Synthesis of γ-Lactams from the
Spontaneous Ring Expansion of β-Lactams

Second-Semester Student

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From β- to γ-lactams through thermal ring expansion: Synthesis of alkene from aldehyde

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Abstract:

During this semester, nine reactions were carried out including the titration of methyl lithium, the distillation of 2-phenylpropionaldehyde and the following reactions in the synthesis of alkenes from an aldehyde and a ketone also known as carbonyl methylenation. The student continued her research with synthesis of 2-phenylpropionaldehyde in order to synthesize N-Chlorosulfonyl β- or γ-lactams from the aldehyde and chlorosulfonylisocyanate. The synthesis of 2-phenylpropionaldehyde is a continuation of the work done in the spring semester of 2001.

Introduction:

In the previous semester, some background of the exposure of the appropriate β-lactone to catalysis by titanium tetrachloride, a Lewis acid, begins ionization of the lactone, where to carboxylate/carbocation intermediate will undergo further reactions to afford the product. This leads us to understand that β-lactams can also undergo the same transformation allowing entry in to the γ-lactam. γ-lactams are commonly encountered in naturally-occurring molecules. Some earlier studies show that the thermal β- to γ-lactam expansion is the base event of this research. This research started with the synthesis of alkenes for carbonyls including ketones and aldehydes. The general overall sequence follows:

\[
\begin{align*}
R_1 & \quad O \\
R_2 & \quad R_1 & \quad R_2 & \quad R_1 & \quad R_2 \\
\end{align*}
\]

The use for β-lactams is due to its simplicity since they are available from a wide variety of synthetic methods. The primary structural goal for the γ-lactam was that the carbonyl group
lie either adjacent to a tertiary or benzylic carbon. The reason for this is that the rearrangement will only occur when a cation of equal (or lesser) energy to the nitrogen-bearing carbon atom is available adjacent to that atom\textsuperscript{1}.

Last semester’s work concentrated on the synthesis of an alkene from the starting material of 2-phenylpropionaldehyde according to methods from a thesis of a prior graduate student of Dr. T. H. Black. This concurs with the first step of the general overall scheme presented above. However, no $\gamma$-lactams were synthesized from $\beta$-lactams through thermal ring expansion.

This semester’s work concentrated on the synthesis of two alkenes from the starting materials of 2-phenylpropionaldehyde and 2-methylcyclohexanone using a new technique since last semester’s work was not producing $\gamma$-lactams. This involved the synthesis of dimethyltitanocene and use of it in the methylenation reactions.

**Results and Discussion:**

The synthesis of dimethyltitanocene is illustrated in the technique shown above. After the titration of methyl lithium to determine its exact molarity, the above reaction was done on a tenth of the scale twice to ensure knowledge of reaction and determine yield. The yield of the first was 65.3\% and the second tenth scale reaction gave 77.7\% yield. Following these two reactions, the synthesis was done on the full scale for use in the following methylenation reactions.

An amount of 11.57 g (46 mmol) of pulverized dicyclopentadienyltitanium dichloride was placed into 200 mL of dry ether and used in the above sequence. The reaction produced
8.12 g of crude product which gave a 84.2% yield. This was a substantial amount available for use in the methylenation reactions. With 7.43 g of the crude product, a .5 M solution was made in THF solution (71.4 mL).

The synthesis of 2-phenylpropionaldehyde is illustrated in the technique shown below.

To ensure purity and to make no question of the carbonyl peak in 2-phenylpropionaldehyde, a distillation was done so that an IR could be taken of the starting aldehyde. This is the first of the attached IR spectrums included. On the attached spectrum sheet, you will see a carbonyl peak at $\delta$ 1723 which is where it should be. Reactions one through four are done with 2-phenylpropionaldehyde and reactions five and six are with 2-methylcyclohexanone.

After the first time the reaction was carried out with 2-phenylpropionaldehyde, no crude product was afforded. The reaction was carried out until the point of dilution with petroleum ether. Accidentally, this mixture was diluted with diethyl ether as well as reactions two and three’s mixture until this realization. Therefore, the reaction was killed and started over.

The second and third reactions using the aldehyde were run simultaneously next to one another to speed up the process and hopefully get decent results. Reaction two was kept at the
correct temperature for about six hours when I returned to find the reaction dead. By this I mean, the magnetic stir bar had overheated and stopped. Also, the reaction temperature was down to room temperature. The solution had been kept from light, but once foil was removed, the solution was noticed to be completely black in color. The boiling point of THF is 65-67 °C which means that since the temperature had never reached over 70 °C, the THF must have boiled off and escaped through the nitrogen inlet and glass joints. This problem was fixed in reaction four of methylenation.

Reaction three remained at the correct constant temperature of 63 °C when returning the next day to finish synthesis. The supposable alkene was black (or deep wine red) and very seemed to be a very oily and sticky solid. Once the ether was poured over it, a orangish-red solution had formed with the solid, still visible, remaining at the bottom. After a few minutes in the ether, all of the solid had dissolved into solution. This, of course, is not suppose to happen. The mixture was put onto the rotovap anyway to get solvent off and see what product was. The resulting product was not a solution (liquid) but instead a solid. This is the point that I realized I was using diethyl ether instead of petroleum ether.

