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COMMUNICATION

CF_2-Containing acetylenephosphonates in heterocyclization reactions: the first synthesis of 2-difluoromethyl azaxanth-3-ylphosphonates†

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Acetylenephosphonates carrying the XCF_2 group have been studied in a base-mediated heterocyclization reaction with selected 2-amino-3-formylchromones to give 2-difluoromethyl azaxanth-3-ylphosphonates. The presence of the fluorinated substituent determined the regioselectivity as well as the reactivity of this process.

Pyridine-containing compounds have been discovered in many naturally occurring molecules as well as being an important scaffold for the design of pharmacologically active substances.[1] Despite the significance of such molecules in the pharmaceutical industry, the introduction of a fluorinated group or a phosphonate motif does remarkably alter their physical, chemical and biological properties.[2] In particular, mefloquine **A** has proven to be a valuable drug against malaria (Fig. 1),[3] whereas compound **B** controls weeds and inhibits plant growth (Fig. 1).[4] In contrast to the fluorinated examples, pyridine derivatives **C** and **D** possessing a phosphonate group, have been recognised as monoamine oxidase-B inhibitors in the treatment of hypertension and have also demonstrated the ability to reverse drug resistance in the multidrug-resistant human carcinoma cell line KB-C2, respectively (Fig. 1).[5] Furthermore, pyridine rings fused with a chromone fragment, namely azaxanthones, are, for instance anti-inflammatory (in the case of **E**), anti-allergic (**F**), anticancer and antitumor agents (**G**) (Fig. 1).[6] Particularly, the tricyclic aminocyanopyridine **E** a mitogen-activated protein kinase-2 (MAPKAP kinase-2) inhibitor prevents autoimmune diseases,[6a,b] and amlexanox **F** is used for cell differentiation, neurogenesis and tumor growth.[6c–g] However, the azapyranoxanthenone amino derivative **G** exhibits cytostatic effects by blocking the entry of the cells in the S-phase.[6h]

Only a few examples of fluorinated azaxanthones have hitherto been mentioned in the literature,[7] while no reports have been published involving a phosphonic group. Therefore a method to tailor biologically active derivatives is to incorporate phosphonate (hydrophilic)[8] moieties along with CF_2-containing (lipophilic)[9] groups. Unlike a phosphate group, a phosphonate linkage is not readily hydrolysed in a biological environment, and this unique property has made these compounds attractive as phosphate analogues in numerous applications.[8,10] Thus, the development of new synthetic methods for azaxanthones modified with both phosphonate and CF_2-containing groups is definitely an important task.

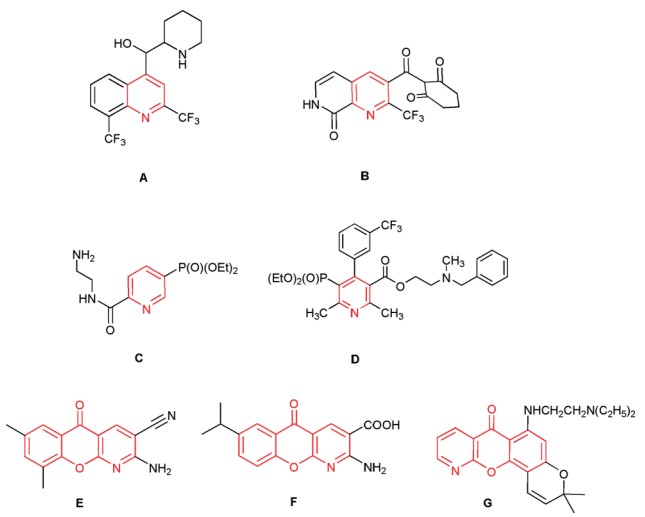

Fig. 1 Pyridine and azaxanthone frameworks in pharmacologically active substances.

The syntheses of azaxanthones have been predominantly carried out *via* condensation (*e.g.* Friedländer-type reaction) utilizing activated methylene compounds reacting with 4-oxo-4*H*-benzopyran-3-carbonitrile or its amino aldehyde precursor.[11] In this case functionalisation of the target product is very limited due to the need for an enolisable substrate. To the best of our knowledge only a few examples using unsaturated compounds to synthesise such azaxanthones have hitherto been reported in the literature.[12] Hence, herein we wish to communicate the application of unsymmetrically substituted electron-poor XCF_2- and phosphonyl-containing alkynes in heterocyclization reaction with 2-amino-3-formylchromones to regioselectively form 2-difluoromethyl azaxanth-3-ylphosphonates.

