A Simple One-Pot Synthesis of 2,6-Disubstituted 4-(Polyfluoroalkyl)pyridines and -pyrimidines by Reaction of 2-Polyfluoroalkylchromones with Aromatic Methyl Ketimines and Amidines

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Abstract: The reaction of 2-polyfluoroalkylchromones with ketimines, derived from aromatic methyl ketones and isopropylamine, gives 2,6-diaryl-4-polyfluoroalkylpyridines in moderate to low yields. Benzamidine and guanidine also react with 2-polyfluoroalkylchromones to afford the corresponding 2,6-disubstituted 4-polyfluoroalkylpyrimidines.

Key words: 2-polyfluoroalkylchromones, ketimines, amidines, 4-polyfluoroalkylpyridines and -pyrimidines

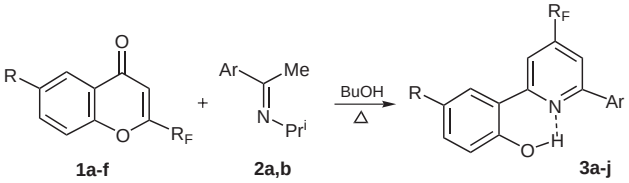
Much attention has been given to the chemistry of R_F-containing N-heterocycles, because they find wide use in various areas of industry, medicine, and agriculture due to their unique physical properties, chemical reactivity, and biological activity.[1,2] In connection with this, remarkable progress has been made in the development of new and efficient methods for the synthesis of polyfluoroalkylated pyridine and pyrimidine derivatives using fluorinated building blocks.

2,6-Diaryl-4-(trifluoromethyl)pyridines have recently been synthesized by the reaction of enamines, prepared from substituted acetophenones and morpholine, with trifluoromethylated β-diketones in the presence of ammonium acetate.[3a] The condensation of CF_3-containing α,β-unsaturated ketones and β-diketones with primary amines, such as β-aminocrotononitrile and ethyl β-aminocrotonates, affords 2- and 4-trifluoromethylpyridines.[3b,c] These compounds were also obtained from the reaction of trifluoromethylated α,β-unsaturated ketones and β-diketones with *N*-silyl-1-azaallyl anions[3d] and by Hantzsch's dihydropyridine synthesis.[3e,f]

2,6-Disubstituted 4-(polyfluoroalkyl)pirimidines were obtained by reactions of amidines with R_F-substituted alkyl ketones,[4a] α,β-unsaturated ketones,[4b] β-diketones,[4c] β-alkoxy-[4d–f] and β-aminovinyl ketones,[4g,h] *N*-aryl acetylenic imines,[4i] iodoalkenes,[4j] and 3-hetarylchromones.[4k] In addition, fluoroalkyl pyrimidines have been synthesized from one-pot reactions of α-fluoroalkyl carbonyl compounds, orthoesters and ammonium carbonate.[4l] The condensation of fluoro-containing nitriles with methyl ketimines[4m] and enamines[4n] provides a simple route to pyrimidines with two polyfluoroalkyl groups.

Recently,[5] in continuation of our studies on the chemical properties of 2-polyfluoroalkylchromones **1**, which turned out to be highly reactive substrates in the reactions with N-,[6a,b] S-,[6c,d] and C-nucleophiles,[6e,f] we investigated the reactions of these compounds with 1,3,3-trimethyl-3,4-dihydroisoquinolines and aromatic N-substituted methyl ketimines capable of reacting with electrophilic substrates as 1,3-C,N-dinucleophiles due to the enamine tautomeric form. We demonstrated that chromones **1** react with dihydroisoquinolines and methyl ketimines to give 2,6-diaryl-4-trifluoromethylpyridines (preliminary communication, see Ref.[5]). This result and the literature data[4k] clearly showed that the present approach could be also applicable to chromones **1** and amidines (1,3-N,N-dinucleophiles), providing the corresponding 4-polyfluoroalkylpyrimidines. Herein, the synthesis of such polyfluoroalkyl-substituted pyridines and pyrimidines with 2-hydroxyaryl substituent is reported in detail.

We have found that 2-R_F-chromones **1a**–**e** react with 1.5 equivalents of *N*-(1-arylethylidene)-2-propanamines **2a,b**, prepared from acetophenone, 2-acetothienone and isopropylamine, by refluxing in anhydrous butanol for 4 hours to afford pyridines **3a**–**i** in 23–67% isolated yields (Equation 1, Table 1). Similar results were obtained by using 1-phenylethan-1-imine (the reaction takes place in a closed flask, without solvent, at 90 °C), but the preparation of N-unsubstituted imines is more tedious. Imines bearing phenyl group at the nitrogen atom and the imine, prepared by action of isopropylamine on 2-hydroxyacetophenone, fail to undergo heterocyclization under the same conditions. Although the reaction affords pyridines **3** in moderate yields, this approach has advantages with regard to ease of operation and the ready availability of starting materials. Since the method is experimentally simple, it may be of value in R_F-containing pyridines chemistry.



1a-f **2a,b** **3a-j**

Ar = Ph (**2a**), 2-C_4H_3S (**2b**)

Equation 1

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Table 1 Synthesis of 2,6-Diaryl-4-polyfluoroalkylpiridines **3a**–**j** by Reaction of Chromones **1a**–**f** with Methylketimines **2a**,**b**

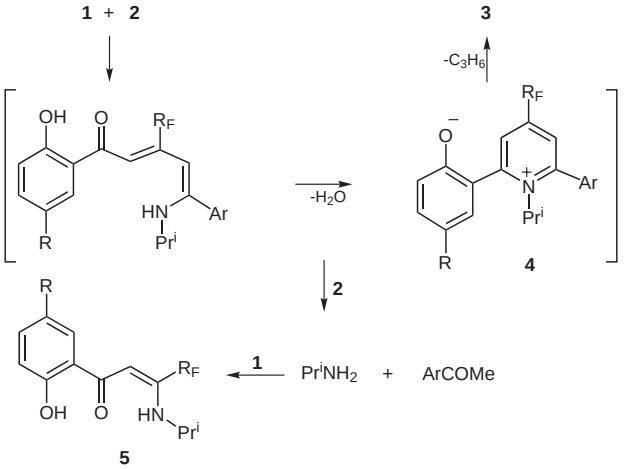
Chromone	R	R_F	Ar	Pyridine	Yield (%)	Mp (°C)
1a	H	CF_3	Ph	**3a**	35	134–135
1a	H	CF_3	2-C_4H_3S	**3b**	27	138–139
1b	MeO	CF_3	Ph	**3c**	23	133–134
1c	NO_2	CF_3	Ph	**3d**	67	193–195
1c	NO_2	CF_3	2-C_4H_3S	**3e**	54	198–200
1d	NO_2	CF_2H	Ph	**3f**	40	227–228
1d	NO_2	CF_2H	2-C_4H_3S	**3g**	36	237–238
1e	NO_2	$(CF_2)_2H$	Ph	**3h**	61	192–194
1e	NO_2	$(CF_2)_2H$	2-C_4H_3S	**3i**	38	215–217
1f	NO_2	H	Ph	**3j**	11	185–186

Note that the reaction is typical only for 2-polyfluoroalkylchromones and does not occur when the R_F group is replaced by the methyl or trichloromethyl group. It is likely that a balance occurs between steric and electronic effects. Unsubstituted chromone does not react under these conditions and the reaction of 6-nitrochromone **1f** with *N*-(1-phenylethylidene)-2-propanamine (**2a**) gives the corresponding pyridine **3j** in only 11% yield. This is probably owing to the lack of R_F group, which enhances the electrophilicity of the substrate and encourages conjugate addition at the initial stage. However, 2-difluoromethyl- and 2-(1,1,2,2-tetrafluoroethyl)chromones fail to react with imine **2a** and the best yields (36–67%) of pyridines **3** were obtained for the 6-nitro-2-R_F-chromone **1c**–**e**, because the electron-withdrawing nitro group favors stabilization of the leaving phenolate anion, thus facilitating the pyrone ring opening. In contrast to the nitro group, the electron-donating methyl and methoxy substituents afflict this reaction. Thus, chromone **1b** provides only 23% of the product **3c**; 7-trifluoromethylnorkhellin[7a] having two methoxy groups in the benzene ring and 5,7-dimethyl-2-trifluoromethylchromone[7b] are not converted into the corresponding pyridine derivatives under the action of imine **2a**.

Although much attention has been paid to the chemistry of the R_F-containing pyridine derivatives, compounds **3a**–**j** were not described in the literature and were unavailable by the known 2,6-diarylpyridine syntheses.[3] The structures of the pyridines **3** compare well with the results of elemental analysis, ^1H, ^{19}F, ^{13}C NMR and IR spectroscopy. The ^1H NMR spectra of these compounds showed signals for the aromatic protons of the aryl substituents, two singlets ranging between 7.74–8.17 and 7.94–8.50 ppm for the protons of the pyridine ring, and a singlet of the OH proton at 11.9–15.4 ppm. In the ^{19}F NMR spectra the trifluoromethyl group of **3a**,**d** manifests itself as a singlet at –66 ppm. The CF_3-substituted carbon atom of 4-CF_3-pyridine **3a** resonates at higher field (C-4, 140.8 ppm, q, $J_{C,F}$ = 33.7 Hz) than that of 2-CF_3-pyridines[3b,d] (C-2, ca. 149 ppm, q, $J_{C,F}$ ca. 35 Hz) in the ^{13}C NMR spectrum.

Most likely, the reaction includes the nucleophilic attack of the enamine tautomer of methyl ketimine **2** at C2 atom of 2-R_F-chromone **1** followed by the opening of pyrone ring and intramolecular cyclization at the keto group (Scheme 1). Taking into account the results of the reaction of chromones **1** with 1,3,3-trimethyl-3,4-dihydroisoquinolines,[5] we could propose that the first step involves the formation of the zwitterionic intermediate **4**, bearing an isopropyl group at the nitrogen atom, followed by elimination of propylene. In fact, in the case of compound **3e**, the zwitterionic compound **4e** (R_F = CF_3, Ar = Ph) was isolated as red crystals (at ca. 20 °C, 1 week in THF and 2 weeks in hexane–toluene). When **4e** was heated in butanol, pyridine **3e** was obtained. This result confirms the intermediacy of **4** in the present formation of pyridines **3**.

Moderate yields of pyridines **3** suggest that imines **2** act not only as a 1,3-C,N-dinucleophiles, but also as a source

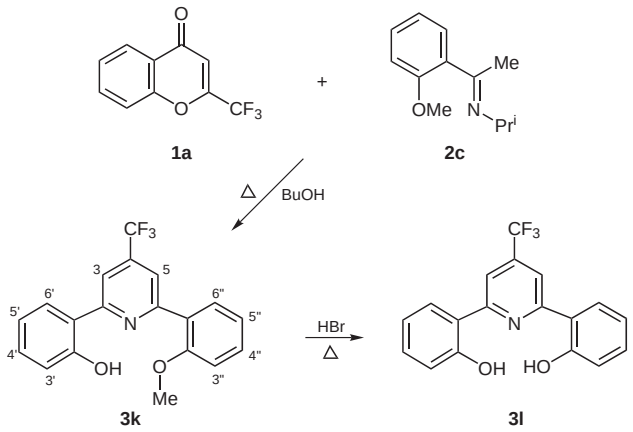


R = NO_2, R_F = CF_3 (**5a**); R = NO_2, R_F = CF_2H (**5b**)

Scheme 1

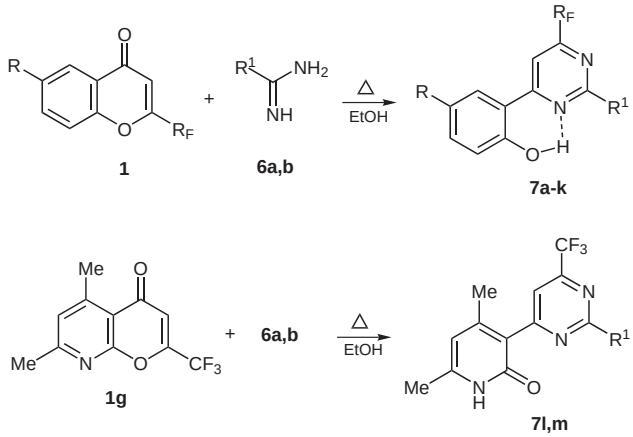
of isopropylamine which destroys the starting chromones. Further support of this hypothesis has been obtained in experiments with chromones **1c**,**d**. Thus, when these compounds reacted with imine **2a** by heating without solvent, besides the desired pyridines **3d**,**f**, a reasonable amount of aminoenones **5a**,**b** has been also isolated by crystallization. Aminoenones **5** are likely the result of the in situ hydrolysis of imine **2a** followed by the attack of isopropylamine at the C2 atom of the corresponding chromone. Aminoenones **5a**,**b** were independently synthesized from chromones **1c**,**d** and isopropylamine in excellent yields.

Using this reaction, we were able to obtain 2-(2-hydroxyphenyl)-6-(2-methoxyphenyl)-4-(trifluoromethyl)pyridine (**3k**) in 43% yield from 2-trifluoromethylchromone (**1a**) and methylketimine **2c**, prepared from 2-methoxyacetophenone and isopropylamine. Demethylation of **3k** to 2,6-bis(2-hydroxyphenyl)-4-(trifluoromethyl)pyridine (**3l**) was achieved in 85% yield by heating with 48% hydrobromic acid at 200 °C in a sealed tube for 10 hours (Scheme 2). These reactions are the most convenient and concise route to pyridine **3l**, which owing to the presence of two *ortho*-OH groups is of great interest and might be employed as an analytical reagent[8a] and organic electroluminescence substance.[8b–8d] Previously, nonfluorinated 2,6-bis(2-hydroxyphenyl)pyridine was obtained by the reaction of 2,6-dibromopyridine with the Grignard reagent from 2-bromoanisole in the presence of $NiCl_2$ as catalyst, followed by demethylation in molten pyridinium chloride.[8b]



Scheme 2

Next, we examined reactions of the 2-polyfluoroalkylchromones **1** with amidines **6a,b** and found that substituted 2-R_F-chromones with both electron-donating and electron-withdrawing substituents are effective in this process, thus creating a fast and efficient route to new py-



R^1 = Ph (**6a**), R^1 = NH_2 (**6b**)

Scheme 3

Table 2 Synthesis of 4-Polyfluoroalkylpirimidines **7a**–**m** by Reaction Chromones **1** with Amidines **6a**,**b**

Chromone	R	R_F	R^1	Pyrimidine	Yield (%)	Mp (°C)
1a	H	CF_3	Ph	**7a**	58	143–144
1b	MeO	CF_3	Ph	**7b**	51	151–152
1c	NO_2	CF_3	Ph	**7c**	92	204–206
1i	Me	CF_3	Ph	**7d**	68	174–176
1j	Cl	CF_3	Ph	**7e**	71	164–165
1k	H	$(CF_2)_2H$	Ph	**7f**	68	163–165
1l	Me	$(CF_2)_2H$	Ph	**7g**	42	157–158
1m	MeO	$(CF_2)_2H$	Ph	**7h**	45	146–147
1n	Cl	$(CF_2)_2H$	Ph	**7i**	75	151–153
1a	H	CF_3	NH_2	**7j**	46	217–218
1c	NO_2	CF_3	NH_2	**7k**	55	265–266
1g	-	CF_3	Ph	**7l**	98	>270 (dec.)
1g	-	CF_3	NH_2	**7m**	58	>300 (dec.)

