(Ph)Br (36.5 mmol) was added via syringe in one portion. The resultant mixture was stirred and warmed to room temperature over 4 h and then refluxed for 24 h. The reaction mixture was cooled to room temperature and then quenched with 100 mL of water. The two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The organic materials were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to give a dark brown residue. Distillation of the residue through a short path distillation apparatus at 134–135 °C (<0.005 mmHg) via a diffusion pump afforded 7.8 g (60% yield) of **12a**. ^{19}F NMR ($CDCl_3$): −188.9 (dd), J_{FCP} = 84 Hz, J_{FCCH} = 34 Hz, and −191.4 (dd), J_{FCP} = 88 Hz, J_{FCH} = 34 Hz. ^{31}P NMR: 10.0 (d), J_{PCF} = 85 Hz, and 10.9 (d), J_{PCF} = 89 Hz. IR: 3080 (sh, w), 3040 (sh, w), 2990 (s), 2940 (s), 1760 (s), 1735 (s), 1600 (w), 1500 (w), 1460 (m), 1380 (m), 1270 (s), 1115 (s), 1000 (s), 775 (m), and 700 (w). Anal. Calcd for $C_{18}H_{28}O_5FP$: C, 57.75; H, 7.54; F, 5.07; P, 8.27. Found: C, 58.40; H, 7.82; F, 5.29; P, 7.59.

Preparation of $(i\text{-PrO})_2P(O)CF[CH(CH_3)_2]COOEt$ (12b). A 100-mL two-necked flask equipped with a septum port, a magnetic stirbar, and a reflux condenser connected to a source of nitrogen was charged sequentially with 50 mL of THF and 6.5 g of **10b** (24 mmol). The resulting solution was stirred and cooled to −78 °C (dry ice/isopropyl alcohol bath), and then 9.6 mL of *n*-butyllithium (24 mmol) was added dropwise via syringe. Stirring at −78 °C was continued for 20 min, and then 4.3 g of $(CH_3)_2CHI$ (25 mmol) was added via syringe in one portion. The resultant mixture was stirred and warmed to room temperature over 4 h and refluxed for 24 h. The reaction mixture was cooled to room temperature and then quenched with 100 mL of water. The two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The organic materials were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to give a dark brown residue. Distillation of the residue through a short-path distillation apparatus at 77–83 °C (<0.005 mmHg) via a diffusion pump afforded 5.4 g (72% yield) of **12b**. ^{19}F NMR ($CDCl_3$): −193.7 (dd), J_{FCP} = 89 Hz, J_{FCCH} = 31 Hz. ^{31}P NMR: 11.4 (d), J_{PCF} = 89 Hz. IR: 2970 (s), 2940 (s), 1755 (s), 1740 (s), 1465 (s), 1380 (m), 1265 (s), 1180 (m), 1140 (s), 1110 (s), 1020 (s), 895 (m), 870 (w), and 750 (m). High-resolution mass spectrum (DIP, EI): mass obtained for $C_{13}H_{27}O_5FP$, $(M + 1)^+$ = 313.158 015 930 0; calculated for $(M + 1)^+$ = 313.155 670 2.

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Comparison of the Tautomerization and Hydrolysis of Some Secondary and Tertiary Enamines

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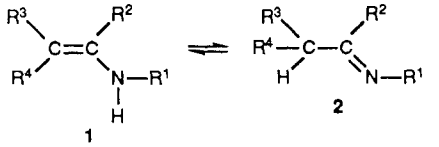
N-Phenylcyclohex-1-en-1-amine, *N*-(*p*-chlorophenyl)cyclohex-1-en-1-amine, the *N*-aryl-2-methylprop-1-en-1-amines, Me_2C = $CHNLC_6H_4X$, L = H,D, X = H, *p*-Cl, *p*-Me, *p*-MeO, *m*-NO_2, the *N*-alkyl-2-methylprop-1-en-1-amines, Me_2C = CHNDR, R = Me, Et, and the (*E*)-*N*-alkylprop-1-en-1-amines, MeHC = CHNDR, R = Me, *t*-Bu, were generated in solution from their *N*-trimethylsilyl derivatives and characterized by NMR spectroscopy. *N*-(*p*-Nitrophenyl)-2-methylprop-1-en-1-amine was isolated from the reaction of isobutyraldehyde and *p*-nitroaniline, and appreciable amounts (>10%) of the *N*-arylcyclohex-1-en-1-amines and *N*-aryl-2-methylcyclohex-1-en-1-amines were found to be present at equilibrium in DMSO-d_6 solution when the aryl group was phenyl, *p*-chlorophenyl, *m*-nitrophenyl, or *p*-nitrophenyl. The kinetics of hydrolysis of all the *N*-aryl secondary enamines obtained in the above ways were measured in aqueous solution and compared with those of the corresponding *N*-methyl tertiary enamines. With all enamines there was a region of pH in which k_{obsd} was proportional to 10^{-pH}, and under such conditions it was considered that the rate-determining step was C-protonation. This was supported by the isotope effect k_{H^+}/k_{D^+} = ca. 3, the observation of general acid catalysis, the much faster rate of hydrolysis of the corresponding imines, and the negative ρ^- values. It was found that in the cyclohexenyl series the secondary and tertiary enamines were hydrolyzed at similar rates when the substituents in the aryl group were the same, but in the 2-methylcyclohexenyl and 2-methylpropenyl series the secondary enamines were hydrolyzed much faster than the corresponding tertiary enamines. This was attributed to the tertiary enamines being hindered from attaining the most favorable conformation for p-π conjugation.

Introduction

The mechanism of hydrolysis of tertiary enamines has been studied by several groups of workers.[1-5] In general at high pHs the rate-limiting step is protonation of the double bond, and when the acidity is increased this changes to being breakdown of the intermediate carbinolamine.

