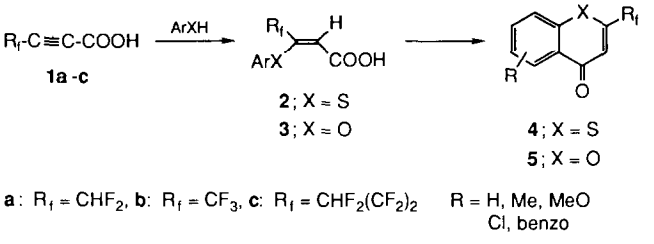
Abstract

A number of 2-(polyfluoroalkyl)-thiochromones (**4**) and -chromones (**5**) have been synthesized in good to excellent yield by an intramolecular Friedel–Crafts acylation of the *Z* isomers of 3-(arylthio)- (**2**) and 3-(aryloxy)polyfluoro-2-alkenoic acids (**3**), which were readily prepared through the Michael addition of arenethiols and phenols to polyfluoro-2-alkynoic acids, $R_f-C\equiv C-COOH$ (**1a**, $R_f=CHF_2$; **1b**, $R_f=CF_3$; **1c**, $R_f=CHF_2CF_2CF_2$), respectively.

Introduction

It is well known that chromones (4*H*-1-benzo[*b*]pyran-4-ones) are widespread in the plant kingdom in a variety of forms and are the parent compounds of important vegetable coloring matters [1], and that some thiochromones (4*H*-1-benzo[*b*]thiopyran-4-ones) have unique biological and pharmacological activities [2]. The synthesis of nonfluorinated chromones and thiochromones has been achieved by various methods [1, 3]. However, there have been only a few papers on the synthesis of chromones having a polyfluoroalkyl group at the 2-poistion. Whalley synthesized 2-(trifluoromethyl)-chromones by cyclizing the condensation products from 2-hydroxyacetophenone derivatives and ethyl trifluoroacetate [4]. Russian chemists obtained 2-(trifluoromethyl)3-arylchromones (isoflavones) by the reaction of 2-hydroxydeoxybenzoins with trifluoroacetic anhydride [5]. To our best knowledge, no reports of the synthesis of 2-polyfluoroalkylated thiochromones have appeared in the literature.

We have recently developed an efficient method for the preparation of polyfluoro-2-alkynoic acids (**1**) [6] and demonstrated their application to the synthesis of polyfluoroalkylated phthalic acids [7] and heterocyclic compounds [8]. As part of our studies to extend further the chemistry and synthetic utility of **1**, we have examined a facile and effective method for synthesizing the title compounds via the Michael reaction between **1** and arenethiols or phenols (ArXH; X=S, O) followed by an intramolecular Friedel–Crafts acylation of the resulting adducts (Scheme 1). In this paper, we would like to report the results of these reactions and the physical properties of the products.



Scheme 1.

Results and discussion

Reactions of 1 with arenethiols and phenols

The perfluorinated acetylenic esters $R_fC\equiv CCOOR$ and ketones of the type $CF_3C(O)C\equiv CR$ are good substrates in Michael addition reactions. Thus, Riess and his coworkers reported the reactions of ethyl perfluoro-2-alkynoates with thiols such as lysin, arginine and cysteine [9]. Cambon and his co-workers obtained a mixture of the *Z* and *E* isomers of Michael adducts from ethyl perfluoro-2-alkynoates and benzenethiol, methyl mercaptoacetate and 3-mercaptoproiolate, and converted the adducts into perfluoroalkylated heterocycles [10]. Bumgardner and his coworkers observed that the reaction of 4,4,4-trifluoro-1-phenyl-2-butyn-1-one with potassium benzenethiolate or phenolate gave the *anti*-Michael adducts in high yield under kinetic controlled conditions (at 25 °C for 6 h) [11]. However, few or no papers have appeared concerning the Michael addition of arenethiolates or phenolates to per- or polyfluorinated acetylenic acids [8].

