Side-chain electrophilic aromatic substitution in 2-alkyloxa- and 2-alkylthiazolines initiated *via* σ-complex formation with super-electrophilic DNBF: a model proinsecticide †

Jean-Claude Cherton,* Sandrine Hamm, Marie-José Pouet, Jean-Claude Halle and François Terrier *

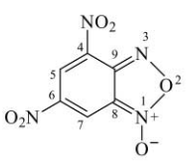
Laboratoire SIRCOB, ESA CNRS 8086, Bâtiment Lavoisier, Université de Versailles, 45, avenue des Etats-Unis, 78035 Versailles Cedex, France. E-mail: cherton@chimie.uvsq.fr. E-mail: terrier@chimie.uvsq.fr

Received (in Cambridge, UK) 28th January 2002, Accepted 27th February 2002
First published as an Advance Article on the web 26th March 2002

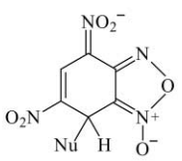
A ^{1}H and ^{13}C NMR study of the reaction of a series of 2-alkyloxa- and 2-alkylthiazolines **3-Xa–c** with 4,6-dinitrobenzofuroxan (DNBF) in DMSO revealed the formation of the C-bonded σ-adducts **5-Xa–c**. Product isolation following addition of Et_3N or KOAc, afforded the Et_3NH^+ or K^+ salts of the DNBF adducts, respectively. The NMR results showed conclusively that coupling of the DNBF moiety with the oxazoline or thiazoline heterocycle occurred at the α position of the 2-alkyl side-chain. A most reasonable mechanism for this coupling involves initial formation of a transient N-bonded adduct between the N-heterocycle and DNBF, which subsequently rearranges through the action of base to the C-bonded adduct as the product of thermodynamic control. The relevance of this work to oxa- and thiazoline-based proinsecticide is emphasized.

Introduction

Despite its neutral character, 4,6-dinitro-2,1,3-benzoxadiazole 1-oxide, commonly referred to as 4,6-dinitrobenzofuroxan (DNBF, **1**), is a 10π-electron heteroaromatic substrate which exhibits an extremely high electrophilic character. This has led to the use of DNBF as an important probe to assess the reactivity of very weak nucleophilic nitrogen, oxygen and sulfur centers as well as carbon centers, with diverse analytical and biological applications.[1–8] In all of these interactions, covalent addition of the anionic or neutral nucleophile occurs at C7 of the carbocyclic ring of DNBF, affording stable anionic or zwitterionic σ-adducts, *e.g.* **2a**–**c**.

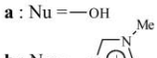


DNBF, **1**

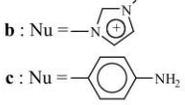


2

a : Nu = —OH



b : Nu =

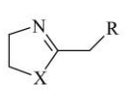


c : Nu =

In this paper, we report on the reaction of DNBF with some 2-alkyloxazolines, **3-O**, and 2-alkylthiazolines, **3-S**, which can be considered as examples of enol ethers (namely imino ethers or imino thioethers) that are known to couple with DNBF.[9] In addition to a contribution to the study of DNBF reactivity, the other objective was to induce modifications of the heterocycles **3-O** and **3-S**, which are presently developed in our laboratory as a "proinsecticide perspective".

The potential of the heterocyclic structure oxazoline **3-O** for the reversible masking of carboxylic acids has been intensively used by Meyers and coworkers for the enantio-selective modification of carboxylic acids by α-ramification.[10] As well, in the prodrug field, Vorbrüggen *et al.* have retained the structures **3-O** and **3-S** for the elaboration of NSAID drugs (non-steroidal anti-inflammatory drugs) based upon carboxylic acids as the active principle.[11] For several years, we have also been working with a series of heterocycles **3-O** and **3-S** differently substituted and designed as contact insecticides due to their high lipophilicity.[12] An efficient unmasking of some biologically active oxazolines and thiazolines was recently demonstrated during *in vitro* assays monitored by ^{19}F NMR [13a,b,d] or modern TLC [13c] in concentrated locust fat-body and mesenteron.

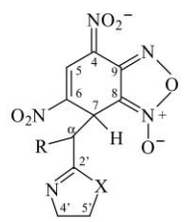
Thus, we wanted to study the impact of the possible modification of the heterocycles **3-O** and **3-S** with super-electrophilic DNBF, upon their metabolization and biological properties.



3-X

X = O or S

a : R = H
b : R = $CH_3(CH_2)_7$
c : R = p-F-$PhCH_2$



5-X

We have discovered that in these systems, σ-complexation takes place at the C_α of the side-chain of these heterocycles to give the C-bonded adducts **5-X**; however adducts resulting from initial coupling at the ring-imino nitrogen atom could not be detected.

Results

In situ complexation of DNBF

The reaction of DNBF with 2-methyloxazoline **3-Oa** was first studied in DMSO-d_6 solution. The ^{1}H NMR spectra recorded

† Electronic supplementary information (ESI) available: the ABX analysis of the CH_2-α and H_2 proton region of the adduct **5-Oa**. See http://www.rsc.org/suppdata/p2/b2/b201045n/

DOI: 10.1039/b201045n

Table 1 ^{1}H and ^{19}F NMR data for σ-adducts **5-X** in DMSO-d_6 [a]

Adduct	H5	H7	Hα [b]	H4′ [b]	H5′ [b]	F
5-Oa [c,d]	8.57	4.58	2.95 2.83	3.5	3.9	—
5-Oa,H [e]	8.60	4.77	3.3 3.1_5	3.9_5	4.8_5	—
5-Sa [d]	8.56	4.62	3.2 3.1	3.9	3.2	—
5-Sa,H [e]	8.60	4.77	3.4_5 3.3	4.2	3.7	—
5-Sa,Et [f]	8.61	4.81	3.5 3.6	4.4_5	3.6	—
5-Ob [c]	8.65 8.53	4.76 4.62	2.8_5 2.9_5 [g]	3.6/3.5	4.1/3.9	—
5-Sb [c]	8.61 8.50	4.75 4.61	3.0 [g,h] 3.2 [h]	3.8_5/4.9_5	3.0 [g,h]/3.2 [h]	—
5-Oc [c]	8.61 8.54	4.83 4.72	3.2 3.2	3.2/3.6	3.9/4.1	−40.80 −40.55
5-Sc [c]	8.60 8.52	4.86 4.70	3.4_5 3.4_5	3.9_5/3.8_5	3.2/3.0_5	−40.80 −40.64