Some secondary enamines are sufficiently stable to exist in detectable amounts in equilibrium with the corresponding imines. Thus, the enamine–imine equilibria (**1** ⇌ **2**) have been studied by Clark and Parker[6] and by Ahlbrecht and his co-workers[7] who showed, as expected, that the enamine is stabilized when R^3 or R^4 is methyl or aryl. It has also been possible to generate less stable



secondary enamines quantitatively or at concentrations greater than those present at equilibrium by methanolysis

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Table I. ^{1}H NMR Spectroscopic Data of *N*-Aryl-2-methylprop-1-en-1-amines and *N*-Aryl-*N*-methyl-2-methylprop-1-en-1-amines

substituent in aryl group	*N*-aryl-2-methylprop-1-en-1-amines[a]				*N*-aryl-*N*-methyl-2-methylprop-1-en-1-amines[b]			
	δ (CH_3)	δ (α-CH)	δ (Ar)	J (NH-C_αH), Hz	δ (CH_3)	δ (α-CH)	δ (Ar)	δ (NCH_3)
H	1.66	6.13	6.4–7.2	9.8	1.67, 1.76	5.78	6.5–7.4	3.0
p-Cl	1.66	6.13	6.96	9.8	1.60, 1.73	5.73	6.86	2.97
p-Me[c]	1.64	6.12	6.78	9.4	1.65, 1.75	5.76	6.83	2.98
p-MeO[d]	1.64	6.11	6.96	9.7	1.63, 1.73	5.67	6.60	2.97
m-NO_2	1.71	6.21	7.1–7.6	9.7	1.63, 1.79	5.78	6.8–7.5	3.08
p-NO_2	1.71	6.30	6.9, 8.0	9.5	1.63, 1.86	5.89	6.8–8.1	3.14

[a] In DMSO-d_6. [b] In $CDCl_3$. [c] δ (*p*-Me) = 2.15 and 2.26 for secondary and tertiary enamines. [d] δ (*p*-MeO) = 3.52 and 3.68 for secondary and tertiary enamines.

Table II. ^{1}H NMR Spectroscopic Data of *N*-Cyclohex-1-enylanilines and *N*-Cyclohex-1-enyl-*N*-methylanilines

substituent in aryl group	*N*-cyclohex-1-enylanilines[a]				*N*-cyclohex-1-enyl-*N*-methylanilines[b]			
	δ (HC=)	δ (CH_2)	δ (Ar)	% enamine	δ (CH=)	δ (CH_2)	δ (Ar)	δ (NMe)
H[c]	5.26	1.6–2.3	6.7–7.3	8	5.40	1.6–2.4	6.6–7.2	3.00
4-Cl[d]	5.22	1.6–2.05	7.05	12	5.45	1.5–2.4	6.78	2.97
3-NO_2	5.55	1.7–2.5	6.8–7.8	28	5.60	1.6–2.3	6.8–7.5	3.01
4-NO_2	5.63	1.6–2.3	6.8–8.11	56	5.60	1.6–2.3	6.58, 7.78	3.04

[a] In DMSO-d_6. [b] In $CDCl_3$. [c] This was also generated from its *N*-trimethylsilyl derivative: ^{1}H NMR δ 0.24 (s, 9 H), 1.6–2.2 (m, 8 H), 5.36 (m, 1 H), and 6.5–7.3 ppm (m, 5 H). Lit.[48] δ 0.25, 1.56–2.04, 5.32, 6.56–7.15 ppm. [d] This was also generated from its *N*-trimethylsilyl derivative: ^{1}H NMR δ 0.24 (s, 9 H), 1.6–2.2 (m, 8 H), 5.41 (m, 1 H), and 6.95 (A_2B_2, 4 H).

of the tin,[8,9] magnesium,[8,9] or lithium[10] derivatives. Primary enamines have been generated by flash thermolysis of their Diels–Alder adducts with anthracene,[11,12] and vinylamine has been generated in the gas phase by pyrolysis of ethylamine[13] and cyclobutylamine.[14]

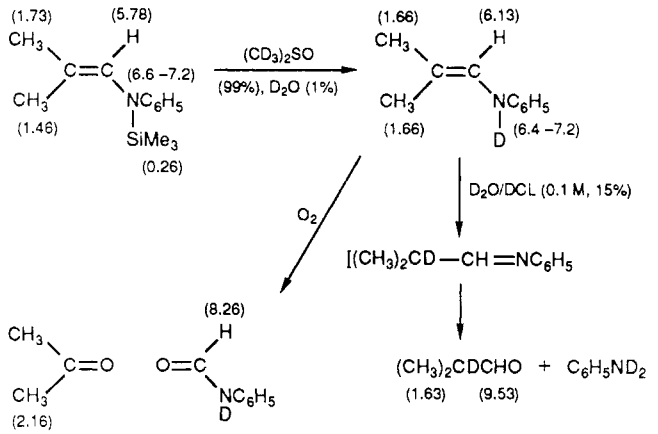
Secondary and primary enamines which carry a sulfinyl,[15] nitrile,[16] ester,[17] or nitro[18] group or two thioether groups[19] on the β-carbon of the double bond are frequently more stable than their imine forms and can be isolated. Kinetic studies on the hydrolysis of secondary enamines with cyano and ethoxycarbonyl groups on the β-carbon have been reported by Coward and Bruice[20] and by Guthrie and Jordan.[21]

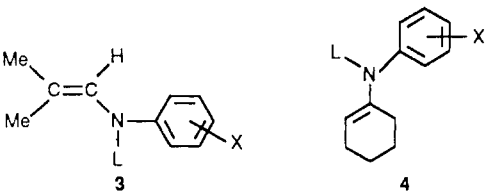
Secondary enamines have also been proposed as intermediates in certain enzymically catalyzed reactions.[22]

In this paper we report a new method for the generation of simple nonconjugated secondary enamines, hydrolysis of their trimethylsilyl derivatives, and a kinetic investigation of their hydrolyses and of the corresponding *N*-methyl tertiary enamines.