rimidine derivatives. Reflux of chromones **1** with benzamidine hydrochloride (**6a**) or guanidinium nitrate (**6b**) in the presence of KOH in ethanol for 3 hours yielded the pyrimidines **7a**–**k** as yellow solids in 45–92% yields. The present reaction could be applicable to the 8-aza-5,7-dimethyl-2-trifluoromethylchromone (**1g**)[9] and amidines **6a**,**b** to afford the corresponding pyrimidines **7l**,**m** with 2-pyridone substituent in 98% and 58% yields, respectively (Scheme 3, Table 2). Note that 5,7-dimethyl-2-trifluoromethylchromone did not react with **6a** and azachromone **1g** gave a complex mixture with imine **2a** in boiling butanol.

The analytical and spectral data of compounds **3** and **7** prepared are given in Tables 3 and 4, respectively.

Table 3 Analytical and Spectral Data for Pyridines **3a**–**l**

Pyridine[a]	^{1}H NMR ($CDCl_3$/TMS) δ, *J*(Hz)	IR (Nujol) (cm^{-1})
3a[b,c]	6.99 (ddd, 1 H, H-5, Ar, ^oJ = 8.1, 7.2, ^mJ = 1.2), 7.08 (dd, 1 H, H-3, Ar, ^oJ = 8.4, ^mJ = 1.2), 7.39 (ddd, 1 H, H-4, Ar, ^oJ = 8.4, 7.2, ^mJ = 1.6), 7.51–7.58 (m, 3 H, C_6H_5), 7.83 (s, 1 $H_{pyridyl}$), 7.88 (dd, 1 H, H-6, Ar, ^oJ = 8.1, ^mJ = 1.6), 7.94–7.97 (m, 2 H, C_6H_5), 8.05 (s, 1 $H_{pyridyl}$), 14.04 (s, 1 H, OH)	1620, 1595, 1570
3b	6.98 (ddd, 1 H, H-5, Ar, ^oJ = 8.1, 7.2, ^mJ = 1.2), 7.09 (dd, 1 H, H-3, Ar, ^oJ = 8.4, ^mJ = 1.2), 7.19 (dd, 1 $H_{thienyl}$, H-4, *J* = 5.0, 3.7), 7.39 (ddd, 1 H, H-4, Ar, ^oJ = 8.4, 7.2, ^mJ = 1.6), 7.52 (dd, 1 $H_{thienyl}$, H-5, *J* = 5.0, 1.1), 7.72 (dd, 1 $H_{thienyl}$, H-3, *J* = 3.7, 1.1), 7.74 (s, 1 $H_{pyridyl}$), 7.84 (dd, 1 H, H-6, Ar, ^oJ = 8.1, ^mJ = 1.6), 7.94 (s, 1 $H_{pyridyl}$), 13.38 (s, 1 H, OH)	1620, 1600, 1575, 1545
3c	3.87 (s, 3 H, CH_3O), 7.02 (d, 1 H, H-3, H-4, Ar, *J* = 1.6), 7.35 (t, 3 H, H-6, Ar, *J* = 1.6), 7.52–7.58 (m, 3 H, C_6H_5), 7.83 (s, 1 $H_{pyridyl}$), 7.94–7.97 (m, 2 H, C_6H_5), 7.98 (s, 1 $H_{pyridyl}$), 13.51 (s, 1 H, OH)	1620, 1575, 1500
3d[d]	7.14 (d, 1 H, H-3, Ar, ^oJ = 9.1), 7.57–7.61 (m, 3 H, C_6H_5), 7.93–7.95 (m, 2 H, C_6H_5), 7.95 (s, 1 $H_{pyridyl}$), 8.16 (s, 1 $H_{pyridyl}$), 8.27 (dd, 1 H, H-4, Ar, ^oJ = 9.1, ^mJ = 2.7), 8.86 (d, 1 H, H-6, Ar, ^mJ = 2.7), 15.21 (s, 1 H, OH)	1625, 1595, 1570, 1535
3e	7.16 (d, 1 H, H-3, Ar, ^oJ = 9.1), 7.27 (dd, 1 $H_{thienyl}$, H-4, *J* = 5.0, 3.8), 7.58 (dd, 1 $H_{thienyl}$, H-5, *J* = 5.0, 1.1), 7.76 (dd, 1 $H_{thienyl}$, H-3, *J* = 3.8, 1.1), 7.86 (s, 1 $H_{pyridyl}$), 8.03 (s, 1 $H_{pyridyl}$), 8.27 (dd, 1 H, H-4, Ar, ^oJ = 9.1, ^mJ = 2.7), 8.82 (d, 1 H, H-6, Ar, ^mJ = 2.7), 14.48 (s, 1 H, OH)	1625, 1590, 1565, 1525
3f[e]	7.18 (d, 1 H, H-3, Ar, ^oJ = 9.1), 7.24 (tt, 1 H, CF_2H, $^2J_{H,F}$ = 55.0), 7.56–7.64 (m, 3 H, C_6H_5), 8.12–8.14 (m, 2 H, C_6H_5), 8.17 (s, 1 $H_{pyridyl}$), 8.24 (dd, 1 H, H-4, Ar, ^oJ = 9.1, ^mJ = 2.9), 8.50 (s, 1 $H_{pyridyl}$), 9.01 (d, 1 H, H-6, Ar, ^mJ = 2.9), 13.9 (br s, 1 H, OH)	1620, 1590, 1570, 1530
