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Competing Diels–Alder reactions of activated nitroethylene derivatives and [3,3]-sigmatropic rearrangements of the cycloadducts

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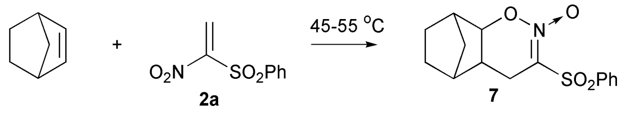
Diels–Alder reaction of nitroethylene derivatives with cyclohexa-1,3-diene afforded three pericyclic products some of which could be converted to others *via* a new [3,3]-sigmatropic rearrangement or *via* a Claisen rearrangement.

Nitroalkenes can function as either dienophiles or as heterodienes in the Diels–Alder (D-A) reaction.[1] Without catalysis by appropriate Lewis acids, nitroalkenes typically react as dienophiles. Likewise, α,β-unsaturated ketones can function as dienophiles or, less commonly, as inverse electron demand (IED) heterodienes.[2] Here we report observations on a competition amongst these various pathways in the reactions of the activated nitroethylene derivatives **2a,b** with cyclohexa-1,3-diene. We also report a new [3,3]-sigmatropic rearrangement of allylic nitronic esters and a Claisen rearrangement of an enol ether, the products of IED D-A reaction of **2a,b**.

Nitroethylene derivative **2a**[3] was generated in the presence of cyclohexa-1,3-diene from the corresponding β-sulfoxide, formed *via* ozonation of the β-sulfide **1a** and added as a solution to a warmed solution of the diene (Scheme 1). When the reaction was carried out in benzene–dichloromethane solution, a mixture of the inseparable α-nitrosulfone adducts **3a** and **4a** was obtained in 46% yield (85 : 15 **3a** : **4a** isomer ratio).[4] Also obtained in 38% yield was the nitronic ester **5a**. When the reaction was carried out in the more polar solvent mixture of acetonitrile–dichloromethane, more of the nitronic ester was obtained (52% yield) at the expense of the α-nitrosulfone adducts **3a**† and **4a** (37% yield). These facts are in accord with formation of the D-A adducts *via* competing non-polar concerted and polar pathways, either non-synchronous concerted or zwitterionic. The nitronic ester was clearly formed *via* the polar pathway as its formation was favored by more polar media.

Nitroethylene derivative **2a** also afforded an IED D-A cycloadduct from a simple alkene (Scheme 2). The nitronic ester **7** was isolated in 55% yield as the *exo* isomer[5] from the reaction of **2a** with norbornylene.

Similar generation and reaction of nitroethylene derivative **2b** in benzene–dichloromethane solution with cyclohexa-1,3-diene afforded products from which a mixture of the diastereomeric nitroketones **3b** and **4b** could be obtained in 39% yield (**3b** : **4b** ratio, 45 : 55).[3] The nitronic ester **5b** was also obtained in 19% yield and the enol ether **6** in 20% yield. Thus, **2b** acted competitively as a dienophile, as a nitroalkene heterodiene, and as an enone heterodiene.



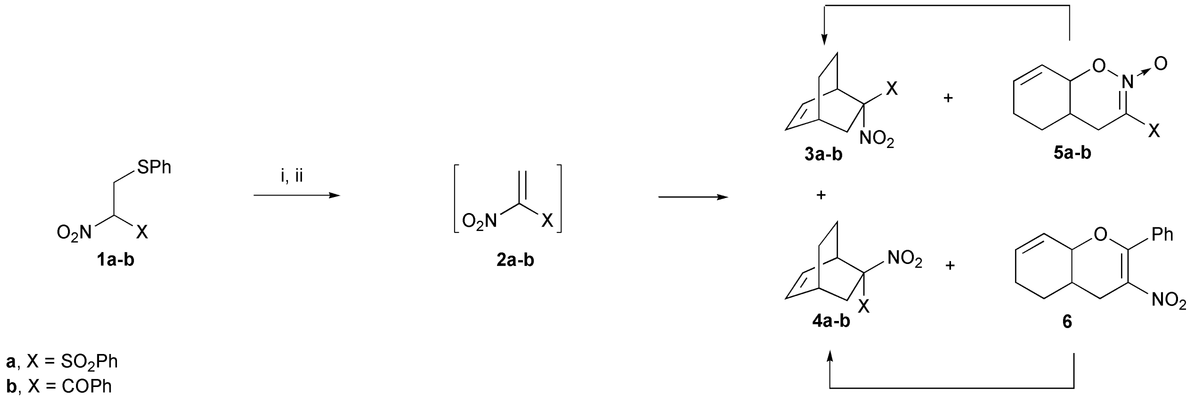
Scheme 2

Warming nitronic ester **5a** at 80 °C in either benzene or ethanol resulted in its conversion to the nitrosulfone **3a** (only the single isomer!) *via* a [3,3]-sigmatropic rearrangement. The reaction cannot be simple thermodynamic equilibration of products *via* a retro D-A reaction since none of isomer **4a** was formed. Also, the nitrosulfone isomers **3a** and **4a** do not interconvert at 80 °C. This appears to be the first reported example of the [3,3]-sigmatropic rearrangement of an *O*-allyl nitronic ester.

