COMMUNICATION

ChemComm
www.rsc.org/chemcomm

A novel reactivity pattern of nitro-benzofuroxans and -benzofurazans: the heterodienic behaviour of the five-membered ring

Régis Goumont,* Muriel Sebban and François Terrier*
Laboratoire SIRCOB, ESA 8086, Institut Lavoisier-Franklin, University of Versailles, 45, Avenue des Etats-Unis, 78035 Versailles Cedex, France. E-mail: goumont@chimie.uvsq.fr

Received (in Cambridge, UK) 30th May 2002, Accepted 2nd August 2002
First published as an Advance Article on the web 21st August 2002

Evidence is presented that the $N_3C_9C_8N$ fragment of the annelated ring of some nitro-activated benzofuroxans and benzofurazans acts as a heterodiene contributor upon treatment with cyclohexadiene, thus highlighting a new facet of the reactivity of this class of heterocycles.

The high susceptibility of nitrobenzofuroxans to undergo covalent nucleophilic addition or substitution processes with very weak nucleophiles has attracted considerable interest over the two last decades leading to numerous synthetic, biological and analytical applications.[1–4] In accord with the idea that this super-electrophilic reactivity is largely the result of a low aromatic character of the benzofuroxan system, recent studies in our laboratory have revealed that nitrobenzofuroxans are in fact very versatile Diels–Alder reagents with the carbocyclic ring being capable of acting as a dienophile,[5] a heterodiene,[5] or a carbodiene[6] depending upon the experimental conditions and the reaction partners employed.[7] Reflecting the potential 1-oxide/3-oxide interconversion of benzofuroxans through the intermediacy of an *o*-dinitroso intermediate,[9–11] diadducts resulting from normal electron-demand Diels–Alder processes involving the N=O double bonds of such intermediates as the dienophile contributors have also been isolated.[12]

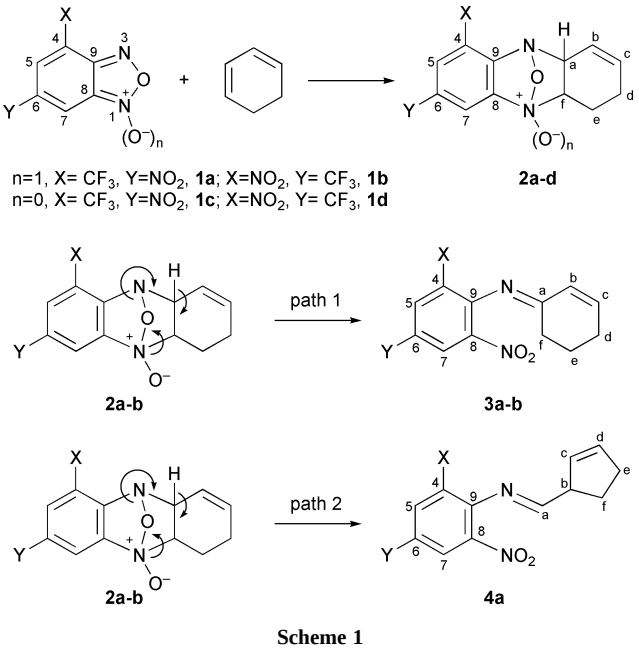
In view of the potential importance of such a multifaceted reactivity as a new approach to synthesis in heterocyclic chemistry, we have looked at how one can modulate the Diels–Alder behaviour of benzofuroxans by modifying the substitution pattern of the carbocyclic ring, eliminating the N-oxide functionality or varying the electron-rich substrate. Here, we report our discovery of another new Diels–Alder pathway that we have identified in the reactions of 6-nitro-4-trifluoromethyl- and 4-nitro-6-trifluoromethylbenzofuroxans **1a** and **1b** with 1,3-cyclohexadiene. The evidence indicates that the $N_3C_9C_8N$ fragment of the annelated furoxan ring of both **1a** and **1b** acts as a heterodiene in these systems to give the adducts **2a** and **2b**. These decompose immediately to afford dinitroarylimines, *i.e.* **3a** and **4a** on the one hand and only **3b** on the other (see Scheme 1).

Treatment of **1a** with excess 1,3-cyclohexadiene at room temperature in CH_2Cl_2 takes place over a week to afford a mixture of **3a** and **4a** (see structures in Scheme 1) in a 9 : 1 ratio (overall yield 94%).[13] Elemental analysis, mass spectrometric data as well as ^1H and ^{13}C NMR data fully agree with the proposed structures.† Among other diagnostic features, it is noteworthy that the proton and carbon resonances pertaining to the activated aromatic ring are very similar for **3a** and **4a**, a reflection of the strong similarity of this moiety in these two molecules. In contrast, the imine fragments of **3a** and **4a** are characterized by quite different sets of carbon resonances with three methylene carbons, two tertiary sp^2 carbons and one quaternary sp^2 carbon for **3a** but two methylene carbons, one tertiary sp^3 carbon and three tertiary sp^2 carbons for **4a**.