3g[e]	7.18 (d, 1 H, H-3, Ar, ^oJ = 9.1), 7.21 (tt, 1 H, CF_2H, $^2J_{H,F}$ = 55.0), 7.26 (dd, 1 $H_{thienyl}$, H-4, *J* = 5.0, 3.7), 7.80 (dd, 1 $H_{thienyl}$, H-5, *J* = 5.0, 1.1), 8.04 (dd, 1 $H_{thienyl}$, H-3, *J* = 3.7, 1.1), 8.15 (s, 1 $H_{pyridyl}$), 8.23 (dd, 1 H, H-4, Ar, ^oJ = 9.1, ^mJ = 2.9), 8.38 (s, 1 $H_{pyridyl}$), 8.97 (d, 1 H, H-6, Ar, ^mJ = 2.9), 13.3 (br s, 1 H, OH)	1620, 1595, 1565, 1525
3h	6.11 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.8, $^3J_{H,F}$ = 1.6), 7.14 (d, 1 H, H-3, Ar, ^oJ = 9.1), 7.56–7.61 (m, 3 H, C_6H_5), 7.89 (s, 1 $H_{pyridyl}$), 7.92–7.96 (m, 2 H, C_6H_5), 8.09 (s, 1 $H_{pyridyl}$), 8.27 (dd, 1 H, H-4, Ar, ^oJ = 9.1, ^mJ = 2.7), 8.86 (d, 1 H, H-6, Ar, ^mJ = 2.7), 15.36 (s, 1 H, OH)	1620, 1590, 1560
3i	6.09 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.8, $^3J_{H,F}$ = 1.7), 7.16 (d, 1 H, H-3, Ar, ^oJ = 9.1), 7.22 (dd, 1 $H_{thienyl}$, H-4, *J* = 5.0, 3.8), 7.57 (dd, 1 $H_{thienyl}$, H-5, *J* = 5.0, 1.1), 7.76 (dd, 1 $H_{thienyl}$, H-3, *J* = 3.8, 1.1), 7.81 (s, 1 $H_{pyridyl}$), 7.97 (s, 1 $H_{pyridyl}$), 8.27 (dd, 1 H, H-4, Ar, ^oJ = 9.1, ^mJ = 2.7), 8.83 (d, 1 H, H-6, Ar, ^mJ = 2.7), 14.62 (s, 1 H, OH)	1620, 1595, 1565, 1525
3j	7.10 (d, 1 H, H-3, Ar, ^oJ = 9.1), 7.50–7.58 (m, 3 H, C_6H_5), 7.77 (dd, 1 $H_{pyridyl}$, ^oJ = 7.3, ^mJ = 1.0), 7.92 (m, 2 $H_{pyridyl}$), 7.99–8.06 (m, 2 H, C_6H_5), 8.22 (dd, 1 H, H-4, Ar, ^oJ = 9.1, ^mJ = 2.6), 8.85 (d, 1 H, H-6, Ar, ^mJ = 2.6), 16.16 (s, 1 H, OH)	1600, 1560
3k	3.93 (s, 3 H, CH_3O), 6.96 (ddd, 1 H, H-5′, ^oJ = 8.1, 7.2, ^mJ = 1.2), 7.04 (dd, 1 H, H-3′, ^oJ = 8.3, ^mJ = 1.2), 7.07 (dd, 1 H, H-3″, ^oJ = 8.3, ^mJ = 1.0), 7.12 (ddd, 1 H, H-5″, ^oJ = 7.5, 7.6, ^mJ = 1.0), 7.36 (ddd, 1 H, H-4′, ^oJ = 8.5, 7.2, ^mJ = 1.6), 7.47 (ddd, 1 H, H-4″, ^oJ = 8.3, 7.5, ^mJ = 1.7), 7.72 (dd, 1 H, H-6″, ^oJ = 7.6, ^mJ = 1.7), 7.85 (dd, 1 H, H-6′, ^oJ = 8.1, ^mJ = 1.6), 7.91 (s, 1 $H_{pyridyl}$), 8.00 (s, 1 $H_{pyridyl}$), 13.87 (s, 1 H, OH)	1620, 1605, 1590, 1570
3l	7.00 (ddd, 2 H, H-5′, H-5″, ^oJ = 7.9, 7.2, ^mJ = 1.2), 7.02 (dd, 2 H, H-3′, H-3″, ^oJ = 8.3, ^mJ = 1.2), 7.37 (ddd, 2 H, H-4′, H-4″, ^oJ = 8.3, 7.2, ^mJ = 1.6), 7.98 (dd, 2 H, H-6′, H-6″, ^oJ = 7.9, ^mJ = 1.6), 8.29 (s, 2 $H_{pyridyl}$), 11.91 (s, 2 H, 2 OH)	1625, 1600, 1595, 1565

[a] Satisfactory microanalyses obtained: C ±0.19, H ±0.42, N ±0.25.
[b] ^{13}C NMR ($CDCl_3$/TMS): δ = 113.29 (q, *J* = 3.7 Hz), 114.06 (q, *J* = 3.5 Hz), 118.11 (s), 118.77 (s), 119.25 (s), 122.78 (q, *J* = 273.8 Hz), 126.60 (s), 126.98 (s), 129.31 (s), 130.42 (s), 132.53 (s), 136.84 (s), 140.78 (q, *J* = 33.7 Hz), 156.53 (s), 159.15 (s), 159.93 (s).
[c] ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ = –66.1 (s, CF_3).
[d] ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ = –66.0 (s, CF_3).
[e] Recorded in DMSO-d_6.

