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4-Chloro-7-nitrobenzofurazan as a Diels–Alder reagent. A facile access to highly functionalized naphthofurazans

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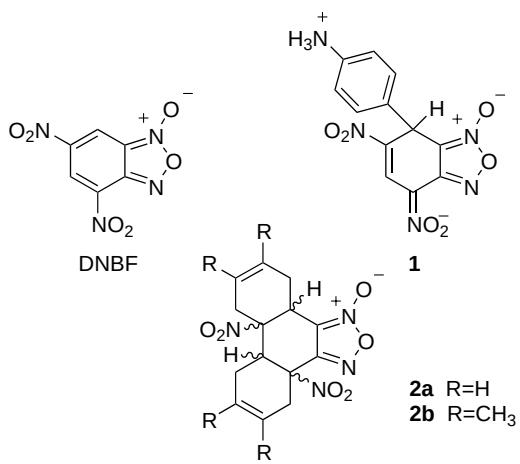
Abstract—4-Chloro-7-nitrobenzo-2-oxa-1,3-diazole (4-chloro-7-nitrobenzofurazan or NBD chloride) is found to react instantaneously and quantitatively with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene), to form regioselectively the silyl enol ether **4**, according to a normal electron-demand Diels–Alder (NEDDA) reaction. This provides the first evidence that this strongly electrophilic heterocycle can also exhibit pericyclic reactivity. Unmasking the enol **4** followed by treatment in the presence of 2 equiv. of base (DBN) leads to 4-chloro-7-hydroxynaphtho[1,2-*c*]furazan **7**. We are thus reporting an easy access to a functionalized hydroxynaphthofurazan, which is obtained under mild conditions in three steps with greater than 80% overall yield.

In the last two decades, much evidence has been accumulated that nitro-2,1,3-benzoxadiazoles and related 1-oxide derivatives, commonly referred to as nitrobenzofurazans and nitrobenzofuroxans, respectively, are 10 π electron heteroaromatic substrates which exhibit an extremely high electrophilic character.[1–7] As a much stronger electrophile than the 4-nitrobenzenediazonium cation,[2c] 4,6-dinitrobenzofuroxan (DNBF) has thus proved to be a suitable probe to assess the reactivity of such weak carbon nucleophiles as benzenoid aromatics or π-excessive heteroaromatics with large negative pK_a^{CH} values, e.g. 1,3-dimethoxybenzene ($pK_a = -9$),[8a] aniline ($pK_a = -6$)[4] or 3-methoxythiophene ($pK_a = -6.5$).[8b] In all of these reactions, covalent addition of the nucleophile takes place at C-7 of the carbocyclic ring of DNBF to give stable σ-adducts of type **1**.[1] Also illustrative of the electrophilic character of nitro-2,1,3-benzoxadiazoles is the high susceptibility of the halogen atom of halonitrobenzofurazans and benzofuroxans to displacement in nucleophilic aromatic SNAr substitutions, leading to diverse analytical, synthetic and biological applications.[9–11] 4-Chloro-7-nitrobenzofurazan (NBD chloride) reacts so readily with amino and thiol functionalities that it is widely used in protein labeling and structure determination of enzymes.[9,11,12]

In 1973, Kresze and Bathelt reported that treatment of DNBF with butadiene and 2,3-dimethylbutadiene afforded, after several weeks, the diadducts **2a** and **2b**, respectively.[13] It was proposed that the formation of these compounds could be accounted for in terms of two consecutive normal electron-demand Diels–Alder type processes; however, the reactions were not further investigated and neither the stereochemistry nor the mechanistic sequence leading to **2a** and **2b** were elucidated.



In this context, our recent discovery that the nitro-substituted carbocyclic ring as well as the annelated ring of nitrobenzofuroxans can be involved in a variety of

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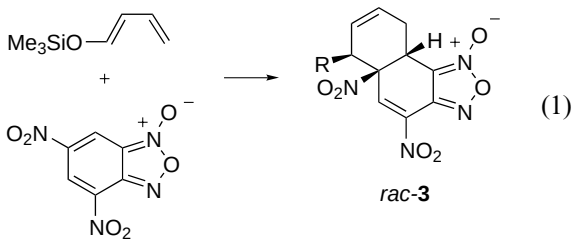
Diels–Alder type reactions is of considerable significance, providing a novel approach to synthesis in heterocyclic chemistry.[14] This potentiality is illustrated in Eq. (1) which shows that the reaction of DNBF with 1-trimethylsilyloxybuta-1,3-diene proceeds with high *endo* stereoselectivity as well as high regioselectivity, giving rise nearly quantitatively to the monoadduct **3** with no evidence for formation of a diadduct of type **2**.[14b]



