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Organic Chemistry

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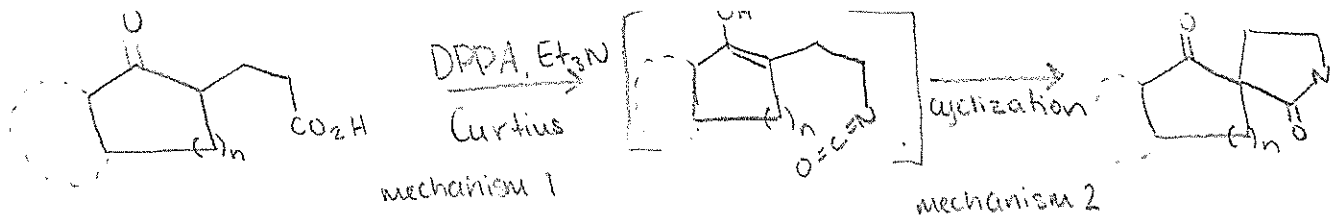
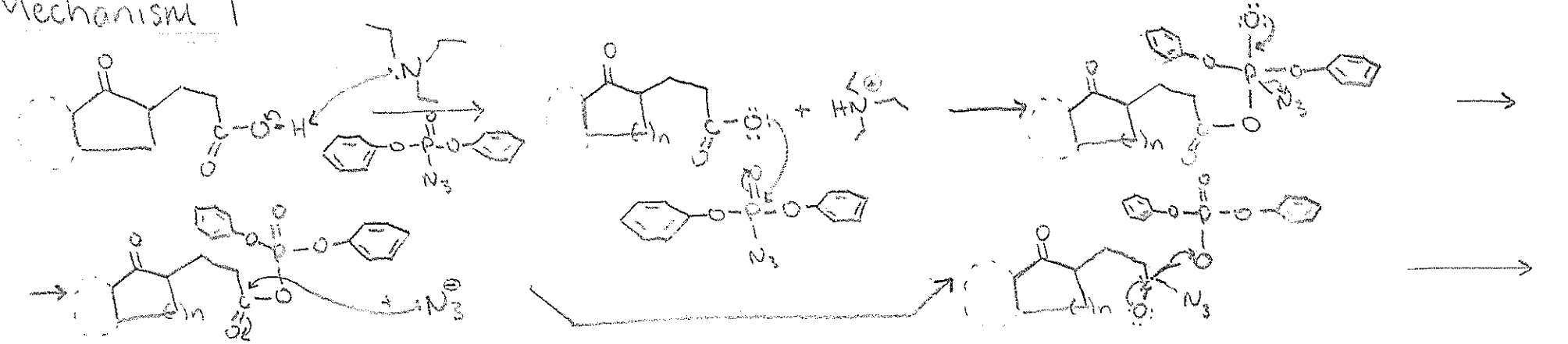
# A Practical Synthetic Method of Synthesizing Spirocyclic Lactams from Beta-Keto Carboxylic Acids

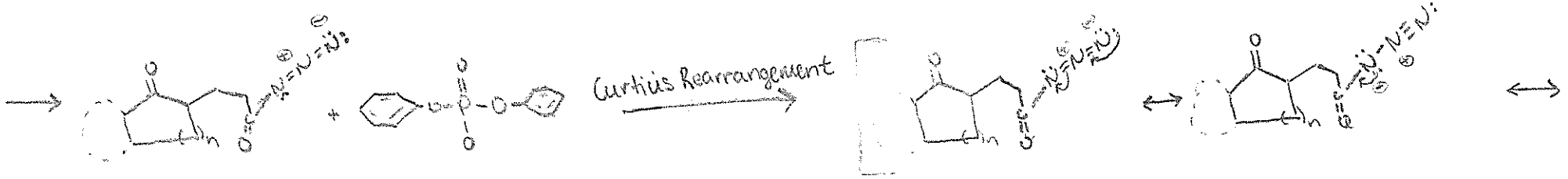
Non-synthetic spirocyclic lactams tend to have a large range of biological functions, including: inhibiting the movement and the morphing of cancer cells, inhibiting MurI, having antimicrobial and anti-fungal properties, and possibly being a treatment of endocrine tumors and acromegaly. There have been multiple synthetic methods reported to create these spirocyclic lactams, including, using a Mn(OAc)3-catalyzed radical cyclization of unsaturated β-keto carboxamides by Cossy, using vinyl selenone as a Michael acceptor for a domino Michael addition/cyclization process by Marini, and varias methods using ruthenium-catalyzed ring-closing metathesis10 and palladium-catalyzed carboxycyclization. These methods suffer some limitations, therefore they are not ideal when synthesizing spirocyclic lactams; the substrate availability and use of metal catalysts that are damaging to the environment are examples of some of these limitations. The researchers for this specific journal article were working on large B-cell lymphoma and triple negative breast cancer, and they were interested in finding a practical way to synthesize multi-substituted spirocyclic lactams using a Curtius rearrangement because of the biological functions of these spirolactams.