Table 4 Analytical and Spectral Data for Pyrimidines **7a–m**

Pyrimidine[a]	^{1}H NMR ($CDCl_3$/TMS) δ, *J*(Hz)	IR (Nujol) (cm^{-1})
7a	7.00 (ddd, 1 H, H-5, Ar, ^oJ = 8.0, 7.2, ^mJ = 1.0), 7.10 (dd, 1 H, H-3, Ar, ^oJ = 8.4, ^mJ = 1.0), 7.46 (ddd, 1 H, H-4, Ar, ^oJ = 8.4, 7.2, ^mJ = 1.5), 7.50–7.60 (m, 3 H, C_6H_5), 7.87 (dd, 1 H, H-6, Ar, ^oJ = 7.8, ^mJ = 1.5), 7.97 (s, 1 $H_{pyrimidyl}$), 8.37–8.42 (m, 2 H, C_6H_5), 13.6 (br s, 1 H, OH)	1590, 1575, 1540
7b	3.86 (s, 3 H, CH_3O), 7.04 (d, 1 H, H-3, Ar, ^oJ = 9.0), 7.10 (dd, 1 H, H-4, Ar, ^oJ = 9.0, ^mJ = 2.9), 7.30 (d, 1 H, H-6, Ar, ^mJ = 2.9), 7.53–7.58 (m, 3 H, C_6H_5), 7.90 (s, 1 $H_{pyrimidyl}$), 8.37–8.40 (m, 2 H, C_6H_5), 13.15 (s, 1 H, OH)	1590, 1575, 1540
7c	7.20 (d, 1 H, H-3, Ar, ^oJ = 9.3), 7.54–7.63 (m, 3 H, C_6H_5), 8.09 (s, 1 $H_{pyrimidyl}$), 8.34 (dd, 1 H, H-4, Ar, ^oJ = 9.3, ^mJ = 2.4), 8.37–8.40 (m, 2 H, C_6H_5), 8.86 (d, 1 H, H-6, Ar, ^mJ = 2.4), 14.59 (s, 1 H, OH)	1595, 1550, 1535
7d	2.36 (s, 3 H, CH_3), 6.98 (d, 1 H, H-3, Ar, ^oJ = 8.4), 7.25 (dd, 1 H, H-4, Ar, ^oJ = 8.4, ^mJ = 1.7), 7.50–7.58 (m, 3 H, C_6H_5), 7.62 (d, 1 H, H-6, Ar, ^mJ = 1.7), 7.94 (s, 1 $H_{pyrimidyl}$), 8.36–8.40 (m, 2 H, C_6H_5), 13.37 (s, 1 H, OH)	1590, 1575, 1540
7e	7.03 (d, 1 H, H-3, Ar, ^oJ = 8.9), 7.39 (dd, 1 H, H-4, Ar, ^oJ = 8.9, ^mJ = 2.5), 7.52–7.58 (m, 3 H, C_6H_5), 7.80 (d, 1 H, H-6, Ar, ^mJ = 2.5), 7.90 (s, 1 $H_{pyrimidyl}$), 8.34–8.37 (m, 2 H, C_6H_5), 13.56 (s, 1 H, OH)	1595, 1575, 1545
7f	6.50 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.1, $^3J_{H,F}$ = 5.4), 7.0–8.0 (m, 6 H, Ar, C_6H_5), 7.90 (dd, 1 H, H-6, Ar, ^oJ = 7.9, ^mJ = 1.7), 8.04 (s, 1 $H_{pyrimidyl}$), 8.30–8.45 (m, 2 H, C_6H_5), 13.6 (br s, 1 H, OH)	1590, 1575, 1540
7g	2.38 (s, 3 H, CH_3), 6.52 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.0, $^3J_{H,F}$ = 5.4), 7.00 (d, 1 H, H-3, Ar, ^oJ = 8.4), 7.28 (dd, 1 H, ;-4, Ar, ^oJ = 8.4, ^mJ = 2.1), 7.53–7.60 (m, 3 H, C_6H_5), 7.68 (d, 1 H, H-6, Ar, ^mJ = 1.4), 8.04 (s, 1 $H_{pyrimidyl}$), 8.34–8.37 (m, 2 H, C_6H_5), 13.47 (s, 1 H, OH)	1590, 1570, 1540
7h	3.88 (s, 3 H, CH_3O), 6.52 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.0, $^3J_{H,F}$ = 5.4), 7.05 (d, 1 H, H-3, Ar, ^oJ = 9.0), 7.11 (dd, 1 H, H-4, Ar, ^oJ = 9.0, ^mJ = 2.9), 7.34 (d, 1 H, H-6, Ar, ^mJ = 2.9), 7.53–7.61 (m, 3 H, C_6H_5), 7.99 (s, 1 $H_{pyrimidyl}$), 8.34–8.38 (m, 2 H, C_6H_5), 13.23 (s, 1 H, OH)	1600, 1575, 1545
7i	6.50 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.0, $^3J_{H,F}$ = 5.2), 7.07 (d, 1 H, H-3, Ar, ^oJ = 8.9), 7.42 (dd, 1 H, H-4, Ar, ^oJ = 8.9, ^mJ = 2.5), 7.54–7.63 (m, 3 H, C_6H_5), 7.87 (d, 1 H, H-6, Ar, ^mJ = 2.5), 8.00 (s, 1 $H_{pyrimidyl}$), 8.33–8.36 (m, 2 H, C_6H_5), 13.7 (br s, 1 H, OH)	1595, 1575, 1545
7j[b]	6.95 (ddd, 1 H, H-5, Ar, ^oJ = 8.1, 7.2, ^mJ = 1.2), 6.97 (dd, 1 H, H-3, Ar, ^oJ = 8.4, ^mJ = 1.2), 7.43 (ddd, 1 H, H-4, Ar, ^oJ = 8.4, 7.2, ^mJ = 1.6), 7.67 (s, 1 $H_{pyrimidyl}$), 7.75 (br s, 2 H, NH_2), 8.13 (dd, 1 H, H-6, Ar, ^oJ = 8.1, ^mJ = 1.6), 13.2 (br s, 1 H, OH)	3470, 3310, 3180, 1645, 1595, 1545
7k[b]	7.17 (d, 1 H, H-3, Ar, ^oJ = 9.2), 7.82 (br s, 2 H, NH_2), 7.87 (s, 1 $H_{pyrimidyl}$), 8.27 (dd, 1 H, H-4, Ar, ^oJ = 9.2, ^mJ = 2.8), 8.90 (d, 1 H, H-6, Ar, ^mJ = 2.8), 13.9 (br s, 1 H, OH)	3430, 3330, 3210, 1660, 1595, 1560
7l[b]	2.25 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 6.16 (s, 1 $H_{pyridyl}$), 7.56–7.61 (m, 3 H, C_6H_5), 8.12 (s, 1 $H_{pyrimidyl}$), 8.39–8.42 (m, 2 H, C_6H_5), 12.0 (br s, 1 H, NHCO)	1655, 1625, 1585, 1530
7m[b]	2.10 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 6.01 (s, 1 $H_{pyridyl}$), 7.01 (s, 1 $H_{pyrimidyl}$), 7.22 (s, 2 H, NH_2), 11.8 (br s, 1 H, NHCO)	3500, 3310, 3200, 1650, 1630, 1590, 1540

