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Reactions of 3-(polyfluoroacyl)chromones with hydroxylamine. The first synthesis of 3-cyano-2-(polyfluoroalkyl)chromones

Vyacheslav Ya. Sosnovskikh,* Vladimir S. Moshkin and Roman A. Irgashev

Department of Chemistry, Ural State University, prosp. Lenina 51, 620083 Ekaterinburg, Russia

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Abstract—Reaction of 3-(polyfluoroacyl)chromones with hydroxylamine proceeds via nucleophilic 1,4-addition followed by opening of the pyrone ring and subsequent cyclization to 4-(polyfluoroalkyl)-4*H*-chromeno[3,4-*d*]isoxazol-4-ols in good yields. On treatment with trifluoroacetic acid, the isoxazole ring of this annulated heterocyclic system opens to give 3-cyano-2-(polyfluoroalkyl)chromones. Reaction of 3-(polyfluoroacyl)chromones with hydroxylamine hydrochloride occurs only at the carbonyl carbon atom connected to the R^F group to give the corresponding oximes in low yields.

The electron-withdrawing acyl group in 2-unsubstituted 3-acylchromones enhances the electrophilicity of the C(2) atom of the pyrone ring, which is usually attacked by nucleophilic reagents. This reactivity has been exploited in both Michael and Diels–Alder reactions of these useful synthetic intermediates.[1] The majority of the reactions with 3-acylchromones are nucleophilic additions with concomitant opening of the pyrone ring leading to various types of heterocyclic products. However, in contrast to well studied 3-formyl-[2] and 3-acylchromones,[3] no data on the chemical properties of 3-(polyfluoroacyl)chromones **1** have been documented. This is quite surprising, especially as these compounds should contain three strong electrophilic centers, that is the C(2) and C(4) atoms of the chromone system and the carbonyl carbon of 3-polyfluoroacyl group.

In view of the unique biological properties displayed by many fluorinated heterocyclic compounds[4] and as an extension of our continuing synthetic studies on the reactivity of R^F-containing chromones,[5] we have focussed our attention on the 3-R^FCO-chromones **1** as a new class of polydentate electrophilic substrates. We reasoned that replacing the hydrogens of the 3-acyl group with fluorine atoms, which are strongly electronegative, would have a positive effect on the reactivity and synthetic utility of these chromone derivatives. In connection with this, we have recently developed an efficient method for the preparation of 3-R^FCO-chromones **1** from readily available, inexpensive starting materials and established their feasibility as novel R^F-containing building blocks for the synthesis of a wide variety of heterocycles.[6,7] It was found that the reactions of chromones **1** with primary amines and indoles proceeded via nucleophilic 1,4-addition with subsequent opening of the pyrone ring and cyclization into 3-(alkyl/arylaminomethylene)-[6] and 3-(indol-3-ylmethylene)-2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones[7] in good yields. One would expect that the reaction of chromones **1** with 1,2-dinucleophilic reagents, such as hydroxylamine, would lead to the possibility of competition between different initial nucleophilic attacks and then towards different cyclization patterns.

The reactions of 3-formylchromone **2a**,[8] 3-benzoylchromone **2b**,[9] and 3-acetylchromone **2c**[10] with hydroxylamine have been shown to give chromone derivatives **3a**,**b** and **4a**–**c** and regioisomeric isoxazoles **5a**–**c** and **6a**,**b**, depending on the reaction conditions (Fig. 1). These products can result from the initial nucleophilic 1,2- or 1,4-additions of hydroxylamine to **2a** and 1,4-addition to **2b**,**c**. In the latter case, no 1,2-addition of hydroxylamine to the PhC=O and MeC=O double bonds was observed.