[a] ^{1}H chemical shifts were reported relative to TMS using the residual solvent signals as internal reference (2.5 ppm for DMSO-d_6). ^{19}F chemical shifts were reported relative to external reference : CF_3COOH (5% v/v in D_2O). [b] "Multiplet" centered at, except for Hα of **5-Oa** for which the assignments of the frequencies concerning the ABX system (Hα, H7) resulted from the sub-spectra method, (*cf.* supplementary material for **5-Oa**). Second order ABXY system (H4′, H5′) was described considering the center of each multiplet of the parts AB and XY. [c] Triethylammonium salt. [d] Potassium salt. [e] *N*-protonated form. [f] *N*-ethylammonium form. [g] Signal masked by the methylenic signal of Et_3N. COSY experiments allow determination of the chemical shifts of these masked signals. [h] CH_2–S and CHα signals are superposed.

immediately after mixing of the two reagents in equimolar amounts, showed a progressive but partial disappearance of the H5 and H7 doublets of DNBF (δ_{H5} = 8.95 ppm, δ_{H7} = 9.27 ppm, $^{4}J_{5,7}$ = 1.9 Hz)[5d] and the concomitant development of a new set of signals which was seen to move regularly downfield as the reaction proceeds. This result, together with the finding that the reaction did not go to completion under the experimental conditions at hand, suggested that the resulting condensation product and the unreacted oxazoline were in fact partners of a proton tranfer equilibrium (Scheme 2, *vide infra*). Consistent with this idea, essentially quantitative conversion of the reagents could be successfully achieved in about 20 minutes when the reaction was carried out in the presence of triethylamine (~1.1 equiv.), a much stronger base than the oxazoline **3-Oa**.[14] At this stage, the ^{1}H NMR spectra showed exclusively the aforementioned new set of signals, *i.e.* a singlet at 8.57 ppm and two complex ABX and ABXY patterns. These data support the formation of an anionic C-bonded adduct of type **5-Oa**. Because of the chirality of the tetrahedral ring carbon C7, the geminal H_α protons are diastereotopic and they therefore appear as the AB part of the ABX system with a slight broadening of the H_B resonance (highfield) which persists in the AB system resulting from irradiation of H_X (H7 triplet-like at 4.58 ppm). Irradiation of N–CH_2 protons entailed the clarification of the AB part, thereby confirming that the broadening of the H_B resonance is the result of a long-range ^{5}J homoallylic-type coupling with the N–CH_2 protons of the oxazoline moiety.[18] The second-order analysis of the ABX system afforded: δ_A = 2.95 ppm, δ_B = 2.83 ppm, δ_X = 4.58 ppm, $^{2}J_{AB}$ = 14.6 Hz, $^{3}J_{AX}$ = 4.8 Hz, $^{3}J_{BX}$ = 3.8 Hz.

As to the ABXY system, it refers to the four methylenic protons of the oxazoline ring and its XY part (N–CH_2 multiplet centered at ~3.5 ppm) is affected by the aforementionned ^{5}J coupling. Clearly, all these data, together with the singlet observed at 8.57 ppm, which is readily assignable to the H5 proton of the carbocyclic ring of the DNBF moiety, fully support the formation of the σ-adduct, structure **5-Oa** (*cf.* Table 1).

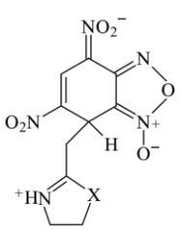
Reaction of DNBF with the two oxazolines **3-Ob**, **3-Oc** and the three thiazolines **3-Sa**, **3-Sb** and **3-Sc**, similarly afforded the adducts **5-Ob,c** and **5-Sa,b,c** in the presence of Et_3N (~1.1 equiv.) in DMSO solution (pK_a = 9.07 for Et_3NH^+ in DMSO[19]). In the case of **5-Sa**, the ^{1}H NMR spectra showed the expected patterns with, however, a reversal in the positions of the H4′ and H5′ resonances as compared with the situation found for the oxygen analogue **5-Oa** (*cf.* Table 1). This reversal is in accord with the relative electronegativities of the oxygen, nitrogen and sulfur atoms and it is in fact observed in the ^{1}H NMR spectra of the parent heterocycles.[13a] In the case of the other DNBF-oxazoline or -thiazoline systems, complexation of DNBF results in the formation of two chiral centers at C7 and Cα, leading to formation of diastereomeric adducts. In agreement with this expectation, the corresponding ^{1}H NMR spectra exhibited two very close but reasonably well-defined sets of H7 and H5 resonances of similar intensities, which leave no doubt as to the formation of adducts **5-Xb,c** as a mixture of two diastereomers. Such a diastereomeric mixture was previously observed in DNBF adducts formed on reaction with cysteine[3c] and cyclopentanone.[3d] Due to this mixture, the resonances of the protons H4′ and H5′ appear as complex patterns (compared to those observed for **5-Oa**) that were difficult to analyse precisely.

The complete assignment of ^{13}C NMR signals for the adducts **5-Xa–c** (*cf.* Table 2) was made on the basis of previously reported ^{13}C NMR data for various DNBF σ-adducts[4c,20] and H–C COSY and *J* modulation experiments.

