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Benzofuroxans

A Synthetic Pathway to Substituted Benzofuroxans through the Intermediacy of Sulfonates: The Case Example of Fluoro-Nitrobenzofuroxans

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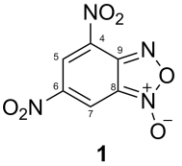
Abstract: Benzofuroxans are well known compounds that continue to attract particular attention since the discovery of 4,6-dinitrobenzofuroxan (DNBF) back in 1899. It has been shown that these compounds possess biological activities that are related to their electronic behaviours and the positioning of substituents borne by the heterocycles. In this paper, we report the first synthesis of 4-fluoro-6-nitrobenzofuroxan and 6-fluoro-4-nitrobenzofuroxan; the altered positions of the substituents enabling us to carry out structural and reactivity comparisons, with DNBF and 4,6-difluorobenzofuroxan. These compounds have been unambiguously characterized through NMR and radiocrystallographic studies. Two main synthetic pathways involving fluoroanisoles and fluorophenols, cheap and easily available chemicals, have been successfully developed. Finally, benzofurazan analogues have been prepared via deoxygenation of corresponding benzofuroxans with triethylphosphite.

Introduction

Since the synthesis of 4,6-dinitrobenzofuroxan **1** in 1899 by Drost,[1] benzofuroxans have attracted particular attention; **1** displays a broad spectrum of biological activities including antibacterial, antifungal and immunosuppressive properties. Importantly, the medicinal properties of **1** and related agents are closely related to the nature and position of the substituent(s) borne by the heterocyclic core.[2] Even though the first members of the benzofuroxans were synthesized at the end of the 19th century, papers in this major field of heterocyclic chemistry continue to be published, adding consistency to the present work.[3,4] The formation of substituted benzofuroxans is readily achieved by heating correspondingly substituted α-nitrophenyl azides. These azides are obtained from the corresponding nitroanilines by diazotization followed by treatment with aqueous solutions of azide or from nucleophilic displacements at chlorinated centers with sodium azide. The experimental conditions depend on the nature of the substituent on the core aromatic scaffold. In the case of electron-withdrawing groups, the S_NAr process of chloride removal is easily achieved under mild conditions (2 h at room temperature) whereas for electron-donating groups, another possible pathway involves oxidative conditions (i.e. sodium hypochlorite in basic alcoholic solution).[5] The fluorine atom, as a substituent in the chemistry of benzofuroxans, can be very interesting because of its amenability to substitution with variously substituted nucleophiles leading to highly functionalized heterocycles.[6] Importantly, fluorine is also known to enhance the ability of organic compounds to penetrate lipid-based membranes.[7] Furthermore, fluorobenzofuroxans also serve as starting points for the synthesis of bioactive compounds. For example, Beirut reaction to 5,6-difluorobenzofuroxan **2** affords fluorinated quinoxaline **3**, a powerful inhibitor of more than 60 tumor cell types.[8]



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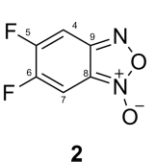

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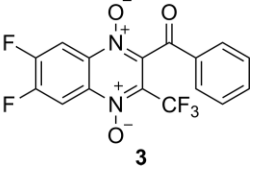

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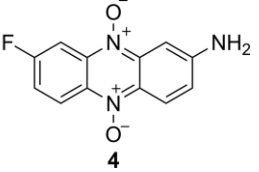
Finally, new fluorinated phenazine-type compound **4** has been shown to be a promising bioreductive antitumor agent. It displayed selective toxicity towards hypoxic V79 cells having an appropriate hypoxic cytotoxicity ratio (HCR = 6.8).[9] Mono- and poly-fluorobenzofuroxans and their benzofurazan analogues are already known and a revisited synthesis of these fluorobenzofuroxans, especially 4,6-difluorobenzofuroxan (DFBF) **5**, has been recently reported by our group.[10]



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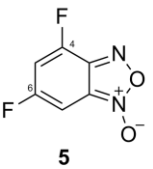

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However, the preparation of fluoronitrobenzofuroxan has been much less often described in the literature. One can refer-

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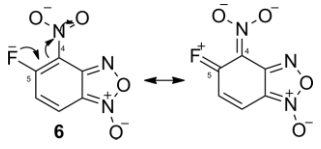
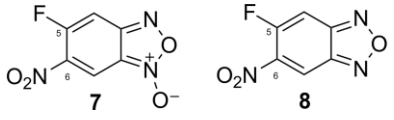
ence the study of 5-fluoro-4-nitrobenzofuroxan (**6**) by Whitehouse and co-workers in 1972. This work highlights an interaction between the scaffold-borne fluoro and nitro groups that diminished the susceptibility of the fluorinated center to undergo substitution chemistry (Scheme 1).[11] Also notable has been work by Okiyama and co-workers to determine the fluorescence properties of 5-fluoro-6-nitrobenzofuroxan (**7**) and its benzofurazan analogue **8**.[12]

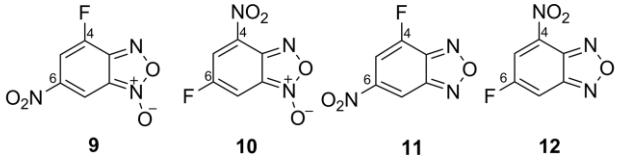


Scheme 1. Interaction of F and NO_2 moieties within benzofuroxan **6**.[11]



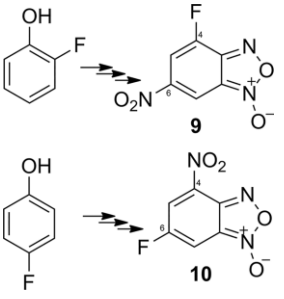
The ability to prepare new substituted fluorinated benzofuroxans is of great interest because: i) it increases the scope of available benzofuroxans, and ii) such species can be used as precursors in the production of new biologically active compounds.

In this paper, we report the first synthesis of two unknown species 4-fluoro-6-nitrobenzofuroxan (**9**) and 6-fluoro-4-nitrobenzofuroxan (**10**) using, for the first time, phenols as starting materials. The 4 and 6 positions of benzofuroxans **9** and **10** have been deliberately chosen for modification in order to better understand the influence of fluoride and nitro group positioning (and interplay) on the reactivity of these heterocycles. Finally, we report the successful synthesis of benzofurazan analogues **11** and **12**, generated via deoxygenation of benzofuroxans **9** and **10**, respectively.