Reaction four was carried out differently than the previous three with the realization of using a condenser with the nitrogen inlet at the top of it to keep the THF at a reflux and noting that the alkene is diluted with petroleum ether and not diethyl ether. An orange-black solution resulted once the petroleum ether was poured over it with a black solid at the bottom of the beaker. The filtrate was removed and the resulting red liquid was placed on the rotovap. An IR was taken which looked promising due to hardly no carbonyl peak present. A TLC was taken with hexane as the eluent. The mixture was mixed with ether in a test tube before placing drops onto the plate. The TLC showed a lot of “junk” that was present with the alkene. There were at least three distinct \( R_f \) values not to mention many that were so faded a \( R_f \) value couldn’t be taken. These numbers were as follows: .431, .514, and .722. The alkene is most likely the .722 but not sufficient proof of that.

Reactions five and six, with 2-methylcyclohexanone, used the same precautions as
reaction four with the condenser, etc. The resulting solution (no solid had formed) was a light orangish-red color with a yellow layer on top. After adding an enormous amount of petroleum ether (50 mL), a definite solid had formed and filtration followed. However, the results showed no alkene in the product. The IR taken of the product looks almost exact to the starting material IR taken before the reaction took place with a peak at δ 1712. The product also looks extremely wet due to the huge peak at δ 3446 which is unexplainable. Only one IR spectrum of these two reactions is attached.

**Conclusion:**

The entire semester’s work was primarily aimed at the synthesis of an alkene from a selected aldehyde (2-phenylpropionaldehyde) and ending with a selected ketone (2-methylcyclohexanone). Upcoming work in the spring semester of 2002 is as follows:

- To try a new approach of synthesizing alkenes with the use of a Wittig Reagent that is prepared fresh each day that reactions are carried out.\(^5\)
- Continuance of the synthesis of the many alkenes in order to go on to the general method for synthesis of N-Chlorosulfonyl β- or γ-lactams from alkenes and chlorosulfonylisocyanate.
- To take a closer look of the lactams structural requirements for more complex substrates.\(^1\)

The simple removal of the N-chlorosulfonyl group will allow for subsequent N-functionalization, allowing for the facile synthesis of a variety of γ-lactams with varying substitution patterns.\(^1\)

**Experimental:**

Preparation of dimethyltitanocene (at the full scale) was carried out under a stream of nitrogen gas. In a 1000 mL round-bottom flask equipped with a magnetic stirrer, a rubber
septum, and thermometer, 11.57 g of pulverized dicyclopentadienyltitanium dichloride was placed with 200 mL of dry ether. The solution was cooled to 10-15 °C where 100 mL of MeLi was added dropwise over a period of 30 minutes. The reaction was stirred while returning to room temperature.

The entire solution was then decomposed by pouring onto ice water. The organic solution was dried over Na₂SO₄ after filtering off the water. The solvents were removed on the rotovap and placed onto the vacuum. A crude amount of 7.43 g was used in the making of a .5 M THF and Cp₂TiMe₂ solution. No purification was done on the dimethyltitanocene.

For the first three reactions ran this semester with the aldehyde, a procedure in German that was translated by Dr. T. H. Black was used. A 50 mL round-bottom flask was set up with a nitrogen inlet, thermometer, and rubber septum. A heating device was set under the round-bottom and a magnetic stirrer was placed inside the flask. In the flask, 2.65 mL of the aldehyde and 8 mL of .5 M pre-made solution were mixed together. The round-bottom was covered completely with foil to keep the solution away from any light source. The solution was then brought to a temperature of 60-65 oC. The reaction was allowed to stir at this heat for approximately 22 hours. The resulting mixture was diluted with diethyl ether instead of petroleum ether which cause two reactions to fail. The second one failed for reasons mentioned above in the results section.

The fourth reaction was done under the same translated procedure used above but with a few changes to look for improvement in the reaction. In a clean, dry, 50 mL three neck round-bottom flask equipped with a condenser (and a nitrogen inlet placed at the top of the condenser), a glass stopper, a magnetic stir bar, and a rubber septum, 2.65 mL of the aldehyde was dissolved in about 5 mL of THF per gram of substrate (13 mL). To this mixture, 12 mL of the .5 M prepared solution was added via syringe. The rubber septum was then replaced with a glass stopper and the flask was covered entirely with Al foil. The reaction was heated to a gentle reflux for 22 hours.

The solution was cooled to room temperature for about six hours and finally placed over
petroleum ether. An orange-black solution resulted with a black solid at the bottom of the beaker. The filtrate was removed and resulting liquid was put onto the rotovap. This was the only reaction of the semester that showed promise from an IR taken and TLC analysis done which results are found above in results section.

The final two reactions ran this semester with the ketone repeated the same procedure used in the fourth reaction. However, only 3.64 mL of 2-methylcyclohexanone were dissolved in about 12 mL of THF. The final 12 mL of the .5 M prepared solution was added to each mixture via syringe and carried out under same conditions and procedures as mentioned above. Results can be found in the above results section of the paper. The procedure’s above have no excuse for not working, but for some reason are not. This is why next semester, a new approach will be taken using a Wittig reagent that is made daily.  

Notes:


