

Late-stage electron-catalyzed perfluoroalkylation of coumarin derivatives—Thermal fluoroalkyl radical production from sodium perfluoroalkyl sulfinate salts



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ABSTRACT

Novel and high-yielding protocols for the late-stage synthesis of 3-perfluoroalkyl-substituted coumarin derivatives employing either perfluoroalkyl iodides R_fI or sodium perfluoroalkylsulfinate salts $NaSO_2R_f$ as perfluoroalkyl R_f radical precursors is presented. The electron-catalyzed methodologies make use of two comparative and parallel protocols as an entry to the production of R_f radicals: (i) from $NaSO_2R_f$ sources and the thermal *tert*-butylhydroperoxide (TBHP) radical initiation in MeCN: CH_2Cl_2 as organic solvent mixture, and (ii) from commercial R_fI and the photoorganocatalyst anthraquinone-2-sulfonic acid as the room-light initiation process in DMF: CH_2Cl_2 as mixture of solvents.

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1. Introduction

The replacement of hydrogen by fluorine or a perfluoroalkyl group R_f in organic compounds may profoundly influence their physical and biological properties [1–4]. Fluorine-containing coumarins are known for their unique properties as fluorophores [5] and laser dyes [6]. As a result of their remarkable fluorescent features [7,8], fluorinated coumarins have been employed in the manufacturing of liquid crystal displays [9,10]. These R_f groups impart an increase in the compound photostability [1] that can be attributed to bathochromic shifts both in the UV and emission spectra as a consequence of the stronger electron-withdrawing nature of the lactone moiety in the 3-(perfluoroalkyl)-substituted derivatives [5]. As opposed to 4-fluoroalkylcoumarins which can be synthesized through polar condensation reactions [11], 3-fluoroalkyl-substituted coumarins can only be accessed through radical reaction protocols (Scheme 1). The synthesis of 3-perfluoroalkyl coumarins has been achieved through different radical-based methodologies, such as the employment of bis-

(heptafluorobutyl) peroxide on the coumarin backbones [12], the use of perfluoroalkyl iodides in the presence of Rongalite [13], perfluoroalkylsulfinate sodium salts in conjunction with Mn(III) in acetic acid [14] or alternative radical methods employing novel, though expensive, fluoroalkylating reagents [15] (Scheme 1).

In this work, we shall report improved, novel and higher-yielding protocols for the synthesis of 3-perfluoroalkyl-substituted coumarin derivatives by electron-catalyzed processes, as an entry to the production of R_f radicals: (i) from sodium perfluoroalkyl sulfinate $NaSO_2R_f$ sources and the thermal *tert*-butylhydroperoxide (TBHP) radical initiation in MeCN: CH_2Cl_2 as organic solvent mixture, and (ii) from commercial perfluoroalkyl iodides R_fI and the photoorganocatalyst anthraquinone-2-sulfonic acid as the room-light initiation process in DMF: CH_2Cl_2 as mixture of solvents.

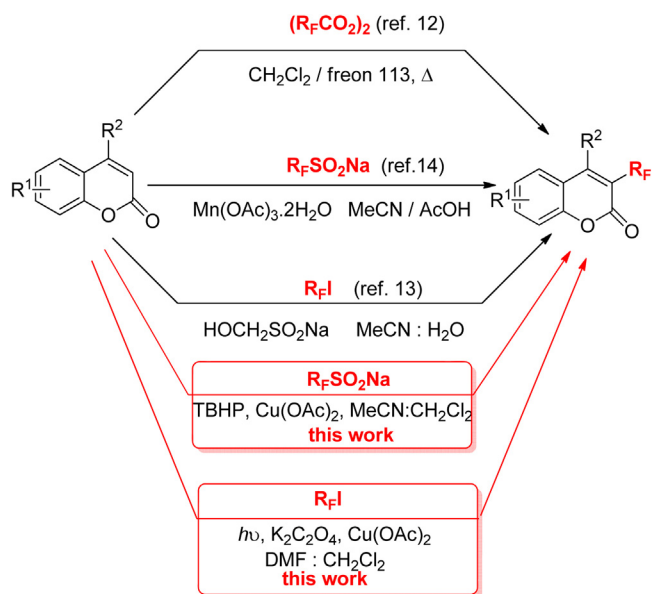
2. Results and discussion

2.1. Light-triggered fluoroalkylation reactions of coumarins

As a first approach, we undertook a series of optimization reaction conditions for the photochemical perfluorobutylation of

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Scheme 1. Different radical methods to achieve 3-fluoroalkyl-substituted coumarins.

7-hydroxy-4-methyl-2*H*-chromen-2-one **1** (4-methyl-7-hydroxy-coumarin), employing different solvents, additives, perfluoroalkyl radical sources, and organophotocatalysts, according to **Table 1**.

Itoh and collaborators have reported on the C–H trifluoromethylation of heteroarenes employing anthraquinone-2-carboxylic acid (ANQ-2C) as photoredox organocatalyst and the Langlois

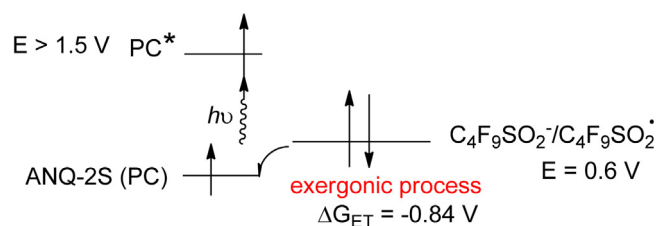


Fig. 1. Oxidation/reduction potential determined by cyclic voltammetry and ΔG_{ET} .

reagent, NaSO_2CF_3 , as the CF_3 radical source [16]. We commenced our studies using anthraquinone-2-sulfonic acid (ANQ-2S) as photocatalyst in the light of its favorable redox potentials [17] ($E_{\text{redANQ}^{\bullet-}/\text{ANQ}^*} = +1.5 \text{ V}$, $E_{\text{redANQ}^{\bullet-}/\text{ANQ}} = -0.883 \text{ V}$) and $\text{NaSO}_2\text{C}_4\text{F}_9$. The synthesis of $\text{NaSO}_2\text{C}_4\text{F}_9$ has been described before [18], and we optimized the reaction yields starting from *n*- $\text{C}_4\text{F}_9\text{I}$ and purified $\text{Na}_2\text{S}_2\text{O}_4$ (see Experimental).

Fig. 1 depicts the scale for the redox potentials involved in the interacting couples. The predicted ΔG_{ET} values of the ET from ANQ-2S* and $\text{C}_4\text{F}_9\text{SO}_2^-$ is ca. -0.84 V , an expected exergonic process (see Discussion of Results). Visible-light irradiation of 7-hydroxy-4-methyl-2*H*-chromen-2-one **1** in the presence of ANQ-2S and $\text{NaSO}_2\text{C}_4\text{F}_9$ ($E_{\text{C}_4\text{F}_9\text{SO}_2^-/\text{C}_4\text{F}_9\text{SO}_2^{\bullet-}} = 0.6 \text{ V}$) does not afford any product (entry 1, **Table 1**). As the radical perfluorobutylation of coumarines in the 3-position would lead to benzyl-type radical intermediates, we envisioned that the presence of R_FI would facilitate the radical adduct oxidation leading to 3-perfluorobutyl-substituted benzyl cations (and R_F radicals) that undergo fast deprotonation to form 3-perfluorobutyl-substituted coumarin derivatives. Thus, we applied

Table 1

Optimization of reaction conditions (24 h.) for the fluoroalkylation of coumarin **1** (0.2 mmol) under photochemical initiation or otherwise noted with an R_F source (3 equiv.) under Ar atmosphere and the presence of an additive (1 equiv., or otherwise noted) in a given solvent system (3 mL).

Entry	Solvent system	R_F source	Illuminated conditions	additive	Substrate Conversion %	Product Yield ^a
1	MeCN	$\text{NaSO}_2\text{C}_4\text{F}_9$	ANQ-2S ^b /CFL ^c	–	–	–
2	MeCN	$\text{NaSO}_2\text{C}_4\text{F}_9$	ANQ-2S ^b /CFL ^c	$\text{Cu}(\text{OAc})_2$	–	–
3	MeCN	$\text{NaSO}_2\text{C}_4\text{F}_9$	ANQ-2S ^{b,d}	–	–	–
4	MeCN	$\text{NaSO}_2\text{C}_4\text{F}_9$	ANQ-2S ^{b,d}	$\text{Cu}(\text{OAc})_2$	–	–
5	MeCN:H ₂ O 1:1	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	<i>hν</i> (254 nm) 2h	–	–	–
6	MeCN:H ₂ O 1:1	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	<i>hν</i> (254 nm) 2h	$\text{Cu}(\text{OAc})_2$	–	–
7	MeCN	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	RB ¹ /CFL ^c	Cs_2CO_3	–	–
8	MeCN	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	RB ^e /CFL ^c 12h	Cs_2CO_3 ^f $\text{Cu}(\text{OAc})_2$ ^g	–	–
9	MeCN	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	ANQ-2S ^b /CFL ^c 12h	$\text{K}_2\text{C}_2\text{O}_4$ ^h $\text{Cu}(\text{OAc})_2$	–	–
10	DMF:CH ₂ Cl ₂ 1:1	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	ANQ-2S ^b /CFL ^c 12h	$\text{K}_2\text{C}_2\text{O}_4$ ^h $\text{Cu}(\text{OAc})_2$ ^g	–	–
11	DMF:CH ₂ Cl ₂ 1:1	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	ANQ-2S ^b /CFL ^c 48h	$\text{K}_2\text{C}_2\text{O}_4$ ^h $\text{Cu}(\text{OAc})_2$ ^g	50	50
12	DMF:CH ₂ Cl ₂ 1:1	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	ANQ-2S ^b /CFL ^c 48h	$\text{Cu}(\text{OAc})_2$ ^g	11	10
13	DMF:CH ₂ Cl ₂ 1:1	<i>n</i> - $\text{C}_4\text{F}_9\text{I}$	ANQ-2S ^b /CFL ^c 24h	$\text{K}_2\text{C}_2\text{O}_4$ ^h $\text{Cu}(\text{OAc})_2$ ⁱ	50	50

^a Isolated yield.

^b ANQ-2S = anthraquinone-2-sulfonic acid, 0.1 equiv.

^c CFL = commercial fluorescent light.

^d Dark reaction, 24 h.

^e 0.1 equiv RB.

^f 1.5 equiv Cs_2CO_3 .

^g 4 equiv $\text{Cu}(\text{OAc})_2$.

^h 3 equiv $\text{K}_2\text{C}_2\text{O}_4$.

ⁱ 0.5 equiv. $\text{Cu}(\text{OAc})_2$.

conditions as shown in entry 2 (Table 1). However, no substitution product was found.

In a previous report [19], we have shown that the direct irradiation (254 nm) of a mixture of *n*-C₄F₉I and olefins or alkynes, in MeCN: H₂O mixtures afford C₄F₉-substituted products with halogen atom transfer (HAT). Applying these reaction conditions to substrate **1**, however, do not lead to substitution product (entries 5,6, Table 1). In a recent report, we have shown that the Rose Bengal (RB) visible-light photocatalyzed reactions [20] of aniline derivatives with *n*-C₄F₉I in the presence of Cs₂CO₃ as additive lead to C₄F₉-substituted anilines, where visible light-excited RB* functions as an electron donor to *n*-C₄F₉I, generating C₄F₉[•] radicals that substitute the arene rings, together with the radical cation of RB [20]. We applied these reaction conditions to substrate **1** in the presence of *n*-C₄F₉I and Cs₂CO₃ as additive [20] in MeCN as solvent (entries 7,8, Table 1). However, no substitution product was encountered. You, Cho and collaborators [21] have shown that the use of CF₃I and an oxalate salt in the presence of an organometallic photoorganocatalyst such as Ru(phen)₃Cl₂ or Ir(dfppy)₂(bpy)PF₆ in conjunction with visible light lead to CF₃-substituted products from olefins. Encouraged by these results [21], we employed K₂C₂O₄, a copper salt, and replaced the metal-photoorganocatalysts for ANQ-2S as an environmentally-friendly option for a readily-available metal-free organophotocatalyst, which can function as a good electron acceptor photoexcited organocatalyst. To our delight, we obtained a 50% yield of substitution product (entries 11 & 13, Table 1). Attempts to improve the substitution yields by this photocatalytic method failed, however.

In order to improve the reaction yields, we proceeded to concentrate our efforts on a thermal radical methodology employing this time NaSO₂C₄F₉/tert-butylhydroperoxide, TBHP, as radical initiator (Table 2).

2.2. Thermal initiation for the perfluoroalkylation reaction of coumarin derivatives

The reaction in the presence of CuSO₄ (entry 1, Table 2) affords 90% yield of product **6** when a 1: 1 mixture of MeCN: CH₂Cl₂ was employed. When CuSO₄ was replaced by Cu(OAc)₂, the yield of product **6** was quantitative (entry 2 Table 2).

The thermal reactions of **1** employing *n*-C₄F₉I and Cs₂CO₃ in different solvent systems, (entries 3–4, Table 2) afford no yields of 3-perfluorobutyl-substituted coumarin derivative. The reactions of **1**, TBHP, and NaSO₂C₄F₉ in H₂O:CH₂Cl₂ (1:1) or H₂O lead to an oligomeric product mixture which could not be identified, with entire substrate conversion (entry 7, Table 2). The reaction in MeCN as solvent, under the same conditions, leads to 50% yield of substrate conversion and only 15% yield of 3-perfluorobutyl-substituted coumarin derivative **6** (entry 8, Table 2). When we changed the reaction solvent to a 1: 1 mixture of MeCN: CH₂Cl₂, the yield of product **6** increased to 30% (entry 9, Table 2). The reaction in the presence of Cu(OAc)₂ (entry 10, Table 2) in a 1: 1 mixture of CH₂Cl₂: H₂O, gives a 35% yield of product **6** (50% substrate conversion).

We therefore employed reaction conditions consisting of coumarin, NaSO₂C₄F₉/TBHP, in Ar-deoxygenated MeCN: CH₂Cl₂ (1: 1) as solvent mixture (entry 2, Table 2) in order to study the scope of the reaction with different coumarin derivatives. We proceeded to evaluate the scope of the perfluorobutylation reaction of coumarins **1–5** employing NaSO₂C₄F₉ under TBHP reaction conditions, according to Table 3. When 7-hydroxy-4-methylcoumarin **1** was subjected to the reaction conditions above (entries 1,2, Table 3), a quantitative yield of 3-perfluorobutyl-7-hydroxy-4-methyl coumarin **6** was obtained.

When the electron rich 5,7-dimethoxy-4-methyl-2H-chromen-2-one (i.e.: 4-methyl-5,7-dimethoxy coumarin) **2** was employed as substrate, the radical reaction initiated with TBHP/NaSO₂C₄F₉ produced 67% yield of perfluorobutyl substitution product **7** in a mixture of MeCN: CH₂Cl₂ (1: 1) as organic media and Cu(OAc)₂ as additive (entry 3, Table 3). We also tried the Langlois reagent (NaSO₂CF₃) under TBHP radical initiation methodology employing substrate **2** with and without Cu(OAc)₂ as additive in MeCN: CH₂Cl₂ as solvent mixture, obtaining the 3-trifluoromethyl-substituted coumarin **8** in 26% isolated yield in the absence of Cu(OAc)₂ as additive (entry 4, Table 3), and a mixture of coumarins **8** and **9** (25% combined yield, **8**: **9** in a 4:1 ratio) in the presence of Cu(OAc)₂ as additive (entry 5, Table 3).

