Experiment 3 – Two-Step Synthesis of Ionones

Additional Reading: Mohrig Section 24 (or other text on UV-vis Spectroscopy)

Ionones are unsaturated ketones responsible for the characteristic fragrance of violets (**Figure 1**). The most abundant isomers, **α- and β-ionone**, can be synthesized in the lab in a two-step process. A concentrated mixture of ionones has a smell that resembles cedarwood. Perfumes from violets are difficult to obtain and have been highly appreciated since the days of Napoleon. An old method for obtaining this perfume consisted of embedding the petals of freshly cut violets between layers of animal fat. The aromatic oils were slowly absorbed by the fat that was then used as a hair cream or ointment.

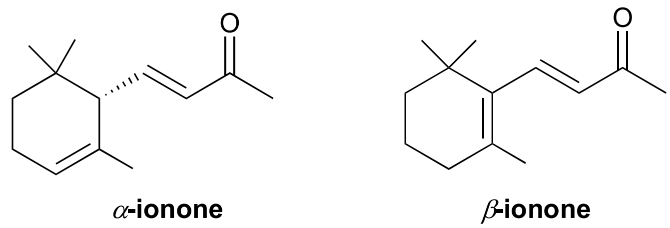

Figure 1. Structures of α- and β-ionone

The synthesis of ionones is an important industrial process. Ionones are not only used in perfumery, but they are also key intermediates in the manufacture of vitamin A. Both ionones can be prepared *via* aldol condensation of citrals with acetone followed by acid treatment (**Figure 2**). Evaluate the structures below to identify which bond is formed by aldol condensation.

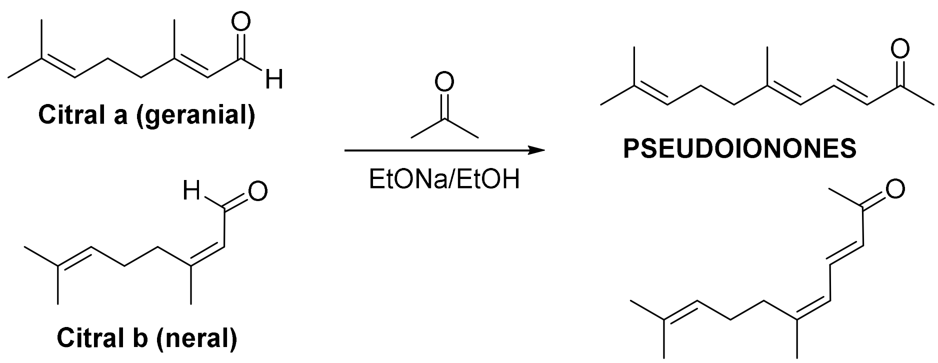

Figure 2. Synthesis of pseudoionones *via* aldol condensation

Citral is a mixture of the two *E*/*Z* stereoisomers of 3,7-dimethyl-2,6-octadienal. **Citral a** or **geranial** (*E* isomer) and **citral b** or **neral** (*Z* isomer) are the main components of lemongrass oil. The aldol condensation of citrals with acetone in the presence of sodium ethoxide gives a mixture of two products, **pseudoionones**, which differ only in the geometry of the double bond between C5 and C6 (**Figure 2**). Note that in making the **pseudoionones**, the newly formed double bond between C3 and C4 has *trans* geometry.

Treatment of **pseudoionones** with acid induces cyclization to **α- and β-ionones** (**Figure 3**). Depending on the nature and concentration of the acid, the formation of one isomer is preferred over the other. The products obtained in the presence of sulfuric or phosphoric acids are different; in each case mainly one isomer, either **α- or β-ionone** is obtained.

