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Reaction of 2-Polyfluoroalkylchromones with 1,3,3-Trimethyl-3,4-dihydroisoquinolines and Methylketimines as a Direct Route to Zwitterionic Axially Chiral 6,7-Dihydrobenzo[*a*]quinolizinium Derivatives and 2,6-Diaryl-4-polyfluoroalkylpyridines

Vyacheslav Ya. Sosnovskikh,*,† Boris I. Usachev,† Aleksei Yu. Sizov,† Ivan I. Vorontsov,‡ and Yurii V. Shklyaev§

Department of Chemistry, Ural State University, 620083 Ekaterinburg, Russia, A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russia, and Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, 614600 Perm, Russia

vyacheslav.sosnovskikh@usu.ru

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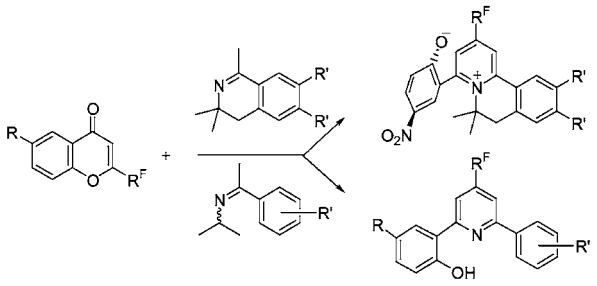
ABSTRACT



2-Polyfluoroalkylchromones react with 1,3,3-trimethyl-3,4-dihydroisoquinolines to give zwitterionic axially chiral 6,7-dihydrobenzo[*a*]quinolizinium derivatives in high yields. In addition, performing this reaction with aromatic methylketimines is a simple and convenient synthesis of 2,6-diaryl-4-polyfluoroalkylpyridines.

Much attention has recently been given to the development of new methods for synthesis of R^F-containing heterocycles, because they find wide use in various areas of industry, medicine, and agriculture due to their unique physicochemical and biological properties.[1,2] In addition, the introduction of the R^F group substantially affects the electron density distribution in organic molecules, and as a result some partially fluorinated substances have become valuable synthons for the construction of novel fluorine-containing heterocyclic compounds.[3]

In continuation of our studies on the chemical properties of 2-polyfluoroalkylchromones,[4] which turned out to be

† Ural State University.
‡ Russian Academy of Sciences.
§ Ural Branch of the Russian Academy of Sciences.

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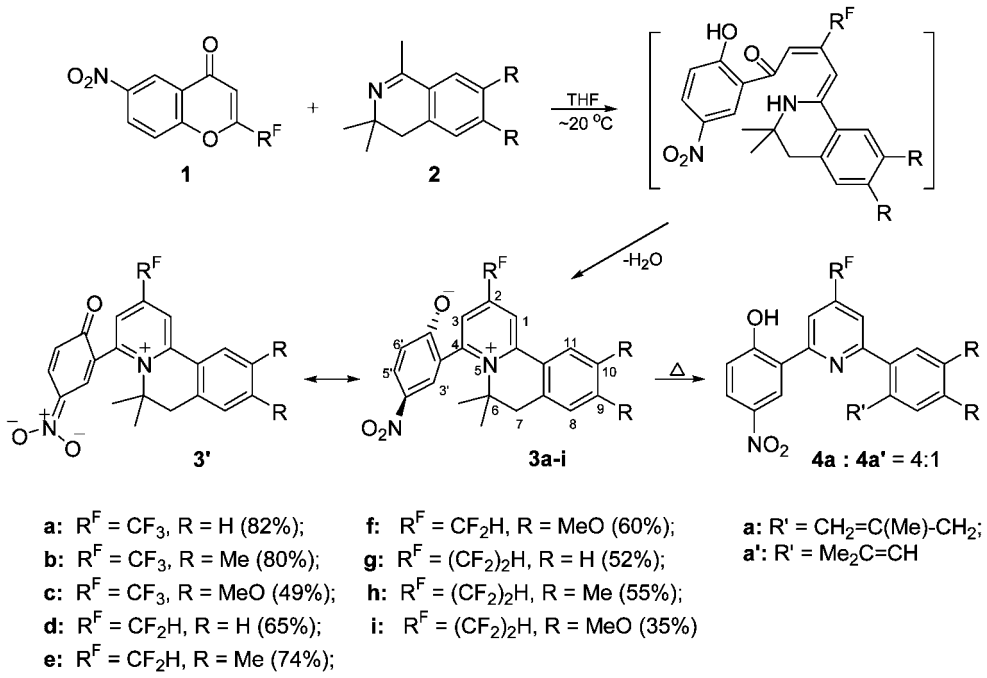
Scheme 1



