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Synthesis of 2-(1-Nitroalkylidene)-cycloalkanones

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SYNTHESIS OF 2-(1-NITROALKYLIDENE)-CYCLOALKANONES

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Abstract : Reaction of 1-(1-nitroalkyl)-cycloalkenes epoxide with silica gel afforded the corresponding 2-(1-nitroalkylidene)-cycloalkanols which were further oxidized with chromic acid-sulfuric acid in 2-(1-nitroalkylidene)-cycloalkanones.

Recently Vankar, Bawa and Kumaravel have reported the synthesis of 3-nitrocyclohex-2-en-1-one (**Ia**), 3-nitrocyclohept-2-en-1-one (**Ib**)[1] and the preparation of interesting synthetic intermediates from the reaction of **Ia** acetal with various nucleophiles.[2] Corey and Estreicher reported the synthesis of **Ia** and 3-nitrocyclopent-2-en-1-one **Ic**.[3] They showed their usefulness in regioselective Diels-Alder chemistry.[3]

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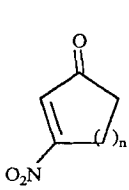
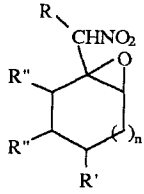
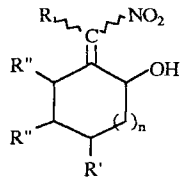


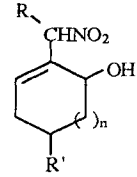
Ia n = 2
b n = 3
c n = 1



III



IV



V

Sakakibara, Manandhar, Ohkita and Ishido performed the oxidation of some 1-nitromethylcycloalkenes into **III** (R = R" = H, R' = H, ^{t}Bu) and studied epoxide ring opening by bases.[4] The exo double bond of the likely kinetically controlled products **IV** readily migrates to the corresponding endo isomers **V** (R = H, R' = H, ^{t}Bu). However pure **IV** was isolated in one case using sodium carbonate (n = 2, R = R' = R" = H, 60 % yield).

We report here a method which ensures regiospecificity in the opening of epoxide ring of **III** and affords exo isomers **IV** in good yields. This was carried out using silica gel usually without solvent (a small amount of CCl_4 was used to dissolve **IIIg**). Oxidation of **IV** with Jones reagent gave β-nitroenones **VI**, except for **IVh** and for E isomers of **IVc-d** which remained unchanged (Table). (Z)-**VI** were the single isomers isolated when R = Me or Et; (E)-**VI** were the main or the single isomers obtained when R = H.

E/Z attributions were carried out as follows:

- by IR[5] : $\nu(NO_2)^{Asym}$ Z = 1532-1524 cm^{-1} > $\nu(NO_2)^{Asym}$ E = 1528-1520 cm^{-1}; $\nu(NO_2)^{Sym}$ Z = 1364-1357 cm^{-1} > $\nu(NO_2)^{Sym}$ E = 1353-1340 cm^{-1}.

- by UV[5] : (E)-γ-hydroxy-α-nitroolefines and (E)-β-nitroenones showed stronger

absorptions than the corresponding (Z)-compounds in the wave length region of 260-275 nm (NO_2 group).

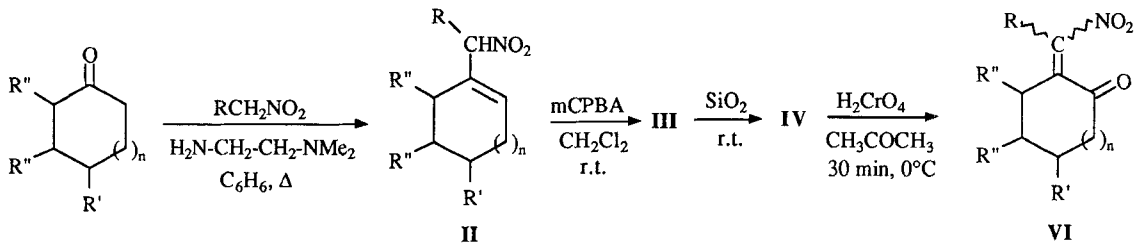
- by ^1H NMR[6] : **IVa-b, e-h** : δ (=C-H)$_E$ = 7.27-7.05 ppm > δ (=C-H)$_Z$ = 7.12-6.82 ppm. **IVa-b, e-g** : δ (C<u>H</u>-OH)$_Z$ = 5.47-5.08 ppm > δ (C<u>H</u>-OH)$_E$ = 4.69-4.20 ppm. **VIa-b, e-h** : δ (=C-H)$_E$ = 7.49-7.33 ppm > δ (=C-H)$_Z$ = 6.84-6.80 ppm.