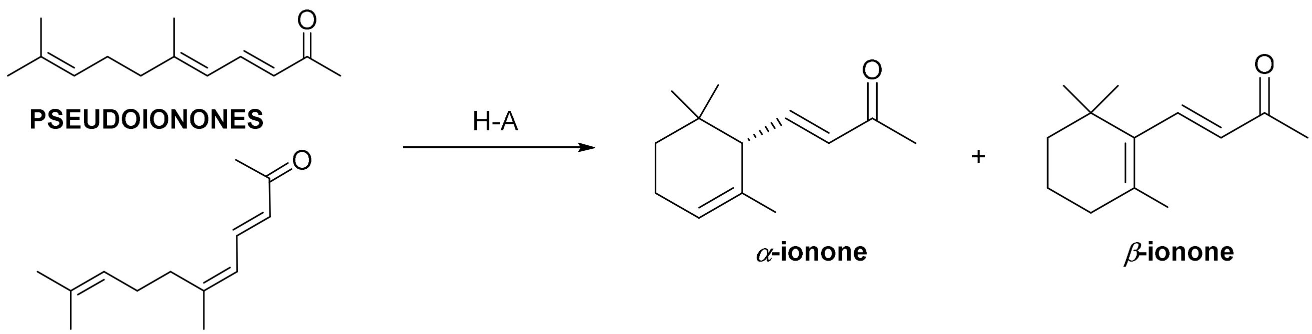

Figure 3. Acid-catalyzed cyclization of **pseudoionones**

The first step in the cyclization of **pseudoionones** is the protonation of C9 by the acid catalyst (**Figure 4**). This is followed by an intramolecular attack from C5 to form a six-membered ring with a tertiary carbocation. Both *E*- and *Z*-pseudoionones form the same carbocation intermediate.

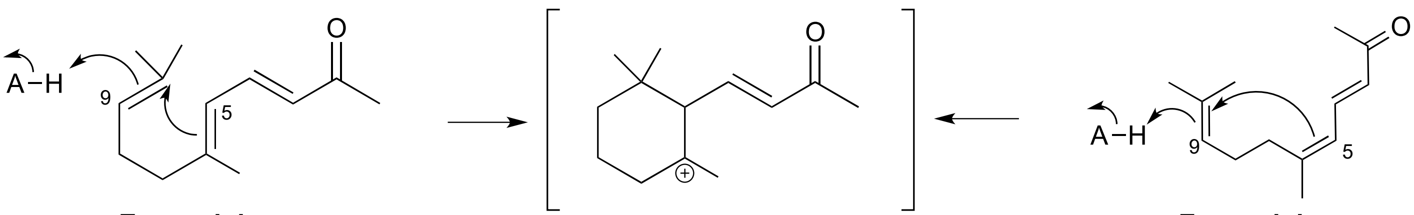

Figure 4. Carbocation formation in ionone synthesis.

The conjugate base of the acid catalyst removes a proton from one of the carbons adjacent to the carbocation, as in the second step of an E1 reaction. This reaction always gives a mixture of products. Depending on the acid catalyst used either α- or β-ionone is favored as the major product (**Figure 5**).

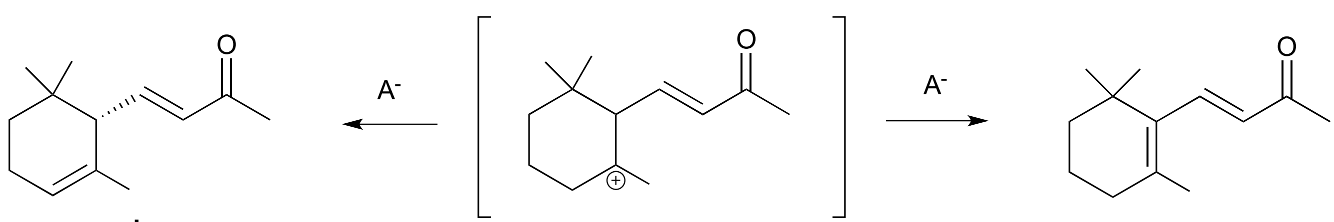

Figure 5. Formation of alkenes in ionones

One of the objectives of the experiment is to determine *why different acids give different isomers*. In this experiment, you will be assigned either sulfuric or phosphoric acid to carry out the cyclization of **pseudoionones** and determine which ionone is the predominant product in your reaction mixture, as determined by IR, GC, and UV-vis spectroscopy.

