EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402692

Revisiting the Synthesis of 4,6-Difluorobenzofuroxan: A Study of Its Reactivity and Access to Fluorinated Quinoxaline Oxides

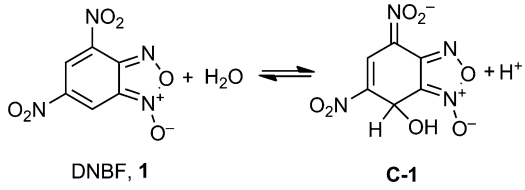
Cyril Jovené,[a] Morgane Jacquet,[a] Jérome Marrot,[a] Flavien Bourdreux,[a] Mikhail E. Kletsky,[b] Oleg N. Burov,[b] Anne-Marie Gonçalves,[a] and Régis Goumont*[a]

Keywords: Synthetic methods / Nucleophilic substitution / Nitrogen heterocycles / Fluorine / Drug discovery

New quinoxaline 1,4-dioxide derivatives have been synthesized from novel fluorinated benzofuroxans such as 4-fluorobenzofuroxan, which is prepared for the first time. Furthermore, the preparation 4,6-difluorobenzofuroxan has been revisited because we were unable to reproduce the reported synthetic method. Several synthetic pathways have thus been investigated, and the optimal way to prepare this disubstituted benzofuroxan was from the 3,5-difluoro-2-nitroaniline. The various synthetic attempts have allowed the isolation of interesting new compounds such as hydroxybenzotriazole-like heterocycles or benzoquinone 2-diazide. In the latter case, our study reveals some interesting features in the mechanism of their formation. The first structural elucidation of benzoquinone 2-diazide through an X-ray crystallographic study is also reported. This study has unambiguously shown that benzoquinone 2-diazide can be involved in Diels–Alder reactions. The first case of a reaction involving a nitro-substituted benzoquinone 2-diazide and cyclopentadiene is also reported. To understand better the influence of the fluorine atoms on the reactivity of benzofuroxans and benzofurazans, a wide array of new fluorinated heterocycles were synthesized together with some already known compounds. This has enabled an extensive investigation of their electrophilic behavior to be undertaken through a theoretical and an electrochemical study. From these studies, it could be deduced that the replacement of nitro groups by fluorine atoms results in a significant decrease in the electrophilic character of benzofuroxan. Nevertheless, these compounds could undergo S_NAr processes, leading to new functionalized heterocycles. The first examples of aromatic nucleophilic substitution of fluorine with these compounds are also described.

Introduction

Substituted benzofuroxans and benzofurazans constitute a class of 10-π heterocyclic compounds that has attracted interest over the past twenty years. It has been shown that they react readily with weak nucleophiles to form stable anionic σ adducts when they are substituted in the 4- and/or 6-position by electron-withdrawing groups. To exemplify this behavior, one can mention the high susceptibility of 4,6-dinitrobenzofuroxan (DNBF, **1**) to undergo σ complexation in the absence of any added base in aqueous solutions to form the hydroxy adduct **C-1** according the Equation (1).[1] More importantly, it has to be noted that the nature of the substituent borne by the six-membered ring is of primary importance in determining how these compounds react with dienes or nucleophiles.



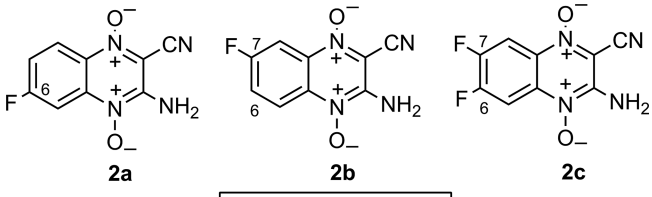
(1)

When benzofuroxans are substituted by electron-releasing substituents, the chemical reactivity is transferred from the carbocyclic ring to the furoxan ring. Such compounds undergo heterocyclic transformations, with the most important transformation being known as the "Beirut reaction", which was described by Haddadin and Issidorides[2,3]. This reaction can be used to prepare quinoxaline 1,4-dioxide, benzimidazole and phenazine derivatives, which are also known to exhibit biological properties. The interaction of substituted benzofuroxans with electron-rich heterocycles or carbanions is the key step in the synthesis of these new biologically active compounds. In 1981, Gosh, Ternai and Whitehouse[4] were the first to publish a review in which the biochemical activity of benzofuroxans was extensively studied. More generally, benzofuroxan derivatives exhibit a broad spectrum of biological activity including antibacterial, antifungal, antileukemic, acaricide, and immunodepressive properties. Recently, a review reporting the pharma-

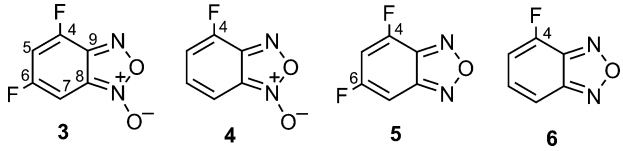
[a] Institut Lavoisier de Versailles, UMR 8180, Université de Versailles,
45 Avenue des Etats-Unis, 78035 Versailles Cedex, France
E-mail: regis.goumont@uvsq.fr
http://www.ilv.uvsq.fr/
[b] Department of Chemistry, Southern Federal University,
Sorge Street 7, 344090 Rostov-on-Don, Russian Federation
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402692.

ceutical properties of benzofuroxans and their derivatives, obtained through reactions involving benzofuroxans themselves, was published.[5,6] Although the first members of the benzofuroxan family were synthesized at the end of the 19th century, papers in this major field of heterocyclic chemistry are still being published, adding some consistency to the present work.[7] Importantly, authors have been able to show that both the medicinal properties and the reactivity of substituted benzofuroxans are closely related to the nature and the position of the substituent(s) borne by these heterocycles.[5] The synthesis and the particular chemistry of quinoxaline and phenazine dioxide derivatives have also attracted considerable attention in the last years. Some of them exhibit biological activities including antiviral, antibacterial, antiinflammatory, antiprotozoal, and anticancer properties.[8–10] A recent review of Cerecetto has been dedicated to the chemistry and the biological activity of these heterocycles.[11]

The peculiar case of fluorinated quinoxaline dioxide **2a**–**c** has been extensively studied; these compounds exhibit biological activity as growth inhibitors of *Trypanosoma cruzy* strains against parasitic diseases such as Chagas disease, tuberculosis or candida disease, which affect approximately 20 million people.[12] Syntheses and studies on the biological activity of 6-fluoro- (**2a**), 7-fluoro- (**2b**), and 6,7-difluoro-quinoxaline (**2c**) derivatives have been reported previously. Nevertheless, other isomers such as 5-fluoro-, 8-fluoro-, 5,7-difluoro, or 6,8-difluoro-quinoxaline derivatives have, to our knowledge, never been prepared, although they could be easily isolated from 4,6-difluoro- and 4-fluorobenzofuroxan (for the numbering of quinoxaline derivatives, see structures above). These new biological agents could be used in future trials to extend the range of biological activity.



In this paper, we report on the revisited synthesis of 4,6-difluorobenzofuroxan **3** and of other new fluorinated benzofuroxans such as 4-fluorobenzofuroxan **4**. We will show that the experimental conditions reported by Leyva[13] to prepare 4,6-difluorobenzofuroxan did not allow the synthesis of this latter compound but could be used to access other interesting derivatives such as hydroxybenzotriazole-like compounds or benzoquinone 2-diazide. Interestingly, we will also show that the reported NMR spectroscopic data in this paper are not those pertaining to 4,6-difluorobenzofuroxan **3**. Together with the first synthesis of these compounds, we will described a theoretical and an electrochemical study of a series of fluoro-substituted benzofuroxans, highlighting, for the first time, their electrophilic behavior.[14] Finally, the use of some of these compounds in S_NAr processes or in the preparation of new quinoxaline dioxides will also be discussed.

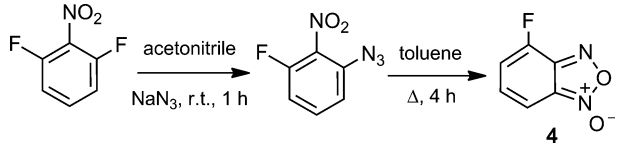


Results and Discussion

The formation of substituted benzofuroxans is readily achieved by heating of the corresponding substituted α-nitrophenyl azides. These azides are obtained from the corresponding nitroanilines either by diazotization ($NaNO_2$ in aqueous acidic media) and subsequent treatment with aqueous solution of azide, or by nucleophilic displacement of a chlorine atom with sodium azide in dimethyl sulfoxide or in a ternary mixture: acetone/methanol/water. The optimal experimental conditions depend on the nature of the substituent: in the case of electron-withdrawing groups the S_NAr process of the chlorine atom removal is easily achieved under mild conditions (2 h at room temperature). Another possible pathway is to prepare benzofuroxan from the corresponding aniline by using oxidative conditions such as the use of sodium hypochlorite in basic alcoholic solution.[15]

Synthesis of Fluoro-Substituted Benzofuroxans

4-Fluorobenzofuroxan **4** was prepared in two steps from 2,6-difluoronitrobenzene. In a first step, heating a solution of 2,6-difluoronitrobenzene in acetonitrile with one equivalent of sodium azide leads to the sole formation of the azido intermediate, which is subsequently heated in toluene to give 4-fluorobenzofuroxan as a pale-yellow solid in quantitative yield (Scheme 1).



Scheme 1. Synthesis of benzofuroxan **4**.

Some similar experimental conditions have been used in the synthesis of 5- and 6-fluorobenzofuroxan and have been improved in the preparation of **4**, replacing dimethyl sulfoxide (DMSO) by acetonitrile.[16] This change results in easier isolation of the benzofuroxan derivative. The ^1H NMR spectra of **4** is characterized by a broad signal at δ = 7.39 ppm for the three protons H-5, H-6, H-7. In accordance with the structure of **4** was the observation in the ^{19}F

NMR spectra of one broad signal at δ = –129.3 ppm, characteristic of the fluorine atom at the fourth position. Interestingly, an X-ray crystallographic study confirmed the structure of the new benzofuroxan **4** in the solid state, revealing a bond length of 1.344 Å for the C(4)–F bond (see Figure 1).

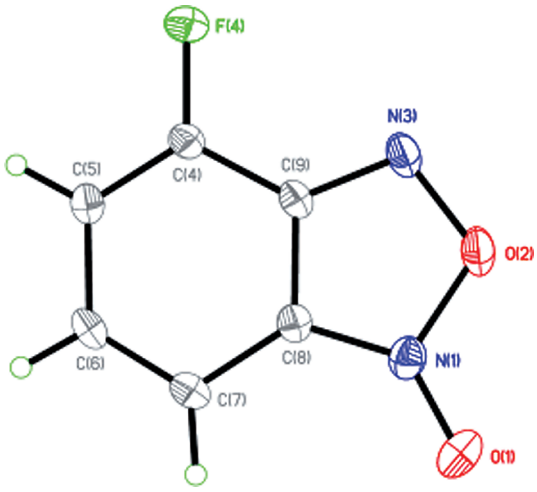
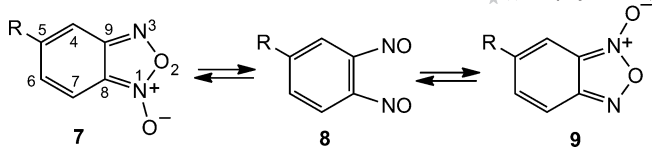


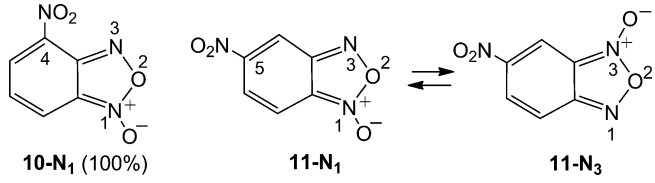
Figure 1. X-ray structure of 4-fluorobenzofuroxan **4**.

The fact that the signals pertaining to benzofuroxan **4** are unresolved is clear evidence of the well-known 1-oxide/3-oxide tautomery. This rearrangement involving substituted benzofuroxan has been extensively studied. Benzofuroxan itself (**7**; R = H) has been shown by low-temperature NMR studies to be a rapidly equilibrating system, with the transformation between the 1- and 3-oxide structure proceeding via *o*-dinitrosobenzene (**8**; R = H) as an intermediate. Ring–chain tautomerism of this type (see Scheme 2) also occurs in substituted benzofuroxans. In the case of benzofuroxans substituted in the 5-position (for the numbering of benzofuroxan, see Scheme 2), the amount of each tautomer is dependent on the nature of R.



Scheme 2. Interconversion between the 1- and 3-oxides of benzofuroxans.