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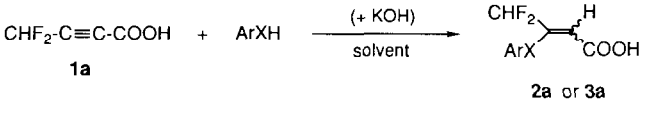
We first investigated the reactions of 4,4-difluoro-2-butynoic acid (**1a**) with arenethiols or phenol under various reaction conditions (Scheme 2). The results are summarized in Table 1.

The acid **1a** was allowed to react with an equimolar amount of benzenethiol in ethanol/water (1:3) at room temperature for 4 h to give a mixture of the geometrical isomers ($Z/E = 82:18$) of 4,4-difluoro-3-(phenylthio)-2-butenoic acid (**2a–I**) in 87% yield (entry 1, Table 1). The structures of the isomers were determined on the basis of a comparison of the chemical shifts of their vinylic hydrogens with those of the Michael adducts between ethyl perfluoro-2-alkynoates and methyl mercaptoacetate [10]. No *anti*-Michael adduct, 4,4-difluoro-2-(phenylthio)-2-butenoic acid, was produced in the present reactions. When the reaction was conducted at reflux temperature (entry 3) or when 2 equimolar amounts of the thiol were used at room temperature (entry 2), the *E* isomer was formed more predominantly than the *Z* isomer.

Using potassium hydroxide (KOH) as the base accelerated the reaction and furnished the *Z* isomer of the Michael adduct exclusively. Thus, when **1a** was treated with an equimolar amount of benzenethiol in the presence of 1.2 equimolar amounts of KOH at room temperature for 0.5 h, the *Z* isomer of **2a–I** was obtained as the sole product in 92% yield (entry 4). Similarly, the reaction of **1a** with 4-methoxybenzenethiol also gave a high yield of the *Z* isomer of the corresponding adduct (**2a–III**) (entry 6). The acceleration of the reaction and the exclusive formation of *Z* isomers under basic conditions could be rationalized in terms of the increase of nucleophilicity of the thiol and preferential *trans* fashion of addition [8, 12].



Scheme 2.

The present addition reaction did not occur in an aprotic solvent such as benzene even at reflux temperature for 24 h (entry 5).

The reaction of **1a** with phenol in ethanol/water (1:3) was carried out under similar conditions to those that gave high yields of the Michael adducts in the reactions with arenethiols. However, none of the desired phenol adduct, 4,4-difluoro-3-phenoxy-2-butenoic acid (**3a–I**), was obtained, an adduct of ethanol, $CHF_2(EtO)C=CHCOOH$, being formed in an 81% yield (entry 7).

Both the use of water as a solvent in place of ethanol/water (1:3) and of a five-fold excess of phenol was found to be critical for the addition of phenol to **1a**. Thus, the treatment of **1a** with 5 equimolar amounts of phenol in the presence of 5 equimolar amounts of KOH in water at 50 °C for 2 h gave one geometrical isomer of the adduct **3a–I** in 84% yield (entry 10). Although the stereochemistry of this adduct could not be determined spectroscopically, the success of its intramolecular cyclization as described below allowed us to assign to it the *Z* configuration.

Synthesis of 2-polyfluoroalkylated thiochromones (4) and chromones (5)

3-(Arylthio)-2-alkenoic acids are useful precursors for the preparation of thiochromones through an intramolecular Friedel–Crafts acylation [13]. However, there have been no reports of the Friedel–Crafts cyclization of polyfluoroalkylated 3-(arylthio)-2-alkenoic acids such as **2**. For this reason, we examined an