The sigmatropic rearrangement clearly favored the strained-ring nitro product over the nitronic ester. Reaction was 40% complete in benzene solution after 2 hours at 80 °C. However, conversion of **5a** to **3a** was > 95% complete in ethanol at 80 °C after 2 hours indicating a polar pathway. Similarly, nitronic ester **8**[3] on standing in deuterochloroform for several days at room temperature converted to the α-nitrosulfone **9** (Scheme 3).

Irreversible Cope[6] and reversible retro-Claisen[7] rearrangements have been reported for related bicyclo[2.2.2]octene derivatives. In these reported cases, the forward reaction has typically been from the bicyclo[2.2.2]octene derivative to the more stable hexahydronaphthalene system. Thus, the [3,3]sigmatropic rearrangement from **5a** to **3a** in the opposite direction is exceptional. Presumably the nitronic ester is substantially less stable than the strained-ring nitro compound. These considerations suggest possibilities for the synthesis of highly functionalized strained-ring systems.

Warming the nitronic ester **5b** at 80 °C in 95% ethanol afforded slow conversion to **3b**, the minor isomer of the nitroketone. Conversion was > 95% complete after 42 hours.



Scheme 1 *Reagents and conditions*: O₃, CH₂Cl₂, −78 °C to 0 °C; ii, add dropwise to a solution of cyclohexa-1,3-diene, 45–55 °C.

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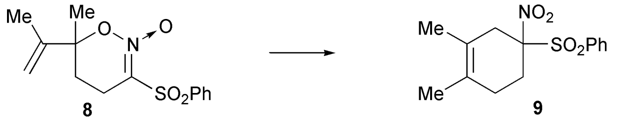
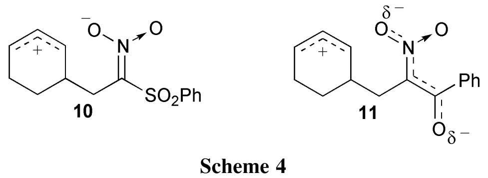


Scheme 3

Neither the enol ether **6** nor the isomeric nitroketone **4b** were formed under these conditions. Conversely, warming the enol ether **6** at 150 °C in DMF for 12 hours afforded the major isomer **4b** exclusively: none of the minor isomer **3b** was formed and, since the nitronic ester **5b** would have rearranged to **3b** under these conditions, **5b** was absent on this reaction pathway. Indeed, pure samples of **3b** and **4b** were obtained only from the rearrangement reactions because the mixture of **3b** and **4b** was not readily separable by simple chromatography. The ability of structural isomers **5b** and **6** to undergo rearrangement affording diastereomeric products appears to be the first example of a previously unrecognized feature of sigmatropic rearrangements. Further examples are being sought as this feature has clear synthetic potential.

It seems likely that the main pathway for formation of the nitrosulfone adducts **3a** and **4a** and the nitroketone adducts **3b** and **4b** is a typical D-A concerted pathway. However, zwitterion intermediates might well be present in the formation of cycloadducts **5a–b** and **6**. Denmark, Cramer, and Sternberg[8] have reported evidence for a zwitterionic intermediate in the $SnCl_4$-catalyzed cycloaddition reaction of 1-nitrocyclohexene and cyclopentene. Similarly, the zwitterion **10** might be present on the pathway leading to nitronic ester **5a** (Scheme 4). The cationic center of **10** would be stabilized by allylic resonance and the anionic center by the combined effects of the nitro and sulfonyl groups. The stabilized zwitterion **11** might be a common intermediate in the formation of both **5b** and **6** if free rotation around the open-chain C–C single bond is possible (however, coulombic attraction would retard free rotation). Since only the *cis*-fused bicyclic isomers **5a–b** and **6** were observed in the D-A reactions, rapidly collapsing cyclic zwitterions[9] rather than extended zwitterions,[9] must be assumed. It is also possible that highly non-synchronous concerted pathways are followed. The rearrangement of nitronic ester **5a** to nitrosulfone **3a** showed strong rate enhancement in polar solution. Consequently, the possibility of the zwitterions **10** and **11** as intermediates in the sigmatropic rearrangements has also been considered. However, only a cyclic zwitterion in which the charged centers never fully dissociate is consistent with the single rearrangement products observed in all cases. There is no evidence countering a highly non-synchronous concerted pathway for any of the three sigmatropic rearrangements. In related Claisen rearrangements, rate enhancement in polar solution has been attributed to a similar highly non-synchronous concerted pathway.[10]



