Honors Cup Synthetic Proposal

Section: 250
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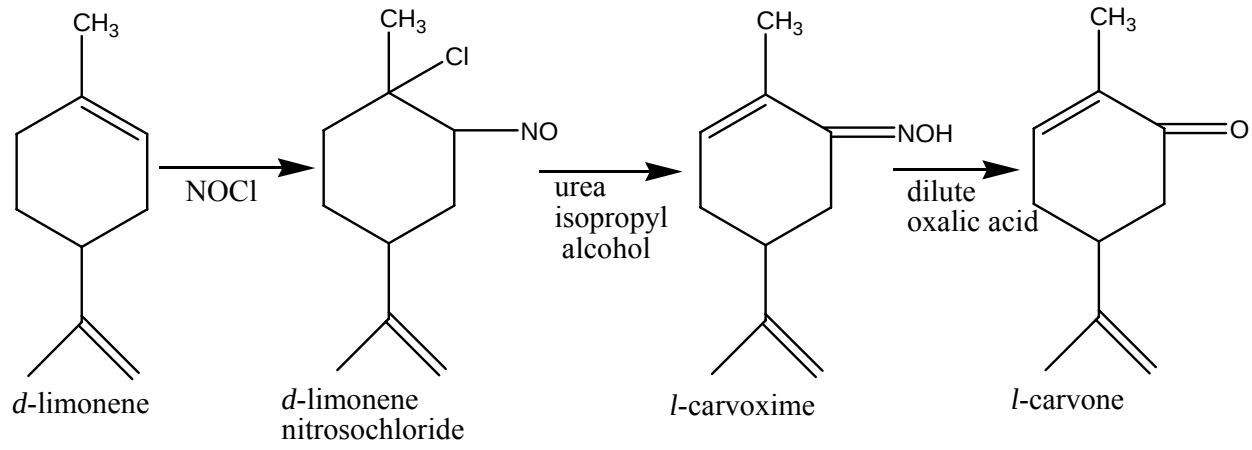
Title: Synthesis of *l*-carvone from *d*-limonene

Introduction:

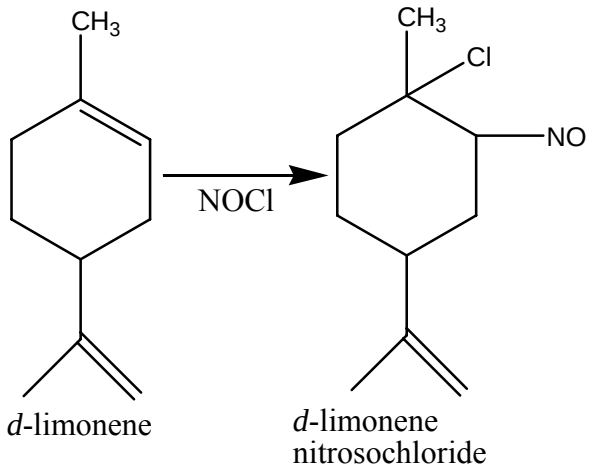
The synthesis of *l*-carvone creates a spearmint scent. It is rather interesting to note that the enantiomer of *l*-carvone, *d*-carvone, smells like caraway seeds. This implies that human olfactory receptors have chiral groups that respond uniquely to the different enantiomers. In addition, *l*-carvone is used to flavor Wrigley's Spearmint gum. The substance is also found in some air fresheners, toothpaste, and medicinal products for its cooling effects.[5] *l*-Carvone was synthesized in a three step mechanism from *d*-limonene, a chemical responsible for the smell of oranges. The intermediates, as labeled below, are *d*-limonene nitrosochloride and *l*-carvoxime. The purpose of this synthesis is to transform the citrus scent into a spearmint scent by altering the chemical properties of the preliminary substance, *d*-limonene.

Overall synthetic reaction scheme:



Step 1

Synthetic transformation 1:



d-limonene

d-limonene nitrosochloride

Experimental 1:

This synthesis was scaled down by a factor of 10.22 from the original text by reducing the molar ratio.

