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σ-Complex formation and oxidative nucleophilic aromatic substitution in 4-nitro-2,1,3-benzoxadiazoles †

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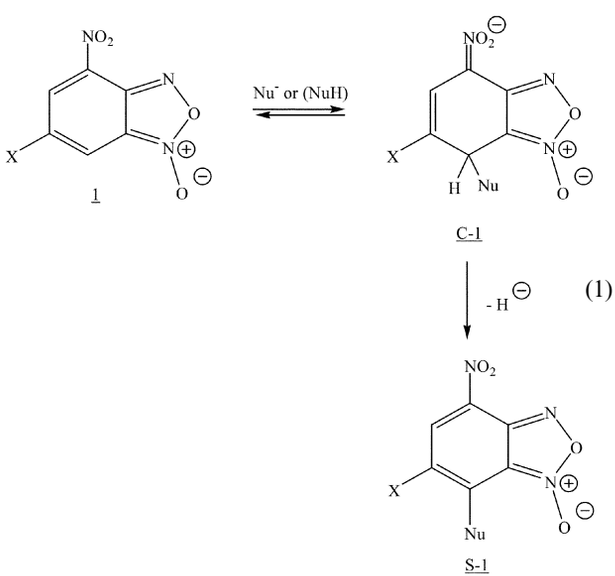
The feasibility of carrying out nucleophilic displacement of hydrogen from highly electron-deficient heteroaromatics has been addressed through a detailed investigation of the interaction of a series of nitrobenzofuroxans *3a–i* and two related heterocycles *5* and *6*, with the 2-nitropropenide anion. Although this series corresponds to a large modulation in the electrophilic properties of the six-membered ring, all reactions first lead to the quantitative formation of the σ-adducts *C-3a–i*, *C-5* and *C-6* arising from covalent addition of the nucleophile to the C-7 carbon. With the exception of the 4-aza substituted member *C-5*, all the adducts have been isolated as pure and very stable alkali salts. Measurements of the oxidation potentials by cyclic voltammetry reveal that the ease of subsequent hydrogen substitution at carbon-7 strongly decreases with increasing electron deficient character of the six-membered ring. The measured E^0 values are in the range 0.5–0.6 V (*vs.* SCE) for the 4-nitro-benzofuroxan and -benzofurazan adducts (*C-3e*, *C-3i*) but they go up to 1.20–1.33 V for the 4,6-dinitro- and 4-nitro-6-trifluoromethanesulfonyl-benzofuroxan adducts (*C-3a,d*) in acetonitrile. Consistently with these E^0 values, only very powerful oxidants such as the Ce^{4+}/Ce^{3+} or the MnO_4^-/Mn^{2+} couples can successfully oxidize the adducts leading to the expected substitution products in moderate to good yields (35–72%). Interestingly, the rearomatization of the 4-nitro substituted benzofuroxan adducts proceeds with a partial Boulton–Katritzky rearrangement of the resulting products. Another noteworthy result is that the 4-nitrobenzofuroxan and 4-nitrobenzofurazan molecules suffer competitive addition of the $(CH_3)_2C{-}NO_2^-$ anion to the 5- and 7- positions under some experimental conditions. This represents the first well-defined example of isomeric addition of a carbon nucleophile to these heterocycles.

Introduction

In the past few years, much evidence has been accumulated that 4,6-dinitro-2,1,3-benzoxadiazole 1-oxide, commonly referred to as 4,6-dinitrobenzofuroxan (DNBF) is an extremely electrophilic heteroaromatic, which undergoes facile covalent addition of many weak anionic or neutral carbon nucleophiles.[1–8] All reactions lead to very stable anionic σ-adducts of type *C-1*. While the ease of formation and isolation of such adducts has led to numerous biological and analytical applications,[7,9–12] it has so far been of little interest for synthetic purposes because of the failure to induce a facile conversion of these species into the corresponding 7-substituted products *S-1* (eqn. (1)).



Two main strategies have been developed to carry out the efficient nucleophilic displacement of a nuclear hydrogen atom of an electron-deficient aromatic while overcoming the difficulty of expelling a highly unstable hydride anion. A first and elegant strategy is the so-called vicarious nucleophilic aromatic substitution pathway depicted in eqn. (2), as discovered by one of us.[13]

In this instance, the rearomatization of the σ-complex intermediate *C-2* is the result of a base-induced β-elimination of a nucleofugal group (L) which must be present at the reactive center of the incoming nucleophile. Owing to the extreme difficulty in achieving the last protonation step of the process, this approach does not work satisfactorily for the nitrobenzoxadiazole series.[14,15] A more general approach is therefore the one dealing with a formal displacement of H^- through chemical oxidation of the σ-complex.[1,16–19] While this strategy has proved to be useful for functionalization of various nitroarenes and nitroactivated heterocycles like nitropyridines or nitronaphthyridines, it has remained rather unsuccessful with nitrobenzofuroxans.[15]

We have reconsidered the feasibility of the overall nucleophilic aromatic substitution process of eqn. (1) by taking advantage of our finding that σ-adducts of type *C-1*, namely the adducts *C-3a–i* can be readily obtained as pure crystalline alkali salts on treatment of a series of 4-nitro-6-X- and 4-X-6-nitro-benzofuroxans or -benzofurazans, *3a–i* with potassium 2-nitropropenide (eqn. (3)).[20]

† Electronic supplementary information (ESI) available: supplementary Tables S1–S4 (complete ^1H, ^{19}F and ^{13}C data). See http://www.rsc.org/suppdata/ob/b3/b302036c/

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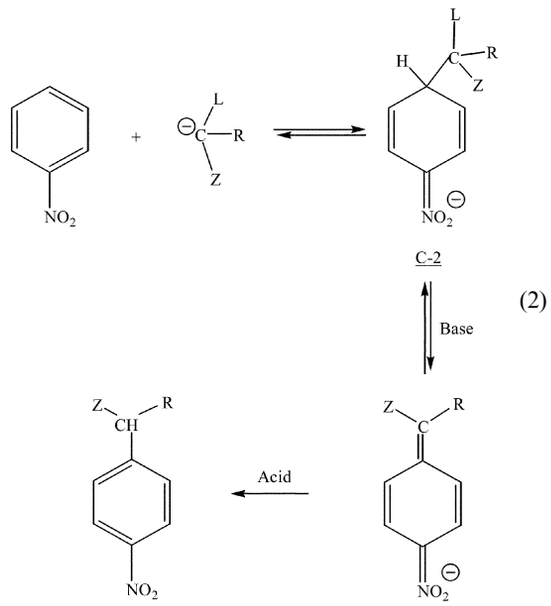
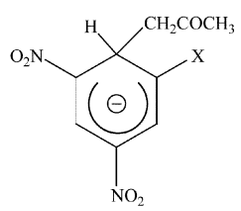