Isolation and protonation of the adducts 5-Oa and 5-Sa

Treatment of DNBF with the oxazoline **3-Oa** and the thiazoline **3-Sa** in the presence of Et_3N in CH_2Cl_2 solution or potassium acetate in acetonitrile solution, followed by the addition of diethyl ether, resulted in the precipitation of adducts **5-Oa** and **5-Sa** in the form of very pure crytalline triethylammonium or potassium salts respectively, whose structures were confirmed by high-resolution mass spectrometry (HRMS), (see Experimental section). Dissolution of these salts in DMSO-d_6 afforded ^{1}H or ^{13}C NMR spectra which were identical to those recorded in the previously discussed adducts generated *in situ* (*cf.* Tables 1 and 2)

The effect of addition of methanesulfonic acid to DMSO-d_6 solutions of the isolated potassium salts of adducts **5-Oa** and **5-Sa** was studied. This induced a downfield shift of all proton resonances, notably those assignable to the methylenic protons of the oxazoline and thiazoline moieties of these initial anionic structures. Importantly, the deshielding effect reached a maximum on addition of 1 equiv. of $MeSO_3H$ (pK_a = 1.76 in DMSO[21]), indicating that at this stage we were dealing with the complete conversion of **5-Oa** and **5-Sa** into their conjugate acids, *i.e.* the zwitterionic adducts **5-Oa,H** and **5-Sa,H**. The NMR data for these two adducts are given in Table 1.



5-X,aH
(X = O, S)

Returning to the experiments carried out in the absence of added Et_3N, it is noteworthy that the various chemical shifts recorded for the partial complexation of DNBF by **3-Oa** always lie between those found for adducts **5-Oa** and **5-Oa,H**. As

Table 2 ^{13}C NMR data for σ-adducts **5-X** in DMSO-d_6 [a]

Adduct	C4	C5	C6	C7	C8	C9	Cα [d]	C2′	C4′	C5′
5-Oa [b,c]	110.2	132.0	124.6	31.6	113.5	149.3	25.0	163.3	54.1	67.0
5-Sa [c]	110.3	132.4	124.3	32.6	113.3	149.3	30.0	167.5	63.6	33.9
5-Ob [b,e]	110.1	132.4	124.0	36.2	111.6	149.5	40.5	165.5	54.0	66.8
	110.3	131.7	124.5	36.2	112.3	149.9	42.8	165.8	53.8	66.6
5-Sb [b,e]	110.7	132.1	124.5	36.9	112.3	150.1	48.0	169.3	64.1	33.3
	110.3	132.7	124.1	37.0	111.8	149.6	46.1	169.2	64.2	33.1
5-Oc [b,e]	110.3	132.6	123.7	36.2	111.8	149.5	42.7	165.0	54.0	67.0
	110.3	131.9	124.3	36.2	112.5	149.7	44.7	165.2	53.8	66.8
5-Sc [b,e]	110.7	132.3	124.4	37.0	112.5	150.0	49.5	168.8	64.1	33.6
	110.5	132.8	123.8	37.0	111.8	149.5	47.7	168.4	64.2	33.4

[a] ^{13}C chemical shifts were reported relative to TMS using the residual solvent signals as internal reference (39.5 for DMSO-d_6). [b] Triethylammonium salt. [c] Potassium salt. [d] $\delta_{C\alpha}$ (DMSO-d_6) in the parent **3-X** molecules : 13.3 for **3-Oa**, 19.7 for **3-Sa**, 27.1 for **3-Ob**, 33.4 for **3-Sb**, 28.9 for **3-Oc**, 35.1 for **3-Sc**. [e] C–H COSY experiments allow determination of the chemical shifts of the Cα and C5 signals.

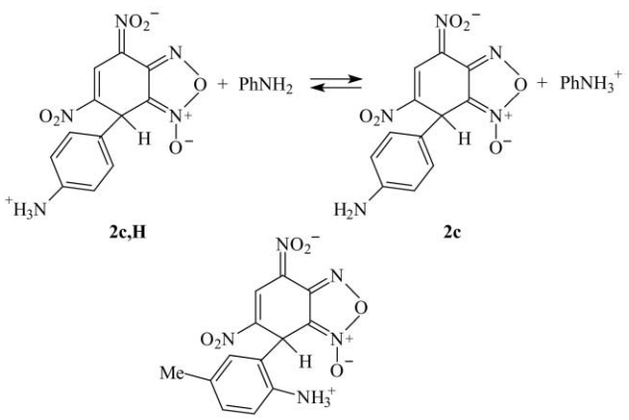
discussed below, this situation confirms the suggestion of an acid–base equilibrium involving these two σ-adducts and the oxazoline acid–base pair **3-Oa,H**–**3-Oa** (*cf.* Scheme 2, *vide infra*).

Discussion

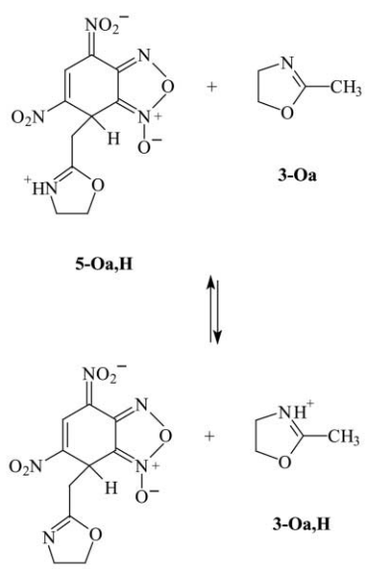
Structural aspects of DNBF adducts

The ^{1}H and ^{13}C NMR parameters in Tables 1 and 2 agree well with the proposed C-bonded anionic **5-X** or zwitterionic **5-X,H** structures. In accord with previous observations for a number of DNBF adducts, the chemical shifts of H5 and C5, located between the two NO_2 groups of the negatively charged DNBF moiety, appear essentially independent of the nature of the bonded oxazoline or thiazoline group.[3–5,20] Importantly, all H_7 resonances lie in the range 4.58–4.86, being in the relatively high-field region which is typical of the reaction of C7 with another carbon atom, but not with an electronegative nitrogen or oxygen atom.[3–6] Besides the strong but expected shielding of C7, reflecting the $sp^2 \longrightarrow sp^3$ rehybridization of this carbon, the data in Table 2 show that the bonding of the DNBF moiety results in a significant downfield shift of the Cα carbon of the side chain of the oxazoline and thiazoline moieties (Cα : $\Delta\delta$ = 10.3–15.8 ppm). This result is a reflection of the strong electron-withdrawing inductive effect which is still exerted by a negatively charged DNBF structure.[1,2,5,6]

