Preparation of 2-Nitromethyl-2-cycloalkenol and 2-Nitromethyl-2-cycloalkenone

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Synopsis. Oxidation of 1-nitromethylcycloalkenes with *m*-chloroperbenzoic acid afforded the corresponding 2-nitromethyl-2-cycloalkenols, which were further converted into 2-nitromethyl-2-cycloalkenones.

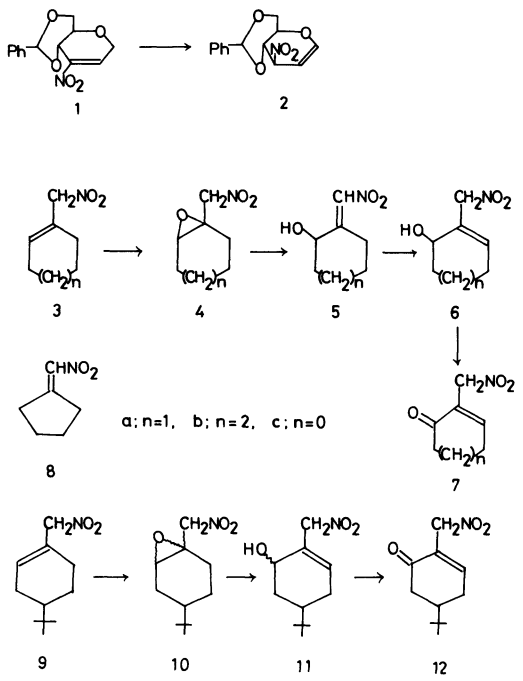
We found that the double bond of α-nitro alkene **1** migrated to give the β-nitro alkene **2** on treatment with triethylamine.[1] In order to clarify if such a facile double bond migration is caused by the conjugation of the double bond formed with the ring oxygen atom, we performed the epoxidation of 1-nitromethylcycloalkenes[2] and subsequent ring opening, anticipating that an exo double bond formed should migrate to the corresponding endo isomer.

Epoxidation of 1-nitromethylcyclohexene (**3a**) with *m*-chloroperbenzoic acid (MCPBA) afforded the epoxide **4a** in 96% yield. As suggested by Takamoto et al. in oxidation of α,β-epoxy ketone oximes,[3] the epoxide ring readily opened by treatment with sodium carbonate to give a mixture of the exo **5a** and endo isomers **6a**. Although complete purification of **5a** was not accomplished, its IR [3500 (OH), 1635 and 1505 cm^{-1} (C=C–NO_2)] and ^1H NMR spectra (olefinic proton at δ=7.17) made us possible to assign the exo structure. In the case of cycloheptene derivative **4b**, the exo isomer **5b** was isolated. Treatment of **4a** with triethylamine afforded **6a** in 83% yield, indicating that, among the hydrogen atoms activated by the nitro alkene moiety, H-1 which attached to the carbon atom having the hydroxyl group is less acidic than the alternative one (H-3). This may be partly attributable to the formation of alkoxide, which should deactivate H-1 and suppress an approach of a base by electrostatic repulsion. Compound **6a** thus formed has potential utility for synthetic purposes, since nitromethyl group thus introduced should be convertible into formyl,[4] nitrile,[5] nitrile oxide,[6] and the nitro group into arylthio,[7] arylsulfonyl groups,[7] and active methylene compounds.[8] Oxidation of **6a** with pyridinium chlorochromate (PCC) afforded the ketone **7a** in 58% yield.

Similar epoxidation of the cycloheptene **3b** gave the epoxide **4b** in 84% yield, of which ring opening with sodium carbonate and triethylamine gave **5b** and **6b** in 60 and 78% yield, respectively. Oxidation of **6b** with PCC afforded the ketone **7b** in 67% yield.

Contrary to the cases of other cycloalkanones, nitromethane condensation of cyclopentanone according to the method described by Eckstein et al.[9] gave a mixture of the exo **8** and endo isomers **3c**. The mixture, without separation, was oxidized with MCPBA to afford the epoxide **4c** and unchanged exo isomer **8**. Epoxide ring opening with triethylamine gave the alcohol **6c** (60%), of which oxidation with PCC gave the ketone **7c** in 41% yield.