TABLE 1. Reaction of **1a** with arenethiols or phenol

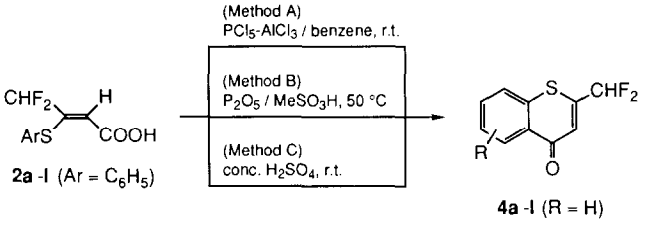
Entry No.	ArXH		Reaction conditions					Product **2a** or **3a**	
	Ar	X	Mole ratio		Solvent	Temp. (°C)	Time (h)	Yield[a] (%)	Isomer ratio[b] (*E*/*Z*)
			ArXH/1	KOH/1					
1	C_6H_5	S	1.0	0	$EtOH/H_2O$	r.t.	4	87	18:82
2	C_6H_5	S	2.0	0	$EtOH/H_2O$	refl.	1.5	84	54:46
3	C_6H_5	S	1.0	0	$EtOH/H_2O$	refl.	0.5	84	62:38
4	C_6H_5	S	1.0	1.2	$EtOH/H_2O$	r.t.	0.5	92	0:100
5	C_6H_5	S	1.0	0	Benzene	refl.	24	NR	–
6	*p*-$MeOC_6H_4$	S	1.0	1.2	$EtOH/H_2O$	r.t.	0.5	98	0:100
7	C_6H_5	O	1.0	1.2	$EtOH/H_2O$	r.t.	24	81[c]	–
8	C_6H_5	O	1.0	1.2	H_2O	60	20	37	0:100
9	C_6H_5	O	5.0	1.2	H_2O	50	24	50	0:100
10	C_6H_5	O	5.0	5.0	H_2O	50	2	84	0:100

[a]Isolated yields.
[b]Determined by ^{19}F NMR spectroscopy.
[c]Yield of ethanol adduct.

intramolecular Friedel–Crafts acylation of **2a** by three methods (A, B and C) as depicted in Scheme 3. The isolated *Z* isomer of **2a–I** was treated with phosphorus pentachloride and then aluminum chloride in benzene at room temperature (method A); with phosphorus pentoxide/methanesulfonic acid (weight ratio 1:10) at 50 °C (method B); and with concentrated sulfuric acid at room temperature (method C).

As can be seen from the results of the reactions of **2a–I** listed in Table 2, method A gave the best yield although any one of the methods afforded good yields (81%–92%) of 2-(difluoromethyl)thiochromone (**4a–I**). The reactions of the other Michael adducts **2a** and 4,4-difluoro-3-phenoxy-2-butenoic acid (**3a–I**) using method A also gave satisfactory results.

The structure of the cyclization product from the Michael adduct of **1a** and 2-naphthalenethiol was tentatively determined to be 3-(difluoromethyl)-1*H*-naphtho[2,1-*b*]thiopyran-1-one [5,6-benzo-3-(difluoromethyl)thiochromone] (**4a–VI**), based upon the higher reactivity of the α-position than that of the β-position in the naphthalene ring and upon the ^{1}H NMR spectrum which exhibited a resonance peak at δ 9.92 ppm of one hydrogen (may be that at the 5-position) which is shifted to lower field than the peaks (δ 7.28–7.92 ppm) of the other five hydrogens on the naphthalene ring due to the additional diamagnetic anisotropy of a carbonyl group [14].

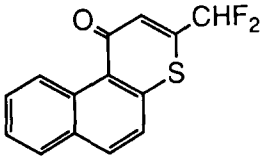


Scheme 3.

TABLE 2. Intramolecular Friedel–Crafts acylation of the isolated adducts **2a** and **3a**

Entry No.	ArXH		Method	Product		
	Ar	X		**4a** or **5a**	R	Yield[a] (%)
11	C_6H_5	S	A	**4a–I**	H	92
12	C_6H_5	S	B	**4a–I**	H	85
13	C_6H_5	S	C	**4a–I**	H	81
14	*p*-MeC_6H_4	S	A	**4a–II**	6-Me	91
15	*p*-ClC_6H_4	S	A	**4a–V**	6-Cl	67
16	β-$C_{10}H_7$	S	A	**4a–VI**	5,6-benzo	73
17	C_6H_5	O	A	**5a–I**	H	76

[a]Isolated yields.



4a -VI

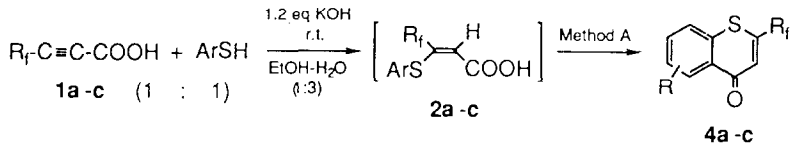
When a mixture of the *Z* and *E* isomers of **2a–I** was subjected to the cyclization reaction using method A, only the *Z* isomer was converted into **4a–I**, the *E* isomer being recovered unchanged. This result provides additional support for the structural assignment of the geometrical isomers of **2a**, which was made by ^{1}H NMR spectral analysis. Similarly, the fact that the one isomer of **3a–I** obtained from the reaction of **1a** with phenol cyclized to afford **5a–I** via method A allows us to assign to it a *Z* geometry.

Attempts were made to simplify the procedure for the synthesis of 2-polyfluoroalkylated thiochromones (**4**) or chromones (**5**). Thus, the alkynoic acids **1a–c** were allowed to react with arenethiols under the same reaction conditions as those of entry 4 in Table 1, followed by simple work-up (see Experimental section) to yield the crude Michael adducts (**2a–c**), which were treated as such via method A to give the corresponding 2-(polyfluoroalkyl)thiochromones (**4a–c–I–VI**) in good to excellent yield (70%–87%). Table 3 summarizes the results of these reactions.

The isolated adduct **3a–I** arising from the addition of phenol to **1a** was subjected to cyclization via method A to give 2-(difluoromethyl)chromone (**5a–I**) in 76% yield (entry 17), whereas cyclization via method A of the crude adduct **3a–I**, prepared by the reaction of **1a** with phenol under the same conditions as those of entry 10 in Table 1 followed by simple work-up (see Experimental section), was unsatisfactory and led to less than 20% yield of **5a–I**. This may be ascribed to inactivation of the chlorinating agent (phosphorus pentachloride) with the phenol remaining in the crude adduct. However, method C was effective for the Friedel–Crafts acylation of crude adducts **3** (see Table 4). Thus, **3a** was treated with sulfuric acid at room temperature for 1 h to give **5a–I** in 76% yield (entry 28). Similar treatment of 4,4-difluoro-3-(3-methoxyphenoxy)-2-butenoic acid (**3a–IV**) furnished two geometrical isomers of the cyclization product, 2-(difluoromethyl)-7- (**5a–IV**) and -5-methoxychromone (**5a–IV**), in a ratio of 3.6:1.

The absorption maxima ($\lambda_{max.}$) in the ultraviolet spectra of all the 2-(polyfluoroalkyl)-thiochromones (**4**) and -chromones (**5**) synthesized in the present study are listed in Table 5, together with those of the fluorine-free thiochromone (**4–III'**: R = 6–MeO, $R_f = CH_3$) and

TABLE 3. Synthesis of thiochromones **4** using the crude adducts **2**

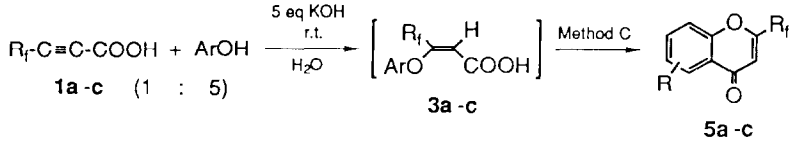


1a-c (1 : 1) **2a-c** **4a-c**

Entry No.	Acid **1**	ArSH	Thiochromone		
			4	R	Yield[a] (%)
18	**1a**	C_6H_5SH	**4a–I**	H	85
19	**1b**	C_6H_5SH	**4b–I**	H	70
20	**1c**	C_6H_5SH	**4c–I**	H	80
21	**1a**	p-MeC_6H_4SH	**4a–II**	6-Me	82
22	**1a**	p-$MeOC_6H_4SH$	**4a–III**	6-MeO	86
23	**1b**	p-$MeOC_6H_4SH$	**4b–III**	6-MeO	70
24	**1c**	p-$MeOC_6H_4SH$	**4c–III**	6-MeO	77
25	**1a**	p-ClC_6H_4SH	**4a–V**	6-Cl	68
26	**1a**	β-$C_{10}H_7SH$	**4a–VI**	5,6-benzo	87
27	**1b**	β-$C_{10}H_7SH$	**4b–VI**	5,6-benzo	72

[a]Yields refer to pure isolated products.