C-2

(2)

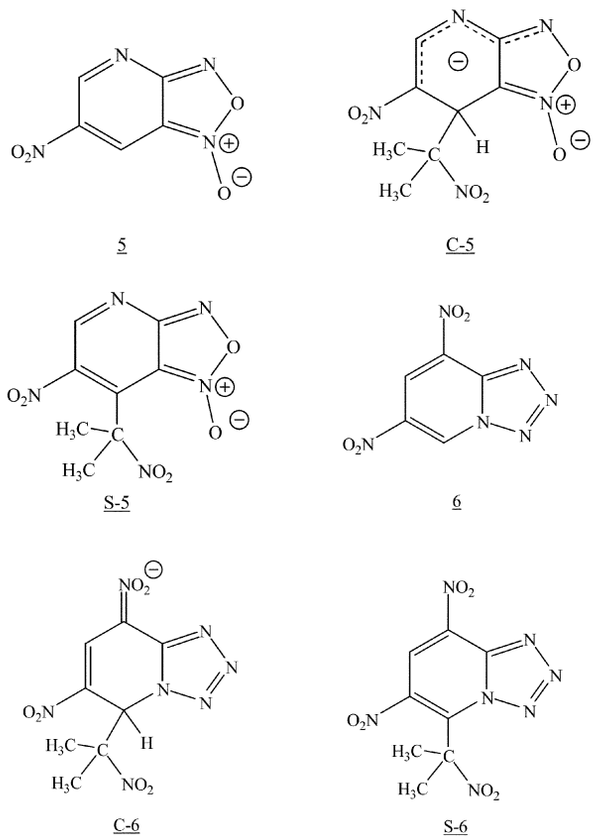
This has recently allowed us to carry out an electrochemical study of the oxidation of some of these species and thus to discover that this process is in fact associated with much higher oxidation potentials than those known to govern the rearomatization of reference nitrobenzene σ-adducts.[20b] The following E^0 values (*versus* SCE) have been obtained in acetonitrile: E^0 = 0.96 V for *C-3b*, E^0 = 1.15 V for *C-3a* and E^0 = 1.33 V for *C-3d* as compared with E^0 values of ~ 0.80 V for 1,3,5-trinitrobenzene adducts, *e.g. C-4a*, in acetone or DMF.[21–23] This finding clearly called for reexamination of the rearomatization of adducts of type *C-3* by using more appropriate chemical oxidants.



C-4

(a) X=NO_2; (b) X=CF_3; (c) X=H

In this paper, we report on the formation, structure and successful chemical oxidation of most of the adducts *C-3a–i*. The behaviour of the two related complexes *C-5* and *C-6* which derive from the addition of the 2-nitropropenide ion to 6-nitro[2,1,3]oxadiazolo[4,5-*b*]pyridine 1-oxide *5* (*i.e.* 4-aza-6-nitrobenzofuroxan) and 4,6-dinitrotetraazolo[1,5-*a*]pyridine *6* is also considered. Among various features of general interest in the context of understanding nucleophilic substitution of a ring hydrogen, our results highlight the existence of a clear inverse relationship between the ease of oxidation and stability of σ-adducts.

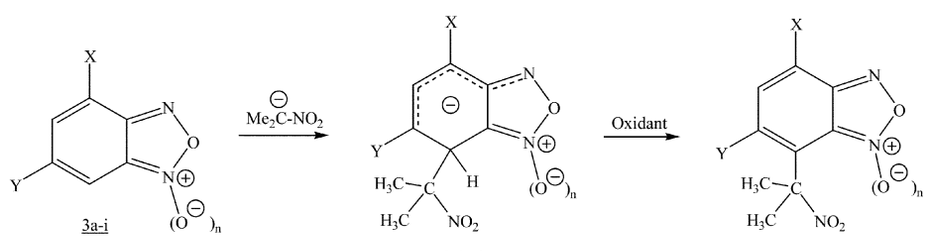


5 C-5 S-5 6 C-6 S-6

Results

σ-Complexation of *3a–i*, *5* and *6*

Intense colors developed immediately upon addition of a 2-nitropropane solution of each of the nitrobenzofuroxan (*3a–g*), nitrobenzofurazan (*3h,i*) and nitropyridine (*5,6*) compounds (1 mmol) to a suspension of potassium 2-nitropropenide (1 eq.) in the same solvent. Except in the case of *5*, yellow to red-orange crystals formed rapidly which were readily collected and found to correspond to an essentially quantitative formation of the σ-adducts *C-3a–i* and *C-6* as crystalline potassium salts. ^{1}H, ^{13}C and ^{19}F NMR spectra recorded after dissolution of these salts in acetone or Me_2SO-*d6* were very clean, consisting of only one set of signals assignable to structures *C-3a–i*, *C-5* and *C-6*. Data needed for our forthcoming discussion are summarized in Table 1. The complete set of ^{1}H and ^{13}C NMR data are provided as supplementary Tables S1 and S2. An X-ray structure of *C-3a* was previously obtained.[20a]



3a-i C-3a-i S-3a-i

(3)

n=1 : (a) X=Y=NO_2 (DNBF); (b) X=NO_2, Y=CN; (c) X=NO_2, Y=CF_3; (d) X=NO_2, Y=SO_2CF_3; (e) X=NO_2, Y=H; (f) X=CN, Y=NO_2; (g) X=CF_3, Y=NO_2

n=0 : (h) X=Y=NO_2 (DNBZ); (i) X=NO_2, Y=H

Table 1 Selected ^{1}H, ^{13}C and ^{19}F NMR data for 2-nitropropenide adducts in Me_2SO-*d6*[a]