Results and Discussion

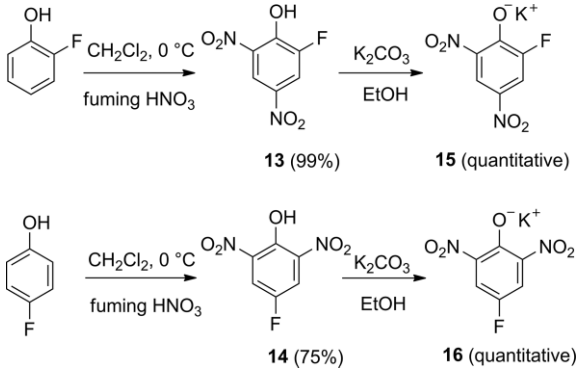
As was mentioned above, one of the most common synthetic approaches to benzofuroxans bearing electron-withdrawing groups entails the reaction of *o*-chloronitrobenzenes with sodium azide followed by the thermal decomposition of the corresponding nitrophenyl azide, leading to the benzofuroxan in nearly quantitative yield.[13] To overcome difficult nitration of chlorofluorobenzenes and to also avoid competitive nucleophilic displacements of Cl vs. F, an alternative synthetic pathway using fluorophenols was undertaken. Phenols are a class of very common chemicals possessing many interesting properties for the synthesis of benzofuroxan: i) fluorophenols are commercially available; ii) the activating hydroxy group enables facile dinitration of the phenyl ring, and iii) the high stability of the nitrophenolate ion allows for possible conversion of the OH into a good leaving group. Accordingly, and as described below, benzofuroxans **9** and **10**, have been prepared from 2-fluorophenol and 4-fluorophenol, respectively (Scheme 2).



Scheme 2. Global synthetic strategy to **9** and **10**.

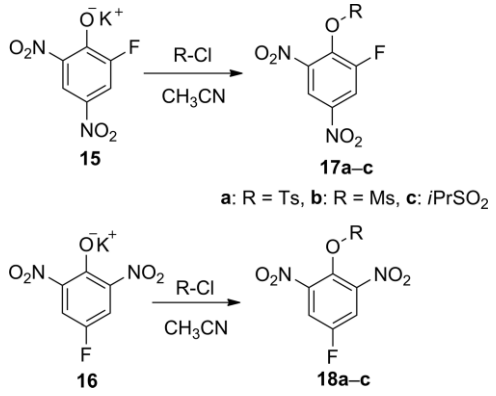
1) Synthesis of Fluorobenzofuroxans 9 and 10

First, the nitration of the two phenols is accomplished under mild conditions in a liquid–liquid two phase system HNO_3 (fuming)/CH_2Cl_2 at 0 °C leading to the dinitro compounds in 99 % and 75 % yields, respectively. The NMR spectroscopic data for these two dinitrophenols are in good agreement with those reported in the literature.[14] The deprotonation of the two dinitrophenols is easily achieved by treating a solution of **13** and **14** in ethanol with potassium carbonate, leading to the precipitation and isolation of highly colored ions **15** and **16** in quantitative yields (Scheme 3).



Scheme 3. Formation of phenolate ions.

The conversion of the phenolate ion to sulfonate analogues has been performed using various sulfonyl chlorides [a: *p*-toluenesulfonyl chloride (TsCl), b: methanesulfonyl chloride (MsCl), and c: isopropylsulfonyl chloride] to understand the influence of the substituent on the subsequent S_NAr process (Scheme 4). Heating of a suspension of the phenolate ion in acetonitrile with the sulfonyl chloride led to formation of compounds **17a–c** and **18a–c** in moderate to good yields as pale yellow solids (Scheme 4, Table 1). The structures of these compounds are in total accord with NMR spectroscopic data recorded in CD_3CN. For example, the ^1H NMR spectra recorded for **17b** and **18b** exhibited singlets at δ = 3.50 and 3.43 ppm, respectively. Similarly, the spectra obtained for **17c** and **18c** revealed a septuplet/doublet system at 3.85/1.56 and 3.80/1.52 ppm, respectively.

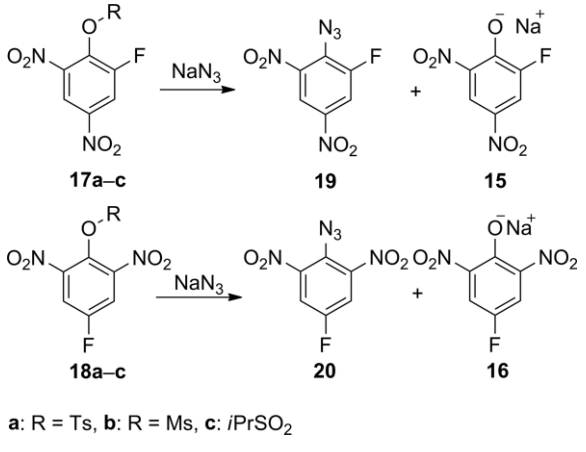


Scheme 4. Synthesis of **17a–c** and **18a–c**.

Table 1. Yields of sulfonates obtained from phenolate ions **15** and **16** as a function of sulfonyl chloride.

Sulfonyl chloride	Reaction with phenolate ion **15**	Reaction with phenolate ion **16**
a, TsCl	**17a**, 90 %	**18a**, 98 %
b, MsCl	**17b**, 70 %	**18b**, 70 %
c, *i*PrSO$_2$Cl	**17c**, 99 %	**18c**, 60 %

The key step in the synthesis of **9** and **10** is the S_NAr process involving sulfonate displacement by NaN_3. Two sets of experimental conditions were tested in which the solvents were either: i) the ternary solvent system (water/ethanol/acetone) usually used in the lab, or ii) pure distilled CH_3CN (Scheme 5).[4] In both cases, the formation of *o*-nitrophenyl azides **19** and **20** was typically accompanied by concomitant formation of ions **15** and **16** as highlighted by the rapid appearance of a deep orange color, yields are summarized in Table 2 for the reaction of **18a–c** with sodium azide. Similar results were obtained for **17a–c** but have been omitted for the sake of clarity.



Scheme 5. Competitive formation of azide vs. phenolate ion.

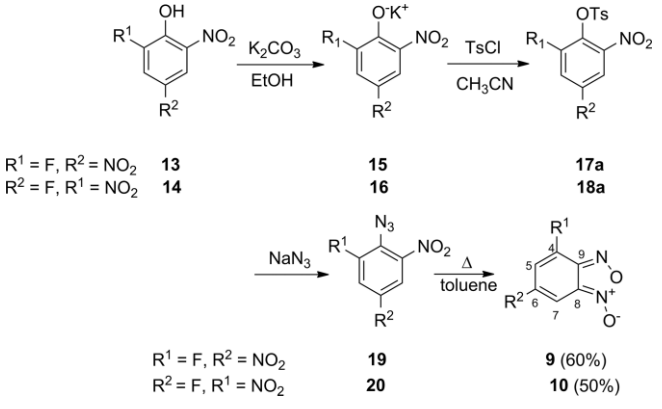
The formation of compound **15** (or **16**) may be rationalized by competitive nucleophilic substitution of the phenolate moiety by the azide group, the driving force being the high degree of stabilization of the phenoxide by both the nitro and fluoro groups. The greater leaving group ability of the sulfonate group compared with the fluorine is clearly a result of the nitro groups

Table 2. Yield of azides and phenolate ions from sulfonates **18a–c**.