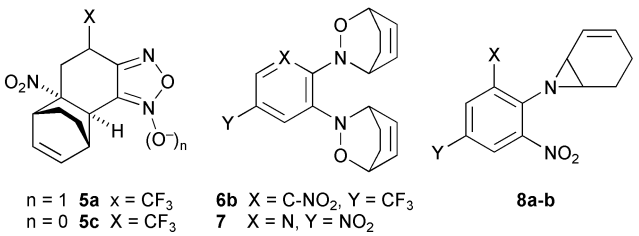
The reaction of the isomeric 4-nitro-6-trifluoromethyl-benzofuroxan **1b** with cyclohexadiene proceeds somewhat differently than that of **1a**, giving rise to the imine **3b** and the diadduct **6b** in a 3 : 1 ratio. The formation of **6b** is reminiscent of that of the adduct **7** recently obtained in the reaction of 4-aza-6-nitrobenzofuroxan with 1,3-cyclohexadiene, being the result of two NEDDA (Normal Electronic Demand) processes in which the N=O double bonds of the *o*-dinitroso intermediate involved in the 1-oxide/3-oxide tautomerism of **1b** play the role of the dienophile contibutors.[12]

Two reasonable mechanisms can be envisoned to account for the formation of the imines **3** and **4**. The first, outlined in Scheme 1, involves the initial formation of the adduct **2** resulting from an inverse electron demand Diels–Alder condensation of a molecule of cyclohexadiene to the $N_3C_9C_8N$ fragment of the furoxan ring acting as a heterodiene contributor. Structure **2** will not be stable, however, being very prone to undergo a 1,2-hydride transfer (path 1) or a 1,2-alkyl group transfer (path 2) with concomitant opening of the furoxan ring and breaking of the N_1C_f bond to give **3** and **4**. The second mechanism is based on a possible nitrenoid reactivity of the 3-nitrogen of **1a,b** with initial formation of the aziridines **8a-b** which will subsequently decompose to **3** and **4**.

Two significant features favor the mechanism of Scheme 1. In accord with the idea that they favorably interact with the oxygen atom of the N-oxide functionality,[14] Lewis acids exert a strong accelerating effect on the imine formation while favoring the hydride transfer. In the presence of $ZnCl_2$, the reaction of **1a** with cyclohexadiene thus proceeds to completion in only 24



Scheme 1



DOI: 10.1039/b205164h

hours, giving exclusively **3a**. More importantly, we were able to isolate an adduct of type **2**, namely **2d**, in removing the N-oxide functionality of **1b** and looking at the reaction of 4-nitro-6-trifluoromethylbenzofurazan **1d** with cyclohexadiene.[15]

Since nitro-benzofuroxans and -benzofurazans behave in general very similarly, we feel that the isolation of **2d** is really a major argument favoring Scheme 1. In contrast, no evidence whatsoever could be obtained for the formation of **8**, despite the expected stabilization of the aziridine structure through conjugation of the nitrogen atom with the strongly electron deficient dinitrophenyl ring.

The formation of the imines **3a**, **4a** and **3b** represents a new reactivity pattern in the chemistry of nitrobenzofuroxans. The fact that the $N_3C_9C_8N$ fragment of the annelated ring of **1a** and **1b** as well as **1d** seems capable to act as a heterodiene further adds to the multifaceted pericyclic reactivity of these heterocycles whose behaviour now appears to be related not only to that of nitroalkenes[16] but also to that of azadienes.[17]

Notes and references

† *General procedure*: To a solution of **1a**–**d** (1 g) in CH_2Cl_2 (10 ml) at room temperature was added an excess (10 equiv.) of cyclohexadiene. The solution turned rapidly orange and the reaction mixture was stirred at room temperature for a few days. Addition of pentane resulted in the immediate formation of a precipitate which was collected by filtration and dried under vacuum and then purified by column chromatography, using pentane–ethylacetate mixtures as eluents.