Adduct	H_5	H_6	H_7	CF_3[b]	C_4	C_5	C_6	C_7	Cα[c]
C-3a[d]	8.69	—	5.27	—	110.61	133.33	120.99	41.32	92.06
C3-b	7.73	—	4.58	—	108.71	140.43	80.52	42.49	92.64
C-3c	7.68	—	4.73	−57.29	106.37	132.64	99.67	40.20	92.51
C-3d	8.22	—	4.56	−78.74	113.31	144.21	90.44	41.29	92.41
C3-e	7.02	4.84	4.37	—	106.21	126.66	104.97	42.22	92.00
C3-e′	5.01	6.20	6.56	—	—	—	—	—	—
C-3f	8.09	—	5.30	—	73.85	141.12	115.10	41.28	92.53
C-3g	7.97	—	5.30	−58.84	91.00	134.19	110.92	41.52	92.75
C-3h	8.80	—	5.56	—	110.58	133.86	121.40	41.30	92.27
C-3i	7.08	4.90	4.57	—	105.98	126.55	106.12	42.52	91.48
C-3i′	4.95	6.24	6.92	—	—	—	—	—	—
C-5	8.61	—	5.30	—	—	157.98	113.43	40.70	92.45
C-6	8.75	—	7.02	—	109.60	132.38	109.65	61.47	93.08

[a] δ in ppm relative to Me_4Si as internal reference. [b] δ in ppm relative to $CFCl_3$ as internal reference. [c] For comparison, $\delta C\alpha$ = 79.20 for 2-nitropropane.[25] [d] Ref. 15*b*.

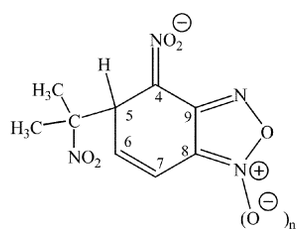
Both noise proton-decoupled and proton-coupled ^{13}C NMR spectra have been recorded for the various adducts. Based on a comparison with chemical shifts and J_{CH} data previously reported for various nitrobenzofuroxan or nitrobenzofurazan adducts, including *C-3a*,[1–8] as well as irradiation and *J*-modulation experiments, the ^{13}C chemical shifts listed in Tables 1 and S2 were unambiguously determined. HETCOR experiments have also been performed in the case of the monosubstituted adducts *C3-e* and *C3-i*. A major diagnostic feature for the addition of the 2-nitropropenide anion to carbon-7 of *3a–i* and *6* is the fact that the value of the $^{2}J_{C_8H_7}$ coupling constant is much higher in the adducts than in the parent molecules, *e.g.* $^{2}J_{C_8H_7}$ = 0.9 Hz for *3h* and 8.1 Hz for *C-3h*.[24] Another important feature is that the resonances for the exocyclic Cα carbon of the adducts are typical of sp^3 carbons bonded to a NO_2 group.[15a,25] Owing to the chirality of the tetrahedral ring C-7 carbon, the two geminal methyl groups of the exocyclic 2-nitropropyl moiety are non-equivalent. This accounts for the finding of two methyl resonances in the ^{13}C as well as ^{1}H NMR spectra of *C3a–i*, *C-5* and *C-6*. The σ-complexation of *3a–i* by the $Me_2C(NO_2)^-$ anion was also studied *in situ* in Me_2SO-*d6* solution. Except for the 4-nitrobenzofurazan system, the ^{1}H and ^{13}C NMR spectra recorded immediately after mixing of equimolar amounts of the reagents confirmed the quantitative formation of the expected C-7 adducts, including the aza adduct *C-5*. The failure to isolate *C-5* as a pure crystalline potassium salt is presumably the result of the high susceptibility of its activated C_5–N_4 double bond to hydration.[26] Two sets of signals with intensities in an approximately 4 : 1 ratio were observed in the ^{1}H NMR spectra pertaining to the σ-complexation of 4-nitrobenzofurazan *3i*. Notably, the predominant set of resonances was identical to the ABX pattern typical of the isolated C-7 adduct *C-3i* and this aids in attributing the AMX system corresponding to the three observed minor peaks to the formation of the *ortho* C-5 carbon-bonded adduct *C′-3i*. With time, only the signals belonging to *C-3i* were present in the spectra, showing that complete isomerization of *C′-3i* to this more stable adduct had occurred.

Carrying out similar *in situ* experiments in methanol allowed us to detect the related C-5 adduct *C′-3e* of 4-nitrobenzofuroxan as a transient species in this solvent (Table 1). Because of their rather short lifetime, ^{13}C NMR spectra of both *C′-3e* and *C′-3i* could not be recorded.

ESI mass spectral experiments confirmed the isolation of the adducts *C-3a–i* and *C-6* as potassium salts. In all instances, base peaks corresponding to the loss of K^+ were observed with no detection of the pseudomolecular ions.

Oxidation of *3a* and *6*

Electrochemical oxidation. Using the same experimental conditions as those recently described for the benzofuroxan adducts *C-3a–g*[20b] we have extended our previous electrochemical investigations to the nitrobenzofurazan adducts *C-3h* and *C-3i* as well as the 4,6-dinitrotetraazolopyridine adduct *C-6*. As found for *C-3a–g*, the cyclic voltammograms obtained at low scan rates (0.2 V s^{-1}) are characterized by well-defined irreversible oxidation waves with the following peak potentials E_p (in V/SCE) in acetonitrile + 0.1 M NBu_4BF_4: 1.07 for *C-3h*; 0.48 for *C-3i*; 1.29 for *C-6*. Interestingly, the reversibility could be observed at high scan rates, *i.e.* 200 V s^{-1} for *C-3h* and 300 V s^{-1} for *C-6*, thereby allowing us to obtain values of the related standard potential (E^0, in V/SCE) as the mid point of the cathodic and anodic peaks: 1.12 for *C-3h*, 0.48 for *C-3i* and 1.29 for *C-6*. These values together with those for the benzofuroxan adducts *C-3a–i* are given in Table 2.



n=1 C'-3e

n=0 C'-3i

Chemical oxidation. In view of the high potentials measured for the oxidation of our series of complexes *C-3a–i* and *C-6*, the Ce^{4+}/Ce^{3+} couple (E^0 = 1.61 V/SHE) appeared to be the most suitable candidate to induce the rearomatization of these species. Addition of 3 equivalents of cerium ammonium nitrate to aqueous solutions of *C-3a–i*, *C-5* and *C-6* resulted in the rapid disappearance of the deep red, orange or yellow color typical of these adducts, suggesting that the oxidation process has actually occurred. Except in the case of the trifluoromethyl and trifluoromethanesulfonyl systems (*C-3c*, *C-3d*), appropriate work up of the final reaction mixtures (see experimental section) afforded the expected substitution products *i.e. S-3a–i*, *S-5* and *S-6*, in moderate to good yields (35–72%). Similar results were obtained with the MnO_4^-/Mn^{2+} couple in 1 M HCl solution (E^0 = 1.51 V/SHE). Less strong oxidizing agents like the tropylium cation, the triphenylmethyl cation, DDQ or more simply $AgNO_3$ were also considered and found to be less or even poorly efficient in rearomatizing disubstituted adducts. However, the conversion of the two monosubstituted adducts *C-3e* and *C-3i* was found to take place satisfactory well when using $AgNO_3$ (E^0 = 0.80 V/SHE) as the oxidant in acetonitrile solution.