a: $R^F = CF_3$, R = H (82%); **b:** $R^F = CF_3$, R = Me (80%); **c:** $R^F = CF_3$, R = MeO (49%); **d:** $R^F = CF_2H$, R = H (65%); **e:** $R^F = CF_2H$, R = Me (74%); **f:** $R^F = CF_2H$, R = MeO (60%); **g:** $R^F = (CF_2)_2H$, R = H (52%); **h:** $R^F = (CF_2)_2H$, R = Me (55%); **i:** $R^F = (CF_2)_2H$, R = MeO (35%)

a: R' = CH_2=C(Me)-CH_2; **a':** R' = Me_2C=CH

highly reactive substrates in the reactions with N-,[5a,b] S-,[5c,d] and C-nucleophiles,[5e] we investigated the reaction of these compounds with 1,3,3-trimethyl-3,4-dihydroisoquinolines capable of reacting with electrophilic substrates as C-nucleophiles[6a,b] or 1,3-C,N-dinucleophiles[6b−d] due to the enamine tautomeric form.

We have found that 6-nitro-2-polyfluoroalkylchromones **1** react with isoquinolines **2** in a THF solution for 4 days at ~20 °C and afford colored (from orange to dark red) crystalline products in high yields. On the basis of the data of elemental analysis and IR and ^{1}H NMR spectroscopies, we ascribed the zwitterionic structure **3** to these compounds (Scheme 1).[7] The structure was confirmed by the X-ray diffraction study of crystals **3d**.[8]

According to the X-ray diffraction data, molecule **3d**, in its crystalline form, is a zwitterion with intramolecular charge separation (Figure 1). Due to steric interactions between the

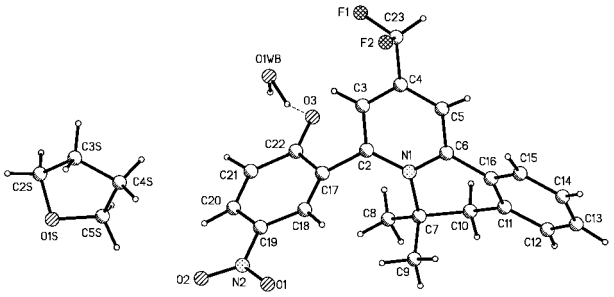


Figure 1. Molecular structure of **3d** (solvate with THF and H_2O molecules).

H(18) atom of the nitrophenoxide ring and the hydrogen atoms of the C(8)H_3 methyl group, the nitrophenoxide ring is not conjugated with the central heterocycle. The planes of these cycles are turned relative to each other by 67.8(5)°, and the C(2)−C(17) bond length of 1.488(6) Å corresponds to the normal nonconjugated C_{sp2}−C_{ar} bond (1.488 Å),[9]

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(7) **Preparation of Compounds 3a−i: General Procedure.** A mixture of chromone **1** (1.9 mmol) and dihydroisoquinoline **2** (2.5 mmol) in THF (3 mL) was allowed to stand at ~20 °C for 4 days. The resulting orange or dark red crystalline product was isolated by filtration, washed with THF, and dried. **Compound 3a:** yield 82%, mp 223−225 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (s, 3H, Me), 1.85 (s, 3H, Me), 2.97 (d, 1H, C*H*H, J = 16.4 Hz), 3.44 (d, 1H, CH*H*, J = 16.4 Hz), 6.63 (d, 1H, H$^{6'}$, ^oJ = 9.6 Hz), 7.40 (d, 1H, H,[8] ^oJ = 7.4 Hz), 7.63 (t, 1H, H^9 or H,[10] ^oJ = 7.5 Hz), 7.69 (td, 1H, H^{10} or H,[9] ^oJ = 7.5 Hz, ^mJ = 1.1 Hz), 7.86 (d, 1H, H,[11] ^oJ = 7.6 Hz), 7.93 (d, 1H, H$^{3'}$, ^mJ = 3.0 Hz), 8.03 (d, 1H, H^1 or H^3, ^mJ = 2.2 Hz), 8.11 (d, 1H, H^3 or H^1, ^mJ = 2.2 Hz), 8.14 (dd, 1H, H$^{5'}$, ^oJ = 9.6 Hz, ^mJ = 3.0 Hz); IR (Nujol) 1650, 1595, 1570, 1520 cm^{-1}. Anal. Calcd for $C_{22}H_{17}F_3N_2O_3$: C, 63.77; H, 4.14; N, 6.76. Found: C, 63.78; H, 4.10; N, 6.73.