β-Ionone has two C-C double bonds conjugated with the ketone, while α-ionone has only one. This structural difference results in different IR stretches and UV-vis spectra (**Figure 6**). β-Ionone has an absorption maximum at longer wavelengths than α-ionone. β-Ionone shows a strong band at 295nm, which is absent in α-ionone; both isomers absorb at 227nm.

α-ionone
Conjugated system with 3π orbitals
Additional vinylic C-H bend: IR 600-900cm^{-1}

β-ionone
Conjugated system with 3π orbitals
Strong UV absorbance at 295nm

Figure 6. IR and UV-vis characterization of ionones.

The IR spectra of both isomers differ in the C-H out-of-plane bending region (600-900 cm^{-1}). α-Ionone, because of it extra vinylic hydrogen, presents several bands in this region that are absent in the IR spectrum of β-ionone (**Table 1**). They can also be distinguished by their GC elution order. In columns of medium polarity they come out in order of increasing boiling points.

Table 1.* Physical properties of α- and β-Ionone and precursors

	α-Ionone	**β-Ionone**	**Citral**	**Pseuodoionones**
b.p. (3 mm Hg)	93 – 95 °C	101 – 103 °C	Approx. 75 °C	120 – 140 °C
λ_{max} (UV-vis spectrum)	227 nm	295 nm	-	-
IR bands, lit. (600 – 900 cm^{-1} range)	620, 738, 800, 827	-	842	-

*re-created from Palleros, D.

<u>Notebook Pages</u> – start before lab, work on it during, turn in with report

- *Purpose*: Reaction scheme – **Figures 2 (week 1) & Figure 3 (week 2) -** starting material, reagents, product, other chemicals used
- *Reagent table:* List the amounts (mg or mL and mmol), molar equivalents (“equiv.”), and physical properties (MW, bp or mp, density, one-word hazard) of each chemical in the reaction scheme.
- *Procedure* (remote) – hand-drawn ‘comic strip’ with diagrams of all equipment and chemicals with amounts. Include pertinent notes from the Clean-up & Safety Table.
    - <u>Week 1</u> – procedure and IR tables with expected values for either of the citrals & pseudoionones (see format from *trans*-cinnamic acid lab)
    - <u>Week 2</u> – include only the procedure assigned to your group based on assignment given by TA in week 1, as well as instructions for IR, GC, and UV-vis analysis.

Clean-up	**Safety**
Solid waste: pipets, filter paper, drying agent	$MgSO_4$, $NaHCO_3$, and citrals are irritants
Liquid Waste: aqueous layers & contents of rota-vap trap	Concentrated sulfuric acid is corrosive; take only what you need with the pipet provided; do not remove from hood
Return equipment to proper place – keep those ring stands organized please!	Acetic acid, phosphoric acid, HCl, and sulfuric acid are corrosive and irritants.
Clean up any snow storms of solids!	Acetone, ethanol, and BME are flammable
Quartz cuvettes for UV-Vis must remain in matched pairs – DO NOT MIX Quartz cuvettes are very expensive. There are no extras. Please be careful!	

EXPERIMENTAL PROCEDURE

Week 1 – Preparation of Pseudoionones

Prepare an ice-salt bath (-8 °C) and place on a stir plate. Weigh 2.25 g of citral (1:1 mixture of citrals a & b) directly into a 25-mL Erlenmeyer flask. Add a magnetic stir bar and 11.25 mL acetone. Stir this solution in the ice-salt bath. Slowly over a period of 10 minutes, add 2.25 mL of 2.25 M NaOEt in ethanol drop-wise (solution prepared for students). Stir for an additional 20 minutes.

Slowly neutralize the reaction with 2 M HCl (approximately 3 mL). The reaction mixture should turn yellow, which is indicative of the highly conjugated product. Transfer the solution to a separatory funnel, using 15 mL of t-butyl methyl ether (BME) to aid in the transfer and to wash the flask. Add 9 mL of water and extract the product into the organic solvent. Separate the layers and extract the aqueous layer with two more portions 5 mL portion of BME. Separate once again and wash the combined organic extracts with a NaCl solution (10% w/v).