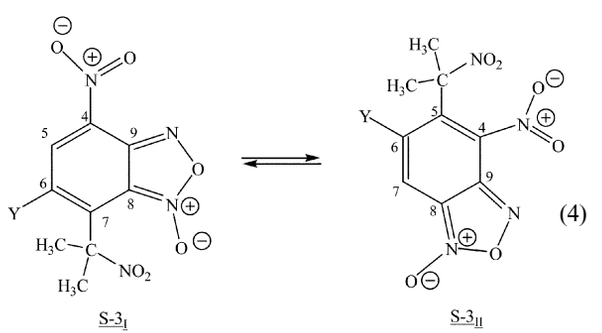
Clear evidence for the successful rearomatization of the benzofuroxan adducts *C-3a*, *C-3b* and *C-3e* was the finding that

Table 2 The effect of complex stability on the oxidation potential of σ-adducts

σ-Adduct	E^0/V (*vs.* SCE)	K^{H_2O} [b]	K^{MeOH} [b]
C-3a	1.15 [a]	2.75×10^{10} [c]	2.1×10^{10} [i]
C-3b	0.96 [a]	3.1×10^{9} [d]	—
C-3c	0.94 [a]	3.2×10^{7} [d]	—
C-3d	1.33 [a]	7.2×10^{10} [e]	—
C-3e	0.59 [a]	4.8×10^{3} [f]	8.5×10^{3} [j]
C-3g	0.91 [a]	6.4×10^{5} [d]	—
C-3h	1.12 [a]	5.5×10^{10} [d]	4.65×10^{10} [i]
C-3i	0.48 [a]	2.2×10^{3} [g]	2.94×10^{3} [j]
C-6	1.29 [a]	3.2×10^{13} [h]	$\sim 5 \times 10^{13}$ [h]
C-10	1.16 [a]	—	—
C-11	1.06 [a]	—	—
C-4a	0.82 [n]	—	23.1 [k]
C-4b	0.53 [n]	—	0.01 [l]
C-4c	0.24 [n]	—	$\sim 10^{-6}$ [m]

[a] In CH_3CN + 0.1 M NBu_4BF_4. [b] K^{H_2O} and K^{MeOH} (in $dm^3\ mol^{-1}$) refer to the equilibrium formation of the similarly substituted hydroxide or methoxide σ-adducts, respectively. [c] Ref. 42*a*. [d] Ref. 42*b*. [e] Ref. 42*d*; [f] Ref. 2*b*. [g] Ref. 42*c*. [h] Unpublished results. [i] Ref. 42*e*. [j] Ref. 34*a*. [k] Ref. 43. [l] Calculated from the value measured in MeOH–Me_2SO 50 : 50 by taking into account the known effect of Me_2SO concentration on complex stability.[37a] [m] Ref. 37*a*. [n] Ref. 21.

both ^1H and ^{13}C spectra of the isolated substitution products consisted of two sets of resonances assignable to the formation of the isomeric structures *S-3*$_I$ and *S-3*$_{II}$. This reflects the occurrence of the Boulton–Katritzky rearrangement outlined in eqn. (4).[27–30]



(4)

From a detailed analysis of the ^1H and ^{13}C NMR spectra recorded in Me_2SO-*d6* and/or acetone-*d6* solutions, *via* in particular 2D HMQC and HMBC experiments, the parameters given in Table 3 as well as in the supplementary Tables S3 and S4 were derived for rearomatized structures *S-3*$_I$ and *S-3*$_{II}$. The well-recognized diagnostic character of the C_8 and C_9 resonances in the benzofuroxan series ($\delta C_8 = 112 \pm 5$; $\delta C_9 = 150 \pm 5$) has been very helpful for the proposed assignments.[31–33] We failed to obtain ^{13}C NMR data for the 5-substituted isomer *S-3e*$_{II}$ because its concentration was too low under the various experimental conditions employed.

In the case of the other nitrobenzofuroxan adducts, *i.e. C-3f* and *C-5* as well as the two nitrobenzofurazan adducts, *i.e. C-3h* and *C-3i*, and the dinitrotetraazolo adduct *C-6*, the oxidation afforded only the expected rearomatized structure, *i.e. S-3f*, *S-3h*, *S-3i*, *S-5* and *S-6*. The NMR parameters for these molecules are also given in Tables 3, S3 and S4.

Mass spectroscopy data as well as elemental analysis data agreed with all structures discussed above (see experimental).

Discussion

Adduct formation — structural features

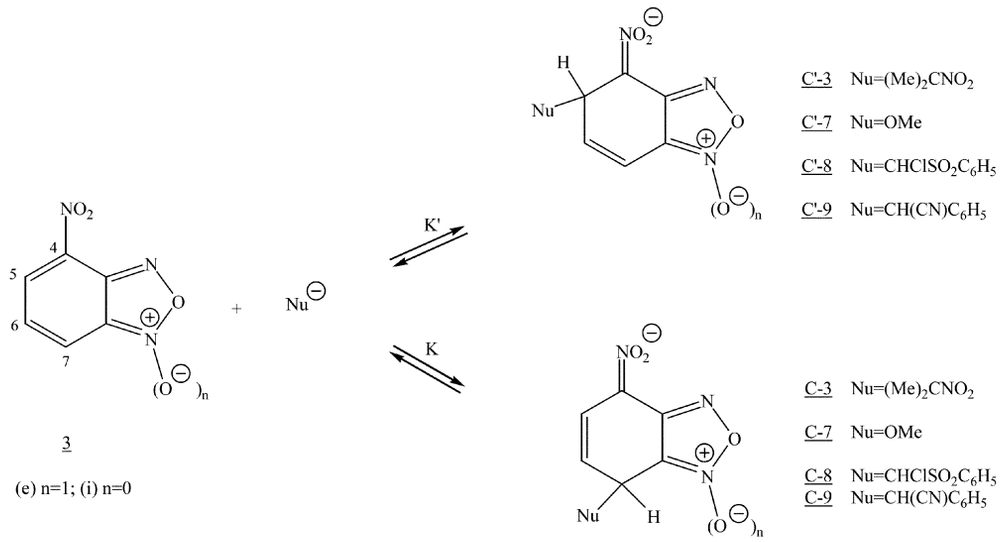
Since they agree well with the proposed structures, the ^1H and ^{13}C NMR data for all the adducts studied in this work do not call for much more comment than given in the results section. As mentioned earlier, the Cα resonance of the exocyclic nitropropane moiety is really typical for an sp^3 carbon bonded to a NO_2 group.[15b,25] Comparison of the data with those for the parent 2-nitropropane ($\delta C_\alpha = 79.20$ ppm, see footnote in Table 1)[25] is noteworthy, however, since it reveals that the presence of the various adjacent nitroactivated heterocyclic structures is always associated with an appreciable shift of this resonance to higher frequency. This implies that all negatively charged structures exert an important −I effect which does not change very much within the series of compounds at hand. This finding is somewhat in contrast with the evidence that the stability of the adducts is notably dependent on the nature of the 4-X and 6-Y substituents of the carbocyclic or hetarene ring (*vide infra*).