3a: Yellow solid; yield 83%; mp 120–121°C; EI MS: *m*/*z* 329 $[M]^{+\cdot}$, 260 $[M - CF_3]^{+\cdot}$; IR ($CHCl_3$, cm^{-1}): 1667 ($\nu_{C=N}$, imine), 1647 ($\nu_{C=C}$), 1550 ($\nu_{NO_2\ as}$), 1347 ($\nu_{NO_2\ s}$). Anal. Calc. for $C_{13}H_{10}F_3N_3O_4$: C, 47.42; H, 3.04; N, 12.76. Found: C, 47.56; H, 3.05; N, 12.68%. ^{1}H NMR ($CDCl_3$, δ): 8.70 (1H, H_5, d, $^4J_{5/7}$ 2.3 Hz), 8.99 (1H, H_7, d, $^4J_{7/5}$ 2.3 Hz), 6.13 (1H, H_b, dt, $^3J_{b/c}$ 10.0, $^4J_{b/d}$ 2.0 Hz), 6.81 (1H, H_c, dt, $^3J_{b/c}$ 10.0, $^3J_{c/d}$ 4.1 Hz), 2.50 (4H, H_d, H_f, m), 2.36 (2H, H_e, m). ^{19}F NMR ($CDCl_3$, δ): −63.65 (CF_3). ^{13}C NMR ($CDCl_3$, δ): 122.76 (C_4), 126.14 (C_5), 140.95 (C_6), 124.31 (C_7), 139.08 (C_8), 149.26 (C_9), 121.72 (CF_3), 171.08 (C_a), 126.56 (C_b), 147.65 (C_c), 25.51 (C_d), 21.68 (C_e), 32.71(C_f).

4a: Yellow oil; yield 11%; EI MS: *m*/*z* 329 $[M]^{+\cdot}$; IR ($CHCl_3$, cm^{-1}): 1670 ($\nu_{C=N}$, imine), 1650 ($\nu_{C=C}$), 1545 ($\nu_{NO_2\ as}$), 1338 ($\nu_{NO_2\ s}$). Anal. Calc. for $C_{13}H_{10}F_3N_3O_4$: C, 47.42; H, 3.04; N, 12.76. Found: C, 47.35; H, 3.20; N, 12.75%.^{1}H NMR ($CDCl_3$, δ): 8.71 (1H, H_5, d, $^4J_{5/7}$ 2.5 Hz), 8.95 (1H, H_7, d, $^4J_{7/5}$ 2.5 Hz), 7.78 (1H, H_a, m), 6.07 (1H, H_c, m), 5.74 (1H, H_d, m), 3.72 (1H, H_b, m), 2.50 (2H, H_e, m), 2.24 (1H, H_f, m), 2.11 (1H, H_f, m). ^{19}F NMR ($CDCl_3$, δ): −63.65 (CF_3). ^{13}C NMR ($CDCl_3$, δ): 123.32 (C_4), 125.80 (C_5), 141.85 (C_6), 123.94 (C_7), 140.24 (C_8), 149.94 (C_9), 121.60 (CF_3), 174.07 (C_a), 52.78 (C_b), 136.05 (C_c), 127.30 (C_d), 32.26 (C_e), 26.06 (C_f).

3b: Yellow solid; yield 82%; mp 110–112° C; EI MS: *m*/*z* 329 $[M]^{+\cdot}$, 249 $[M - C_6H_8]^{+\cdot}$; IR ($CHCl_3$, cm^{-1}): 1662 ($\nu_{C=N}$, imine), 1637 ($\nu_{C=C}$), 1565 ($\nu_{NO_2\ as}$), 1352 ($\nu_{NO_2\ s}$). Anal. Calc. for $C_{13}H_{10}F_3N_3O_4$: C, 47.42; H. 3.04; N. 12.76. Found: C, 47.65; H, 3.09; N, 12.62%. ^{1}H NMR ($CDCl_3$, δ): 8.37 (2H, $H_{5/7}$, s), 6.17 (1H, H_b, dt, $^3J_{b/c}$ 10.0, $^4J_{b/d}$ 2.0 Hz), 6.80 (1H, H_c, dt, $^3J_{b/c}$ 10.0, $^3J_{c/d}$ 4.1 Hz), 2.53 (2H, H_f, m), 2.39 (2H, H_d, m), 2.02 (2H, H_e, m). ^{19}F NMR ($CDCl_3$, δ): −63.53 (CF_3). ^{13}C NMR ($CDCl_3$, δ): 140.91 ($C_{4/8}$), 126.24 ($C_{5/7}$), 124.08 (C_6), 143.35 (C_9), 125.63 (CF_3), 172.87 (C_a), 126.87 (C_b), 147.47 (C_c), 29.66 (C_d), 21.64 (C_e), 33.06 (C_f).

