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Organic Chemistry

Dr. Yeagley

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Hutton, C.; "Synthesis of β -Hydroxy- β -(fluoronitrophenyl)alanines: Vital Components in the Assembly of Biologically Active Cyclic Peptides," *Org. Lett.* **1999**, 1, 295.

1) Where is the author from (What University)? (3 pts)

The author is from the School of Chemistry, The University of Sydney

2) What is the specific problem/issue(s) that the researchers are attempting to address? (5 pts)

The author is trying to address the nucleophilic aromatic substitution reactions and how it has recently been shown to provide a general method for the formation of such ether linkages, and consequently the synthesis of functionalized fluoronitro-substituted aromatic amino acids is of great interest. Also, the author is addressing the herein which is a method of the stereospecific synthesis of 3-fluoro-4-nitro- and 4-fluoro-3-nitro-threo- β - hydroxyphenylalanine

3) In the Introduction, what has the author given the reader that helps the reader to understand the work's role/place in the recent literature? (5 pts)

In the introduction the author provides more background information on nucleophile aromatic substitution reaction of fluoronitro-substituted aromatic amino. Also, it mentions 4-fluoro-3-nitro- β -hydroxyphenylalanine and how it has been used extensively in synthesis of vancomycin and its analogues.

4) How did the author successfully prove or disprove their hypothesis surrounding the problem/issue they are addressing? What data was pivotal to this success, all of it is not an answer? (5 pts)

For the author to prove its hypothesis figures and references were illustrated and analyzed for the reader to understand the research. Figure 1 demonstrates that the hydrolysis of N-phthaloyl- β -bromoarylalanine methyl esters provides the corresponding β -hydroxyarylalanine derivatives, with the selectivity being controlled by facially selective stabilization of the intermediate benzylic cation by the neighboring ester moiety. Also Figure 1b illustrates the increased magnitude of the neighboring group effect by the amide moiety.

5) Is all the data relevant to the issue the author is attempting to address? (5 pts)

Yes, all the data provided in this article relates to the issue that the author is attempting to address.

6) Do you think that the conclusion(s) they found have truly advanced "our" knowledge of the field? (5 pts)

Yes, I do believe that this article does advance our knowledge of the field with the conclusion in which the procedures provide the rapid, stereospecific synthesis of β -hydroxy- β -(fluoronitrophenyl)alanines which are suitable for incorporation into syntheses of a variety of biologically active ether-bridged cyclic peptides such as vancomycin.

Questions specific to your article or references within:

7) What is a hydrolysis reaction? (3 pts)

hydrolysis is a chemical reaction in which water is used to break down the bonds of a substance. Hydrolysis can also be thought of as the exact opposite reaction to condensation, which is the process whereby two molecules combine to form one larger molecule.

8) Is this group the first to present this hydrolysis strategy to similar molecules? (3 pts)

This group was one of the first to introduce the hydrolysis strategy to similar molecules.

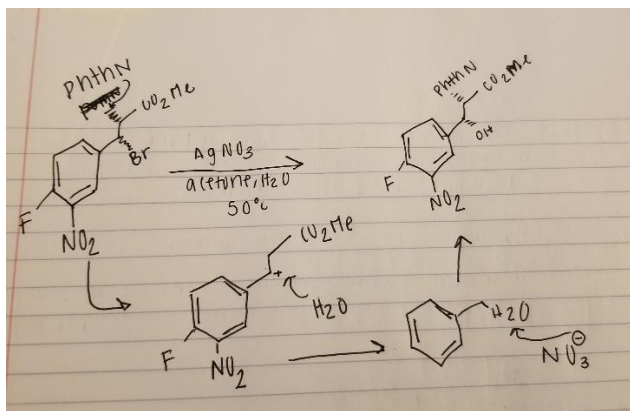
9) Is the substitution process SN1 or SN2? What controls the stereochemical outcome of the product? (5 pts)

The substitution process was SN1. The neighboring group has an impact of controlling the stereochemistry outcome of the product.

10) Is this process then stereoselective or stereospecific? (3 pts)

The process is stereoselective.

11) Draw the arrow pushing mechanism for the conversion of 3 to 4. (8 pts)



- 12) In attempting to convert 3 to 4 the major product is 5, how does compound 5 come about? That is by what reaction mechanism? (3 pts)

Indicating that elimination of hydrogen bromide becomes competitive with production of the corresponding and the cation does form because the elimination comes from the concerted reaction which give or elimination which also indicates E2.

- 13) The authors blame “sufficiently electron withdrawing aromatic substituents” for the formation of 5. They are trying to say the side reaction (from question 11) is more prevalent when the reaction changes from unimolecular to bimolecular. Why might electron withdrawing groups be expected to cause the reaction to change from unimolecular to bimolecular? (3 pts)

Electron withdrawing group be expected to cause the reaction to change from unicellular to bimolecular because the cation never forms. The reaction happens in concerted reaction with is E2.

- 14) Based on question 12, why might exchanging the fluoro and nitro groups to the 3-fluoro-4- nitrophenyl derivatives have a larger propensity for forming 5? You will need to remember that resonance effects "trump" inductive effects. (3 pts)

Based on question 12, the compound contains E2 which indicated that the compound had a strong base which means that their a larger probability that propensity will form.

