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The first example of a preparative 1,4-perfluoroalkylation using (perfluoroalkyl)trimethylsilanes☆

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Abstract—Reactions of 2-perfluoroalkylchromones with (perfluoroalkyl)trimethylsilanes proceed as a 1,4-nucleophilic perfluoroalkylation to give 2,2-bis(perfluoroalkyl)chroman-4-ones in high yields after acid hydrolysis. Oxidation of 2,2-bis(trifluoromethyl)-6-methylchroman-4-one with $K_2S_2O_8$ leads to fluorinated analogs of natural lactarochromal and the corresponding acid. © 2003 Published by Elsevier Science Ltd.

Regioselective perfluoroalkylation of organic compounds using various fluorinating agents is a well established methodology for the synthesis of partially fluorinated materials applicable for agrochemistry and the pharmaceutical industry.[1] The unique properties of (trifluoromethyl)trimethylsilane (Ruppert's reagent) as a nucleophilic trifluoromethylating agent are well known.[2] The reactions of aldehydes, ketones, α-keto amides and esters with CF_3SiMe_3 in the presence of a nucleophilic initiator proceed as a 1,2-addition of the CF_3 group at the carbonyl carbon atom to give trifluoromethylated alcohols or trifluoromethyl ketones in excellent yields following acid hydrolysis.[3]

So far, a straightforward method for a preparative 1,4-trifluoromethylation of α,β-unsaturated systems has not been developed. All attempts with different reagents (CF_3SiMe_3/Nu, adducts of CF_3H and *N*-formylmorpholine/CsF or $CF_3H/N(SiMe_3)_3$/DMF/Me_4NF) exclusively lead to products of a 1,2-addition.[3,4] The only example known to us, where a 1,4-addition takes place to a certain extent is observed in the reaction of *trans*-1-benzoyl-2-(dimethylamino)ethylene with $CF_3H/N(SiMe_3)_3$/DMF/Me_4NF. However, in this reaction the 1,4-trifluoromethylation was followed by the elimination of dimethylamine[4a] and the initial product of 1,4-addition could not be isolated. Thus, this reaction proceeding as an A_N–E process could not be strongly considered a successful nucleophilic 1,4-trifluoromethylation.

Here, we wish to report that (perfluoroalkyl)trimethylsilanes can be employed to generate compounds with a *gem*-bis(perfluoroalkyl) group by 1,4-nucleophilic perfluoroalkylation of 2-perfluoroalkylchromones **1**. In our initial studies, we optimized the reaction conditions by using 2-trifluoromethylchromone **1a** and R^FSiMe_3 and monitored the reaction progress by ^{19}F NMR. When chromone **1a** was treated with 1.2 equiv. of R^FSiMe_3 in dry THF in the presence of a catalytic amount of anhydrous Me_4NF (2 mol%) as a nucleophilic initiator for 4 h at 0°C, ^{19}F NMR analysis of the reaction mixture showed almost quantitative formation of the trimethylsilyl ethers **2a**,**b** and **3a**,**b** with high regioselectivity (Scheme 1). Surprisingly, no trifluoromethylation was observed in the case of CF_3SiMe_3/Bu_4NF. When the temperature was decreased from 25 to −30°C, the regioselectivity increased by 5 and 10% for $R^F = CF_3$ and C_2F_5, respectively, but at −78°C the conversion was only about 20% after 3 h.

The reactions of 2-R^F-chromones with R^FSiMe_3 are very dependent on the size of the R^F group. For example, upon increasing the length of the perfluoroalkyl chain in the Ruppert's reagent to C_2F_5 (compounds **2b**,**3b**) the regioselectivity drops, most likely due to steric repulsion between R^F moieties. Similarly, the reaction of 2-perfluoroethylchromone **1c**

Keywords: 2-perfluoroalkylchromones; (perfluoroalkyl)trimethylsilanes; 2,2-bis(perfluoroalkyl)chroman-4-ones; trifluoromethylated analogues of natural lactarochromal and corresponding acids.

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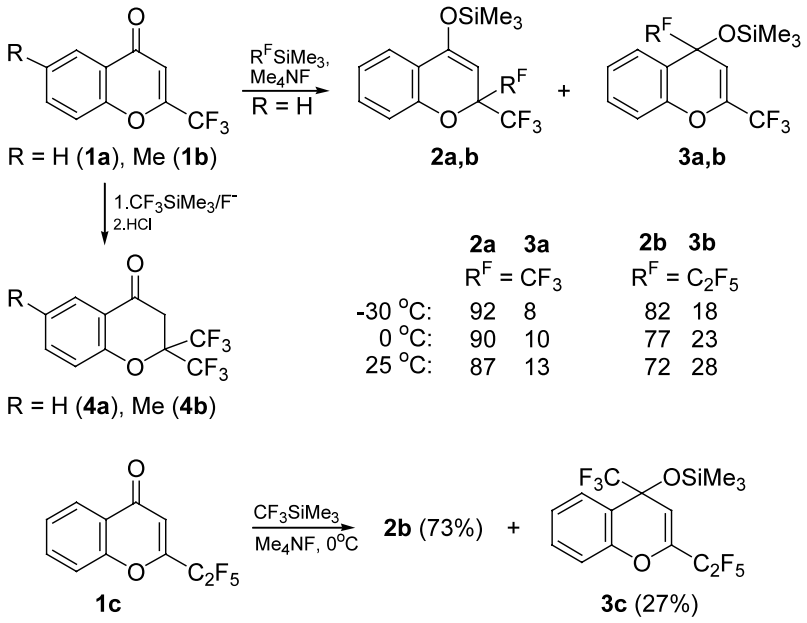


