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Generation and in situ Diels–Alder reactions of activated nitroethylene derivatives†

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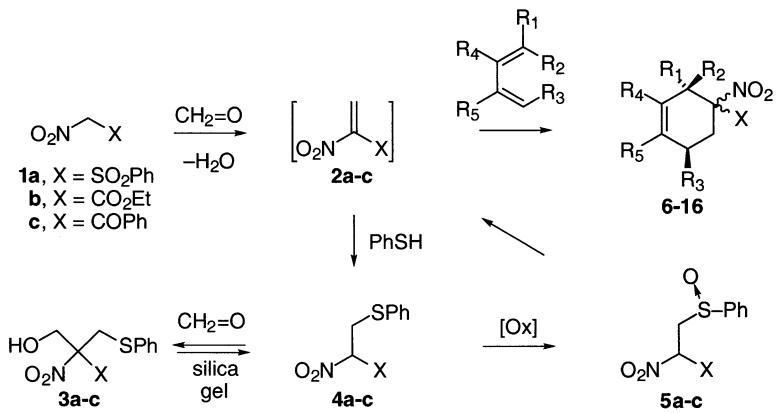
Abstract—Dienes readily undergo Diels–Alder reaction with CH_2=C(NO_2)SO_2Ph (**2a**), CH_2=C(NO_2)CO_2Et (**2b**), and CH_2=C(NO_2)COPh (**2c**), all observed in situ by ^{1}H NMR. The cycloadducts of **2a** undergo $S_{RN}1$ reactions. © 2002 Elsevier Science Ltd. All rights reserved.

Although isolable,[1] nitroethylene is of somewhat limited stability, readily undergoing polymerization and conjugate addition with weak nucleophiles. Ethylene derivatives in which one of two geminal W-groups is nitro have never been isolated[2] and only three of their in situ Diels–Alder (D–A) reactions have ever been reported.[2,3] Here we describe a protocol for conducting routine D–A reactions using the nitroethylene derivatives **2a–c** possessing a second electron attracting group at the α-position.

In a simple, practical route to the D–A adducts of nitroethylene derivatives **2a–c**, the commercially available nitromethane derivatives **1a–c** were condensed with formalin in the presence of dienes and acetic acid (Scheme 1). An excess of the nitromethane derivative was routinely employed (three-fold excess of **1a**, six-fold excess of **1b–c**) and yields are based on the starting diene as the limiting reagent (Table 1). The presence of acetic acid appears to serve two functions: facilitated dehydration of the intermediate nitroaldol[4] and control of the reaction pH lowering potential side reactions of the nitroethylene derivative. At no time were the nitroethylene derivatives **2a–c** observed under these conditions. Uncharacterized polar compounds were also present in the crude products.



Scheme 1.

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† Dedicated to Professor Henry Feuer on the occasion of his 90th birthday.

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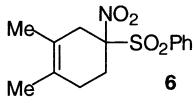
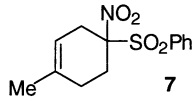
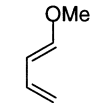
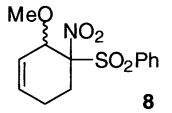
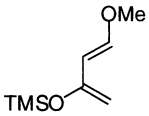
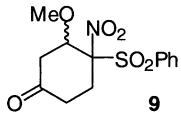
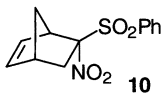
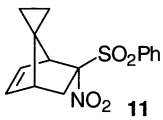
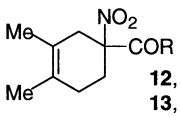
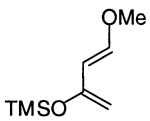
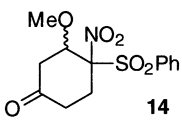
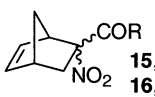
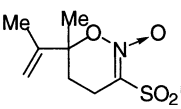
Table 1. Diels–Alder adducts obtained from **2a**–**2c**

Dienophile Precursor	Diene	Cycloadduct	Yield, %	Isomer Ratio
1a		 **6**	90	
4a			91[a]	
1a		 **7**	55	>97:3 *p* / *m*
1a		 **8**	84	80:20 *endo* / *exo* (>97:3 *o* / *m*)
4a		 **9**	57[b]	85:15 *endo* / *exo*
1a			0	
1a		 **10**	99[c]	>97:3 *endo* / *exo*
4a			97	
1a		 **11**	93[d]	>97:3 *endo* / *exo*
1b		 **12**, R = OEt	68	
4b			80	
1c		**13**, R = Ph	62	
4c			84	
4b		 **14**	61[b]	70:30 *endo* / *exo*
1b		 **15**, R = OEt	80[d]	85:15
1c		**16**, R = Ph	82[c]	70:30 *endo* / *exo*

[a]Also isolated in 3% yield was nitronic ester **17**:  [b]The product was sensitive: loss of MeOH occurred readily. [c]Major isomer determined from crystallographic data: *endo* nitro (reference 7). [d]Major isomer determined from spectral data: *endo* nitro.