- 15) The authors decide to change the ester of 2 to the amide of 7. Based on the transition state provided (Figure 1) why do you think that the amide is a better choice for the transformation? (4 pts)

Amides are the most unreactive of all carboxylic acid derivative. This is because of its slight double bond characteristic that reduces the leaving group ability of the nitrogen. This resonance form more prevalent among amide than it is for carboxylic acid, esters, or anhydrides.

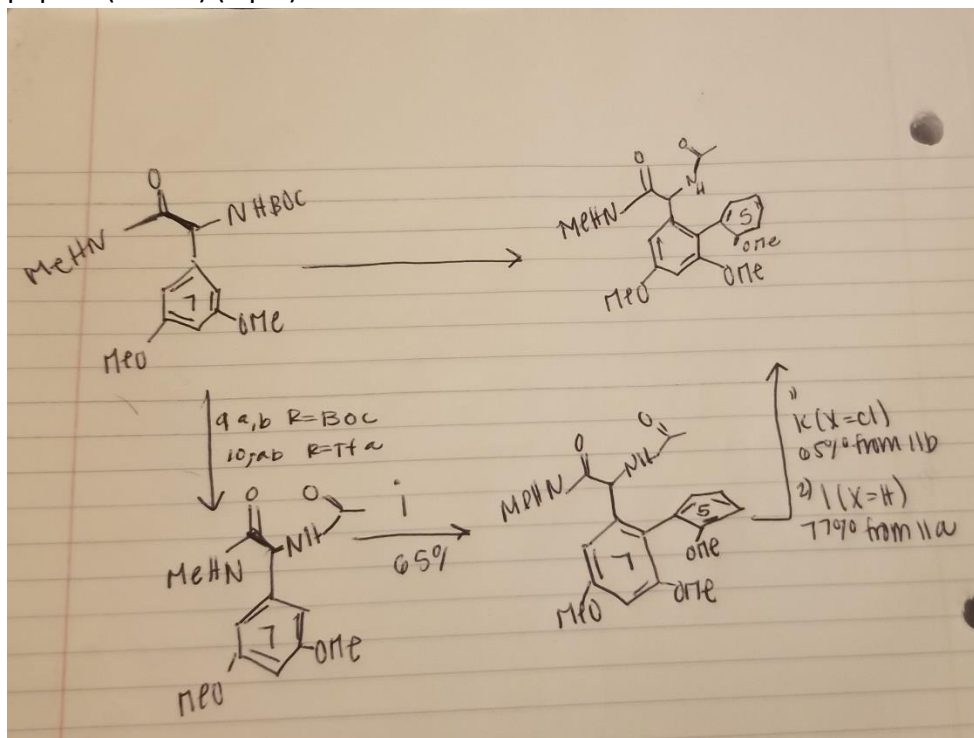
- 16) Using the percent yields in the text, what was the overall yield of 9a from 1a? (4 pts)

$1a/9a * 100 = \text{percent yields}$ $0.82 / 0.85 * 100 = 96\%$

- 17) What is Vancomycin? (ref. 2a) (2 pts)

Vancomycin is a treatment of Gram-positive bacterial infections that is used as an antibiotic.

- 18) David Evans uses his chiral auxiliary to prepare a very similar compound in his synthesis of vancomycin. Draw the step, starting material and product, that Evan's uses his auxiliary to prepare the same alcohol stereocenter as that prepared in the Hutton paper? (ref. 2a) (3 pts)



- 19) Instead of using directing groups or chiral auxiliaries the Wong group showed that an enzyme can be made to perform a similar reaction in a flask and provide enantiopure products. What is an enzyme and what is the name of the enzyme that can perform this transformation? (ref 7) (5 pts)

Enzymes are catalysts that drive reaction rates forward. Most catalysts, but not all, are made up of amino acid chains called proteins that accelerate the rate of reactions in chemical systems. The functionality of a catalyst depends on how the proteins are folded, what they bind to, and what they react with. Throughout this experiment, they were two enzymes used in this experiment, one was *Escherichia coli* L-threonine aldolase (LTA; EC 2.1.2.1) and the other one is *Xanthomonas oryzae* D-threonine aldolase (DTA).

- 20) Using "biology" to perform organic chemistry brings many challenges, what challenge did the use of DMSO help the Wong lab overcome? Hint: Simply making it fast is not correct, why has the reaction become faster? (ref 7) (3 pts)

Some of the challenges that DMSO help the Wrong lab overcome was slightly increased the yield, but the effect was not as significant compared to acetaldehyde. The increased yield in the case of hydrocinnamaldehyde might be due to the acceleration effect and the increase of substrate solubility. Since isobutyraldehyde was a poor substrate, the amount of enzyme was increased to improve the yield, but the diastereoselectivity was dramatically decreased. Use of excess amount of glycine, however, increased the yield without loss of the diastereoselectivity. Aromatic aldehydes usually gave relatively high yields but low diastereoselectivity.