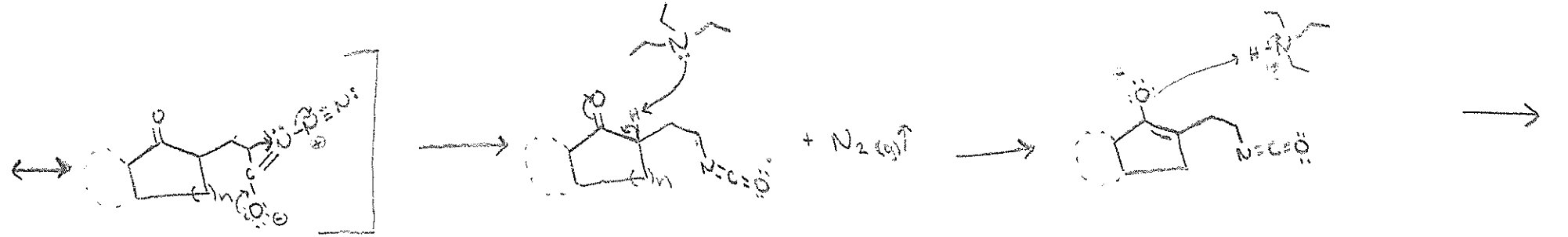
The Curtius rearrangement mechanism that they preformed used DPPA and triethylamine (Et3N) to form an intermediate, and through a cyclization this intermediate produced multi-substituted spirocyclic lactams. The mechanisms began with the Et3N deprotonating the carboxylic acid, then the lone pairs on this negatively charged oxygen attacked the Phosphorus of DPPA. Through neighboring group participation, the N3 came off the DPPA. It the attacked the Carbon that is double bonded to the oxygen and through neighboring group participation again, the rest of the DPPA came off. A Curtius rearrangement of the Nitrogens caused N2 to come off as a gas, and the group became a Nitrogen double bonded to a Carbon that is double bonded to an Oxygen. The Et3N attacked the alpha hydrogen of the 5-membered ring, causing a double bond and a negatively charged Oxygen. The electrons then pulled the Hydrogen off the Et3N to form an -OH group. The cyclization happened and then through a proton transfer the spirocyclic lactams was formed. These two mechanisms are highlighted on the following page.

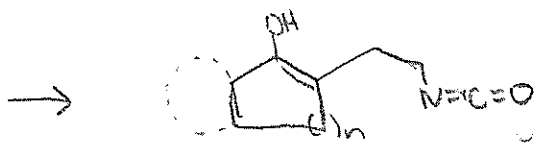

DPPA, Et3N
Curtius
mechanism 1
cyclization
mechanism 2

## Mechanism 1




Curtius Rearrangement





To discover the reagents and starting materials that the researchers needed in order to make these spirolactams, they began by finding they ideal conditions to generate 3-acetylpyrrolidin-2-one from 5-oxohexanoic acid. As entry number 4 in Table 1 shows, using *t*-BuOH as a solvent, with Et3N as a base, at 50 degrees Celsius, produced a yield of 65%, the greatest out of any of the others tried. Then they began experimenting with different starting materials and analyzing what the products of each were; scheme 2 shows which ones they used and the resulting yield from those. The results showed that when using a starting material with electron donating and withdrawing substituents on the phenyl ring, the reaction was favorable; it also shows that the products with halogen substituents can be used to create more complex structures. As observed in Scheme 2 with compounds 4a-b vs. 4i-j, the structures of 4a and 4i are relatively similar, along with 4b and 4j, however there is a difference in the yields of these. To account for this, the researchers studied the geometric preferences of the intermediates of these compounds. This was found to be explained by the distance between C1—C2. Figure 1 displays this, but the main reason was because 4a-4b had shorter C1—C2. By observing Scheme 2 and Figure 1, it can be concluded that five-membered rings had shorter interactions in the intermediates, so the yield would be greater with these. Overall, this synthesis of small spirocyclic lactams is necessary because they can be precursors to build drug-like compounds.

The researchers found that by using this method, they achieved yields of 55-73% proving that by using the β-keto carboxylic acid they can synthesize high yields of they spirocyclic lactams. While not the original goal, it was also found that this method produced fused lactams along with the spirocyclic lactams when using these β-keto carboxylic acids. They tested this in

Scheme 4 and found that there was impressive yields when Cu-mediated coupling of amide with 1-iodo-2-nitrobenzene was followed by the reduction of the nitro group to offer the pentacyclic spirolactam 9 in Scheme 4, where a new fused ring was made. Future work to be done includes trying to control the chirality of the quaternary carbon in the center of the spirolactams to see if there is a connection between the chirality and the percent yield of the product.

According to the article, the methods and research done seem to be accurate, thorough, and well thought out. They used their understanding of Chemistry to find the starting material and reagents that would produce the best yield of the product they wanted, and they provided their reasoning in a clear, well-developed way; however, there may be one minor flaw with the article itself. It seems to answer the question of practicability indirectly, but it doesn't necessarily say whether or not there is something negative that occurs because of this particular reaction. For the examples of this synthesis that other people had done prior, they stated the negative affects, but for their own, they didn't state any. Does this mean that there is none, or that they are too insignificant to announce, or that they just didn't want people to know? Knowing that these researchers put so much time into this experiment, it is unlikely that they just simply omitted the negatives of it, so it can be assumed that the synthesis of spirocyclic lactams from β-keto carboxylic acids has few to no negatives outcomes, and if there are any negative effects, they are negligible.

References

Yang, Wei, Xianyu Sun, Wenbo Yu, Rachita Rai, Jeffery R. Deschamps, Lauren A. Mitchell, Chao Jiang, Alexander D. MacKerell, Jr., and Fengtian Xue. "Facile Synthesis of Spirocyclic Lactams from β-Keto Carboxylic Acids." *Organic Letters*. ACS Publications, 4 June 2015. Web. 17 Oct. 2015.