TABLE 4. Synthesis of chromones **5** using the crude adducts **3**



1a-c (1 : 5) **3a-c** **5a-c**

Entry No.	Acid **1**	ArOH	Chromone		
			5	R	Yield[a] (%)
28	**1a**	C_6H_5OH	**5a–I**	H	76
29	**1b**	C_6H_5OH	**5b–I**	H	70
30	**1c**	C_6H_5OH	**5c–I**	H	58
31	**1a**	p-$MeOC_6H_4OH$	**5a–III**	6-MeO	64
32	**1b**	p-$MeOC_6H_4OH$	**5b–III**	6-MeO	51
33	**1c**	p-$MeOC_6H_4OH$	**5c–III**	6-MeO	63
34	**1a**	m-$MeOC_6H_4OH$	**5a–IV**	7-MeO	54
				5-MeO	15

[a]Yields refer to pure isolated products.

chromones (**5–I′**: R = H, $R_f = CH_3$; **5–III′**: R = 6–MeO, $R_f = CH_3$). The $\lambda_{max.}$ values for 6-methoxy-substituted thiochromones (**4–III**) and chromones (**5–III**) were observed at *c.* 360 and 330 nm, exhibiting bathochromic shifts of *c.* 20 and 30 nm relative to those of other **4** and **5** compounds, respectively. No remarkable differences in the absorption properties, the $\lambda_{max.}$ value and the extinction coefficient were observed between fluorinated and nonfluorinated **4** and **5** compounds despite differences in the number of polyfluoroalkyl groups.

Experimental

Infrared (IR) spectra were recorded on a Shimadzu IR-400IR spectrophotometer. ^1H NMR spectra were obtained with Hitachi R-24B (60 MHz) and/or GE QE-300 (300 MHz) spectrometers in chloroform-*d* ($CDCl_3$) or $CDCl_3$ acetone-d_6 (CD_3COCD_3) solution using tetramethylsilane as an internal reference. A Hitachi R-24F (56.466 MHz) spectrometer was used to measure the ^{19}F NMR spectra in $CDCl_3$ with trifluoroacetic acid as an external reference. Mass spectra (MS) were taken