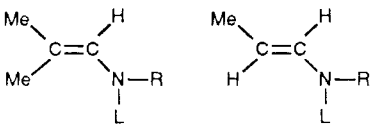
Generation of Secondary Enamines. The secondary enamines **3**, **4**, and **5** (L = D) were generated from their trimethylsilyl derivatives by hydrolysis in DMSO-d_6 (99%, v/v) and D_2O (1%, v/v). Under these conditions at room temperature the enamine was generated quantitatively in 5–10 min as demonstrated by ^{1}H NMR spectroscopy. Thus, for the generation of *N*-isobutenylaniline (**3a**, L = D) the signal of the *N*-trimethylsilyl group at δ 0.25 was replaced by that of trimethylsilanol (or hexamethyl-

Scheme I





a, X = H; b, X = *p*-Cl; c, X = *p*-MeO; d, X = *p*-Me; e, X = *m*-NO_2; f, X = *p*-NO_2. L = H, D, Me



5a: R = Me
b: R = Et
L = H or D

6a: R = Me
b: R = Bu^t
L = H or D

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Table III. ^{1}H NMR Spectroscopic Data on *N*-(2-Methylcyclohex-1-enyl)anilines and *N*-(2-Methylcyclohex-1-enyl)-*N*-methylanilines

substituent in aryl group	*N*-(2-methylcyclohex-1-enyl)anilines[a]				*N*-(2-methylcyclohex-1-enyl)-*N*-methylanilines[b]			
	δ (MeC=)	δ (CH_2)	δ (Ar)	% enamine	δ (MeC=)	δ (CH_2)	δ (Ar)	δ (NMe)
H	c	1.6–2.4	6.6–7.3	10	1.52	1.6–2.2	6.5–7.4	2.93
4-Cl	c	1.5–2.4	6.98	15	1.51	1.6–2.2	6.82	2.92
3-NO_2	1.57	1.6–2.5	7.0–81	30	1.53	1.6–2.3	6.6–7.5	3.01
4-NO_2	1.54	1.6–2.4	6.58, 8.1	60	1.49	1.6–2.4	6.78, 8.05	3.03

[a] In DMSO-d_6. [b] In $CDCl_3$. [c] Obscured by the signals of the CH_2 group.

Table IV. UV Absorption Maxima of *N*-Aryl-2-methylprop-1-en-1-amines (3, L = H) and *N*-Aryl-*N*-methyl-2-methylprop-1-en-1-amines (3, L = Me) [Aqueous Solutions]

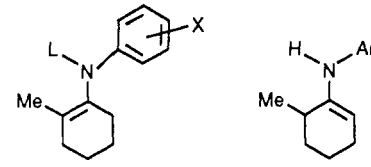
substituent	*N*-aryl-2-methylprop-1-en-1-amines λ_{max}, nm	*N*-aryl-*N*-methyl-2-methylprop-1-en-1-amines λ_{max}, nm
H	271	262
4-Cl	279	267
4-Me	270	263
4-MeO	276	260
3-NO_2	268	260
4-NO_2	432	424

disiloxane) at δ 0.05, the signal of H(1) at δ 5.78 by a signal at δ 6.13 and the two signals of the methyl groups at δ 1.46 and 1.73 by a broad singlet at δ 1.66 (see Scheme I). The solution obtained is stable for several hours, but over a period of 2–3 days the enamine is oxidized to acetone and *N*-phenylformamide.[23] If 15% (v/v) D_2O/DCl (0.1 M) is added to the solution the enamine is converted into 2-[$^2H_1$]isobutyraldehyde and aniline without the detection of any intermediates. Enamine **3a** (L = H) was also generated under conditions of slow exchange from the *N*-trimethylsilyl derivative in DMSO-d_6 (99%, v/v)–H_2O (1%, v/v) which contained 4×10^{-5} M HCl. Now a double multiplet (J = 9.8 Hz) was observed at δ 6.13 for the α-proton, and a signal at δ 7.2 was observed for the N-H. Irradiation of the latter caused the double multiplet at δ 6.13 to collapse to a single multiplet.

The other secondary enamines **3b–e**, **4a,b**, and **5** were generated similarly in DMSO-d_6 (99% v/v)–D_2O (1% v/v) solution. Their ^{1}H NMR data are given in Tables I and II (footnotes c, d). However it was not necessary to use this technique to generate the secondary enamine **3f**, which is analogous to **3a** but has a *p*-nitro substituent, as this tautomer, rather than the imine, is isolated from the condensation of isobutyraldehyde and *p*-nitroaniline.

Although the *N*-alkyl secondary enamines **5** could be generated by the acid-catalyzed hydrolysis of their *N*-trimethylsilyl derivatives those with one fewer methyl group on the double bond (**6**) could not, presumably because they are much more sensitive to acid-catalyzed hydrolysis. However if tetrabutylammonium fluoride was used as catalyst the trimethylsilyl group could be removed faster than the enamine was hydrolyzed.

The *N*-arylcyclohexenamines **4a,b,e,f**, could also be generated in DMSO-d_6 solution in equilibrium with their imine tautomers. Although the NMR spectra of the latter in $CDCl_3$ solution showed only the presence of imines, the spectra of solutions in DMSO-d_6 showed the presence of both tautomers (see Table II). The percentage of the enamine tautomer increased with increasing electron-withdrawing power of the substituent in the aryl ring, and no enamine tautomer could be detected with **4c** and **4d** when the substituent was *p*-methyl or *p*-methoxy. The *N*-aryl-2-methylcyclohexenamines (**7**, L = H) could also be generated in this way. Thus, the ^{1}H NMR spectrum of the corresponding imines in DMSO-d_6 showed a reduced intensity for the signal of the 2-methyl group and a new broad singlet at δ 1.54, which was not observed in the spectrum of a solution in $CDCl_3$ (Table III). This chemical shift was close to that of the methyl group of the corresponding tertiary enamines (δ 1.52). As with the latter[24] no vinyl signal could be detected which would indicate the presence of the tautomeric trisubstituted enamine (**8**).