The reaction of 2-amino-3-formylchromone derivatives **1a–c** with a series of unsymmetrical alkynes **2a–e** regioselectively led to CF_2-containing azaxanth-3-ylphosphonates **3a–o** in good to excellent yields (51–94%). Table 2 summarises all accomplished results. The heterocyclization process carried out in dry DMSO at ambient temperature proceeded well in the presence

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† Electronic supplementary information (ESI) available: Experimental details and copies of ^1H, ^{13}C, ^{19}F, ^{31}P NMR and MS (HRMS) spectra of new compounds. See DOI: 10.1039/c1ob06379k

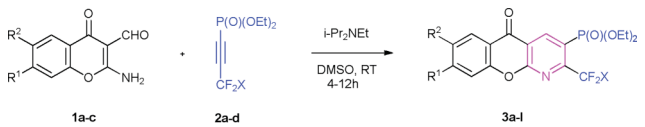
Table 1 XCF_2–C≡C–P(O)$(OEt)_2$ **2a–e** in the reaction with 2-amino-3-formylchromone **1a** in dry DMSO: screening of different bases

Entry	X	Product	Base				
			DBU	DABCO	K_2CO_3	*i*-Pr_2NEt	NEt_3
1	F	**3a**	95[a] (20[b])	93 (32)	92 (36)	99 (94)	45 (15)
2	Cl	**3d**	93 (22)	92 (25)	90 (27)	89 (84)	40 (10)
3	Br	**3m**	91 (16)	90 (20)	90 (19)	82 (10)	36 (8)
4	H	**3g**	85 (14)	81 (15)	88 (13)	75 (51)	30 (~5)
5	CF_3	**3j**	90 (18)	84 (16)	89 (20)	86 (77)	38 (12)

[a] Conversion of the substrate in % was established by ^{19}F and ^{31}P NMR after 10 h at RT; [b] Isolated yield in %.

of a base. The conversion of acetylenes **2a–e** was monitored by ^{19}F and ^{31}P NMR spectroscopy and appropriate products were purified by flash column chromatography. The cyclisation performed in the absence of a base led to the target products only in traces according to NMR data; hence different basic catalysts (mediators), for instance diazabicycloundecene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), K_2CO_3, *i*-Pr_2NEt and NEt_3 were examined (Table 1).

The use of stronger bases, such as K_2CO_3, DBU and DABCO in dry DMSO resulted in an almost excellent conversion of the appropriate acetylene within a few hours. However, monitoring the reaction showed the presence of many by-products due to the decomposition of **2a–e**. On the other hand, NEt_3 mediated such a heterocyclization insufficiently and even after 24 h the conversion of substrates did not reach 50%, resulting in very low yield. Interestingly, taking *i*-Pr_2NEt as a mediator in dry DMSO (assigned as **Method A**) we optimised the reaction conditions, furnishing the azaxanthyl ring in moderate to excellent yields (Scheme 1, Table 2).



R^{1-2} = H, CH_3, Cl; X = F (**2a**), Cl (**2b**), H (**2c**), CF_3 (**2d**)

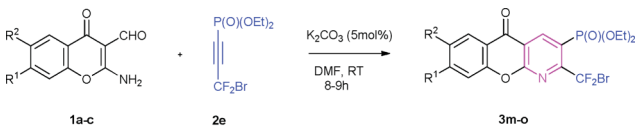
Scheme 1 The reaction of 2-amino-3-formylchromones **1a–c** with CF_2X-containing acetylenephosphonates **2a–d**.

Subsequently numerous solvents such as tetrahydrofuran (THF), dichloromethane (DCM), dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO) were investigated, as presented in Table 3. We found that the more polar the solvent, the better were the results (Table 3). DMSO was indeed a well-suited solvent for this heterocyclization reaction (75–99%). Dichloromethane, as a weak solvating agent gave very low conversion of substrates (25–50%), whereas the more polar DMF provided the target product with slightly lesser yields (55–90%) compared with those achieved using DMSO; and in THF no azaxanthyl ring was formed at all.

It should be noted that the reaction of an acetylenephosphonate possessing a -CF_2Br group **2e** with **1a** according to **Method A**, provided **3m** as a sole product with very good conversion (82%) (Entry 3, Table 3).

However, the isolation process required extraction with water and afforded the target product in only 10% yield. This phenomenon can be explained by the fact that **3m** underwent possible hydrolysis in the presence of an excess amount of water.[13]

The optimum reaction conditions, which were found to give **3m** in moderately good yield, were taking K_2CO_3 as a catalyst (5 mol%) in dry DMF at ambient temperature (assigned as **Method B**, Scheme 2). The removal of the solvent under reduced pressure without heating and an isolation process in the absence of water provided diethyl (2-(bromodifluoromethyl)-5-oxo-5*H*-chromeno-[2,3-*b*]-pyridin-3-yl)phosphonate **3m** in 62% isolated yield (Entry 13, Table 2).