TABLE 5. Physical properties of thiochromones **4** and chromones **5**

4 or 5	M.p. (°C)	IR (cm^{-1})[a] ($\nu_{C=O}$)	UV (nm)[b] [$\lambda_{max.}$ (log ϵ)]	^1H NMR δ (ppm) (J, Hz)	^{19}F NMR δ (ppm)[c] (J, Hz)
4a–I	83–84	1640	339 (4.04)	6.50 (1 H, t, J=55.0); 7.08 (1H, m); 7.42–7.68 (3H, m); 8.44 (1H, m)	−34.2 (d, J=55)
4b–I	50–52	1630	340 (3.96)	7.27 (1H, m); 7.64 (3H, m); 8.42 (1H, m)	14.2 (s)
4c–I	60–61	1620	342 (4.01)	6.14 (1H, tt, J=51.8, 5.4); 7.26 (1H, m); 7.68 (3H, m); 8.45 (1H, m)	−32.3 (2F, m); −49.8 (2F, m); −57.2 (2F, dm, J=51.8)
4a–II	109–110	1625	346 (4.00)	2.47 (3H, s); 6.56 (1H, t, J=55.8); 7.11 (1H, m); 7.49 (2H, m); 8.29 (1H, m)	−34.3 (2F, d, J=55.8)
4a–III	95–96	1625	361 (3.93)	3.88 (3H, s); 6.56 (1H, t, J=55.2); 7.09 (1H, m); 7.23–7.58 (2H, m); 7.84 (1H, m)	−33.9 (d, J=55.2)
4b–III	79–81	1620	363 (3.93)	3.92 (3H, s); 7.25 (1H, m); 7.12–7.58 (2H, m); 7.82 (1H, m)	14.5 (s)
4c–III	123–125	1610	365 (3.94)	3.93 (3H, s); 6.12 (1H, tt, J=51.7, 5.3); 7.21 (1H, m); 7.11–7.59 (2H, m); 7.85 (1H, m)	−32.2 (2F, m); −50.0 (2F, m); −57.2 (2F, dm, J=51.7)
4a–III'[d]	96–98		355 (4.00)	2.40 (3H, s); 3.84 (3H, s); 6.73 (1H, s); 7.08 (1H, dd, J=8.8, 2.6); 7.33 (1H, d, J=8.8); 7.82 (1H, d, J=2.6)	
4a–V	114–116	1625	346 (3.99)	6.50 (1H, t, J=54.6); 7.04 (1H, m); 7.51 (2H, m); 8.30 (1H, m)	−34.3 (d, J=54.6)
4a–VI	125–127	1620	339 (3.90)	6.49 (1H, t, J=55.2); 7.16 (1H, m); 7.28–7.92 (5H, m); 9.92 (1H, m)	−33.9 (d, J=55.2)
4b–VI	134–135	1625	339 (3.89)	7.30 (1H, m); 7.23–7.90 (5H, m); 9.83 (1H, m)	14.9 (s)
5a–I	94–95	1665	303 (3.84)	6.44 (1H, t, J=53.4); 6.57 (1H, s); 7.28–7.88 (3H, m); 8.19 (1H, m)	−44.8 (d, J=53.4)
5b–I	88–90	1650	298 (3.84)	6.72 (1H, s); 7.30–7.82 (1H, m); 8.20 (1H, m)	6.60 (s)
5c–I	44–45	1670	299 (3.87)	6.09 (1H, tt, J=52.0, 5.0); 6.69 (1H, s); 7.21–7.85 (3H, m); 8.15 (1H, m)	−40.3 (2F, m); −50.5 (2F, m); −57.7 (2F, dm, J=52.0)
5–I'[e]	68–70 (73)[f]		294 (3.87) (298 (3.84))[f]	2.37 (3H, s); 6.10 (1H, s); 7.15–7.65 (3H, m); 8.14 (1H, m)	
5a–III	98–100	1650	330 (3.84)	3.86 (3H, s); 6.41 (1H, t, J=53.0); 6.51 (1H, s); 7.32 (2H, m); 7.45 (1H, m)	−44.2 (d, J=53.0)
5b–III	84–86	1670	331 (3.84)	3.89 (3H, s); 6.63 (1H, s); 7.34 (2H, m); 7.45 (1H, m)	6.68 (s)
5c–III	80–81	1665	333 (3.84)	3.88 (3H, s); 6.09 (1H, tt, J=51.2, 5.0); 6.65 (1H, s); 7.33 (2H, m); 7.48 (1H, m)	−40.2 (2F, m); −50.5 (2F, m); −57.7 (2F, dm, J=51.2)
5–III'[g]	101–103		333 (3.87)	2.35 (3H, s); 3.85 (3H, s); 6.10 (1H, s); 7.22 (2H, m); 7.46 (1H, m)	
5a–IV (7-isomer)	146–148	1665	300 (4.03)	3.90 (3H, s); 6.37 (1H, t, J=53.2); 6.48 (1H, s); 6.80–7.05 (2H, m); 8.03 (1H, m)	−44.4 (d, J=53.2)
5a–IV (5-isomer)	179–181	1675	315 (3.76)	3.97 (3H, s); 6.36 (1H, t, J=53.8); 6.45 (1H, s); 6.74–7.07 (2H, m); 7.56 (1H, m)	−44.9 (d, J=53.8)

[a]Measured in the form of KBr pellets.
[b]Measured in ethanol.
[c]Chemical shifts upfield from external CF_3COOH are expressed negative in ppm.
[d]Prepared from tetrolic acid and 4-methoxybenzenethiol according to the present method.
[e]Prepared from *o*-hydroxyacetophenone and ethyl acetate according to the previous method [15].
[f]Ref. 16.
[g]Synthesized from tetrolic acid and 4-methoxyphenol according to the present method.

on a Hitachi M-80B mass spectrometer operating at an ionization potential of 70 eV. Ultraviolet (UV) spectra were recorded on a Hitachi U-3410 spectrophotometer. All melting points are uncorrected.

Polyfluoro-2-alkynoic acids (**1a–c**) were prepared according to the method reported recently by us [6]. All chemicals were of reagent grade.