In this context, we decided to study the interaction of 3-(polyfluoroacyl)chromones **1** with hydroxylamine with the emphasis on the synthesis of the hitherto unknown

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* Corresponding author. Tel.: +7 343 261 68 24; fax: +7 343 261 59 78; e-mail addresses: Vyacheslav.Sosnovskikh@usu.ru; svy@etel.ru

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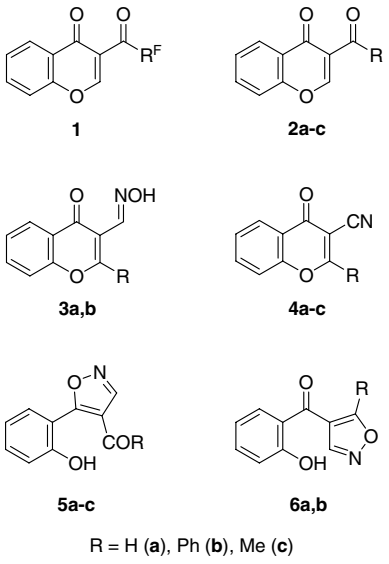
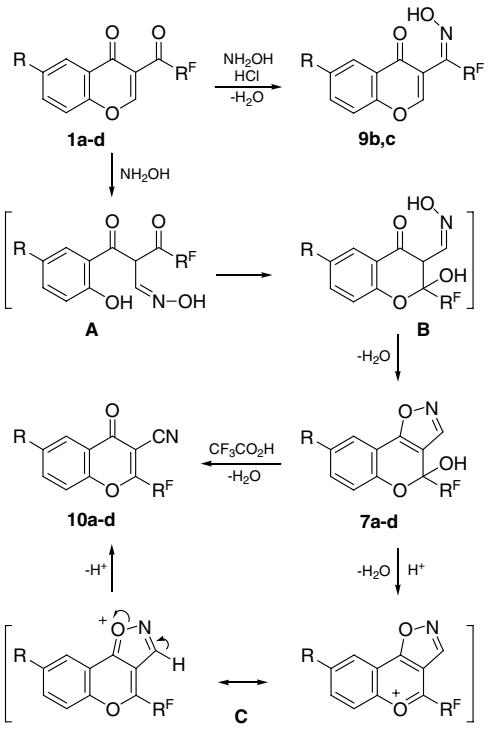


Figure 1.

3-cyano-2-(polyfluoroalkyl)chromones. We found that 3-R^FCO-chromones **1a–d** smoothly reacted with hydroxylamine to afford chromeno[3,4-*d*]isoxazoles **7a–d** in good yields (Table 1).[11] All the reactions were carried out in methanol at room temperature using hydroxylamine obtained in situ from the corresponding hydrochloride after reaction with potassium hydroxide. Furthermore, the same products were obtained in lower yields when chromones **1** were treated with a combination of $NH_2OH{\cdot}HCl$ and AcONa.

A plausible reaction pathway involves an initial attack of hydroxylamine at the electrophilic C(2) atom followed by ring opening to intermediate **A**, which then leads to **B** by cyclization between the phenolic hydroxyl and the R^FCO group. Intermediate **B** then undergoes cyclodehydration to give chromeno[3,4-*d*]isoxazoles **7** (Scheme 1). The alternative cyclization of **A** involving the oxime hydroxyl and the carbonyl carbon connected to the R^F group to give isoxazolines **8** does not occur (Fig. 2). In this case, the R^F group hinders the dehydration and, therefore, the formation of the aromatic isoxazole ring is prevented.

When the same reaction was carried out with chromones **1b**,**c** and hydroxylamine hydrochloride in the presence of a catalytic amount of concentrated HCl in 95% ethanol,[8a,e] the only products obtained were the corresponding oximes **9b**,**c** (yields 19–24%),[12] formed undoubtedly by nucleophilic 1,2-addition of hydroxylamine to the R^FCO group. This result is in marked contrast to those obtained by Eiden et al.[9] and Ghosh



Scheme 1.

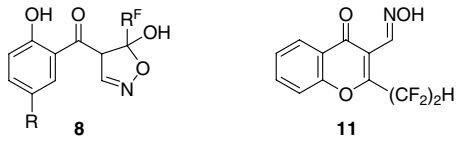


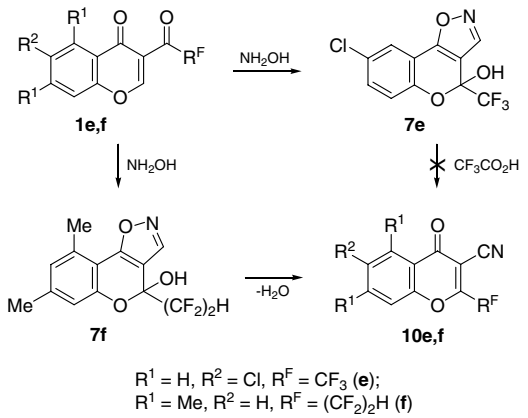
Figure 2.

et al.,[10] in which they found that the addition of hydroxylamine to 3-benzoylchromone and 3-acetylchromone occurred exclusively at the 2-position (Fig. 1, compounds **3b–6b**, **4c**, **5c**).