(1)

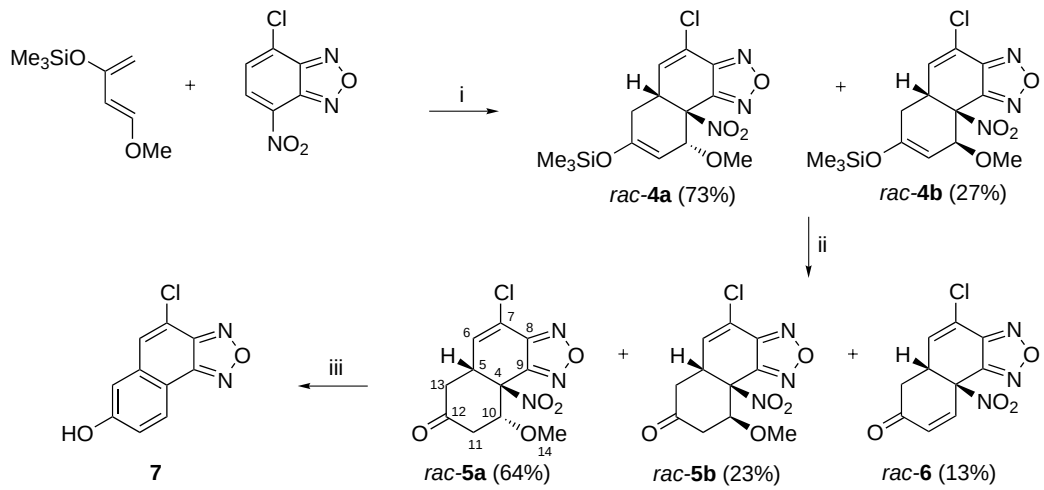
We now report that the reaction of 4-chloro-7-nitrobenzofurazan with the electron-rich Danishefsky diene affords the first step of a new and efficient access to a series of functionalized hydroxynaphthofurazans (Scheme 1).

Treatment of NBD chloride with the Danishefsky diene,[15] at room temperature in dichloromethane, resulted in rapid and quantitative formation of two diastereomers, **4a** and **4b** (Scheme 1) in 73:27 ratio, respectively.[16] Isomer **4a** can be selectively extracted into pentane and is obtained as white crystals after evaporation of the solvent; whereas isomer **4b** could not be obtained in pure form. Compounds **4a** and **4b** were characterized by ^{1}H and ^{13}C NMR analysis and the stereochemistry attributed through NOE experiments.[16] The two species **4a** and **4b** can be considered respectively as the *exo* and *endo* isomers of a regioselective Diels–Alder addition on a nitro alkene functionality. The reactivity of nitroalkenes in Diels–Alder reactions has been very elegantly described and used by Denmark et al.[17] To our knowledge, this is the first example of a Diels–Alder reaction with NBD chloride, acting as a dienophile in such mild conditions and provides evidence for the low aromaticity of this substrate.

In a second step the mixture **4a**,**b** was hydrodesilylated in acetonitrile, yielding a mixture of the two ketones **5a**,**b** as well as a small amount of the enone derivative **6**.[18] Compound **5a** was recrystallized from CH_2Cl_2 affording monocrystals which showed a triclinic system with two different motifs in the unit cell. The X-ray structure determination[19] confirmed the stereochemistry which had been assigned to **4a** through NMR: as depicted on the ORTEP view (Fig. 1), the methoxy and nitro groups have a *trans* relationship, thus confirming the previous *exo* configuration of **4a**. The mixture **5a**,**b** and **6** in THF was then allowed to react with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), following the procedure reported by Corey for aromatization of nitrocycloalkenone derivatives.[20] After acidification and work up of the reaction, the substituted phenol **7** was obtained as a single product.[21] Based on a previously reported chemical shift (δ_{OH})-pK_a correlations for phenolic derivatives, a value of 7.1 can be established for the pK_a of **7** in aqueous solution.[22] Overall, our work provides the first example of an easy access to a functionalized hydroxynaphthofurazan,[23] which can be obtained under mild conditions in three steps with greater than 80% yield. Moreover, one could anticipate further electrophilic aromatic substitution of the phenolic ring (halogenation, nitration,...) and nucleophilic aromatic substitution of chlorine in the erstwhile NBD chloride moiety, thus giving access to new functionalizations of the ring system.

Supplementary material

Crystallographic data for compound **5** are available free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].



Scheme 1. *Reagents and conditions*: (i) CH_2Cl_2, rt, 15 min, quantitative; (ii) HF aq. 30% 5 equiv., acetonitrile, rt, 60 min; (iii) DBN 2 equiv., THF, rt, 60 min, 95%, two steps.

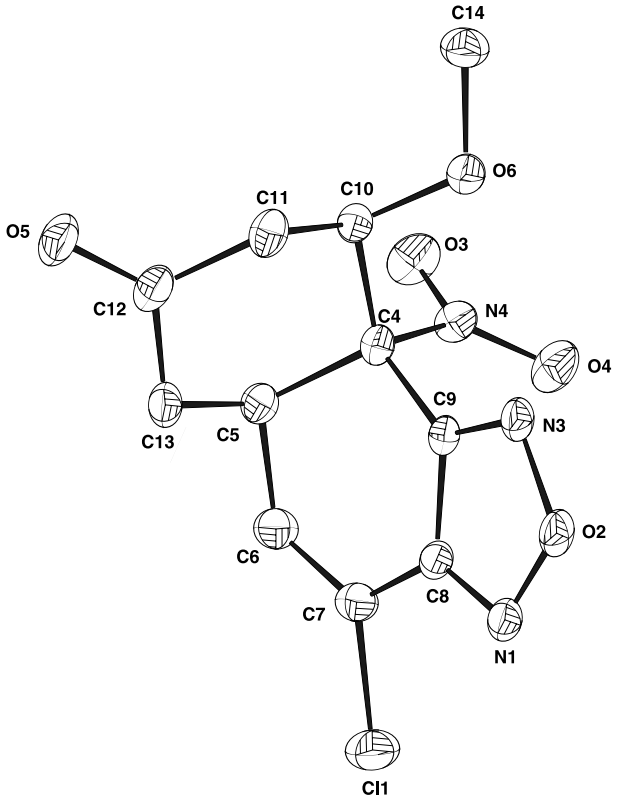


Fig. 1. Molecular structure of **5a** showing the atom labeling scheme. Hydrogen atoms are omitted for clarity.

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16. NBDCl (4.056 g, 20.03 mmol) were dissolved in 20 mL of freshly distilled dichloromethane. Upon addition of 3.90 mL of *trans*-1-methoxy-3-trimethlysilyloxybuta-1,3-diene (20.0 mmol) at room temperature, the solution rapidly became red and gradually dark yellow after 15 min. The mixture was then evaporated to dryness, yielding quantitatively as a pale yellow solid, a mixture of **4a**,**b** in a 73:27 ratio, respectively. Washing the solid with pentane resulted in dissolution of isomer **4a**, which was subsequently isolated in pure form. Compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 6H, $OSi(CH_3)_3$, 1.67 (ddt, 1H, H-13, $J_{5-13}=9.5$, $J_{13a-13b}=18$, $J=1.4$), 2.59 (dd, 1H, H-13, $J_{5-13}=7.4$), 3.40 (s, 3H, OCH_3), 3.89 (ddd, 1H, H-5, $J_{5-6}=6.1$), 5.02 (m, 2H, H-10, H-11), 6.47 (d, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ −0.10 ($Si(CH_3)_3$), 34.87 (C-13), 40.18 (C-5), 58.43 (OCH_3), 79.85 (C-10), 88.87 (C-4), 101.03 (C-11), 120.58 (C-7), 134.02 (C-6), 146.75 (C-9), 149.62 (C-8), 150.14 (C-12). Compound **4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 6H, $OSi(CH_3)_3$, 1.57 (ddt, 1H, H-13, $J_{5-13}=10.4$, $J_{13a-13b}=18.4$, $J=1.6$),

2.70 (dd, 1H, H-13, $J_{5-13}=7.7$), 3.35 (s, 3H, OCH_3), 4.16 (ddd, 1H, H-5, $J_{5-6}=6.6$), 5.16 (dt, 1H, H-11, $J_{10-11}=6.1$), 6.82 (d, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ −0.05 ($Si(CH_3)_3$), 35.14 (C-13), 34.72 (C-5), 56.55 (OCH_3), 74.05 (C-10), 87.73 (C-4), 98.13 (C-11), 118.55 (C-7), 138.50 (C-6), 146.91 (C-9), 148.11 (C-8), 154.49 (C-12).