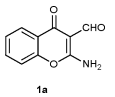
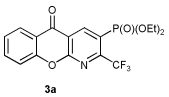
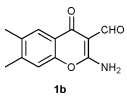
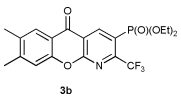
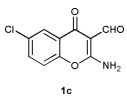
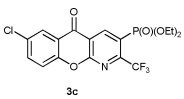
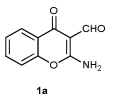
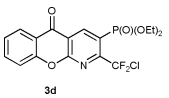
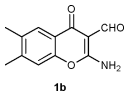
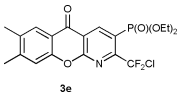
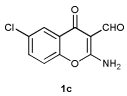
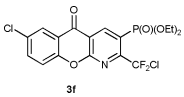
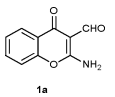
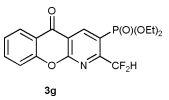
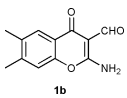
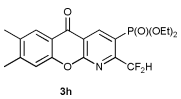
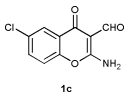
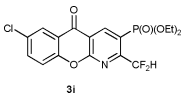
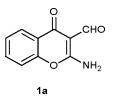
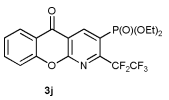
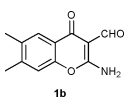
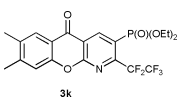
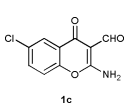
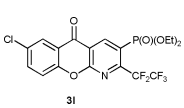
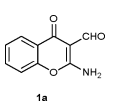
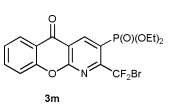
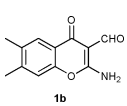
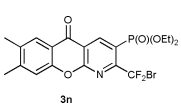
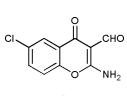
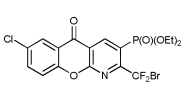
R^{1-2} = H, CH_3, Cl

Scheme 2 The synthesis of CF_2Br-containing azaxanth-3-ylphosphonates **3m–o**.

Next we studied the effect of substituents in various CF_2-containing acetylenephosphonates **2a–e** as well as in 2-amino-3-formylchromones **1a–c**. In addition, one of the advantages of this synthetic route is that substituents, such as -Me **1b** and -Cl **1c** on the aryl ring were well tolerated and therefore did not affect the heterocyclization. On the other hand, fluorinated groups in alkynes **2a–e** were found to influence the reaction either electronically or sterically. The acetylene **2a** bearing a CF_3 group directly attached to the triple bond was revealed to be superior and gave **3a** with almost quantitative conversion and consequently excellent yields (Entry 1, Table 3 and Entries 1–3, Table 2). It is worth noting that the less electron-withdrawing the fluorinated group is, for instance -CF_2Cl **2b** and -CF_2Br **2e**, the lower the reactivity that is observed in the heterocyclization reaction, furnishing the respective products with reduced yields as compared to the -CF_3 group **2a** (Entries 2–3, Table 3; Entries 4–6 and 13–15, Table 2). Moreover a CF_2H **2c**, as the weakest EWG group in this series, provided the corresponding products in only 49–51% isolated yields (Entries 7–9, Table 2). The F_5C_2-group **2d** with comparable electronic properties to CF_3, was found to affect such a process rather sterically than electronically. As a result, the azaxanth-3-ylphosphonate **3j** bearing a pentafluoroethyl group was obtained in 77% yields (Entry 10, Table 2; Entry 5, Table 3). These findings are in agreement with other cyclisation reactions of perfluorinated alkynes (*e.g.* 1,3-dipolar cycloaddition, Diels–Alder reaction).[14,15]

Below we describe a plausible mechanism for the formation of the azaxanthyl ring. Scheme 3 illustrates that the base-activated 2-amino-3-formylchromone **4** regioselectively reacts *via*

Table 2 XCF_2-containing azaxanth-3-ylphosphonates **3a–o**

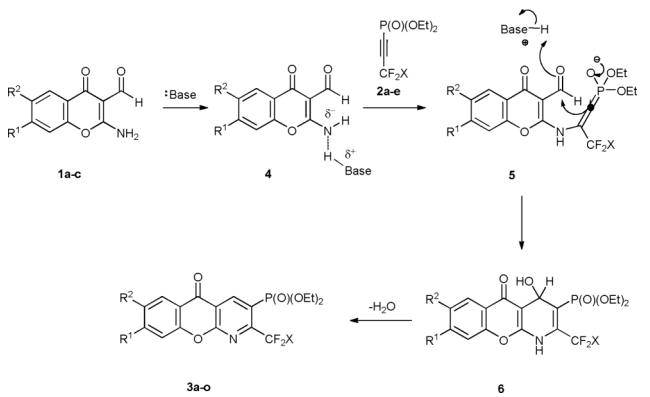
Entry	Substrate	X	Product	Time (h)	Yield[c] (%)
1[a]	 **1a**	F	 **3a**	4	94
2[a]	 **1b**	F	 **3b**	4	93
3[a]	 **1c**	F	 **3c**	4	94
4[a]	 **1a**	Cl	 **3d**	6	84
5[a]	 **1b**	Cl	 **3e**	7	84
6[a]	 **1c**	Cl	 **3f**	6	85
7[a]	 **1a**	H	 **3g**	11	51
8[a]	 **1b**	H	 **3h**	12	49
9[a]	 **1c**	H	 **3i**	12	51
10[a]	 **1a**	CF_3	 **3j**	7	77
11[a]	 **1b**	CF_3	 **3k**	7	76
12[a]	 **1c**	CF_3	 **3l**	8	78
13[b]	 **1a**	Br	 **3m**	8	62
14[b]	 **1b**	Br	 **3n**	8	62
15[b]	 **1c**	Br	 **3o**	8	63

[a] According to **Method A**; [b] According to **Method B**; [c] Isolated yield.

Table 3 Screening of various different solvents in the reaction of a series of acetylenes XCF_2–C≡C–P(O)$(OEt)_2$ **2a–e** with 2-amino-3-formylchromone **1a**

			Convn[a] (%)		
Entry	X	Product	DCM	DMF	DMSO
1	F	**3a**	50	90	99
2	Cl	**3d**	45	80	89
3	Br	**3m**	40	63	82
4	H	**3g**	25	55	75
5	CF_3	**3j**	39	64	86

[a] The reaction was performed in a dry solvent at ambient temperature in the presence of *i*-Pr_2NEt and checked by ^{19}F and ^{31}P NMR spectra after 10 h.



Scheme 3 A plausible mechanism for the formation of CF_2-containing azaxanth-3-ylphosphonates **3a–o**.

a Michael-type addition with the more electrophilic carbon of the acetylenephosphonate's triple bond containing -CF_2X group. Accordingly, a dipolar allene[14] **5** is formed which intramolecularly cyclises into the dihydropyridine derivative **6** and after the dehydration process leads to CF_2-containing azaxanth-3-ylphosphonates **3a–o**. The use of the polar solvent (DMSO) plays a crucial role due to possible interactions and stabilisation of the intermediate **5** formed during this process.[16]

The structures of 2-difluoromethyl azaxanth-3-ylphosphonates **3a–o** were well established by ^1H, ^{13}C, ^{19}F and ^{31}P NMR spectroscopy and mass spectrometry (ESI). In the ^1H NMR a characteristic doublet at around δ 9.5 ppm with the coupling constant $^3J_{H-P} \approx 14$ Hz was assigned to a proton at the 4-position. Moreover the two fluorine nuclei of the CF_2H- group split the proton into a triplet at δ 7.4 ppm with $^2J_{H-F} \approx 53$ Hz. In the ^{13}C NMR spectra a quartet of doublets *C*(*2*)-CF_3 at around δ 152 ppm with $^2J_{C-F} \approx 37$ and $^2J_{C-P} \approx 11$ Hz for molecules **3a–c** was observed and a triplet of doublet *C*(*2*)-CF_2X ($^2J_{C-F} \approx 33$ Hz, $^2J_{C-P} \approx 10$ Hz) for compounds **3d–o**. The *C*(*3*)-P(O)$(OEt)_2$ and *C*(*4*)-H carbon nuclei of **3a–o** were detected as doublets at around δ 121 ppm with $^1J_{C-P} \approx 190$ Hz and at δ 117 ppm with $^2J_{C-P} \approx 12$ Hz, respectively.

In conclusion, we have reported a regioselective and efficient synthetic approach to afford XCF_2-containing azaxanth-3-ylphosphonates *via* a simple cyclisation reaction of 2-amino-3-formylchromones with XCF_2-substituted acetylenephosphonates. The use of the *i*-PrNEt–DMSO system gave the best results in this heterocyclization in the case of X = F, Cl, H and CF_3; while for X = Br only K_2CO_3–DMF showed the optimal results. Factors that influenced the reaction progress were also discussed. Finally, the novel series of azaxanthones will likely show potential biological activity.

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