[a] Satisfactory microanalyses obtained: C 0.31, H ±0.30, N ±0.25.
[b] Recorded in DMSO-d_6.

In conclusion, we have demonstrated that 2-(2-hydroxyaryl)-6-(het)aryl-4-polyfluoroalkylpyridines can be easily prepared from readily available 2-polyfluoroalkylchromones and aromatic methyl ketimines. In spite of the moderate yields, the method has advantages, particularly with regard to ease of operation and applicability to the concise synthesis of useful materials. In addition, the reaction with benzamidine and guanidine is a simple and convenient synthesis of 2,6-disubstituted 4-polyfluoroalkylpyrimidines, which are difficult to prepare by other methods.

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (^{1}H at 400.1 MHz, ^{19}F at 376.5 MHz, and ^{13}C at 100.6 MHz) with TMS and $CFCl_3$ as internal standards. The IR spectra were measured on an IKS-29 instrument as suspensions in Nujol. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. The starting 2-polyfluoroalkylchromones **1a–f** were prepared by reaction of the appropriate 2-hydroxyacetophenones and 3-acetyl-4,6-dimethyl-2-pyridone with R_FCO_2Et according to described procedures.[6a,9] The starting imines **2a–c** were prepared by direct condensation of the appropriate carbonyl compound and isopropylamine according to described procedure.[10] 1-Phenylethan-1-imine was obtained from benzonitrile and CH_3MgI according to known method.[11] Pyridines **3k,l** were described earlier.[5]

2,6-Diaryl-4-polyfluoroalkylpyridines (3); General Procedure

To a solution of chromone **1** (2.0 mmol) in butanol (4 mL) was added methylketimine **2** (3.0 mmol), and the mixture was refluxed for 4 h. Then, the reaction mixture was concentrated to ca. 2 mL and cooled to r.t. The resulting precipitate was filtered, washed with EtOH, and recrystallized from butanol or ethanol to give pyridine **3** as a yellow solid (see Tables 1 and 3).

Reactions Chromones 1a,c with 1-Phenylethan-1-imine
To chromone **1a** or **1c** (2 mmol) was added 1-phenylethan-1-imine (0.52 g, 4.4 mmol), and the mixture was heated at 90 °C for 4 h in a closed flask. Then the reaction mixture was diluted with 70% EtOH (5 mL) and the crystalline material was collected by filtration to give pyridines **3a** and **3d** in 29 and 32% yields, respectively.