Unfortunately, stereoselectivity of epoxidation was low; oxidation of 1-nitromethyl-4-*t*-butylcyclohexene (**9**) with MCPBA afforded a 3:1 mixture of the epoxides **10** (based on ^1H NMR spectroscopy) in 90% yield. Without separation of the mixture, it was treated with triethylamine to afford the allyl alcohol **11** in 97% yield and subsequent oxidation gave the ketone **12** (53% overall yield from **9**).



Experimental

IR spectra were recorded with a Hitachi 285 Infrared Spectrophotometer on sodium chloride plate. ^1H NMR spectra were determined in chloroform-*d* with tetramethylsilane as an internal standard with a Varian EM360A NMR Spectrometer. Column chromatography was carried out on silica gel (Wakogel, C-300). Analytical samples except for **12** were prepared by bulb to bulb distillation at the oven temperature as described.

General Procedure for the Epoxidation of 1-Nitromethylcycloalkene. To a solution of **3b** (1.55 g, 10 mmol) in dichloromethane (20 ml) was added MCPBA (1.9 g, 11 mmol), and the mixture was stirred until the starting material **3b** had disappeared in TLC (ca. 1 h) and then

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diluted with water. The aqueous layer was extracted with dichloromethane and the combined organic layers were successively washed with saturated aqueous sodium hydrogen carbonate, aqueous sodium hypochlorite, and saturated aqueous sodium chloride, dried, and evaporated to a syrup. It was purified by flash column chromatography with 3:1 (v/v) cyclohexane–benzene to give 1.44 g (84%) of 1-nitromethylcycloheptene oxide (**4b**): bp 117 °C (0.35 Torr, 1 Torr=133.322 Pa); IR 1540 cm^{-1} (NO_2); ^1H NMR δ=4.38 (2H, s, CH_2NO_2), 3.07 (1H, t, $J_{2,3}=J_{2,3'}=4.5$ Hz, H-2); Found: C, 55.76; H, 7.40; N, 7.81%. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18%.

1-Nitromethylcyclohexene Oxide (4a): Yield 96%, bp 78—80 °C (0.2 Torr); IR 1545 cm^{-1} (NO_2); ^1H NMR δ=4.38 (2H, s, CH_2NO_2), 3.13 (1H, t, $J_{2,3}=J_{2,3'}=2.0$ Hz, H-2); Anal. ($C_7H_{11}NO_3$) C, H, N.

1-Nitromethylcyclopentene Oxide (4c). Similar treatment of cyclopentenone (1 mmol) with nitromethane (1.5 mmol) and piperidine (0.2 ml) for 10 h gave a mixture of exo- and endo-products in the ratio of 1:2. Epoxidation of the crude product, followed by column chromatography with 9:1 (v/v) cyclohexane–benzene, gave successively the unreacted exo isomer (900 mg) and 1.05 g (72% yield, based on the starting endo isomer) of **4c**. Compound **4c**: bp 100 °C (0.35 Torr); IR 1550 cm^{-1} (NO_2); ^1H NMR δ=5.08, 4.61, 4.58, 4.11 (2H, AB type, CH_2NO_2), 3.40 (br. s, 1H, H-2); Anal. ($C_6H_9NO_3$) C, H, N.

2-Nitromethylene-1-cycloheptanol (5b). A mixture of **3b** (325.5 mg, 2.1 mmol), MCPBA (725 mg, 4.2 mmol), and dichloromethane (20 ml) was stirred for 1 h. To the mixture was added saturated aqueous sodium carbonate (20 ml) and the mixture was stirred for 8 h. Conventional work up gave a syrup, which was chromatographed with 3:1 (v/v) benzene–cyclohexane to give **6b** (8%) and **5b** (60%) in turn. Compound **5b**: bp 122 °C (0.35 Torr); IR 3450 (broad OH), 1635 and 1515 cm^{-1} (C=C-NO_2); ^1H NMR δ=7.29 (1H, s, $CHNO_2$), ca. 4.45 (1H, m, H-1); Anal. ($C_8H_{13}NO_3$) C, H, N.

General Procedure for Preparation of 2-Nitromethyl-2-cycloalkenol (6b). A solution of the epoxide **4b** (1.52 g, 8.9 mmol) in chloroform (10 ml) in the presence of triethylamine (0.1 ml) was kept at room temperature for 0.5 h. Conventional work up afforded a syrup. It was chromatographed with 3:1 (v/v) benzene–cyclohexane to give 1.19 g (78%) of the alcohol (**6b**), which was pure as judged from TLC and ^1H NMR spectroscopy: bp 125 °C (0.35 Torr); IR 3450 (broad OH), 1540 cm^{-1} (NO_2); ^1H NMR δ=6.05 (1H, br. t, $J_{3,4}=J_{3,4'}=6.5$ Hz, H-3), 4.99 (2H, s, CH_2NO_2), 4.55 (1H, m, H-1), 2.97 (1H, s, OH); Anal. ($C_8H_{13}NO_3$) C, H, N.

