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Nitronaphthalenes as Diels–Alder dienophiles

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Abstract

1-Nitronaphthalene, 2-nitronaphthalene and 1,3-dinitronaphthalene react with Danishefsky diene as normal electron demand Diels–Alder dienophiles to give hydroxyphenanthrene derivatives as principal products in reasonable yields. The aromatization is an expected behavior in thermal reactions involving nitro-substituted compounds. However, it was possible to isolate the primary cycloadducts when using 1,3-dinitronaphthalene, although in very low yields. Other less reactive dienes do not undergo cycloaddition.

The Diels–Alder (D–A) reaction is one of the most useful methods in preparative organic chemistry. It provides the chemist with one of his best tools for the rapid preparation of cyclic compounds having a six-membered ring, in a one-step inter- or intramolecular reaction. This reaction can establish large numbers of stereochemical centers in one synthetic step and thus it has had great utility in natural product synthesis.

While a great effort has been dedicated to the development and use of aromatic compounds as dienes for the D–A reaction, in general their use as dienophiles has been considered less probable, mainly because aromatic and heteroaromatic compounds have proved to be relatively unreactive as dienophiles.

Recently we reported the high dienophilicity of *N*-tosyl-3-nitroindole in a normal D–A reaction.[1] The compounds involved as the diene partner were very reactive [(*N*-acetyl-*N*-propylamino)-1,3-butadiene,[1] Danishefsky diene[2]]. We have continued exploring this reaction using nitronaphthalenes as dienophiles. 1-Nitronaphthalene has proven to be only reactive with anthracene at 300°C.[3] Naphthalene itself behaves as a dienophile in an inverse demand reaction with hexachlorocyclopentadiene.[4] Despite this behavior, naphthalene and its derivatives have usually been forced to behave as dienes under hyperbaric or thermal conditions. The nitronaphthalenes used in this work were 1-nitronaphtalene **1**, 2-nitronaphthalene, and 1,3-dinitronaphthalene **5**.

The reaction conditions included both elevated temperatures (80–150°C) and high pressure (12 kbar) (only for **1**), evaluating different diene:dienophile molar ratios, solvents and times of reaction

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in order to improve the rate and/or the yields of the reaction.[1,2†] This allowed us to compare not only the relative reactivity of the 1- and 2-substitution of the aromatic ring, but also the regioselectivities and stereoselectivities in the case of successful cycloaddition.

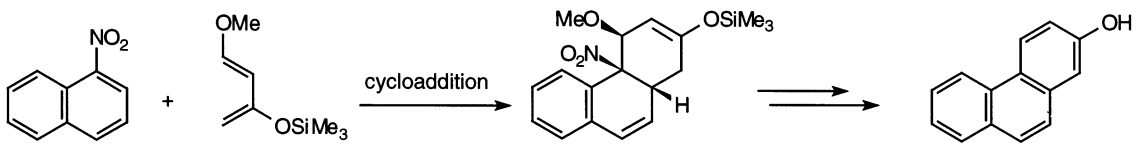
The diene components were *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene diene **2** (Danishefsky diene), (1*Z*,3*E*)-1,4-dimethoxy-1,3-butadiene,[5] chosen for their higher reactivity compared to the other readily available dienes isoprene, *trans*-1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene, *trans*-1-methoxy-1,3-butadiene, which proved to be unreactive toward cycloaddition under the reaction conditions studied.

When 1- and 2-nitronaphthalene were reacted with the Danishefsky diene under all conditions (see Table 1) the observed products were 2-hydroxyphenanthrene **4a**[6] and 3-hydroxyphenanthrene **4b**,[7] respectively, with traces of their regioisomers (16:1 ratio of 2-hydroxy to 3-hydroxyphenanthrene, entry 4, Table 1). These products resulted from the expected aromatization of the nitro-adducts.[8] Attempts to isolate the primary adducts were unsuccessful because of their unstability. The first exploratory experiment using **1** and **2** under hyperbaric conditions (entry 4) led to the highest yields at 2-hydroxyphenanthrene. In this case, the 75 MHz ^{13}C NMR analysis of the crude product mixture immediately after decompression and solvent evaporation, showed the presence of the substituted adduct **3**‡ which rapidly decomposed to the corresponding phenanthrene. When 2-nitrosubstituted, naphthalene evidenced a significantly lower reactivity.§ This fact, in addition to it being a strong cancer suspect agent, persuaded us to discard this isomer for further reactions (Scheme 1).

