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Mechanistic studies of amination of ketenimines: change of rate-determining step by N-substituents through electronic effects

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Abstract—Vinylidenediamine intermediate was not found in amination reactions of *N*-*i*-propyl-*p*-substituted-phenylketenimines **3a**–**3e** with *n*-$BuNH_2$, but it was found in amination reactions of *N*-*p*-substituted-phenylphenylketenimines **1a**–**1c** with *n*-$BuNH_2$ by low-temperature ^1H NMR spectrometer, indicating that the rate-determining step is changed from the first step (C═N addition) to the second step (tautomerization) when N-substituent of the ketenimines is changed from *i*-propyl group to *p*-substituted-phenyl group. Amination reactions of ketenimines **5** and **10** in a solvent with $\varepsilon=35.9$ were designed to explore electronic effects of N-substituents on the amination reactions by means of ab initio calculations. Computation results at level of MP2/6-31+G*//HF/6-31+G* (Onsager model) show that significant electronic stabilization of the first transition state involving C═N addition by *N*-phenyl group is the major factor causing the change of the rate-determining step for the amination reactions.

1. Introduction

Chemistry of ketenes and ketenimines has been intensely studied for a century.[1] They are important reactive intermediates, which may occur as transients in many thermal and photochemical reactions.[1,2] There has been intense interest in their addition reactions, including cycloadditions,[3] nucleophilic additions,[2b,f,4] electrophilic additions,[5] and radical additions.[6] Both amination of ketenes[2f,4c–f] and hydration of ketenimines[2b,4h,i] generate the amide functional group, which is a repeating unit in peptides and other synthetic polymers like nylon.

There was a mechanistic controversy regarding where an initial addition occurs on ketenes and ketenimines when they reacts with amines.[2f,4c–f,7,8] Recent results[2f,4c–f,7] confirm that they are two-step reactions and involve an initial addition of an amine to C═O or C═N, followed by tautomerization. In the recent literatures regarding amination reactions of ketenimines[7] or ketenes,[2f,4d,e] intermediates of vinylidenediamines or enol amides were found, indicating that the rate-determining step is the second step involving tautomerization.

In our previous research, we found that reaction of *N*-phenylphenylketenimine **1a** with *n*-butylamine involves two steps including an initial addition to C═N, followed by tautomerization to give amidine **2a**.[7] The reaction runs fast at room temperature, so the metastable intermediate of vinylidenediamine was caught and identified by means of low-temperature proton NMR. In the low-temperature proton NMR experiment, it was found that the second step involving tautomerization is much slower than the first addition step.[7] On the other hand, when we changed N-substituent of the ketenimine from phenyl group to *i*-propyl group **3a** and did the same amination reaction, surprisingly no intermediate was found at all by means of the low-temperature proton NMR. In this article, we designed model reactions and used ab initio calculations to inspect how and why the rate-determining step of these amination reactions is changed. To our knowledge, this is the first example to demonstrate change of rate-determining step in the reactions of ketenimines and ketenes (Scheme 1).

2. Computational details

All the calculations reported here were performed with Gaussian98 program.[9] The Onsager self-consistent reaction field (SCRF) model has been used to monitor systems in a solvent with dielectric constant of 35.9 which is close to that of acetonitrile. The model treats the solvent as a continuum of uniform dielectric constant (the reaction field) and the solute is placed into a fixed spherical cavity of radius a_0 within the solvent. The radius a_0 of the cavity for each solute was evaluated based on its optimized structure in the gas

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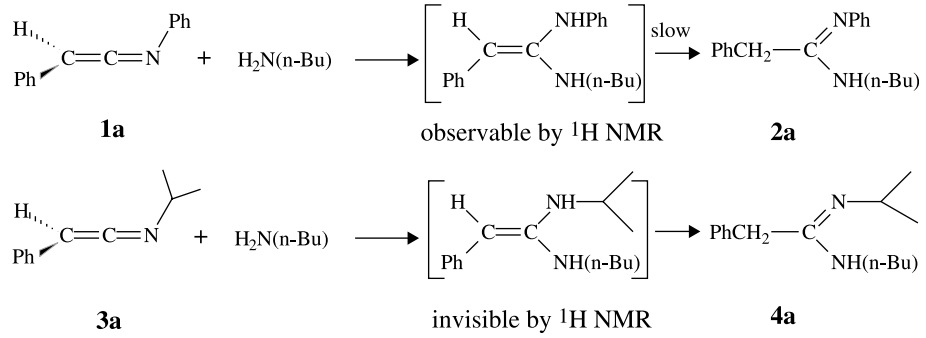


Scheme 1.

phase. SCRF geometry optimizations of **5–14** were carried out at level of HF/6-31+G* in solvent (ε=35.9) without any symmetry restriction. Many possible conformations have been optimized for each of these configurations, and the conformation with the lowest energy was chosen for each configuration. Their optimized structures are shown in Figure 1. An SCRF frequency calculation at each of SCRF optimized structures was run at the same level and analytical