A most significant finding is that the reactions of the 2-nitropropenide anion with 4-nitrobenzofuroxan *3e* and 4-nitrobenzofurazan *3i* initially give rise to a mixture of the carbon-5 and carbon-7 adducts, namely *C′-3e,i* and *C-3e,i* respectively, under some experimental conditions. This situation can be appropriately compared with that encountered in the interaction of these two compounds with some oxygen and nitrogen nucleophiles. In particular, extensive NMR and kinetic studies of the reactions of *3e* and *3i* with the methoxide ion have been made in methanolic solution.[34] These have been found to result in rapid MeO^- attack at the 5-position to give the adducts *C′-7e,i* followed by slow isomerization of these species to the thermodynamically more stable 7-methoxy complexes *C-7e,i*, as outlined in Scheme 1. In these systems, about 5% of *C′-7e* and *C′-7i* remained present in the solutions at final equilibrium, in accord with the finding that the difference in stability of the two isomeric adducts is not very large; the ratio *K*/*K′* of the equilibrium constants for their formation is about 20.[34a]

Table 3 Selected ^1H and ^{13}C NMR data for the 5- or 7-substituted benzofuroxans and benzofurazans *S-3a–i* and related heterocycles *S-5* and *S-6* in Me_2SO-d_6 [a]

Compound	H_5	H_6	H_7	C_4	C_5	C_6	C_7	Cα	CH_3
S-3a$_I$	8.52	—	—	137.74	123.15	148.75	130.00	90.05	27.31
S-3a$_{II}$	—	—	8.92	139.21	127.78	145.91	128.62	89.35	26.36
S-3b$_I$	8.75	—	—	138.32	135.58	116.75	140.69	90.14	28.18
S-3b$_{II}$	—	—	8.41	137.36	142.33	114.34	129.06	91.00	27.95
S-3e$_I$	8.59	7.70	—	137.13	126.15	132.48	133.59	87.48	26.47
S-3e$_{II}$	—	7.76	8.21	—	—	—	—	—	—
S-3f	8.62	—	—	111.26	132.92	148.61	128.04	89.31	26.85
S-3g	8.28	—	—	117.45	124.85	147.78	127.18	88.89	26.53
S-3h	9.01	—	—	138.32	127.95	148.36	131.52	90.84	29.03
S-3i	8.51	7.63	—	137.15	129.85	126.53	137.39	88.55	26.54
S-5	9.04	—	—	—	151.40	146.41	134.66	89.63	26.01
S-6	9.22	—	—	140.78	135.40	155.20	134.73	92.12	27.99

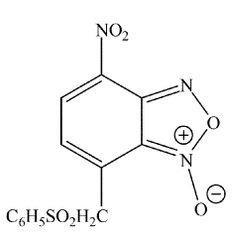
[a] δ in ppm relative to Me_4Si as internal reference.



Scheme 1

Scheme 1 applied in a recent study by Crampton *et al.* of the reaction of *3e* with various aliphatic and alicyclic amines in DMSO solution.[35] In these instances, the 7-adducts were considerably more thermodynamically stable than the 5-isomers so that the latter had essentially disappeared at completion of the interaction. Contrasting with the above findings, NMR studies of the reaction of *3e* with aryloxide anions have revealed the exclusive formation of 7-aryloxy adducts which are preferred both kinetically and thermodynamically.[8] Obviously, the characterization of the short-lived 5-adducts *C′-3e* and *C′-3i* implies that the interaction of *3e* and *3i* with the 2-nitropropenide ion proceeds through the two competitive reactions shown in Scheme 1. As in the case of the amine nucleophiles, the 7-adducts *C-3e* and *C-3i* are much more thermodynamically stable than their 5-isomers, *i.e. C′-3e* and *C′-3i*, and they are the only products obtained at completion of the reactions.

The competitive formation of the adducts *C′-3* and *C-3* in the reactions of *3e* and *3i* with the $Me_2CNO_2^-$ anion represents the first-well-defined example of isomeric addition of a carbon nucleophile to the activated 5- and 7-positions of 4-nitrobenzofuroxan and 4-nitrobenzofurazan. Based on a TLC analysis of the reaction mixture, it has been previously suggested that the vicarious nucleophilic aromatic substitution of *3e* with the carbanion of chloromethylphenylsulfone might proceed initially through competitive formation of the two adducts *C′-8e* and *C-8e* in Me_2SO solution.[15a] However, only the corresponding rearomatized 7-substituted product *V-8e* could be isolated and firmly identified after work up of the reaction mixture.



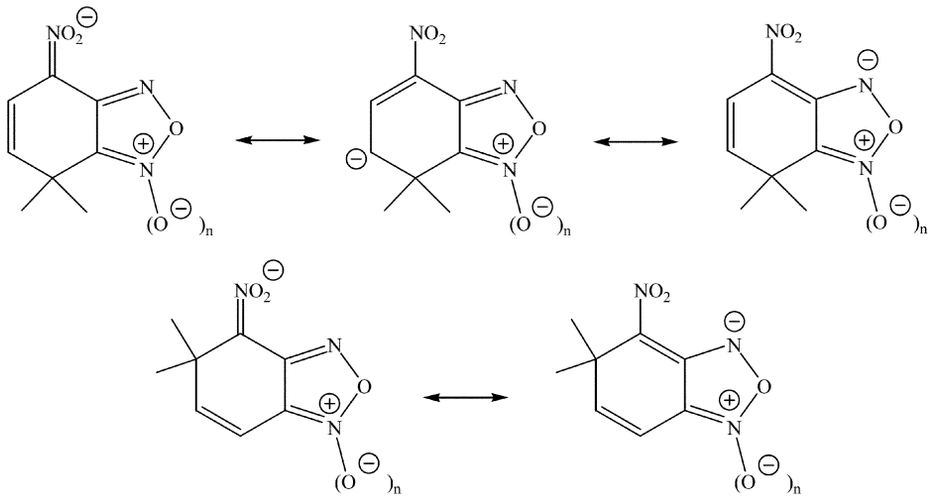
V-8e

Contrasting with this situation, Atherton *et al.* have shown that they were dealing with the formation of the 5-isomer *C′-9e* in a kinetic study of the reaction of *3e* with the benzylcyanide anion in methanol.[36] However, the possible conversion of this adduct into the 7-isomer *C-9e* was not investigated.