7 **8**

The coupling constants J (NH-C_αH) of all of the *N*-aryl-2-methylprop-1-en-1-amines were in the range 9.4–9.8 Hz. This is similar to the value of J (OH-C_αH) found for vinyl alcohol[25] and suggests that the HN-C_αH dihedral angle is approximately 180°.

It has been reported that the *N*-isobutylideneanilines spontaneously tautomerize in CCl_4 solution to yield 15–18% of the enamines (**3**).[26] The evidence for this was the observation in the ^{1}H NMR spectrum of signals at δ 1.60 and 1.70 attributed to the protons of the methyl groups of the enamine and of a signal at δ ca. 7.70 attributed to the vinyl proton. These proposed enamines are the same as those that we have generated in DMSO-d_6 solution from their trimethylsilyl derivatives, but the chemical shift of the vinyl proton, δ ca. 6.12 (see Table I), that we find is quite different. We have re-examined the ^{1}H NMR spectrum of *N*-isobutylideneaniline in the CCl_4 solution and found similar results to those previously reported.[26] However, a solution in the $CDCl_3$ showed only signals of the imine, but when 10% (v/v) CCl_4 was added the signals at δ 1.6–1.7 and 7.7 were formed rapidly. When a solution of *N*-isobutylideneaniline in CCl_4 was left overnight it turned red, indicating that the compound was decomposing. It was therefore thought that the new signals at δ 1.6–1.7 and 7.7 are due to the formation of decomposition products of the imine in CCl_4 rather than the presence of the enamine tautomer.[27] A solution of *N*-isobutylidene-3-nitroaniline in $CDCl_3$ contains about 40% enamine at equilibrium and this shows a chemical shift δ 1.6 and 1.7 for the two methyl groups, but δ 6.10 for the vinylic proton. These are similar to the chemical shifts in DMSO-d_6 solution (see Table I) when 85% of the enamine is present at equilibrium.

UV and ^{1}H NMR Spectra of Secondary and Tertiary Enamines. As discussed frequently before[28–30] one

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Table V. ^{1}H NMR Spectroscopic Data of *N*-Alkyl-2-methylprop-1-en-1-amines and *N*-Alkylprop-1-en-1-amines and Their *N*-Trimethylsilyl Derivatives

	N-alkyl-2-methylprop-1-en-1-amines								
	N-trimethylsilyl derivatives					free enamines			
N-alkyl group	δ [$(CH_3)_2C$=]		δ (α-CH)	δ (alkyl)	δ (Me_3Si)	δ [$(CH_3)_2C$=]		δ (α-CH)	δ (alkyl)
methyl	1.63		5.56	2.54	0.08	1.57, 1.46		5.42	2.53
ethyl	1.58		5.30	2.64, 0.92	0.07	1.55, 1.44		5.45	2.77, 0.98
	N-alkylprop-1-en-1-amines								
	δ (CH_3C=)	δ (β-CH)	δ (α-CH)	δ (alkyl)	δ (Me_3Si)	δ (CH_3C=)	δ (β-CH)	δ (α-CH)	δ (alkyl)
methyl	1.67	4.25	6.28	2.54	0.10	*a*	4.17	6.08	2.46
tert-butyl	1.61	4.96	5.88	1.16	0.13	*a*	4.46	5.84	1.10

[a] Peak obscured.

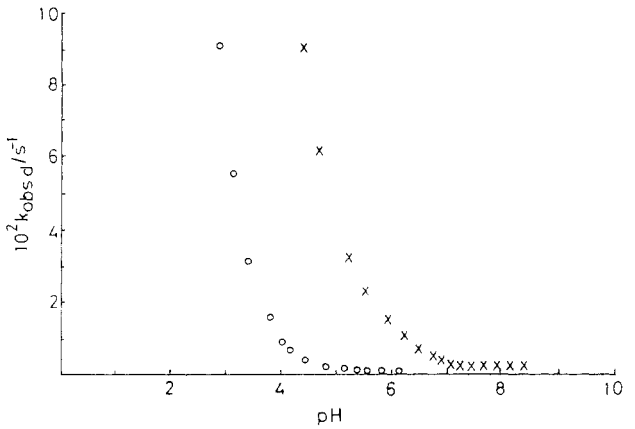
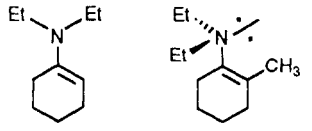


Figure 1. pH–rate profiles for the hydrolysis of *N*-phenyl-2-methylprop-1-en-1-amine (crosses) and of *N*-methyl-*N*-phenyl-2-methylprop-1-en-1-amine (circles) in water at 25.0 °C (I = 1.00 M).

of the most important factors in determining the physical and chemical propertis of enamines is the ability of the system to achieve a near to planar conformation and to maximise overlap between the π-orbital of the double bond and the lone-pair orbital on the nitrogen. Bulky substituents on the double bond and the nitrogen make it difficult for the system to achieve the most favorable conformation in the ground state or the transition state and hence have a large effect on the chemical[31,32] and physical properties.[33] This has been demonstrated very nicely by Anderson, Casarini, and Lunazzi[34] recently who showed that whereas 1-(diethylamino)cyclohexene (**9**) exists in a conformation with the lone pair "near to orthogonal to the π-plane (LPO), and the nitrogen pyramid considerably flattened so that the two nitrogen substituents are near the plane" 2-(diethylamino)-1-methylcyclohexene exists in a conformation (**10**) with the lone pair near the plane (LPP).



9 **10**

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The most important structural difference between secondary and tertiary enamines is of course that the former always carry one small substituent, a hydrogen, on the nitrogen. Hence the largest difference between secondary and tertiary enamines might be expected when the latter are hindered by the substituents on the nitrogen and on the double bond from attaining the LPO conformation.

An effect of this type is clearly indicated by the UV and NMR spectra. As shown in Table IV the λ_{max}s for the secondary enamines **3** (L = H) occur at 7–16 nm longer wavelengths than those of the corresponding *N*-methyl tertiary enamines **3** (L = Me). Since pπ conjugation of the enamine double bond would be expected to cause a bathochromic shift, these results indicate greater conjugation in the secondary than in the tertiary enamines.