The structure of oxime **9c** was established by consideration of the $^3J_{H,F}$ value of 5.3 Hz for the terminal proton of the $(CF_2)_2H$ group. This value agrees well with the data for compounds with a $(CF_2)_2H$ group at the oxime carbon atom ($^3J_{H,F} = 5.4$ Hz in the case of oximes[13] and $^3J_{H,F} = 3.0–3.8$ Hz in the case of 2-(1,1,2,2-tetrafluoroethyl)chromones[14]). This allowed us to reject the alternative structure **11** (Fig. 2), which can result from intermediate **B**. The *E*-configuration of the C=N bond was suggested from the ^{19}F NMR chemical shift of the CF_3 group in oxime **9b** (93.4 ppm, C_6F_6). According to published data,[15] the signal for this group in the spectra of *Z*-isomers of trifluoromethylated oximes

Table 1. Isolated yields for compounds **7a–d** and **10a–d**

Chromone	R	R^F	Isoxazole	Yield (%)	Mp (°C)	Nitrile	Yield (%)	Mp (°C)
1a	H	CF_3	**7a**	72	144–145	**10a**	83	118–119
1b	Me	CF_3	**7b**	65	143–144	**10b**	72	149–150
1c	H	$(CF_2)_2H$	**7c**	70	105–106	**10c**	85	138–139
1d	Me	$(CF_2)_2H$	**7d**	57	117–118	**10d**	71	186–187



Scheme 2.

and hydrazones appeared at 97–99 ppm, whereas for the *E*-isomers it appeared at 92–96 ppm.

Next, we examined the possibility of preparing 3-cyano-2-(polyfluoroalkyl)chromones from compounds **7**. 3-Cyanochromones are important intermediates in the synthesis of biologically interesting compounds.[16] On the other hand, due to the powerful electron-withdrawing ability of R^F groups, the insertion of polyfluoroalkyl substituents into the 2-position of chromones activates these molecules and 2-R^F-chromones are highly reactive substrates in reactions with *N*-, *S*-, and *C*-nucleophiles.[5] To the best of our knowledge, there have been no reports on the preparation of 2-polyfluoroalkyl substituted 3-cyanochromones, despite the possible enhancement of their reactivity due to the presence of the R^F group, however, 3-cyano-2-methylchromones are known.[10,17]

Attempts to obtain 3-cyano-2-(polyfluoroalkyl)chromones **10** from chromeno[3,4-*d*]isoxazoles **7** in the presence of KOH in ethanol, conditions that had previously been used for the preparation of carbonitrile **4b** from **3b**, **5b**, and **6b**,[9] proved fruitless. However, it was found that the required compounds **10** could be easily prepared by refluxing isoxazoles **7** in trifluoroacetic acid for 15 min (only starting material **7b** was recovered from a similar reaction in acetic acid). Thus, isoxazoles **7a**–**d** are easily ring opened to give 3-cyano-2-(polyfluoroalkyl)chromones **10a**–**d** in high yields (Table 1).[18] This result probably represents a specific property of fused isoxazoles **7** because only base-induced ring-opening reactions have been reported for non-fluorinated analogues **5** and **6**.[8a,e,9] The most likely, intermediate in the trifluoroacetic acid ring opening of **7** is the aromatic benzopyrylium cation **C**, which undergoes deprotonation to give **10** (Scheme 1).

Surprisingly, isoxazole **7e** failed to provide the corresponding carbonitrile **10e** under the same reaction conditions. Besides the starting material, a small amount (~20%) of 5-(5-chloro-2-hydroxyphenyl)isoxazole was detected by ^{1}H NMR spectroscopy. This product is the result of the detrifluoroacetylation of **7e**. On the other hand, chromone **1f** bearing two electron-donating methyl groups reacted with hydroxylamine to afford a 3:1 mixture of **7f** and **10f**, which was converted to carbonitrile **10f** by simple crystallization from toluene (**7f** was converted to **10f** during crystallization). Thus, it appears that electronic effects play an important role in the ring opening of isoxazoles **7** (Scheme 2). This observation is consistent with our assumption that the reaction proceeds via the intermediate benzopyrylium cation **C**. An investigation of the scope and limitations of the transformation **7** → **10** is now in progress.