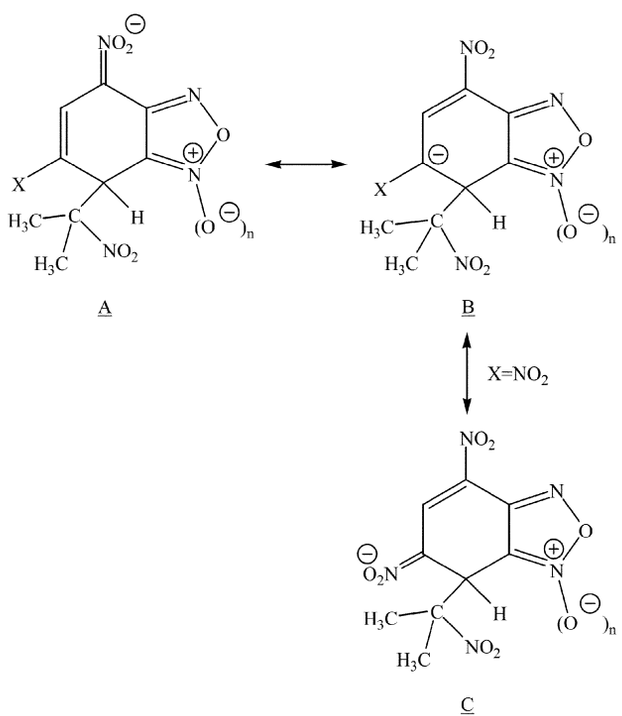
The observed thermodynamic preference for 7-attack in the 4-nitrobenzofuroxan and 4-nitrobenzofurazan systems can be reasonably understood in terms of the extent of charge delocalization possible in the adducts. Comparison in Scheme 2 of the resonance forms available clearly shows the possibility of greater charge delocalisation in the 7-adducts. The accumulated evidence is also that a *para*-NO_2 group is more efficient than an *ortho*-NO_2 group in delocalizing electrons by resonance interaction.[1,37] This will not only result in greater stability of the 7-adducts but also in a higher kinetic barrier to their formation, as compared with that for the 5-adducts, *i.e.* the situation that is actually observed.

That a large portion of the negative charge of the adducts *C-3e* and *C-3i* is localized onto the oxygen atoms of the 4-nitro group is supported by the finding that the σ-complexation of *3e* and *3i* induces a strong shielding of the C_4 carbon: $\Delta\delta C_4 = -19$ for *3e*; $\Delta\delta C_4 = -36$ for *3i*. This shielding is reminiscent of that reported in ^{13}C studies of the formation of picryl σ-adducts of type *C-4*. In these instances, theoretical calculations have been made which indicate that the σ-complexation process results in increases in π-electron density at the 2-,4- and 6-positions as well as on the related NO_2 substituents, accounting well for the variations observed in the corresponding chemical shifts: $\Delta\delta C_{2,6} = -17$; $\Delta\delta C_4 = -29$.[1,38,39] In addition, the calculations confirmed the predominant role of a *para*-NO_2 group in the delocalization of the negative charge of σ-adducts. That the $\Delta\delta C_4$ value is here lower for the addition to *3e* than to *3i* reflects the fact that electron-donation from the *N*-oxide group to the carbocyclic ring is operating in the benzofuroxan series,[28a] so that the C_4 carbon is already initially more shielded in *3e* (δC_4 = 125.2) than in *3i* (δC_4 = 137.0).

Consistent with the results discussed above, the σ-complexation of the two 4,6-dinitrosubstituted molecules *3a* and *3h* is also associated with strong shielding of the C_4 and C_6 carbons. In contrast with the situation which prevails in the trinitrobenzene series, the effect appears to be rather similar at these *para* and *ortho*-like positions ($\Delta\delta C_4 = -26.11$; $\Delta\delta C_6 = -23.64$ for DNBF; $\Delta\delta C_4 = -25.97$; $\Delta\delta C_6 = -26.59$ for DNBZ). Also noteworthy is that a much higher shielding of the *ortho* C_6 carbon than of the nitro-bearing carbon C_4 is observed upon complexation of 4-nitro-6-trifluoromethanesulfonylbenzofuroxan *3d*: $\Delta\delta C_4 = -24.77$; $\Delta\delta C_6 = -37.28$. In as much as the strong ability of an SO_2CF_3 group to stabilize a negative charge is known to derive from polarization effects rather than conjugative effects,[40] the above figures suggest that the resonance structure *B* must contribute importantly to the stabilization of the adducts *C-1a*, *C-1h* and *C-1d*. The reasoning also applied to the 6-cyano substituted system ($\Delta\delta C_4 = -28.34$; $\Delta\delta C_6 = -29.50$), confirming recent conclusions that the activating effect of a CN group is essentially the result of a polar effect.[41]



