

A Kinetic Study on Michael-Type Additions of Substituted Anilines to 3-Butyn-2-one

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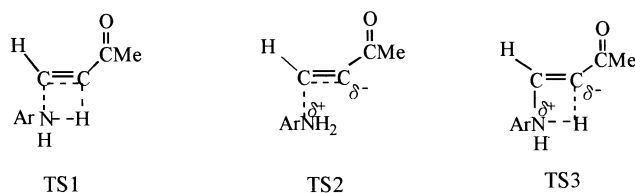
Enaminones are highly valuable intermediates, particularly in the synthesis of heterocyclic compounds and α,β -unsaturated ketones.¹⁻³ Enaminones of physiologically active amines are also known to be attractive synthons for medicinal chemists.^{1,4} Therefore, the properties and synthetic applications of enaminones have been intensively investigated.¹⁻⁵ Enaminones can be prepared from various methods, *i.e.*, from the reaction of acetone with *N,N*-dimethylformamide dimethylacetal,⁶ substitution of the chlorine in 2-chlorovinyl ketones by an amine,⁷ acetylation of aliphatic enamines⁸ and palladium assisted amination of methyl vinyl ketones.⁹ Enaminones can be also synthesized from addition of amines to an activated acetylenic moiety.^{5,10}

Although reactions of activated acetylenes with amines were reported to produce the corresponding addition products, enaminones, the kinetic study for the formation of enaminones has not been much investigated.^{5,10} We recently performed the Michael-type addition reaction of 3-butyn-2-one (**1**) with a series of aliphatic primary amines RNH₂ including α -effect nucleophiles such as NH₂NH₂ and MeONH₂, and found that the reaction yields enaminones quantitatively.^{5a,b} We also found unusually small α -effect in this system and suggested plausible reasons for the small α -effect in the acetylenic system.^{5a,b} We now expand our study to reactions of **1** with a series of aromatic primary amines ArNH₂ as shown in Scheme 1 and wish to report the reaction mechanism.

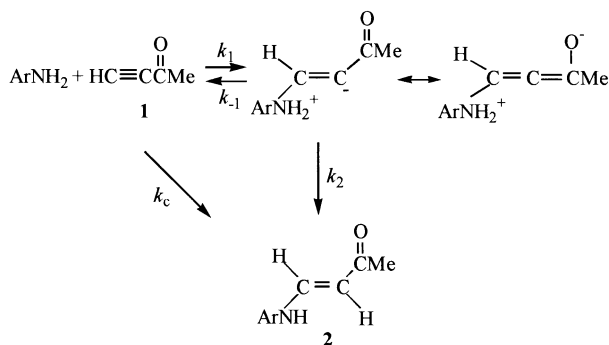
Our preliminary ¹H NMR study revealed that the nucleophilic attack by ArNH₂ occurs only at the acetylenic carbon atom to produce the enaminone **2**, but not at the carbonyl carbon atom to produce the corresponding imine. The kinetic studies were performed spectrophotometrically under pseudo-first-order conditions in which the concentration of ArNH₂ was at least 20 times in excess. Pseudo-first-order rate con-

stants (k_{obs}) were calculated from the well known equation, $\ln(A_{\infty} - A_t) = -k_{\text{obs}}t + C$, in which A_{∞} and A_t represent the absorbance at the infinite time (10 half lives) and at time t , respectively. In Table 1 are summarized the reaction conditions and k_{obs} values. Plots of k_{obs} vs [ArNH₂] are linear, and pass through the origin, indicating that general base catalysis by the second ArNH₂ molecule is absent. Second-order rate constant (k_N) values have been calculated from the slope of the linear plots of k_{obs} vs ArNH₂ concentration. The uncertainty in the k_N values is estimated to be less than 3% from the replicate runs.

The reaction of **1** with ArNH₂ may proceed through either one step concertedly with a transition state similar to TS1 (without an intermediate) or stepwisely with an intermediate as shown in Scheme 1.⁵ In the latter mechanism, two different transition states TS2 and TS3 are possible, *i.e.*, TS2 represents the transition state in the rate-determining formation of the intermediate, while TS3 applies to the rate-determining proton transfer to produce the product **2**.



