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Stork enamine synthesis pdf

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The Stork enamine alkylation is a reaction sequence in organic chemistry that involves the addition of an enamine to a Michael acceptor or another electrophile, resulting in the formation of an alkylated iminium product. This product can then be hydrolyzed by dilute aqueous acid to produce the corresponding alkylated ketone or aldehyde. The overall process is known as the Stork enamine synthesis and offers a selective monoalkylation of a ketone or aldehyde, which may be challenging to achieve directly. The reaction also applies to acyl halides as electrophiles, resulting in the formation of 1,3-diketones (Stork acylation). Additionally, activated sp3 alkyl electrophiles, including benzylic, allylic/propargylic, and α-carbonyl alkyl halides, can be used. However, nonactivated alkyl halides generally yield low to moderate amounts of the desired alkylation product. The reaction was named after its inventor, Gilbert Stork, and has been modified to include anionic versions of enamines, such as azaenolates or metalloenamines, which can be used with less reactive electrophiles. In one variation, a carbonyl compound is condensed to form a Schiff base, which then reacts with a Grignard reagent to form a Hauser base. This species' negative charge allows for the displacement of a less reactive alkyl halide, including methyl and ethyl groups. Hydrolysis of the resulting product yields the alkylated ketone or aldehyde. The Stork enamine reaction is a useful method in biological chemistry that involves the formation of enamines as nucleophiles. These are electronically similar to enolate ions, making them behave similarly in various reactions. Enamines can be prepared by reacting ketones with secondary amines, and their increased electron density on the α carbon atom makes them nucleophilic. In the Stork enamine reaction, an enamine adds to an α,β-unsaturated carbonyl acceptor, followed by hydrolysis to yield a 1,5-dicarbonyl compound. This process is particularly advantageous over traditional enolate-ion-based reactions due to its neutrality and ease of preparation and handling. The Stork enamine reaction has applications in biological pathways, allowing for the Michael addition of ketones to α,β-unsaturated carbonyl compounds. For instance, cyclohexanone reacts with pyrrolidine to form an enamine, which can then react with an enone like 3-buten-2-one and undergo hydrolysis to yield a 1,5-diketone. This method has two key advantages: enamines are easier to handle than charged enolate ions, and they can be prepared from monoketones, whereas only enolate ions from β-dicarbonyl compounds can be used. A collection of organic compounds H2C═CHCO2Et, H2C═CHCHO, and CH3CH═CHCOCH3 are listed, along with their potential synthesis using an enamine reaction. Enamines are formed from the combination of a secondary amine and an aldehyde or ketone. This process involves the breaking of a C-O bond and the formation of a new C-C pi bond. The resulting enamine is nucleophilic due to its resonance form, featuring a negative charge on the alpha carbon. It can undergo reactions with electrophiles like alkyl halides and Michael acceptors. However, enamines are hydrolyzed with strong acid. Stepwise mechanisms involve positively charged nitrogen species. Recall that acid catalysis promotes protonation, which turns species into better leaving groups. In our case, water is the leaving group. Proton transfer from nitrogen to oxygen occurs through Deprotonation of nitrogen followed by Protonation of OH to give OH2(+). A base (B) acts as a shuttle to pick up and drop off the proton. Now that there's a free lone pair on nitrogen and a good leaving group (OH2), the stage is set for Elimination of water, resulting in an iminium salt under mildly acidic conditions. This is usually the rate-determining step. Deprotonation at the alpha-carbon can result in formation of a C-C pi bond, breaking the C-N pi bond. The final deprotonation step gives us our neutral enamine species and a molecule of water. The mechanism follows the steps Protonation Addition Deprotonation Protonation Elimination Deprotonation - PADPED! When an unsymmetrical ketone is used, the tendency is for the less-substituted enamine to be formed. Enamines have special properties because their nitrogen lone pair makes them capable of funky reactions. The nitrogen combines with the pi bond to give an extended pi system that can resonate. The nitrogen lone pair acts as a strong electron donor, forming a new C-N pi bond and resulting in resonance forms with negative charges on carbon. This property is known as "pi donation". As a result, enamines are highly nucleophilic. Hovering over an ortho carbon on an aromatic ring, for instance, would reveal similarities between an enamine and a strongly activated aromatic ring. By this analogy, we'd expect enamines to be excellent nucleophiles and react with electrophiles, which is indeed the case! The nitrogen in an enamine adopts a trigonal planar geometry due to its sp2 hybridization, allowing maximum overlap of p orbitals and facilitating delocalization that compensates for steric hindrance. Interestingly, the alkene carbon in enamines exhibits more basic properties than the nitrogen itself, as observed when treating an enamine with D+ (deuterium), resulting in the formation of a carbon-deuterium bond. Well, most primary alkyl halides react well. It's an alternative to forming C-C bonds through ketone enolate alkylation. Enamines also perform conjugate additions with alpha, beta unsaturated species like methyl vinyl ketone. The usual procedure is to add aqueous acid after the reaction, resulting in hydrolysis of the enamine and formation of a new ketone. Nucleophilic enamines can form bonds with pi-acceptors like C=O bonds, making alkenes more electrophilic. Enamines react with alpha, beta unsaturated ketones to form new ketones after proton transfer. They will also perform aldol reactions with aldehydes but this is not covered as much and the article is long enough already. Enamines are easily hydrolyzed back into aldehydes/ketones using aqueous acid (H2SO4/H2O). The reaction