Reactions of 1a–c with arenethiols

To a solution containing specified amounts of benzenethiol (1–2 mmol) or *p*-methoxybenzenethiol (1 mmol) and of KOH (0–1.2 mmol) in 4 ml of ethanol/water (1:3) or benzene was gradually added acid **1a** (1 mmol) at 0 °C and the mixture stirred at room or reflux temperature for 0.5–24 h (see Table 1). The

reaction mixture was made weakly acid with dilute hydrochloric acid and extracted with diethyl ether (3×10 ml). When the reactions were performed in the absence of KOH, the mixture was subjected to extraction without acidification. The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with benzene as eluent to give analytically pure product **2a–I** (a mixture of the *E* and *Z* isomers, 84–92% yield) or **2a–III** (the *Z* isomer alone, 98% yield). The results of these reactions are summarized in Table 1.

4,4-Difluoro-3-(phenylthio)-2-butenoic acid (**2a–I**): *Z* isomer: m.p. 117–118 °C. IR (KBr) (cm^{-1}): 1675 (C=O); 1585 (C=C). ^1H NMR ($CDCl_3$) δ: 5.73 (1H, t, J=53.5 Hz); 6.33 (1H, s); 7.38 (5H, m); 11.21 (1H, br, s) ppm. ^{19}F NMR ($CDCl_3$) δ: −36.1 (d, J=53.5 Hz) ppm. MS (*m/z*): 230 (M^+); 94 (100%). *E* isomer: M.p. 145–147 °C. IR (KBr) (cm^{-1}): 1680 (C=O); 1600 (C=C). ^1H NMR ($CDCl_3$) δ: 5.20 (1H, s); 7.37 (1H, t, J=54.0 Hz); 7.44 (5H, m); 9.67 (1H, br, s) ppm. ^{19}F NMR ($CDCl_3$) δ: −37.4 (d, J=54.0 Hz) ppm. MS (*m/z*): 230 (M^+); 94 (100%).

4,4-Difluoro-3-(4-methoxyphenylthio)-2-butenoic acid (**2a–III**): *Z* isomer: m.p. 134–135 °C IR (KBr) (cm^{-1}): 1680 (C=O); 1590 (C=C). ^1H NMR ($CDCl_3$/CD_3COCD_3) δ: 3.86 (3H, s); 5.95 (1H, t, J=54.4 Hz); 6.35 (1H, s); 6.97 (2H, d, J=8.6 Hz); 7.57 (2H, d, J=8.6 Hz); 9.96 (1H, br, s) ppm. ^{19}F NMR ($CDCl_3$/CD_3COCD_3) δ: −37.1 (d, J=54.4 Hz) ppm. MS (*m/z*): 260 (M^+, 100%).

*Reactions of **1a–c** with phenols*

A mixture consisting of **1a** (1 mmol), phenol (1 mmol), KOH (1.2 mmol) and 4 ml of ethanol/water (1:3) was stirred at room temperature. After stirring for 24 h, the ^{19}F NMR spectrum of the reaction mixture showed the complete disappearance of the peak due to **1a** and one doublet due to the product. The mixture was made weakly acidic with dilute hydrochloric acid and extracted with diethyl ether (3×10 ml). The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated by evaporation. Column chromatography (silica gel/chloroform) of the residue gave the ethanol adduct, 3-ethoxy-4,4-difluoro-2-butenoic acid [8], in 81% yield.

To a solution consisting of specified amounts of phenol (1–5 mmol) and KOH (1.2–5.0 mmol) in 4 ml of water was gradually added acid **1a** (1 mmol) at 0 °C and the mixture stirred at 50 °C or 60 °C for 2–24 h (see Table 1). This mixture was worked-up in similar manner to that described above and the crude products were purified by column chromatography (silica gel/chloroform). The *Z* isomer of the Michael adduct **3a–I** was isolated in 37%–84% yield. The results are summarized in Table 1.

4,4-Difluoro-3-phenoxy-2-butenoic acid (**3a–I**): *Z* isomer: m.p. 94–95 °C IR (KBr) (cm^{-1}): 1705 (C=O), 1665 (C=C). ^1H NMR ($CDCl_3$) δ: 5.92 (1H, s), 5.97 (1H, t, J=53.7 Hz), 7.13 (5H, m), 10.10 (1H, br, s) ppm. ^{19}F NMR ($CDCl_3$) δ: −42.9 (d, J=53.7 Hz) ppm. MS (*m/z*): 214 (M^+), 94 (100 %).