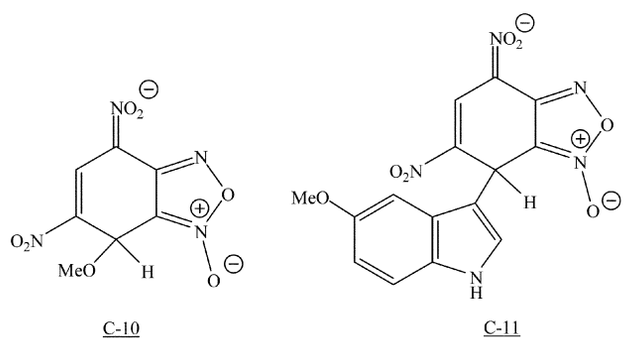
Scheme 2



A B C

Oxidation of the adducts

The chemical feasibility of the oxidation of our series of 2-nitropropenide adducts can be readily understood with reference to the oxidation potentials pertaining to rearomatization of these species in acetonitrile. Inspection of Table 2 clearly shows that E^0 increases strongly but regularly on going from the 4-nitro-benzofuroxan and -benzofurazan 2-nitropropenide adducts *C-3e* and *C-3i* to the 4,6-dinitro or 4-nitro-6-trifluoromethanesulfonyl analogues *C-3a*, *C-3h* and *C-3d* and to the 4,6-dinitrotetraazolopyridine adduct *C-6*. This suggests that the potentiality of charge delocalization in the cyclohexadienyl-type moiety of the adducts, and therefore the stability of these species, is a major factor governing the ease of the oxidation process. Consistent with this idea are the two following features: (1) the oxidation potential appears to depend very little on the moiety bonded at the sp^3 carbon, being for example similar for the three DNBF adducts *C-3a*, *C-10* and *C-11*;[20b] (2) the observed changes in E^0 within our series of 2-nitropropenide adducts parallel very well those in their thermodynamic stability, as reflected by a comparison of the equilibrium constants measured for formation of the related hydroxide σ-adducts, which have just became available in aqueous solution.[42b,d] To be noted, is that a similar situation emerges in the benzene series when the E^0 values for oxidation of the three *C-4* adducts are compared with the equilibrium constants for formation of the corresponding methoxide adducts in methanol.[37a,43]



C-10 C-11

Comparing the two series further, it is noteworthy that the 4-nitrobenzofuroxan and 4-nitrobenzofurazan adducts are more stable by about two pK_a units but oxidize more readily than the TNB adducts ($\Delta E^0 \sim 0.3$ V). In view of the accumulated evidence that the aromatic character of a benzoxadiazole moiety is much lower than that of a benzene ring, the above trend is readily accounted for.[1,16,35] The important point, however, is that the E^0 values fit well our finding that the adducts *C-3e* and *C-3i* are efficiently rearomatized using the same mild oxidizing agents, *e.g.* Ag^+ or 2,3-dichloro-5,6-dicyanoquinone, as those successfully employed for a number of TNB adducts.[44]

Focusing on the other σ-adducts listed in Table 1, they are all notably more stable and therefore more resistant to oxidation than *C-3e* and *C-3i*. In particular, we note that there is a 10^6–10^7 increase in the equilibrium constant for adduct formation on going from 4-nitrobenzofuroxan to the superelectrophilic 4,6-dinitrobenzofuroxan compound. As can be seen in Table 2, this huge gain in adduct stability goes along with a 0.56 V increase in the oxidation potential, bringing E^0 to such a level that only very strong oxidizing agents will be able to induce rearomatization of the carbocyclic ring. As a matter of fact, the experimental evidence is that chemical conversion of the DNBF adduct *C-3a* as well as of the similarly stable 4-aza-6-nitrobenzofuroxan and 4,6-dinitrobenzofurazan adducts *C-5* and *C-3h* can be achieved only with couples like Ce^{4+}/Ce^{3+} or MnO_4^-/Mn^{2+} (at pH = 0). Also remarkable is the especially powerful activating effect of the SO_2CF_3 group which makes the 4-nitro-6-trifluoromethanesulfonyl adduct *C-3d* the most stable σ-complex studied in the benzofuroxan series.[42b] In this instance, the E^0value is so high (E^0 = 1.33 V/SCE) that the oxidation of *C-3d* does not proceed satisfactorily well with the

two aforementioned couples, affording a so far unidentified high molecular weight compound rather than the expected substitution product *S-3d* previously obtained from preparative electrolysis experiments.[20b] In view of the lower E^0 value of 0.94 V/SCE for this process, it also remains to elucidate why we failed to achieve the chemical oxidative conversion of the trifluoromethyl adduct *C-3c* to *S-3c* with the two strong oxidants above.

Apart from the two latter systems, it is clear from all our results that the difficulty in carrying out oxidative nucleophilic aromatic substitutions in the nitrobenzofuroxan and related series is primarily a reflection of the especially strong electron-deficient character of the six membered ring of these heterocycles. As a matter of fact, Remenniko *et al.* have recently shown that this type of compound ranks among the strongest non charged electrophiles, comparable in reactivity to stabilized carbocations and cationic metal-π-complexes.[45]

Boulton–Katritzky rearrangement

A major feature of the oxidation of the 4-nitrobenzofuroxan adducts is that some of the resulting substituted products, namely *S-3a,b* and *S-3e*, undergo the Boulton–Katritzky rearrangement depicted in eqn. (4). A similar situation was found to prevail with the two compounds *S-3c* and *S-3d* as obtained by electrochemical oxidation. Such a rearrangement has been the subject of many studies, including through a recent theoretical approach.[27–29] The available experimental and theoretical evidence is that strain and steric effects are of significant importance in determining the relative amounts of the two tautomers at final equilibrium. In this regard, it is noteworthy that the ratio of the two structures $S\text{-}3_I$ and $S\text{-}3_{II}$ is seen here to decrease from the 4,6-dinitro compound (1 : 1) to the 6-cyano-nitro compound (~4 : 1) to the 4-nitro compound (94 : 6) at room temperature in DMSO solution. This trend gives further support to the idea that the bulkiness of the 6-substituent in the 7-tautomer of type $S\text{-}3_I$ is one of the key factors driving the isomerization equilibrium towards the 5-tautomer.

Experimental

General

Melting points were determined on a Reichert-type microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer. Chemical shifts are reported in ppm (*J* values in Hertz) relative to internal Me_4Si for ^{1}H and ^{13}C NMR and $CFCl_3$ for ^{19}F NMR. Electronic impact mass spectra (EI, 70 eV) were obtained using a Hewlett-Packard 5989B and a NERMAG R10–10C spectrometer equipped with a quadrupole. Elemental analyses were determined by the Microanalytical Laboratory of the University Pierre et Marie Curie, France. Electrochemical measurements pertaining to the oxidation of the adducts *C-3h*, *C-3i* and *C-6* were carried out with the same electrochemical equipment as described previously.[20b]

Materials

σ-Adducts as crystalline potassium salts. Samples of the potassium salts of the adducts *C-3a–g* used in this paper were the same as those employed in our previous electrochemical investigation of the oxidation of these species.[20b] The potassium salts of the two nitrobenzofurazan adducts *C-3h* and *C-3i* as well as of the 4,6-dinitrotetraazolo adduct *C-6* were prepared and isolated as stable crystals upon treatment of the parent molecules, *i.e. 3h*, *3i* and *6*, with potassium 2-nitropropenide (1 eq.) in 2-nitropropane, as described in detail for C-*3a–g*. As is the case for most alkali salts of σ-adducts of nitrobenzofuroxans,[3–6,42] including those of *C-3a–g*, attempts to obtain satisfactory elemental analysis of $C\text{-}3h,K^+$, $C\text{-}3i,K^+$ and *C-6*, K^+ have failed. To be noted is that these three salts decompose violently upon heating (*ca.* 155–200 °C). In all cases, satisfactory mass spectra were obtained, base peaks corresponding to the loss of K^+ were observed, for example *m*/*z* 314 for *C3-a*, with no detection of the pseudomolecular ions. A detailed NMR study has been made and the data are summarized in Tables 1, S1 and S2.