In conclusion, we have shown that the reaction of 3-(polyfluoroacyl)chromones with hydroxylamine is a simple and practical method for introduction of a CN group at the 3-position of 2-(polyfluoroalkyl)-chromones. The resulting 3-cyano-2-(polyfluoroalkyl)-chromones are of considerable interest as reactive precursors in the synthesis of other useful organic materials containing polyfluoroalkyl groups.

Acknowledgments

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11. *Preparation of* **7**. To a solution of hydroxylamine, prepared from $NH_2OH{\cdot}HCl$ (1.0 mmol) and KOH (0.9 mmol) in MeOH (3 mL), 3-R^FCO-chromone **1** (0.5 mmol) was added. The resulting mixture was allowed to stand for 18–24 h at room temperature and then diluted with water (5 mL) containing AcOH (1.5 mmol). After cooling, the precipitate that formed was filtered off, washed with water, dried and recrystallized from toluene–hexane (1:7) to give **7** as colorless crystals.
4-(Trifluoromethyl)-4H-chromeno[3,4-d]isoxazol-4-ol **7a**. IR (KBr) 3105, 1651, 1608, 1573, 1515, 1470, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (br s, 1H, OH), 7.17–7.22 (m, 2H, H-6, H-8), 7.47 (ddd, 1H, H-7, $^oJ = 8.5$, 7.6 Hz, $^mJ = 1.6$ Hz), 7.77 (dd, 1H, H-9, $^oJ = 7.6$ Hz, $^mJ = 1.6$ Hz), 8.40 (s, 1H, H-3); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 76.47 (d, CF_3, $J = 0.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.58 (q, *C*–CF_3, $^2J_{C,F} = 36.3$ Hz), 104.17, 110.49, 117.24, 121.38 (q, CF_3, $^1J_{C,F} = 285.7$ Hz), 122.58, 123.29, 133.04, 146.61, 151.25, 163.26. Anal. Calcd for $C_{11}H_6F_3NO_3$: C, 51.38; H, 2.35; N, 5.45. Found: C, 51.09; H, 2.12; N, 5.46.
12. *1-(4-Oxo-4H-chromen-3-yl)-2,2,3,3-tetrafluoropropan-1-one oxime* **9c**. Yield 24%, mp 186–187 °C, colorless crystals; IR (KBr) 3225, 1649, 1622, 1602, 1570, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (tt, 1H, CF_2CF_2H, $^2J_{H,F} = 52.8$ Hz, $^3J_{H,F} = 5.3$ Hz), 7.48 (ddd, 1H, H-6, $^oJ = 7.9$, 7.3 Hz, $^mJ = 0.9$ Hz), 7.53 (d, 1H, H-8, $^oJ = 8.3$ Hz), 7.75 (ddd, 1H, H-7, $^oJ = 8.6$, 7.2 Hz, $^mJ = 1.7$ Hz), 8.01 (s, 1H, H-2), 8.26 (dd, 1H, H-5, $^oJ = 8.0$ Hz, $^mJ = 1.6$ Hz), 8.78 (s, 1H, OH). Anal. Calcd for $C_{12}H_7F_4NO_3$: C, 49.84; H, 2.44; N, 4.84. Found: C, 49.73; H, 2.46; N, 4.74.
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18. *4-Oxo-2-(trifluoromethyl)-4H-chromene-3-carbonitrile* **10a**. IR (KBr) 2245, 1667, 1637, 1610, 1580, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (ddd, 1H, H-6, $^oJ = 8.0$, 7.3 Hz, $^mJ = 1.0$ Hz), 7.64 (d, 1H, H-8, $^oJ = 8.6$ Hz), 7.89 (ddd, 1H, H-7, $^oJ = 8.7$, 7.2 Hz, $^mJ = 1.7$ Hz), 8.28 (dd, 1H, H-5, $^oJ = 8.0$ Hz, $^mJ = 1.5$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 93.67 (s, CF_3). Anal. Calcd for $C_{11}H_4F_3NO_2$: C, 55.24; H, 1.69; N, 5.86. Found: C, 55.20; H, 1.46; N, 5.87.