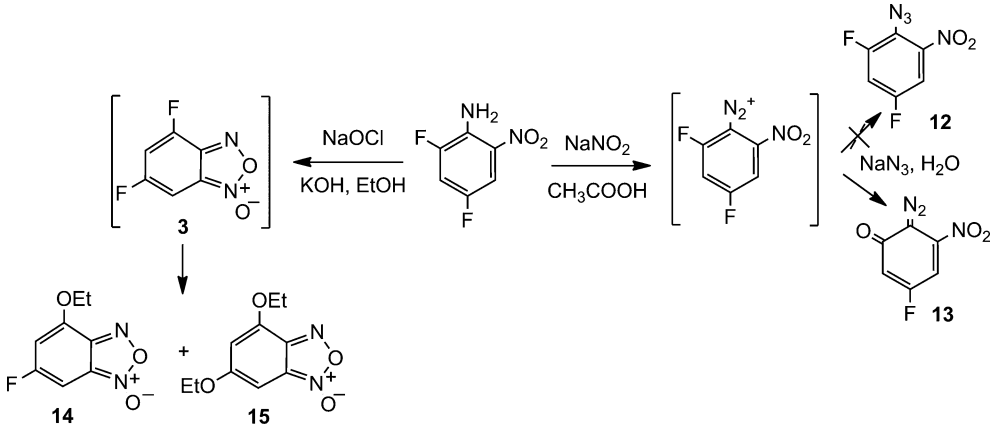
When R is an electron donor, structure **7** is more abundant, whereas an electron-withdrawing group favors structure **9**. When an electron-withdrawing group is located in the 4-position (as in the case of the 4-nitrobenzofuroxan, **10**), the benzofuroxan exists in one form with the *N*-oxide in the 1-position at all temperatures.[17,18] When the nitro group is in the 5-position, as in the case of 5-nitrobenzofuroxan **11**, both isomers exist at room temperature (Scheme 3).



Scheme 3. Interconversion of 5-nitrobenzofuroxan **11**.

The synthesis of 4,6-difluorobenzofuroxan **3** has been reported by Leyva[13]. It was mentioned that heterocycle **3** can be prepared from 4,6-difluoro-2-nitroaniline by using either basic or acidic conditions (Scheme 4). Keeping in mind that 4,6-difluorobenzofuroxan will be used further in the synthesis of new quinoxaline compounds, we attempted to reproduce the reported experimental conditions.

By using first the diazotization methodology (right part of Scheme 4), the synthesis of the diazonium salt was performed, followed by the addition of one equivalent of sodium azide in water. This step led to the isolation of a dark-red solid in 85% yield. However, the ^{19}F NMR spectra recorded in $CDCl_3$ was not consistent with the structure of



Scheme 4. Synthetic pathways developed by Leyva.

the postulated azide **12**. These spectra revealed the presence of only one signal, pertaining to one fluorine atom, at δ = –94.0 ppm. This was confirmed by the ^{13}C NMR spectra, which also showed only one doublet pertaining to a quaternary carbon substituted by a fluorine atom at δ = 167.15 ppm ($^{1}J_{C,F}$ = 268 Hz). By using 2D NMR techniques such as HMQC and HMBC experiments, the structure of this unexpected product was easily determined. This compound can be formulated as the substituted benzoquinone 2-diazide **13**, the formation of which can be accounted for in terms of substitution of a fluorine atom by water during the formation of the diazonium salt. Among the structural data, typical diagnostic features for the structure of **13** are: (1) the presence of two doublet of doublets that are characteristic of the protons H-5 and H-7; (2) two signals pertaining to carbons C-1 and C-2 at δ = 79.4 and 175.7 ppm, respectively. The presence of two electron-withdrawing groups such as a nitro group and the diazonium moiety borne by the aromatic ring favors facile nucleophilic aromatic substitution of a fluorine atom.[19] As this synthetic pathway does not allow 4,6-difluorobenzofuroxan **3** to be prepared, a second method using sodium hypochlorite in basic media was envisioned. These synthetic conditions have often been used to prepare substituted benzofuroxans and especially the unsubstituted benzofuroxan **7** (R = H).[20] In this case also, the experimental conditions described by Leyva[13], i.e., the use of sodium hypochlorite in ethanolic solution of base (sodium or potassium hydroxide), did not lead to the formation of 4,6-difluorobenzofuroxan **3** but to the formation of a mixture of two compounds **14** and **15**, in 80% yield. Their formation can be interpreted in terms of substitution of one or both fluorine atoms in 4,6-difluorobenzofuroxan by one or two ethoxide moieties. Decreasing the concentration of sodium or potassium hydroxide together with the reaction time resulted in the sole formation of monosubstituted compound **14**, with approximately 20% aniline remaining in the crude mixture. NMR spectra were in complete agreement with the structure of benzofuroxans **14** and **15**, revealing broad signals that confirm a benzofuroxan structure and, more particularly, the presence of quadruplet/triplet systems characteristic of the ethyl groups. Interestingly, the structure of **14** was also firmly established by an X-ray crystallographic study (Figure 2).

These results provide clear evidence for the intermediate formation of 4,6-difluorobenzofuroxan in the reaction mixture but also show that this compound is not stable in basic media, in which it undergoes facile nucleophilic aromatic substitution, as could be expected.

As it was impossible for us to reproduce the experimental conditions of Leyva to prepare 4,6-difluorobenzofuroxan **3**, new synthetic pathways, involving other starting materials, were investigated.

First, to prevent the formation of the benzoquinone 2-diazide, a synthesis of **3** starting from hydrazine **17** was performed. It has been reported that aromatic hydrazine could undergo diazotization to lead to azide formation.[21] Hydrazine **17** was easily prepared by treatment of the corresponding anisole **16**[22] with hydrazine hydrate in ethanol at reflux.[23] ^{1}H and ^{19}F NMR spectra recorded in acetonitrile exhibited characteristic signals such as two multiplets at δ = 8.41 and 7.66 ppm for the two aromatic protons, and two signals at δ = –110.1 and –123.8 ppm for the two fluorine atoms, respectively. Surprisingly, the diazotization of **17** leads to total recovery of the starting material, leading to the conclusion that compound **17** could not be the expected hydrazine **17**.

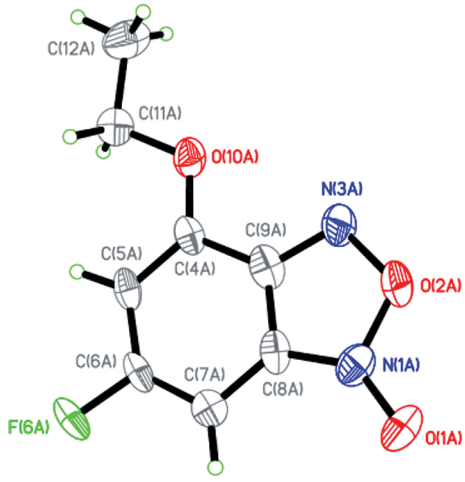
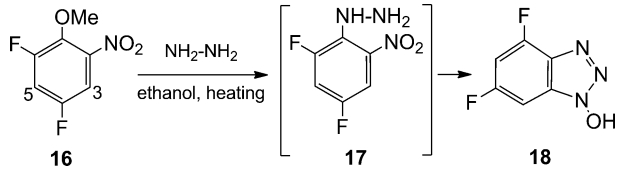
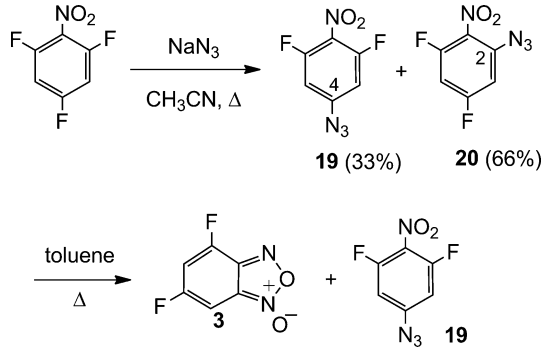


Figure 2. ORTEP view of benzofuroxan **14**.

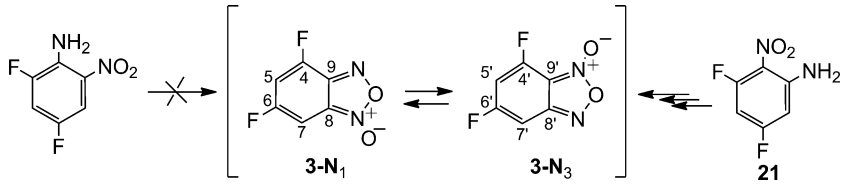
A more detailed structural study showed that the nitro group was absent, leading to a strong shielding of the two tertiary carbon atoms C-5 and C-7, at δ = 102.1 and 93.3 ppm, respectively. A mechanism in which the nitro group and the hydrazine moiety are involved is reminiscent of the mechanism of formation of substituted 1-hydroxybenzotriazole (HOBt). The intramolecular dehydration involving **17** leads to **18**, which has been postulated to have a



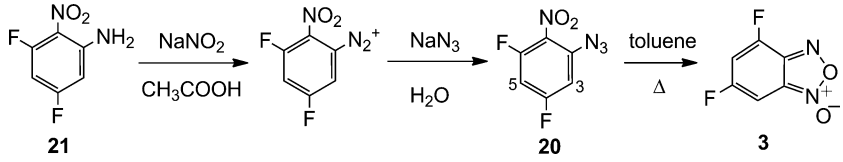
Scheme 5. Synthesis of HOBt-like compound **18**.



Scheme 6. Synthesis of benzofuroxan **3** from 1,3,5-trifluoronitrobenzene.



Scheme 7. Tautomer equilibrium of benzofuroxane **3**.



Scheme 8. Diazotization of **21** and definitive formation of benzofuroxan **3**.

HOBt-like structure (Scheme 5).[24] The NMR spectroscopic data are in complete agreement with this structure and HRMS data were also consistent, exhibiting a peak at *m*/*z* 172.0323 (*m*/*z* calcd. for $C_6H_4N_3OF_2$: 172.0322).

The second attempt to prepare benzofuroxan **3** was performed from 2,4,6-trifluoronitrobenzene by using the developed experimental conditions for the synthesis of 4-benzofuroxan. Heating of one equivalent of 2,4,6-trifluoronitrobenzene[25] with one equivalent of sodium azide in acetonitrile led to the formation of a mixture of two substituted azides **19** and **20** in a 1:2 ratio, respectively. The overall yield was around 65% and the mixture of compounds was obtained as an orange solid. The ^{19}F NMR spectra of the minor azide were consistent with the symmetrical structure of **19** ($\delta F_{2,6}$ = –118.5 ppm). The formation of this latter azide resulted from substitution of the fluorine atom at the 4-position (Scheme 6).

Unfortunately, separation of the two isomers **19** and **20** was not possible and this mixture of azides was heated overnight to reflux in toluene. The crude reaction mixture was obtained as a pale-orange liquid in 40% yield but in this case also, it was not possible to separate the remaining symmetrical azide from benzofuroxan **3** through column chromatography on silica or alumina gel. Although this synthesis does not lead to pure benzofuroxan, the first NMR results are consistent with the structure of **3**. The ^{19}F NMR spectra, recorded in [D_6]acetone, exhibited four broad signals corresponding to the two tautomers **3-N$_1$** and **3-N$_3$** at δ = –101.7/–126.2 ppm for the minor isomer and at δ = –104.9/–124.2 ppm for the major tautomer. At this stage it was not possible to determine which tautomer corresponded to which isomer (Scheme 7). These data are not consistent with those reported by Leyva. Nevertheless, the fact that the NMR spectroscopic data are consistent with the structure of azides and that the cyclization step takes place in neutral media, i.e., a cyclization step in toluene at reflux, make these results consistent.[5]

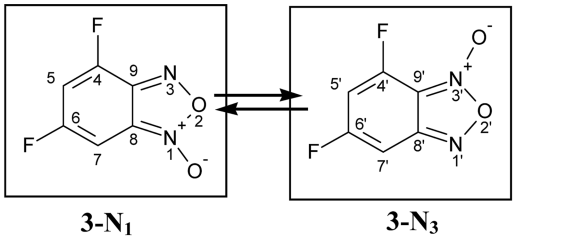
To obtain definitive evidence for the structure of **3**, a final synthesis was carried out. As shown in Scheme 7, the two tautomers **3-N$_1$** and **3-N$_3$** coexist in solution. If 4,6-difluoro-2-nitroaniline does not lead to **3-N$_1$**, due to the formation of benzoquinone 2-diazide **13**, one could postulate that 3,5-difluoro-2-nitroaniline **21** could lead to **3-N$_3$**. Importantly, the switch of the two positions bearing the nitro and the amino groups reduces the likelihood of nucleophilic aromatic substitution of a fluorine atom by water (see below). The diazotization of **21** in acetic acid followed by the addition of sodium azide in water led to the quantitative formation of **20**. Importantly, the NMR spectroscopic data pertaining to this compound were similar to those obtained above. The ^1H NMR spectra reveal two signals at δ = 7.37 and 7.23 ppm, which were characteristic of the two aromatic protons H-3 and H-5, respectively. The ^{19}F NMR spectra exhibit two signals at δ = –103.4 and –120.6 ppm for the two fluorine atoms. Finally, heating of **20** to reflux in toluene led to the exclusive formation of benzofuroxan **3** as an orange liquid in 90% yield (Scheme 8). The NMR spectroscopic data were also similar to those obtained previously.