As a nice illustration of this −I effect, it has been found that a $DNBF^-$ moiety increases the acidity of various neighbouring groups. For example, the pK_a value for ionization of the OH group of the hydroxy σ-adduct **2a** is 11.8,[2a] *i.e.* almost 4 pK units lower than that for the ionization of water (pK_a = 15.74). As expected, this acid-strengthening effect depends markedly on how remote the ionizable site is from C7. Thus, Crampton and Rabbitt have measured increases in acidity of about 0.5 and 1 pK unit in comparing the pK_a values for ionization of the *para*- and *ortho*-NH_3^+ groups of the zwitterionic σ-adducts **2c**,**H** and **2d**,**H** with those for the anilinium and 4-methylanilinium cations, respectively, in DMSO.[6a] As a matter of fact, these authors observed that the mixing of equimolar amounts of DNBF and aniline in this solvent eventually resulted in a mixture of the two zwitterionic and anionic σ-adducts **2c**,**H** and **2c** in rapid equilibrium (Scheme 1). Obviously, our results regarding the interaction of DNBF with the oxazoline **3-Oa** in the absence of Et_3N (Scheme 2) are in accord with Crampton and Rabbitt's work as well as other work in this area.[3a,b,5] In the resulting zwitterionic σ-adduct **5-Oa,H**, the positively charged iminium group is as remote as the *ortho*-NH_3^+ group in **2d**,**H**, with, however, a less favorable situation due to the presence of the sp^3 Cα carbon. The result is that a stronger base is needed to shift the equilibrium to the right.



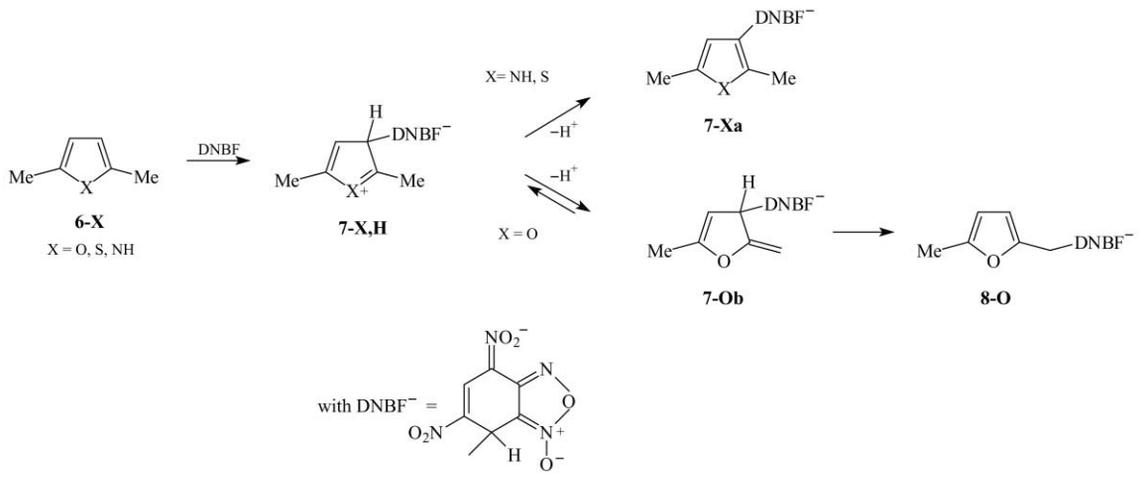
Scheme 1



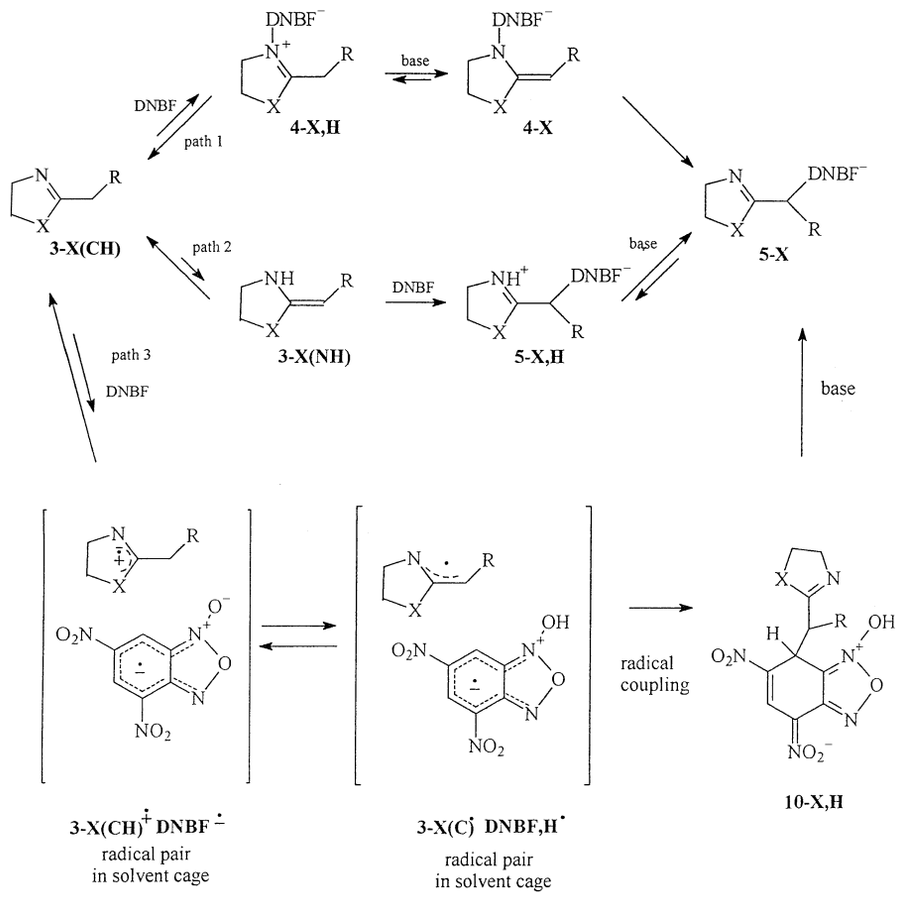
Scheme 2

Side-chain substitution of 3-X : reaction pathways and mechanisms

It is not the first time that reaction of DNBF with the side-chain of a heterocyclic compound has been observed since we have reported earlier a similar electrophilic substitution in the 2,5-dimethylfuran **6-O**/DNBF system.[5b] In this instance, the adduct **8-O** was obtained as the sole product of reaction. The mechanism depicted in Scheme 3 was proposed because



Scheme 3



Scheme 4

conventional C_β S_EAr reactions were observed with the homologous thiophene **6-S** and pyrrole **6-NH** compounds, leading to the adducts **7-Xa**.