Sulfonate	Experimental conditions	Azide **20**	Phenolate **16**
18a	ternary solvent system	40 %	60 %
	pure CH_3CN	77 %	23 %
18b	ternary solvent system	28 %	72 %
	pure CH_3CN	50 %	50 %
18c	ternary solvent system	94 %	6 %
	pure CH_3CN	79 %	21 %

in the *ortho*/*para* positions.[15] It is well established that the presence of two nitro groups in these positions leads to increased stabilization of the Meisenheimer complex. According to the results summarized in Tables 1 and 2, the superior experimental conditions involve the use of the tosyl chloride and execution of the S_NAr process in pure acetonitrile at room temperature; the overall yield for the two steps being around 75 %.

Finally, heating of **19** and **20** in boiling toluene leads to the exclusive formation of benzofuroxans **9** and **10** as pale yellow solids in 90 % yield. This translates to overall yields of 60 % and 50 % (Scheme 6) for compounds **9** and **10**, respectively. The numbering of the various atoms is given in Scheme 6; this system is typically used by our group and others in describing benzofuroxan chemistry. It is important to keep this non-conventional numbering system in mind so as to enable appropriate comparisons with other papers.



Scheme 6. Global scheme for formation of benzofuroxans **9** and **10**.

The ^1H NMR spectra of these heterocycles are characterized by two deshielded protons around 8 ppm. The chemical shifts of the two protons H^5/H^7 for **9** and **10** are summarized in Table 3 together with those of DNBF, **1** and DFBF, **5**. Interestingly, the signals of the two protons H^5/H^7 are doublet of doublets for **10** (H^5: $^3J_{H5H7}$ = 2.1, $^3J_{H5F}$ = 8.4 Hz; H^7: $^3J_{H7H5}$ = 2.1, $^3J_{H7F}$ = 6 Hz) while those for **5** are a broad singlet (H^7) and a broad doublet (H^5: $^3J_{H5F}$ = 6.3 Hz, vide infra). As has been previously reported, the ^{13}C NMR spectra of compounds **9** and **10** show some characteristic features. The complete assignment was easily obtained using one- and two-dimensional techniques including HMQC and HMBC experiments. The two resonances corresponding to C^5 and C^7 are readily determined whereas the resonances of C^8 and C^9 are key features of NMR spectra of benzofuroxans. In fact, with chemical shifts of 145 and 115 ppm, respectively, the signals of C^9 and C^8 are quite independent of the position and nature of the substituent, and

are easily assigned (Table 3). The data summarized in Table 3 clearly show that signals corresponding to C^8 and C^9 are in close agreement with those peviously reported for DNBF, **1** and DFBF, **5**. Finally, an average $^1J_{CF}$ value of 250–260 Hz has been measured for the carbon atom bearing the fluorine atom in compounds **9** and **10**, this value being close to that measured for difluorobenzofuroxan, **5**.[10] Also, in accordance with the structures of **9** and **10** was the observation in the ^{19}F NMR spectra of broad signals at –118.6 and –107.7 ppm, respectively, characteristic of the aromatic ring fluoride. Finally, UV/Visible spectra were recorded in CH_3CN and found to exhibit maximum absorptions at wavelengths of 390 and 405 nm for **9** and **10**, respectively; such values are typical for the benzofuroxan moiety.[16]

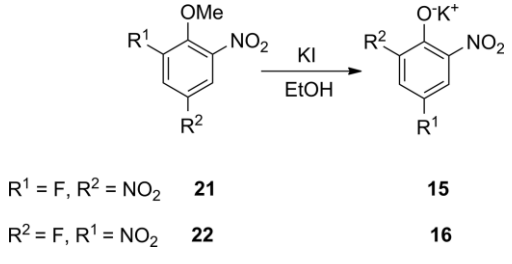
Table 3. ^1H NMR and characteristic ^{13}C NMR chemical shifts of DNBF, **1**, DFBF, **5** and benzofuroxans **9** and **10**.[a]

Heterocycle	δH^5 (ppm)	δH^7 (ppm)	δC^8 (ppm)	δC^9 (ppm)
1[b]	9.12	8.82	116.6	144.8
5[c]	7.05	7.05	116.8	145.6
9[b]	7.85	8.33	114.4	146.3
7[b]	8.41	7.65	117.5	145.4

[a] Relative to internal $SiMe_4$. [b] CD_3CN. [c] Acetone-d_6, see ref.[10].

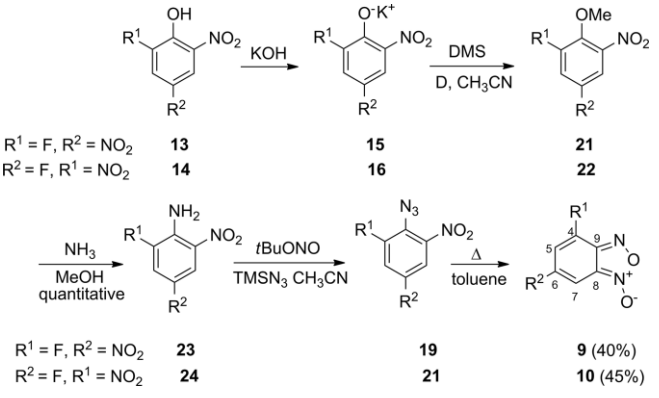
Also interesting in this methodology, is that this synthetic pathway can be extended to fluoroanisoles when phenols are not available. In such cases, the methoxy group, being electron-donating, enables facile dinitration leading to dinitrofluoroanisoles **21** and **22** in moderate yields. Interestingly, the NMR spectroscopic data for these compounds are in agreement with those reported previously in the literature.[17]

Phenoxide ions **15** and **16** (as their potassium salts) can then be obtained in quantitative yields by heating a solution of the dinitroanisoles in ethanol in the presence of potassium iodide (Scheme 7). The next steps remain identical to those previously described in Scheme 6. The yields for anisole nitration are lower than those for phenol nitration; the global yield for the synthesis of the benzofuroxans **9** and **10** are 40 % and 45 %, respectively.



Scheme 7. Formation of phenolate ions from dinitroanisoles.

Dinitroanisole can also be used in an efficient one-step synthesis of the corresponding dinitroaniline analogues. As a matter of fact, the nitration step of aniline often requires protection of the amino group as an amide and subsequent deprotection of the dinitroamide intermediate in acidic media following nitration. The overnight heating of the dinitroanisole with excess ammonia solution in MeOH results in quantitative formation of anilines **23** and **24**.[18] This latter reaction is simpler and more efficient than nitration of the aniline. The formation of benzofuroxans from anilines has been extensively described and used in the literature and may represent a useful alternative pathway in cases where the current benzofuroxan synthesis is not compatible with phenol or anisole precursors. The two conventional methods, i) diazotization in acidic media/subsequent treatment with NaN_3/heating, and ii) application of sodium hypochlorite in basic methanolic media, do not afford heterocycles **9** and **10**. It is difficult to rationalize this behavior due to the presence of the fluorine atom, assuming that the fluorinated center enables aromatic nucleophilic substitutions. This type of reaction has been previously reported in the synthesis of 4,6-difluorobenzofuroxan (**5**), for which the nucleophilic displacement of the fluorine atom by water and hydroxide ion has been observed and highlighted.[10] A water-free synthesis in neutral experimental conditions, implying the use of *tert*-butyl nitrite (*t*Bu*ONO*) as nitrosation agent with $TMSN_3$, has been employed leading to azides **19** and **20** in 90 % yield (Scheme 8).[19] Finally, heating these azides in boiling toluene affords 4-fluoro-6-nitrobenzofuroxan (**9**) and 6-fluoro-4-nitrobenzofuroxan (**10**) in 40 % and 45 % yields, respectively. The NMR spectroscopic data for these species are also similar to previously obtained data sets.



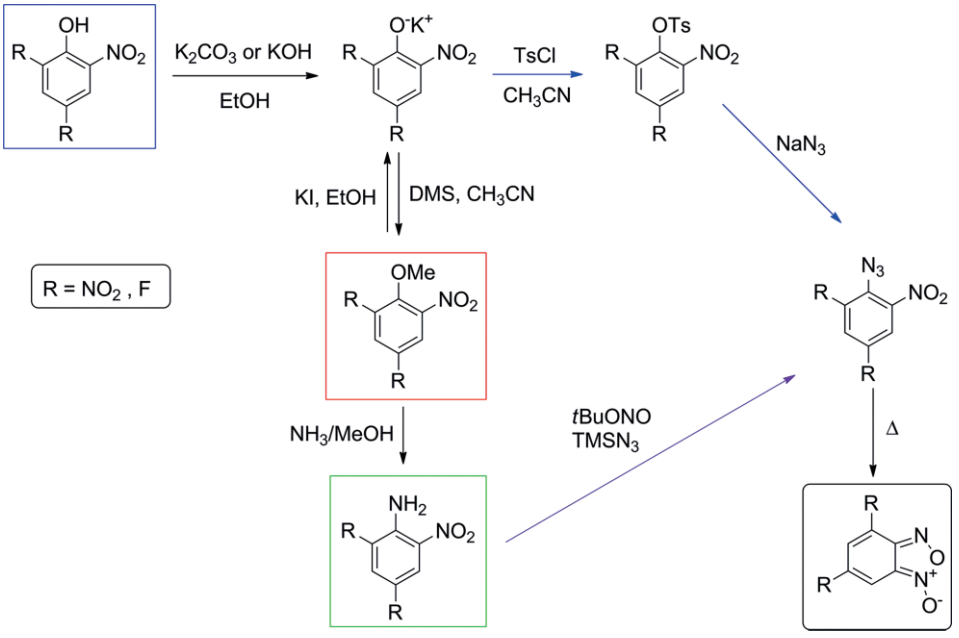
Scheme 8. Synthesis of benzofuroxans **9** and **10** from anilines.

Finally, if anisole is not available to prepare the aniline, one can prepare the anisole via methylation of the phenolate ion obtained from the phenol. The heating of a solution of phenolate with dimethyl sulfate (DMS) in acetonitrile affords the corresponding anisole in a 80 % yield (Scheme 8).[20]

The yields for compounds **9** and **10** obtained using the three synthetic pathways are gathered in Table 4. The main message emerging from these data is that the synthetic pathway starting from fluorophenols provides optimal results but that the two other pathways give similar, and still respectable, yields. Notably, Scheme 9 summarizes the various strategies available

Table 4. Summary of yields for production of 4-fluoro-6-nitrobenzofuroxan (**9**) and 6-fluoro-4-nitrobenzofuroxan (**10**) using the three differernt approaches detailed herein.

Product	Yield from phenols (%)	Yield from anisoles (%)	Yield from anilines (%)
9	60 %	40 %	40 %
10	50 %	45 %	45 %



Scheme 9. Global synthesis of benzofuroxans **9** and **10**.

to prepare 4-fluoro-6-nitrobenzofuroxan (**9**) and 6-fluoro-4-nitrobenzofuroxan (**10**).

2) Structural Study of Benzofuroxans 9 and 10

The structure of **9** was further validated through a radiocrystallographic study revealing that the length of the C^6=C^7 double bond is found to be 1.355 Å whereas that of the C^4=C^5 linkage is 1.333 Å (Figure 1). Interestingly, this value is reminiscent of that found in 4-nitrobenzodifuroxan **25** which possesses a bond length of 1.339 Å.[21]

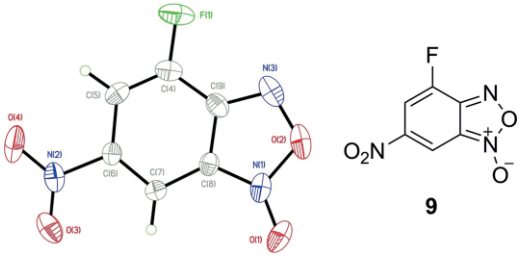
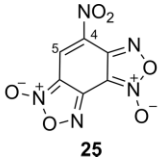
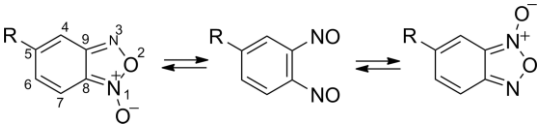


Figure 1. X-ray structure of benzofuroxan **9**.