Discussion

Variable-Temperature NMR experIments

Most of the benzofuroxans prepared in this study have been structurally studied by conducting variable-temperature NMR experiments. In this discussion, we will focus on the peculiar case of 4,6-difluorobenzofuroxan **3**, with the ^1H, ^{13}C and ^{19}F NMR spectra being recorded in acetonitrile[D_3] from 233 to 343 K together with 2D NMR experiments. The numbering of the carbon atoms of both tautomers is given in Scheme 7. The various spectra are summarized in Figures 3, 4, and 5. At room temperature (298 K), ^1H, ^{13}C and ^{19}F NMR spectra of **3** showed very broad signals due to the tautomeric equilibrium highlighted in Scheme 7. When NMR experiments are carried out at low temperature (233 K) the aromatic region exhibited narrow peaks, corresponding to both tautomers. In acetonitrile solution (approximately 10% w/v) at 343 K, the spectra reveal signals pertaining to only one isomer due to a complete coalescence. The recording of a complete series of spectra at low and high temperature allowed straightforward attri-

bution of all the resonances and a determination of the ratio between the two isomers at low temperature. It should be mentioned that, at 343 K, it has not been possible to observe signals pertaining to the two quaternary carbons C-8 and C-9. Low-temperature ^{1}H NMR spectra show signal of characteristic shape. For example, the shape of signals at δ = 7.21 and 6.95 ppm (pseudo-triplet), which can be attributed to H-5 and H-5′, respectively, could be due to the quite close couplings between H-5 (or H-5′) with the two fluorine atoms. Interestingly, it is known that the ^{13}C NMR spectra of benzofuroxans show some characteristic features.[26] The resonances of C-9 and C-8 appear to be the key features of the ^{13}C NMR spectra of benzofuroxans. With chemical shift of δ = 150 and 110 ppm, respectively, the signals of C-9 and C-8 are quite independent of the position and of the nature of the substituent. The position of the signal pertaining to C-8 compared with that of C-9



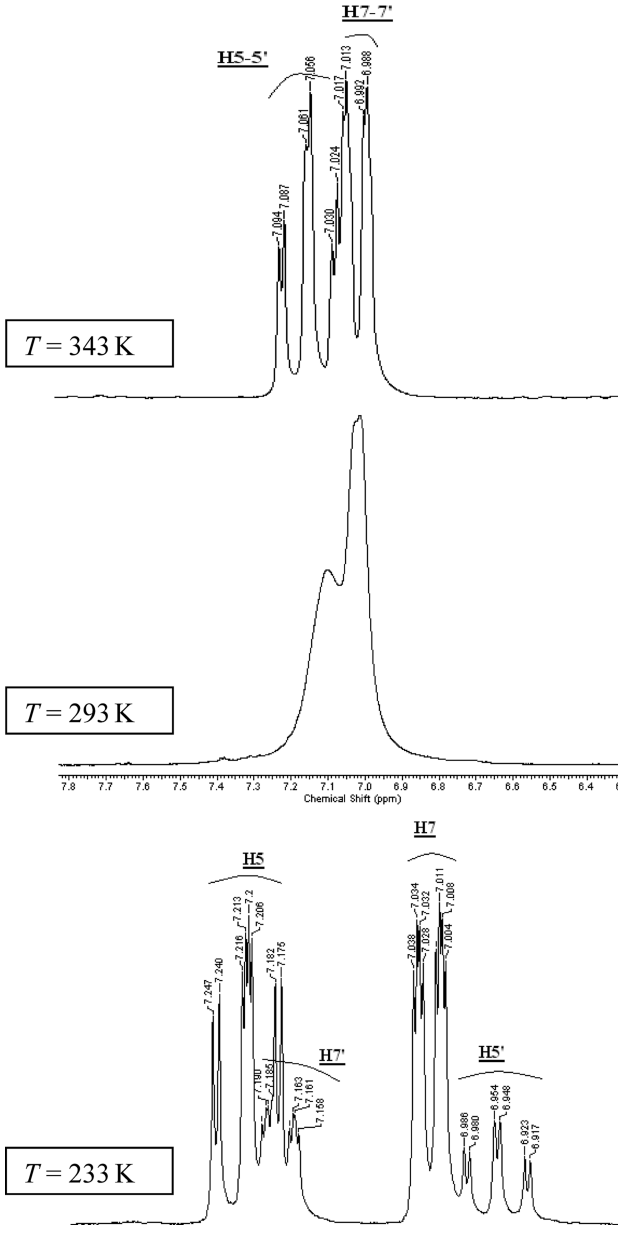
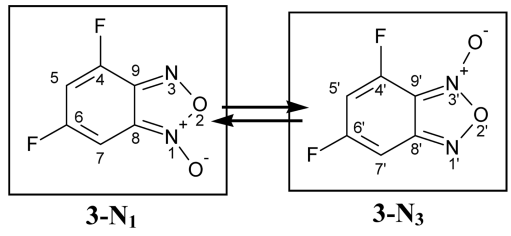


Figure 3. ^{1}H NMR of **3** in CD_3CN from 343–233 K.



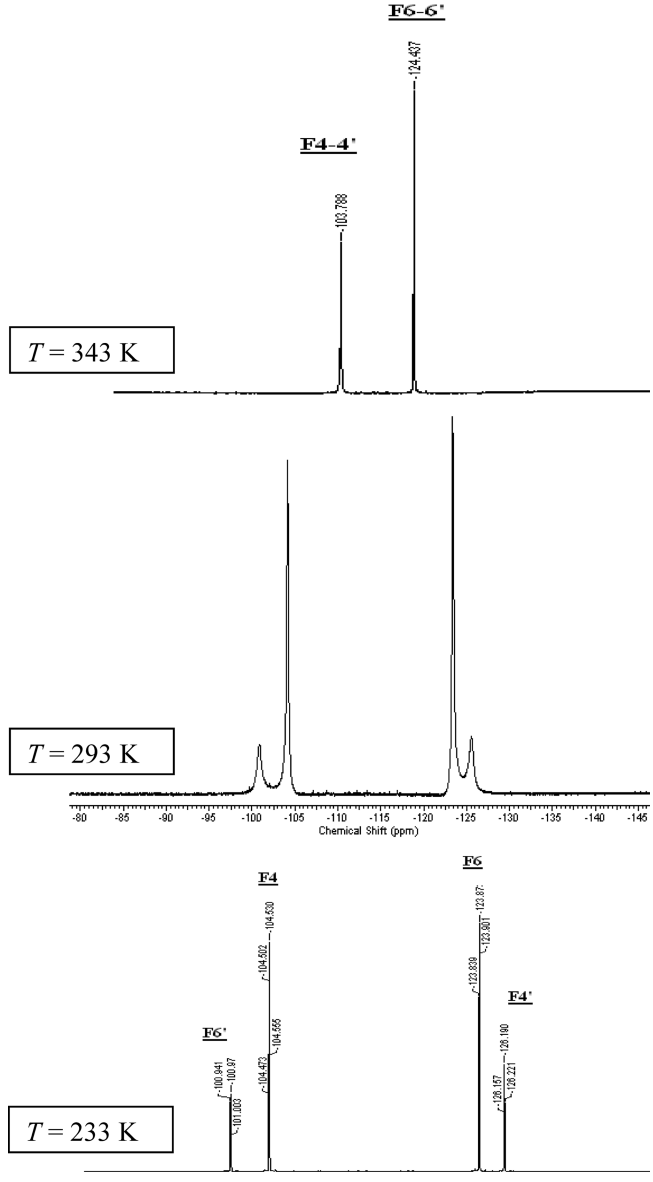


Figure 4. ^{19}F NMR of **3** in CD_3CN from 343–233 K.

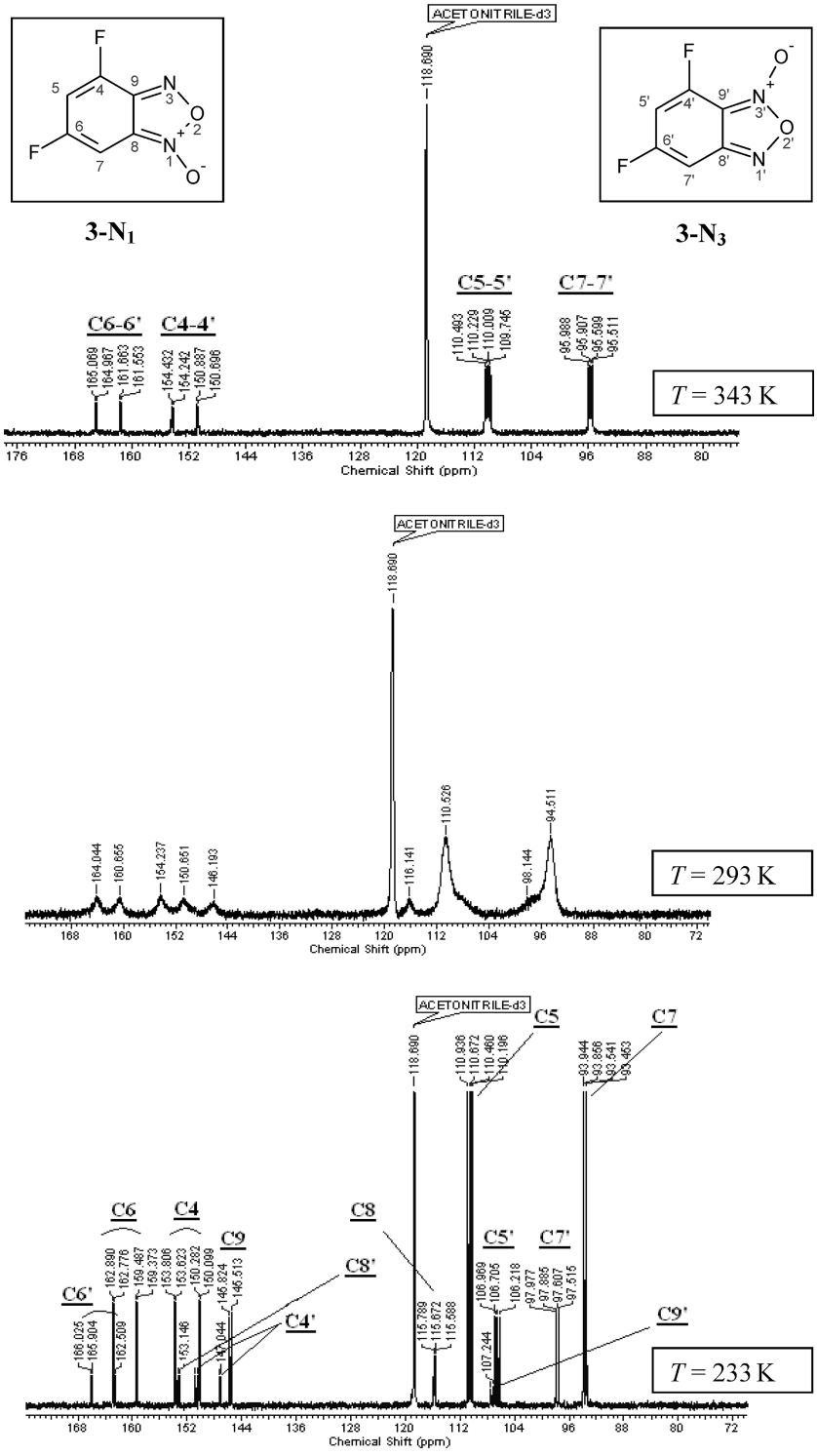
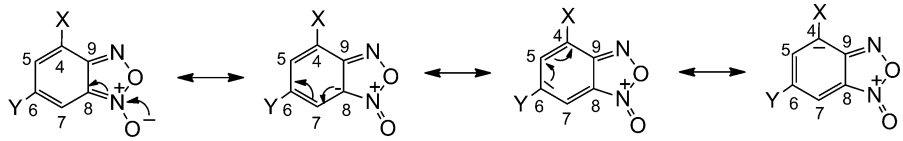


Figure 5. ^{13}C NMR of **3** in CD_3CN from 343–233 K.

could be explained by the mesomeric effect of the *N*-oxide functionality (Scheme 9).[27]

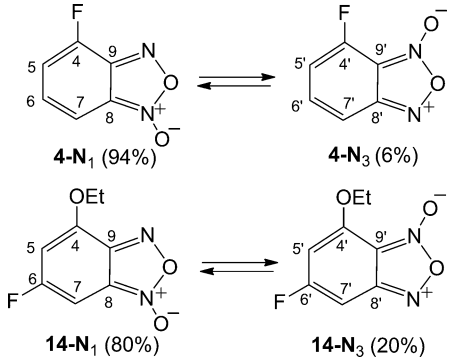
This substituent effect has been attributed to the presence of a partial negative charge on C-8 resulting from a significant contribution of the second resonance form described in Scheme 9, whereas C-9, which is more distant from the *N*-oxide function, remains unaffected or is only slightly affected.[26]

HMBC spectra recorded for these compounds exhibit characteristic correlations. For example, two correlations between C-9 ($\delta \approx 145$ –150 ppm) and H-7 ($J_{C9,H7} = 5$ Hz) and H-5 ($J_{C9,H5} = 7$–9 Hz), respectively, can be observed, whereas C-8 ($\delta \approx 110$–115 ppm) is only correlated with H-7 ($J_{C8,H7} = 2$–3 Hz).[26] The HMBC spectra recorded for **3** in acetonitrile showed nice correlations as follows: (1) C-9 ($\delta = 145.7$ ppm) is correlated with H-7 ($\delta = 7.01$ ppm) and H-



Scheme 9. Tautomeric forms of substituted benzofuroxans.

5 (δ = 7.21 ppm); (2) C-8′ (δ = 153.2 ppm) is only correlated with H-7′ (δ = 7.19 ppm). Similarly, the correlations between C-6 (or C-6′) with both protons H-5 and H-7 (or H-5′ and H-7′) allow a rapid discrimination between the resonances of C-4 and C-6. Such two-dimensional correlations have been also used to determine the regioselectivity of addition of diene on both isomers involved in the *N*-oxide interconversion.[6] Finally, from these results, it has been determined that the major isomer was **3-N$_1$** and that the ratio in its favor was approximately 3:1. Similar studies performed with **4** and **14** also revealed that the major isomer has the *N*-oxide functionality at the N-1 position and that the ratios are 15:1 and 4:1, respectively (Scheme 10, low- and high-temperature NMR spectra for these benzofuroxans are given in the Supporting Information, Figures S1–S14).