***d*-Limonene nitrosochloride**. A solution of 3.91 mL (0.051 mol) of isopropyl alcohol and 4.00 g (0.030 mol) of *d*-limonene was prepared in a 100 mL three necked round bottomed flask. An ice bath was used to cool the solution below 10 ^{0}C and the round bottomed flask was capped with a septum. 7.82 mL (0.102 mol) of isopropyl alcohol, a concentrated aqueous solution of 2.03 g of sodium nitrite (0.030 mol), and 11.74 mL (0.386 mol) of concentrated hydrochloric acid were added drop wise (simultaneously) using three addition funnels. Preliminary temperature was maintained. The solution was stirred for 15 minutes after the components were added and then the mixture was cooled in the refrigerator for one hour. The substance was filtered using vacuum filtration. Ethanol was placed in an ice bath until properly chilled. The resultant white slurry left over from the vacuum filtration was then washed two times with the chilled ethanol. A proton NMR was used to determine a change in the shift of the proton at the site where a new carbon to nitrogen bond was formed: this proton moved up field due to the loss of the double bond.[1,3]

Expected yield: 80.7 % 15.8 g

Safety, disposal and green issues 1:[6,8,9]

R-(+)-limonene is an irritant and dangerous for the environment. This compound is flammable, a skin irritant, a skin sensitizer, toxic for aquatic organisms, and eventually greatly affects the aquatic environment. For safety reasons, avoid contact with skin by wearing rubber gloves. This compound is not environmentally safe, and must be prevented from being released into the environment. R-(+)-Limonene is considered hazardous, and must be disposed of in the hazardous waste container.

Isopropyl alcohol is highly flammable. This compound is also a skin and eye irritant. Wear rubber gloves and safety goggles. In case of eye contact, wash eye thoroughly with water and seek help. Isopropyl alcohol should be disposed as hazardous waste in the appropriate container.

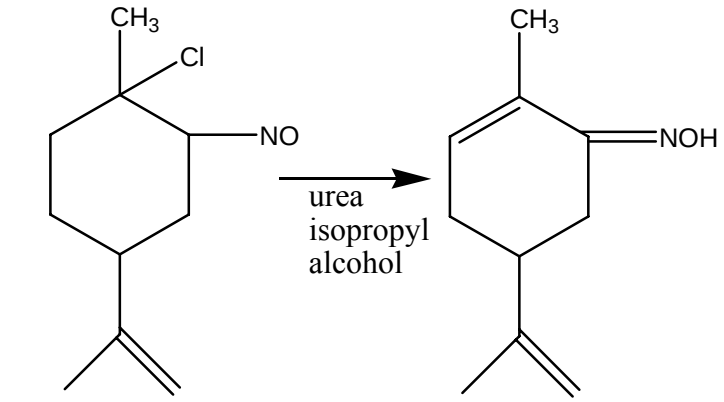
Hydrochloric acid is a corrosive substance. This compound causes burns and irritates the respiratory system. In case of eye contact, wash eye thoroughly with water and seek help. You must wear protective clothing, rubber gloves, and safety goggles. If there is an explosion or fire involving hydrochloric acid, then do not breathe in the fumes. Be sure to wear protective respiratory equipment when spraying or fumigating. Hydrochloric acid should be disposed as hazardous waste in the appropriate container.

Sodium nitrite is dangerous for the environment, toxic, and an oxidizing agent. If sodium nitrite is put in contact with combustible material, there could be a fire. Do not swallow, because of this compound's toxicity. This compound is especially toxic towards aquatic organisms. Seek help if this substance is involved in an accident. This compound is not environmentally safe, and must be prevented from being released into the environment. Sodium nitrite should be disposed as hazardous waste in the appropriate container.

Ethanol is highly flammable. The container ethanol is in must be kept closed, dry, and under the hood. Be sure to keep the substance under the hood, and do not smoke near it because of possible ignition. Keep ethanol away from food and beverages. Ethanol should be disposed as hazardous waste in the appropriate container.

Step 2

Synthetic transformation 2:



d-limonene nitrosochloride

l-carvoxime

Experimental 2:

This synthesis was scaled down by a factor of ten from the original text by reducing the molar ratio.