Table 1
Diels–Alder reactions of nitronaphthalenes derivatives and Danishefsky diene

Entry	Dienophile	Diene:dienophile ratio	Conditions	Isolated product (yield%)[a]
1	**1**	2:1	Benzene, 80°C, 6 d, ampoule	**4a** (traces)
2	**1**	2:1	Benzene, 120°C, 3 d, ampoule	**4a** (51)
3	**1**	2:1	Xylene, 150°C, 6 d, reflux	**4a** (46)
4	**1**	12:1	Dichloromethane, 40°C, 50 h, 12 kbar	**4a** (76), **4b** (5)
5	**5**	2:1	Benzene, 80°C, 6 d, ampoule	**10** (12), **11** (15), **8** (4), **9** (2)
6	**5**	2:1	Benzene, 120°C, 3 d, ampoule	**10** (14), **11** (65), **8**, **9** (traces)

[a] Based on consumed dienophile.



1 **2** **3** **4a**

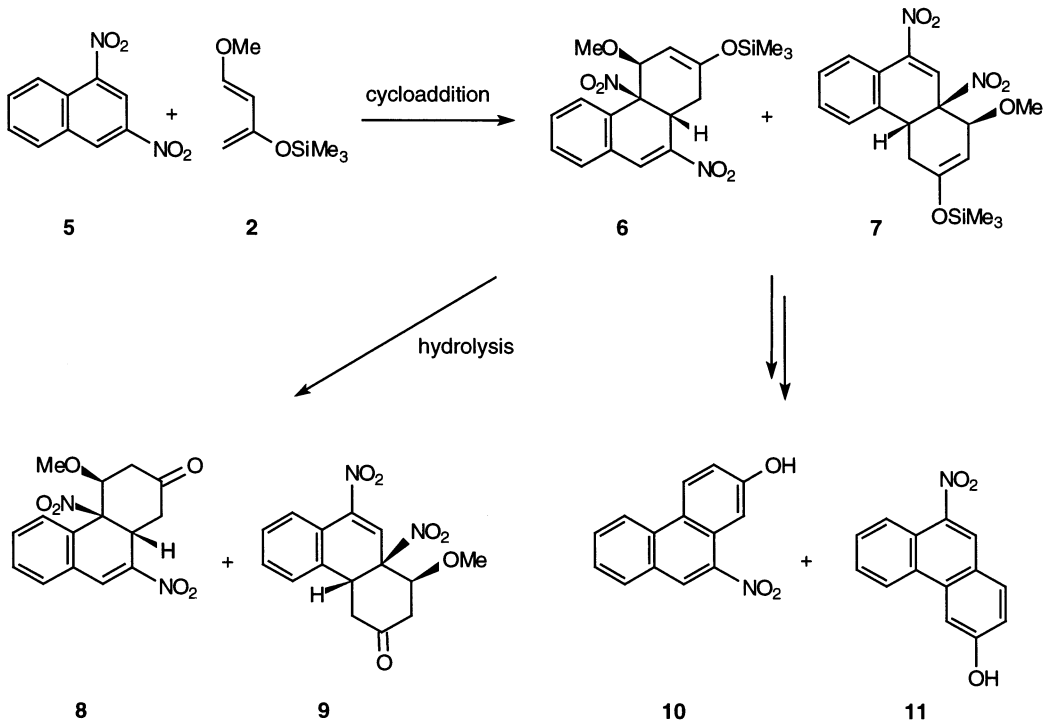
Scheme 1.

† Experimental conditions can be found in these references.

‡ ^{13}C NMR (75 MHz, Cl_3CD) 57.2 OMe, 76.34-C, 92.2 quat C–NO_2.

§ This result agrees with the observed unreactivity of 2-nitronaphthalene in its reaction with anthracene at 300°C.[3]

The higher reactivity expected for 1,3-dinitronaphthalene **5** is a consequence of its lower LUMO compared to the mononitrated naphthalenes. Moreover, according to MM+ calculations, the higher electronic deficiency in this dienophile is at C4 (due to the presence of two electronwithdrawing groups in a 1,3 relation), indicating a more favored cycloaddition process at the C3–C4 bond than at the C1–C2 bond. The reaction of **5** with Danishefsky diene (Scheme 2) led to a mixture of 2-hydroxy-10-nitrophenanthrene **10**[¶] and 3-hydroxy-9-nitrophenanthrene **11.**[‖] At higher temperatures, compound **11** is clearly the major product (Table 1, entry 6).



Scheme 2.