In the ^{1}H-NMR spectra the signals of the α-vinyl protons of the secondary enamines **3** (L = H) appear at about 0.35–0.45 ppm lower than those of the corresponding tertiary enamines **3** (L = Me) (Table I). The pπ conjugation of the enamine system can be represented as resonance between two structures **11** and **12**. The more important the zwitterionic structure **12** in which the α-vinylic proton has an imine-like environment the more downfield its chemical shift would be expected to be. The lower chemical shift of the α-proton of the secondary enamines **3** (L = H) compared to the tertiary enamines **3** (L = Me) (see Table I) therefore suggests a greater contribution of structure B with the former, i.e. greater pπ conjugation.

11 **12**

Even with secondary enamines, however, it does not appear that pπ conjugation is always maximized as the chemical shift of the α-vinyl proton of **5a**, L = D (δ 5.42), is at 0.66 ppm higher field than that of **6a**, L = D (δ 6.08), in which the methyl group cis to the nitrogen is replaced by a hydrogen (see Table V). Further, replacement of the *N*-methyl group of **6a**, L = D, by a *tert*-butyl group as in **6b**, L = D, causes an upfield shift to δ 5.84. It is interesting that there is a large difference in chemical shift between that of the β-proton of **6b**, L = D (δ 4.46), and that of the β-proton of its trimethylsilyl derivative (δ 4.96) whereas the chemical shifts of the β-protons of **6a**, L = D, and its trimethylsilyl derivative are very similar (δ 4.17 and 4.25) (see Table V). It seems that although there is a hydrogen cis to the amino group of the trimethylsilyl derivative of **6b**, L = D, the presence of two large groups on the nitrogen, trimethylsilyl and *tert*-butyl, cause a reduction in the pπ conjugation.

A Comparison of the Kinetics of the Hydrolysis of Analogous Secondary and Tertiary Enamines. The

Table VI. Second-Order Rate Constants (k_{H^+}, M^{-1} S^{-1}) for the Hydrolysis of Enamines at 25 °C

		2-methylprop-1-en-yl series[a]		cyclohex-1-enyl series[b]		2-methylcyclohex-1-enyl series[b]	
substituent	σ	sec	tert	sec	tert	sec	tert
p-MeO	−0.27	7.44×10^5	951	–	–	–	30.5
p-Me	−0.17	7.79×10^4	262	–	–	–	12.5
H	0	1.69×10^4	97.4	6.78×10^6	4.02×10^6	1.78×10^6	4.28
p-Cl	0.23	1.53×10^3	24.6	1.99×10^6	1.74×10^6	4.85×10^5	1.18
m-NO_2	0.71	47.2	2.34	1.59×10^4	3.82×10^4	2.24×10^3	0.167
p-NO_2	0.81 1.23[c]	3.29	0.0353	560	489	76.4	5.42×10^{-3}
ρ(esd)[d]		−4.07 (0.41)	−2.54 (0.21)	−3.81 (0.50)	−2.94 (0.46)	−4.20 (0.59)	−2.25 (0.18)
ρ^-(esd)[e]		−3.43 (0.33)	−2.77 (0.14)	−3.45 (0.25)	−3.26 (0.23)	−3.71 (0.32)	−2.38 (0.11)

[a] I = 1.00 M (maintained constant with KCl). [b] I = 0.10 M (maintained constant with KCl). [c] σ^- value. [d] ρ omitting point for *p*-nitro compound. [e] ρ^-.

Table VII. Second-Order Rate Constants (k_{D^+} and Solvent Isotope Effects (k_{H^+}/k_{D^+}) for the Hydrolyses of *N*-Aryl-2-methylprop-1-en-1-amines and *N*-Aryl-*N*-methyl-2-methylprop-1-en-1-amines at 25 °C (I = 1.00 M KCl)

	N-aryl-2-methylprop-1-en-1-amines		*N*-aryl-*N*-methyl-2-methylprop-1-en-1-amines	
substituent in aryl group	k_{D^+}, M^{-1} s^{-1}	k_{H^+}/k_{D^+}	k_{D^+}, M^{-1} s^{-1}	k_{H^+}/k_{D^+}
H	4.48×10^3	3.77	30.8	3.16
m-NO_2	15.5	3.05	0.838	2.79
p-NO_2	1.04	3.16	0.0104	3.39

pH–rate profile for the hydrolysis of *N*-phenyl-2-methylprop-1-en-1-amine (**3a**, L = H) (Figure 1) was determined at 25.0 °C in solutions of ionic strength 1.00 M by following the disappearance of the enamine absorption at 271 nm. This is similar to the pH–rate profile for the hydrolysis of tertiary enamines, previously reported, in having a region at high pH (>7) at which the rate is independent of pH and a region (pH 7 to pH 5) in which the rate increases with decreasing pH, indicating catalysis by hydronium ion. The results at pHs >5 follow eq 1, but at pHs lower than

$$k_{obsd} = k_{H^+} \times 10^{-pH} + k_{H_2O} \quad (1)$$

5 deviations from the linear relationship were observed with the measured rates falling below the straight line. The pH–rate profile for the analogous tertiary enamine *N*-phenyl-*N*-methyl-2-methylprop-1-en-1-amine (**3a**, L = Me) was similar, but displaced to lower pHs by about 2 pH units (Figure 1).

Similar pH–rate profiles were obtained for the hydrolysis of the other members of these two series of enamines (Table VI) and for the secondary and tertiary enamines derived cyclohexanone (**4**, L = H and Me) and 2-methylcyclohexanone (**7**, L = H and Me). The kinetic results are summarized in Tables VI and VII.

Under these conditions no evidence was obtained for the accumulation of any intermediates. Comparison of the infinity UV spectra with those of authentic samples of the carbonyl compound and the anilines indicated that the enamines are hydrolyzed directly into the latter under these conditions. Tight isobestic points were always observed, and an investigation of the hydrolysis of *N*-isobutylideneaniline, the imine tautomer of *N*-phenyl-2-methylprop-1-en-1-amine (**3a**, L = H), showed that it was hydrolyzed much faster than the latter under these conditions. Thus k_{H^+} for the imine is 9.09×10^7 M^{-1} s^{-1} whereas k_{H^+} for the enamine (**3a**, L = H) is 1.69×10^4 M^{-1} s^{-1} at 25 °C (see Table VI).

Plots of log k_{H^+} for the hydrolyses of the enamines against the σ-values of the substituents yielded straight lines if the points for the *p*-nitro compounds were omitted. If the σ^- constant was used, the points for the *p*-nitro compounds fell on these lines. The ρ values are given in Table VI.

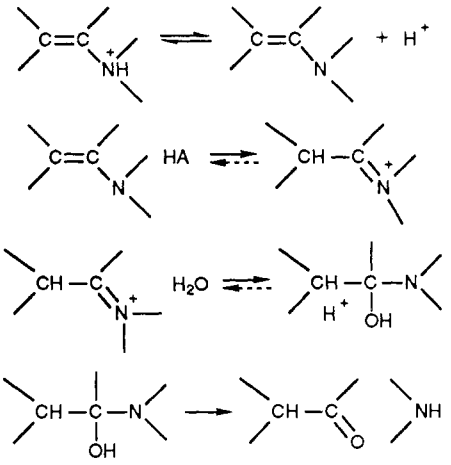
The pD–rate profiles for the secondary and tertiary enamines were also determined for the unsubstituted compounds (**3a**) and for those with *m*- and *p*-nitro substituents. The variation of k_{obsd} with pD followed eq 2, and the values of the rate constants and the isotope effects are given in Table VII.

$$k_{obsd} = k_{D^+} \times 10^{-pD} + k_{D_2O} \quad (2)$$

General acid catalysis of the hydrolysis of the *m*-nitro compounds (**3e**, L = H and Me) by acetic acid was investigated. The catalytic constant, k_{HOAc}, of the hydrolysis of the secondary enamine (**3e**, L = H) (6.43×10^{-2} M^{-1} s^{-1} at 25 °C) was 23 times greater than that for the tertiary enamine (**3e**, L = Me) (2.28×10^{-3} M^{-1} s^{-1} at 25 °C).

Discussion of Kinetic Results

As discussed by previous workers[1-5] the kinetic results obtained for the hydrolysis of tertiary enamines are best explained by the mechanism shown in eqs 3–6. Usually at high pHs the rate-determining step is C-protonation (eq 4), but this changes as the pH is lowered to hydration of immonium ion or breakdown of the carbinolamine. The pH at which this change occurs of course depends on the structure of the enamine.



In the pH range in which the rate increases linearly with acid concentration it appears that the rate-determining step in the hydrolysis of all the secondary and tertiary *N*-arylenamines studied in this investigation is C-protonation (eq 4). This fits the rate law and is in agreement with the solvent deuterium isotope effect (k_{H^+}/k_{D^+} = ca. 3, see Table VII) and the observation of general acid catalysis. It is also consistant with the negative ρ values found on substitution in the *N*-aryl group.

As with ketonization of simple enols, C-protonation of secondary enamines could proceed by a concerted (eq 7) or nonconcerted (eqs 8, 9) mechanism. However unlike with simple enols where this is a matter of controversy,[35-37] all evidence is in favor of the nonconcerted process. The concerted mechanism (eq 7) would require proton abstraction from the nitrogen of the enamine by a base or water. This is chemically unreasonable for simple enamines in view of the fact that the acidity of the N-H of an enamine would be expected to be much lower than that of an enol. For the ketonization of vinyl alcohol, the rate constant for catalysis by hydroxide ion (k_{HO^-}) is ca. 7.5×10^5 times greater than that for catalysis by hydronium ion (k_{H^+}).[35] No base catalysis, however, could be detected for the hydrolysis of secondary enamines in this study. For example, the rates of hydrolysis of *N*-phenylcyclohex-1-en-1-amine at pH 9.9 and 12.1 are, within experimental error, identical. On the other hand, the intermediate formed on C-protonation of a secondary enamine, i.e. the immonium ion **13** is thermodynamically stable species. The stepwise mechanism is therefore energetically favored. There is not a potential unstable intermediate like the O-protonated carbonyl compound in the ketonization of enols that would be avoided by a concerted mechanism.[38] This conclusion is in agreement with the isotope effects k_{H^+}/k_{D^+} which are similar for the secondary and tertiary enamines (see Table VII).

The effect of solvent composition on the k_{H^+} for hydrolysis in DMSO–H_2O mixtures also favors a nonconcerted process. Kreevoy and Williams found that k_{H^+} for the hydrolysis of ethyl vinyl ether in DMSO–H_2O mixtures decreased by a factor of about 50 on going from 0 to 60–70 mol % DMSO and then increased slightly with increasing DMSO concentration.[39] This dependence is very similar to that shown by the acidity of the medium as measured by protonation of 4-nitroaniline and is also similar to that shown by k_{H^+} for reactions which follow the A-1 mechanism.[40] On the other hand k_{H^+} for reactions which follow the A-2 mechanism[41] and k_{H^+} for the ketonization of simple enols[35,36] show a quite different dependence. The variation of k_{H^+} with solvent composition for the hydrolysis of *N*-(*p*-nitrophenyl)-2-methylprop-1-enamine and *N*-methyl-*N*-(4-nitrophenyl)-2-methylprop-1-enamine in DMSO–H_2O mixture is shown in Figure 2 along with the previously determined[35] values for the hydrolysis of ethyl vinyl ether and the ketonization of vinyl alcohol. It is seen that the secondary and tertiary enamines show similar variations with DMSO composition to one another and to that shown by ethyl vinyl ether, but quite different from the variation of k_{H^+} for the ketonization of vinyl alcohol. This evidence therefore also rules out a concerted mechanism for the reaction of the secondary enamine shown in eq 7. One might speculate that the transition state for protonation of the secondary enamine in a nonconcerted process (eq 8) would be expected to enjoy stronger H-bonding from $=^{\delta+}$N-H to DMSO than to water. However this does not appear to be important as the variation of k_{H^+} with solvent composition is so similar for the secondary and tertiary enamines.

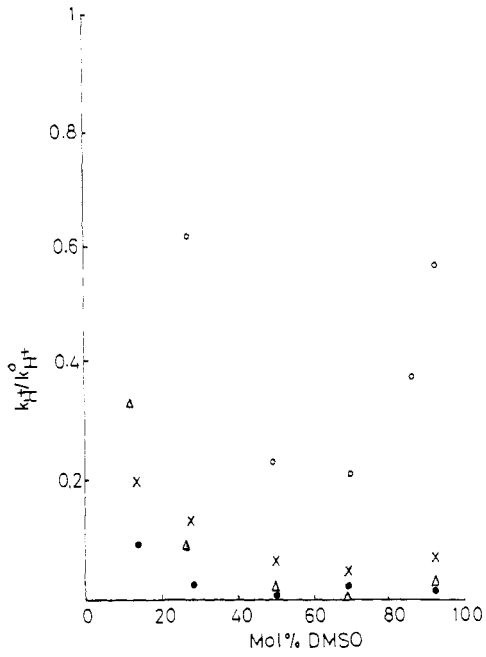


Figure 2. Dependence of rate constants for some acid-catalyzed reactions in DMSO–H_2O mixtures: hydrolysis of *N*-(*p*-nitrophenyl)-2-methylprop-1-enamine (filled circles); hydrolysis of *N*-methyl-*N*-(*p*-nitrophenyl)-2-methylprop-1-en-amine (crosses); hydrolysis of ethyl vinyl ether (triangles); and ketonization of vinyl alcohol (open circles).

The rates of hydrolysis of the relatively sterically unhindered cyclohexenyl enamines (**4**, L = H and Me) are almost the same when the substituent is the same in the secondary and tertiary series. The maximum rate ratio is 2.5 (k_{tert}/k_{sec}) found with the m-nitro compounds and the ρ^- values are very similar (−3.45 and −3.26, see Table VI). It is suggested that these enamines like 1-(diethylamino)cyclohexene[34] exist in a LPO conformation and can easily attain a transition state in which positive charge is delocalized on to nitrogen.

When a methyl group is introduced into the double bond as in (**7**, L = H and Me) the rate of hydrolysis of the secondary series is only decreased slightly. The rate decrease increases as the electron-withdrawing ability of the substituent (X) increases, and is a maximum of 7.33 when

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the substituent is *p*-nitro. This is reflected in the more negative ρ^- value (−3.71) for the series with the methyl substituent on the double bond (**4**, L = H) compared to the series without it (**4**, L = H) (−3.45). It seems that the methyl substituent can have little effect on the conformation of the ground state or transition state of this series of secondary enamines.

In contrast to the above behavior, when a methyl group is introduced onto the double bond of the tertiary enamines (**4**, L = Me) to give **7** (L = Me) there is a large (10^5–10^6) decrease in k_{H^+} for hydrolysis. Also the ρ^- value becomes less negative, changing from −3.20 to −2.38. It has been shown[34] that there is a change in conformation of 1-(diethylamino)cyclohexene from LPO to LPP when a methyl substituent is placed on the double bond. Our results suggest that a similar change takes place on going from the series of tertiary enamines (**4**, L = Me) to the methyl-substituted series (**7**, L = Me). If the latter series had a LPP conformation, attainment of the transition state for C-protonation with positive charge delocalized on to nitrogen would be more difficult and the reaction would be slower. Also the less negative ρ^- values for hydrolysis of the methyl-substituted series suggest that there may be less positive charge delocalized on nitrogen in the transition state.

Similar behavior is found with the 2-methylprop-1-en-1-yl enamines (**3**), but the difference in the rate of hydrolysis of the secondary and tertiary series is less; $k_{H^+}{}^{sec}/k_{H^+}{}^{tert}$ varies from 782 for the unsubstituted compounds to 20 for the *m*-nitro compounds. Again the ρ^- value for the tertiary series (−2.77) is less negative than for the secondary series (−3.43). As discussed above the UV and NMR spectra of these compounds suggest that the secondary enamines (**3**, L = H, D) are predominently in a LPO conformation and that the tertiary enamines (**3**, L = Me) are in a LPP conformation and, as in the methyl-substituted cyclohexenyl series, this has an effect on the rate of C-protonation.

The high reactivity of the secondary enamines may be illustrated by comparing their rates of hydrolysis with the rates of ketonization of the corresponding enols. Thus, k_{H^+} for the hydrolysis of *N*-phenylcyclohex-1-en-1-amine (6.78×10^6 M^{-1} s^{-1} at 25 °C) is ca. 1.2×10^4 times greater than k_{H^+} for the ketonization of cyclohex-1-en-1-ol (5.8×10^2 M^{-1} s^{-1}),[42] and k_{H^+} for the hydrolysis of *N*-phenyl-2-methylprop-1-en-1-amine (1.69×10^4 M^{-1} s^{-1} at 25 °C) is ca. 2.9×10^4 times greater than k_{H^+} for the ketonization of 2-methylprop-1-en-1-ol (0.59 M^{-1} s^{-1}).[42]

Tidwell and his co-workers have developed a linear free energy relationship to correlate the rate constants for the protonation of double bonds.[43] The most precise correlation was obtained for substituted cyclohexenes, and we are now able to add an additional point to this, that for the phenyl amino group, so that the reactivity range has been increased from 10^9 to greater than 10^{14} (Table VIII). The results are now correlated by

$$\log k_{H^+} = -10.2\sigma_p{}^+ - 6.9$$

where the standard deviation of the slope and intercept are 5.2 and 0.4%; $\nu = 0.9946$; $T = 19.2$ which for 4 degrees of freedom implies a confidence level of less the 0.1%.[44]

Table VIII. Rate Constants for Protonation of 1-Substituted Cyclohexenes at 25 °C

substituent	σ^+_p[a]	log k_{H^+}, M^{-1} s^{-1}
H[b]	0	−7.35
Me[b]	−0.31	−3.52
AcNH[c]	−0.65[d]	−0.74
OMe[e]	−0.78	1.63
OEt[e]	−0.82	1.90
NHPh	−1.4	6.83

[a] From Exner, O. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; pp 482–484. [b] Reference 45. [c] Reference 43. [d] Average value quoted in reference 43. [e] Reference 46.