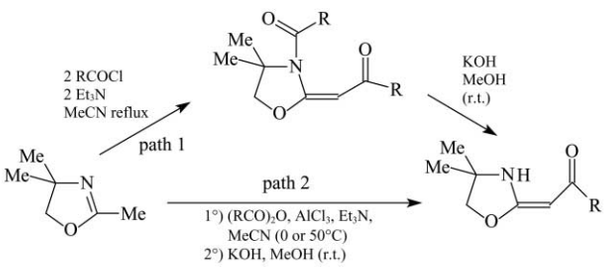
As can be seen, the key to the formation of **8-O** is the methylenic deprotonation of the **7-O,H** intermediate which is favored by the low aromaticity of the furan ring (as compared with the pyrrole and thiophene rings) and strengthened by the important −I effect of the $DNBF^-$ moiety.[2] On this basis, we can envisage a similar activation to account for the formation of **5-X**.

Two possible mechanisms are shown in Scheme 4. In path 1, the first step involves quaternisation of nitrogen by DNBF giving the N-adduct **4-X,H**. It is known that N-bonded adducts, formed under kinetic control, are thermodynamically less stable than their C-bonded counterparts.[3a,4,6a] In the present system, there was no NMR evidence for the accumulation of such N-bonded adducts. Low-temperature experiments using MeCN-d_3 were unsuccessful due to solubility problems. Moreover, attempts to detect N-bonded adducts between DNBF and oxazolines lacking a proton at the α-position, *e.g.* 2-phenyloxazoline, and without a C2-substituent as in 4,4-dimethyloxazoline, failed. These results indicate that adducts **4-X,H** are thermodynamically unstable relative to the reactants. Nevertheless, this does not preclude their participation in the reaction pathway as low-concentration intermediates.

It is expected that quaternisation of nitrogen in **4-X,H** will result in considerable enhancement of acidity for hydrogens on the α-carbon. An example illustrating the large magnitude of this effect is the increase by 19 pK units in the acidity of the methyl group in 2-methylbenzothiazole (pK_a = 27.4 in DMSO)

following *N*-methylation to give 2,3-dimethylbenzothiazolium iodide (pK_a = 8.5 in DMSO).[22] Such an enhancement in acidity of the hydrogen at the α-carbon of **4-X,H** will allow deprotonation by weak bases such as Et_3N or **3-X** itself. Then, rearrangement of the N-bonded adduct **4-X** affords the thermodynamically more stable C-adduct **5-X**; product formation is faster in the presence of Et_3N. This would be in accord with path 1 with either (a) rate-limiting deprotonation of the α-carbon followed by rapid isomerisation of **4-X** to **5-X**, or (b) formation of **4-X** as a low-concentration intermediate whose concentration increases with base concentration, followed by rate-limiting isomerisation of **4-X** to **5-X**.

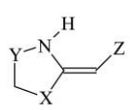
A similar oxazoline–nitrogen reactivity was previously observed by Tohda *et al.* who isolated diacetylated products derived from 2,4,4-trimethyloxazoline (Scheme 5 path 1).[23a,b] In



Scheme 5

this instance, there is no doubt that the primary *N*-acylation favors deprotonation of the C–H position (pK_a (Et_3NH^+/Et_3N) = 18.5 in MeCN[24]), thereby inducing the Cα acylation process. In contrast with acetyl chloride, acid anhydrides are not effective under the same experimental conditions, activation by $AlCl_3$ being required to achieve the reaction[23c] (Scheme 5 path 2).

Direct formation of **5-X** from the enaminic tautomer **3-X(NH)** can also be envisaged as being the operative pathway (Scheme 4, path 2). However, it is noteworthy that only ketene N,X-acetals of type **9-X**, where Y (carbonyl group, for example[25]) and/or Z (COR, CO_2Et, $CONH_2$, CN)[23b,25] are electron-withdrawing −M moieties, have been observed so far.



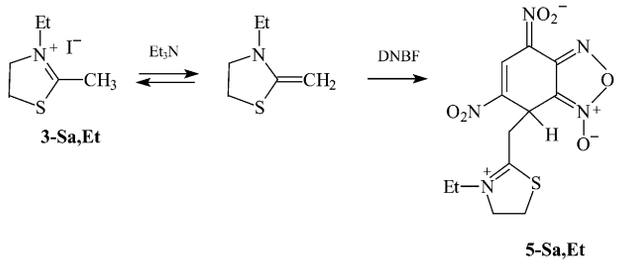
9-X

X = O, S

Based on the absence of such stabilizing substituents in **3-X(NH)**, one can reasonably anticipate that the population of this tautomer will be very low, thus rendering path 2 unfavorable, even though **3-X(NH)** is not devoid of appreciable carbon nucleophilicity.

There are in fact two additional arguments which do not favor path 2. The first is the observation that formation of the C-adducts **5-X** is markedly accelerated by the addition of an external base. Should path 2 be the correct pathway, this catalysis would mean that the rate-limiting step in the overall complexation process would be deprotonation of the iminium moiety of **5-X,H**, which is unlikely. A second argument deals with our finding that C-complexation of DNBF by the 2-methyl-3-ethylthiazolinium cation **3-Sa,Et** actually takes place in the presence of Et_3N in DMSO solution (Scheme 6).

Hence, the condensation necessarily involves deprotonation of the α-methyl group prior to the coupling with the DNBF molecule. As can be seen in Table 1, the NMR chemical shifts for **5-Sa,Et** are deshielded relative to **5-Sa**, in agreement with the zwitterionic structure of this adduct.



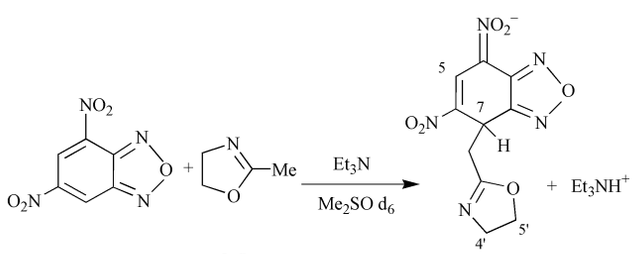
3-Sa,Et **5-Sa,Et**

Scheme 6

Finally, there is to be considered the possibility of a single electron-transfer (SET) mechanism as an alternative to the polar mechanisms considered hitherto. Since DNBF is an extremely electron-deficient substrate, the formation of a radical anion upon interaction with electron-rich heterocycles and other basic moieties is not an unreasonable assumption. While there has been so far, to our knowledge, no reports of the detection of nitrobenzofuroxan radical anions through EPR spectroscopy, recent electrochemical work has pointed out the marked instability of these species which give very rapidly unidentified decomposition products.[26] Nevertheless, it remains possible in our systems that when formed in a cage together with a radical cation, further reaction through the intermediacy of a $DNBF^{-\bullet}$ species could be feasible. Such a possible mechanism is illustrated in Scheme 4, as path 3.

Central to the SET mechanism is initial electron transfer from the heterocycle **3-X(CH)** to DNBF yielding the radical pair, followed by proton transfer to the *N*-oxide functionality within a solvent cage, $N^+–O^- \longrightarrow N^+–OH$. Coupling between the resulting overall **DNBF,H$^\bullet$** radical and the heterocyclic **3-X(C)$^\bullet$** radical at the α-carbon would yield the C-bonded adduct **10-X,H** which would be deprotonated by base to give the observed product **5-X**.

In view of the possible radical mechanism considered above it was decided to perform a similar reaction to the one investigated herein, but changing the electron-deficient molecule to the 4,6-dinitrobenzofurazan (DNBZ) structure. The course of the observed reaction with **3-Oa**, shown in Scheme 7, was the



DNBZ **3-Oa** **11**

Scheme 7

formation of the analogous C-bonded adduct **11** which has been fully characterized (see Experimental section). This shows that the proton transfer $N^+–O^- \longrightarrow N^+–OH$, between the radical pair is not a prerequisite for C-adduct formation, thus eliminating the SET mechanism.

Conclusions

Our study has shown conclusively that the heterocycles **3-O** and **3-S** can sucessfully be modified via σ-complex formation with super-electrophilic DNBF, to afford C-bonded adducts **5-X**. The resulting modification of the α-position has been achieved under mild conditions as compared with the general method of metalation/alkylation of heterocyclic structures.[10]

In the utilization of the synthesized structures **5-X** as proinsecticides, a potential problem could possibly arise due to

a lowering of lipophilicity arising from the DNBF moiety, in which case an alternative testing procedure, *i.e.* ingestion *versus* direct contact,[27] would have to be developed. However, this possible problem may be ameliorated through the use of a large organic cation such as Bu_4N^+. Testing of the reaction products is currently underway and the results will be reported in due course.

Experimental

Materials

4,6-Dinitrobenzofuroxan (DNBF) was prepared according to the procedure reported by Drost: mp 173 °C (lit.,[4b,5,28] mp 172–174.5 °C). 2-Methyloxazoline, 2-methylthiazoline, 2-methyl-3-ethylthiazolinium iodide, 2-phenyloxazoline and 4,4-dimethyloxazoline (Aldrich) were used as received. Preparations of 2-nonyloxazoline, 2-nonylthiazoline, 2-[2-(*p*-fluorophenyl)ethyl]oxazoline and 2-(2-(*p*-fluorophenyl)ethyl]thiazoline have been reported previously.[13a,b]

Preparation of 5-X adducts

Et_3NH^+ and K^+ salts of 5-Oa. To a stirred solution of DNBF (226 mg, 1 mmol) in CH_2Cl_2, (4 ml), 2-methyloxazoline (87 mg, 1.02 mmol) and triethylamine (115 mg, 1.15 mmol) were added. The solution turned orange and some minutes later, diethyl ether (10 ml) was added to precipitate the salt. The resulting orange crystals were filtered, washed with diethyl ether and vacuum dried over P_2O_5: mp 112 °C dec. (85%), UV (MeOH): λ = 362 nm (ε = 6530 dm^3 mol^{-1} cm^{-1}), λ = 474 nm (ε = 21000 dm^3 mol^{-1} cm^{-1}).

The K^+ salt of **5-Oa** was prepared in a similar way, replacing CH_2Cl_2 with MeCN (5 ml). The red K^+ salt began to precipitate as soon as potassium acetate (~1.1 equiv.) was added: mp 192 °C dec. (95%), UV (MeOH): λ = 362 nm (ε = 6350 dm^3 mol^{-1} cm^{-1}), λ = 474 nm (ε = 21450 dm^3 mol^{-1} cm^{-1}); mass spectrum FAB (negative mode) *m*/*z* = 310. It should be noted that a potassium kryptand (crown ether: Kriptofix 21 (Merck)) must be added to the glycerol–thioglycerol matrix.

K^+ salts of 5-Sa. These dark red crystals were obtained by the same protocol as for **5-Oa,K** but a longer reaction time (2 h 30 min) is needed to improve the yield (76%): mp 212 °C dec., UV (MeOH): λ = 365 nm (ε = 6850 dm^3 mol^{-1} cm^{-1}), λ = 474 nm (ε = 21000 dm^3 mol^{-1} cm^{-1}); mass spectrum FAB (negative mode with Kriptofix 21) *m*/*z* = 326.

Similarly, attempts to perform HRMS determination for the anions of **5-Oa** and **5-Sa** by the LSIMS method were unsuccessful, but satisfactory results were finally obtained by using the MALDI-TOF technique, with the 1,8,9-trihydroxyanthracene (dithranol)–$CHCl_3$ matrix, as follows: for **5-Oa** anion, *m*/*z* found 310.0383, calc. 310.0422, $\Delta M/M$ = 12.6 ppm; for **5-Sa** anion, *m*/*z* found 326.0211, calc. 326.0194, $\Delta M/M$ = 52 ppm

As is the case for most DNBF adducts, attempts to obtain satisfactory elemental analysis for **5-Xa Et_3NH^+** or **K^+** salts, have failed.

In situ detection of adduct 11

Et_3NH^+ salt of 11. To a stirred solution of DNBZ (0.152 mmol) in DMSO-d_6 (0.5 ml), 2-methyloxazoline (0.142 mmol) and triethylamine (0.148 mmol) were added. The solution turned brown and some minutes later the ^{1}H NMR spectrum was recorded.

^{1}H NMR (DMSO-d_6) δ ppm/residual ^{1}H signal of DMSO at 2.5, mutiplicity and coupling constants *J* in Hertz: 8.63 (H5, s), 4.91 (H7, dd, ^3J = 6.6, ^3J = 3.9), 4.00 (H5′, m), 3.55 (H4′, m), 2.94 (HαA, dd, J_{gem} = −14.9, ^3J = 6.6), 2.75 (HαB, ddt, J_{gem} = −14.9, ^3J = 3.9, $J_{\text{homoallylic-like}}$ = 1.5).

Measurements

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker AC 300 spectrometer equipped with an Aspect 3000 computer, and operating at 300.13, 75.47 and 282.38 MHz, respectively.The experiments were conducted either by dissolving the isolated salt **5-Xa** or by adding **3-Xb,c** (1 equiv.) and Et_3N (1.1 equiv.) to a DMSO-d_6 solution of DNBF (1 equiv., c = 0.06 mol l^{-1} for ^{1}H and ^{19}F NMR). For recording ^{13}C spectra of **5-Xb,c**, the concentration was 0.1 mol l^{-1}. ^{1}H and ^{13}C chemical shifts were reported in ppm relative to TMS using the residual solvent signals as internal reference. ^{19}F chemical shifts were reported relative to external reference : CF_3COOH (5% v/v in D_2O). Two dimensional experiments were acquired using the standard Bruker software for 2D H–H COSY[29] and C–H COSY.[30]

FAB negative mode mass spectra were obtained using a JEOL AX 500 spectrometer (resolution of 500) equipped with a PDP11 data system. MALDI-TOF High Resolution spectra were obtained using an Applied Biosystems Spectrometer (Voyager-STR model) nitrogen laser (λ = 337 nm), resolution 6000. Preparation of the sample was carried out by spotting 1 µl of product solution in $CHCl_3$–MeOH (50 : 50), (about 1 µg µl^{-1}) onto a 1 µl matrix composed of 1,8,9-trihydroxyanthracene in $CHCl_3$ (10 g l^{-1}).

Acknowledgements

The authors are grateful to Professors Erwin Buncel (Queen's University, Kingston, Canada) and Michael Crampton (Durham, England) for helpful discussions during the writing of this paper.

References

1 (*a*) F. Terrier, in *Nucleophilic Aromatic Displacement*, ed. H. Feuer, VCH, New York, 1991, pp. 18 and 138; (*b*) E. Buncel, M. R. Crampton, M. J. Strauss and F. Terrier, in *Electron-Deficient Aromatic and Heteroaromatic Base Interactions*, Elsevier, Amsterdam, 1984, pp. 166 and 296; (*c*) F. Terrier, *Chem. Rev.*, 1982, **82**, 77; (*d*) E. Buncel, J. Dust and F. Terrier, *Chem. Rev.*, 1995, **95**, 2261.

2 (*a*) F. Terrier, F. Millot and W. P. Norris, *J. Am. Chem. Soc.*, 1976, **98**, 5883; (*b*) F. Terrier, A.-P. Chatrousse, Y. Soudais and M. Hlaibi, *J. Org. Chem.*, 1984, **49**, 4176.

3 (*a*) M. J. Strauss, R. A. Renfrow and E. Buncel, *J. Am. Chem. Soc.*, 1983, **105**, 2473; (*b*) E. Buncel, R. A. Renfrow and M. J. Strauss, *J. Org. Chem.*, 1987, **52**, 488; (*c*) M. J. Strauss, A. de Fusco and F. Terrier, *Tetrahedron Lett.*, 1981, **22**, 1945; (*d*) F. Terrier, M.-P. Simonnin, M.-J. Pouet and M. J. Strauss, *J. Org. Chem.*, 1981, **46**, 3537.

4 (*a*) R. J. Spear, W. P. Norris and R. W. Read, *Tetrahedron Lett.*, 1983, **24**, 1555; (*b*) W. P. Norris, R. J. Spear and R. W. Read, *Aust. J. Chem.*, 1983, **36**, 297; (*c*) R. W. Read, R. J. Spear and W. P. Norris, *Aust. J. Chem.*, 1984, **37**, 985.

5 (*a*) F. Terrier, J.-C. Hallé, M.-J. Pouet and M.-P. Simonnin, *J. Org. Chem.*, 1986, **51**, 410; (*b*) F. Terrier, J.-C. Hallé, M.-J. Pouet and M.-P. Simonnin, *J. Org. Chem.*, 1984, **49**, 4363; (*c*) F. Terrier, E. Kizilian, J.-C. Hallé and E. Buncel, *J. Am. Chem. Soc.*, 1992, **114**, 1740; (*d*) F. Terrier, J.-C. Hallé, P. MacCormack and M.-J. Pouet, *Can. J. Chem.*, 1989, **67**, 503.

6 (*a*) M. R. Crampton and L. C. Rabbitt, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1669; (*b*) M. R. Crampton, L. C. Rabbitt and F. Terrier, *Can. J. Chem.*, 1999, 639; (*c*) M. R. Crampton and L. C. Rabbitt, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2169.

7 (*a*) J. Kind and H. J. Niclas, *Synth. Commun.*, 1993, **23**, 1569; (*b*) H. J. Niclas, B. Göhrmann and E. Gründemann, *Synth. Commun.*, 1991, **21**, 909.

8 (*a*) M. I. Evgen'yev, S. Y. Garmonov, I. I. Evgen'yeva, S. M. Goryunova, V. I. Pogorel'tsev and F. S. Levinson, *Talanta*, 1998, **45**, 1465; (*b*) M. I. Evgen'yev, S. Y. Garmonov, I. I. Evgen'yeva and H. C. Budnikov, *Talanta*, 1995, **42**, 1465; (*c*) M. I. Evgen'yev, S. Y. Garmonov, I. I. Evgen'yeva and L. S. Gazizullina, *J. Anal. Chem.*, 1998, **53**, 571 and references therein.

9 (*a*) J.-C. Hallé, D. Vichard, M.-J. Pouet and F. Terrier, *J. Org. Chem.*,

1997, **62**, 7178; (*b*) D. Vichard, J.-C. Hallé, B. Huguet, M.-J. Pouet, D. Riou and F. Terrier, *Chem. Commun.*, 1998, 791.
10 (*a*) A. I. Meyers, G. Knaus and K. Kamata, *J. Am. Chem. Soc.*, 1974, **96**, 268; (*b*) M. Reuman and A. I. Meyers, *Tetrahedron*, 1985, **41**, 837; (*c*) A. I. Meyers, *J. Heterocycl. Chem.*, 1998, **35**, 991; (*d*) J.-C Cherton, M. Lanson, D. Ladjama, Y. Guichon and J.-J. Basselier, *Can. J. Chem.*, 1990, **68**, 1271; (*e*) P. Beak and V. Snieckus, *Acc. Chem. Res.*, 1982, **15**, 306.
11 (*a*) H. Vorbrüggen and K. Krolikievicz, *Tetrahedron Lett.*, 1981, **22**, 4471; (*b*) H. Vorbrüggen and K. Krolikievicz, *Tetrahedron*, 1993, **49**, 9353.
12 (*a*) J. C. Cherton, M. Amm, R. Oumeddour, D. Ladjama and O. Convert, *Analusis*, 1990, **18**, 37I; (*b*) J. C. Cherton, D. Ladjama and D. Soyez, *Analusis*, 1990, **18**, 71.
13 (*a*) S. Hamm, *PhD Thesis*, University of Versailles, 1999; (*b*) J.-C. Cherton, S. Hamm, J.-C. Hallé, L. Menguy and M. Beaufour, *J. Fluorine Chem.*, 2001, **107**, 387; (*c*) M. Beaufour, J.-C. Cherton, A. Carlin Sinclair and S. Hamm, *J. Chromatogr. B: Biomed. Appl.*, 2001, **761**, 35; (*d*) J.-C. Cherton, M. Beaufour, L. Menguy and B. Merelli, *Spectrosc. Lett.*, 2002, in press.
14 In water, pK_a = 10.87, 5.52 and 5.22, respectively for Et_3NH^+ [15] **3-Oa,H** [16] and **3-Sa,H**.[17].
15 R. A. Robinson and R. H. Stokes, in *Electrolyte Solution*, Butterworth, London, 2nd edn. (revised), 1965, p. 525.
16 M. A. Weinberger and R. Greenhalgh, *Can. J. Chem.*, 1963, **41**, 1038.
17 R. B. Martin, S. Lowey, E. L. Elson and J. T. Edsall, *J. Am. Chem. Soc.*, 1959, **81**, 5089.
18 T. W. Hambley, C. J. Hawkins, M. F. Lavin, A. van den Brenk and D. J. Watters, *Tetrahedron*, 1992, **48**, 341.
19 M. R. Crampton and I. A. Robotham, *J. Chem. Res.*, 1997, **5**, 22.
20 (*a*) J.-C. Hallé, M.-J. Pouet, M.-P. Simonnin and F. Terrier, *Tetrahedron Lett.*, 1983, **22**, 2255; (*b*) F. Terrier, R. Goumont, M.-J. Pouet and J.-C. Hallé, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1629; (*c*) E. Kizilian, F. Terrier, A.-P. Chatrousse, K. Gzouli and J.-C. Hallé, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2667; (*d*) F. Terrier, M.-J. Pouet, K. Gzouli, J.-C. Hallé, F. Outurquin and C. Paulmier, *Can. J. Chem.*, 1998, **76**, 937.
21 R. L. Benoit and C. Buisson, *Electrochim. Acta*, 1973, **18**, 105.
22 F. G. Bordwell, A. V. Satisch, F. Jordan, C. B. Rios and A. C. Chang, *J. Am. Chem. Soc.*, 1990, **112**, 792.
23 (*a*) Y. Todha, T. Kawashima, M. Ariga, R. Akiyama, H. Shudoh and Y. Mori, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2329; (*b*) Y. Todha, T. Yanagidani, S. Hiramatsu, N. Nishiwaki, K. Tani, K. Imagawa and M. Ariga, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 2781; (*c*) Y. Todha, M. Morikawa, T. Kawashima, M. Ariga and Y. Mori, *Chem. Lett.*, 1986, 273.
24 I. M. Kolthoff, M. K. Chantooni, Jr. and S. Bhowmik, *J. Am. Chem. Soc.*, 1968, **90**, 23.
25 J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, in *The Tautomerism of Heterocycles*, ed. A. R. Katritzky and A. J. Boulton, Academic Press, New York, Advances in Heterocyclic Chemistry series, suppl. 1, 1976, pp. 369 and 491.
26 G. Moutiers, J. Pinson, F. Terrier and R. Goumont, *Chem. Eur. J.*, 2001, **7**, 1712.
27 G. D. Prestwich, A. K. Gayen, S. Phirwa and T. B. Kline, *BioTechnology*, 1983, **1**, 62.
28 P. Drost, *Liebigs Ann. Chem.*, 1899, **307**, 49.
29 A. Bax and M. F. Summer, *J. Am. Chem. Soc.*, 1986, **108**, 2093.
30 A. Bax and D. G. Davis, *J. Magn. Reson.*, 1985, **65**, 355.