[¶] ^{1}H NMR (300 MHz Cl_3CD+$DMSO_{d6}$) δ 7.28 (dd, 1H, $J_{34}=9.0$ Hz, $J_{31}=2.6$ Hz, 3-H), 7.51 (t, 1H, $J_{76}=J_{78}=7.4$ Hz, 7-H), 7.68 (t, 1H, $J_{65}=J_{67}=7.4$ Hz, 6-H), 7.87 (d, 1H, $J_{87}=7.2$ Hz, 8-H), 7.79 (d, 1H, $J_{13}=2.6$ Hz, 1-H), 8.37 (s, 1H, 9-H), 8.49 (d, 1H, $J_{43}=9.0$ Hz, 4-H), 8.53 (d, 1H, $J_{56}=7.4$ Hz, 5-H); ^{13}C NMR (75 MHz, Cl_3CD+$DMSO_{d6}$) δ 106.1, 117.9, 121.1, 123.7, 123.7 quat, 124.1 quat, 124.7, 125.2, 126.3 quat, 128.9, 129.3, 131.4 quat, 138.5 quat, C-NO_2, 156.8 quat C–OH].

[‖] ^{1}H NMR (300 MHz Cl_3CD+$DMSO_{d6}$) δ 7.25 (dd, 1H, $J_{21}=8.5$ Hz, $J_{24}=2.4$ Hz, 2-H), 7.70 (m, 2H, 6-H and 7-H), 7.9 (d, 1H, $J_{12}=8.5$ Hz, 1-H), 8.02 (d, 1H, $J_{42}=2.4$ Hz, 4-H), 8.47 (s, 1H, 10-H), 8.56–8.57 (m, 2H, 5-H and 8-H); ^{13}C NMR (75 MHz Cl_3CD+$DMSO_{d6}$) δ 105.0, 116.8, 120.1 quat, 120.9, 121.5 quat, 121.7, 124.4, 125.0, 125.9, 128.0 quat, 130.2, 132.4 quat, 140.6 quat C-NO_2, 157.7 quat C–OH.

In this reaction system it was possible to isolate a small amount of products **8** and **9**** derived by hydrolysis of the enol ethers **6** and **7**, considered to be precursors of the isolated aromatic compounds. An *endo* approach in both addition processes leads to a *cis* arrangement of nitro and methoxy groups, consistent with only minor steric repulsions in the transition state.

In the reactions of 1-nitronaphthalene and 1,3-dinitronaphthalene with (1*Z*,3*E*)-1,4-dimethoxy-1,3-butadiene (similar conditions than cited in Table 1), no cycloaddition products were observed. In these cases, we noted only the presence of the corresponding *N*-naphthyl-pyrrole, e.g. 1-nitronaphthalene yields 1-(1′-naphthyl)-pyrrole.††

Conclusions. It has been demonstrated that naphthalene, when substituted at positions 1- or 2- with a nitro group (strong electron withdrawing), can undergo cycloaddition on the C1–C2 bond with Danishefsky's diene. The substitution at the 1-position proved to be better in the ability to induce the dienophilic behavior of the aromatic compound. When 1,3-dinitrosubstituted, naphthalene produced higher yields of products by addition to the C3–C4 bond, due to the higher dienophilicity of this position. Compared with our former results using *N*-tosyl-3-nitroindol, nitronaphthalene demonstrates a lower reactivity because of its higher *aromaticity*.

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** Compound **8** ^{1}H NMR (300 MHz, Cl_3CD) δ 3.44 (s, 3H OMe), 4.45 (dd, 1H, $J_{10a\text{-}1}=10.7$, 5.46 Hz, 10a-H), 4.97 (t, 1H, $J_{43}=3.05$ Hz, 4-H); ^{13}C NMR (75 MHz Cl_3CD) δ 90.2 quat C–NO_2; 204.8 C=O; compound **9** ^{1}H NMR (300 MHz Cl_3CD): δ 5.31 (brt, 1H, $J_{12}=6.10$ Hz, 1-H); 5.57 (d, 1H, $J_{4a4}=9.32$ Hz, 4a-H). The separation was achieved by preparative TLC, which leads to the lower proportion or rate of aromatization.

†† ^{1}H NMR (300 MHz Cl_3CD) δ 6.40 (t, 2H, $J_{32}=J_{34}=J_{45}=2.2$ Hz, 3-H and 4-H), 6.98 (t, 2H, $J_{23}=J_{54}=2.2$ Hz, 2-H and 5-H), 7.42–7.52 (m, 7H, 3′-H, 5′-H, 6′-H, 7′-H), 7.74 (d, 1H, $J_{43}=8.42$ Hz, 4′-H), 7.84 (d, 1H, $J_{23}=7.96$ Hz, 2′-H), 7.88 (d, 1H, $J_{87}=8.68$ Hz, 8′-H); ^{13}C NMR (75 MHz Cl_3CD) δ 109.1, 123.2, 123.3, 125.3, 126.5, 126.9, 127.8, 128.1, 129.9 quat 9′-C, 134.3 quat 10′-C, 138.3 quat C–N. We observed similar products in the reactions of nitronaphthalenes and the above cited dienes, with improved yields at higher temperature.