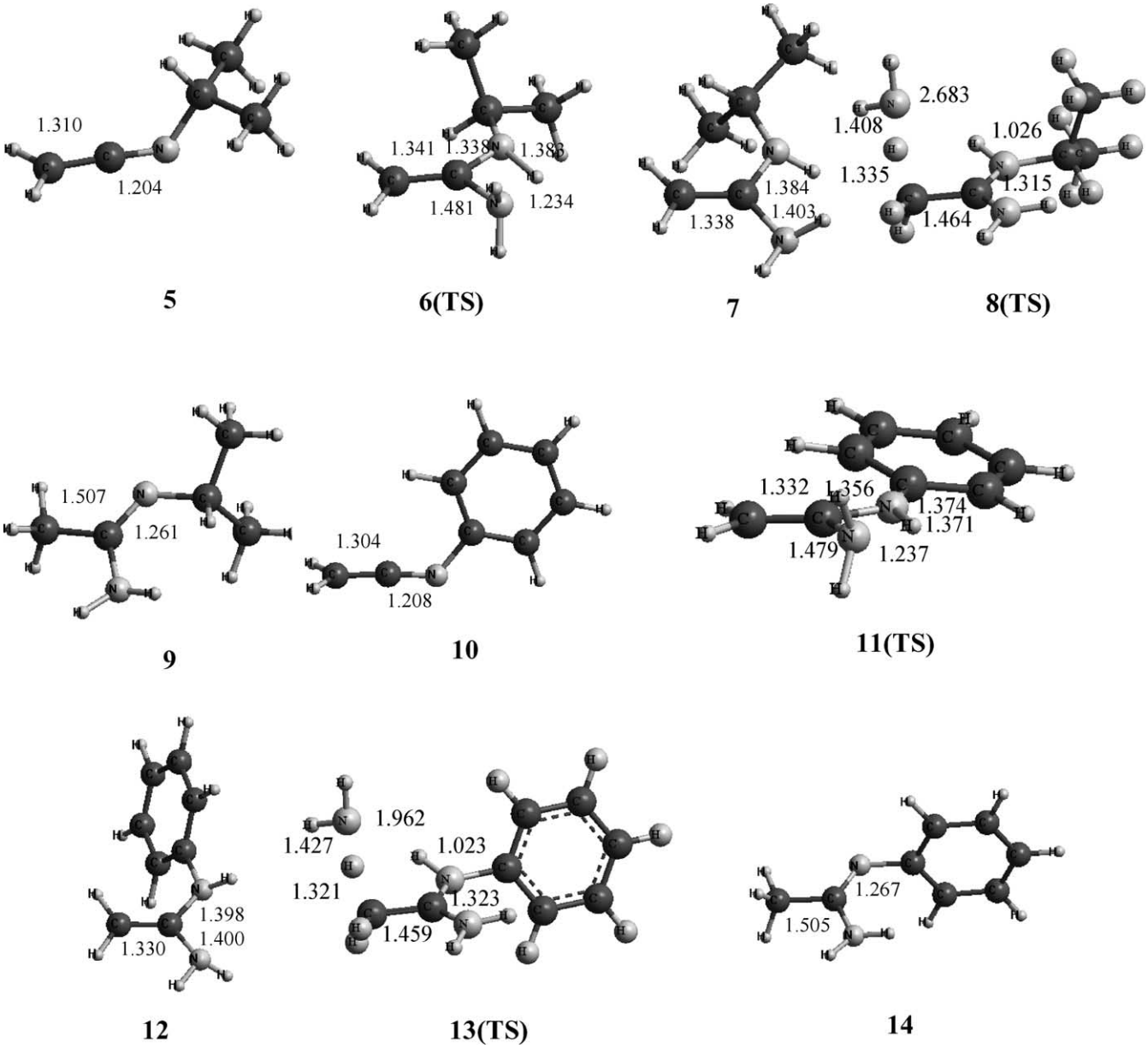


Figure 1. SCRF optimized structures of **5–14** at level of HF/6-31+G* (Onsager) in a solvent (ε=35.9). Bond lengths are in Å.

Table 1. Calculated energies (hartree), imaginary frequencies (cm^{-1}), and spherical cavity of radius a_0 (Å) of stationary points along amination of ketenimines in solvent ($\varepsilon=35.9$) at MP2/6-31+G*//HF/6-31+G* Level (Onsager model)

Stationary point	a_0	Energy	Imaginary frequency	Stationary point	a_0	Energy	Imaginary frequency
5	3.86	−249.66817		**10**	4.04	−362.47773	
6(**TS**)	4.29	−305.95331	−2109	**11**(**TS**)	4.66	−418.77114	−2115
7	4.06	−306.02672		**12**	4.41	−418.83987	
8(**TS**)	4.23	−362.31219	−1880	**13**(**TS**)	4.60	−475.12451	−1825
9	4.22	−306.05061		**14**	4.46	−418.86874	
NH_3	2.77	−56.33085					

vibration frequencies were calculated to determine the nature of the located stationary points. Thus, all the stationary points found were properly characterized by evaluation of the harmonic frequencies. The energies of all the stationary points were calculated at MP2/6-31+G* with scale zero-point vibration energies included, and population analyses of **5** and **10** were carried out at the same level. (Table 1) The scale factor of 0.9135 for zero-point vibration energies is used according to the literatures.[10] As shown in Table 2,[10] it was reported that the Onsager model at MP2/6-31+G* level gives the best prediction results for the energy difference between the *gauche* and *trans* conformers of dichloroethane in several solvents.[10] Therefore, the Onsager model at MP2/6-31+G* level was used in this research to predict the reaction mechanism of the amination of ketenimines.

Table 2. Predicted energy differences (ΔE) between the *gauche* and *trans* conformers of dichloroethane in four solvent environments

Medium	ΔE (kcal/mol)			
	Onsager		IPCM	Exp.
	HF/6-31+G*	MP2/6-31+G*	B3LYP/6-31+G*	
Gas phase	1.96	1.51	1.76	1.20
Cyclohexane	1.32	0.99	1.45	0.91
Pure liquid	0.50	0.29	0.90	0.31
Acetonitrile	0.30	0.13	0.73	0.15

3. Results and discussion

When we studied the amination of *N*-phenylphenylketenimine **1a** with *n*-butylamine in CD_3CN at −10 °C by proton NMR spectrometer, the vinylidenediamine intermediate was caught and we found that it involves two steps, C=N addition and tautomerization, and the second step is much slower than the first step.[7] The same reaction mechanism was found for amination of other *N*-*p*-substituted-phenyl-phenylketenimines **1b** and **1c** with *n*-$BuNH_2$ by monitoring the reactions with proton NMR spectrometer in CD_3CN at −10 °C Scheme 2). One representative example is shown in Figure 2.[7] On the other hand, reactions of *N*-*i*-propyl-*p*-substituted-phenylketenimines **3a**–**3e** with *n*-$BuNH_2$ in CD_3CN are much slower than those of **1a**–**1c** with *n*-butylamine, so they were monitored by proton NMR spectrometer at 10 °C Scheme 3). Surprisingly, there is no intermediate found for each of the reactions, and one representative example is shown in Figure 3. To find out this strange result, reactions of ketenimines **5** and **10** with NH_3 were monitored by ab initio calculations in the solvent with $\varepsilon=35.9$.

The major structure difference between **1a**–**1c** and **3a**–**3e** is N-substituent. To avoid inaccurate calculations due to too many atoms,[10] the investigated molecules need to be simplified, so ketenimines **5** and **10** were chosen as model substrates in order to inspect N-substituent effects on the amination reactions. Amination reactions of **5** and **10** with NH_3 were monitored at the MP2/6-31+G* level in the solvent with dielectric constant of 35.9.

In early studies, theoretical[8a,b] and kinetic studies[8c–e] of amination of ketenes were interpreted as involving initial addition to the C=C bond of ketenes. Later on, high-level ab initio calculations[4c,e] and kinetic studies[2f,4d–f,l–m] overthrew the previous mechanism and suggested the amination reactions proceed via amine addition across the C=O bond of ketenes, followed by tautomerization. Meanwhile, some labile intermediate of amide enols from amination of ketenes were caught by IR[2f,4e,l] and UV[4m] spectrometers, and a stable amide enol from the amination of a crowded diarylketene was even isolated.[4f] Similarly, the amination of ketenimines was found to proceed via amine addition across the C=N bond, followed by tautomerization, much easier than via amine addition across the C=C bond by high-level ab initio calculations in both gas phase and solution,[7] and the metastable intermediate of vinylidenediamine was caught and identified by means of low-temperature proton NMR spectrometer.[7] Therefore, the amination reactions of **5** and **10** were designed to involve the two steps, C=N addition and tautomerization (Scheme 4).