*Intramolecular Friedel–Crafts acylation of the isolated Z isomer of **2a** or **3a** by various methods*

Method A

To a benzene solution (6 ml) of the *Z* isomer of **2a–I** (1 mmol) was gradually added PCl_5 (1.4 mmol) at room temperature. After stirring for 0.5 h under an argon atmosphere, $AlCl_3$ (2.0 mmol) was added slowly to the mixture. The whole mixture was stirred for an additional 0.5 h and then poured into ice/water. The organic layer was extracted with diethyl ether (3×25 ml). The ethereal extracts were washed with a saturated aqueous solution of sodium bicarbonate (20 ml) and with brine (2×20 ml), dried over sodium sulfate, filtered and then concentrated by evaporation. Column chromatography (silica gel/chloroform) of the residue gave analytically pure product **4a–I** in 92% yield.

Method B

To a 1:10 phosphorus pentoxide/methanesulfonic acid solution, prepared by adding phosphorus pentoxide (1.6 g) to freshly distilled methanesulfonic acid (16 g) and then stirring for 1 h [17], was gradually added **2a–I** (1.0 mmol) at room temperature. The mixture was stirred at 50 °C for 6 h and then poured into ice/water containing sodium hydrogen carbonate. The organic layer was extracted with dichloromethane (3×20 ml), dried over sodium sulfate, filtered and concentrated under vacuum. Column chromatography (silica gel/chloroform) of the residue gave analytically pure product **4a–I** in 85% yield.

Method C

To concentrated sulfuric acid (4 ml) was gradually added **2a–I** (0.23 g, 1.0 mmol) at room temperature. The mixture was stirred at room temperature for 1 h and then poured into ice/water. The organic layer was extracted with diethyl ether (3×20 ml), dried over sodium sulfate, filtered and then concentrated under vacuum. Column chromatography (silica gel/chloroform) of the residue gave analytically pure product **4a–I** in 81% yield.

*Intramolecular Friedel–Crafts acylation of the isolated mixture of E and Z isomers of **2a** by method A*

A mixture of the *E* and *Z* isomers of **2a–I** (*E*/*Z* = 45:55) was treated according to method A. Usual work-up

followed by column chromatography (silica gel/chloroform) of the crude product gave analytically pure thiochromone (**4a–I**) in 86% yield (based on the *Z* isomer) and the unreacted *E* isomer quantitatively.

Synthesis of 2-polyfluoroalkylated thiochromones (4) and chromones (5) using crude 2 and 3

Reactions of **1a–c** (1 mmol) with arenethiols (1 mmol) in the presence of KOH (1.2 mmol) were carried out under the same reaction conditions as those of entry 4 in Table 1. The reaction mixtures were made weakly acidic with dilute hydrochloric acid and were then extracted with diethyl ether. The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residues (crude **2a–c–I–VI**) were subjected to the following reaction without further purification by column chromatography. The crude Michael adducts **2a–c–I–VI** were cyclized intramolecularly via method A. The reaction mixtures were worked-up by the procedure described above in method A. The cyclization products (**4a–c–I–VI**) were purified by column chromatography (silica gel/chloroform). The results of the reactions are summarized in Table 3.

In a similar manner, the crude Michael adducts **3a–c–I–VI**, prepared by the reaction of **1a–c** (1 mmol) with phenol (5 mmol) in the presence of KOH (5 mmol) under the same reaction conditions as those of entry 10 in Table 1, were treated via method C. The reaction mixtures were worked-up by the procedure described above in Method C. Column chromatography (silica gel/chloroform) of the crude products gave analytically pure chromones (**5a–c–I–VI**). The results of the reactions are summarized in Table 4.

The melting points, IR, IV, ^1H and ^{19}F NMR spectral data of all thiochromones (**4**) and chromones(**5**) prepared are listed in Table 5. Their elemental analyses for carbon and hydrogen showed agreement between calculated and found values to within $\pm 0.3\%$.

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