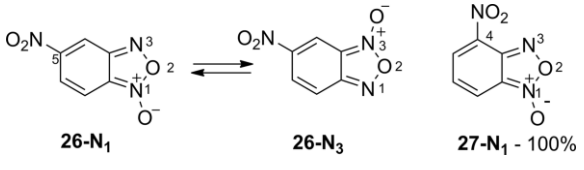


This is also typical of a nitro-olefinic fragment as it was reported for DNBF **1** where values of 1.370 and 1.400 Å have been measured for the two potentially reactive C^6=C^7 and C^4=C^5 double bonds, respectively.[22] This first experimental finding reflects the low degree of aromatic character for the benzofuroxan structure as has been previously demonstrated for other substituted benzofuroxans.[23]

That the signals corresponding to benzofuroxan **9** are unresolved provides clear evidence of the well-known 1-oxide/3-oxide tautomeric relationship. Ring-chain tautomerism of this type occurs in benzofuroxan itself (R = H, Scheme 10) and also in substituted benzofuroxans. In the case of benzofuroxans substituted at the 5 position (for the numbering of benzofuroxan, see Scheme 2), the amount of each tautomer is dependent on the nature of R. When the nitro group is in the 5 position, as in 5-nitrobenzofuroxan **26**, both isomers exist at room temperature. An electron-donating group, whatever its position, always favors this equilibrium with the co-existence of the two isomers. Also in accordance with the presence of two tautomers for **9**, was the observation in the ^{19}F NMR spectra of two broad signals at –118.6 and –121.1 ppm, characteristic of the aryl fluoride moiety in both tautomers. This equilibrium could be the result of a greater influence imposed by electron-donating effects relative to those of fluorine-associated electron-withdrawing effects (Scheme 11).



Scheme 10. 1-oxide/3-oxide interconversion for benzofuroxans.



Scheme 11. 1-oxide/3-oxide interconversion for 5-nitrobenzofuroxan **26**.

When an electron-withdrawing group is located at the 4 position (4-nitrobenzofuroxan, **27**), the benzofuroxan exists in one form with the *N*-oxide in the 1 position at all temperatures; this explains why the NMR spectra of 4-nitro-6-fluorobenzofuroxan (**10**) exhibit sharp signals.[24–26]

3) Synthesis of Benzofurazan Analogues 11 and 12

The formation of benzofurazans is usually achieved from corresponding benzofuroxan analogues using triphenylphosphine or triethylphosphite in toluene or ethanol. The optimal experimental procedure for generating benzofurazans **11** and **12** has been to heat fluorinated benzofuroxans in boiling toluene with 1.2 equiv. of triethyl phosphite (Scheme 12). Benzofurazans are easily purified and obtained in moderate to good yields. NMR spectra are in full agreement with the structure of benzofurazan and with the disappearance of the *N*-oxide functionality. Some ^{1}H NMR and characteristic ^{13}C NMR chemical shifts of **11** and **12** are summarized in Table 5 and compared with those of DNBZ (4,6-dinitrobenzofurazan) **28**, and DFBZ (4,6-difluoroben-

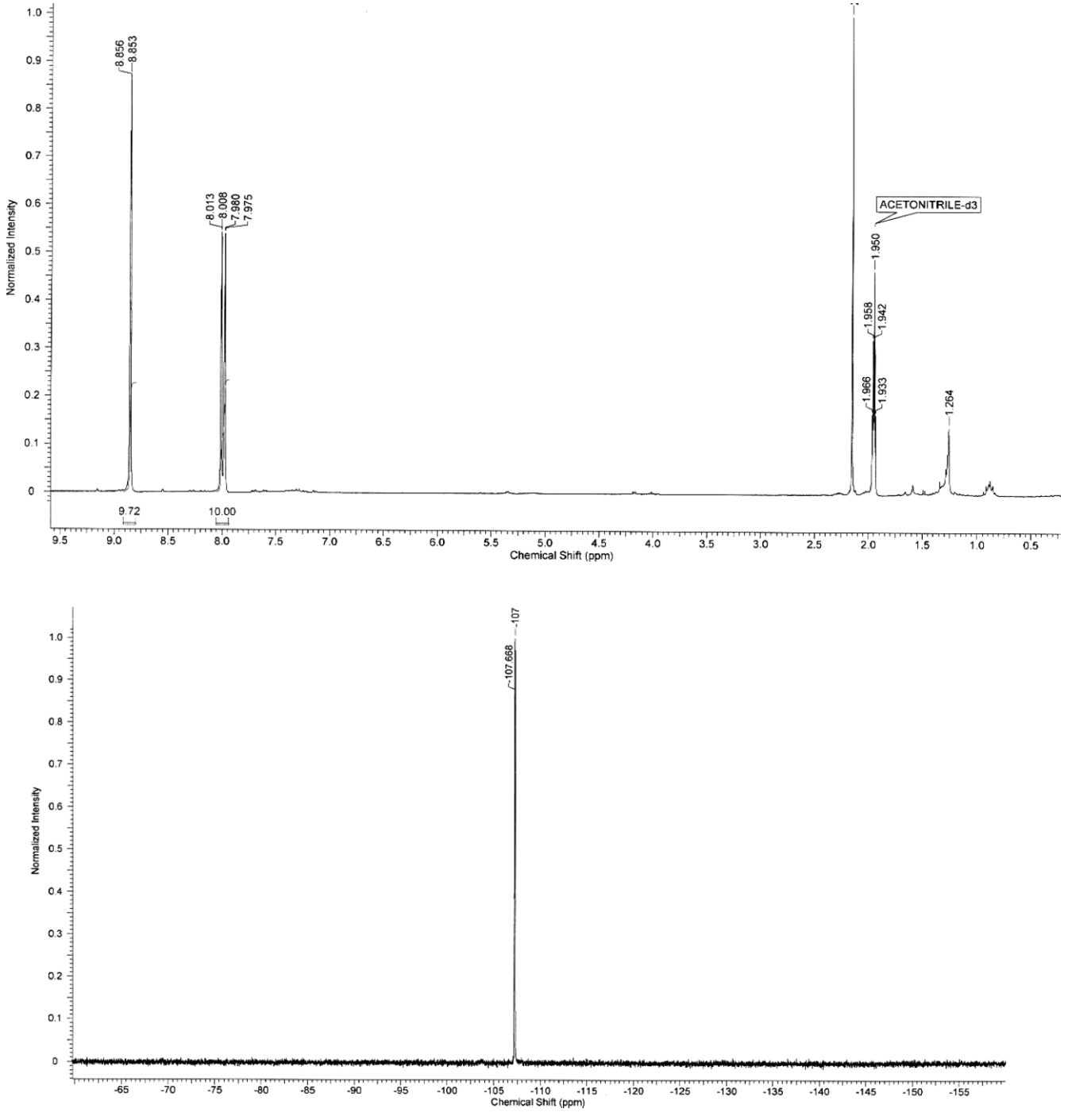
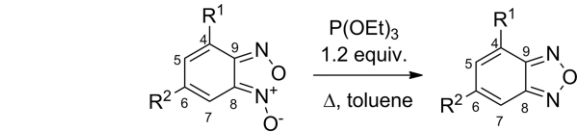


Figure 2. Characteristic NMR spectra. Upper part: ^{1}H NMR spectra of **11** in CD_3CN; lower part ^{19}F NMR spectra of **11** in CD_3CN.



