Blattellaquinone

Synthesis of a Cockroach Pheromone

In this experiment, the cockroach pheromone Blattellaquinone is synthesized in a two step process; an esterification reaction followed by an oxidation.

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Blattellaquinone

The German cockroach, *Blattella germanica*, can be found all over the world and is a major food-associated and residential pest.

There are several methods available for the control the infestations of cockroaches. One of them is the use of insecticides. Unfortunately, cockroaches are very resilient and they can easily become resistant to insecticides. Additionally, some of the insecticides which are in use at the moment pose a threat to both humans and the environment. An alternative which circumvents these problems is the “bait-and trap” strategy, which is generally easier on the environment than the mass application of insecticides. The perfect
bait is a system which attracts only specific insects without conditioning these insects with continued use. Available baits for cockroaches include food compounds such as sugars or protein hydrolysates (Hydrolysates are predigested, partially hydrolyzed whey proteins). Unfortunately, these baits are not specific for cockroaches and they lose their effectiveness as cockroaches learn to refuse the attractants employed.

**Pheromones**

A pheromone is a chemical which is used for communication between individuals of the same species. Insects, for instance, make heavily use of pheromones in order to communicate between each other. Insects use pheromones to send alarms, mark territories or paths to food, cause individuals to keep apart or come together, and very important for the preservation of the species, to find and attract mates. A great advantage of using pheromones as a bait is that they only attract target insects and the insects do not learn to refuse it. Usually, the cost to produce pheromones is higher than the cost for traditional pesticides but much less pheromone needs to be applied in order to control the insect population.

**Blattellaquinone**. also known as gentisyl quinone isovalerate, is a sex pheromone of the German cockroach.

In 1993, researchers reported that a German cockroach sex pheromone is located in the pygidia of virgin females. The isolation and identification of this pheromone proved difficult, since each insect only has about a nanogram \(10^{-9}\) g). It took until 2005 for Nojima et al. to report the identification of the pheromone as gentisyl quinone isovalerate. They combined and extracted the pygidia of about 15,000 virgin female cockroaches, subjected the extracts to a series of chromatographic procedures, and determined which chromatographic fractions contained the pheromone by observing the behavior of male cockroaches in olfactory tubes.

Patty L. Feist  
*The Synthesis of a Cockroach Pheromone*  

**Synthesis of Blattellaquinone**

The synthesis of blattellaquinone requires two steps. The first step is the reaction of 2,5-dimethoxybenzyl alcohol with isovaleryl chloride. This reaction is a nucleophilic acyl substitution reaction and yields the ester 2,5-dimethoxybenzyl 3-methylbutanoate.
The above reaction has to be carried out in the presence of a weak base (triethylamine) in order to trap the HCl which is formed during the reaction because the acid can promote the hydrolysis of the ester, undoing the esterification reaction. After the esterification reaction is complete, the work-up of the mixture includes a wash with aqueous ammonium chloride to remove the amine.

The second step in the synthesis of blattellaquinone is the oxidation of 2,5-dimethoxybenzyl 3-methylbutanoate with ceric ammonium nitrate (CAN) to form the pheromone blattellaquinone.

Ceric ammonium nitrate is an oxidizing agent and its ability to oxidize p-dimethoxybenzene derivatives to the corresponding benzoquinones has been known since the 1970s. CAN has a lot of advantages, e.g., it is inexpensive, non-hygroscopic, and very easy to handle. Since it is not very soluble in organic solvents, the reaction is carried out and a mixture of acetonitrile (organic solvent) and water.
Pre-Lab Questions

1. In both steps of the reaction, one of the reactants is added slowly using an addition funnel. Suggest why this is the case, rather that adding all the reactants at once.

2. A convenient way to synthesize esters is to react an acyl chloride with an alcohol (see step one of the synthesis). Give the acyl chloride and the alcohol that would be required to form the ester shown below. What other compound would be included in the reaction mixture to facilitate the reaction?