Scheme 10. 1-/3-Oxide interconversion of benzofuroxans **4** and **14**.

From variable-temperature NMR experiments, the rate constant k_c of the coalescence process and the activation parameters for the dynamic equilibrium could be readily obtained. A complete line-shape analysis was not always necessary to extract these data, and simplified equations could be used to estimate k_c and $\Delta G^{\neq}$ values.[28] For the coalescence temperature T_c, the rate constant k_c is given by Equation (2).

$$k_c = \frac{\pi\Delta\nu}{\sqrt{2}} = 2.22\ \Delta\nu\ (s^{-1}) \quad (2)$$

with $\Delta\nu$ being the separation in Hz between the two signals in the absence of exchange.

Free enthalpies of activation $\Delta G^{\neq}$ were obtained from the coalescence temperature T_c by the application of Equation (3), derived from Eyring's equation:

$$\Delta G^{\neq} = RT_c\,[22.96 + \ln(\frac{Tc}{\Delta\nu})]\ (J\,mol^{-1}) \quad (3)$$

It is also possible to describe $\Delta G^{\neq}$ values by Equation (4). In this equation, k_c values are used instead of $\Delta\nu$.

$$\Delta G^{\neq} = 19.14T_c\,[10.32 + \log(\frac{Tc}{kc})]\ (J\,mol^{-1}) \quad (4)$$

The coalescence temperatures T_c, k_c, and $\Delta G^{\neq}$ values are summarized in Table 1 for compounds **3**, **4**, and **14**.

Table 1. k_c and $\Delta G^{\neq}$ parameters for fluorobenzofuroxans **3**, **4**, and **14**.

	T_c [K][a]	$\Delta\nu$ [Hz][b]	k_c [s^{-1}]	$\Delta G^{\neq}$ (kcal mol^{-1}) [Eq. (3)][c,d]	ΔG [cal mol^{-1}] in favor of N_1[e]
3	303	60	133.2	14.8 (14.5)	520
4	293	14	31.1	15.1 (15.9)	1340
14	313	58	128.8	15.3 (16.0)	790

[a] T_c values $\pm$ 5 K. [b] Average value. [c] $\Delta G^{\neq} \pm 0.5$ kcal mol^{-1}. [d] $\Delta G^{\neq}$ values from Equation (4) are identical, values in parentheses are theoretical values. [e] $\Delta G = -RT\ln(K)$, where T is the temperature below which well-resolved spectra could be recorded, $K = \frac{[\%N_1]}{[\%N_3]}$.

The estimated values for fluorobenzofuroxans **3**, **4**, and **14** are of approximately the same magnitude (ca. 15 kcal mol^{-1}) as those of the benzofuroxans reported earlier (10–15 kcal mol^{-1}) by Katritzky.[29] For example, $\Delta G^{\neq}$ values of 15 kcal mol^{-1} are reported for benzofuroxan and 5,6-dinitrobenzofuroxan and a value of 13.6 kcal mol^{-1} is determined for 5-nitrobenzofuroxan **11**.[28] Interestingly, the estimated experimental values for free enthalpies of activation $\Delta G^{\neq}$ are in close agreement with those determined theoretically (values in parentheses, Table 1). More important, these values are also all in accord with those reported for variously substituted benzofuroxans.[28,29]

Formation of Benzoquinone 2-Diazide

The formation of benzoquinone 2-diazide **13** deserves comment. Although the formation of this compound has been previously reported, some interesting data have been determined in our study and should be mentioned. Camps et al. have shown that benzoquinone 2-diazide **13** formed during their attempted synthesis of 2-amino-4,6-difluorobenzonitrile by a Sandmeyer cyanation of 2,4-difluoro-6-nitrobenzene-diazonium cation.[19] The authors mention that diazonium salts having leaving groups at the *ortho* and *para* position can give products derived from nucleophilic substitution of the diazo group by nucleophiles (hydroxide for example) present in the reaction medium, in competition with the expected nucleophilic substitution by the cyanide moiety. In fact, no further nucleophile is needed to form the benzoquinone 2-diazide **13**. In our case, even when

sodium azide was added as a solid, the formation of benzoquinone 2-diazide could not be avoided, which suggests that this reaction arises from adventitious water or from water produced during the formation of NO^+. A completely water-free synthesis, involving the use of tertiobutyl nitrite (*t*BuONO) as nitrosation agent, in acetonitrile was employed, but that also led to the sole formation of the benzoquinone 2-diazide.[30] The structure of **13** was also confirmed through an X-ray crystallographic study, which revealed that the length of the C(2)=C(3) double bond was 1.355 Å (Figure 6). Interestingly, this bond length is reminiscent of that of NBDF **22**, with a bond length of 1.339 Å.[31] This is typical of a nitro-olefinic fragment and contrasts with the situation reported for DNBF **1** for which values of 1.37 and 1.40 Å have been measured for the two potentially reactive C(6)=C(7) and C(4)=C(5) double bonds, respectively.[31]

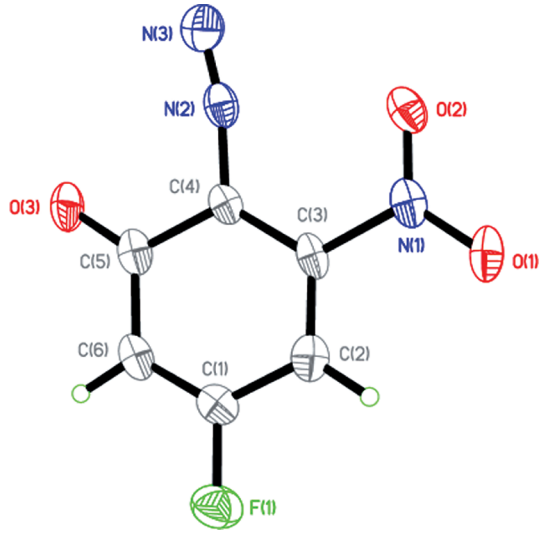
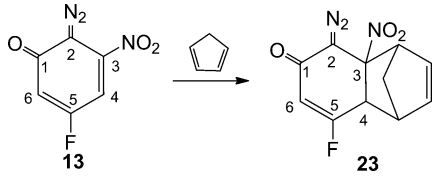


Figure 6. ORTEP view of benzoquinone 2-diazide **13**.

A first interesting result confirming the nitro-activated character of the C(2)=C(3) double bond is that compound **13** reacts easily with cyclopentadiene to give cycloadduct **23** in quantitative yield (Scheme 11). This result is of significant importance because it opens synthetic routes to new, highly functionalized compounds. The result also highlights, for the first time, the dienophilic character of the nitro-activated double bound of benzoquinone 2-diazide. More interestingly, these aryl diazoketones may also be used in the organic synthesis of highly functionalized compounds such as Azamerone, a pyridazine natural product.[32]

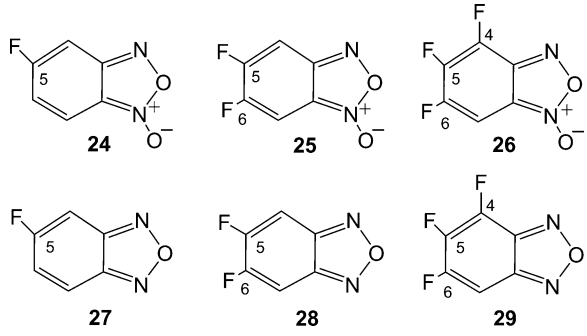


Scheme 11. Dienophilic behavior of the C(2)=C(3) double bond of **13**.

Benzofurazan Synthesis

The formation of benzofurazans is usually achieved from the corresponding benzofuroxan analogues by using triphenylphosphine or triethylphosphite in toluene or in ethanol. The best experimental procedure to obtain benzofurazan **5** and **6** has been to heat fluorinated benzofuroxans to reflux in toluene with one equivalent of triethylphosphite. The synthesis of **6** from 2,6-difluoroaniline with the intermediate formation of an unstable nitroso compound has been reported.[33] Nevertheless, in our case, the deoxygenation process of **4** is easily carried out and the synthesis leads to **6** in one step in a very good yield compared with methods reported previously.[33] The benzofurazans were easily purified and were obtained in fair to moderate yields. NMR spectra were in full agreement with the structure of benzofurazan and with the disappearance of the *N*-oxide functionality. Two major points have to be mentioned: The NMR spectra reveal well-defined signals because of the absence of tautomery, and a large deshielding of the resonance pertaining to C-8 going from δ = 110 ppm in benzofuroxan to 155 ppm in benzofurazan.[26]

To understand better the influence of the position of the fluorine atom on the reactivity and electrophilicity of polyfluorobenzo-furoxan and -furazan, the syntheses of known 5-fluoro- (**24**),[34] 5,6-difluoro- (**25**),[35] and 4,5,6-trifluorobenzofuroxan (**26**)[13] were performed. To complete this study, the syntheses of the new benzofurazan analogues **27**–**29** of the previous heterocycles were carried out (Scheme 12). The fluorobenzofurazans were fully charac-



Scheme 12. Structure of fluorobenzofuroxans and of the furazan analogues.

Table 2. ^1H[a] and ^{19}F NMR[b] parameters for fluorobenzofurazans.

	H-4	H-5	H-6	H-7	F
5	–	7.39	–	7.58	–101.6
					–117.7
6[c]	–	7.33	7.62	7.82	–122.9
27	7.66	–	7.52	8.11	–104.7
28[d]	8.00	–	–	8.00	–123.8
29	–	–	–	7.95	–121.0
					–121.9
					–146.9
					–150.9

[a] Relative to internal $SiMe_4$, δ in ppm; solvent [D_6]acetone. [b] Relative to internal $CFCl_3$, δ in ppm; solvent [D_6]acetone. [c] Shifts δ are in agreement with those reported previously.[31] [d] Shifts δ are in agreement with those reported previously.[33]

terized by NMR experiments; it should be noted that liquid fluorobenzofurazans are highly volatile and that care must be taken to limit the loss of those compounds, for example through slow evaporation of reaction solvent under an inert gas stream. The NMR spectroscopic data are summarized in Tables 2 and 3. Only the ^{1}H NMR spectroscopic data of **28** were previously reported. This work allows a complete NMR characterization of the symmetrical 5,6-difluorobenzofurazan.[36]

Table 3. ^{13}C NMR parameters for fluorobenzofurazans.[a]

	C-4	C-5	C-6	C-7	C-8	C-9
5	152.0	109.9	164.5	97.8	151.2	143.2
6[b]	150.8	115.21	133.9	114.1	152.7	144.3
27	99.5	164.7	126.9	120.5	148.6	150.6
28[c]	102.2	155.4	155.4	102.2	147.2	147.2
29	138.7	143.1	156.4	98.7	146.9	142.7

[a] Relative to internal $SiMe_4$, δ in ppm; solvent [D_6]acetone. [b] Shifts δ are in agreement with those reported previously.[31] [c] This work.

Electrophilicity of Fluorobenzofuroxan and Benzofurazan: Theoretical and Electrochemical Studies

Recent density functional theory (DFT) studies on Diels–Alder (DA) reactions have shown that the classification of the diene/dienophilic pairs on a unique electrophilicity scale is a convenient way to predict the feasibility and the polar characteristics of the cycloaddition processes. The question has been especially addressed by Domingo et al.,[37] using the global electrophilicity index ω, introduced by Parr and defined by Equation (5).[38] In this equation, the electronic chemical potential μ and the chemical hardness η of a substrate are two parameters that were evaluated in terms of the one-electron energies of the frontier molecular orbitals (FMO) HOMO and LUMO at the ground state of the molecules.[39] Another index used by Domingo et al. is the so called ΔN_{max} parameter, defined by Equation (6), which is a measure of the maximum amount of electronic charge that the electrophilic partner can accept.[37] According to the model, the polar character of a DA interaction can be assessed from the difference, $\Delta\omega$, in the global electrophilicities of the two reagents as well as by the ΔN_{max} values for the system at hand.[36]

$$\omega = \frac{\mu^2}{2\eta} \quad (5)$$

$$\Delta N_{max} = -\frac{\mu}{\eta} \quad (6)$$

The various parameters required to compare the electrophilicity of the fluorobenzo-furoxans and -furazans studied in this work are collected in Table 4. An important message of Table 4 is that the ω values associated with all substrates are very low, being in the range 2.6–3.2 eV. This compares in particular with ω values for nitroalkenes (e.g., ω = 2.61 eV for nitroethylene), and cyano-activated olefins (e.g., ω = 2.99 eV for benzylidenemalononitriles) or 1,1-dinitro-2,2-diphenylethylene (ω = 3.16 eV).[40] This shows that the electrophilicity of the fluorinated heterocycles is dramatically decreased upon substitution of a nitro group by a fluorine atom (ω = 3.0 eV for **3** and 5.46 eV for DNBF, **1**; ω = 2.8 eV for **4** and 4.21 for 4-NBF, **10**). The replacement of two nitro groups in compound **1** and of one nitro group in **10** results in a $\Delta\omega$ of 2.5 and 1.4 eV, respectively, leaving no doubt that these compounds will be unreactive towards common dienes such as cyclopentadiene in Diels–Alder reactions or towards neutral nucleophiles in nucleophilic substitution, such as water or methanol. Roughly, substitution of one nitro group by a fluorine atom results in a decrease in the electrophilicity of more than one ω unit. Previous studies have allowed the demarcation line for σ complexation and DA reactivity to be defined as a ω value of roughly 3.5–3.8 as the boundary between super- and normal-electrophiles and between reactive dienophiles and inert partners in Diels–Alder reactions.[39] In fact, polyfluorobenzofuroxans and furazans fall below the border of super- and normal electrophilic behavior, indicating a low electrophilic character.