2-[1-Isopropyl-6-phenyl-4-(trifluoromethyl)pyridinium-2-yl]-4-nitrophenolate (4e)
A mixture of chromone **1c** (0.26 g, 1.0 mmol) and imine **2a** (0.16 g, 1.0 mmol) in THF (1 mL) was allowed to stand with stirring for 1 week at ca. 20 °C. After evaporation of solvent at ca. 20 °C, the residue was diluted with a mixture (7 mL) of hexane–toluene (1:1) and kept again for 2 weeks at ca. 20 °C. The solid product was separated by filtration to give the title compound as red crystals; yield: 12%; mp 149–151 °C.

IR (Nujol): 1590, 1515 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.42–1.48 (m, 6 H, 2 CH_3), 5.52 (sept, 1 H, CH, J = 6.9 Hz), 6.55 (d, 1 H, H-3′, ^oJ = 9.6 Hz), 7.57–7.65 (m, 5 H, C_6H_5), 7.69 (d, 1 $H_{pyridyl}$, J = 2.0 Hz), 8.08 (d, 1 $H_{pyridyl}$, J = 2.0 Hz), 8.13 (dd, 1 H, H-4′, ^oJ = 9.6 Hz, ^mJ = 3.0 Hz), 8.22 (d, 1 H, H-6′, ^mJ = 3.0 Hz).

Anal. Calcd for $C_{21}H_{17}F_3N_2O_3$: C, 62.69; H, 4.26; N, 6.96. Found: C, 62.46; H, 4.40; N, 6.66.

4,4,4-Trifluoro-1-(2-hydroxy-5-nitrophenyl)-3-(isopropylamino)but-2-en-1-one (5a); Typical Procedure
A mixture of chromone **1c** (1.30 g, 5.0 mmol) and imine **2a** (0.90 g, 5.6 mmol) was heated in a sealed tube at 90 °C for 6 h. The reaction mixture was cooled and diluted with MeOH (5 mL). The precipitate formed (0.52 g) was filtered off and recrystallized from butanol to give pyridine **3d** as light yellow needles (39%). After removal of the solvent from the filtrate, the residue was purified by recrystallization from hexane to give aminoenone **5a** as light yellow needles; yield: 15%; mp 129–130 °C (EtOH). Treatment of chromone **1c** with isopropylamine in EtOH at ca. 20 °C for 1 h gives **5a** in 90% yield.

IR (Nujol): 1615, 1580 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.37 (d, 6 H, 2 CH_3, J = 6.4 Hz),), 4.02 [d sept q, 1 H, CH, $J_{CH,NH}$ = 10.4 Hz, J(CH,CH_3) = 6.4 Hz, J(CH,CF_3) = 1.3 Hz], 6.17 (s, 1 H, =CH), 7.03 (d, 1 H, H-3, ^oJ = 9.2 Hz), 8.27 (dd, 1 H, H-4, ^oJ = 9.2 Hz, ^mJ = 2.7 Hz), 8.60 (d, 1 H, H-6, ^mJ = 2.7 Hz), 10.56 (br s, 1 H, NH), 13.62 (s, 1 H, OH).

Anal. Calcd for $C_{13}H_{13}F_3N_2O_4$: C, 49.06; H, 4.12; N, 8.80. Found: C, 49.33; H, 4.12; N, 8.54.

4,4-Difluoro-1-(2-hydroxy-5-nitrophenyl)-3-(isopropylamino)but-2-en-1-one (5b)
This compound was obtained similarly to **5** in 18% yield as a light yellow needles, mp 147–148 °C (EtOH). Treatment of chromone **1d** with isopropylamine in EtOH at ca. 20 °C for 1 h gave **5b** in 94% yield.

IR (Nujol): 1610, 1580 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.36 (d, 6 H, 2 CH_3, J = 6.4 Hz), 4.06 [d sept, 1 H, CH, $J_{CH,NH}$ = 10.3 Hz, J(CH,CH_3)= 6.3 Hz], 5.96 (s, 1 H, =CH), 6.28 (t, 1 H, CF_2H, ^2J = 53.2 Hz), 7.01 (d, 1 H, H-3, ^oJ = 9.2 Hz), 8.24 (dd, 1 H, H-4, ^oJ = 9.2 Hz, ^mJ = 2.7 Hz), 8.60 (d, 1 H, H-6, ^mJ = 2.7 Hz), 10.40 (br d, 1 H, NH, $J_{NH,CH}$ = 8.3 Hz), 13.89 (s, 1 H, OH).

Anal. Calcd for $C_{13}H_{14}F_2N_2O_4$: C, 52.00; H, 4.70; N, 9.33. Found: C, 51.76; H, 4.75; N, 9.31.

4-Polyfluoroalkylpyrimidines (7); General Procedure
Benzamidine or guanidine (2.0 mmol), prepared from **6a**,**b** and KOH, was dissolved in EtOH (5 mL). To this solution was added chromone **1** (1.6 mmol), and the mixture was refluxed for 3 h (for chromones **1a**–**n**) or 1 h (for azachromone **1g**). After the reaction mixture was cooled to the r.t., the resulting precipitate was filtered, washed with H_2O, and recrystallized from toluene to give pyrimidine **7** as a yellow solid (see Tables 2 and 4).

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