The reaction of 7-methoxy-2H-chromen-2-one (i.e.: 7-methoxy-coumarin) **3**, and 1,1'-(4-methyl-2-oxo-2H-chromene-6,7-diyl)diethanone (i.e.: 6,7-diacetoxy-4-methyl coumarin) **4**, under TBHP- radical initiation conditions with NaSO₂C₄F₉ as

Table 2

Optimization of reaction conditions (24 h. or otherwise noted) for the fluoroalkylation of coumarin **1** (0.2 mmol) under thermal initiation with an R_F source (3 equiv.) and additive (1 equiv. or otherwise noted) under Ar atmosphere in a given solvent system (3 mL).

Entry	Solvent system	R _F source	Conditions/initiator	Additive	Conversion substrate (%)	Product Yield (%) ^a
1	MeCN:CH₂Cl₂ 1:1	NaSO₂C₄F₉	TBHP^b, 0–5 °C	CuSO₄^e	90	90
2	MeCN:CH₂Cl₂ 1:1	NaSO₂C₄F₉	TBHP^b, 0–5 °C	Cu(OAc)₂^e	99	99
3	1,4-Dioxane	<i>n</i> -C ₄ F ₉ I	100 °C	Cs ₂ CO ₃	–	–
4	MeCN: 1,4-dioxane	<i>n</i> -C ₄ F ₉ I	100 °C	Cs ₂ CO ₃	–	–
5	1,4-Dioxane	<i>n</i> -C ₄ F ₉ I	100 °C	Cs ₂ CO ₃ Cu(OAc) ₂ ,	–	–
6	H ₂ O	NaSO ₂ C ₄ F ₉	TBHP ^b , 0–5 °C	–	–	–
7	H ₂ O:CH ₂ Cl ₂ 1:1	NaSO ₂ C ₄ F ₉	TBHP ^b , 0–5 °C	–	100	– ^c
8	MeCN	NaSO ₂ C ₄ F ₉	TBHP ^b , 0–5 °C	–	50	15
9	MeCN:CH ₂ Cl ₂ 1:1	NaSO ₂ C ₄ F ₉	TBHP ^b , 0–5 °C	–	30	30 ^d
10	H ₂ O:CH ₂ Cl ₂ 1:1	NaSO ₂ C ₄ F ₉	TBHP ^b , 0–5 °C	Cu(OAc) ₂ ^e	50	35

Bold values refer to optimized yields; reaction conditions that will be employed hereafter.

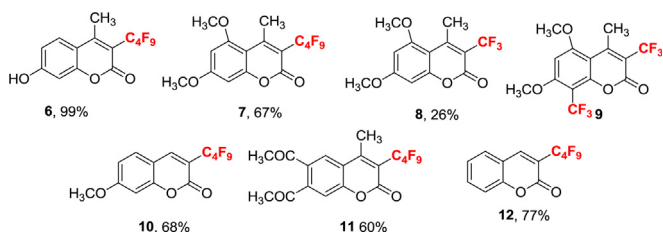
^a Isolated yield.

^b TBHP = tert-butyl hydroperoxide, 5 equiv.

^c Ratio C3:C5C₄F₉-substitution = 3:1.

^d In the presence of air.

^e 4 equiv. of additive.

Table 3Reactions of coumarins **1–5** (0.2 mmol) with NaSO₂C₄F₉ (3 equiv.)/TBHP(5 equiv.) and additive (4 equiv.) in Ar-deoxygenated MeCN/CH₂Cl₂ (1:1) as solvent mixture.

Entry	Coumarin	R _f source	Additive	Substrate conversion(%)	Product yield, (%) ^a
1	1	NaSO ₂ C ₄ F ₉	CuSO ₄	90	6 , 90
2	1	NaSO ₂ C ₄ F ₉	Cu(OAc) ₂	99	6 , 99
3	2	NaSO ₂ C ₄ F ₉	Cu(OAc) ₂	67	7 , 67
4	2	NaSO ₂ CF ₃	–	30	8 , 26
5	2	NaSO ₂ CF ₃	Cu(OAc) ₂	30	8 , 9 (4:1) 25
6	3	NaSO ₂ C ₄ F ₉	Cu(OAc) ₂	75	10 , 68
7	4	NaSO ₂ C ₄ F ₉	Cu(OAc) ₂	75	11 , 60 ^b
8	5	NaSO ₂ C ₄ F ₉	Cu(OAc) ₂	88	12 , 77

Bold values refer to optimized yields; reaction conditions that will be employed hereafter.

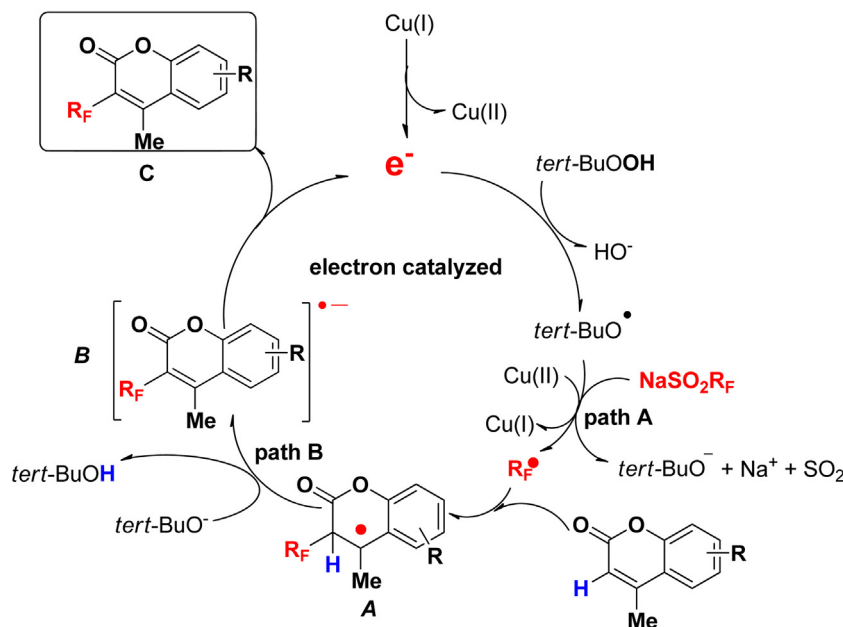
^a Isolated yield.^b Ratio C3:C5C₄F₉-substitution = 4:1.

radical source afford 68 and 60% yields of substitution products **10** [22] and **11**, respectively (entries 6,7, Table 3). 2H-chromen-one (i.e.: coumarin) **5** affords 67% yield of 3-perfluorobutyl 2H-chromen-one **12** (entry 8, Table 3).

The thermal reaction (NaSO₂C₄F₉/TBHP/Cu(OAc)₂) proceeds by an electron-catalyzed mechanism [23a] in which TBHP is able to carry on the radical chain with many substrates (i.e.: **1**). The addition of Cu(OAc)₂ improves the radical chain process, as observed from entry 2, Table 2, probably through Cu(II)-mediated oxidation of NaSO₂R_F. An experiment was conducted with TEMPO

as radical scavenger in order to probe for the presence of radicals. When the reaction under thermal conditions was carried out in the presence of TEMPO (1 equiv.) and coumarin **1**, the yield of substituted coumarin was 10%. Another experiment was conducted in the presence of 1,4-dinitrobenzene, a known radical anion scavenger under reaction conditions of Table 3 [23b]. Under these reaction conditions, a very reduced yield of coumarin **6** was found. This result is supportive of the presence of radical anion intermediates.

The proposed reaction mechanism is shown in Scheme 2 below.

**Scheme 2.** Proposed reaction mechanism for the TBHP-initiated 3-perfluoroalkylation of coumarins.

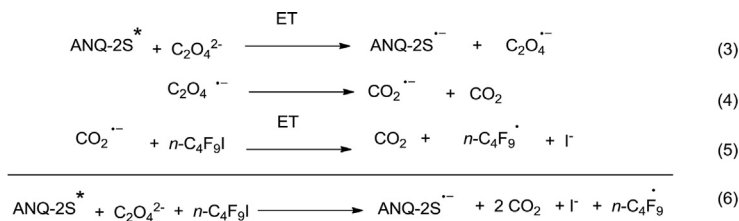
The initiation entails an electron injection from traces of Cu(I), which in turn induce decomposition of *tert*-BuOOH into *tert*-BuO[•] radicals (Scheme 2). R_F radicals are produced by ET reaction from NaSO₂R_F and *tert*-BuO[•] radicals (path A), generating *tert*-butoxide anion as well. R_F radicals add to the coumarin forming intermediate A, which can suffer re-aromatization by proton loss with *tert*-butoxide anion (path B), affording the radical anion of the substitution product B. Radical anion B transfers an electron into the electron-catalyzed cycle, affording the thermoneutral substituted product C. The proton abstraction is made from the benzylic-type radical intermediate A (Scheme 2), as proposed by Studer and co-workers [23a] (see Scheme S1 & S2, in Supporting information) for the re-aromatization process of the radical intermediate. Deprotonation of radical intermediate A leads to a radical anion species. This process is termed PT-ET sequence (Proton Transfer-Electron Transfer sequence), and a thorough explanation is given in Section II.D., SI.

We observed that for the electron rich 5,7-dimethoxy-coumarin derivative 2, the reaction gives the perfluoroalkyl-substituted product in fairly good yields upon addition of Cu(OAc)₂ (Table 3, entry 3), whereas in the absence of Cu(OAc)₂, no product is formed (not shown).

Interestingly, Zou and co-workers postulated a Wheland intermediate in the Mn(III)-mediated trifluoromethylation reaction of coumarins with NaSO₂CF₃ in glacial acetic acid as solvent [24]. Being our reaction medium strongly basic (i.e.: *tert*-butoxide anion), it is considered more likely that intermediate A underwent deprotonation [23a] to afford a radical anion intermediate such as B rather than an ET event to afford a Wheland intermediate as

Regarding the mechanism involving the photocatalyst, the ground and excited redox states of anthraquinone-2-sulfonic acid, AQN-2S, an electron transfer mediator, are relevant for the formation of the electron poor perfluorobutyl radical (C₄F₉•), which functions as an oxidant of the substrate and an active species for the formation of perfluorobutylated coumarins. The photoinduced downhill electron transfer from C₄F₉SO₂⁻ to the excited state of AQN-2S (AQN-2S*, E_{LUMO} – E_{HOMO} = 2.33 eV [17,25]) is expected to efficiently generate C₄F₉• and AQN-2S^{•-} radical anions on the basis of their redox potentials (E_{AQN-2S/AQN-2S^{•-}} = –883 mV). The calculated ΔG_{ET} from the Rehm Weller equation [26,27], is < –0.84 V (ΔG_{ET} < –0.84 V > E_{C₄F₉SO₂⁻/C₄F₉SO₂^{•-}} – E_{AQN-2S*/AQN-2S^{•-}} – E_{o,o} + 0.06). However, no product is obtained under these reaction conditions (entries 1,2, Table 1, see also Fig. 1).