R^1 = F, R^2 = NO_2 **9** — **11** (83%)
R^2 = F, R^1 = NO_2 **10** — **12** (64%)

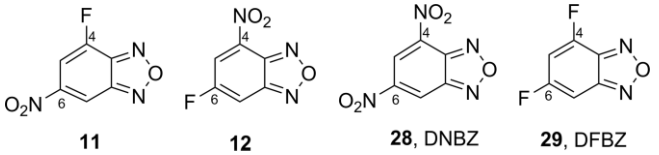
Scheme 12. Formation of **11** and **12** upon deoxygenation of **9** and **10** by $P(OEt)_3$ in toluene.

Table 5. ^1H NMR and characteristic ^{13}C NMR chemical shifts (ppm) of DNBZ, **28**, DFBZ, **29** and benzofurazans **11** and **12**.[a]

Heterocycle	δH^5	δH^7	δC^8	δC^9
28[b]	9.04	9.80	150.0	143.3
29[c]	7.39	7.58	151.2	144.3
11[d]	8.00	8.86	149.6	143.4
12[d]	8.08	8.50	149.8	141.2

[a] Relative to internal $SiMe_4$. [b] [D_6]DMSO, see ref.[5a] [c] [D_6]Acetone, see ref.[10] [d] CD_3CN.

zofurazan) **29**. The disappearance of the electron releasing effect of the *N*-oxide has two major effects upon NMR spectra: i) it induces well defined signals due to the absence of tautomerism, and ii) it induces large deshielding of the resonance corresponding to C^8 [shift from 110 ppm in benzofuroxan to 155 ppm in benzofurazan (see Tables 3 and 5)].[5] This is exemplified by Figure 2 which displays ^1H and ^{19}F NMR spectra of compound **11** in CD_3CN. The isolation and unambiguous NMR characterization of substituted benzofurazans **11** and **12** also provide indirect support for the structural elucidation of benzofuroxans **9** and **10**.



11 **12** **28**, DNBZ **29**, DFBZ

Conclusions

For the first time, the synthesis of fluoronitrobenzofuroxans and especially of 4-fluoro-6-nitrobenzofuroxan and 6-fluoro-4-nitrobenzofuroxan has been performed using several synthetic strategies. This study has shown that these fluoronitrobenzofuroxans can be prepared from fluorophenols and fluoroanisoles and, more specifically, from a sulfonate intermediate. These compounds are easily available and both families possess an electron-donating group that facilitates the key nitration step. Various sulfonyl chlorides were employed to convert phenols or anisoles into good leaving groups; the use of TsCl proved optimal. This synthetic strategy can also be extended to the preparation of other benzofuroxans. Substituted dinitroanisoles are the starting point for an efficient one-step synthesis of amino analogues proceeding in good yields and eliminating the classical protection/deprotection steps associated with aniline dinitration-based approaches. Classical procedures for converting anilines into benzofuroxans have not been efficient, and the synthesis of aromatic azides from the corresponding amines has been accomplished under mild conditions with *tert*-butyl nitrite and azidotrimethylsilane. Finally, we have shown here that benzofurazans can be readily prepared by deoxygenation of benzofuroxans using triethyphosphite.

Experimental Section

General: ^1H, ^{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 (^1H and ^{13}C NMR) or $CFCl_3$ (^{19}F NMR). Abbreviations used are: br. s = broad signal; d = doublet; m = multiplet, sept = septuplet. Melting points (M.p.) were determined with a Büchi B-545 and are uncorrected. Starting materials were obtained from commercial sources and were used without further purification. UV/Visible spectra were recorded using a conventional Hewlett–Packard spectrophotometer.

General Procedure for Dinitration of Phenols: To a solution of the appropriate phenol in dichloromethane at 0 °C was added dropwise a fuming nitric acid solution (2.3 equiv.). The reaction medium was stirred at room temperature for 18 h. The residue was diluted in water and extracted with dichloromethane to give the nitro compound which was purified by column chromatography on silica gel using PE/AcOEt as eluent. Experimental data for both dinitrophenols **13** and **14** are in agreement with those previously reported.[14b]

Compound 13: Yield 99 %. ^1H NMR (CD_3CN): δ = 8.30 (dd, *J* = 3, 10 Hz, 1 H); 8.73 (m, 1 H) ppm. ^{19}F NMR (CD_3CN): δ = –129.2 (d, *J* = 10 Hz, 1 F) ppm.

Compound 14: Yield 75 %. ^1H NMR (CD_3CN): δ = 8.13 (d, *J* = 8.5 Hz, 2 H), 8.78 (br. s, OH) ppm.

^{19}F NMR (CD_3CN): δ = –122.0 (t, *J* = 8.5 Hz, 1 F) ppm.

General Procedure for the Deprotonation of Phenols: To a solution of the appropriate phenol in ethanol was added a solution of K_2CO_3 (1.1 equiv.) dissolved in the minimum volume of water. The reaction medium was stirred at room temperature for 10 min. The resulting phenolate was filtered off and the colored solid was dried under vacuum.

Salt 15: Yield 99 %. Red solid. Decomposition before melting. ^1H NMR ([D_6]DMSO): δ = 7.68 (dd, *J* = 3.0, 12.0 Hz, 1 H); 8.53 (dd, *J* = 1.4, 3.0 Hz, 1 H) ppm. ^{19}F NMR ([D_6]DMSO): δ = –129.9 (br. s, 1 F) ppm.

Salt 16: Yield 99 %. Yellow solid. Decomposition before melting. ^1H NMR ([D_6]DMSO): δ = 7.72 (d, *J* = 9 Hz, 2 H) ppm. ^{19}F NMR ([D_6]DMSO): δ = –139.7 (t, *J* = 9 Hz, 1 F) ppm.

General Procedure for the Formation of Sulfonates: To a solution of the appropriate phenolate ion in dry acetonitrile at room temperature was added 1.1 equiv. of sulfonyl chloride. The reaction medium was stirred at room temperature for 18 h. The solvent was removed under vacuum to yield a crude mixture containing the sulfonate which was isolated and purified by column chromatography with PE/AcOEt as eluent. HRMS data have been determined only for sulfonates **17a** and **18a** derived from TsCl. Compound **17a** shows some tendency to decompose.