indicating that the electron density is not delocalized along the bond between the cycles considered. A comparison of the geometric parameters of the *p*-nitrophenoxide fragment in structure **3d** with the published data on seven *p*-nitrophenoxide-containing organic salts found by us in CCDC (Table 1, see Supporting Information) shows that their geometries are comparable, but the resonance *p*-quinoid structure **3′** contributes more significantly to the zwitterionic nature of molecule **3d**. Thus, compounds **3** might exist as atropisomers due to restricted rotation about the C(2)−C(17) bond. Note that atropisomeric compounds are of considerable interest due to their presence in a number of biologically active natural products and their utility as directing groups in asymmetric synthesis.[10]

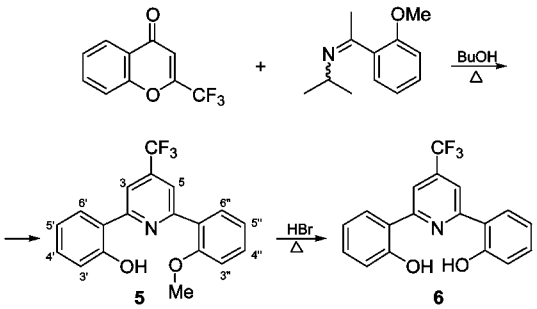
The chirality and the zwitterionic structure proposed for compounds **3a**−**i** agree well with the ^{1}H NMR spectroscopic data. The protons of the CH_2 group are diastereotopic and appear as doublets at δ 2.85−2.97 and 3.33−3.44 ppm with $^2J_{AX}$ = 16.4−16.5 Hz. In the phenoxide fragment of zwitterions **3**, the H(6′) proton is shielded by ∼0.5 ppm, and the ortho and meta constants were increased by 0.4−0.5 Hz compared to those in phenols **4**; in the pyridinium ring the H(1) and H(3) protons appear as doublets with ^mJ = 1.8−2.2 Hz, whereas in the pyridine ring they appear as singlets.

Most likely, the reaction includes the nucleophilic attack of the enamine tautomer of dihydroisoquinoline **2** to C(2) atom of 2-R^F-chromone **1** followed by the pyrone cycle opening and intramolecular cyclization at the keto group (Scheme 1). Note that the reaction is typical only for 6-nitro-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.

On heating compound **3a** to melting or on refluxing **3a** in butanol for 4 h, N−C(6) bond cleavage occurs to a afford a mixture of isomeric 2,6-diarylpyridines shown as **4a** and **4a′** (yield 80%). Steric hindrance in **3a** may provide a driving force for cleavage of the N−C(6) bond. This result clearly shows that the present methodology could be applicable to 2-polyfluoroalkylchromones and aromatic N-substituted methylketimines, providing the corresponding 2,6-diaryl-4-polyfluoroalkylpyridines.

Indeed, using this reaction, we were able to obtain 2-(2-hydroxyphenyl)-6-(2-methoxyphenyl)-4-(trifluoromethyl)pyridine (**5**) in 41% yield from readily available 2-trifluoromethylchromone[4] and methylketimine, prepared from 2-methoxyacetophenone with isopropylamine (boiling in butanol for 4 h). Taking into account the results of the reaction of **1** with **2**, we can propose that the first step involves the formation of the zwitterionic intermediate, bearing an isopropyl group at the nitrogen atom, followed by elimination of propylene. Demethylation of **5** to 2,6-bis(2-hydroxyphenyl)-4-(trifluoromethyl)pyridine (**6**) can be achieved by heating with 48% hydrobromic acid at 200 °C in a sealed tube for 10 h (yield 85%)[11] (Scheme 2). Although much

Scheme 2



attention has been paid to the chemistry of the CF_3-containing pyridine derivatives,[12] these compounds were not described in the literature and were unavailable by the known 2,6-diarylpyridines syntheses.[12d−f] At the same time, pyridines **5** and **6** due to the *ortho*-OH group are of great interest as analytical reagents[13] and organic electroluminescence substances.[14]

The present method could be applicable to the 6-substituted (MeO, NO_2) 2-R^F-chromones and *N*-(1-arylethylidene)-2-propanamines to afford the corresponding analogues of pyridine **5** in good to moderate yields. Notably, the nitro group that appears to be so important in the reaction of **1**