When thiophenol was substituted for the diene in the above reactions, the β-sulfides **4a**–**c** and hydroxymethyl β-sulfides **3a**–**b** were obtained.[5] During silica gel chromatography, **3a** and **3b** were converted to **4a** and **4b**. In the case of **4c**, little hydroxymethyl β-sulfide **3c** was obtained but acid-catalyzed elimination of benzoic acid was a troublesome side reaction.[5] Thus, β-sulfides **4a**–**c** were readily obtained in 67–88% yield.[6] These β-sulfides proved useful, stable precursors to the corresponding nitroethylene derivatives.

Oxidation with either MCPBA or ozone provided the β-sulfoxides **5a**–**c** as unstable intermediates undergoing β-sulfoxide elimination at 0–40°C. In each case, MCPBA oxidation of the β-sulfide **4a**–**c** gave the β-sulfoxide **5a**–**c** (two diastereomers) and the nitroethylene derivative **2a**–**c** that could be detected in CD_2Cl_2 solution by ^1H NMR.[8] Warming the sample briefly afforded the nitroethylene derivative at the expense of the sulfoxide in each case. The NMR signals attributed to the geminal olefinic protons are characteristic: in all three cases, the proton *cis* to the nitro group gave a sharp doublet while the proton *trans* to the nitro group was broadened, presumably owing to greater quadrapole coupling from the N-atom.[9] Concentration of solutions containing **2a** at 0–5°C led to complete decomposition of both the sulfoxide and the nitroethylene derivative although solutions containing

2b could be concentrated at 20°C and reconstituted without destruction of **2b** and its sulfoxide precursor.

Nitroethylene derivatives **2a–c** were then cleanly generated for in situ cycloaddition in the following manner. A CH_2Cl_2 solution of the corresponding purified β-sulfide was oxidized with ozone at −78°C and the preformed cold solution was then added dropwise to a warmed solution of diene. Under these conditions, D–A cycloadducts were obtained in 57–97% yield based on the β-sulfide as the limiting reagent.[10,11] For example, the Danishefsky diene worked well under these anhydrous conditions affording the sensitive cycloadducts **9** and **14** on work-up. Loss of methanol from **9** and **14** occurred readily.

In the cases involving cyclopentadiene and its derivatives, cycloaddition of $CH_2{=}C(NO_2)SO_2Ph$ (**2a**) occurred with a high preference for placing the nitro group *endo* in the resulting adduct (cycloadducts **10–11** >97:3 isomer ratio). This high stereoselectivity was surprising in view of the fact that *E*-$PhSO_2CH{=}CHNO_2$ has been reported to give a 75:25 mixture of diastereomers on reaction with cyclopentadiene.[12] MM2 calculations[13] suggested a preferred conformation of **2a** where the phenyl group of the sulfone moiety is perpendicular to the C,C double bond (Fig. 1) allowing easier access to a transition state with *endo*-placement of the nitro group. For reactions of the planar species **2b–c** where this effect would be absent, substantially less biased *endo*/*exo* mixtures were obtained (cycloadducts **15–16**). In all cases, regioselectivity was high (only one regioisomer for cycloadducts **7**, **8**, **9**, and **14** was detected). In one case, reaction of **2a** with 2,3-dimethyl-1,3-butadiene, a 3% yield of a periisomer, the nitronic ester **17**, was obtained in addition to the α-nitrosulfone **6**.

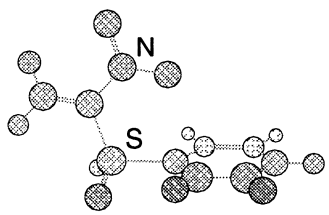
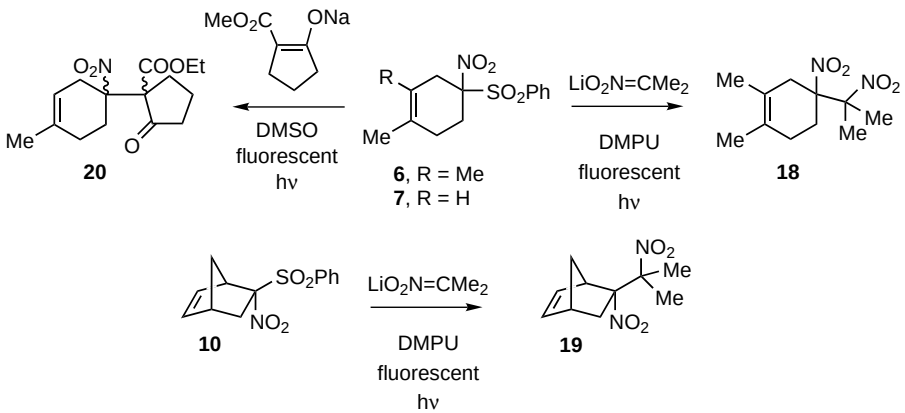


Figure 1. MM2 calculation: preferred conformation of **2a**.

