Pergamon

Tetrahedron Letters 42 (2001) 4499–4501

TETRAHEDRON LETTERS

A remarkably facile oxygen transfer in a nitrobenzofuroxan structure activated through σ-complex formation

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Received 5 April 2001; accepted 10 May 2001

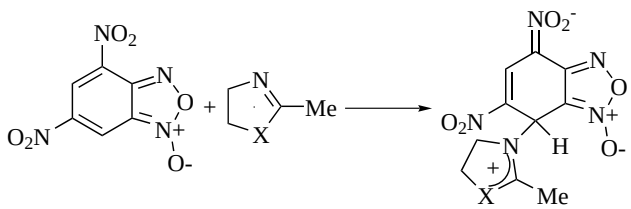
Abstract—Treatment of 4,6-dinitrobenzofuroxan (DNBF) with the imidazoline **1-NR$_f$** is found to afford a zwitterionic nitrogen-bonded complex (**2-NR$_f^{\pm}$**) which, in the presence of base (Et_3N), undergoes a slow but quantitative transformation to give 7-hydroxy-4,6-dinitrobenzofurazan (**5**) as the final product. Overall, an oxygen transfer has thus occurred from the *N*-oxide function to the carbocyclic moiety of DNBF. The key point in this transformation is shown to be a facile abstraction of the sp^3 hydrogen bonded at C-7 of **2-NR$_f^{\pm}$**, providing important new evidence that the parent DNBF structure is extremely electron-withdrawing ('super-electrophile'). The overall conversion is also an unusual case of a catalytic process in which the catalysts (both **1-NR$_f$** and Et_3N) partake to form covalent reaction intermediates and thereby lower the activation energy, resulting in a facile reaction. © 2001 Elsevier Science Ltd. All rights reserved.

In a long range program in our laboratories,[1,2] we have been investigating the reactions of electron-deficient heteroaromatics like 4-nitrobenzofuroxan (NBF), 4,6-dinitrobenzofuroxan (DNBF) and 2-(2′,4′,6′-trinitrophenyl)-4,6-dinitrobenzotriazole 1-oxide (DNBT-Pic) with electron-rich reagents like anilines or phenols as well as heteroaromatics such as pyrrole, indole, thiophene or furan derivatives.[3] The results have revealed in part the highly electrophilic behavior of DNBF and DNBT-Pic which have therefore been termed as super-electrophiles.[4–8] One aspect of interest is the hypothesis by Ghosh and Whitehouse that σ-complex formation with intracellular nucleophiles may be responsible for antileukemic activity of compounds such as NBF.[9]

In connection with a search for new potential proinsecticides,[10] we have recently undertaken studies of the series of compounds **1-X** (X = O, S, NH) reacting with DNBF in which the first step is nucleophilic addition at C_7 of the carbocyclic ring according to Eq. (1). In order to realize lipophilic systems, we have extended the series to **1-NR$_f$**[11] where **R$_f$** is $-(CH_2)_6-F$, also taking advantage of a possible monitoring of the reactions through ^{19}F NMR.[10]

While the reaction of DNBF with **1-NR$_f$** afforded rapidly and quantitatively the zwitterionic σ-complex **2-NR$_f$**,[12] we found rather unexpectedly that this adduct is very sensitive to the presence of base, undergoing a slow but facile and irreversible transformation to afford 7-hydroxy-4,6-dinitrobenzofurazan **5** as the final product.[14] Overall, an oxygen transfer has thus occurred from the *N*-oxide function to the carbocyclic moiety of DNBF. This represents a rare example of the occurrence of a formal intramolecular oxygen transfer, which calls for an explanation of the processes involved.

Scheme 1 outlines the proposed mechanism. Following the formation of the zwitterionic adduct **2-NR$_f^{\pm}$** in



DNBF **1-X** **2-X**

X = O, S, NH, NR_f

(1)

Keywords: nitrobenzofuroxans; imidazolines; anionic σ-adducts; Meisenheimer complexes; intramolecular oxygen transfers.

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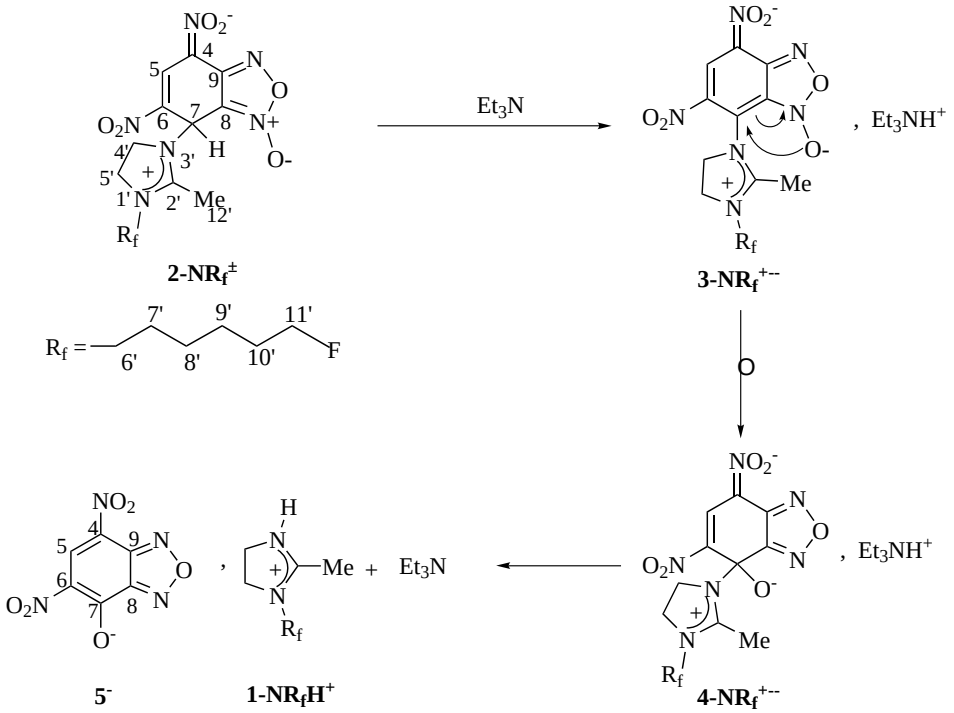
PII: S0040-4039(01)00774-2



Scheme 1.

Me_2SO solution, the addition of Et_3N (1 equiv.) or another tertiary amine like *N*-methylimidazole induces a rapid evolution of the NMR spectra, which eventually consist of the resonances ascribable to the formation of the anion $\mathbf{5}^{-}$[15] of 7-hydroxy-4,6-dinitrobenzofurazan **5** and protonated **1-NR$_f$**.

The key point in the conversion of **2-NR$_f^{\pm}$** to $\mathbf{5}^{-}$ is abstraction by Et_3N of the hydrogen bonded at sp^3 C-7 of the adduct **2-NR$_f^{\pm}$** to give the anion **3-NR$_f^{+--}$**. Here, two major factors favor this ionization process: (1) H_7 in **2-NR$_f^{\pm}$** benefits from being activated both by the positively charged imidazolinium moiety as well as by the DNBF$^-$ moiety. Despite its negative charge, the accumulated evidence is that this latter heterocyclic structure exerts a strong –I effect.[2,3,8] (2) Extensive through-conjugation is operating in **3-NR$_f^{+--}$**, contributing strongly to the stability of this species.

There follows an intramolecular concerted process in which the *N*-oxide functionality attacks at the electron deficient C_7 center in a four-centered transition state, resulting in the observed transfer of the oxygen to C-7 and the formation of the intermediate σ-complex, **4-NR$_f^{+--}$**. Last, expulsion of the imidazolinium moiety, as an excellent leaving group,[8a] occurs to afford $\mathbf{5}^{-}$ and the starting imidazoline **1-NR$_f$**, which undergoes immediate protonation on reaction with Et_3NH^+.

Besides the novelty of the observed oxygen transfer, the reaction mechanism depicted in Scheme 1 includes two other remarkable features in terms of organic reactivity: (1) Because protonated aza structures are associated with good nucleofugalities in S_NAr reactions,[8a,16] σ-adducts resulting from the addition of tertiary amine groups to electron-deficient aromatics are generally not stable.[8a] On this ground, the formation of **2-NR$_f^{\pm}$** as a relatively stable zwitterionic σ-adduct is a noteworthy finding with very few precedents in the context of σ-complex chemistry.[4c,13,17] (2) Examples of proton abstractions by relatively weak bases at the sp^3 carbon of a σ-complex are so far unknown in the literature. The only instance known to us of a well demonstrated proton abstraction from a σ-adduct is that involving the less electron-deficient NBF system where the much stronger base MeO^- was required.[18] Interestingly, relevant cases are those discussed by Krivun and Katritzky who reported that 4H-pyrans can undergo deprotonation at the 4-position when they benefit from activation by a triphenylphosphonium or a benzotriazole moiety.[19,20] In most cases, it is through a base-catalyzed E_2-type elimination process involving a leaving group which is initially present in the incoming nucleophile moiety that proton abstraction from the sp^3 carbon of a σ-adduct is achieved, i.e. the so-called vicarious nucleophilic aromatic substitution of hydrogen, as discovered by Makosza.[21] It is also noteworthy that though formally an 'isomerization', it does not appear to be possible to propose an allowed mechanism for the direct transformation of DNBF to **5**. The isomerization becomes possible, however, through the reaction sequence of σ-complex formation and the subsequent deprotonation, both of which depend on the extraordinary electron deficient nature of the DNBF structure. The overall transformation is quite an unusual case of a catalytic process (both **1-NR$_f$** and Et_3N are regenerated) in which the catalysts partake to form covalent reaction intermediates and thereby lower the activation energy, resulting in a facile reaction.