3. Compare and contrast the reactants and reaction conditions that would be used to synthesize the ester in question 2 via a Fisher esterification.
Procedure

Precautions

1.) Isovaleryl chloride is flammable, corrosive, and can cause burns. It is also an irritant to the respiratory system and a lachrymator! Most importantly, isovaleryl chloride has a noxious odor. Work in a fume hood while handling this reagent.

2.) 2,5-Dimethoxybenzyl alcohol is an irritant: do not breathe its vapor and avoid contact with skin and eyes.

3.) Triethylamine is flammable, corrosive, and harmful.

4.) Ammonium chloride is as irritant and harmful if swallowed.

5.) Ceric ammonium nitrate is an irritant and an oxidizer

Wear gloves and protecting clothing throughout the experiment.

2,5-Dimethoxybenzyl 3-methylbutanoate

1. Dissolve 10 mmoles of 2,5-dimethoxybenzyl alcohol in 40 mL of methylene chloride and place this mixture in a round bottom flask. Place over a stir motor and add a stir bar. Add 11 mmoles of triethylamine and stir until everything is in solution.

2. Secure an addition funnel over the flask, then place 13 mmoles of isovaleryl chloride in the funnel. Add the isovaleryl chloride dropwise to the mixture in the flask; it should take 10-15 min to add all of this reactant. After all the isovaleryl chloride has been added, continue to stir the reaction for 45 min.

3. Transfer the reaction mixture to a separatory funnel and wash the organic layer sequentially as follows: Once with 10 mL of saturated sodium bicarbonate, twice with 10 mL of 10% ammonium chloride, and once with 10 mL of saturated sodium chloride. Dry the organic layer over sodium sulfate or magnesium sulfate.

4. Filter the organic layer and remove the methylene chloride with a rotary evaporator. After the solvent has been removed, you should expect to have about 2 mL of a light tan liquid with some sediment in it. This crude intermediate, 2,5-dimethoxybenzyl 3-methylbutanoate, can be used directly in the next step. Take an IR of the 2,5-dimethoxybenzyl 3-methylbutanoate and submit a sample for NMR.
Blattellaquinone

5. Add the crude 2,5-dimethoxybenzyl 3-methylbutanoate to 40 mL of a mixture of acetonitril/water (50:50) and place this solution in a round bottom flask. Place over a stir motor and add a stir bar. Secure an addition funnel over the flask and dissolve 30 mmoles of ceric ammonium nitrate (CAN) in 20 mL of water. Place this solution in the addition funnel, and then add it dropwise over 10-15 min while stirring vigorously. After all the CAN has been added, continue to stir the reaction mixture for 45 min.

6. After the reaction period, use gravity filtration to remove any solids that have formed. Then, add solid sodium chloride until the solution is saturated. Carefully decant into a separatory funnel. Extract three times (3 x 30 mL) with methylene chloride.

**Note:** Usually the organic layer is on top for the first extraction, but sometimes it is not; check the layers against water and save both layers in case you make a mistake.

7. Combine the three methylene chloride extracts and wash sequentially as follows: Twice with 25 mL of saturated sodium bicarbonate and once with 25 mL of saturated sodium chloride. Dry the organic layer over sodium sulfate or magnesium sulfate.

8. Filter the organic layer and remove the methylene chloride with a rotary evaporator. After all the solvent has been removed, a few drops of a viscous brown liquid will remain in the flask. Spread this product on a large watch glass or evaporating dish for a few minutes and scrape it with a spatula until all the solvent evaporates and a tarnish solid appears. This solid is blattellaquinone.

Spectroscopy

1. Obtain a NMR spectrum of the product. Consult with your laboratory instructor about how to do this.

2. Assign all the NMR peaks in the spectrum.
Post-Lab Questions

1. Give the products of the acid catalyzed hydrolysis of each of the following esters.

   (a) ![Diagram of an ester](image1)

   (b) ![Diagram of an ester](image2)

2. Give the mechanism of esterification of a general carboxylic acid $RCOOH$ with methanol in which the alcohol oxygen is labeled with the $^{18}O$ isotope ($CH_3^{18}OH$). Does the labeled oxygen appear in the ester or in the water product?

3. **Challenging question:**

   Explain the following results mechanistically:

   ![Chemical reaction](image3)