According to preliminary results of kinetic studies for the amination reactions of **1a**–**1c** and **3a**–**3e** with *n*-$BuNH_2$ in CH_3CN, C=N addition of these ketenimines involves one molecule of *n*-$BuNH_2$.[11] Therefore, C=N addition of **5** and **10** are designed to involve one molecule of NH_3. Because suprafacial 1,3-hydrogen shift is thermally forbidden,[12] tautomerization of vinylidenediamines **7** and **12** without catalyst is unlikely. Therefore, we designed tautomerization of **7** and **12** to be catalyzed by one molecule of NH_3, forming amidines **9** and **14**.

Calculated activation enthalpies, activation entropies, activation free energies, enthalpies, entropies, and free energies for the amination reactions of **5** and **10** with NH_3 are shown in Table 3. Both C=N addition of **5** and tautomerization of **7** are exothermic reactions, and activation free energy of the former is 5.1 kcal/mol more than that of the latter. This indicates that the first step involving C=N addition is a rate-determining step in the amination reaction of **5** with NH_3. That is the reason why there is no intermediate found by low-temperature proton NMR spectrometer in the amination reactions of **3a**–**3e** with

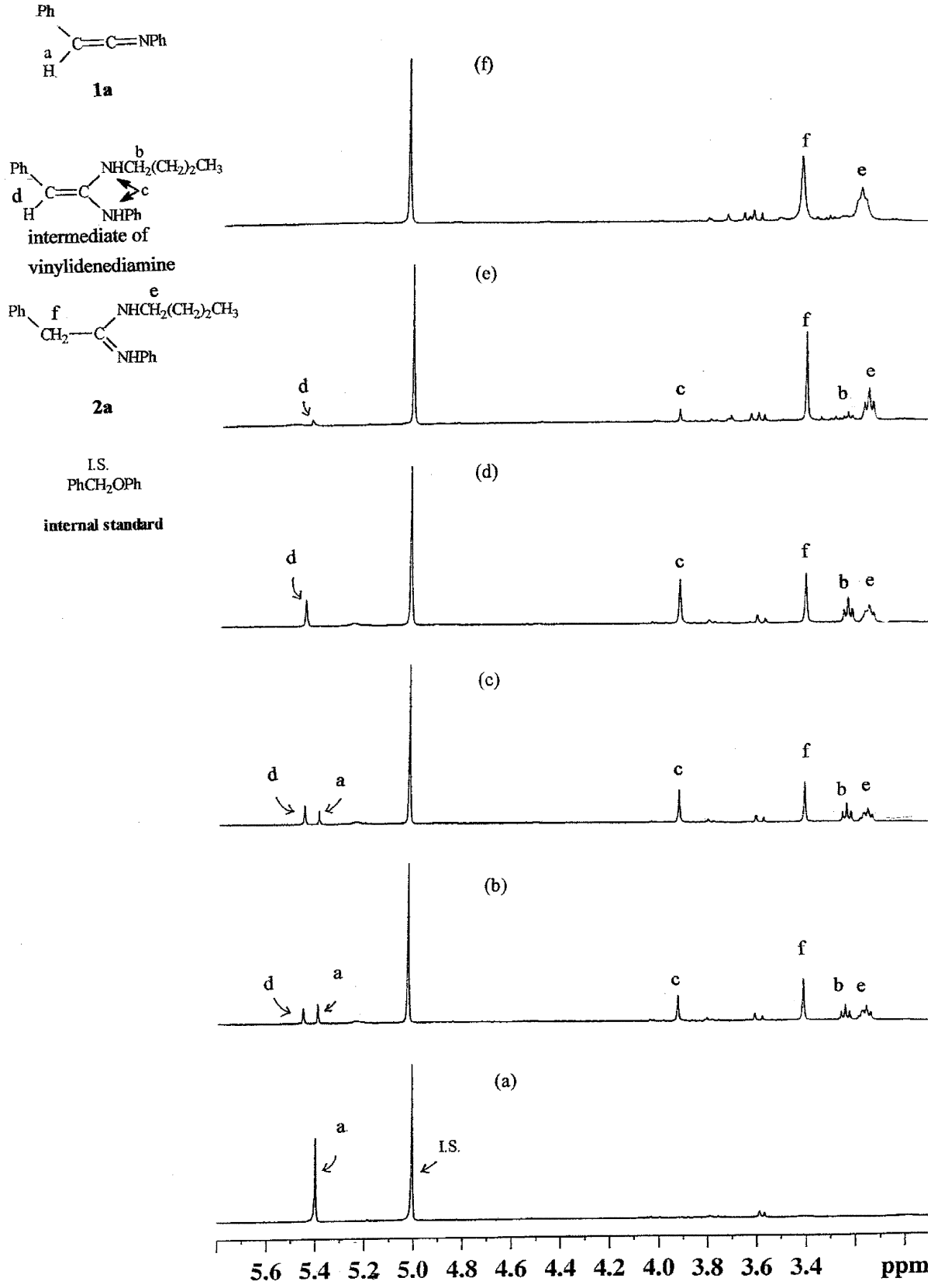


Figure 2. Part of ^{1}H NMR (CD_3CN) spectra for the reaction of **1a** with *n*-butylamine in the presence of an internal standard (benzyl phenyl ether) at −10 °C (a) before adding *n*-butylamine, (b) at 10 min after mixing the solution, (c) at 14 min, (d) at 45 min, (e) at 19 h, and (f) at 30 min after increasing the temperature to 25 °C.