Table 4. Global properties and global electrophilicity scale and first reduction potentials[a] for fluorobenzofuroxans involved in this work.

	LUMO, a.u.	HOMO, a.u.	ω [eV]	ΔN_{max}	$E^I_{1/2}$ [V]
3	–0.10497	–0.23425	3.0	1.312	–1.31
4	–0.10010	–0.23084	2.8	1.266	–1.22
5	–0.10095	–0.25861	2.8	1.140	–1.03
6	–0.09565	–0.25249	2.6	1.110	–1.30
24	–0.10040	–0.22940	2.9	1.278	–1.13
25	–0.10408	–0.23644	3.0	1.286	–1.13
26	–0.10924	–0.24060	3.2	1.339	–1.35
27	–0.09592	–0.25743	2.6	1.093	–1.26
28	–0.09958	–0.26452	2.7	1.104	–1.33
29	–0.10516	–0.26394	2.9	1.163	–1.28
13	–0.13537	–0.25172	4.4	1.6635	–

[a] In V vs. SRE in CH_3CN at room temperature.

The first half wave reduction potentials ($E^I_{1/2}$) associated with a reversible monoelectronic transfer process of a large set of substituted benzofuroxans can be determined through a detailed electrochemical approach in acetonitrile with a network of microelectrode by using ferrocene as an internal reference potential. The electrochemical data pertaining to the series of fluorobenzofuroxans are summarized in Table 4. As can be seen, the major result emerging from this study is that the reduction potentials are in the same range (i.e., –1.03 to –1.33 V), confirming that these benzofuroxan derivatives possess low electrophilicity comparable to that of benzotrithiadiazole ($E^I_{1/2}$ = –1.00 V) and of nitrobenzothiadiazole ($E^I_{1/2}$ = –0.90 V).[14] Qualitatively, it has been shown that the $E^I_{1/2}$ scale fits well the DA reactivity of this type of heteroaromatic derivative, and $E^I_{1/2}$ values below –0.4 V confirm that fluorobenzofuroxan cannot be engaged in Diels–Alder reactions but can be used in S_NAr processes with strong nucleophiles such as amines or alkoxides (see below).[14]

Microelectrodes have already proved to be efficient tools for the investigation of reversible electrode reactions ac-

cording rapid electron transfer kinetics.[14] When measuring time becomes sufficiently long, the current density reaches a steady-state value because of mass transport to the microelectrode. Because the current at this potential is half the current limiting value, the potential is called the reversible half-wave potential ($E^{I}_{1/2}$), which can be associated with the reversible formal potential of the Ox/Red couple ($E°$). Typical cyclic voltammograms obtained by this method for three electron acceptors, **24** and **27**–**28** are presented in Figure 7.

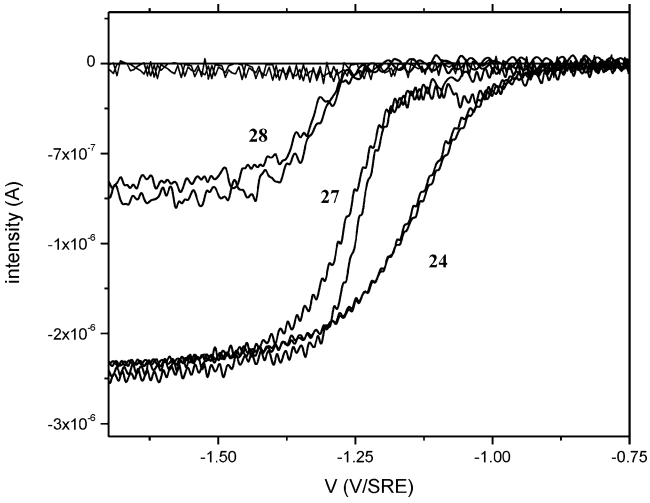
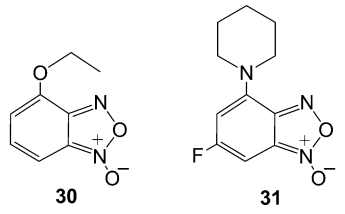


Figure 7. Linear scan voltammetry (20 mV/s) of a solution of the supporting electrolyte (tributylammonium perchlorate) in CH_3CN under argon without benzofuroxan (linear curve) and of **24** (10^{-2} mol·dm^{-3}, $E^{I}_{1/2}$ = –1.13 V vs. SRE), **27** (9×10^{-3} mol·dm^{-3}, $E^{I}_{1/2}$ = –1.26 V vs. SRE), and **28** (4×10^{-3} mol·dm^{-3}, $E^{I}_{1/2}$ = –1.33 V vs. SRE).

With a $E^{I}_{1/2}$value close to zero, DNBF **1** remains the most electron deficient heterocycle of the series, with an electrophilicity of the same order of magnitude as tetranitrofluorenone ($E^{I}_{1/2}$ = –0.06 V vs. SRE).[14]

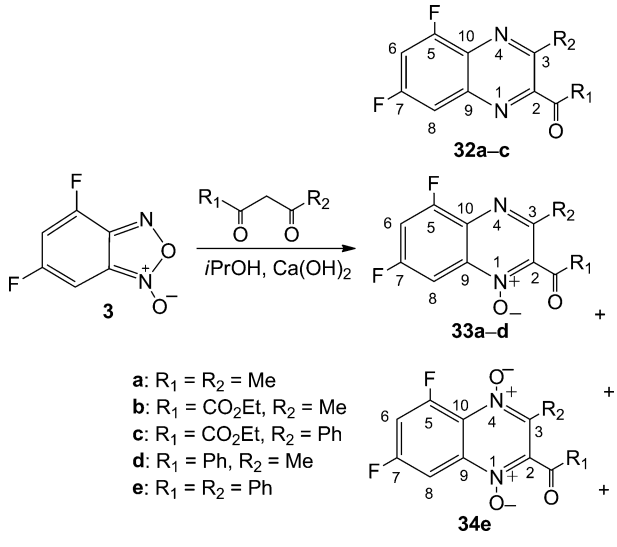
S_NAr Processes

Here we highlight the first examples of nucleophilic aromatic substitution involving 4,6-difluorobenzofuoxan. First, as mentioned above, their low electrophilic character does not allow reaction with either methanol or water. Nevertheless, 4,6-difluorobenzofuoxan reacts readily with one equivalent of sodium ethoxide, as described in the beginning of this paper, to give **14** in quantitative yield. The regioselectivity of this addition has been unambiguously assigned through an X-ray study (Figure 2). The addition of a second equivalent of sodium ethoxide leads to the substitution of the second fluorine atom at the 6-position to afford 4,6-diethoxybenzofuroxan in quantitative yield. The same reaction has been performed with 4-fluorobenzofuroxan. This reaction also leads to the quantitative formation of 4-ethoxybenzofuroxan **30**. Some other nucleophiles are currently being tested to extend the reactivity of fluorobenzofuroxans and furazans to the synthesis of new functionalized compounds. For example, the reaction involving 4,6-difluorobenzofuroxan and piperidine led to quantitative formation of 4-amino-substituted benzofuroxan **31**. The regioselectivity of the substitution was confirmed by ^{13}C NMR spectroscopic analysis. For example, the signal of the characteristic carbon C-9 at δ = 148.2 ppm appears as a singlet, revealing that the fluorine at the 4-position has been removed, leading to the disappearance of the $^{2}J_{C9,F}$ coupling. Such S_NAr reactions involving fluorobenzofuroxans and alkoxide ion or amines have been reported previously.[35] These first examples of substitution are of great relevance because they lead to the regioselective formation of highly functionalized compounds from appropriate nucleophiles.



4,6-Difluorobenzofuroxan 3 in the Synthesis of Quinoxalines

As mentioned in the introduction of this paper, one of the goals of this study was to synthesize biologically active compounds derived from fluorobenzofuroxans. To obtain variously substituted quinoxalines, the reaction of 4,6-difluorobenzofuroxan with dicarbonylated compounds such as ethyl acetylacetate or acetylacetone, was taken as the prototype reaction to establish the appropriate experimental conditions. Interestingly, heating of 4,6-difluorobenzofuroxan with a slight excess of carbonylated compound in 2-propanol, in the presence of a catalytic amount of $Ca(OH)_2$, led to the formation of three types of new substituted quinoxalines **32**–**34**, differing in the number of *N*-oxide functionalities (Scheme 13).[41]



Scheme 13. Formation of quinoxalines in 2-propanol.

The NMR spectroscopic data are in complete agreement with the proposed structures of these quinoxalines. The ^{1}H NMR spectra reveal two multiplets for the two protons H-6 and H-8, with the signal of H-6 being an apparent triplet because of the two similar ^3J coupling constants with the fluorine atoms. The two fluorine atoms, which are two useful probes, together with the HMBC spectra, allow straightforward assignment of the carbon atoms and especially the quaternary atoms. The two carbon atoms C-9/C-10 are clearly discriminated from the C-3/C-2 atoms through their couplings with F-5 and F-7, and C-10 is assigned through the two long-range ^{13}C–^{1}H heteronuclear shift correlations, revealed by the HMBC spectra and typical for the two ^3J couplings between C-10 and H-6 and between C-10 and H-8. Similarly, the two doublet of doublets, characteristic of C-5 and C-7 have been assigned through the HMBC spectra and especially through the two correlations between C-7 and H-8 and H-6, shown by the HMBC spectra. Finally, C-3 is assigned through the observation of a small ^4J coupling with F-5.

With all the quaternary carbon atoms being assigned, it became easier to determine whether the quinoxaline bears none, one, or two *N*-oxide functionalities. As was the case for the benzofuroxan series, the presence of an *N*-oxide group resulted in significant shielding of the carbon next to the nitrogen atom bearing the oxygen.[26] When the NMR spectroscopic data of **32a** are compared with those of **33a**, the resonance pertaining to the carbon C-2 shifts from δ = 148.8 ppm in **32a** to δ = 139.0 ppm in **33a** ($\Delta\delta \approx 10$ ppm) whereas the chemical shift of carbon C-3 remains unaffected, confirming the position of the *N*-oxide group in the 1-position. The chemical shift of C-9 follows a similar trend: δ = 140.9 in **32a** to δ = 136.6 ppm in **33a** ($\Delta\delta \approx 4.5$ ppm). The addition of a second *N*-oxide group in the 4-position results in a shielding of both C-10 and C-3 carbon atoms [δ_{C10} = 133.1 ppm in **33c** and δ_{C10} = 127.7 ppm in **34e** ($\Delta\delta \approx 5.5$ ppm); δ_{C3} = 152.9 ppm in **33c** and δ_{C3} = 140.3 ppm in **34e** ($\Delta\delta \approx 10.5$ ppm)]. Surprisingly, the quinoxaline-1,4 dioxides were obtained in only one case; in most cases, a mixture of quinoxaline and quinoxaline-1 oxide was obtained. These observations contradict previously reported results. In fact, the use of these experimental conditions (i.e., heating for one night in 2-propanol with a catalytic amount of $Ca(OH)_2$), only leads to the formation of quinoxaline-1,4-dioxides. Modification of the experimental conditions leads to similar results. One could anticipate that the formation of quinoxaline **32** and quinoxline-1 oxide **33** arises from the instability of the dioxide compounds **34**, which suffer either one or two deoxygenation processes. Experiments are in progress to understand better the mechanism leading to the unexpected formation of both **33** and **34**. The regioselectivity of the reaction has been unambiguously assigned through the two X-ray structures of **32a** and **33b**, showing that the fluorine atoms are in the 5- and 7-positions and the carbonyl moiety is in the 2-position. More importantly, in the case of quinoxaline monoxides **33a**–**d**, the X-ray study has revealed that the *N*-oxide functionality is located on the nitrogen atom N-1 (Figure 8).

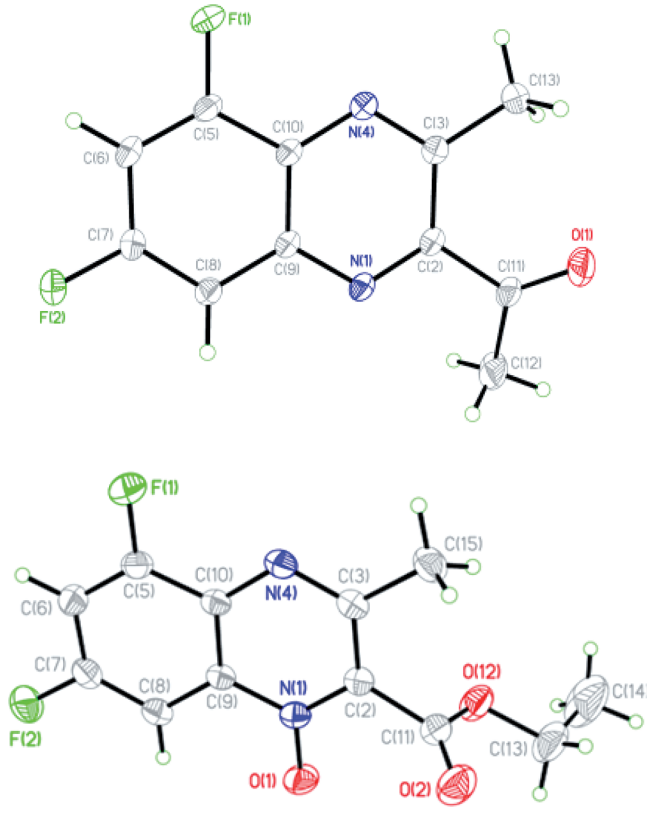


Figure 8. ORTEP views of quinoxaline **32a** (top) and **33b** (bottom).

Conclusions

For the first time, the synthesis of 4,6-difluorobenzofuroxan has been performed, using several synthetic strategies. This study has shown that previous work reporting the synthesis of this benzofuroxan was erroneous. Variable-temperature NMR experiments confirm its structure and allow the quantification of the two tautomers **3-N$_1$** and **3-N$_3$**, which undergo *N*-oxide interconversion, in a 3:1 ratio. The various experimental pathways allow the isolation and characterization of new compounds such as HOBt-like compounds **18**, which will be used in peptide couplings. Perhaps more important, it has been shown that benzoquinone 2-diazide **13** can be used as a dienophile in Diels–Alder reactions involving cyclopentadiene. This reactivity is in complete agreement with a ω value of 4.4 eV, determined by using the Parr methodology, revealing the high electrophilic character of **13**. To our knowledge, this is the first example of Diels–Alder reaction involving benzoquinone diazide. We have also shown that these compounds can be prepared by using water-free conditions such as tertiobutylnitrite in acetonitrile, indicating that water formed during the diazotization process is sufficient for substitution of the fluorine atom. Although the substitution of the nitro groups of DNBF (**1**) by fluorine atoms results in a large decrease of the electrophilic character of fluorobenzofuroxans, the new fluorinated benzofuroxans could be used to prepare new quinoxaline derivatives, which will be biologically tested in further trials. Both the electrochemical and the theoretical

studies have shown that the electrophilicity of fluorobenzofuroxans falls below the border demarcating super and normal electrophilic behavior, indicating a low electrophilic character comparable to that of benzotrithiadiazole.

Experimental Section

General: ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with Bruker 200 and 300 MHz spectrometers. All spectroscopic data are reported in ppm in the δ-scale relative to internal TMS (^{1}H and ^{13}C NMR) or $CFCl_3$ (^{19}F NMR). Abbreviations used are: br. s = broad signal; d = doublet; m = multiplet. Melting points were determined with a Büchi B-545 and are uncorrected. Starting materials were obtained from commercial sources and were used without further purification. Substituted benzofuroxans **24**–**25** were obtained according to reported procedures.[13,32,35]

4,6-Difluorobenzofuroxan (3): Obtained from 3,5-difluoro-2-nitroaniline (**21**).

3,5-Difluoro-2-nitroaniline (21): 3,5-Difluoroaniline (11.16 g, 86.4 mmol) was added to acetic anhydride (15 mL, 155.5 mmol) at 0 °C and the mixture was stirred for 1 h at room temperature. Water (30 mL) was then added and the mixture was stirred for 30 min at room temperature. The precipitate was filtered off to obtain 3,5-difluoroacetanilide as a white solid (14 g, 95%; m.p. 130 °C), which was used without further purification. 3,5-Difluoroacetanilide (7 g, 41 mmol) was dissolved in dichloromethane (50 mL) and a mixture of fuming nitric acid (3.9 mL, 94 mmol), and sulfuric acid (3.9 mL) was added dropwise at 0 °C. The mixture was stirred for 18 h at room temperature, then the residue was diluted in water and extracted with dichloromethane to give a mixture of two products as a white-yellow solid, which was separated by column chromatography on silica gel (ErOAc/petroleum ether, 1:20) to obtain 3,5-difluoro-2-nitroacetanilide (6 g, 68%, m.p.99.6 °C) and 3,5-difluoro-4-nitroacetanilide (1 g, 11%, m.p. 137 °C).

3,5-Difluoro-2-nitroacetanilide: ^{1}H NMR ([D$_6$]acetone): δ = 7.84 (m, 1 H, H-6), 7.15 (m, 1 H, H-4) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –102.5 (m, 1 F, F-5), –117.6 (m, 1 F, F-3) ppm. ^{13}C NMR ([D$_6$]-acetone): δ = 169.8 (C-7), 164.7 (d, J = 252.1 Hz, C-5), 156.9 (d, J = 258.6 Hz, C-3), 135.9 (C-1), 129.1 (C-2), 107.0 (C-6), 101.4 (C-4), 24.3 (CH_3) ppm. HRMS: m/z calcd. [MH$^+$] 217.0425; found 217.0425.

3,5-Difluoro-4-nitroacetanilide: ^{1}H NMR ([D$_6$]acetone): δ = 7.58 (d, J = 12 Hz, H-2–5), 2.16 (s, 3 H, CH_3) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –119.41 (d, J = 12 Hz, F-3–5) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 170.68 (C-7), 156.8 (d, J = 255.8 Hz, C-3–5), 145.7 (C-1), 125.2 (br. s, C-4), 103.7 (C-2–5), 24.8 (CH_3) ppm. HRMS: m/z calcd. for [MH$^+$] 217.0425; found 217.0417.

3,5-Difluoro-2-nitroacetanilide (9 g, 41.65 mmol) was then heated at reflux in HCl (3 M, 200 mL) for 4 h at 100 °C. The mixture was diluted with water (300 mL) and filtered to obtain 3,5-difluoro-2-nitroaniline **21** (6.5 g, 89%; m.p. 108 °C) as yellow solid, which was engaged in the next step without further purification. ^{1}H NMR ([D$_6$]acetone): δ = 6.61 (m, 1 H, H-6), 6.42 (m, 1 H, H-4) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –103.2 (m, 1 F, F-5), –114.4 (m, 1 F, F-3) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 166.1 (d, J = 250.9 Hz, C-5), 159.9 (d, J = 259.9 Hz, C-3), 149.2 (C-1), 121.0 (C-2), 100.1 (C-6), 94.1 (C-4) ppm.

3,5-Difluoro-2-nitroaniline **21** (6.5 g, 37.4 mmol) was dissolved in a mixture of acetic acid (40 mL) and sulfuric acid (20 mL). The reaction mixture was cooled to 0 °C, then a solution of sodium nitrite (2.84 g, 41.14 mmol) in water (10 mL) was added dropwise, immediately followed by the addition of a solution of sodium azide (3.40 g, 52.36 mmol) in water (10 mL). The mixture was stirred for 1 h at room temperature, then water (200 mL) was added to obtain 3,5-difluoro-2-nitrophenylazide **20** (5.15 g, 70%; m.p. 55 °C) as a yellow solid. ^{1}H NMR ([D$_6$]acetone): δ = 7.37 (m, 1 H, H-6), 7.23 (m, 1 H, H-4) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –103.4 (m, 1 F, F-5), –120.6 (m, 1 F, F-3) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 164.2 (d, J = 254.2 Hz, C-5), 156.1 (d, J = 256.1 Hz, C-3), 138.2 (C-1), 129.4 (C-2), 105.2 (C-6), 102.3 (C-4) ppm.

3,5-Difluoro-2-nitrophenylazide **20** (5.15 g, 25.75 mmol) was heated at reflux in toluene for 15 h. After cooling, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/petroleum ether, 1:50) to obtain 4,6-difluorobenzofuroxan **3** (4.36 g, 98%) as an orange liquid. ^{1}H NMR ([D$_3$]acetonitrile, r.t.): δ = 7.05 (br. s, 2 H, H-5–7) ppm. ^{19}F NMR ([D$_3$]acetonitrile, r.t.): δ = –104.6 (br. s, 1 F, F-4), –123.9 (br. s, 1 F, F-6) ppm.

4-Fluorobenzofuroxan (4): A mixture of 1,3-difluoro-2-nitrobenzene (450 mg, 2.83 mmol) and sodium azide (202 mg, 3.11 mmol) was heated at reflux in anhydrous CH_3CN (35 mL) for 15 h. The solution was then cooled and the solvent was evaporated under reduced pressure. The residue was heated at reflux in toluene for an additional period of 5 h to complete the cyclization of the remaining azide. After evaporation of toluene, the residue was purified by column chromatography on silica gel (EtOAc/petroleum ether, 1:10) to obtain 4-fluorobenzofuroxan **4** (435 mg, 99%; m.p. 45 °C) as an orange solid. ^{1}H NMR ([D$_3$]acetonitrile): δ = 7.25 (br. s, 3 H, H-5–7) ppm. ^{19}F NMR ([D$_3$]acetonitrile): δ = –129.3 (br. s, 1 F, F-4) ppm.

2-Diazo-5-fluoro-3-nitrobenzoquinone (13): 2,4-Difluoro-6-nitroaniline (650 mg, 3.74 mmol) was dissolved in a mixture of acetic acid (20 mL) and sulfuric acid (10 mL). The solution was cooled to 0 °C and a solution of sodium nitrite (284 mg, 4.11 mmol) in water (5 mL) was added dropwise. The mixture was stirred for 1 h at room temperature. After the removal of the solvent under reduced pressure, the residue was extracted with EtOAc to obtain, after evaporation, 2-diazo-5-fluoro-3-nitrobenzoquinone **13** (428 mg, 63%; m.p. 75 °C) as an orange solid. ^{1}H NMR ($CDCl_3$): δ = 7.18 (dd, J = 7.8 Hz, H-4), 6.68 (dd, J = 10.8 Hz, H-6) ppm. ^{19}F NMR ($CDCl_3$): δ = –94.1 (m, 1 F, F-5) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.6 (C-1), 167.2 (d, J = 267.3 Hz, C-5), 142.8 (C-2), 114.3 (C-4), 107.8 (C-6), 79.4 (C-3) ppm. HRMS: m/z calcd. for [MH$^+$] 184.0158; found 184.0160. The experimental data were in agreement with those reported previously.[19]

4-Ethoxy-6-fluorobenzofuroxan (14) and 4,6-Diethoxybenzofuroxan (15): Obtained from 4,6-difluorobenzofuroxan (**3**) upon treatment with sodium ethoxide in ethanol. To a solution of **3** in ethanol was added sodium ethoxide (1 equiv.). After 30 min at room temperature, ethanol was evaporated to give **14** (90%; m.p. 79 °C) as a pale-yellow solid. ^{1}H NMR ([D$_3$]acetonitrile): δ = 6.62 (br. s, 2 H, H-5–7), 4.28 (q, J = 7.0 Hz, 2 H, CH_2), 1.50 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR ([D$_3$]acetonitrile): δ = –104.4 (br. s, 1 F, F-5) ppm. HRMS: m/z calcd. for [MH$^+$] 199.0519; found 199.0516.

Compound **14** was then poured into ethanol and sodium ethoxide (1 equiv.) was added. After 30 min stirring and the evaporation of ethanol, 4,6-diethoxybenzofuroxan (**15**; quantitative) was isolated as a yellow solid [m.p. 224 °C (decomp.)]. ^{1}H NMR ([D$_6$]acetonitrile): δ = 6.32 (br. s, 1 H, H-7), 6.04 (br. s, 1 H, H-5), 4.10 (q, J = 7.0 Hz, 2 H, CH_2), 3.54 (q, J = 7.0 Hz, 2 H, CH_2), 1.41 (t, J = 7.0 Hz, 3 H, CH_3), 1.13 (t, J = 7.0 Hz, 3 H, CH_3) ppm. HRMS: m/z calcd. for [MH$^+$] 225.0875; found 225.0878.

The same compounds were also obtained during the synthesis of **3** using basic and oxidative conditions.

2,4-Difluoro-6-nitroanisole (16): Potassium 2,4-difluoro-6-nitrophenoxide (3 g, 14 mmol) was dissolved in anhydrous CH_3CN. Dimethylsulfate (1.6 mL, 16.8 mmol) was added and the mixture was then heated at 40 °C for 15 h until the red color disappeared. The yellow reaction mixture was then cooled and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether) to obtain 2,4-difluoro-6-nitroanisole **16** (1.3 g, 50%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 7.36 (m, 1 H, H-5), 7.15 (m, 1 H, H-7) ppm. ^{19}F NMR ($CDCl_3$): δ = –112.9 (m, 1 F, F-4), –121.6 (d, J = 10.4 Hz, F-2) ppm. ^{13}C NMR ($CDCl_3$): δ = 156.5 (CF_{Ar}), 156.3 (CF_{Ar}), 144.2 (C-6), 139.1 (C-1), 109.7 (C-3), 107.6 (C-5), 62.9 (CH_3) ppm.

4,6-Difluoro-1-hydroxybenzotriazole (18): Hydrazine hydrate (0.1 mL, 2.92 mmol) was added to a solution of 2,4-difluoro-6-nitroanisole (500 mg, 2.65 mmol) in absolute ethanol and the mixture was heated at reflux for 15 h. After cooling and evaporation of the solvent, the residue was washed with chloroform and the solid was filtered to obtain 4,6-difluoro-1-hydroxybenzotriazole **18** (295 mg, 65%; m.p. 100 °C) as a red powder. ^{1}H NMR ([D$_6$]DMSO): δ = 7.53 (d, J = 8.4 Hz, H-7), 7.40 (m, 1 H, H-5) ppm. ^{19}F NMR ([D$_6$]-DMSO): δ = –117.8 (s, 1 F, F-4), –125.3 (s, 1 F, F-6) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 157.4 (d, J = 239.8 Hz, C-6), 151.7 (d, J = 256.4 Hz, C-4), 130.2 (C-9), 128.4 (C-8), 98.0 (C-5), 92.7 (C-7) ppm. HRMS: m/z calcd. for [MH]$^+$ 172.0322; found 172.0323.

