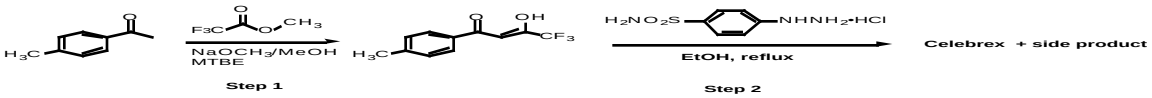
Organic Cumulative Exam

June 1999

Synthesis of Old and New NSAIDs

1. What does the acronym NSAID stand for?

2. Antiinflammatory agents are perhaps the most widely consumed type of drug in the world. These drugs represent a 5 billion dollar per year market. Thus, the organic chemistry of these drugs is medicinally and commercially important. For drugs that are produced on such a large scale, it is very important to identify simple and efficient syntheses. We will consider the syntheses of two medicinally important NSAIDs. First let's take a look at the synthesis of the new drug celebrex (celecoxib). John Talley of Monsanto/Searle told us about this drug in his talk at Organic Chemistry Day '99.



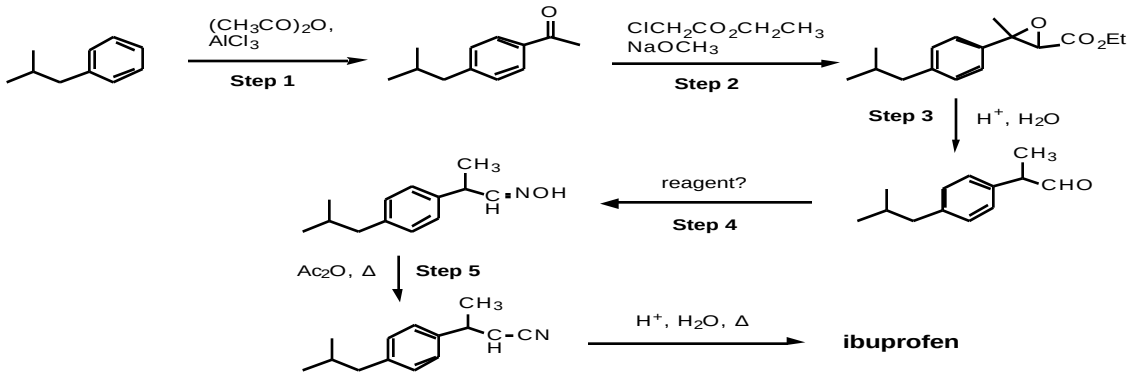
J. Med. Chem. **1997**, *40*, 1349&1356.

a) Show a detailed, arrow-pushing mechanism for Step 1.

b) Show the two major products of Step 2 and offer a detailed mechanism for their formation.

c) According to the information provided by Dr. Talley, why does celebrex represent a significant improvement over existing NSAIDs?

3. Ibuprofen is not a new drug, but it is an important NSAID. Please answer the following questions regarding the commercial synthesis of ibuprofen shown below.



(a) Show a mechanism for Step 1. What side products would you expect? What is the name of this type of reaction?

(b) Step 2 involves what is known as a Darzen's condensation. Propose a mechanism for this reaction.

(c) Provide a complete, detailed, step-by-step mechanism for Step 3.

(d) Provide the reagent and conditions required for Step 4. What is the general name for this type of product?

(e) Provide a mechanism for Step 5.

(f) Given the conditions for the final step of the synthesis draw the structure of ibuprofen.

(g) Does ibuprofen possess a stereogenic center? If so, do you think that the synthesis shown provides optically active drug?

(h) Offer a simple (1-3 step) synthesis for the aromatic starting material for this process.