In conclusion, the present work featuring proton abstraction at C_7 of **2-NR$_f^{\pm}$** by a weak base, provides important new evidence that the parent DNBF structure is extremely electron-deficient, and justifies our terminology of a super-electrophile accorded to it.[8] Moreover, the overall reaction affords a ready functionalization of the heterocycle carbocyclic ring which is otherwise difficult to accomplish.

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11. Fluorinated imidazoline **1-NR$_f$** has been prepared by *N*-alkylation of commercial 2-methyl-2-imidazoline. A mixture of 2-methyl-2-imidazoline (300 mg, 3.56 mmol) and ω-bromo-fluorohexane (325 mg, 1.77 mmol) obtained from the corresponding ω-chlorohexanol (Pattison, F. L. M.; Howell, W. C.; McNamara, A. J.; Schneider, J. C.; Walker, J. F. *J. Org. Chem.* **1956**, *21*, 739) was dissolved in toluene and heated to reflux for 3 hours. After cooling, the mixture was treated with aqueous NaOH then extracted with ether. After solvent evaporation, the residue was distilled under reduced pressure $Eb_{0.5\ mmHg}=130°C$; 35%. IR (NaCl) cm^{-1}: 1616, 1024; HRCIMS (isobutane) m/z 187.1607 $(M+H)^+$, $C_{10}H_{20}N_2F$ requires 187.1610; ^1H NMR (300 MHz, Me_2SO-d_6, TMS) δ (ppm, J(Hz)) 4.45 (dt, $^3J_{10'-11'}=6.1$, $^2J_{H-F}=47.3$, 2H, $H_{11'}$), 3.64 (t, $^3J_{4'-5'}=9.6$, 2H, $H_{4'}$), 3.26 (t, $^3J_{4'-5'}=9.6$, 2H, $H_{5'}$), 3.06 (t, $^3J_{6'-7'}=7.1$, 2H, $H_{6'}$), 1.9 (t, $^5J_{12'-4'}=1.2$, 3H, $H_{12'}$), 1.71 (dt, $^3J_{H-F}=25.5$, 2H, $H_{10'}$), 1.47 (m, 6H, $H_{7'-9'}$); ^{13}C NMR (75 MHz, Me_2SO-d_6) δ 164.6 ($C_{2'}$), 84.0 ($^1J_{C-F}=164.2$, $C_{11'}$), 52.0 ($C_{4'}$), 49.9 ($C_{5'}$), 46.9 ($C_{6'}$), 30.3 ($^2J_{C-F}=19.8$, $C_{10'}$), 28.5, 26.4 ($C_{7'-8'}$), 25.0 ($^3J_{C-F}=5.1$, $C_{9'}$), 14.4 ($C_{12'}$); ^{19}F NMR (282 MHz, Me_2SO-d_6), δ (relative to external reference CF_3COOH/D_2O, 5:95, v/v) -140.8_5.
12. As many other zwitterionic nitrogen-bonded σ-adducts in the DNBF as well as the 1,3,5-trinitrobenzene (TNB) series, **2-NR$_f$** is so strongly sensitive to moisture in the solid state that efforts to characterize this complex by standard analytical techniques have failed. In contrast, **2-NR$_f$** is very stable in Me_2SO solution, where very clear ^1H and ^{13}C NMR spectra were recorded. The chemical shifts given below leave no doubt as to the structure of **2-NR$_f$**, showing some remarkable similarities with those observed for similar N-bonded species, e.g. the zwitterions obtained in the reactions of DNBF with *N*-methylimidazole or imidazole in the same solvent.[13] ^1H NMR (300 MHz, Me_2SO-d_6, TMS) δ 8.78 (s, 1H, H_5), 6.84 (s, 1H, H_7), 4.45 (dt, 2H, $H_{11'}$), 3.80 (m, 2H, $H_{4'}$), 3.40 (m, 4H, $H_{5'-6'}$), 2.57 (s, 3H, $H_{12'}$), 1.60 (m, 2H, $H_{10'}$), 1.59 (m, 2H, $H_{7'}$), 1.34 (m, 4H, $H_{8'-9'}$); ^{13}C NMR (75 MHz, Me_2SO-d_6, TMS) δ 165.7 ($C_{2'}$), 148.1 (C_9), 133.3 (C_5), 117.0 (C_6), 110.0 (C_4), 108.9 (C_8), 83.7 ($C_{11'}$), 48.0 (C_7), 47.2 ($C_{4'}$), 46.2, 42.7 ($C_{5'-6'}$), 29.7 ($C_{10'}$), 26.3, 25.2 ($C_{7'-8'}$), 24.3 ($C_{9'}$), 10.8 ($C_{12'}$); ^{19}F NMR (282 MHz, Me_2SO-d_6), δ (relative to external reference CF_3COOH/D_2O, 5:95, v/v) −140.79.
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