Experimental Section

Melting points were determinated on a Tottoli melting points apparatus and are reported uncorrected. Infrared spectra were recorded on Perkin-Elmer VP 1750 and System 2000 spectrophotometers. Proton NMR spectra were recorded at 400 MHz on a Brücker AM-400 instrument. ^1H NMR shifts are given in parts per million from Me_4Si in $CDCl_3$ solvent. Allylic nitrocompounds **II** were prepared from the corresponding ketones and nitroalcanes according to the procedure of Tamura, Sato and Oda.[7]

Preparation of nitroepoxides III. Nitroepoxides **III** were prepared by oxidation of the corresponding allylic nitrocompounds with 1.1 eq. of mCPBA in methylene chloride under an inert atmosphere.[8]

General procedure for the opening of nitroepoxides III. Preparation of IV. Silica gel (Merck 70-230 Mesh ASTM) (4.35 g, $7.25.10^{-2}$ mol) was added at room temperature to the nitroepoxide **III** (4.35 g). The resulting mixture was mechanically stirred during 15 min and allowed to stand at room temperature for the time indicated in Table. 100 ml of ether were then added and the reaction mixture filtered off. Silica gel was washed several times with ether and methylene chloride. The combined organic layers were concentrated under reduced pressure at room



					II		III	IV			VI	
Entry	n	R	R'	R"	E/Z[a]	Yield[b] %	Yield[b] %	Time (h)	E/Z	Yield[c] %	E/Z	Yield[c] %
a	0	H	H	H	100/0	54	70	6	83/17	86	100/0	20
b	1	H	H	H	"	95	90	8	73/27	88	92/8	89
c	1	Me	H	H	"	45	77	18	25/75	78	0/100	73
d	1	Et	H	H	"	55	96	48	35/65	64	0/100	63
e	1	H	Me	H	"	89	80	24	84/16	90	100/0	91
f	2	H	H	H	"	71	92	8	83/17	91	82/18	87
g	7	H	H	H	72/28	99	99	8	74/26	77	75/25	87
h	1	H	H	C_6H_4	100/0	68	99	8	100/0	81	-	-

(a) Determined by ^1H NMR after purification ; (b) Yields of distillated products ; (c) Yields after chromatography.

temperature and the resulting γ-hydroxy-α-nitroolefine **IV** purified by column chromatography.

IVa : (E) and (Z)-2-nitromethylene cyclopentanol. E/Z = 83/17. IR : 3420, 1640, 1521 and 1345 cm-1. ^{1}H NMR : E (δ) : 7.22 (br s, 1 H); 4.72-4.65 (m, 1 H); 3.08-3.02 (m, 2 H); 2.26-1.59 (m, 4 H). Z (δ) : 7.12 (br s, 1 H); 5.19-5.14 (m, 1 H); 3.08-3.02 (m, 2 H); 2.26-1.59 (m, 4 H).

IVb : (E) and (Z)-2-nitromethylene cyclohexanol. E/Z = 73/27. IR : 3425, 1641, 1517 and 1345 cm-1. ^{1}H NMR : E (δ) : 7.22 (br s, 1 H); 4.26-4.22 (m, 1 H); 3.65-3.60 (m, 1 H); 2.30-1.40 (m, 8 H). Z (δ) : 6.83 (br s, 1 H); 5.49-5.46 (m, 1 H); 3.65-3.60 (m, 1 H); 2.30-1.40 (m, 8 H).