$S_{RN}1$ reactions. The secondary α-nitrosulfone D–A adducts are highly functionalized and would be expected to be useful synthetic intermediates. For example, secondary nitrosulfones, formerly of limited availability, have been reported to undergo $S_{RN}1$ substitution reactions in which the sulfone group can be replaced by a nucleophile.[14] We have accordingly subjected nitrogen-degassed DMPU solutions containing excess lithium 2-nitropropanate and α-nitrosulfones **6** and **10** to visible light (Scheme 2). The substitution products **18** and **19** were formed in 87–90% yield. Interestingly, **19** was formed as a single isomer (presumably with the nitro group *endo*) despite the radical intermediate present in such reactions. Similarly, reaction of α-nitrosulfone **7** with the sodium enolate of ethyl 2-oxocyclopentanecarboxylate in DMSO solution afforded substitution product **20** (mixture of diastereomers) in 40% yield.

Representative procedures. **Synthesis of 6**: **procedure A**. A solution containing **1a** (0.74 g, 3.7 mmol), 2,3-dimethyl-1,3-butadiene (0.10 g, 1.2 mmol), 37% formalin (0.99 g), and HOAc (0.73 g) in THF (5 mL) was heated at 35–40°C for 1 day. Volatiles were removed in vacuo and the residue partitioned between CH_2Cl_2 and 10% brine. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel (CH_2Cl_2 elution) followed by recrystallization from 95% ethanol afforded 0.33 g (90% yield) of **6**:[7,15] mp 97–98°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.6–7.9 (m, 5H), 2.9–3.1 (m, 2H), 2.68 (dd, 1H, J = 13.7, 5.7 Hz), 2.3–2.45 (m, 1H), 2.05–2.3 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 135.1, 132.7, 130.5, 129.1, 125.1, 120.3, 106.3, 33.2, 27.9, 25.5, 18.7, 18.2.

Synthesis of 6: **procedure B**. Through a cold (−78°C) solution of β-sulfide **4a** (325 mg, 1.0 mmol) and HOAc (63 mg) in CH_2Cl_2 (10 mL) over 30 min was passed a stream of ozone in O_2 (excess ozone). This solution (kept cold) was stirred for an additional 30 min, purged with N_2, and transferred dropwise over 45 min to a



Scheme 2.

warmed solution (50–55°C bath temp.) of 2,3-dimethyl-1,3-butadiene (167 mg, 2.0 mmol) in benzene (10 mL). Heating was continued an additional 30 min, volatiles were removed, and the crude product was purified as in procedure A: 270 mg (91% yield).