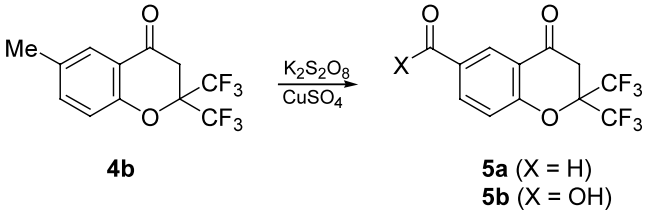
Scheme 1.

with CF_3SiMe_3 at 0°C leads to a mixture of the 1,4- and 1,2-addition products in the molar ratio **2b**:**3c** = 73:27. Note that steric hindrance in the carbonyl compounds is also a limiting factor in the reactions of R^FSiMe_3.[3b]

Next, we applied this reaction for the preparative synthesis of chromanones **4a**,**b**. When chromones **1a**,**b** were treated with CF_3SiMe_3/Me_4NF for 4 h at −10°C followed by acid hydrolysis (dilute HCl), 2,2-bis(trifluoromethyl)chroman-4-ones **4a**,**b** were obtained as oils after vacuum distillation in 86 and 61% isolated yields, respectively.[5] Each product contained as an admixture ~10% trimethylsilyl ethers **3**, which are more stable than ethers **2** (Scheme 1).

The approach described here represents the best overall route to fluorinated analogs of natural chromanones and chromenes with *gem*-dimethyl groups at the C(2) atom, which are widely abundant in nature.[6] For example, 4-oxo-2,2-bis(trifluoromethyl)chroman-6-carbaldehyde **5a**, the analog of natural lactarochromal, a metabolite of the fungus *Lactarius deliciosus*[7] in which both methyl groups are replaced by the trifluoromethyl groups, was synthesized by the oxidation of the 6-Me group of chromanone **4b** with a mixture of $K_2S_2O_8$ and $CuSO_4$ in aqueous acetonitrile[8] in 17% yield (the reaction conditions are not optimized). In addition to hexafluorolactarochromal **5a**, this reaction gave the corresponding hexafluoroacid **5b** (yield 35%), which is also a fluorinated analog of the natural acid isolated from *Chrysothamnus viscidiflorus* (Scheme 2).[9]

In summary, the reaction of 2-trifluoromethylchromones with Ruppert's reagent is a simple and efficient method for the synthesis of 2,2-dimethylchroman-4-ones in which the *gem*-dimethyl group is replaced with a *gem*-bis(trifluoromethyl) moiety. This



Scheme 2.

approach is the first example of a successful preparative regioselective 1,4-trifluoromethylation of a conjugated enone system and can be used for the synthesis of fluorinated analogs of natural compounds.

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5. *2,2-Bis(trifluoromethyl)chroman-4-one (**4a**).* Colorless liquid, 86% yield, bp 94–97°C (15 Torr); ^{1}H NMR (400 MHz, $CDCl_3$) δ **4a** (89%): 3.22 (s, 2H, CH_2), 7.13 (dd, 1H, $J=8.4$, 1.0 Hz, H^8), 7.17 (ddd, 1H, $J=8.4$, 7.3, 1.0 Hz, H^6), 7.60 (ddd, 1H, $J=8.4$, 7.3, 1.8 Hz, H^7), 7.89 (dd, 1H, $J=7.8$, 1.8 Hz, H^5), **3a** (11%): −0.03 (s, 9H, $SiMe_3$), 5.81 (s, 1H, =CH), 7.18 (dd, 1H, $J=8.4$, 1.1 Hz, H^8), 7.27 (ddd, 1H, $J=8.4$, 7.3, 1.1 Hz, H^6), 7.44 (ddd, 1H, $J=8.4$, 7.3, 1.7 Hz, H^7), 7.72 (d quint, 1H, $J=8.0$ Hz, $^mJ=^5J_{H,F}=1.4$ Hz, H^5); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ **4a**: −77.78 (s, CF_3), **3a**: −73.70 (s, C^2–CF_3), −81.98 (s, C^4–CF_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ **4a**: 34.65 (s, C^3), 80.03 (sept, $^2J_{C,F}=30.9$ Hz, C^2), 117.46 (s, C^8), 119.15 (s, C^{4a}), 121.91 (q, $^1J_{C,F}=287.8$ Hz, CF_3), 123.41 (s, C^6), 126.48 (s, C^5), 137.13 (s, C^7), 157.21 (s, C^{8a}), 184.52 (s, C^4); IR (neat) 1710 (C=O), 1670, 1615, 1590 (arom.) cm^{-1}.
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