IVc : (E) and (Z)-2-methyl-2-nitromethylene cyclohexanol. E/Z = 25/75. mp_E = 66°C; mp_Z = 46°C. IR : 3418, 1652, 1521 and 1358 cm-1. ^{1}H NMR : Z (δ) : 4.63 (br t, J = 3 Hz, 1 H); 2.22 (d, J = 1.8 Hz, 3 H); 2.50-1.25 (m, 9 H). E (δ) : 4.60 (br t, J = 3 Hz, 1 H); 2.17 (d, J = 1.5 Hz, 3 H); 2.50-1.25 (m, 9 H).

IVd : (E) and (Z)-2-ethyl-2-nitromethylene cyclohexanol. E/Z = 35/65. mp_E = 54°C. IR : 3425, 1650, 1521 and 1365 cm-1. ^{1}H NMR : Z (δ) : 4.64 (br t, J = 3 Hz, 1 H); 2.60 (br q, J = 7.5 Hz, 2 H); 2.34-2.26 (m, 2 H); 2.08-1.20 (m, 6 H); 1.10 (t, J = 7.5 Hz, 3 H). E (δ) : 4.51 (br t, J = 3 Hz, 1 H); 2.54 (br q, J = 7.5 Hz, 2 H); 2.34-2.26 (m, 2 H); 2.08-1.20 (m, 6 H); 1.10 (t, J = 7.5 Hz, 3 H).

IVe : (E) and (Z)-5-methyl-2-nitromethylene cyclohexanol. E/Z = 84/16. IR : 3468, 1638, 1517 and 1347 cm-1. ^{1}H NMR : E (δ) : 7.05 (br s, 1 H); [7.23 (br s, 1 H)]; 4.34-4.20 (m, 1 H); 3.78-3.72 (m, 1 H); 3.11-3.03 (m, 1 H); 2.85-2.69 (m, 1 H); 2.33-1.70 (m, 4 H); 1.57-1.48 (m, 1 H); 0.98 (d, J = 6.7 Hz, 3 H); [0.96 (d, J = 6.7 Hz, 3 H)]. Z (δ) : 6.82 (br s, 1 H); 5.22-5.08 (m, 1 H); 3.78-3.72 (m, 1 H); 3.11-3.03 (m, 1 H); 2.85-2.69 (m, 1 H); 2.33-1.70 (m, 4 H); 1.57-1.48 (m, 1 H); 0.91 (d, J = 6.4 Hz, 1 H).

IVf : (E) and (Z)-2-nitromethylene cycloheptanol. E/Z = 83/17. IR : 3461, 1631, 1518 and 1344 cm-1. 1H NMR : E (δ) : 7.27 (br s, 1 H); 4.48-4.41 (m, 1 H); 1.83-1.74 (m, 2 H); 1.56-1.47 (m, 2 H); 1.36-1.26 (m, 6 H). Z (δ) : 6.97 (br s, 1 H); 5.13-5.07 (m, 1 H); 1.83-1.74 (m, 2 H); 1.56-1.47 (m, 2 H); 1.36-1.26 (m, 6 H).

IVg : (E) and (Z)-2-nitromethylene cyclododecanol. E/Z = 74/26. IR : 3453, 1634, 1520 and 1347 cm-1. 1H NMR : E (δ) : 7.26 (br s, 1 H); 4.47-4.43 (m, 1 H); 2.89-1.25 (m, 20 H). Z (δ) : 6.94 (br s, 1 H); 5.55-5.50 (m, 1 H); 2.89-1.25 (m, 20 H).

IVh : (E)-2-nitromethylene dihydronaphtalenol. IR : 3468, 1613, 1514 and 1329 cm-1. 1H NMR (δ) : 7.60-7.24 (m, 5 H); 5.44 (br t, J = 4.2 Hz, 1 H); 3.19-3.11 (m, 1 H); 2.72-2.66 (m, 1 H); 2.18-1.95 (m, 2 H).