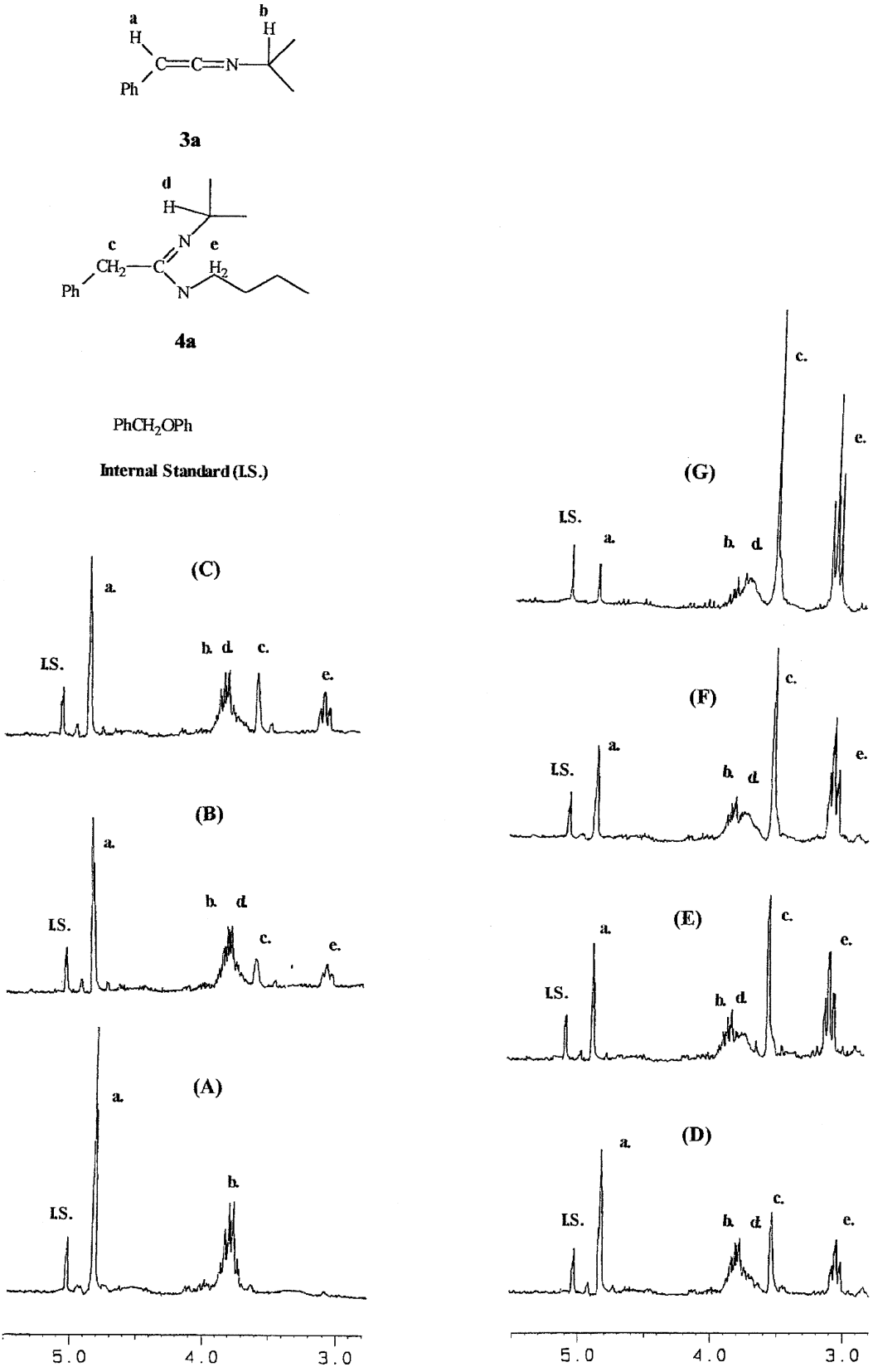
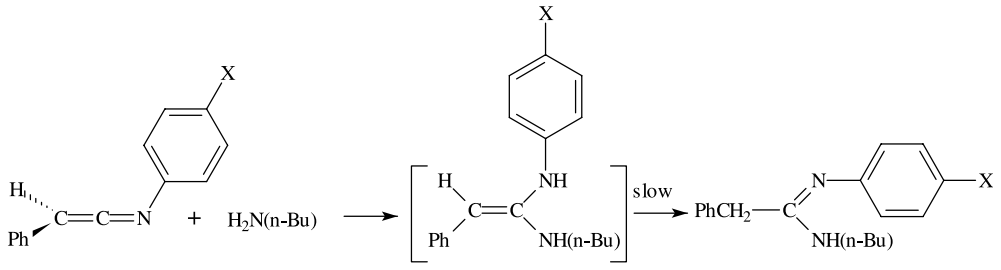
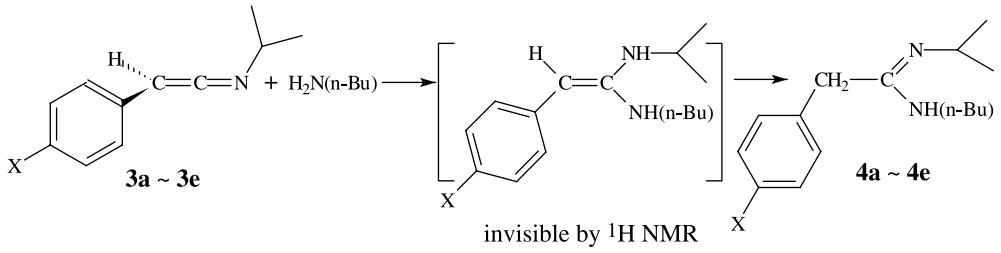


Figure 3. Part of ^{1}H NMR (CD_3CN) spectra for amination of **3a** with *n*-$BuNH_2$ in the presence of benzyl phenyl ether as an internal standard at 10 °C (A) before adding *n*-$BuNH_2$, (B) at 5 min after mixing the solution, (C) at 20 min, (D) at 40 min, (E) at 100 min, (F) at 130 min, (G) at 250 min.



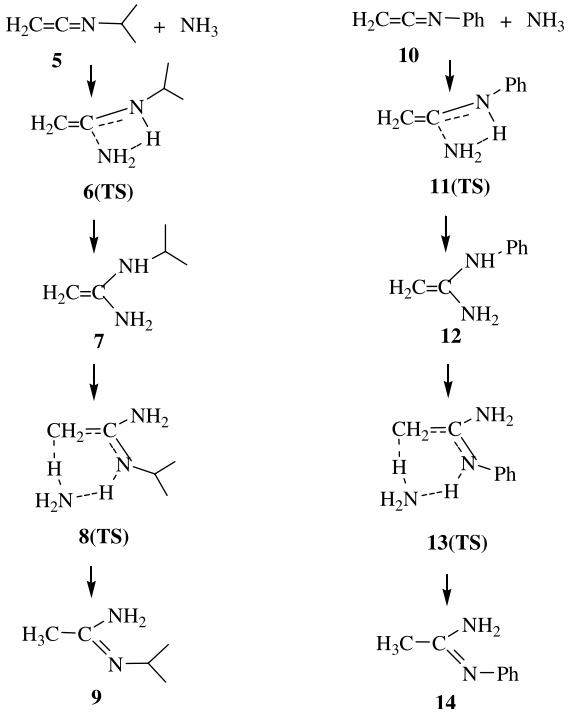
1a, **2a**: X = H ; **1b**, **2b** : X = OMe ; **1c**, **2c** : X = Br

Scheme 2.