2-Nitromethyl-2-cyclohexenol (6a): Yield 83%, bp 125 °C (0.35 Torr); IR 3350 (OH), 1550 cm^{-1} (NO_2); ^1H NMR δ=6.03 (1H, br. t, $J_{3,4}=J_{3,4'}=3.3$ Hz, H-3), 5.16 (1H, d, J=14 Hz, $CHNO_2$), 4.76 (1H, d, $CHNO_2$), 4.25 (1H, br. t, $J_{1,6}=J_{1,6'}=4.0$ Hz, H-1), 3.20 (1H, br. s, OH); Anal. ($C_7H_{11}NO_3$) C, H, N.

2-Nitromethyl-2-cyclopentenol (6c): Yield 60%, bp 115 °C (0.35 Torr); IR 3370 (OH), 1550 cm^{-1} (NO_2); ^1H NMR δ=6.05 (1H, br. s, H-3), 5.04 (2H, s, CH_2NO_2), 4.81 (1H, m, H-1), 2.80 (1H, s, OH); Anal. ($C_6H_9NO_3$) C, H, N.

General Procedure for Preparation of 2-Nitromethyl-2-cycloalkenone (7b). To an ice-cooled solution of PCC (500 mg, 2.3 mmol) in dichloromethane (20 ml) was added dropwise a solution of the alcohol **6b** (164 mg, 0.96 mmol) in dichloromethane (2 ml) under a nitrogen atmosphere and the mixture was stirred for additional 3 h at ambient temperature and diluted with diethyl ether. After removal of a solid material by filtration, the filtrate was evaporated and the residue was chromatographed with 9:1 (v/v) benzene–ethyl acetate to give 109 mg (67%) of the ketone **7b**, which was pure as judged from TLC and ^1H NMR spectroscopy: bp 120 °C (0.35 Torr); IR 1670 (CO), 1550 cm^{-1} (NO_2); ^1H NMR δ=6.77 (t, 1H, $J_{3,4}=J_{3,4'}=6.0$ Hz, H-3), 5.03 (s, 2H, CH_2NO_2); Anal. ($C_8H_{11}NO_3$) C, H, N.

2-Nitromethyl-2-cyclohexenone (7a): Yield 58%, bp 120 °C (0.35 Torr); IR 1680 (CO), 1550 cm^{-1} (NO_2); ^1H NMR δ=7.09 (1H, t, $J_{3,4}=J_{3,4'}=4.0$ Hz, H-3), 4.95 (2H, s, CH_2NO_2); Anal. ($C_7H_9NO_3$) C, H, N.

2-Nitromethyl-2-cylopentenone (7c): Yield 41%, bp 95 °C (0.35 Torr); IR 1705 (CO), 1550 cm^{-1} (NO_2); ^1H NMR δ=7.81 (1H, br. s, H-3), 5.06 (2H, s, CH_2NO_2); Anal. ($C_6H_7NO_3$) C, H, N.

5-*t*-Butyl-2-nitromethyl-2-cyclohexenone (12): According to the method described by Eckstein et al.[9] **9** was obtained in 60% yield from 4-*t*-butylcyclohexanone; bp 115 °C (0.45 Torr); IR 1550 cm^{-1} (NO_2); ^1H NMR δ=5.89 (1H, br.s, H-2) and 4.77 (2H, s, CH_2NO_2); Anal. ($C_{11}H_{19}NO_2$) C, H, N.

Similar epoxidation of **9** afforded a 3:1 mixture of **10** as judged from its ^1H NMR spectrum, the epoxide ring of which was opened by treatment with triethylamine, followed by oxidation with PCC, to give **12** in 53% overall yield (from **9**); syrup, purified by column chromatography without distillation; IR 1675 (CO), 1550 cm^{-1} (NO_2); ^1H NMR δ=7.1 (1H, m, H-3), 4.98 (2H, s, CH_2NO_2); Found: C, 62.82; H, 8.08; N, 6.28%. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63%.

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