General procedure for the preparation of β-nitroenones VI. To an ice-cooled solution of the nitroalcohol **IV** (20.10^{-3} mol) in dry acetone (5 ml) was added dropwise Jones reagent (7.40 ml) under a nitrogen atmosphere. The mixture was stirred at 0°C until the starting material disappeared (TLC, 10-30 min) then diluted with water. The aqueous layer was extracted twice with ether. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo at room temperature. The resulting β-nitroenone **VI** was purified by flash column chromatography.

VIa : (E)-2-nitromethylene cyclopentanone. IR : 1734, 1642, 1525 and 1350 cm-1. 1H NMR (δ) : 7.49-7.47 (m, 1 H); 3.27 (td, J = 7.30 Hz, 2 H); 2.51 (t, J = 7.8 Hz, 2 H); 2.16-2.06 (m, 2 H).

VIb : (E) and (Z)-2-nitromethylene cyclohexanone. E/Z = 92/8. IR : 1709, 1620, 1528 and 1347 cm-1. 1H NMR : E (δ) : 7.41 (t, J = 2.3 Hz, 1 H); 3.12 (2 t, J = 6.7 Hz, 2 H); 2.58 (t, J = 6.7 Hz, 2 H); 2.00-1.92 (m, 2 H); 1.89-1.82 (m, 2 H).

Z (δ) : 6.82 (br s, 1 H); 3.12 (2 t, J = 6.7 Hz, 2 H); 2.58 (t, J = 6.7 Hz, 2 H); 2.00-1.92 (m, 2 H); 1.89-1.82 (m, 2 H).

VIc : (Z)-2-methyl-2-nitromethylene cyclohexanone. mp = 37°C. IR : 1702, 1645, 1528 and 1368 cm-1. 1H NMR (δ) : 2.56 (t, J = 6.7 Hz, 2 H); 2.54 (2 t, J = 6.7 Hz, 2 H); 2.32 (t, J = 1.6 Hz, 3 H); 1.99-1.91 (m, 2 H); 1.86-1.78 (m, 2 H).

VId : (Z)-2-ethyl-2-nitromethylene cyclohexanone. IR : 1702, 1638, 1528 and 1361 cm-1. 1H NMR (δ) : 2.67 (q, J = 7.7 Hz, 2 H); 2.52 (t, J = 6.6 Hz, 2 H); 2.49 (t, J = 6.6 Hz, 2 H); 1.97-1.88 (m, 2 H); 1.84-1.76 (m, 2 H); 1.10 (t, J = 7.7 Hz, 3 H).

VIe : (E)-5-methyl-2-nitromethylene cyclohexanone. IR : 1709, 1620, 1525 and 1351 cm-1. 1H NMR (δ) : 7.42 (br s, 1 H); 3.54-3.45 (m, 1 H); 2.80-2.70 (m, 2 H); 2.23-1.96 (m, 3 H); 1.52-1.40 (m, 1 H); 1.09 (d, J = 6.4 Hz, 3 H).

VIf : (E) and (Z)-2-nitromethylene cycloheptanone. E/Z = 82/18. IR : 1709, 1617, 1530 and 1350 cm-1. 1H NMR : E (δ) : 7.33 (br s, 1 H); 2.88-2.86 (m, 2 H); 2.74-2.69 (m, 2 H); 1.88-1.77 (m, 6 H). Z (δ) : 6.84 (br s, 1 H); 2.78-2.73 (m, 2 H); 2.42-2.37 (m, 2 H); 1.88-1.77 (m, 6 H).

VIg : (E) and (Z)-2-nitromethylene cyclododecanone. E/Z = 75/25. IR : 1709, 1615, 1526 and 1348 cm-1. 1H NMR : E (δ) : 7.45 (br s, 1 H); 2.95-2.89 (m, 2 H); 2.77-2.72 (m, 2 H); 1.84-1.25 (m, 16 H). Z (δ) : 6.80 (br s, 1 H); 2.82-2.77 (m, 2 H); 2.42-2.36 (m, 2 H); 1.84-1.25 (m, 16 H).

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