3a, **4a**: X = H ; **3b**, **4b** : X = CH_3 ; **3c**, **4c** : X = OMe ; **3d**, **4d** : X = Cl ; **3e**, **4e** : X = NO_2

Scheme 3.



Scheme 4.

n-$BuNH_2$ in CD_3CN. On the other hand, both C═N addition of **10** and tautomerization of **12** are exothermic reactions, and activation free energy of the former is 0.33 kcal/mol less than that of the latter, indicating that the second step involving taumomerization becomes a rate-determining step in the amination reaction of **10** with NH_3. This is consistent with the experimental results that the metastable vinylidene-diamine intermediates were caught by low-temperature proton NMR spectrometer in the amination reactions of **1a**–**1c** with n-$BuNH_2$ in CD_3CN.

Activation free energy for tautomerization of **7** is very close to that for tautomerization of **12**, indicating that electronic effects of N-substituent make little difference in the tautomerization processes. In contrast, activation free energy for C═N addition of **5** with NH_3 is 4.69 kcal/mol more than that for C═N addition of **10** with NH_3, indicating that *N*-phenyl group strongly stabilizes the transition state in the C═N addition process of **10** with NH_3. This is the major reason why the rate-determining step is changed from the first step (C═N addition) to the second step (tautomerization) when N-substituent of the ketenimines is changed from *i*-propyl group **3a**–**3e** to *p*-substituted-phenyl group **1a**–**1c** in the amination reactions. Because steric effect of phenyl group is very close to that of *i*-propyl group,[13] it turns out that electronic effects, instead of steric effect, control the change of the rate-determining step in these amination reactions.

Table 3. Calculated activation enthalpies (kcal/mol), activation entropies (cal/mol K), activation free energies (kcal/mol), enthalpies (kcal/mol), entropies (cal/mol K), and free energies (kcal/mol) for amination of **5** and **10** in the solvent ($\varepsilon=35.9$) at MP2/6-31+G*//HF/6-31+G* level (Onsager model)

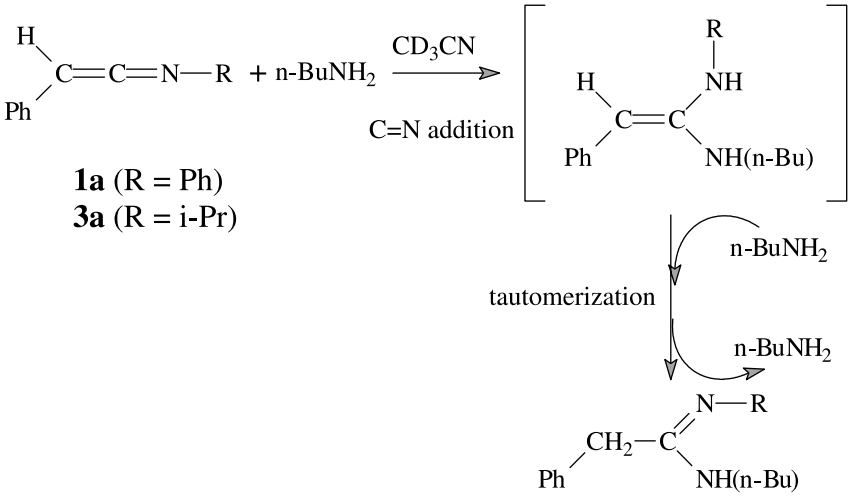
	$\Delta H^{\ddagger}$ (298 K)	$\Delta S^{\ddagger}$ (298 K)	$\Delta G^{\ddagger}$ (298 K)	ΔH (298 K)	ΔS (298 K)	ΔG (298 K)
Process: **5**+NH_3→**6**(**TS**)→**7**						
	28.25	−40.44	40.30	−13.85	−40.54	−1.77
Process: **7**+NH_3→**8**(**TS**)→**9**+NH_3						
	25.27	−33.31	35.20	−15.37	1.99	−15.96
Process: **10**+NH_3→**11**(**TS**)→**12**						
	23.46	−40.78	35.61	−16.07	−39.67	−4.25
Process: **12**+NH_3→**13**(**TS**)→**14**+NH_3						
	25.62	−34.61	35.94	−18.52	3.22	−19.48

Rate constants for the amination reactions of ketenimines **1a** and **3a** with *n*-$BuNH_2$ in CD_3CN were measured by means of low-temperature proton NMR spectrometer and their results are shown in Table 4. The rate constants of the first steps (C=N addition) for the amination of ketenimines **1a** and **3a** were measured by following disappearance of ketenimines. Their pseudo-first-order rate constants are $1.52\times10^{-3}\ s^{-1}$ (at −10 °C) for the amination of **1a** and $9.18\times10^{-5}\ s^{-1}$ (at 10 °C) for the amination of **3a**, and the corresponding second-order rate constants are $3.04\times10^{-3}\ M^{-1}\ s^{-1}$ (at −10 °C) and $1.84\times10^{-4}\ M^{-1}\ s^{-1}$ (at 10 °C), respectively, indicating that *N*-phenyl ketenimine makes the C=N addition step much faster during the amination reaction than *N*-*i*-propyl ketenimine does. These experimental results are well consistent with our computation results that *N*-phenyl group strongly stabilizes the transition state in the C=N addition process of amination of ketenimines.

The rate constant of the second step (tautomerization) for the amination of ketenimine **1a** was measured by following appearance of amidine product. The pseudo-first-order rate constant are $3.00\times10^{-5}\ s^{-1}$ (at −10 °C), and the corresponding second-order rate constants are $6.00\times10^{-5}\ M^{-1}\ s^{-1}$ (at −10 °C), indicating that the tautomerization is much slower than the corresponding C=N addition, resulting in accumulation of the vinylidenediamine intermediate. On the other hand, in the case of amination of ketenimine **3a**, the C=N addition step is very slow and presumably slower than the next tautomerization step, leading to no accumulation of the vinylidenediamine intermediate. All the experimental results are consistent with our computation results that the rate-determining step is changed from the first step (C=N addition) to the second step (tautomerization) when N-substituent of the ketenimines is changed from *i*-propyl group to phenyl group in the amination reactions.