Presumably because of a high propensity to hydration of the activated N_4–C_5 double bond, we failed to isolate the adduct *C-5* of 4-aza-6-nitrobenzofuroxan *5* as a crystalline alkali salt. However, the NMR spectra recorded after dissolution in Me_2SO-d_6 of the viscous oil obtained after reaction of potassium 2-nitropropenide (1 eq.) with *5* leave no doubt that the adduct *C-5* was quantitatively formed. The fact that the oxidative treatment of *C-5* afforded the expected substitution product *S-5* was definitive evidence for a successful σ-complexation (*vide infra*). Also, a mass spectrum (ESI) could be obtained which confirmed structure *C-5*.

The parent benzofurazans (*3h*, *3i*), benzofuroxan (*5*) and tetraazolopyridine (*6*) compounds were prepared and purified as reported in the literature.[31,42,46–48]

Oxidative treatment of the σ-adducts. Preparation of the 7-substituted products *S-3a–i*, *S-5* and *S-6*.

Oxidation of the 4,6-disubstituted adducts *C-3a–b*, *C-3f–h*, *C-5* and *C-6*. To an aqueous solution of the σ-adduct in water were added three equivalents of cerium ammonium nitrate. The initially orange-red colored solution turned rapidly to yellow. After overnight stirring, the aqueous solution was extracted three times with 50 cm^3 of ethyl acetate. After washing twice with water (20 cm^3), the organic layer was dried on $MgSO_4$ and then evaporated under reduced pressure, affording in most cases a brown solid which was purified by column chromatography (florisil), using pentane–ethyl acetate mixtures as eluents. Selected analytical data for the substitution products obtained are given below, except for the ^{1}H and ^{13}C NMR data which are collected in Tables 3, S3 and S4.

Oxidation of the monosubstituted adducts *C-3e* and *C-3i*. Three equivalents of silver nitrate were added to a solution of the adduct in 15 cm^3 of acetonitrile. A black mirror of silver appeared rapidly but the mixture was kept under stirring for 15 hours. Evaporation of the solvent afforded a residue which was purified by column chromatography as above. ^{1}H and ^{13}C NMR data for *S-3e* and *S-3i* are given in Tables 3, S3 and S4. Other analytical data are given below.

Selected data

***S-3a*.** Yellow solid; yield 55%; mp 172–3 °C; MS (EI): *m*/*z*: 313 $[M]^{+\bullet}$, 267 $[M - NO_2]^{+\bullet}$, 237 $[M - 2CH_3 - NO_2]^{+\bullet}$. Anal. Calc. for $C_9H_7N_5O_8$: C, 34.52; N, 22.36; H, 2.25. Found: C, 34.59; N, 22.06; H, 2.15%.

***S-3b*.** Yellow oil; yield 68%; MS (EI): *m*/*z*: 293 $[M]^{+\bullet}$, 247 $[M - NO_2]^{+\bullet}$, 217 $[M - 2CH_3 - NO_2]^{+\bullet}$. Anal. Calc. for $C_{10}H_7N_5O_6$: C, 40.95; N, 20.47; H, 2.38. Found: C, 41.09; N, 20.36; H, 2.35%.

***S-3e*.** Yellow solid; yield 35%; mp 103 °C; MS (EI): *m*/*z*: 268 $[M]^{+\bullet}$, 222 $[M - NO_2]^{+\bullet}$, 206 $[M - NO_2 - O]^{+\bullet}$. Anal. Calc. for $C_9H_8N_4O_6$: C, 40.29; N, 20.89; H, 2.98. Found: C, 40.59; N, 21.06; H, 2.95%.

***S-3f*.** Yellow solid; yield 72%; mp 128 °C; MS (ESI): *m*/*z*: 310 $[(M + NH_4^+) - H]^-$, 294 $[(M + NH_4^+) - H - O]^-$. Anal. Calc. for $C_{10}H_7N_5O_6$: C, 34.52; N, 22.36; H, 2.25. Found: C, 34.59; N, 22.06; H, 2.15%.

***S-3g*.** Yellow solid; yield 67%; mp 117 °C; MS (EI): *m*/*z*: 336 $[M]^{+\bullet}$, 290 $[M - NO_2]^{+\bullet}$. Anal. Calc. for $C_{10}H_7F_3N_4O_6$: C, 35.71; N, 16.66; H, 2.08. Found: C, 36.02; N, 17.06; H, 2.15%.

***S-3h*.** Yellow solid; yield 65%; mp 172–3 °C; MS (EI): *m*/*z*: 251 $[M - NO_2]^{+\bullet}$. Anal. Calc. for $C_9H_7N_5O_7$: C, 36.37; N, 23.57; H, 2.37. Found: C, 36.70; N, 23.48; H, 2.39%.

***S-3i*.** Yellow solid; yield 35%; mp 103 °C; MS (EI): *m*/*z*: 206 $[M - NO_2]^{+\bullet}$. HRMS calculated for $C_9H_8N_4O_5$: 206.0566 $[M\text{-}NO2]^{+\bullet}$. Found: *m*/*e* 206.0565.

***S-5*.** Orange solid; yield 70%; mp 130 °C; MS (EI): *m*/*z*: 269 $[M]^{+\bullet}$, 207 $[M - NO_2 - O]^{+\bullet}$. Anal. Calc. for $C_8H_7N_5O_6$: C, 35.68; N, 26.02; H, 2.60. Found: C, 35.92; N, 26.66; H, 2.75%.

***S-6*.** Yellow solid; yield 60%; mp 90 °C; MS (EI): *m*/*z*: 297 $[M]^{+\bullet}$, 251 $[M - NO_2]^{+\bullet}$. Anal. Calc. for $C_8H_7N_7O_6$: C, 32.32; N, 32.99; H, 2.35. Found: C, 34.02; N, 32.19; H, 2.55%.

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