23: 2-Diazo-5-fluoro-3-nitrobenzoquinone (100 mg, 0.55 mmol) was dissolved in dichloromethane (10 mL). Cyclopentadiene (1.4 mL, 16.5 mmol) was added and the reaction mixture was stirred for 3 d at room temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/petroleum ether, 1:10) to obtain **23** (24 mg, 18%; m.p. 88 °C) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ = 6.60 (m, 1 H, H-8), 6.05 (m, 1 H, H-9), 5.93 (d, J = 13.2 Hz, H-6), 3.63 (m, 2 H, H-4–10), 3.43 (s, 1 H, H-7), 1.85 (s, 2 H, CH_2) ppm. ^{19}F NMR ($CDCl_3$): δ = –82.1 (m, 1 F, F-5) ppm. ^{13}C NMR ($CDCl_3$): δ = 179.8 (C-1), 171.6 (d, J = 281.8 Hz, C-5), 140.3 (C-8), 132.5 (C-9), 108.6 (C-6), 93.4 (C-3), 68.7 (C-2), 54.0 (C-10), 47.3 (C-7), 46.5 (CH_2), 45.7 (C-4) ppm. HRMS: m/z calcd. for [MH]$^+$ 250.0628; found 250.0634.

Synthesis of Substituted Fluorobenzofurazan. General Procedure: Substituted fluoro-benzofuroxan (1 equiv.) was heated at reflux with triethylphosphite (1.2 equiv.) in toluene overnight. After cooling, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether) to give the substituted fluorobenzofurazan.

4,6-Difluorobenzofurazan 5: Yield 50 mg (18%); pale-yellow, highly volatile liquid. ^{1}H NMR ([D$_6$]acetone): δ = 7.58 (m, 1 H, H-7), 7.39 (m, 1 H, H-5) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –101.6 (d, J = 8.7 Hz, F-4), –117.7 (m, 1 F, F-6) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 164.5 (d, J = 256.5 Hz, C-6), 152.0 (d, J = 267.0 Hz, C-4), 151.2 (C-8), 143.2 (C-9), 109.9 (C-5), 97.8 (C-7) ppm.

4-Fluorobenzofurazan (6): Yield 42%; colorless, highly volatile liquid. ^{1}H NMR ([D$_6$]acetone): δ = 7.82 (d, J = 9.0 Hz, H-7), 7.62 (m, 1 H, H-6), 7.33 (m, 1 H, H-5) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –122.9 (m, 1 F, F-4) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 152.7 (C-8), 150.8 (d, J = 254.9 Hz, C-4), 144.3 (C-9), 133.9 (C-6), 115.2 (C-5), 114.1 (C-7) ppm.

5-Fluorobenzofurazan (27): Yield 75%; yellow oil. ^{1}H NMR ([D$_6$]-acetone): δ = 8.11 (m, 1 H, H-7), 7.66 (d, J = 8.4 Hz, H-4), 7.52 (m, 1 H, H-6) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –104.7 (m, 1 F, F-5) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 164.7 (d, J = 256.0 Hz, C-5), 150.6 (C-9), 148.6 (C-8), 126.9 (C-6), 120.5 (C-7), 99.5 (C-4) ppm.

5,6-Difluorobenzofurazan (28): Yield 62%; white solid; m.p. 114 °C. ^{1}H NMR ([D$_6$]acetone): δ = 8.00 (m, 2 H, H-4–7) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –122.4 (m, 2 F, F-5,6) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 155.4 (d, J = 262.5 Hz, C-5,6), 147.2 (C-8–9), 102.2 (C-4–7) ppm.

4,5,6-Trifluorobenzofurazan (29): Yield 87%; colorless, highly volatile liquid; ^{1}H NMR ([D$_6$]acetone): δ = 7.95 (m, 1 H, H-7) ppm. ^{19}F NMR ([D$_6$]acetone): δ = –121.9 (m, 1 F, F-5), –146.9 (m, 1 F, F-4), –150.9 (m, 1 F, F-6) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 156.4 (d, J = 261.5 Hz, C-6), 146.9 (C-8), 143.1 (C-5), 142.7 (C-9), 138.7 (C-4), 98.7 (C-7) ppm.

4-Ethoxy-6-fluorobenzofuroxan (30): Prepared in quantitative yield by following the procedure used for the synthesis of **14**. ^{1}H NMR ([D$_6$]acetone): δ = 7.24 (br. s, 1 H, H-6), 6.93 (br. s, 1 H, H-7), 6.75 (br. s, 1 H, H-5), 4.30 (q, J = 7.0 Hz, 2 H, CH_2), 1.48 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 149.9 (C-4), 131.8 (C-6), 116.6 (C-8), 109.6 (C-5), 105.0 (C-7) ppm. Were were unable to determine the chemical shift of the C-9 carbon even by recording ^{13}C NMR spectra in other solvents. HRMS: m/z calcd. for [MH$^+$] 181.0613; found 181.0616.

6-Fluoro-4-piperidinobenzofuroxan (31): A mixture of 3,5-difluorobenzofuroxan (200 mg) and piperidine (1.2 equiv.) in THF (20 mL) was stirred at room temperature until completion of the reaction (3 d). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 0–10%) to give **31** (56%) as an orange solid; m.p. 82.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.26 (dd, J = 6.7, 1.7 Hz, 1 H), 6.08 (d, J = 12.2 Hz, 1 H), 3.71–3.52 (m, 4 H), 1.85–1.63 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.6 (d, J = 253.4 Hz), 148.2, 142.5 (d, J = 12.8 Hz), 115.3 (d, J = 16.5 Hz), 101.1 (d, J = 34.5 Hz), 83.4 (d, J = 30.9 Hz), 50.5, 25.5, 24.3 ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –103.19 (dd, J = 12.2, 6.7 Hz) ppm.

Synthesis of Substituted Quinoxalines 32–34. General Procedure: 4,6-Difluorobenzofuroxan (200 mg, 1 equiv.) and carbonylated compound (1.2 equiv.) was heated at reflux in the presence of calcium hydroxide (2.3 mg) in 2-propanol (5 mL) for 18 h. The hot mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 0–5%) to give the product in fair to modest yield. When fair yields were obtained, the starting 4,6-difluorobenzofuroxan was recovered.

32a: Yield 16%; white powder; m.p. 100.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.4 Hz, 1 H, H-8), 7.36 (td, J = 9.5, 2.3 Hz, 1 H, H-6), 2.68 (s, 3 H, H-13), 2.63 (s, 3 H, H-12) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.2 (s, C-11), 162.0 (dd, J = 255.6, 12.0 Hz, C-7), 158.2 (dd, J = 244.9, 18.9 Hz, C-5), 152.3 (d, J = 1.7 Hz, C-3), 139.0 (s, C-2), 136.7 (d, J = 12.0 Hz, C-9), 132.7 (dd, J = 14.8, 2.4 Hz, C-10), 108.4 (dd, J = 29.3, 22.3 Hz, C-6), 100.1 (dd, J = 27.4, 5.1 Hz, C-8), 29.7 (s, C-12), 22.3 (s, C-13) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –103.1 (dd, J = 8.4 Hz, F-5), –116.4 (dd, J = 13.7, 5.7 Hz, F-7) ppm. HRMS: m/z = 223.0681.

32b: Yield 14%; pale-yellow solid; m.p. 116.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, 1 H, H-8), 7.35 (ddd, J = 11.4, 2.2, 1.1 Hz, 1 H, H-6), 4.55 (q, J = 6.7 Hz, 2 H, H-12), 2.95 (s, 3 H, H-14), 1.48 (t, J = 7.1 Hz, 3 H, H-13) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.2 (s, C-11), 162.1 (dd, J = 218.8, 13.3 Hz, C-7), 156.9 (dd, J = 230.2, 13.3 Hz, C-5), 152.5 (t, J = 2.8 Hz, C-3), 146.6

(s, C-2), 141.0 (dd, J = 14.8, 2.1 Hz, C-9), 130.7 (dd, J = 12.1, 1.9 Hz, C-10), 109.5 (dd, J = 22.0, 5.3 Hz, C-8), 107.6 (dd, J = 29.9, 22.2 Hz, C-6), 62.9 (s, C-12), 23.6 (s, C-14), 14.3 (s, C-13) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –105.3 (dd, J = 16.2, 8.4 Hz, F-5), –120.4 (t, J = 8.3 Hz, F-7) ppm. HRMS: m/z = 253.0791.

32c: Yield 13%: yellow powder; m.p. 93.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (dd, J = 4.5, 2.3 Hz, 2 H, Ar-H), 7.66 (d, J = 8.7 Hz, 1 H, H-8), 7.51 (dd, J = 3.9, 2.3 Hz, 3 H, Ar-H), 7.37 (td, J = 9.4, 2.3 Hz, 1 H, H-6), 4.34 (q, J = 7.1 Hz, 2 H, H-12), 1.18 (t, J = 7.1 Hz, 3 H, H-13) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2 (s, C-11), 162.2 (dd, J = 253.8, 12.1 Hz, C-7), 157.9 (dd, J = 265.6, 14.4 Hz, C-5), 151.6 (d, J = 2.3 Hz, C-3), 147.8 (s, C-2), 141.0 (dd, J = 14.8, 1.8 Hz, C-9), 137.0 (s, C-14), 130.6 (dd, J = 12.1, 1.5 Hz, C-10), 130.1 (s, C-17), 128.84 (s, C-Ar), 128.80 (s, C-Ar), 109.3 (dd, J = 22.1, 5.3 Hz, C-8), 107.6 (dd, J = 30.0, 22.1 Hz, C-6), 62.8 (s, C-12), 13.8 (s, C-13) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –103.9 (dd, J = 16.6, 8.5 Hz, F-5), –119.1 (t, J = 8.4 Hz, F-7) ppm.

33a: Yield 21%; yellow powder; m.p. 114.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.7 Hz, 1 H, H-8), 7.34 (td, J = 9.4, 2.5 Hz, 1 H, H-6), 2.96 (s, 3 H, H-12), 2.81 (s, 3 H, H-13) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.9 (s, C-11), 161.6 (dd, J = 252.5, 12.2 Hz, C-7), 157.2 (dd, J = 264.1, 14.4 Hz, C-5), 152.9 (t, J = 2.9 Hz, C-3), 148.8 (s, C-2), 140.9 (dd, J = 14.6, 2.2 Hz, C-9), 130.8 (dd, J = 11.8, 2.0 Hz, C-10), 109.4 (dd, J = 21.6, 5.3 Hz, C-8), 107.7 (dd, J = 29.9, 22.3 Hz, C-6), 27.9 (s, C-12), 24.4 (s, C-13) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –105.9 (dd, J = 15.8, 8.5 Hz, F-5), –120.4 (dd, J = 12.4, 4.6 Hz, F-7) ppm. HRMS: m/z = 223.0684.

33b: Yield 14%; white solid; m.p. 116.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.6 Hz, 1 H, H-8), 7.34 (td, J = 9.4, 2.7 Hz, 1 H, H-6), 4.55 (q, J = 7.1 Hz, 2 H, H-12), 2.67 (s, 3 H, H-14), 1.43 (t, J = 7.1 Hz, 4 H, H-13) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7 (dd, J = 253.5, 11.25 Hz, C-7), 161.3 (s, C-11), 158.2 (dd, J = 262.0, 11.4 Hz, C-5), 152.0 (dd, J = 2.9, 1.1 Hz, C-3), 136.6 (dd, J = 12.8, 3.6 Hz, C-9), 135.0 (s, C-2), 132.7 (dd, J = 14.8, 2.4 Hz, C-10), 108.4 (dd, J = 29.3, 22.3 Hz, C-6), 100.3 (dd, J = 27.5, 5.1 Hz, C-8), 63.5 (s, C-12), 22.0 (s, C-14), 14.41 (s, C-13) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –103.2 (dd, J = 8.4 Hz, F-5), –116.5 (dd, J = 38, 1.5 Hz, F-7) ppm. HRMS: m/z = 253.0784.

33c: Yield 15%; white solid; m.p. 102.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.6 Hz, 1 H, H-8), 7.77 (dd, J = 6.8, 1.3 Hz, 2 H, H-Ar), 7.48 (m, 3 H, H-Ar), 7.40 (td, J = 8.8, 2.7 Hz, 1 H, H-6), 4.40 (q, J = 7.1 Hz, 2 H, H-12), 1.21 (t, J = 7.1 Hz, 3 H, H-13) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2 (dd, J = 255.2, 10.0 Hz, C-7), 161.4 (s, C-11), 158.9 (dd, J = 255.2, 10.0 Hz, C-5), 152.9 (dd, J = 2.9, 1.2 Hz, C-3), 136.6 (dd, J = 12.9, 3.3 Hz, C-9), 135.6 (s, C-2), 135.0 (s, C-14), 133.1 (dd, J = 15.0, 2.3 Hz, C-10), 130.8 (s, C-17), 129.0 (s, C-Ar), 128.6 (s, C-Ar), 108.7 (dd, J = 29.4, 22.2 Hz, C-6), 100.4 (dd, J = 27.5, 5.2 Hz, C-8), 63.4 (s, C-12), 13.8 (s, C-13) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –103.1 (q, J = 8.4 Hz, F-5), –116.4 (m, F-7) ppm.

33d: Yield 30%; pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (td, J = 10.6, 4.2 Hz, 1 H, H-8), 7.81 (d, J = 10.6, 4.2 Hz, 2 H, H-13), 7.66 (dd, J = 10.6, 4.2 Hz, 1 H, H-12), 7.51 (t, J = 7.7 Hz, 2 H, H-14), 7.39 (ddd, J = 9.4, 8.5, 2.8 Hz, 1 H, H-6), 2.59 (s, 3 H, H-16) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.6 (s, C-11), 161.9 (dd, J = 251.1, 7.6 Hz, C-7), 158.3 (dd, J = 259.3, 8.7 Hz, C-5), 153.0 (dd, J = 2.9, 1.1 Hz, C-3), 138.4 (s, C-2), 136.8 (dd, J = 12.7, 3.9 Hz, C-9), 135.3 (s, C-15), 134.4 (s, C-12), 133.0 (dd, J = 14.8, 2.4 Hz, C-10), 129.6 (s, C-14), 129.0 (s, C-13), 108.4 (dd, J = 29.2, 22.3 Hz, C-6), 100.3 (dd, J = 27.4, 5.1 Hz, C-8), 22.1 (s, C-16) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –103.1 (q, J = 8.4 Hz, F-5), –116.4 (m, F-7) ppm.

34e: Yield 54.5%; yellow powder; m.p. 100.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.1 Hz, 1 H, H-8), 7.77 (d, J = 7.5 Hz, 2 H, H-13), 7.60 (t, J = 7.2 Hz, 1 H, H-15), 7.41 (m, 9 H, H-6 and Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.1 (s), 163.2 (dd, J = 258.7, 11.6 Hz), 156.3 (dd, J = 273.1, 12.9 Hz), 141.7 (dd, J = 3.8, 2.6 Hz), 140.3 (s), 140.1 (s), 135.2 (s), 134.5 (s), 131.0 (s), 130.1 (s), 129.4 (s), 129.1 (s), 129.0 (s), 127.7 (m), 126.2 (s), 109.7 (dd, J = 28.7, 24.7 Hz), 102.6 (dd, J = 27.8, 5.7 Hz) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –99.1 (m, F-5), –108.1 (m, F-7) ppm. HRMS: m/z = 379.0898.

X-ray Structural Analysis: X-ray intensity data were collected with a Bruker X8-APEX2 CCD area-detector diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Data reduction was accomplished using SAINT V7.03. The substantial redundancy in data allowed a semiempirical absorption correction (SADABS V2.10)[42] to be applied, on the basis of multiple measurements of equivalent reflections. The structure was solved by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix least-squares on all F^2 data using SHELXTL V6.12.[43] Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms.

Computational Information: Full geometry optimizations for the dienes and dienophiles not previously studied have been performed at the B3LY8/6-31G* level of theory,[44–46] which is implemented in the Gaussian 03 package of programs.[46] The global electrophilicity power (ω) was evaluated by means of Equation (4). The electronic chemical potential (μ) and chemical hardness (η) values were approximated in terms of the one-electron energies of the frontier molecule orbitals (FMO), ε_H and ε_L, respectively, by using $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta = \varepsilon_H - \varepsilon_L$,[39] respectively, at the ground state (GS) of the molecules.

Crystal Structure Analysis: See the Supporting Information. The crystal structures (Figure 1, Figures 2 and 8) have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC-977343 (for **13**), -977344 (for **14**), -977345 (for **4**), -996899 (for **32a**), and -996900 (for **33b**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H, ^{13}C, and ^{19}F NMR spectra of the key intermediates together with the low- and high-temperature NMR spectra of the two benzofuroxans **4** and **14**.

Acknowledgments

The authors are grateful for the support of this research by the Centre National de la Recherche Scientifique (CNRS) and the Ministry of Research of Russia (grant RCF 14-13-00103).

[1] a) F. Terrier, S. Lakhdar, R. Goumont, T. Boubaker, *Chem. Commun.* **2004**, 2586–2587; b) L. Forlani, A. Tocke, E. Del Vecchio, S. Lakhdar, R. Goumont, F. Terrier, *J. Org. Chem.* **2006**, *71*, 5527–5537; c) S. Kurbatov, R. Goumont, V. Minkin, F. Terrier, *Chem. Commun.* **2006**, 4279–4281; d) S. Lakhdar, M. Westermaier, R. Goumont, T. Boubaker, H. Mayr, F. Terrier, *J. Org. Chem.* **2006**, *71*, 9088–9095; e) L. Forlani, E. Del Vecchio, R. Goumont, F. Terrier, *Chem. Eur. J.* **2007**, *13*, 9600–9607; f) R. Goumont, E. Jan, M. Makosza, F. Terrier, *Org.*

Biomol. Chem. **2003**, *1*, 2192; g) S. Kurbatov, P. Rodrigez-DaFonte, R. Goumont, F. Terrier, *Chem. Commun.* **2003**, 2150–2151; h) M. Sebban, R. Goumont, J. C. Halle, J. Marrot, F. Terrier, *Chem. Commun.* **1999**, 1009–1010.

[2] a) M. J. Haddadin, C. H. Issidorides, *Heterocycles* **1976**, *4*, 767; b) M. J. Haddadin, C. H. Issidorides, *J. Org. Chem.* **1966**, *31*, 4067–4068.

[3] H. Suzuki, T. A. Kawakami, *Synthesis* **1997**, 855–857.

[4] P. Ghosh, B. Ternai, M. Whitehouse, *Med. Res. Rev.* **1981**, *1*, 159–187.

[5] C. Jovene, E. Chugunova, R. Goumont, *Mini-Rev. Med. Chem.* **2013**, *13*, 1089–1136.

[6] C. Jovene, M. Sebban, J. Marrot, R. Goumont, in: *Targets in Heterocyclic Systems*, Chemical Society of Italy, Rome, Italy, **2012**, vol. 16, p. 90–112.

[7] a) S. D. Jorge, F. Palace-Berl, K. F. M. Pasqualoto, M. Ishii, A. K. Ferreira, C. M. Berra, R. V. Bosh, D. A. Maria, L. C. Tavares, *Eur. J. Med. Chem.* **2013**, *64*, 200–214; b) L. Wang, C. Li, Y. Zhang, C. Qiao, Y. Ye, *J. Agric. Food Chem.* **2013**, *61*, 8632–8640.

[8] J. B. Laursen, J. Nielsen, *Chem. Rev.* **2004**, *104*, 1663–1685.

[9] Y. Deepika, P. Surendra Nath, K. Sachin, S. Shewta, *Int. J. Curr. Pharm. Rev. Res.* **2011**, *1*, 33–46.

[10] A. Carta, P. Corona, M. Loriga, *Curr. Med. Chem.* **2005**, *12*, 2259–2272.

[11] a) M. Gonzales, H. Cerecetto, A. Monge, *Top. Heterocycl. Chem.* **2007**, *11*, 179–211; b) M. Gonzales, H. Cerecetto, *Expert Opin. Ther. Pat.* **2012**, *22*, 1289–1302.

[12] a) J. J. Cazzulo, *Curr. Top. Med. Chem.* **2002**, *2*, 1261–1271; b) P. Hotez, D. H. Molyneux, A. Fenwick, J. Kumaresan, S. E. Sachs, J. D. Sachs, L. N. Savioli, *N. Engl. J. Med.* **2007**, *357*, 1018–1027.

[13] S. Leyva, V. Castanedo, E. Leyva, *J. Fluorine Chem.* **2003**, *121*, 171–175.

[14] G. Berionni, A. M. Gonçalves, C. Mathieu, T. Devic, A. Etcheberry, R. Goumont, *Phys. Chem. Chem. Phys.* **2011**, *13*, 2857–2869.

[15] P. B. Ghosh, M. W. Whitehouse, *J. Med. Chem.* **1968**, *11*, 305–311.

[16] P. B. Ghosh, B. Ternai, M. W. Whitehouse, *J. Med. Chem.* **1972**, *15*, 255–260.

[17] a) A. J. Boulton, P. B. Gosh, *Adv. Heterocycl. Chem.* **1969**, *10*, 1–41; b) A. Gasco, A. J. Boulton, *Adv. Heterocycl. Chem.* **1981**, *29*, 251–340.

[18] P. B. Ghosh, M. W. Whitehouse, *J. Med. Chem.* **1968**, *11*, 305–311.

[19] P. Camps, J. Morral, D. Munoz-Torrero, *J. Chem. Res. Synop.* **1998**, 144–145.

[20] F. B. Mallory, *Org. Synth.* **1963**, *4*, 74–75.

[21] M. Y. Hang, V. Huynh, M. A. Hiskey, D. E. Chavez, R. D. Gilardi, *J. Energ. Mater.* **2005**, *23*, 99–106.

[22] S. C. Waller, Y. A. He, G. R. Harlow, Y. Q. He, E. A. Mash, J. R. Halpert, *Chem. Res. Toxicol.* **1999**, *12*, 690–699.

[23] M. D. Coburn, *J. Heterocycl. Chem.* **1974**, *11*, 1099–1100.

[24] F. Novelli, F. Sparatore, *Farmaco* **2002**, *57*, 871–882.

[25] G. C. Finger, F. H. Reed, J. L. Finnerty, *J. Am. Chem. Soc.* **1951**, *73*, 153–155.

[26] M. Sebban, C. Jovene, P. Sepulcri, D. Vichard, F. Terrier, R. Goumont, in: *Magnetic Resonance Spectroscopy* (Ed.: Donghyun Kim.), INTECH Publisher, Croatia, **2012**, chapter 10, p. 183–206.

[27] a) F. Terrier, J. C. Hallé, P. MacCormack, M. J. Pouet, *Can. J. Chem.* **1989**, *67*, 503–507; b) F. A. L. Anet, I. Yavari, *Org. Magn. Reson.* **1976**, *8*, 158–160.

[28] a) H. Friebolin in: *Basic One- and Two-Dimensional NMR Spectroscopy*, Wiley-VCH, Weinheim, Germany, **1998**, chapter 10; b) H. Gunther in: *NMR Spectroscopy*, 2nd ed., Wiley, Chichester, UK, **1995**, chapter 9.

[29] a) A. R. Katritzky, M. F. Gordeev, *Heterocycles* **1993**, *35*, 483–518; b) A. J. Boulton, P. J. Halls, A. R. Katritzky, *J. Chem. Soc. B* **1970**, 636–1970; c) A. J. Boulton, A. R. Katritzky, M. J. Sewell, B. Wallis, *J. Chem. Soc. B* **1967**, 914–919.

[30] K. Barral, A. D. Moorhouse, J. E. Moses, *Org. Lett.* **2007**, *9*, 1809–1811.

[31] a) S. Kurbatov, R. Goumont, S. Lakhdar, J. Marrot, F. Terrier, *Tetrahedron* **2005**, *61*, 8167–8176; b) E. A. Chugunova, A. D. Voloshina, R. E. Mukhamatdinova, I. V. Serkov, A. N. Proshin, E. M. Gibadullina, A. R. Burilov, N. V. Kulik, V. V. Zobov, D. B. Krivolapov, A. B. Dobrynin, R. Goumont, *Lett. Drug Des. Discovery* **2014**, *11*, 502–512.

[32] J. M. Winter, A. L. Jansma, T. M. Handel, B. S. Moore, *Angew. Chem. Int. Ed.* **2009**, *48*, 767–770; *Angew. Chem.* **2009**, *121*, 781.

[33] M. E. Jung, T. A. Dong, X. Cai, *Tetrahedron Lett.* **2011**, *52*, 2533–2535.

[34] S. Uchiyama, K. Takeshira, S. Kohtani, T. Santa, R. Nakagaki, S. Tobita, K. Imai, *Phys. Chem. Chem. Phys.* **2001**, *4*, 4514–4522.

[35] S. K. Kotovskaya, S. A. Romanova, V. N. Charushin, M. I. Kodess, O. N. Chupakhin, *J. Fluorine Chem.* **2004**, *125*, 421–428.

[36] E. Pretsch, P. Bühlmann, M. Badertscher, in: *Structure Determination of Organic Compounds*, Springer, Berlin/Heidelberg, **2009**, p. 109–260.

[37] a) P. Arroyo, M. T. Picher, L. R. Domingo, *J. Mol. Struct.* **2004**, *709*, 45–52; b) L. R. Domingo, M. J. Aurell, P. Perez, R. Contreras, *Tetrahedron* **2002**, *58*, 4417–4423; c) L. R. Domingo, M. J. Aurell, P. Perez, R. Contreras, *J. Phys. Chem. A* **2002**, *106*, 6871–6875; d) P. Perez, L. R. Domingo, M. J. Aurell, R. Contreras, *Tetrahedron* **2003**, *59*, 3117–3125.

[38] R. G. Parr, L. Von Szentpaly, S. Liu, *J. Am. Chem. Soc.* **1999**, *121*, 1922–1924.

[39] a) R. G. Parr, W. Yang, in: *Density Functional Theory of Atoms and Molecules*, Oxford University Press, New York, **1989**. b) R. G. Parr, R. G. Pearson, *J. Am. Chem. Soc.* **1983**, *105*, 7512–7516.

[40] S. Lakhdar, G. Berionni, R. Goumont, F. Terrier, *Lett. Org. Chem.* **2011**, *8*, 108–118.

[41] A. F. Kluge, M. L. Maddox, G. S. Lewis, *J. Org. Chem.* **1980**, *45*, 1909–1914.

[42] G. M. Sheldrick, *SHELXTL*, version 5.1, Bruker AXS Inc., Madison, WI, USA, **1999**.

[43] *APEX2*, version 1.0–8, Bruker AXS, Madison, WI, **2003**.

[44] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.

[45] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.

[46] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, T. Vreven Jr., K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, revision B.04, Gaussian, Inc., Pittsburgh PA, **2003**.

Received: June 4, 2014
Published Online: September 4, 2014