Due to lack of special NMR sample-injection system, we had problem to inject CD_3CN solution of ketenimine into a thermostated NMR tube inside a NMR spectrometer, which contained CD_3CN solution of *n*-$BuNH_2$ and internal standard and had finished shimming. To compensate this deficiency, we added *n*-$BuNH_2$, CD_3CN, internal standard, and ketenimine together in a NMR tube at liquid nitrogen temperature, and let them warm up to a preset temperature inside a NMR spectrometer for further rate-constant measurement. As shown in Table 4, this method did provide

Table 4. Pseudo-first-order and second-order rate constants of the C=N addition and tautomerization for the amination reactions of ketenimines **1a** and **3a** with *n*-$BuNH_2$ in CD_3CN by means of proton NMR spectrometer[a]



R	Temperature	C=N Addition		Tautomerization	
		k_{obs} (s^{-1})	k_2 ($M^{-1}\ s^{-1}$)	k_{obs} (s^{-1})	k_2 ($M^{-1}\ s^{-1}$)
Ph	−10 °C	1.52×10^{-3}	3.04×10^{-3}	3.00×10^{-5}	6.00×10^{-5}
i-Pr	10 °C	9.18×10^{-5}	1.84×10^{-4}	—	—

[a] All rate constants were measured at least in duplicate with maximum deviations of ±5%.

acceptable results in distinguishing N-substituent effects for the amination of ketenimines. However, this method is not accurate enough to measure temperature and concentration effects on the rate constants and linear free energy relationship (LFER) for the amination of ketenimines. Therefore, we couldn't get experimental data of activation parameters for the amination of ketenimines, which may be used to fit our computational results. Nevertheless, literature data can be used for the comparison purpose. Base-catalyzed hydration of **3a** was reported to have observed first-order rate constant of 1.3×10^{-3} s^{-1} at pH=10 and 25 °C in water,[4i] which is faster than the amination of **3a** in CD_3CN ($k_{obs}=9.18\times10^{-5}$ s^{-1} at 10 °C). Presumably, it is because water concentration in the base-catalyzed hydration reaction is much more than *n*-$BuNH_2$ concentration in the amination reaction. The base-catalyzed hydration of **3a** was reported to have the experimental activation enthalpy of 15.2 kcal/mol,[4i] which is smaller than that for the amination of **5** in acetonitrile (calculated $\Delta H^{\ddagger}$(298 K) =28.25 kcal/mol). It was reported that water solvent is involved in the transition state of base-catalyzed hydration of **3a**,[4i] and it is likely that involvement of water solvent in the transition state reduces its activation enthalpy.

Calculated activation barriers for hydration of ketenimine with H_2O and $(H_2O)_2$ addition across C=N bond in solution by PCM model at MP2/6-31G(d,p) level were reported to be 44.5 and 27.0 kcal/mol, respectively.[14] Calculated activation barriers for amination of ketene with NH_3 and $NH_3\cdot H_2O$ addition across C=O bond in gas phase at MP2/6-31G* level were reported to be 30.03 and 2.86 kcal/mol, respectively.[4c] These two examples indicate that involvement of additional water molecule in the transition states significantly reduce activation barrier. Compared with the experimental rate constants for the amination reactions of ketenimines **1a** and **3a**, the calculated activation free energies for the amination of ketenimines **5** and **10** are somewhat big, indicating that additional water molecule is likely involved in the transition states of the amination of ketenimines **1a** and **3a** during the NMR studies. Nevertheless, this does not change the finding that *N*-phenyl group strongly stabilizes the transition state in the C=N addition process of amination of ketenimines.

LUMO of ketenimines lies in the ketenimine plane with a large coefficient on C_α, so amination of ketenimine involves an in-plane nucleophilic attack on the ketenimine LUMO at C_α.[7] This can be easily seen from the optimized transition structures **6**(**TS**) and **11**(**TS**). LUMO energies of **5** and **10** were calculated to be 1.95 and 1.83 eV at MP2/6-31+G* level in the solvent with dielectric constant of 35.9 (Onsager model), indicating that *N*-phenyl substituent decreases LUMO energy of ketenimine. According to PMO theory,[12,15] *N*-phenyl ketenimine **10** with low-lying LUMO is more reactive toward nucleophilic amines than *N*-*i*-propyl ketenimine **5**, and this is consistent with both our experimental and computational results.

In the optimized transition structure of **11**(**TS**), dihedral angle between *N*-phenyl substituent and ketenimine (or enamine) plane is 12.8°, and the *N*-phenyl group is conjugated with the enamine backbone, making electron delocalization go through these groups. Bond distances in these groups can be an evidence for this electron delocalization. It is very likely that this electron delocalization provides one of ways to stabilize **11**(**TS**) significantly.

4. Conclusion

The rate-determining step of the amination reactions of **3a–3e** is the first addition step, so the vinylidenediamine intermediate cannot be found naturally. In contrast, due to electronic stabilization of the transition state of the first C=N addition step by *N*-phenyl group, the rate-determining step of the amination reactions of **1a–1c** switches to the second tautomerization step, resulting in accumulation of the vinylidenediamine intermediate. Therefore, the vinylidenediamine intermediate can be caught in the amination reactions of **1a–1c**. *N*-phenyl substituent decreases LUMO energy of ketenimine, and that makes *N*-phenyl ketenimine more reactive toward nucleophilic amines than *N*-*i*-propyl ketenimine. The transition state **11**(**TS**) for the C=N addition of *N*-phenyl ketene **10** is significantly stabilized by electron delocalization through the system.

5. Experimental

5.1. General

Ketenimines **1a** is known and other ketenimines **1b–1c** and **3a–3e** were prepared by a known procedure.[4h,i,7]

5.2. General method to prepare ketenimines 1b–1c and 3a–3e

Phosphorus pentachloride (7 mmol) was added to a solution of *N*-substituted-*p*-substituted-phenylacetamide (7 mmol) in dry benzene (20 mL). The solution was refluxed for 1 h, and the benzene and by-product of phosphorus oxychloride were removed in high vacuum. The green-yellow residue was dissolved in dry ether (20 mL) and dry triethylamine (6 mL) was added to the solution to give an instant color change to red. The reaction was refluxed for 6 h. The solution was filtered to remove insoluble ammonium chloride under nitrogen atmosphere. After evaporation of the solvent and triethylamine, crude ketenimine was obtained as red oil, and it was purified by sublimation in high vacuum with finger temperature at −196 °C. The ketenimine was diluted with hexane for storage.