Tosylate 17a: Yield 90 %. White solid, m.p. 101 °C. ^1H NMR (CD_3CN): δ = 2.50 (s, 3 H); 7.49 (d, *J* = 8.0 Hz, 2 H), 7.80 (d, *J* = 8.0 Hz, 2 H), 8.39 (dd, *J* = 2.4, 8.5 Hz, 1 H), 8.63 (t, *J* = 2.4 Hz, 1 H) ppm. ^{19}F NMR (CD_3CN): δ = –118.7 (bd, *J* = 8.5 Hz, 1 F) ppm. ^{13}C NMR (CD_3CN): δ = 20.8, 128.2, 130.2, 130.4, 134.9, 144.0, 145.2, 147.7, 155.0 (d, *J* =

259.2 Hz) ppm. HRMS (electrospray, Na^+): Calculated for $C_{13}H_9N_2O_7FS$: 379.0012, found 379.0012.

Mesylate 17b: Yield 70 %. Pale yellow solid, m.p. 92 °C. ^1H NMR (CD_3CN): δ = 3.50 (s, 3 H); 8.52 (dd, J = 4.0, 10.0 Hz, 1 H), 8.68 (t, J = 2 Hz, 1 H) ppm. ^{19}F NMR (CD_3CN): δ = –118.5 (br. s, 1 F) ppm.

Isopropylsulfonate 17c: Yield 99 %. Pale yellow solid. 106 °C. ^1H NMR (CD_3CN): δ = 1.56 (d, J = 6.8 Hz, 6 H); 3.85 (sept, J = 6.8 Hz, 1 H), 8.50 (dd, J = 4.0, 6.0 Hz, 1 H), 8.65 (t, J = 2.4 Hz, 1 H) ppm. ^{19}F NMR (CD_3CN): δ = –118.4 (br. s, 1 F) ppm.

Tosylate 18a: Yield 98 %. White solid, m.p. 85 °C. ^1H NMR (CD_3CN): δ = 2.49 (s, 3 H); 7.46 (d, J = 8.0 Hz, 2 H), 7.68 (d, J = 8.0 Hz, 2 H), 8.08 (d, J = 7.4 Hz, 2 H) ppm. ^{19}F NMR (CD_3CN): δ = –107.5 (t, J = 7.4 Hz, 1 F) ppm. ^{13}C NMR (CD_3CN): δ = 20.5, 118.1 (d, J = 28 Hz), 128.7, 129.5, 130.7, 130.9, 145.3, 148.3, 158.5 (d, J = 250.0 Hz) ppm. HRMS (electrospray, Na^+): Calculated for $C_{13}H_9N_2O_7FS$: 379.0012, found 379.0011.

Mesylate 18b: Yield 70 %. Pale yellow solid, m.p. 92 °C. ^1H NMR (CD_3CN): δ = 3.43 (s, 3 H); 8.17 (d, J = 8.0 Hz, 2 H) ppm. ^{19}F NMR (CD_3CN): δ = –107.7 (br. s, 1 F) ppm.

Isopropylsulfonate 18c: Yield 60 %. Pale yellow solid, m.p. 74 °C. ^1H NMR (CD_3CN): δ = 1.53 (d, J = 6.9 Hz, 6 H); 3.79 (sept, J = 6.6 Hz, 1 H), 8.13 (d, J = 7.0 Hz, 2 H) ppm. ^{19}F NMR (CD_3CN): δ = –107.6 (br. s, 1 F) ppm. ^{13}C NMR (CD_3CN): δ = 15.4, 54.8, 117.7, 118.1, 128.5, 145.7, 157.5 (d, J = 255.4 Hz) ppm.

General Procedure for Formation of Azides from Sulfonates

1. In a Ternary Acetone/Methanol/Water Mixture: To a solution of sulfonate (1 mL per mmol of sulfonate) in an acetone/methanol mixture (v/v, 1:1), was added a solution of sodium azide (1.1 equiv.) in a mixture water/methanol in a ratio 1:2, the volume of water being equal to the volume of acetone. The reaction medium was stirred and protected from light for 18 h. The solvent was removed under vacuum to yield a crude mixture containing the azide which was isolated by column chromatography with PE/AcOEt as eluent.

2. In Dry Acetonitrile: To a solution of the appropriate sulfonate in acetonitrile at room temperature was added 1.1 equiv. NaN_3. The reaction mixture was stirred and heated at reflux overnight. The solvent was removed under vacuum to yield a crude mixture which was purified by column chromatography with PE/AcOEt as eluent.

Azide 19: Yield 80 %, m.p. 82 °C (decomposition). ^1H NMR (CD_3CN): δ = 8.33 (dd, J = 2.6, 11.0 Hz, 1 H); 8.54 (m, 1 H) ppm. ^{19}F NMR (CD_3CN): δ = –118.3 (br. s, 1 F) ppm.

Azide 20: Yield 77 %, m.p. 64 °C (decomposition). ^1H NMR (CD_3CN): δ = 7.87 (d, J = 8.6 Hz, 2 H) ppm. ^{19}F NMR (CD_3CN): δ = –111.1 (br. s, 1 F) ppm.

General Procedure for Dinitration of Anisoles: To a solution of the appropriate anisole in sulfuric acid (20 mL) at 0 °C was added dropwise a fuming nitric acid solution (2.5 equiv.) in sulfuric acid (10 mL). The reaction medium was stirred at room temperature for 1 h. The residue was diluted with an ice/water mixture and the precipitate was filtered off and dried. The dinitroanisoles were purified by column chromatography on silica gel using PE/AcOEt as eluent. Experimental data for both dinitrophenols **21** and **22** are in agreement with those previously reported.[17]

Anisole 21: Yield 45 %. ^1H NMR (CD_3CN): δ = 4.21 (d, J = 3.6 Hz, 3 H), 8.33 (dd, J = 3.0, 11.5 Hz, 1 H), 8.49 (br. s, 1 H) ppm. ^{19}F NMR (CD_3CN): δ = –123.5 (br. s, 1 F) ppm.

Anisole 22: Yield 65 %. ^1H NMR (CD_3CN): δ = 3.97 (s, 3 H), 8.00 (d, J = 8 Hz, 2 H) ppm. ^{19}F NMR (CD_3CN): δ = –113.8 (br. s, 1 F) ppm.

General Procedure for Formation of Anilines from Anisoles: The appropriate anisole was added to an excess of ammonia solution in MeOH (7 M) and the mixture was heated at reflux for 15 h. The solvent was removed under vacuum to yield the aniline which was used without further purification.