***l*-Carvoxime**. 5.0 g (0.025 mol) of *d*-limonene nitrosochloride and 2.0 g (0.033 mol) of urea were dissolved in 25.0 mL (0.326 mol) of isopropyl alcohol in an appropriately sized round bottomed flask. The solution was heated under reflux in a sand bath for one hour. The solution was poured into an excess of water, where the desired product separated from the aqueous layer. The resultant oil layer crystallized upon standing. The mixture was separated using vacuum filtration. The product was washed with water and dried. An IR and a proton NMR were run to prove the presence of the hydroxyl group and the removal of the two hydrogen atoms from the ring at the sites of the new double bonds. [1,4]

Expected yield: 99 % 4.07 g

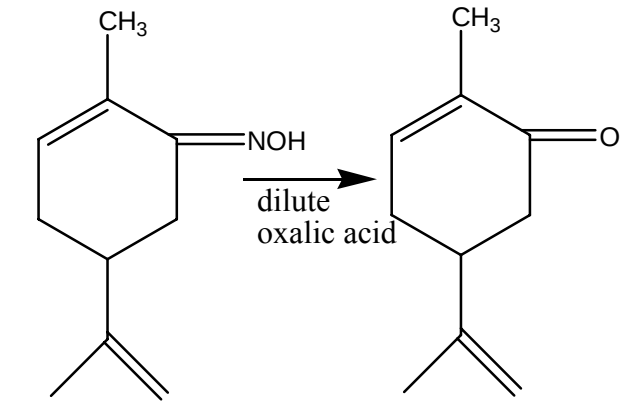
Safety, disposal and green issues 2: [6,8,9]

Isopropyl alcohol is highly flammable. This compound is also a skin and eye irritant. Wear rubber gloves and safety goggles. In case of eye contact, wash eye thoroughly with water and seek help. Isopropyl alcohol should be disposed as hazardous waste in the appropriate container.

There are no safety precautions necessary for urea.

Step 3

Synthetic transformation 3:



l-carvoxime *l*-carvone

Experimental 3:

This synthesis was scaled down by a factor of five from the original text by reducing the molar ratio.

***l*-Carvone.** 2.00 g (0.012 mol) of *l*-carvoxime and a 20 mL aqueous solution of 5 % oxalic acid were added to an appropriately sized round bottom flask. The mixture was heated under reflux in a sand bath for two hours. The mixture was then steam distilled, and the distillate was extracted with ether. Using sodium sulfate, the ethereal solution was dried and then fractionally distilled. The product was tested using proton NMR and IR to prove the existence of the carbonyl group and a change in the number hydrogen atoms, confirming that *l*-carvone was truly made. These spectra were compared against the confirmed spectra of *l*-carvone (see figure **1** for the proton NMR spectrum). The optical activity of *l*-carvone is -61^{o} and can be determined as different from its enantiomer by testing its optical rotation. [3,4]

Expected yield: 78 % 1.42 g

Safety, disposal and green issues 3: [6,8,9]

Oxalic Acid is a harmful substance. This compound is harmful in contact with skin and harmful if swallowed. Avoidance with skin and eyes can be prevented by wearing rubber gloves and safety goggles. Oxalic acid should be disposed of in a proper waste container, and it is not considered hazardous waste.

Diethyl ether solution is extremely flammable and harmful. Precaution must be taken with this substance because when mixed with oxidizing substances the result could be explosive. The substance is harmful if swallowed. Be sure to keep the substance under the hood, and do not smoke near it because of possible ignition. Do not dispose of the substance through the drains. Diethyl ether should be disposed of as hazardous waste in the appropriate container.

***l*-Carvone** is harmful if swallowed and should be disposed of in a proper waste container, however, it is not considered hazardous waste.

Sodium Sulfate is hygroscopic and must be stored in a dry environment. This compound should be disposed of in a proper waste container, but it is not considered hazardous waste.

Overall budget:

Chemical	Supplier	Cost	Amt. Needed	Total
R-(+)-Limonene	Sigma Aldrich	$29.00/100 mL	4.0 g (density = 0.842 g/mL)	$1.38
Isopropyl alcohol	Sigma Aldrich	$6.50/100 mL	36.73 mL	$2.39
Urea	Sigma Aldrich	$13.10/100 g	2.0 g	$0.26
Hydrochloric acid	Sigma Aldrich	$34.30/500 mL	11.74 mL	$0.81
Sodium nitrite	Sigma Aldrich	$68.20/25 g	2.03 g	$5.54
Oxalic Acid	Sigma Aldrich	$27.30/50 g	1.00 g	$0.55
Diethyl ether	Sigma Aldrich	$21.00/100 mL	~20 mL	$4.20
Ethanol	Sigma Aldrich	$56.80/ 1 gallon	~20 mL	$0.30
l-carvone	Sigma Aldrich	$55.00/kg	(only if wanted to test with for a TLC plate)	(not necessary to order)
Sodium sulfate	Sigma Aldrich	$403.00/100 g	~1 g	$4.03

Total costs per synthesis: $19.46

References:

(1) Bordenca, C.; Allison, R. K.; *Ind. Eng. Chem.;* **1951**; *43*; 1196-1198.

(2) Linder, S. M.; Greenspan, F.P; *J. Org. Chem.;* **1957**; *22*; 949-951.

(3) Reitsema, R.; *J. Org. Chem.;* **1958**; *23*; 2038-2039.

(4) Royals, E. E.; Horne, S. E.; *J. Am. Chem. Soc.;* **1951**; *73*; 5856-5857.

Note: We ended up not using the Linder article for the reaction steps because the synthesis of *l*-carvone required the use of completely different methods, such as oxidation of limonene.

Other references:

(5) "Carvone." Wikipedia. 27 Dec. 2005. 4 Feb. 2006 <http://en.wikipedia.org/wiki/Carvone>.

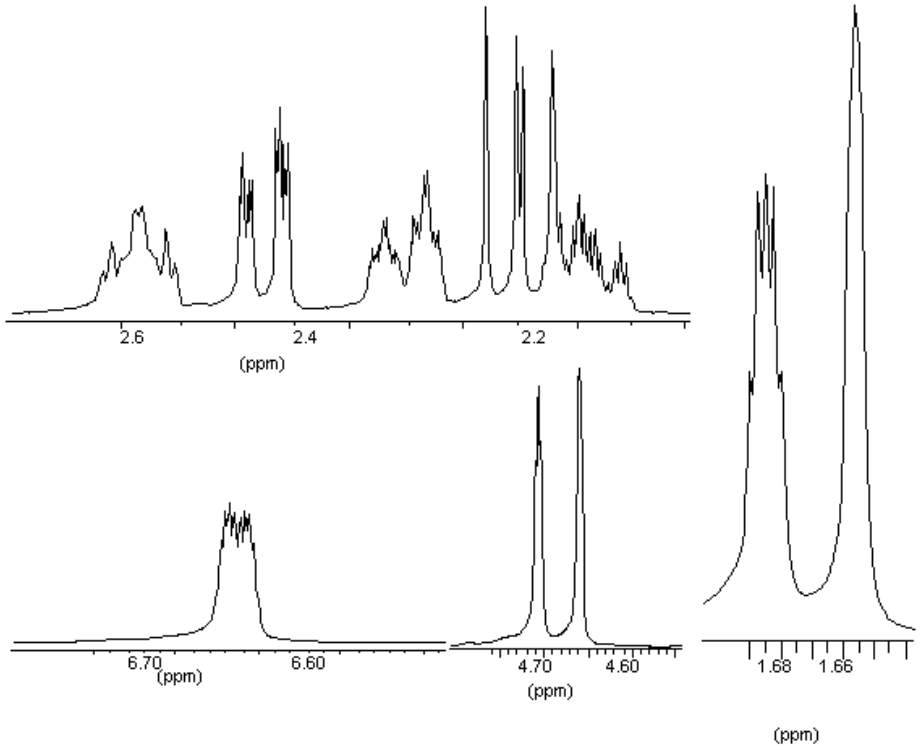
(6) Chemical and Other Safety Information. 4 Feb. 2006 <http://www.physchem.ox.ac.uk/MSDS/>.

(7) GC-MS & NMR. 4 Feb. 2006 <http://www.agr.hokudai.ac.jp/ms-nmr/>.

(8) J. T. Baker. 4 Feb. 2006 <http://www.jtbaker.com/>.

(9) Sigma-Aldrich. 5 Feb. 2006 <http://www.sigmaaldrich.com/Area_of_Interest/The_Americas/United_States.html>.

Spectrum for *l*-carvone:



^{1}H-NMR spectrum

Figure **1** [7]