(8) **Compound 3d** ($C_{22}H_{18}F_2N_2O_3 \cdot C_4H_8O \cdot 0.5H_2O$; CCDC no. 213183): triclinic, space group *P*-1 with a = 10.032(3) Å, b = 10.206(3) Å, c = 12.847(3) Å; α = 74.002(6)°, β = 85.066(6)°, γ = 65.669(5)°, V = 1151.6(5) Å^3, Z = 2; R_1 = 0.085 (based on F for 2190 reflections with $I > 2\sigma(I)$); wR_2 = 0.288 (based on F^2 for all 4000 reflections). Full details on the crystal structure of **3d** are available in Supporting Information.

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(11) **2-(2-Hydroxyphenyl)-6-(2-methoxyphenyl)-4-(trifluoromethyl)-pyridine (5):** yield 41%, yellow needles, mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H, MeO), 6.96 (ddd, 1H, H$^{5'}$, ^oJ = 8.1, 7.2 Hz, ^mJ = 1.2 Hz), 7.04 (dd, 1H, H$^{3'}$, ^oJ = 8.3 Hz, ^mJ = 1.2 Hz), 7.07 (dd, 1H, H$^{3''}$, ^oJ = 8.3 Hz, ^mJ = 1.0 Hz), 7.12 (ddd, 1H, H$^{5''}$, ^oJ = 7.5, 7.6 Hz, ^mJ = 1.0 Hz), 7.36 (ddd, 1H, H$^{4'}$, ^oJ = 8.5, 7.2 Hz, ^mJ = 1.6 Hz), 7.47 (ddd, 1H, H$^{4''}$, ^oJ = 8.3, 7.5 Hz, ^mJ = 1.7 Hz), 7.72 (dd, 1H, H$^{6''}$, ^oJ = 7.6 Hz, ^mJ = 1.7 Hz), 7.85 (dd, 1H, H$^{6'}$, ^oJ = 8.1 Hz, ^mJ = 1.6 Hz), 7.91 (s, 1H, H^3 or H^5), 8.00 (s, 1H, H^5 or H^3), 13.87 (s, 1H, OH); IR (Nujol) 2800−3300, 1620, 1595, 1570 cm^{-1}. Anal. Calcd for $C_{19}H_{14}F_3NO_2$: C, 66.09; H, 4.09; N, 4.06. Found: C, 66.15; H, 4.12; N, 3.94. **2,6-Bis(2-hydroxyphenyl)-4-(trifluoromethyl)pyridine (6):** yield 85%, dark yellow crystals, mp 170−171 °C (toluene−hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.00 (ddd, 2H, H$^{5'}$, H$^{5''}$, ^oJ = 7.9, 7.2 Hz, ^mJ = 1.2 Hz), 7.02 (dd, 2H, H$^{3'}$, H$^{3''}$, ^oJ = 8.3 Hz, ^mJ = 1.2 Hz), 7.37 (ddd, 2H, H$^{4'}$, H$^{4''}$, ^oJ = 8.3, 7.2 Hz, ^mJ = 1.6 Hz), 7.98 (dd, 2H, H$^{6'}$, H$^{6''}$, ^oJ = 7.9 Hz, ^mJ = 1.6 Hz), 8.29 (s, 2H, H^3, H^5), 11.91 (s, 2H, 2 OH); IR (Nujol) 3300, 1625, 1600, 1565 cm^{-1}. Anal. Calcd for $C_{18}H_{12}F_3NO_2$: C, 65.26; H, 3.65; N, 4.23. Found: C, 65.14; H, 3.70; N, 3.98.

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with **2** is not necessary for the ketimine examples. Further studies on the regioselective synthesis of polyfluoroalkylated 2,6-disubstituted pyridines are now in progress.

In conclusion, we have presented zwitterionic 6,7-dihydrobenzo[*a*]quinolizinium derivatives with axial chirality because of hindered rotation about the C(2)−C(17) bond, which are easily available from 2-polyfluoroalkylchromones and 1,3,3-trimethyl-3,4-dihydroisoquinolines. On the other hand, this reaction with aromatic methylketimines is a simple and convenient synthesis of 2,6-diaryl-4-polyfluoroalkylpyridines with potential use in the preparation of complexes with various metals useful as electroluminescence materials.[14]

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Supporting Information Available: X-ray data for compound **3d**; spectral and analytical data of compounds **3b**−**i** and **4a**; and ^{1}H NMR spectra for compounds **3b**, **3c**, **3f**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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