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18. A crude mixture of 7.43 g of **4a**,**b** (20.0 mmol) was dissolved in 10 mL of acetonitrile and added at room temperature to 5 equiv. of HF in a 30% aqueous solution. The darkened solution was maintained under stirring for 1 h. After evaporation of acetonitrile and addition of dichloromethane, the organic phase was washed with water and dried over magnesium sulfate. The evaporation of dichloromethane yielded 5.77 g of a brown–yellow solid (96% yield). The ^1H NMR analysis showed the presence of three compounds **5a**, **5b** and **6** in a 64, 23, 13% ratio. The amount of **6** was found to vary slightly from one experiment to another. A pure form of **5a** could be obtained by starting with a pure sample of **4a** and recrystallized from a dichloromethane solution, leading to the formation of pale yellow monocrystals. Compound **5a**: mp 105°C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.97 (ddd, 1H, H-13b, $J_{5-13b}=13.1$, $J_{13a-13b}=15.6$, $J_{11b-13b}=0.5$), 2.74 (ddd, 1H, H-13a, $J_{5-13a}=5.4$, $J_{11a-13a}=2.0$), 2.74 (ddd, 1H, H-11b, $J_{10-11b}=11.3$, $J_{11a-11b}=14.9$), 3.08 (ddd, 1H, H-11a, $J_{10-11a}=4.4$), 3.47 (s, 3H, OCH_3), 3.85 (ddd, 1H, H-5, $J_{5-6}=6.2$), 4.61 (dd, 1H, H-10), 6.44 (d, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.05 (C-5), 42.20 (C-11), 42.53 (C-13), 58.76 (OCH_3), 79.69 (C-10), 89.04 (C-4), 121.00 (C-7), 132.29 (C-6), 145.76 (C-9), 149.32 (C-8), 200.18 (C-12). Anal. calcd for $C_{11}H_{10}ClN_3O_5$: C, 44.07; H, 3.34; N, 14.02. Found: C, 44.25; H, 3.30; N, 14.05%. Compound **5b**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.88 (ddd, 1H, H-13b, $J_{5-13b}=13.1$, $J_{13a-13b}=15.8$, $J_{11b-13b}=0.5$), 2.74 (ddd, 1H, H-13a, $J_{5-13a}=5.4$, $J_{11a-13a}=2.0$), 2.74 (ddd, 1H, H-11b, $J_{10-11b}=11.3$, $J_{11a-11b}=14.9$), 3.08 (ddd, 1H, H-11a, $J_{10-11a}=4.4$), 3.47 (s, 3H, OCH_3), 3.85 (ddd, 1H, H-5, $J_{5-6}=6.2$), 4.61 (dd, 1H, H-10), 6.44 (d, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.31 (C-5), 40.10 (C-11), 42.53 (C-13), 57.85 (OCH_3), 79.72 (C-10), 87.08 (C-4), 118.98 (C-7), 136.53 (C-6), 146.29 (C-9), 148.09 (C-8), 200.60 (C-12). Compound **6**: ^1H NMR (300 MHz, $CDCl_3$): δ 2.15 (dd, 1H, H-13b, $J_{5-13b}=13.3$, $J_{13a-13b}=16.6$), 2.87 (ddd, 1H, H-13a, $J_{5-13a}=4.6$, $J_{11-13a}=0.8$), 4.22 (ddd, 1H, H-5, $J_{5-6}=5.7$), 3.08 (ddd, 1H, H-11a, $J_{10-11a}=4.4$), 6.53 (dd, 1H, H-6), 6.48 (dd, 1H, H-10 or H-11, $J=10.3$ and 0.7), 7.35 (dd, 1H, H-11 or H-10, $J=10.3$ and 0.8).
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21. A mixture of 5.62 g of **5a**,**b** and **6** (18.8 mmol) was dissolved in 10 mL of THF. DBN (4.94 mL, 39.9 mmol, 2.1 equiv.) was added and the black solution was stirred for 1 h at room temperature. The solvent was removed by rotary evaporation, and the residue was dissolved in water and neutralized with acid (HCl, 5N). The product was extracted into diethyl ether and dried over magnesium sulfate. After filtration, the solvent was evaporated to dryness giving **7** (3.94 g, 95% yield) as a yellow solid. Compound **7**: mp 273°C; MS (EI, m/z) 220 (M^+); ^1H NMR (300 MHz, CD_3COCD_3): δ 7.37 (d, 1H, H-11, $J_{10-11}=8.5$, $J_{11-13}=2.5$), 7.37 (d, 1H, H-13), 7.89 (s, 1H, H-6), 8.34 (d, 1H, H-10), 9.60 (s, 1H, OH); ^{13}C NMR (75 MHz, CD_3COCD_3): δ 112.74 (C-4), 114.98 (C-13), 119.02 (C-7), 119.40 (C-11), 128.07 (C-10), 134.33 (C-6), 136.31 (C-5), 148.45 (C-8), 149.44 (C-9), 161.10 (C-12). Anal. calcd for $C_{10}H_5ClN_2O_2$: C, 54.42; H, 2.27; N, 12.70. Found: C, 54.32; H, 2.35; N, 12.65%.
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