Supporting Information (7 pages)

Factors on Regioselectivities of the Ene Reaction with Trisubstituted Cycloalkenes – A Comparison of the Enophiles Singlet Oxygen, Triazolinedione and Nitrosoarene

Waldemar Adam, Nils Bottke, Oliver Krebs

Institut für Organische Chemie, Universität Würzburg, Am Hubland,
D-97074 Würzburg, Germany

Experimental Section

General Aspects. The elemental analyses were performed by the Microanalytical Division of the Institute of Inorganic Chemistry, University of Würzburg. For quantitative NMR analysis, tetrachloroethane was used as internal standard. To obtain well-resolved NMR spectra of the hydroxylamine products, diphenylhydrazine or phenylhydrazine were added to the $CDCl_3$ solution as scavenger of paramagnetic impurities. TLC analyses were conducted on precoated silica-gel foils Polygram SIL G/UV254 (40 × 80 mm) from Machery and Nagel, Düren, Germany. TLC Spots were visualized by UV light (254 nm) or by phosphomolybdic acid or sodium hydroxide staining (in the case of hydroxyl amines). Silica gel (20-63 μm, Woelm) was used for flash chromotography.

Materials. 1-Methylcyclopentene and 1-methylcyclohexene are commercially available. 1-Methylcycloheptene, *Z*-1-methylcyclooctene and *E*-1-methylcyclooctene were prepared according to literature procedures.[12] *p*-Nitronitrosobenzene was made by oxidation of *p*-nitroaniline with Curox (potassium monoperoxysulfate, kindly supplied by Peroxid-Chemie GmbH, Pullach bei München, Germany) according to the literature procedures.[13] 4-Phenyl-1,2,4-triazoline-3,5-dione was obtained according to the literature procedure.[14]

General Procedure for the Ene Reaction with 4-Nitronitrosobenzene. To a solution of the alkene (13.2 mmol) in 200 mL of dry dichloromethane was added 1.00 g (6.58 mmol) of 4-nitronitrosobenzene at 0 ° C. The reaction mixture was stirred at this temperature for 24 h to achieve complete conversion (TLC detection, 2:1 petroleum ether/ethyl ether). The product was extracted from the organic layer with 4% aqueous sodium hydroxide solution (3 x 50 mL). After acidification with 30% sulfuric acid, the water layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water (1 x 50 mL), dried over anhydrous Na_2SO_4, and the solvent removed (40 ° C, 700 mbar). The crude ene products were purified by silica-gel flash chromatography (5:1 petroleum ether/dichloromethane as eluent).

1-Methylcyclopentene (1). The reaction was conducted on 1.08 g (13.2 mmol) of **1** according to the above general procedure. The ene product was isolated and characterized; 325 mg (21% yield); orange powder (85 : 15 mixture of the two regioisomers **1a** and **1b**).

***N*-[2-Methyl-2-cyclopentenyl]-*N*-4-nitrophenylhydroxylamine** (**1a**) **and *N*-[2-Methenylcyclopentyl]-*N*-4-nitrophenylhydroxylamine** (**1b**)

IR (KBr) 3310, 2910, 1592, 1490, 1281, 1113, 827 cm^{-1}; mp 56 - 56.5 ° C; Anal. Calcd. for $C_{12}H_{14}N_2O_3$ (234.3): C, 61.53; H, 6.02; N, 11.96; Found: C, 61.17; H, 5.96; N, 11.98.

1a: ^{1}H-NMR (600 MHz): δ = 1.61 (s, 3H), 1.86 (m, 1H), 2.00 (m, 1H), 2.18 (m, 1H), 2.33 (m, 1H), 4.72 (m, 1H), 5.59 (m, 1H), 7.01 (m, 2H), 8.03 (m, 2H), OH signal not detectable; ^{13}C-NMR (150 MHz): δ = 14.5 (q), 25.4 (t), 30.8 (t), 73.5 (d), 112.3 (d), 113.9 (d), 125.3 (d), 136.7 (s), 140.5 (s), 156.8 (s);

1b: ^{1}H-NMR (600 MHz): δ = 1.50 (m, 1H), 1.64 (m, 1H), 1.73 (m, 1H), 1.86 (m, 1H), 2.18 (m, 1H), 2.33 (m, 1H), 4.63 (m, 1H), 4.94 (br s, 1H), 5.05 (br. s, 1H), 6.84 (m, 2H), 7.95 (m, 2H), OH signal not detectable; ^{13}C-NMR (150 MHz): δ = 23.4 (t), 27.1 (t), 32.6 (t), 67.2 (d), 108.0 (t), 113.5 (d), 126.1 (d), 140.5 (s), 148.8 (s), 156.3 (s).

1-Methylcyclohexene (2). The reaction was conducted on 9.50 g (99.0 mmol) of **2** according to the above general procedure. The ene product **2a** was isolated and characterized; 279 mg (17% yield); red oil.

***N*-[2-Methyl-2-cyclohexenyl]-*N*-4-nitrophenylhydroxylamine** (**2a**)
IR (film) 3382, 2935, 2663, 1591, 1495, 1319, 1112, 837 cm^{-1}; Anal. Calcd. for $C_{13}H_{16}N_2O_3$ (248.3): C, 62.89; H, 6.50; N, 11.28; Found: C, 62.79; H, 6.80; N, 10.82; ^{1}H-NMR (600 MHz): δ = 1.49 (m, 1H), 1.52 (s, 3H), 1.67-1.98 (m, 5H), 4.22 (m, 1H), 5.66 (m, 1H), 6.94 (d, *J* = 9.3 Hz, 2H), 8.01 (d, *J* = 9.3 Hz, 2H), OH signal not detectable; ^{13}C-NMR (150 MHz): δ = 21.0 (q), 21.1 (2 x t), 25.0 (t), 63.1 (d), 112.1 (d), 112.7 (2 x d), 125.5 (2 x d), 132.2 (s), 140.0 (s), 156.8 (s).

1-Methylcycloheptene (3). The reaction was conducted on 724 mg (6.58 mmol) of **3** according to the above general procedure. The ene product was isolated and characterized; 432 mg (25% yield); orange powder (94 : 6 mixture of the two regioisomers **3a** and **3b**).

***N*-[2-Methyl-2-cycloheptenyl]-*N*-4-nitrophenylhydroxylamine** (**3a**) **and**
***N*-[2-Methenylcycloheptyl]-*N*-4-nitrophenylhydroxylamine** (**3b**)
IR (KBr): 3356, 2922, 2850, 1595, 1479, 1282, 1101, 828 cm^{-1}; mp 117-117.5 °C; Anal. Calcd. for $C_{14}H_{18}N_2O_3$ (262.3): C, 64.11; H, 6.92; N, 10.68; Found: C, 63.81; H, 6.60; N, 10.64;
3a: ^{1}H-NMR (600 MHz): δ = 1.71 (s, 3H), 1.48-2.37 (m, 8H), 4.45 (dd, J_1 = 9.7 Hz, J_2 = 5.7 Hz, 1H), 5.77 (t, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 9.3 Hz, 2 H), 8.13 (d, *J* = 9.3 Hz, 2H), OH signal not detectable; ^{13}C-NMR (150 MHz): δ = 22.6 (q), 25.6 (2 x t), 25.9 (t), 28.8 (t), 67.3 (d), 112.3 (d), 112.5 (2 x d), 125.6 (2 x d), 136.9 (s), 139.8 (s), 155.8 (s);
3b: ^{1}H-NMR (600 MHz): δ = 1.22-2.44 (m, 10H), 4.35 (m, 1H), 4.96 (br. s, 1H), 5.07 (br. s, 1H), 7.04 (d, *J* = 9.3 Hz, 2H), 8.06 (d, *J*= 9.0 Hz, 2H), OH signal not detectable; ^{13}C-NMR (150 MHz): δ = 21.0 (t), 21.1 (2 x t), 25.0 (2 x t), 63.1 (d), 112.1 (t), 113.5 (2 x d), 126.3 (2 x d), 139.8 (s), 152.6 (s), 155.8 (s).

Nitroso Ene Reaction with *Z*-1-Methylcyclooctene (*Z*-4). The reaction was conducted on 816 mg (6.58 mmol) of Z-**4** according to the above general procedure. The ene product was isolated and characterized; 432 mg (24% yield); orange powder (35 : 65 mixture of the two regioisomers **4a** and **4b**).

_N_-[2-Methyl-2-cyclooctenyl]-_N_-4-nitrophenylhydroxylamine (4a) and _N_-[2-Methenylcyclooctyl]-_N_-4-nitrophenylhydroxylamine (4b)

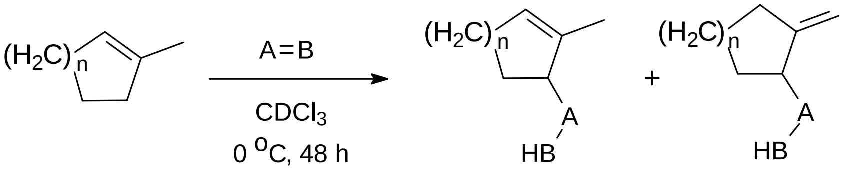
IR (KBr): 3450, 2920, 2850, 1585, 1480, 1290, 1180, 1110, 835, 755, 695 cm^{-1}; mp 94-100 ° C; Anal. Calcd. for $C_{15}H_{20}N_2O_3$ (276.3): C, 65.20; H, 7.30; N, 10.14; Found C, 65.44; H, 7.59; N, 9.85;

4a: ^{1}H-NMR (400 MHz): δ = 1.20-1.84 (m, 3H), 2.12-2.45 (m, 9H), 4.71 (dd, J_1 = 4.0 Hz, J_2 = 11.6 Hz, 1H), 5.49 (t, J = 8.6 Hz, 1H), 6.82 (m, 2H), 8.02 (m, 2H), OH signal not detectable; ^{13}C-NMR (100 MHz): δ = 18.5 (q), 24.4 (t), 27.2 (t), 27.3 (t), 30.4 (t), 31.0 (t), 61.1 (d), 111.9 (d), 125.3 (d), 126.2 (d), 140.1 (s), 148.9 (s), 155.8 (s);

4b: ^{1}H-NMR (400 MHz): δ = 1.20-1.84 (m, 3H), 2.12-2.45 (m, 10H), 4.20 (dd, J_1 = 3.6 Hz, J_2 = 11.4 Hz, 1H), 4.93 (s, 1H), 4.96 (s, 1H), 6.82 (m, 2H), 8.02 (m, 2H), OH signal not detectable; ^{13}C-NMR (100 MHz): δ = 25.8 (t), 25.9 (t), 26.1 (t), 27.5 (t), 30.3 (t), 33.6 (t), 68.3 (d), 113.9 (d), 116.4 (t), 125.2 (d), 134.6 (s), 151.0 (s), 156.2 (s).

General Procedure for the Ene Reaction with 4-Nitronitrosobenzene on the NMR Scale. Under an argon-gas atmosphere, the alkene (2.88 or 1.44 mmol) was dissolved in 5.00 mL of $CDCl_3$ and saturated with argon gas. To this solution were added 50.0 µL of tetrachloroethane as internal standard and a 0.5-mL aliquot of this stock solution was taken as reference spectrum. To the remaining stock solution was added the 4-nitronitrosobenzene (1.30 mmol) at 0 ° C, and the reaction mixture was stirred at this temperature for 24 h. The conversion, mass balance and regioselectivity were determined by ^{1}H-NMR analysis directly on the crude reaction mixture; the results are summarized in Table 1.

Table 1. Regioselectivities of the Ene Reaction of *p*-Nitronitrosobenzene (ArNO), 4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) and Singlet Oxygen ($^1O_2$) with the 1-Methylcycloalkenes **1-4**.