Photocatalysis, however, is achieved employing the additive or co-reactant potassium oxalate. The co-reactant C₂O₄²⁻ employed in reaction conditions depicted in entries 11–13, Table 1, (E_{ox} = 0.21 V vs SCE, MeCN) undergoes a one-electron oxidation event induced by the excited photocatalyst (E_{AQN-2S*/AQN-2S^{•-}} > 1.5 V), provoking the fast homolytic cleavage of the C–C bond in oxalate, yielding the radical anion of CO₂^{•-}, and thermoneutral CO₂ [21]. This latter process has a favorable Gibbs energy for the ET [27] (ΔG_{ET} < –1.29 V > E_{C₂O₄²⁻/C₂O₄^{•-}} – E_{AQN-2S*/AQN-2S^{•-}} + E_{o/o} + 0.06 eV). In turn, CO₂^{•-} has a very large negative oxidation potential itself [28] (E_{ox} = –2.20 V vs SCE) capable of reducing *n*-C₄F₉I to C₄F₉• radicals and iodide anion, rendering thermoneutral CO₂. This other one-electron reduction process is also exergonic (ΔG_{ET} = –0.99 V = E_{CO₂^{•-}/CO₂} – E_{C₄F₉I/C₄F₉•}). These redox processes are depicted in Fig. 2.



proposed in glacial acetic acid as solvent [24]. From Table 2, entries 6,7, it is observed that in proton-solvents, the substitution yields drop significantly, or no reaction is observed, in agreement with an intermediate with electronic characteristics such as B.

According to entry 12, Table 1, C₄F₉• radicals could also be generated in the absence of C₂O₄²⁻, albeit in lower yields (11% of product is accumulated). Generation of C₄F₉ radicals can be accounted for either from the direct reduction by CO₂^{•-}, or by the

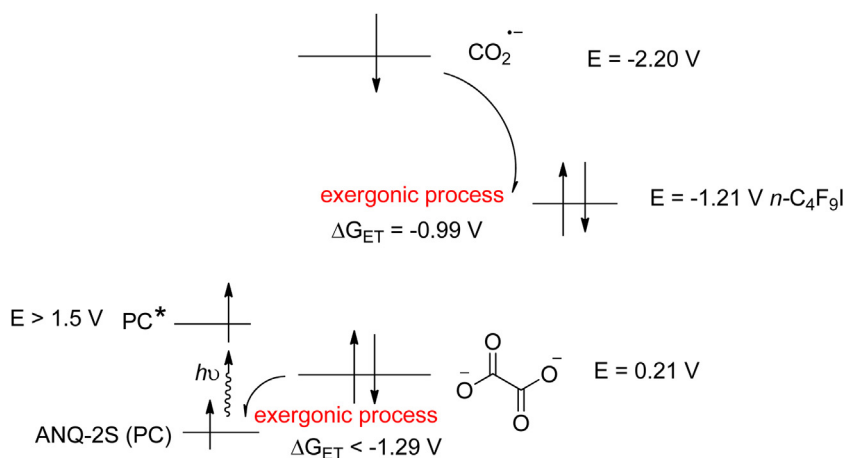
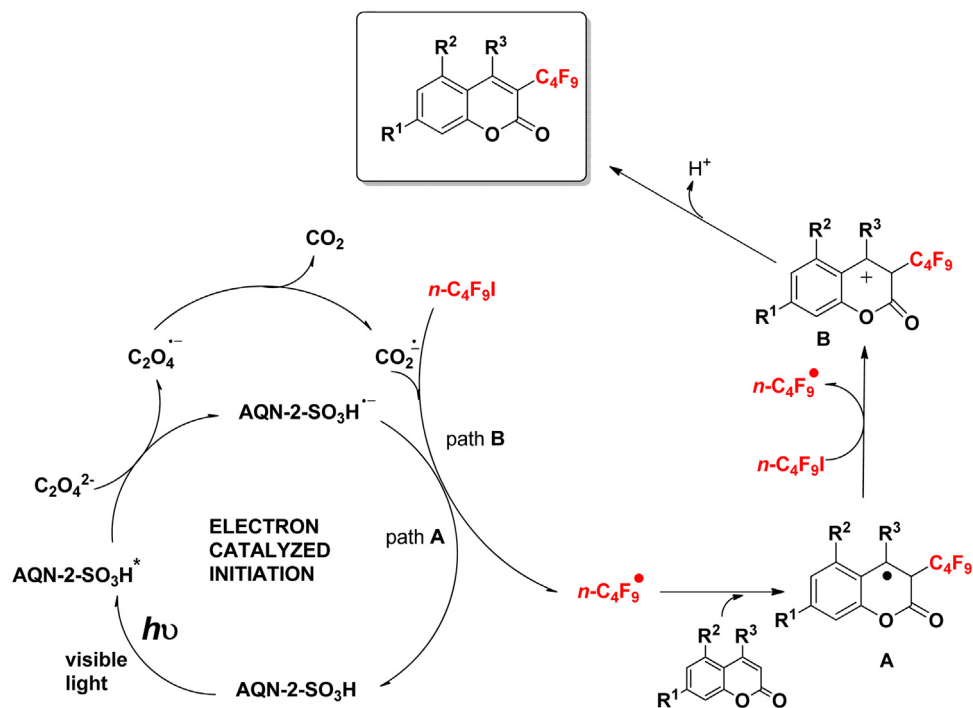
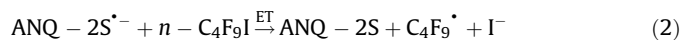
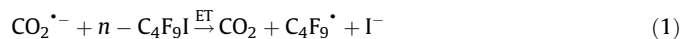


Fig. 2. ET from C₂O₄²⁻ to excited ANQ-2S* generating the highly reductant CO₂^{•-} radical anion capable of reducing *n*-C₄F₉I to C₄F₉ radicals.



Scheme 3. Proposed reaction mechanism for the photocatalyzed perfluorobutylation of coumarin derivatives with *n*-C₄F₉I.

radical anion of ANQ-2S^{•-}. This scenario introduces the possibility that processes illustrated in Eqs. (1) & (2) may be operating simultaneously:



The proposed mechanism is described in Scheme 3 below.

Irradiation of photocatalyst ANQ-2S by visible light leads to the triplet excited manifold of ANQ-2S*, which readily accepts an electron from ground state C₂O₄²⁻ to generate the radical anion of the photocatalyst (i.e.: ANQ-2S^{•-}) and the radical anion of oxalate (*vide supra*, Fig. 2). The radical anion of the photocatalyst ($E_{\text{ANQ-2S}^{\bullet-}/\text{ANQ-2S}} = -0.883\text{ V}$) ANQ-2S^{•-} is capable of donating an electron to *n*-C₄F₉I to generate C₄F₉[•] radicals, according to path A, Scheme 3. However, the calculated Gibbs parameter of the ET from the radical anion of ANQ-2S^{•-} to *n*-C₄F₉I is almost endergonic ($\Delta G_{\text{ET}} = 0.327\text{ V}$). In turn, the radical anion of oxalate, i.e.: C₂O₄^{•-}, however, readily undergoes dissociation into CO₂^{•-} radical anion and thermoneutral CO₂-CO₂^{•-} radical anion also acts as a potent reductant to *n*-C₄F₉I to generate C₄F₉[•] radicals, according to path B, Scheme 3. This process is calculated to be highly exergonic (the one-electron reduction of *n*-C₄F₉I by CO₂^{•-}) with a value of $\Delta G_{\text{ET}} = -0.99\text{ V} = \text{CO}_2^{\bullet-}/\text{CO}_2 - E_{\text{C}_4\text{F}_9\text{I}/\text{C}_4\text{F}_9^{\bullet}}$. C₄F₉[•] radicals, in turn, substitute the 3- position of the coumarin derivative to yield intermediate A (Scheme 3), which is oxidized by R₁I to intermediate B, which ultimately suffers deprotonation and yields the substitution product.

Interestingly, oxalate is acting as a two-electron reductant in the overall process, according to the ET sequence shown in Eqs. (3)–(6) below:

We postulate a Wheland intermediate such as B (Scheme 3) unlike intermediate B (Scheme 2) due to the absence of base under

these reaction conditions, and the likely oxidation of adduct A (Scheme 3) by *n*-C₄F₉I.

3. Conclusions

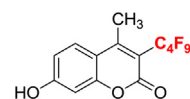
Although the thermal radical initiation methodology renders higher yields of C₄F₉-substituted products derived from coumarins than the photocatalyzed process, a study is underway to attempt the photocatalysis with other visible-light photoorganocatalysts, towards a more benign method, circumventing the use of chemical radical initiators. Although there have been some reported methods for the direct or late-stage perfluorobutylation of coumarins, the herein reported strategies should be considered higher yielding and milder methods, and the chemical initiation protocol using *tert*-butylhydroperoxide the synthetic choice to achieve such substitutions.

4. Experimental section

For general synthetic procedures, purification protocols, and characterizations and methods, please refer to Supporting information.

4.1. Characterization of compounds

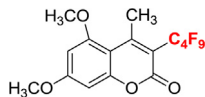
7-Hydroxy-4-methyl-3-(perfluorobutyl)-2H-chromen-2-one, **6**, 99%, 35 mg



¹H NMR (DMSO, δ_H: ppm): 11.13 (1H, s), 7.89 (1H, d, *J* = 8.95 Hz), 6.88 (1H, dd, *J* = 8.92 Hz, *J* = 1.60 Hz), 6.73 (1H, d, *J* = 1.6 Hz), 2.58 (3H, s). ¹³C NMR (DMSO, δ_C: ppm): 163.6, 159.3, 155.9, 154.8, 128.9, 114.0, 111.2, 101.7, 16.2. ¹⁹F-NMR (DMSO, δ_F: ppm): -80.4, -101.9,

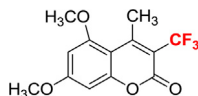
–121.1, –125.8. **HRMS**: mass calculated for $C_{14}H_7F_9O_3$: 394.02515. Mass found: 394.0265.

5,7-Dimethoxy-4-methyl-3-(perfluorobutyl)-2H-chromen-2-one, **7**, 67% yield, 88 mg. Eluant: Hexane:CH₂Cl₂ 1:2



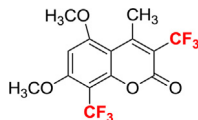
¹H-NMR (CDCl₃, δ_H: ppm): 6.42 (1H, d, *J* = 2.4 Hz), 6.33 (1H, d, *J* = 2.4 Hz), 3.89 (3H, s), 3.87 (3H, s), 2.71 (3H, t, *J* = 2.5 Hz). **¹³C-NMR** (CDCl₃, δ_C: ppm): 154.6, 161.0, 160.5, 156.7, 156.2, 104.9, 96.3, 93.0, 56.0, 55.9, 21.0, **C-C₄F₉** unobserved. **¹⁹F-NMR** (CDCl₃, δ_F: ppm): –80.8, –101.3, –120.7, –126.1. **HRMS**: mass calculated for $C_{16}H_{11}F_9O_4$: 438.05136. Mass found: 438.0521.

