Organic Cumulative Exam April 1998

The Schmidt Reaction

There are actually several related reactions in organic chemistry that have been given the moniker "The Schmidt Reaction" or "Schmidt Rearrangement". We'll look at a couple of them here.

1. The Schmidt Reaction of carboxylic acids involves in the conversion of an acid to an amine. Show the reagents used to effect this transformation and suggest a mechanism for the reaction. (10pts)

2. In an effort to trim down the amount of chemistry that students learn, many undergraduate textbooks no longer include the Schmidt Reaction. Most do include, however, the closely related Hofmann Rearrangement. Show a Hofmann rearrangement. (6pts)

3. Ureas are common side products formed in the Schmidt and Hofmann reactions described above. For example, when butanamide is subjected to these Hofmann reaction conditions, N,N-dipropylurea is isolated along with the desired product. Suggest how this urea forms. (6 pts)

4. What did the experiments shown below tell early researchers about the mechanism of the Schmidt and Hofmann rearrangements? (What alternate mechanism(s) do these observations rule out?) (6 pts)



5. Now for a <u>different</u> Schmidt reaction: the Schmidt reaction of ketones. The major product resulting from addition of hydrazoic acid to cyclohexanone is shown below. Suggest a mechanism for this Schmidt Reaction. (7pts)



6. A Schmidt Reaction utilizing ALKYL azides has recently been developed independently by Aube and Pearson. Aube's version is shown below. Predict the product and propose a mechanism for its formation. (10pt)

7. In the intramolecular Schmidt Reaction utilizing alkyl azides, aldehydes behave differently than ketones. The reaction shown below yields <u>two</u> products each with molecular formulas of C_5H_9NO . Spectroscopic evaluation reveals that one contains an aldehyde group and the other an amide. Suggest what the two major products are and rationalize their formation with mechanisms.(6pt)

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8. Aube expressed surprise (*JACS* **1995**, *117*, 10449) that the Schmidt reaction of alkyl azides was not developed until the 1990s, given that the "standard" Schmidt reaction has been widely used for a very long time. To explain the longstanding lack of interest in this area he suggested that the early attempts at carrying out intermolecular Schmidt reactions with alkyl azides which were quite <u>un</u>successful must have discouraged further work. Early unsuccessful attempts involved intermolecular addition of alkyl azides to ketones. Aube notes that he and Pearson have succeeded in their recent attempts largely because intramolecular Schmidt reactions are much more facile than intermolecular versions.

a) Suggest why the intramolecular Schmidt Reaction of Alkyl Azides is more facile than intermolecular versions. (4 pts)

b) Aube's group has also shown that the intermolecular Schmidt Reaction of alkyl azides can proceed if <u>titanium tetrachloride</u> is used as a catalyst (again, in explaining why this interesting reaction lay undiscovered for so long, he notes that in the 1950's the use of titanium tetrachloride was not all that common - so early researchers did not attempt titanium tetrachloride-catalyzed version of this reaction). What is the general role of $TiCl_4$? (3 pts)

c) In the old literature there is <u>one example</u> of a high-yielding Schmidt reaction using an alkyl azide. The successful reaction uses hydroxyethyl azide. The reaction with ethyl azide does <u>not</u> work. Given what we now know about this general reaction, suggest why the reaction with hydroxyethyl azide works. Show a mechanism (5 pts)



10. Pearson's group has developed related Schmidt-type chemistry (*J. Heterocyclic Chem.* **1996**, *33*, 1489). For our final question, lets take a quick look at Pearson's chemistry.



Suggest a mechanism for this transformation (7 pts).