2d: Yellow solid; yield 83%; mp 120–121°C; EI MS: *m*/*z* 297 $[M - O]^{+\cdot}$. HRMS: calc. for $C_{13}H_{10}F_3N_3O_2$: *m*/*z* 297.0726 $[M - O]^{+\cdot}$, found: *m*/*z* 297.0725. IR ($CHCl_3$, cm^{-1}): 1657 ($\nu_{C=C}$), 1555 ($\nu_{NO_2\ as}$), 1336 ($\nu_{NO_2\ s}$). ^{1}H NMR ($CDCl_3$, δ): 7.62 (1H, H_5, d, $^4J_{5/7}$ 1.1 Hz), 6.81 (1H, H_7, d, $^4J_{7/5}$ 1.1 Hz), 6.60 (1H, H_b, m), 5.57 (1 H, H_a, m), 6.19 (1H, H_c, dt, $^3J_{b/c}$ 7.35, $^3J_{c/d}$ 5.88 Hz), 2.34 (2H, H_d, H_e, m), 2.36 (2H, H_d, H_e, m), 4.91 (1H, H_f, m). ^{19}F NMR ($CDCl_3$, δ): −65.57 (CF_3). ^{13}C NMR ($CDCl_3$, δ): 140.97 (C_4), 105.72 (C_5), 134.95 (C_6), 107.50 (C_7), 143.44 (C_8), 148.62 (C_9), 122.90 (CF_3), 54.82 (C_a), 130.97 (C_b), 129.55 (C_c), 23.67 (C_d), 20.69 (C_e), 70.98 (C_f).

1 (*a*) F. Terrier, In *Nucleophilic Aromatic Displacement*, ed. H. Feuer, VCH, New York, 1991; (*b*) F. Terrier, E. Kizilian, J. C. Hallé and E. Buncel, *J. Am. Chem. Soc.*, 1992, **114**, 1740.
2 E. Buncel, R. A Manderville and J. M. Dust, *J. Chem. Soc. Perkin Trans. 2*, 1997, 1019, and references therein.
3 M. R. Crampton and L. C. Rabbitt, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1669, and references therein.
4 P. B. Ghosh, B. Ternai and M. Whitehouse, *J. Med. Chem.*, 1972, **15**, 255.
5 (*a*) D. Vichard, J. C. Hallé, B. Huguet, M. J. Pouet, D. Riou and F. Terrier, *Chem. Commun.*, 1998, 791; (*b*) P. Sepulcri, J. C. Hallé, R. Goumont, D. Riou and F. Terrier, *J. Org. Chem.*, 1999, **64**, 9254.
6 P. Sepulcri, J. C. Hallé, R. Goumont, D. Riou and F. Terrier, *J. Chem. Soc., Perkin Trans. 2*, 2000, 51.
7 The formation of diadducts resulting from normal electron demand reactions at the two nitroactivated double bonds has been reported in the DNBF-2,3-dimethylbutadiene system but their stereochemistry was not elucidated.[8]
8 G. Kresze and H. Bathelt, *Tetrahedron*, 1973, **29**, 1043.
9 (*a*) A. R. Katritzky and M. V. Gordeev, *Heterocycles*, 1993, **35**, 483; (*b*) A. Gasco and A. J. Boulton, *Adv. Heterocycl. Chem.*, 1981, **29**, 252.
10 (*a*) I. R. Dunkin, M. A. Lynch, A. J. Boulton and N. Henderson, *J. Chem. Soc., Chem. Commun.*, 1991, 1178; (*b*) S. Murata and H. Tomioka, *Chem. Lett.*, 1992, 57; (*c*) N. Hacker, *J. Org. Chem.*, 1991, **56**, 5217.
11 (*a*) J. W. Mc Farland, *J. Org. Chem.*, 1972, **36**, 1842; (*b*) A. B. Bulacinski, E. F. V. Scriven and H. Suschitzky, *Tetrahedron Lett.*, 1975, 3577; (*c*) J. Gallos and E. Malamidou-Xenikaki, *Heterocycles*, 1994, **37**, 193.
12 M. Sebban, R. Goumont, J. C. Hallé, J. Marrot and F. Terrier, *Chem. Commun.*, 1999, 1009.
13 In some experiments, a trace of the monoadduct **5a** was observed.
14 S. Yamabe, T. Dai and T. Minato, *J. Am. Chem. Soc.*, 1995, **117**, 10994.
15 Consistent with structure **2d** was in particular: (1) the presence in the ^{1}H NMR spectra of two low field doublets for the aromatic H_5 and H_7 protons and four multiplets in the range 4.50–6.95 ppm assignable to the ethylenic protons H_b and H_c and to the junction protons H_a and H_f; (2) the presence in the ^{13}C NMR spectra of two resonances at 54.82 and 70.98 ppm assignable to the two tertiary α-nitrogen-substituted carbons C_a and C_f, respectively. Contrasting with its analogue **1d**, the benzofurazan **1c** reacted only as a dienophile to afford **5c**. Satisfactory analytical data were obtained for **5c** as well as its analogue **5a**.
16 S. E. Denmark and J. J. Cottell, *J. Org. Chem.*, 2001, **66**, 4276 and references therein.
17 D. L. Boger, *Chemtracts-Organic Chemistry*, 1996, **9**, 149.