Dry the organic layer over $MgSO_4$, gravity filter with a glass funnel into a pre-weighed RBF, and concentrate using a rota-vap. Weigh the product and calculate the percent yield of the synthesis of pseudoionones. Obtain the IR spectrum of the product and compare to the provided IR spectrum of citrals (in lab). Analyze the citrals and products by GC to determine percent conversion to product. Save the remaining product in a labeled vial for next week.

Week 2 – Cyclization with Sulfuric and Acetic Acids ~~(pairs closer to the chalk board)~~

Prepare an ice-water bath and place on a stir plate. In a 50-mL Erlenmeyer flask equipped with stir bar, add 1.95 mL of glacial acetic acid then slowly add 2.55 mL of concentrated sulfuric acid (98% w/w). Be especially careful when using these solutions in the fume hood and change your gloves immediately after, regardless of whether you think they're contaminated.

Weigh 1.4 g of pseudoionones (week 1 product) into a test tube. If the week 1 product yield was less than 1.4 g, use the entire product. Add the pseudoionones to the acidic solution drop-wise over a period of 20 minutes. Record observations, including color changes and visible changes to the viscosity of the mixture. After the addition is complete, stir at room temperature for 20 minutes.

Prepare a mixture of 30 mL of cold water and 6 mL of BME in a flask. Swirl, then transfer to the reaction mixture, mix, and transfer it to a separatory funnel. Extract the product into the organic layer. Separate the layers and extract the aqueous layer with an additional 6 mL of BME. Wash the combined organic layers with 2 x 12 mL of an aqueous solution containing $NaHCO_3$ (5% w/v) and NaCl (10% w/v).

Check the pH of the aqueous solution to ensure it is basic before disposing. If necessary, adjust the pH with a $NaHCO_3$ solution and wait for bubbling to subside before transferring to waste. Dry the organic layer over $MgSO_4$, filter into a pre-weighed RBF, and concentrate with a rota-vap. Proceed to IR, GC, and UV-vis analysis.

Week 2 – Cyclization with Phosphoric Acid ~~(pairs closer to the windows)~~

In a 25-mL Erlenmeyer flask equipped with stir bar and immersed in a water bath (30 °C), place 4.0 mL of concentrated phosphoric acid (85% w/w). Be especially careful when using this solution in the fume hood and change your gloves immediately after, regardless of whether you think they're contaminated.

Weigh 1.4 g of pseudoionones (week 1 product) into a test tube. If the week 1 product yield was less than 1.4 g, use the entire product. Add the pseudoionones to the acidic solution drop-wise over a period of 20 minutes. Record observations, including color changes and visible changes to the viscosity of the mixture. After the addition is complete, stir in the water bath for 20 minutes.

Add 30 mL of aqueous NaCl (10% w/v) and transfer the mixture into a separatory funnel. Wash the flask with 15 mL of BME and transfer the wash to the separatory funnel. Mix and separate the layers. Extract the aqueous layer again with 15 mL of BME. Wash the combined organic layers first with 15 mL of an aqueous solution containing $NaHCO_3$ (5% w/v) and NaCl (10% w/v), followed by 15 mL of aqueous NaCl.

Check the pH of the aqueous solution to ensure it is basic before disposing. If necessary, adjust the pH with a $NaHCO_3$ solution and wait for bubbling to subside before transferring to waste. Dry the organic layer over $MgSO_4$, filter into a pre-weighed RBF, and concentrate with a rota-vap. Proceed to IR, GC, and UV-vis analysis.

Analysis (Week 2, all groups)

Weigh the product and calculate the percent yield of ionones. Obtain the IR of product and analyze the product by GC. Do not inject thick products as this may damage the column. Instead, dilute a small sample of your product with acetone a few drops at a time in a vial or test tube until the solution is freely flowing, then inject the solution. Compare your sample to the provided 1:1 standard of α- and β-ionone, using boiling points for peak identification. Determine the percent conversion to product as well as percent composition of α- and β-ionone.

Dissolve 5 mg (±0.1 mg) of the ionones product in a 10-mL volumetric flask. Dilute to 10 mL with 100% ethanol. Perform a 1:20 dilution by dissolving 500 μL of the solution with 100% ethanol in a separate 10-mL volumetric flask. Follow TA instructions to obtain the UV-vis spectrum of this solution in the range 200-400 nm. If the absorbances at 227 and 295 nm are greater than 2, dilute the solution with ethanol and measure again.