5,7-Dimethoxy-4-methyl-3-(trifluoromethyl)-2H-chromen-2-one, **8**, 26% yield, 15 mg. Eluant system: Hexane:CH₂Cl₂ 1:2



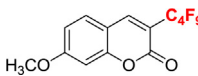
¹H-NMR (CDCl₃, δ_H: ppm): 6.42 (1H, d, *J* = 2.4 Hz), 6.32 (1H, d, *J* = 2.4 Hz), 3.90 (3H, s), 3.87 (3H, s), 2.73 (3H, q, *J* = 2.1 Hz). **¹³C-NMR** (CDCl₃, δ_C: ppm): 164.4, 160.4, 158.9, 156.6, 155.9, 104.5, 96.3, 93.0, 56.1, 55.9, 20.4, **C-C₄F₉** unobserved. **¹⁹F-NMR** (CDCl₃, δ_F: ppm): –55.3. **HRMS**: mass calculated for $C_{13}H_{11}F_3O_4$: 288.0609. Mass found: 288.0611.

5,7-Dimethoxy-4-methyl-3,8-bis(trifluoromethyl)-2H-chromen-2-one, **9**, 25% yield, 18 mg. Eluant system: Hexane:CH₂Cl₂ 1:2.



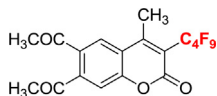
¹H-NMR (CDCl₃, δ_H: ppm): 6.40 (1H, s), 4.05 (3H, s), 4.01 (3H, s), 2.75 (3H, q, *J* = 2.1 Hz). **¹³C-NMR** (CDCl₃, δ_C: ppm): 162.5, 160.5, 157.8, 156.0, 153.9, 104.2, 93.0, 91.6, 56.5, 56.2, 20.77, **C-C₄F₉** unobserved. **¹⁹F-NMR** (CDCl₃, δ_F: ppm): –54.6, –55.7. **HRMS**: mass calculated for $C_{14}H_{10}F_6O_4$: 356.04833. Mass found: 356.0483.

7-Methoxy-3-(perfluorobutyl)-2H-chromen-2-one, **10**, 68% yield, 53 mg. Eluant system: Hexane:AcOEt 2:1.



¹H-NMR (CDCl₃, δ_H: ppm): 8.07 (1H, s), 7.53 (1H, d, *J* = 8.7 Hz), 6.95 (1H, dd, *J* = 8.7 Hz, *J* = 2.4 Hz), 6.87 (1H, d, *J* = 2.4 Hz), 3.94 (3H, s). **¹³C-NMR** (CDCl₃, δ_C: ppm): 165.3, 157.2, 155.8, 146.3, 130.6, 113.9, 110.7, 100.5, 56.1, **C-C₄F₉** unobserved. **¹⁹F-NMR** (CDCl₃, δ_F: ppm): –80.8, –110.9, –121.7, –125.8. **HRMS**: mass calculated for $C_{14}H_7F_9O_3$: 394.0251. Mass found: 394.0255.

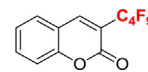
1,1'-(2-oxo-3-(perfluorobutyl)-2H-chromene-6,7-diyl)diethanone, **11**, 60% yield, 55 mg. Eluant system: Hexane:AcOEt 1:1.



¹H-NMR (CDCl₃, δ_H: ppm): 7.66 (1H, s), 7.30 (1H, s), 2.64 (3H, s), 2.37 (6H, s). **¹³C-NMR** (CDCl₃, δ_C: ppm): 168.1, 167.2, 156.5, 155.2, 151.0, 146.7, 139.1, 120.3, 117.3, 112.2, 20.6, 20.5, 16.8, **C-C₄F₉**

unobserved. **¹⁹F-NMR** (CDCl₃, δ_F: ppm): –80.8, –103.4, –121.2, –126.0. **HRMS**: mass calculated for $C_{18}H_{11}F_9O_4$: 462.0513. Mass found: 462.0522.

3-(Perfluorobutyl)-2H-chromen-2-one, **12**, 77% yield, 56 mg. Eluant system: Hexane:AcOEt 2:1.



¹H-NMR (DMSO-*d*₆, δ_H: ppm): 8.84 (1H, s), 7.96 (1H, d, *J* = 7.4 Hz), 7.81 (1H, t, *J* = 7.4), 7.51 (1H, d, *J* = 8.22), 7.47 (1H, t, *J* = 7.2, 6.8). **¹³C-NMR** (CDCl₃, δ_C: ppm): 160.8, 154.1, 143.4, 131.8, 127.9, 124.4, 118.8, 116.9, **C-C₄F₉** unobserved. **¹⁹F-NMR** (DMSO-*d*₆, δ_F: ppm): –80.4, –110.2, –121.4, –125.6. **HRMS**: mass calculated for $C_{13}H_5F_9O_2$: 364.1632. Mass found: 364.1628.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jfluchem.2017.03.005>.

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