1,3-Dipolar Cycloaddition-A Case study

From the results of our present study, it is clear that two 1,3-dipoles, azomethine oxide and azomethine imine, belonging to the same category exhibit a dramatic variation in their reactivity pattern with a common dipolarophile. In this section, we include our arguments to account for the observed selectivity.

As mentioned in the introductory chapter, three distinct reaction mechanisms were proposed originally for 1,3-dipolar cycloaddition. Huisgen proposed the first mechanism, which involves concerted bond formation between the dipole and the dipolarophile. Firestone proposed a stepwise mechanism involving a diradical intermediate. To date, however, no convincing experimental evidence has been reported that supports the diradical mechanism. The third possible pathway is via a zwitterionic intermediate. Huisgen experimentally proved this possibility and he described them as exceptional cases. This was the background of our present study. We deliberately selected two 1,3-dipoles, namely azomethine oxides (nitrones) and azomethine imines, belonging to allyl anion type; and a common dipolarophile, dibenzoylacetylene, an acetylene with anion stabilizing groups.

The dipole moment measurement as well as its reactions with ketenes, ketenimines, etc shows that nitrones can behave like nucleophiles. So we reasoned that if the dipolarophile contains anion stabilizing groups, it will definitely open the door to the stepwise reaction. If such an alternate pathway is possible, in addition to the electronic parameters, the steric parameters will also influence the course of the reaction. To verify this, we employed nitrones
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with varying substituents on the α–C. The experimental results confirmed the proposed mechanism, i.e., zwitterion mediated two-step reaction.

To verify the proposed mechanism involving initial nucleophilic attack, we selected azomethine imines, where we changed the electronic environment of the dipole, especially the nucleophilicity. Nucleophilicity of azomethine imine is reduced by anchoring a cyano group - an electron withdrawing group - to the nucleophilic terminus of the dipole. Here we observed the cyclisation of the zwitterionic intermediate as the most probable reaction pathway.

According to Huisgen the term concerted does not necessarily imply that the two new σ bonds are developed in the transition state to precisely the same extent. The perfect synchrony is possible to observe only in the case of systems with high symmetry in 1,3-dipole and dipolarophile. The 1,3-dipole that differs in the electrophilic and nucleophilic properties of the termini, and dipolarophile polarized by their substitution pattern, will undergo concerted but not necessarily synchronous cycloaddition (Figure 1)

**Figure 1.** Energy Profiles for concerted and stepwise mechanisms of 1,3-dipolar cycloaddition reactions.
The experimental observations can be explained by considering steric as well as electronic parameters of dipoles and dipolarophiles. In the case of nitrone cycloaddition, the significant observations are:

i) The major product formed is a 1:1 adduct when $\alpha-C$ of nitrone is sterically hindered.

ii) Formation of this 1:1 adduct can be explained only by considering a zwitterion mediated reaction pathway.

iii) The other two compounds obtained as minor became the major when steric barrier offered by the $\alpha-C$ is reduced.

iv) Sum of the $m/z$ values of minor products is exactly equal to sum of the masses of 1:1 adduct and H$_2$O. This means that hydrolysis of nitrone-DBA adduct is taking place at some stage of the reaction.

v) The isolated 1:1 adduct was separately subjected to mild hydrolysis and the set of products formed was different from the one obtained in the nitrone-DBA cycloaddition reaction. This ruled out the possibility for the hydrolysis of the isolated 1:1 adduct under the reaction condition.

vi) When the same reaction was conducted in acetonitrile containing water as well as in methanol, no noticeable change in product distribution was observed. Hence the hydrolysis step manifests at a later stage in the reaction sequence.

Together with these experimental observations, the lability/instability of $N$-aryl substituted isoxazolines and oxazolines prompted us to propose a mechanism which involves two competing pathways (Figure 2).
The pronounced nucleophilic nature of N-fluorenylidene-N-aryl nitrones as well as N-diphenylmethylene-N-aryl nitrones makes their nucleophilic attack on the acetylenic dipolarophile a rather fast process. The anion stabilizing group gives some thermodynamic stability for the zwitterionic intermediate whereas steric hindrance on $\alpha$–C of nitrones kinetically retards intramolecular cyclisation. Additionally, isoxazolines generated by direct cyclisation are unstable molecules. Since intramolecular cyclisation of the zwitterion is kinetically retarded, the system prefers other alternative pathways involving comparatively lower energy transition states where such steric hindrance is not expected. Our experimental observations are in good agreement with this argument. When substantial crowding is present on $\alpha$-C, [3,3]-sigmatropic shift was the major reaction pathway. When steric hindrance on the $\alpha$-C of nitrone is gradually reduced, intramolecular cyclisation of the zwitterion becomes more and more prominent. In the case of N-phenylmethylene-N-aryl nitrones, intramolecular cyclisation of the zwitterion is the only observed reaction pathway.

**Figure 2** Energy profile for stepwise mechanism with competing pathways.
If the rate of formation of the zwitterion lags behind the rate of its intramolecular cyclisation and if the product thus obtained is fairly stable, there is every chance for the reaction to pass through a single intramolecular pathway (Figure 3). One of the factors which influence the rate of initial nucleophilic attack is the nucleophilicity of the dipole. The rate of attack is expected to decrease with decreasing nucleophilicity of the dipole. Azomethine imine with an electron withdrawing group, for e.g., cyano group attached to the nucleophilic terminus of the dipole is employed for this purpose. The experimental observations i.e., the formation of pyrazolines as the sole product, verified our arguments.

**Figure 3.** Energy profile for a stepwise cycloaddition reaction leading to a reasonably stable compound.

Finally, we conclude that dipolar additions can follow a zwitterionic mechanism. In the absence of a favorable alternative, cycloaddition is the only observed transformation. When stage is set for lower energy alternatives, other transformations of zwitterionic intermediates might manifest.

Were we the first to observe stepwise addition in alleged 1,3-cycloadditions? The answer here is NO! Several investigators encountered but failed to recognize stepwise reaction sequences since it was
presumed that all 1,3-additions are concerted. We have shown that more credible alternative mechanisms can be proposed for the generation of products formed in some of these reactions. We suggest that a paradigm shift is obligatory here: Based on findings reported in this thesis, 1,3-dipolar addition reactions, especially those employing nitrones should not be \textit{a priori} classified as cycloadditions. These might better qualify as stepwise reactions and alternative mechanism should be considered for the generation of various products in these reactions.

Over the past several years, our group maintained an active research program on the generation of 2(3\textsubscript{\textit{H}})- and 3(2\textsubscript{\textit{H}})-furanones. Most surprisingly, while investigating the course of 1,3-dipolar additions, we serendipitously discovered facile routes for the synthesis of pharmacologically as well as synthetically significant 3(2\textsubscript{\textit{H}})-furanones through hitherto unknown pathways. We could also generate novel routes for the synthesis of highly substituted quinoline derivatives by the hydrolysis of a few 3(2\textsubscript{\textit{H}})-furanones synthesized by us.

\textit{“No great discovery was ever made without a bold guess”}.  

\textbf{Sir Isaac Newton}