1 - 4 **1a - 6a** **1b - 6b**

entry	olefin (equiv)	n	enophile A=B	convn[a,b) [%]	mb[a,b) [%]	regioselectivity[a] twix		regioselectivity[a] twin	
1	**1** (2.0)	1	ArNO	24	88	82	(**1a**)	18	(**1b**)
2	**2** (2.0)	2	ArNO	22	82	> 95	(**2a**)	< 5	(**2b**)
3	**3** (2.0)	3	ArNO	35	85	91	(**3a**)	9	(**3b**)
4	*Z*-**4** (2.0)	4	ArNO	26	88	31	(**4a**)	69	(**4b**)
5	*Z*-**4** (2.0)	4	PTAD	50	97	16	(**5a**)	84	(**5b**)
6	*E*-**4** (1.0)	4	ArNO	> 95	75	> 95	(**4b**)	< 5	(**4a**)
7	*E*-**4** (1.0)	4	PTAD	> 95	70	> 95	(**5b**)	< 5	(**5a**)
8	*E*-**4** (1.0)	4	$^1O_2$	> 95	81	94	(**6b**)	< 5	(**6a**)

a) Conversion and mass balance (mb) relative to the olefin. b) Determined by ^{1}H-NMR spectroscopy, error ±5% of the stated value.

1-Methylcyclopentene (1). The reaction was conducted on 238 mg (2.88 mmol) of **1** according to the above general procedure. The results are given in Table 1 (entry 1).

1-Methylcyclohexene (2). The reaction was conducted on 278 mg (2.88 mmol) of **2** according to the above general procedure. The results are given in Table 1 (entry 2).

1-Methylcycloheptene (3). The reaction was conducted on 319 mg (2.88 mmol) of **3** according to the above general procedure. The results are given in Table 1 (entry 3).

***Z*-1-Methylcyclohexene (*Z*-4).** The reaction was conducted on 358 mg (2.88 mmol) of *Z*-**4** according to the above general procedure. The results are given in Table 1 (entry 4).

***E*-1-Methylcyclooctene (*E*-4).** The reaction was conducted on 179 mg (1.44 mmol) of *E*-**4** according to the above general procedure. The results are given in Table 1 (entry 6).

General Procedure for the Ene Reaction with 4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) on the NMR Scale. The alkene (150 or 300 μmol) was dissolved in 500 μL argon-saturated $CDCl_3$. To this solution were added 10 μL tetrachloroethane as internal standard and an ^{1}H-NMR spectrum was measured. Subsequently, 4-phenyl-1,2,4-triazoline-3,5-dione (52.5 mg, 300 μmol) was added at 0 ° C and the reaction mixture was stirred at this temperature for 24 h. The conversion, mass balance, and regioselectivity (*twix/twin*) were determined by ^{1}H-NMR analysis and are given in Table 1.[15]

***Z*-1-Methylcyclohexene (*Z*-4).** The reaction was conducted on 18.6 mg (150 μmol) of *Z*-**4** according to the above general procedure. . The results are given in Table 1 (entry 5).

***E*-1-Methylcyclohexene (*E*-4).** The reaction was conducted on 37.2 mg (300 μmol) of *E*-**4** according to the above general procedure. The results are given in Table 1 (entry 7).

Singlet-Oxygen Ene Reaction with *E*-1-Methylcyclohexene (*E*-4). A sample (37.2 mg, 300 μmol) of the cyclooctene *E*-**4** and 5 mol% of tetraphenylporphin were dissolved in 1 mL argon-saturated $CDCl_3$. To this solution were added 10 μL tetrachloroethane as internal standard and an ^{1}H-NMR spectrum was measured. The solution was irradiated with two Osram Violax NAV-T 400-W sodium lamps at -5 ° C, while a stream of dry oxygen gas was passed continuously through the reaction mixture. After 3 h, the conversion, mass balance, and regioselectivity (*twix/twin/lone*) were determined by ^{1}H-NMR analysis. The results are given in Table1 (entry 8).

Additional References

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