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## 1,3-Dipolar-Cycloaddition of Benzylazide to (+)-Limonene: A Protection Cycle for the 8,9-Double Bond.

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Abstract. A method for protecting the 8,9-double bond of (+)-limonene (1) is described. The key step is the 1,3-dipolar-cycloaddition of benzylazide to 1, which affords N-benzyl-N-[9-(1-p-menthenylidene)]-amine (2) and N-benzyl-N-[8,9-(1-p-menthenylidene)]-amine (3).

(+)-Limonene (1) can be easily obtained from orange peels in high purity,<sup>1</sup> which led to its being chosen as a starting material in our laboratories <sup>2,3</sup>. In some reactions there were serious problems due to the competition between the 1,2- and the 8,9-double bonds of  $1^{-3}$ . In order to avoid loss of time and material a strategy was devised to protect the 8,9-double bond: using the 1,3-dipolar cycloaddition of benzylazide to 1 which should lead to the imine 2, reducible to the amine 4; after methylation of 4 to produce 5, Hoffman or Cope Elimination conditions could be used to regenerate 1. As a bonus it was hoped that 1-p-menthen-9-al, a natural product found in some plants,<sup>4</sup> and a potentialy useful starting material for preparation of bisabolanes,<sup>5</sup> would be obtained through the hydrolysis of 2.



Usually imines do not react with azides, but their tautomers, the enamines, react very quickly<sup>6</sup>. In order to avoid the reaction of benzylazide with the enamine tautomer of 2, a large excess of 1 was used: 189.13 g (1.39 mol) of 1 and 30.69 g (0.23 mol) of benzylazide were heated at 160 °C for 3.0 h, under N<sub>2</sub> atmosphere. The excess 1 was distilled off at 118-122 °C/42 Torr, and the residual liquid was distilled at 115-145 °C/1 Torr to afford 46.71 g of a pale yellow liquid. Through flash chromatography of 800 mg , with AcOEt/hexane (1:4) as eluent, 296 mg of 3,<sup>7</sup> (31.2 % yield<sup>8</sup>) were isolated.

With GC-MS three main peaks were observed during the analysis of the yellow liquid. Two of them were due to the diastereoisomers of 3, and the third was attributed to the imine  $2,^9$  that decomposed under the conditions used for its purification. IR and <sup>1</sup>H NMR spectra<sup>10</sup> of the yellow liquid were also in agreement with the structures proposed for 2 and 3.

As expected the cycloaddition ocurred mainly at the 8,9-double bond (the <sup>1</sup>H NMR of the yellow liquid presented very weak signals in the region of the position 9 of 1), probably due to steric effects <sup>6</sup>. Based on the literature about thermal decomposition of triazolines, <sup>6</sup> possible mechanisms for the formation of 2 and 3 are depicted below. We strongly agree with the suggestion of the referee that homolysis followed by rearrangement of 1,3-diradicals would also explain the products and is energetically more plausible.



Another possible route for the formation of 3 would be the decomposition of the benzylazide to the corresponding nitrene, that can add to the double bond of 1. But the low rate of decomposition of benzylazide when heated in decalin seems to rule out this possibility.

Although the yield of 2 was low (the <sup>1</sup>H NMR spectrum suggests a 2/3 molar ratio of 1:1), we reacted 23.66 g of the yellow liquid with 14.00 g (0.35 mol) of NaBH<sub>4</sub> 95% (NaBH<sub>4</sub>/2  $\ge$  3.5) in 580 ml of dry <sup>1</sup>PrOH at 30 °C for 48 h under anhydrous atmosphere. After the usual work up procedures, the residue was distilled at 110-135 °C/1 Torr to afford 19.67 g of a clear, colorless liquid. From 700 mg of this liquid, 263 mg of 3,<sup>7</sup> (26% yield<sup>8</sup>) and 324 mg of 4,<sup>11</sup> (32% yield,<sup>8</sup>) were isolated by flash chromatography with AcOEt/hexane (1:1) as eluent.

To 10.65 g of the crude reduction product (distilled at 110-155  $^{\circ}$ C/1 Torr), cooled at 0 $^{\circ}$ C, 9.34 ml (0.18 mol) of HCO<sub>2</sub>H 88% and 9.24 ml of formol (0.12 mol of formaldehyde) were added and, after 2 min , the flask was imersed in boiling water for 2 min<sup>12</sup>. 160 ml of NaOH 10% were added and the mixture was extracted with hexane (3 x 50 ml). After drying and removing the hexane, the residue was distilled at 119-144  $^{\circ}$ C/1 Torr to afford 6.38 g of clear liquid. No 3 could be detect by GC, and 370 mg of 5<sup>13</sup> (29% yield<sup>8</sup>) were isolated from 470 mg of the crude product by flash chromatography using AcOEt/hexane (1:4) as eluent.

1.519 g of crude 5 (distilled at 119-144 °C/1 Torr), 4 ml of <sup>t</sup>BuOH and 1.8 ml ( $\cong$ 6 mmol) of H<sub>2</sub>O<sub>2</sub> 30% were stirred at 25 °C for 110 h. 5 mg of MnO<sub>2</sub> were added to destroy the excess H<sub>2</sub>O<sub>2</sub>, and the mixture was filtrered on Celite. The solvent was evaporated and the residue was kept at 25°C/1Torr for 7 h. After that, it was heated at 150°C/1 Torr for 1 h, and the liquid condensed in a trap cooled at - 78°C was purified by column chromatography with hexane as eluent, <sup>14</sup> yielding 200 mg of 1 (7.3% total yield<sup>8</sup>).