5.2.1. *N*-*p*-Methoxyphenylphenylketenimine (1b). Yield: 74%; ^{1}H NMR ($CDCl_3$) δ 3.83 (3H, s, OCH_3), 5.24 (1H, s, CH), 6.92 (2H, d, J=8.2 Hz, PhH), 7.19 (2H, d, J=8.2 Hz, PhH); 7.26–7.34 (5H, m, PhH); ^{13}C NMR ($CDCl_3$) δ 55.5, 60.9, 114.6, 125.1, 125.2, 125.5, 128.9, 132.9, 133.0, 159.2, 189.4; IR (hexane) 2007 (C=C=N) cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0999. Anal. Calcd for $C_{15}H_{13}NO$: C 80.68, H 5.87, N 6.28. Found: C 80.70, H 5.81, N 6.22.

5.2.2. *N*-*p*-Bromophenylphenylketenimine (1c). Yield: 62%; ^{1}H NMR ($CDCl_3$) δ 5.30 (1H, s, CH), 7.10–7.53 (9H, m, PhH); ^{13}C NMR ($CDCl_3$) δ 61.3, 121.3, 125.4,

125.6, 125.7, 129.0, 131.9, 132.6, 139.6, 191.9; IR (hexane) 2016 (C═C═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{14}H_{10}BrN$ 270.9996, found 270.9995. Anal. Calcd for $C_{14}H_{10}BrN$: C 61.99, H 3.72, N 5.17. Found: C 61.93, H 3.77, N 5.10.

5.2.3. *N*-*i*-Propylphenylketenimine (3a). Yield: 78%; ^1H NMR ($CDCl_3$) δ 1.35 (6H, d, $J=8.5$ Hz, CH_3), 3.85 (1H, m, CH), 4.82 (1H, d, $J=2.4$ Hz, CH), 7.08–7.30 (5H, m, PhH); ^{13}C NMR ($CDCl_3$) δ 23.5, 54.6, 58.4, 124.4, 124.7, 128.7, 134.3, 184.7; IR (hexane) 2026 (C═C═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{13}N$ 159.1048, found 159.1049. Anal. Calcd for $C_{11}H_{13}N$: C 82.96, H 8.23, N 8.80. Found: C 82.92, H 8.19, N 8.89.

5.2.4. *N*-*i*-Propyl-*p*-methylphenylketenimine (3b). Yield: 66%; ^1H NMR ($CDCl_3$) δ 1.33 (6H, d, $J=5.2$ Hz, CH_3), 2.30 (3H, s, CH_3), 3.83 (1H, m, CH), 4.79 (1H, d, $J=1.8$ Hz, CH), 7.00 (2H, d, $J=8.0$ Hz, PhH), 7.07 (2H, d, $J=8.0$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 21.4, 23.5, 54.7, 58.6, 124.7, 129.4, 130.9, 134.1, 185.8; IR (hexane) 2026 (C═C═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{15}N$ 173.1204, found 173.1206. Anal. Calcd for $C_{12}H_{15}N$: C 83.18, H 8.73, N 8.09. Found: C 83.10, H 8.80, N 8.10.

5.2.5. *N*-*i*-Propyl-*p*-methoxyphenylketenimine (3c). Yield: 71%; ^1H NMR ($CDCl_3$) δ 1.30 (6H, d, $J=2.6$ Hz, CH_3), 3.80 (3H, s, OCH_3), 3.82 (1H, m, CH), 4.79 (1H, d, $J=2.0$ Hz, CH), 6.80 (2H, d, $J=5.0$ Hz, PhH), 7.00 (2H, d, $J=5.0$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 23.5, 54.7, 55.2, 58.3, 114.4, 121.1, 125.8, 157.0, 186.6; IR (hexane) 2026 (C═C═N) cm^{-1}; MS (EI) *m/z* 196 (30, M^+), 140 (45), 99 (100), 84 (25), 57 (70); HRMS (EI) *m/z* calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1153. Anal. Calcd for $C_{12}H_{15}NO$: C 76.14, H 7.99, N 7.40. Found: C 76.10, H 8.18, N 7.35.

5.2.6. *N*-*i*-Propyl-*p*-chlorophenylketenimine (3d). Yield: 59%; ^1H NMR ($CDCl_3$) δ 1.30 (6H, d, $J=2.6$ Hz, CH_3), 3.85 (1H, m, CH), 4.76 (1H, d, $J=2.0$ Hz, CH), 7.03 (2H, d, $J=5.9$ Hz, PhH), 7.20 (2H, d, $J=5.9$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 23.5, 54.7, 58.0, 125.8, 129.1, 130.6, 132.7, 183.7; IR (hexane) 2026 (C═C═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{12}ClN$ 193.0658, found 193.0656. Anal. Calcd for $C_{11}H_{12}ClN$: C 68.37, H 6.26, N 7.25. Found: C 68.40, H 6.19, N 7.31.

5.2.7. *N*-*i*-Propyl-*p*-nitrophenylketenimine (3e). Yield: 45%; ^1H NMR ($CDCl_3$) δ 1.33 (6H, d, $J=5.2$ Hz, CH_3), 3.88 (1H, m, CH), 4.76 (1H, d, $J=1.7$ Hz, CH), 7.06 (2H, d, $J=7.0$ Hz, PhH), 7.98 (2H, d, $J=7.0$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 23.3, 54.6, 57.7, 123.7, 129.9, 134.9, 143.8, 177.3; IR (hexane) 2032 (C═C═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{12}NO_2$ 190.0868, found 190.0870. Anal. Calcd for $C_{11}H_{12}NO_2$: C 69.44, H 6.36, N 7.37. Found: C 69.51, H 6.42, N 7.39.

5.3. NMR study of amination of ketenimines 1b–1c and 3a–3e

A NMR tube filled with 1 mL of a CD_3CN solution of a ketenimine (0.01 mmol) and benzyl phenyl ether (0.033 mmol, serving as an internal standard with δ 5.0 ppm) was cooled by liquid nitrogen. Pure *n*-butylamine (50 μL, 0.5 mmol) was injected into the NMR tube through a rubber cap. The solution in the NMR tube was shaken in a cold bath and then put into the NMR spectrometer. Then the reaction was monitored by proton NMR spectrometer at −10 °C for **1b–1c** and 10 °C for **3a–3e** until all the ketenimine and most of intermediate (if it exists) were consumed, and then the temperature was raised to 25 °C. Monitored ^1H NMR spectra for amination of **1a–1c** look alike with vinylidenediamine intermediate involved and one representative of them was shown in Figure 2.[7] Monitored ^1H NMR spectra for the amination of **3a–3e** look alike without any detected intermediate and one representative of them is shown in Figure 3. Final products of amidines were identified as follows.

5.4. Product analysis for amination of 1b–1c and 3a–3e with *n*-$BuNH_2$

5.4.1. *N*-Butyl-*N′*-(*p*-methoxyphenyl)-2-phenylacetamidine (2b). ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, $J=7.2$ Hz, CH_3), 1.27–1.43 (4H, m, CH_2), 3.16 (2H, t, $J=7.0$ Hz, CH_2), 3.44 (2H, s, CH_2), 6.93–7.30 (9H, m, PhH); ^{13}C NMR ($CDCl_3$) δ 13.77, 20.07, 31.17, 36.19, 41.02, 55.20, 114.21, 114.52, 125.14, 128.28, 128.43, 142.82, 143.88, 151.01, 158.53; IR (thin film) 1655 (N–═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{24}N_2O$ 296.1889, found 296.1888.

5.4.2. *N*-Butyl-*N′*-(*p*-bromophenyl)-2-phenylacetamidine (2c). ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, $J=7.2$ Hz, CH_3), 1.29–1.45 (4H, m, CH_2), 3.17 (2H, t, $J=6.8$ Hz, CH_2), 3.46 (2H, s, CH_2), 7.11–7.50 (9H, m, PhH); ^{13}C NMR ($CDCl_3$) δ 13.70, 20.12, 31.07, 36.39, 41.25, 110.63, 116.29, 125.55, 128.30, 128.74, 131.36, 142.72, 145.04, 157.09; IR (thin film) 1651 (N–═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{21}N_2$ 265.1705, found 265.1703.

5.4.3. *N*-Butyl-*N′*-*i*-propyl-2-phenylacetamidine (4a). ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, $J=7.2$ Hz, CH_3), 1.17 (6H, d, $J=6.4$ Hz, CH_3), 1.31–1.52 (4H, m, CH_2), 3.07 (2H, t, $J=6.8$ Hz, CH_2), 3.50 (2H, s, CH_2), 3.78 (1H, m, CH), 7.06–7.15 (5H, m, PhH); ^{13}C NMR ($CDCl_3$) δ 13.71, 19.73, 20.11, 31.13, 36.25, 41.30, 46.02, 125.81, 128.02, 128.83, 142.51, 157.91; IR (thin film) 1663 (N–═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{24}N_2$ 232.1939, found 232.1941.

5.4.4. *N*-Butyl-*N′*-*i*-propyl-2-(*p*-methylphenyl)acetamidine (4b). ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, $J=7.2$ Hz, CH_3), 1.17 (6H, d, $J=6.4$ Hz, CH_3), 1.31–1.52 (4H, m, CH_2), 2.31 (3H, s, CH_3), 3.13 (2H, t, $J=7.0$ Hz, CH_2), 3.64 (2H, s, CH_2), 3.80 (1H, m, CH), 7.00 (2H, d, $J=8.0$ Hz, PhH), 7.07 (2H, d, $J=8.0$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 13.75, 20.10, 21.30, 32.34, 36.65, 41.01, 46.82, 126.23, 128.52, 134.73, 141.51, 153.91; IR (thin film) 1662 (N–═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{26}N_2$ 246.2096, found 246.2095.

5.4.5. *N*-Butyl-*N′*-*i*-propyl-2-(*p*-methoxyphenyl)acetamidine (4c). ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, $J=7.2$ Hz, CH_3), 1.18 (6H, d, $J=6.5$ Hz, CH_3), 1.31–1.52 (4H, m, CH_2), 3.06 (2H, t, $J=7.0$ Hz, CH_2), 3.48 (2H, s, CH_2), 3.70 (3H, s, OCH_3), 3.80 (1H, m, CH), 6.80 (2H, d, $J=5.0$ Hz, PhH), 7.00 (2H, d, $J=5.0$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 13.95, 19.81, 20.30, 32.13, 36.95, 41.43, 46.71, 113.81,

128.82, 129.13, 154.51, 157.91; IR (thin film) 1661 (N–═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{26}N_2O$ 262.2045, found 262.2044.

5.4.6. *N*-Butyl-*N′*-*i*-propyl-2-(*p*-chlorophenyl)acetamidine (4d). ^1H NMR ($CDCl_3$) δ 0.97 (3H, t, $J=7.2$ Hz, CH_3), 1.08 (6H, d, $J=6.4$ Hz, CH_3), 1.31–1.52 (4H, m, CH_2), 3.13 (2H, t, $J=7.1$ Hz, CH_2), 3.61 (2H, s, CH_2), 3.80 (1H, m, CH), 7.03 (2H, d, $J=5.9$ Hz, PhH), 7.20 (2H, d, $J=5.9$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 14.05, 19.80, 20.90, 31.83, 36.75, 41.22, 46.53, 128.71, 130.42, 131.11, 136.53, 153.62; IR (thin film) 1662 (N–═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{23}ClN_2$ 266.1550, found 266.1549.

5.4.7. *N*-Butyl-*N′*-*i*-propyl-2-(*p*-nitrophenyl)acetamidine (4e). ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, $J=7.2$ Hz, CH_3), 1.11 (6H, d, $J=6.5$ Hz, CH_3), 1.31–91.52 (4H, m, CH_2), 3.04 (2H, t, $J=7.0$ Hz, CH_2), 3.64 (2H, s, CH_2), 3.80 (1H, m, CH), 7.05 (2H, d, $J=7.0$ Hz, PhH), 7.95 (2H, d, $J=7.0$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 14.55, 20.81, 20.98, 33.21, 37.05, 41.11, 46.57, 123.81, 129.82, 146.10, 147.26, 154.10; IR (thin film) 1660 (N–═N) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{23}N_3O_2$ 277.1790, found 277.1787.

5.5. Rate-constant measurement for amination of ketenimines 1a and 3a

Setup for the rate-constant measurement is the same as the one shown in NMR study of amination of ketenimines **1b–1c** and **3a–3e**. The rate constant for the first step, C═N addition, of the amination of ketenimine **1a** was measured at −10 °C by following disappearance rate of characteristic resonance peak at δ 5.39 which is assigned vinyl proton of ketenimine **1a**. The rate constant for the second step, tautomerization, of the amination of ketenimine **1a** was measured at −10 °C after complete consumption of **1a** by following appearance rate of characteristic resonance absorption at δ 3.42 which is assigned methylene protons of the corresponding amidine product. The rate constant for the first step, C═N addition, of the amination of ketenimine **3a** was measured at 10 °C by following disappearance rate of characteristic resonance peak at δ 4.82 which is assigned vinyl proton of ketenimine **3a**. Integration of the characteristic resonance peaks is divided by that of the characteristic resonance peak at δ 5.0 of the internal standard. Combination of the ratios with the corresponding measured time generated first-order exponential decay or rise. The Sigma Plot software was used to fit the plots in order to get first-order rate constants. All rate constants were measured at least in duplicate with maximum deviations of $\pm$5%.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.119

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