Scheme 4

Notes and references

† *Selected physical and spectroscopic data:* **3a**: mp 153–154 °C; δ_H (250 MHz, $CDCl_3$) 7.55–7.85 (m, 5H), 6.37 (app. t, 1H, J = 7.2 Hz), 6.01 (app. t, 1H, J = 7.2 Hz), 3.55–3.65 (m, 1H), 2.85–2.95 (m, 1H), 2.78 (broad d, 1H, J = 15.7 Hz), 2.63 (d, 1H, J = 15.7 Hz), 2.35–2.55 (m, 1H), 1.65–1.85 (m, 1H), 1.25–1.40 (m, 2H); δ_C (62.9 MHz, $CDCl_3$) 136.6, 134.8, 134.1, 130.1, 129.8, 129.0, 111.6, 35.9, 31.3, 29.4, 23.1, 19.4; IR ν(KBr)/cm^{-1} 1550, 1365, 1151 (Calc. for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.16; N, 4.78. Found: C, 57.04; H, 5.01; N, 4.60). **3b**: δ_H (250 MHz, $CDCl_3$) 7.4–7.9 (m, 5H), 6.43 (app. t, 1H), 6.30 (app. t, 1H), 3.76 (m, 1H), 2.8–2.9 (m, 1H), 2.59 (dd, 1H, J = 14.6, 2.2 Hz), 2.48 (d, 2H, J = 14.6 Hz), 1.7–1.85 (m, 1H), 1.4–1.55 (m, 1H), 1.1–1.4 (m, 2H). **4b**: δ_H (250 MHz, $CDCl_3$) 7.35–7.76 (m, 5H), 6.51 (dd, 1H, J = 6.7, 7.8 Hz), 6.18 (app. t, 1H), 3.51–3.53 (m, 1H), 3.28 (dd, 1H, J = 14.5, 2.6 Hz), 2.75–2.85 (m, 1H), 1.75–1.9 (m, 2H), 1.2–1.6 (m, 3H); δ_C (62.9 MHz, $CDCl_3$) 189.4, 133.7, 132.8, 132.7, 132.1, 128.8, 128.6, 38.7, 37.0, 29.3, 22.4, 20.5. **5a**: mp 86–88 °C; δ_H (250 MHz, $CDCl_3$) 7.5–8.1 (m, 5H), 6.08–6.18 (m, 1H), 5.65–5.75 (m, 1H), 4.65–4.72 (m, 1H), 3.28 (dd, 1H, J = 8.6, 19.5 Hz), 2.66 (dd, 1H, J = 3.1, 19.5 Hz), 2.3–2.45 (m, 1H), 2.05–2.3 (m, 2H), 1.65–1.8 (m, 2H); δ_C (62.9 MHz, $CDCl_3$) 137.0, 136.9, 134.4, 129.5, 128.8, 123.7, 120.7, 78.3, 30.1, 28.5, 24.4, 23.7; HRMS (M + H): calc m/z 294.0800, found m/z 294.0795. **5b**: δ_H (250 MHz, $CDCl_3$) 7.40–7.85 (m, 5H), 6.19–6.26 (m, 1H), 5.85–5.95 (m, 1H), 4.85–4.95 (m, 1H), 3.08 (dd, 1H, J = 8.8, 19.0 Hz), 2.55 (dd, 1H, J = 3.6, 19.0 Hz), 2.1–2.45 (m, 3H), 1.75–1.95 (m, 2H); δ_C (62.9 MHz, $CDCl_3$) 189.5, 136.6, 133.7, 128.8, 128.7, 121.5, 119.9, 77.9, 29.9, 29.0, 24.4; 24.3; HRMS (M + Na): calc m/z 280.0950, found m/z 280.0945. **6**: δ_H (250 MHz, $CDCl_3$) 7.3–7.6 (m, 5H), 6.0–6.1 (m, 1H), 5.85–6.0 (m, 1H), 4.55–4.65 (m, 1H), 2.96 (dd, 1H, J = 7.3, 17.2 Hz), 2.79 (dd, 1H, J = 3.9, 17.2 Hz), 2.1–2.4 (m, 3H), 1.65–1.85 (m, 2H); HRMS (M + Na): calc m/z 280.0950, found m/z 280.0952. **7**: δ_H (250 MHz, $CDCl_3$) 7.40–8.05 (m, 5H), 4.37 (d, 1H, J = 6.0 Hz), 3.39 (dd, 1H, J = 6.4, 14.4 Hz), 2.4–2.5 (m, 1H), 2.1–2.35 (m, 3H), 1.85 (broad d, 1H, J = 10.7 Hz), 1.5–1.7 (m, 2H), 1.05–1.35 (m, 3H); HRMS (M + Na): calc m/z 330.0776, found m/z 330.0769.

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4 Structure assignment was based in part on spectral comparison to cyclopentadiene adducts (ref. 3) and is consistent with the sigmatropic rearrangement results.
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10 For a discussion of the mechanistic implications of rate enhancement in polar solution for the Claisen rearrangement, see: E. Brandes, P. A. Grieco and J. J. Gajewski, *J. Org. Chem.*, 1989, **54**, 515 and references therein.