The enaminones obtained in the present reactions were identified to be the *E*-isomer from ¹H NMR spectra. Since TS1 and TS3 would result in the *E*-isomer only, one can suggest that TS1 or TS3 is favored as the transition state in the present system. The proton transfer is involved in the rate-determining step for the reaction whose transition state is either TS1 or TS3. Therefore, one should have observed a large primary kinetic isotope effect (KIE), if the reaction proceeded through TS1 or TS3.^{5,11} However, in fact, deuter-

ArNH₂ = Z-C₆H₄NH₂ ;

Z = 4-CN, 3-Cl, 4-Cl, 3-MeO, H, 3-Me, 4-Me, 4-MeO, 4-OH

Scheme 1

Table 1. Experimental conditions and pseudo-first-order rate constants (k_{obs}) for Michael-type additions of Z-C₆H₄NH₂ to 3-butyn-2-one in H₂O at 25.0 ± 0.1 °C

Z	[ArNH ₂]/10 ⁻³ M	$k_{\text{obs}}/10^{-3}$ s ⁻¹
4-CN	19.9-24.9	0.250-0.325
3-Cl	4.98-24.9	0.81-4.16
4-Cl	6.10-24.4	1.48-6.17
3-OMe	4.87-17.9	1.45-5.47
H	18.2-66.9	6.93-25.2
3-CH ₃	4.54-16.7	2.52-8.98
4-OMe	4.62-17.0	6.40-22.4
4-OH	2.70-9.89	4.37-15.1

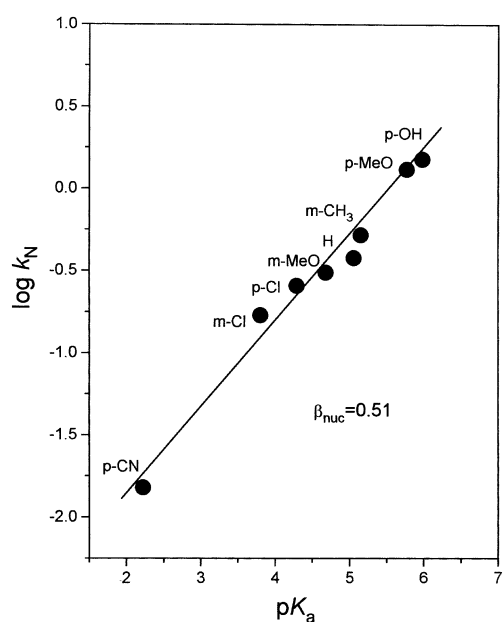


Figure 1. Brønsted-type plot for Michael-type additions of $Z\text{-C}_6\text{H}_4\text{NH}_2$ to 3-buten-2-one in H_2O at 25.0 ± 0.1 °C.

ated aniline in D_2O was found to be more reactive than aniline in H_2O , resulting in an inversed KIE ($k_{\text{N}}^{\text{H}}/k_{\text{N}}^{\text{D}} = 0.92$). The inversed KIE clearly suggests that the proton transfer is not involved in the rate-determining step but occurs rapidly after the rate-determining step. Accordingly, one can exclude TS1 and TS3, and the remaining TS2 is considered to be the most plausible transition state in the present reaction system.

In order to obtain more information on the reaction mechanism as well as the structure of the transition state, a Brønsted-type plot was constructed. As shown in Figure 1, the logarithmic second-order rate constants ($\log k_{\text{N}}$) are linearly correlated with the $\text{p}K_{\text{a}}$ values of the conjugated acids of anilines. A linear Brønsted-type plot indicates that there is no mechanism change upon changing the basicity of the nucleophiles, while a break or a curvature in a Brønsted-type plot is suggestive of a change in the reaction mechanism or in the rate-determining step of a multistep reaction.¹² Therefore, one can suggest that the reaction mechanism does not change upon changing the basicity of ArNH_2 in the present system, *i.e.*, the transition state is similar to TS2 and the rate-determining step is the k_1 step in Scheme 1.

The magnitude of β_{nuc} values has been suggested to represent relative degree of bond formation between the substrate and nucleophiles or relative degree of charge development on the nucleophilic atom at the rate-determining transition state.¹² The β_{nuc} value in the present system has been calculated to be 0.51, which is much larger than the one obtained from the reaction of **1** with RNH_2 ($\beta_{\text{nuc}} = 0.32$).^{5a} Therefore, one can suggest that the degree of bond formation between the substrate and nucleophile or the degree of positive charge developed on the nitrogen atom of amines is more significant for the reaction with ArNH_2 than with RNH_2 .

The magnitude of β_{nuc} values has been also used as a measure of the selectivity parameter.¹²⁻¹⁴ It has been generally

known that more reactive reaction system results in smaller β_{nuc} value for a variety of reactions and vice versa. Therefore, the reactivity-selectivity relationship has been accepted as a principle.^{13,14} However, this principle is no longer regarded as general because many exceptions have been found.^{13,14} In fact, ArNH_2 is found to be more reactive than RNH_2 in the reaction with **1**. Since the more reactive ArNH_2 results in a larger β_{nuc} value than the less reactive RNH_2 , the reactivity-selectivity principle is not valid in the present system.

In conclusion, enaminones **2** can be prepared quantitatively from the reaction of **1** with ArNH_2 without general base catalysis. The enaminone formation reaction proceeds stepwisely through TS2 and the rate-determining step is the k_1 step. The reactivity-selectivity principle is not valid in the reactions of **1** with ArNH_2 and RNH_2 .

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