The yields presented are not satisfactory for a good protection cycle, but we believe that considerable improvements can be made.

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## **References and notes.**

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- (7) m/z (70 eV) 241 (4%), 226 (10%), 173 (15%), 147 (50%), 91 (100%); IR (neat) 3026, 2962-2860, 1449, 1382, 1150, 2000-1660 (harmonics of monosubstituted benzene), 1603-1494, 797 (characteristic of the 1,2-double bond of 1), 731 and 697 (monosubstituted benzene) cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.18 (s, CH<sub>3</sub>), 1.22 (d, J= 4.2 Hz, aziridine ring), 1.61 (s, CH<sub>3</sub>C=C), 1.72 (s, CH<sub>3</sub>C=C), 1.83 (d, J= 4.2 Hz, aziridine ring), 3.63 (s, CH<sub>2</sub>Ph), 3.65 (s, CH<sub>2</sub>Ph), 5.35 (s, CH=C), 7.2-7.3 (CH aromatic); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  12 (CH<sub>3</sub> linked to the aziridine ring), 24 (CH<sub>3</sub>), 25.5 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 27.6 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 30.9 (CH<sub>2</sub>), 39.7 and 37.9 (CH<sub>2</sub> from the aziridine ring), 42.3 (C from the aziridine ring), 42.9 and 43.1 (saturated CH), 57.0 and 57.2 (CH<sub>2</sub>Ph), 120.5 and 120.8 (CH olefinic), 126.6-140.8 (aromatic ring), 133.5 and 133.9 (C olefinic).
- (8) Isolated yield normalized for benzylazide.
- (9) m/z (70 eV) 241 (5%), 173 (10%), 147 (100%), 132 (30%), 118 (15%), 91 (90%), 79 (10%), 65 (20%).
- (10) Yellow liquid: IR (neat) 3100 2850, 1650 (C=N or C=C-N axial), 1450, 1380 1300, 798 (characteristic of the 1,2-double bond of 1), 732 and 697 (monosubstituted benzene) cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.08 (d, J= 5.7 Hz, CH<sub>3</sub>CH of 2), 1.10 (d, J=5.7 Hz, CH<sub>3</sub>CH of 2), 1.17 (s, CH<sub>3</sub> linked to the aziridine ring of 3), 1.22 (d, J= 4.2 Hz, CH<sub>2</sub> of the aziridine ring of 3), 1.61 1.64 (CH<sub>3</sub>C=C), 1.83 (d, J= 4.2 Hz, CH<sub>2</sub> of the aziridine ring), 3.64 (CH<sub>2</sub>Ph of 3), 4.56 (CH<sub>2</sub>Ph of 2), 5.35 (CH=C; characteristic of the 1,2-double bond of 1), 7.25 7.32 (CH aromatic).
- (11) m/z (70 eV) 243 (20%), 186 (10%), 120 (80%), 107 (15%), 91 (100%), 65 (10%); IR (neat) 3330 (NH), 3000 2890, 1451, 1376, 1120 900, 798 (characteristic of the 1,2-double bond of 1), 736 and 698 (monosubstituted benzene) cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.88 (d, J= 6.9, CH<sub>3</sub>CH), 0.91 (d, J= 6.6 Hz, CH<sub>3</sub>CH), 1.57 (NH), 1.63 (s, CH<sub>3</sub>C), 2.4 2.7 (m, CHCH<sub>2</sub>N), 3.7 (dd, J= 13.33 Hz and J= 13.43Hz, NCH<sub>2</sub>Ph), 5.36 (CH=C, characteristic of the 1,2-double bond of 1), 7.3 (m, aromatic); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 14.67 and 15.05 (CH<sub>3</sub>), 23.70 (CH<sub>3</sub>C=C), 25.52 (CH<sub>2</sub>), 27.40 (CH<sub>2</sub>), 27.63 (CH<sub>2</sub>), 29.84 (CH<sub>2</sub>), 30.85 (CH<sub>2</sub>), 31.00 (CH<sub>2</sub>), 36.68 (CH), 36.89 (CH), 37.66 (CH), 37.87 (CH), 53.56 (CH<sub>2</sub>N), 53.71 (CH<sub>2</sub>N), 54.32 (CH<sub>2</sub>N), 120.92 (CH olefinic), 126.82 128.35 (CH aromatic), 133.94 (CH olefinic), 140.7 (C aromatic).
- (12) Adapted from: Clarke, H.T.; Gillespie, H.B.; Weisshauss, S.Z. J. Am. Chem. Soc. 1933, 55, 4571-87.
- (13) m/z (70 eV) 257 (6%), 134 (60%), 91 (100%), 65 (20%); IR (neat) 3100 2850, 1945 1680 (harmonics characteristic of monosubstituted benzene), 1650, 1602, 1451, 1366, 1050, 798 (characteristic of the 1,2-double bond of 1), 737 and 697 (monosubstituted benzene) cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  0.862 (d, J= 6.9 Hz, CH<sub>3</sub>CH), 0.865 (d, J= 6.9 Hz, CH<sub>3</sub>CH), 1.637 (s, CH<sub>3</sub>C), 2.146 (s, CH<sub>3</sub>N), 2.156 (s, CH<sub>3</sub>N), 2.070 2.360 (m, CH<sub>2</sub>N), 3.35 3.55 (CH<sub>2</sub>Ph), 5.36 (s, CH olefinic), 7.27 7.29 (CH aromatic),
- (14) Adapted from: Cope, A.C.; Trumbull, E.R. Org. React. 1960, 2, 317 493.

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