References

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3. (a) There are no reports of in situ D–A reactions of α-nitro-vinyl sulfones, but see: Zeilstra, J. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1974**, *39*, 3215; (b) 1,1-Dinitroethene: Gold, M. H.; Hamel, E. E.; Klager, K. J. *J. Org. Chem.* **1957**, *22*, 1665.
4. Wade, P. A.; Murray, J. K., Jr.; Shah-Patel, S.; Palfey, B. A.; Carroll, P. J. *J. Org. Chem.* **2000**, *65*, 7723.
5. β-Sulfide **2a** was prepared in DMSO at 35°C. β-Sulfides **2b** and **2c** were prepared in THF at 65°C. The THF solution of crude **2c** was diluted with CH_2Cl_2 and washed (several portions of water) to remove the bulk of HOAc *before* concentration: otherwise substantial elimination of benzoic acid occurred.
6. ^{1}H NMR (250 MHz, $CDCl_3$) data. **4a**: δ 7.55–7.9 (m, 5H), 7.25–7.45 (m, 5H), 5.44 (dd, 1H, $J=11.7$, 2.8 Hz), 3.72 (dd, 1H, $J=14.9$, 2.8 Hz), 3.50 (dd, 1H, $J=14.9$, 11.7 Hz). **4b**: δ 7.25–7.45 (m, 5H), 5.02 (dd, 1H, $J=8.1$, 6.8 Hz), 4.19 (q, 2H, $J=7.2$ Hz), 3.4–3.6 (m, 2H), 1.21 (t, 3H, $J=7.2$ Hz). **4c**: δ 7.30–7.75 (m, 10H), 6.09 (dd, 1H, $J=8.5$, 5.5 Hz), 3.75 (dd, 1H, $J=14.6$, 8.5 Hz), 3.59 (dd, 1H, $J=14.6$, 5.5 Hz).
7. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic data Centre as supplementary publication numbers CCDC 178872 (**10**) and 178873 (**16**). Copies of the data can be obtained, 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].
8. ^{1}H NMR (250 MHz, CD_2Cl_2) olefinic signals. **2a**: δ 7.25 (d, 1H, $J=3.2$ Hz), 7.20 (broad d, 1H). **2b**: δ 6.47 (d, 1H, $J=2.6$ Hz), 6.43 (broad s, 1H). **2c**: δ 6.88 (d, 1H, $J=2.7$ Hz), 6.21 (broad s, 1H). ^{1}H NMR (250 MHz, CD_2Cl_2) data. **5a** (50:50 diastereomer mixture) δ 7.35–8.1 (m, 10H), 6.08 (dd, 1H, $J=9.2$, 2.6 Hz, isomer i) 5.89 (dd, 1H, $J=11.4$, 1.9 Hz, isomer ii) 3.9–4.05 (m, 1H, both isomers), 3.73 (dd, 1H, $J=14.8$, 9.2 Hz, isomer i), 3.50 (dd, 1H, $J=14.8$, 1.9 Hz, isomer ii).
9. The published spectrum of nitroethylene (Ref. 1) also shows the same effect but without explanation.
10. Representative ^{1}H NMR (250 MHz, $CDCl_3$) data. **7**: δ 7.55–7.9 (m, 5H), 5.31 (m, 1H), 2.9–3.2 (m, 2H), 2.7–2.85 (m, 1H), 2.35–2.5 (m, 1H), 2.0–2.3 (m, 2H), 1.63 (s, 3H). **11**: δ 7.5–7.85 (m, 5H), 6.53 (dd, 1H, $J=5.7$, 3.0 Hz), 6.01 (dd, 1H, $J=5.7$, 3.0 Hz), 3.38 (m, 1H), 3.14 (dd, 1H, $J=13.8$, 3.5 Hz), 2.55–2.60 (m, 2H), 1.15–1.25 (m, 1H), 0.84–0.94 (m, 1H), 0.45–0.6 (m, 2H). **12**: δ 4.23 (q, 2H, $J=7.2$ Hz), 2.85 (broad d, 1H, $J=17.6$ Hz), 2.68 (broad d, 1H, $J=17.6$ Hz), 2.5–2.65 (m, 1H), 2.2–2.35 (m, 1H), 2.04 (app. broad s, 2H), 1.64 (s, 3H), 1.58 (s, 3H), 1.26 (t, 3H, $J=$ 7.2 Hz). **16** (*endo* NO_2): δ 7.4–7.9 (m, 5H), 6.59 (dd, 1H, $J=5.5$, 2.9 Hz), 5.95 (dd, 1H, $J=5.5$, 2.9 Hz), 3.94 (broad s, 1H), 3.10 (broad s, 1H), 2.82 (dd, 1H, $J=13.5$, 3.2 Hz), 2.26 (dd, 1H, $J=13.5$, 3.2 Hz), 1.67–1.77 (m, 2H). **17**: δ 7.5–8.0 (m, 5H), 4.83 (m, 1H), 4.79 (s, 1H), 2.90–3.05 (m, 1H), 2.63–2.85 (m, 1H), 2.30–2.41 (m, 1H), 1.89–2.0 (m, 1H), 1.64 (d, 3H, $J=0.5$ Hz), 1.42 (s, 3H).
11. Representative ^{13}C NMR (62.9 MHz, $CDCl_3$) data. **7**: δ 135.1, 133.9, 132.8, 130.6, 129.1, 114.9, 105.7, 28.3, 26.6, 25.3, 22.6. **11**: δ 142.3, 135.3, 134.8, 134.0, 130.1, 129.1, 116.9, 55.4, 48.6, 44.9, 35.2, 12.0, 5.6. **12**: δ 166.9, 124.8, 121.0, 92.0, 62.5, 37.1, 29.0, 28.0, 18.5, 18.3, 13.6. **16** (*endo* NO_2): δ 191.2, 142.0, 133.8, 131.6, 128.8, 101.2, 53.2, 50.3, 42.7, 37.5.
12. Ono, N.; Kamimura, A.; Aritsune, K. *J. Org. Chem.* **1986**, *51*, 2139.
13. MM2 calculation: CHEM-3D™ program.
14. (a) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734; (b) Kornblum, N.; Boyd, S. D.; Ono, N. *J. Am. Chem. Soc.* **1974**, *96*, 2580.
15. Anal. calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.81; N, 4.75. Found: C, 56.67; H, 5.61; N, 4.56%.