Aniline 23: Yield 99 %, m.p. 156 °C (ref.[18a] 156–157 °C). ^1H NMR (CD_3CN): δ = 7.3 (br. s, 2 H, NH_2), 8.14 (dd, J = 11.0; 2.4 Hz, 1 H), 8.80 (t, J = 2.4 Hz, 1 H) ppm. ^{19}F NMR (CD_3CN): δ = –128.6 (d, J = 11.0 Hz, 1 F) ppm.

Aniline 24: Yield 90 %, m.p. 126–129 °C. (ref.[18b] 133–4 °C). ^1H NMR ($CDCl_3$): δ = 8.36 (d, J = 7.8 Hz, 2 H) ppm. ^{19}F NMR ($CDCl_3$): δ = –125.5 (t, J = 7.8 Hz, 1 F) ppm.

General Procedure for the Formation of Azides from Anilines: The appropriated aniline (200 mg, 2.14 mmol) was dissolved in CH_3CN (4 mL) in a 25 mL round-bottomed flask and cooled to 0 °C in an ice bath. To this stirred mixture was added *t*BuONO (331 mg, 380 µL, 3.21 mmol) followed by $TMSN_3$ (300 mg, 340 µL, 2.56 mmol) dropwise. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by column chromatography using various PE/AcOEt mixtures. The experimental data of **19** and **20** are in accord with those reported above.

General Procedure for Benzofuroxan Formation: The appropriate azide was dissolved in toluene and heated at reflux for 3–4 h. The solvent was removed under vacuum to yield the benzofuroxan which was purified by column chromatography on silica gel using PE/AcOEt as eluent. Unfortunately, no satisfactory high-resolution mass data have been obtained for these benzofuroxans maybe because of their high tendency to decompose. Due to very slow relaxation processes and coupling with the fluorine atom, signals correlating to NO_2-tethered carbons have not been found even when using increased relaxation delays.

Benzofuroxan 9: Yield 90 %, m.p. 120–121 °C. UV (CH_3CN, c = 5×10^{-5} mol L^{-1}): λ_{max} = 390 nm ($\varepsilon \approx 25000$ mol^{-1} L cm^{-1}). ^1H NMR ($CDCl_3$): δ = 8.33 (br. s, H7); 7.85 (d, J = 6.3 Hz, H5) ppm. ^{19}F NMR ($CDCl_3$): δ = –118.6 (br. s, F^4) ppm. ^{13}C NMR ($CDCl_3$): δ = 146.3 (C9); 129.3 (d, J = 259.0 Hz, C4); 114.4 (C8); 109.7 (C5); 108.7 (C7) ppm.

Benzofuroxan 10: Yield 90 %, m.p. 128–129 °C. UV (CH_3CN, c = 5×10^{-5} mol L^{-1}): λ_{max} = 405 nm ($\varepsilon \approx 20000$ mol^{-1} L cm^{-1}). ^1H NMR (CD_3CN): δ = 7.65 (dd, J = 2.1; 6.0 Hz, H7); 8.41 (dd, J = 2.1; 8.4 Hz, H5) ppm. ^{19}F NMR (CD_3CN): δ = –107.7 (br. s, F^6) ppm. ^{13}C NMR (CD_3CN): δ = 160.0 (d, J = 257.2 Hz, C6); 145.4 (C9); 127.1 (C5); 117.5 (C8); 106.1 (C7) ppm. ^1H NMR ($CDCl_3$): δ = 7.46 (dd, J = 2.2, 5.3 Hz, H5); 8.25 (br. s, H7) ppm. ^{19}F NMR ($CDCl_3$): δ = –104.3 (br. s, F^6) ppm.

General Procedure for Benzofurazan Production: One equiv. of the substituted fluorobenzofuroxan was heated with 1.2 equiv. of triethylphosphite overnight in boiling toluene. After cooling, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using PE to afford expected fluorobenzofurazan as a pale yellow solid. Unfortunately, no satisfactory high-resolution mass data have been obtained for these benzofuroxans; this is likely attributable to their propensity for decomposition.

Benzofurazan 11: Yield 83 %, m.p. 138 °C. ^1H NMR (CD_3CN): δ = 8.00 (dd, J = 1, 10 Hz, H5); 8.86 (d, J = 1 Hz, 1 H, H7) ppm. ^{19}F NMR (CD_3CN): δ = –117.6 (1 F) ppm. ^{13}C NMR (CD_3CN): δ = 150.4 (d, J = 267.0 Hz, C4), 150.2 (C6), 149.6 (C9), 143.4 (C8), 111.7 (C7), 108.8 (C5) ppm.

Benzofurazan 12: Yield 64 %, m.p. 113 °C. ^1H NMR (CD_3CN): δ = 8.08 (dd, J = 1.4, 5 Hz, H5); 8.50 (dd, J = 1.4, 6 Hz, H7) ppm. ^{19}F

NMR (CD_3CN): δ = –104.1 (1 F) ppm. ^{13}C NMR (CD_3CN): δ = 161.0 (d, J = 257.0 Hz, C6), 149.8 (C8), 141.2 (C9), 137.6 (C4), 124.4 (C5), 106.2 (C7) ppm.

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)[27] 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 $F2$ data using SHELXTL V6.12.[28] Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms.

Crystal Structure Analysis: CCDC 1469138 (for **9**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Supporting Information (see footnote on the first page of this article): Copies of ^1H, ^{19}F and ^{13}C NMR and UV spectra of the key intermediates together with the cif file for crystallographic structure **1**.

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Keywords: Synthetic methods · Tautomerism · Fluorine · Phenols · Azides

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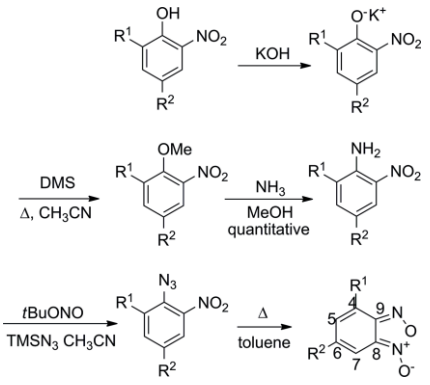
Benzofuroxans



4-Fluoro-6-nitrobenzofuroxan and 6-fluoro-4-nitrobenzofuroxan have been prepared, for the first time, from fluorophenols and fluoroanisoles, two families of cheap and readily available chemicals. Due to the presence of methoxy and hydroxy groups, the key nitration step is easily achieved and dinitro compounds are obtained in good yields; these can then be used to prepare the phenyl azide intermediate.

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