References

Hibbert, H.; Cannon, L. T. *J. Amer. Chem. Soc*. **1924**, *46*, 119-130.

Kimel, W., *et. al*. *J. Org. Chem*. **1957**, *22*, 1611-1618.

Krishna, H. J. V.; Joshi, B. N. *J. Org. Chem.* **1957**, *22*, 224-226.

Palleros, D. R. *Experimental Organic Chemistry*; Wiley: New York, **2000**; pp. 520 – 530.

Royals, E. E. *Ind. Engineer. Chem.* **1946**, *38*, 546-548.

Introduction: Pre-Lab Questions

Week 1

1. Draw the mechanism for the aldol condensation of geranial (citral a) *or* neral (citral b) with acetone and sodium ethoxide. Why is the *trans*-isomer preferred for the *newly formed* alkene?

2. What *changes* do you expect in the IR spectrum of citrals and pseudoionones?

3. What is the purpose of HCl in the reaction work-up? Of NaCl?

4. Calculate the theoretical yield of pseudoionones. Show your work (including calculations for moles of starting materials).

Week 2

5. Draw the cyclization mechanism for either the *E*- or *Z*-pseudoionone.

6. Briefly explain why there is a difference in the absorbance max (λ_{max}) of α- and β-ionone.

7. Calculate the theoretical yield of ionones. Show your work.

Prepare a draft of the abstract and bring to week 2 for TA feedback.

Results: Post-Lab Questions – typed and turned in with lab report

1. (*5 points*) Report the yield (mg) and % yield for both steps.

2. (*10 points*) Report the corrected GC retention times, integration, and percent composition for each chromatogram. Be sure to identify the peaks. Report your data in table format and briefly comment on the success of reaction and purity of products. Attach the chromatogram(s) to the back of the report or refer to your lab partner's report.

3. (*10 points*) Interpret the IR spectra of citral, pseudoionones, and the ionones. Report your analysis in table format (see *trans*-cinnamic acid prep notes). What are the distinguishing peaks in each? Attach the IRs to the back of the report or refer to your lab partner's report.

4. (*5 points*) Report whether the cyclization was performed with acetic or phosphoric acid. Discuss your GC results with a neighboring group to collect percent composition data for the reactions done with both acids. How can the acid strength (acetic or phosphoric) be used to explain why different cyclization products are favored?

5. (*5 points*) Report the observed peaks and absorbances in the UV-vis spectra. Does this result support your answer to questions 2 & 4? Explain.

6. (*20 points*) Interpret the ^{1}H NMR of α- and β-ionone (same format and instructions as in the *trans*-cinnamic acid lab). Assign as many peaks as possible. Which peak in the ^{1}H NMR spectrum is best to use to distinguish α- and β-ionone from each other?

CHEM 110L
Exp 3 - Synthesis of Ionones

Name ______________________________

Section Day _____ Time _____

TA Name ___________________________

RUBRIC & STUDENT CHECKLIST (DO NOT TURN IN)

SECTION	INSTRUCTOR COMMENTS	POINTS ASSIGNED
IN-LAB QUIZZES		**/ 10**
INTRODUCTION Original responses to pre-lab questions		/ **35**
LAB REPORT – Due dates in syllabus & Canvas		
ABSTRACT One paragraph, four sentences: Purpose, procedure, main result(s), and conclusion(s).		**/ 30**
RESULTS The main results are stated, as outlined in the in-lab questions, using complete sentences.		/ **55**
EXPERIMENTAL METHODS The experimental details (including final amount used and obtained) are *briefly* described in a few sentences.	NONE	0 / 0
NOTEBOOK PAGES Proper format: reaction scheme, chemical info table, procedure, waste and clean-up procedure.		/ **30**
NEATNESS AND ORGANIZATION Proper order and format (see syllabus for full descriptions of each section).		**/ 20**
ZOOM PARTICIPATION Attendance & participation in chat, questions, reactions, etc. 10 pts per day		**/ 20**
	LAB REPORT TOTAL	**/ 200**