starts with PADPED: Protonation of the enamine, Addition of water to the resulting iminium ion, Deprotonation of oxygen, Protonation of nitrogen (making it a better leaving group), Elimination of neutral HNR2, and finally Deprotonation of oxygen to give the neutral carbonyl. Enamines can be formed through addition of secondary amine to enolizable aldehyde/ketone in mild acid presence. Enamines, which are generated from ketones or aldehydes, exhibit unique reactivity patterns. They can participate in alkylation reactions at the carbon atom with alkyl halides and also undergo conjugate addition, known as Michael reactions. Furthermore, enamines can be hydrolyzed back to their original ketone or aldehyde form using aqueous acid. This process can be thought of as a circular journey that starts with a relatively simple ketone or aldehyde. The addition of a secondary amine transforms it into an enamine, endowing it with enhanced nucleophilic properties. This allows the formation of a bond with a desired electrophile. The resulting product can then undergo hydrolysis, removing the secondary amine and restoring the original ketone or aldehyde, albeit with some modifications. This sequence bears a resemblance to the Hero's Journey concept. What would be particularly impressive is if the secondary amine could be combined with an acid catalyst to create a catalytic cycle. Interestingly, this has been achieved in certain instances, such as in the development of asymmetric organocatalysis. The 2021 Nobel Prize in Chemistry was awarded to Benjamin List and David MacMillan for their work on this topic. Some early research in this area includes the use of L-proline by List's group to perform aldol reactions with chiral enamines, as well as Macmillan's group using a chiral amine to facilitate electrophilic addition to highly reactive iminium ions. Despite being covered in second-semester organic chemistry courses, these functional groups remain an active area of research. Enamines exhibit distinct chemical properties, including proton chemical shifts, UV-vis spectra, rotation barriers, X-ray crystal structures, and acid-base reactions. The vinyl proton's chemical shift is inversely related to electron density on the carbon bearing a proton, with lower shifts indicating greater overlap. An alternative approach involves analyzing the UV-vis spectrum, which reveals that enamines absorb light at longer wavelengths than comparable alkenes due to conjugation. Another method involves observing rotation barriers, where overlap between the nitrogen lone pair and the alkene results in "partial double bond" character of the C-N bond, leading to small rotation barriers. X-ray crystal structures of enamines demonstrate sp2 hybridized nitrogen, serving as a conclusive indicator. However, comparing the basicity of the nitrogen in enamines versus their corresponding amines reveals that enamines are generally less basic due to delocalization of the nitrogen lone pair into the pi bond of the alkene. In contrast, the carbon atom in an enamine tends to be stronger base than its amine counterpart. This is attributed to the high basicity of carbon, which is enhanced by electron-withdrawing groups attached to the amines. Enamines are also capable of acid-base reactions with water, as evidenced by their measured pKa values. The positive charge in enamines is delocalized between nitrogen and carbon, differing from the protonated nitrogen. Furthermore, comparing the nucleophilicity of enamines versus enol ethers reveals significant differences, with enamines exhibiting a higher order of magnitude difference according to the Mayr Reactivity Scale. Enamine formation through alkylation or Michael addition can lead to the creation of a new enamine, which is considered the "less substituted" form due to minimized allylic strain. This new enamine can undergo easy hydrolysis with water and mild acid, making it prone to degradation if not properly handled. However, in Stork's 1963 paper, strongly electrophilic alkyl halides such as allyl, benzyl, and methyl halides were found to provide the best yields for this reaction. Enamines can also participate in various reactions, including aldol reactions with aldehydes and ketones. One notable example is the Hajos-Parrish-Eder-Sauer-Wiechert reaction, which uses L-proline as a catalyst to produce an optically enriched enone (the Hajos-Parrish ketone) used in steroid synthesis. This reaction involves an enamine that performs an intramolecular aldol reaction. References Norman Collie, Ueber die Einwirkung des Ammoniaks auf Acetessigester (1884) Georg Wittig, Hermann Blumenthal, Über die Einwirkung von Ammoniak und Ammoniak-Derivaten auf o-Acetylaceto-phenole (1927) C. Mannich, H. Davidsen, Über einfache Enamine mit tertiär gebundenem Stickstoff (1936) Gilbert Stork, Ross Terrell, and Jacob Szmuszkovicz, A New Synthesis of 2-Alkyl and 2-Acyl Ketones (1954) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, The Enamine Alkylation and Acylation of Carbonyl Compounds (1963) Enamines can be alkylated via their enamines, but yields are better with allyl halides. Allyl simple halides give almost entirely N-quaternary salts. Simply adding water to an enamine usually suffices to hydrolyze it to the corresponding carbonyl compound, unlike enol ethers which remain stable in water. This highlights the basicity of enamines towards water. All reactions involving enamines must be conducted with rigorous exclusion of water. The first step in a procedure involves synthesizing an enamine. A study on the basicity of some mono- and bicyclic enamines found that six-membered ring enamines are only slightly stronger bases than corresponding saturated amines, whereas five-and seven-membered ring enamines are much stronger bases. Pyrrolidine enamines exhibit large rotation barriers due to greater orbital overlap. The hydrolysis mechanism of tertiary enamines in acidic medium has been studied. In weakly acidic solutions, the rate of hydrolysis is determined by the addition of water to the C=N bond. In the pH range of 3 to 14 at 25°C, carbinolamine formation occurs. In weakly acidic solutions (pH 1-6), the process is slowed down by an uncatalyzed attack of water, acting as a rate-limiting factor.