Experimental Section

General. Boiling points and melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 157G spectrophotometer. ^1H NMR spectra at 60 MHz were measured on a Varian EM 360 or Hitachi Perkin-Elmer R-20 NMR spectrometer and at 90 MHz on a JEOL FX-90Q spectrometer. Chemical shifts are given in δ, in ppm downfield from internal tetramethylsilane. Low-resolution mass spectra were recorded on a Hitachi RMS-4 mass spectrometer and high-resolution spectra on a VG 70-70F spectrometer. Microanalyses were performed either by the Butterworth Laboratories Ltd. UK or by the Australian Mineral Development Laboratories.

Substituted Isobutylideneanilines. Equimolar amounts of isobutyraldehyde and the substituted aniline in toluene were refluxed on a Dean–Stark apparatus for 3–8 h.[47] The products were purified by fraction distillation under reduced pressure or by recrystallization. The ^1H NMR spectra (Table S1 of the supplementary material) indicated that all compounds existed in the imine form except the *m*-nitro compound which existed a mixture of imine and enamine in $CDCl_3$ solution and the *p*-nitro compound which was isolated as the enamine form. An enamine was also isolated from the condensation of 2-ethylbutyraldehyde and *p*-nitroaniline.

***N*-Aryl-*N*-(trimethylsilyl)-2-methylprop-1-en-1-amines.** Trimethylsilyl trifluoromethanesulfonate (12 mmol) was added with stirring to a solution of the imine (10 mmol) and triethylamine (2 g) in light petroleum (bp 40–60 °C), (20 mL) under nitrogen. After stirring for 20–60 h two layers separated, the upper layer was concentrated under reduced pressure, and the product was fractionally distilled.[48] The products were characterized by their ^1H NMR spectra and high-resolution mass spectra (Table S2 and S3, supplementary material).

***N*-Alkyl-*N*-(trimethylsilyl)enamines.** The corresponding imines were prepared by adding ice-cold isobutyraldehyde or propionaldehyde dropwise to the ice-cold amine with stirring. Potassium hydroxide was added, and the solution was set aside for several hours.[49] Two layers separated, and the upper was distilled from potassium hydroxide and treated with trimethylsilyl trifluoromethanesulfonate as described above except that much shorted reaction times (ca. 5 min) were needed for the *N*-methyl and *N*-ethyl derivatives, but not for the *N*-*tert*-butyl compound (60 h). The NMR spectral data are given in Table V.

Substituted Cyclohexylidene- and (2-Methylcyclohexylidene)anilines. A mixture of cyclohexanone or 2-methylcyclohexanone (100 mmol) and the substituted aniline (100 mmol) in toluene was refluxed in the presence of zinc chloride (20 mg) in a Dean–Stark apparatus. The reaction mixture was filtered, the solvent was removed, and the product was fractionally distilled.[50] The ^1H NMR spectral data are given in Table S4 (supplementary material).

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***N*-Aryl-*N*-(trimethylsilyl)cyclohex-1-en-1-amines.** The unsubstituted and *p*-chloro compounds were prepared by treatment with trimethylsilyl trifluoromethanesulfonate as described above for periods of 5 and 30 min. The ^{1}H NMR spectral data are given in Table II (footnotes *c*, *d*).

***N*-Aryl-*N*-methylcyclohex-1-en-1-amines and *N*-Aryl-*N*,2-dimethylcyclohex-1-en-1-amines.** Molar equivalents of cyclohexanone or 2-methylcyclohexanone and the ring-substituted *N*-methylaniline were heated in toluene in the presence of toluene-*p*-sulfonic acid (2 mg/mmol) in a Dean–Stark apparatus. When separation of water was complete, the reaction mixture was concentrated and the product was distilled.[52] The physical properties of the enamines are given in Table S5 (supplementary material).

NMR Spectroscopic Detection of Secondary Enamines. The trimethylsilyl derivative (ca. 20 mg) was dissolved in the solvent (usually DMSO-d_6), and the spectrum was run on a Varian EM 360, Hitachi-Perkin, or JEOL FX 90Q NMR spectrometer. Deuterium oxide or water containing a small amount of acid or tetrabutylammonium fluoride as stated was then added, and the formation and decay of the secondary enamine was monitored by running the spectrum at convenient time intervals.

Kinetic Measurements. Stock solutions of the secondary enamines, prepared as described, or of the tertiary enamines in dimethyl sulfoxide or acetonitrile (ca. 5×10^{-3} M, 20–25 μL) were added to 2.0 μL of the thermally equilibrated reaction solution contained in the curette in the thermostated cell hold of a Shimadzu UV 250 spectrophotometer which was operated on line through an IEEE interface with an Apple II or Hewlett-Packard 85 B microcomputer. Reactions were normally followed to greater than 90% completion (40–80 data points), and first-order rate constants were calculated using a generalized least-squares method.[54] The standard deviations for most of the first-order rate constants were less than 0.5% and those runs with an error of greater than 2% were discarded. Second-order constants for the [H$^+$]-catalyzed reactions were obtained as the slopes of plots of the first-order constants against 10^{-pH} using a linear least-squares method. Ten to fifteen points were used for each compound, and standard deviations of the slopes were normally less than 2%.

Reaction solutions, whose ionic strengths were maintained constant with potassium chloride (I = 1.00 M or 0.100 M), had their pHs adjusted with low concentrations of HCl, sodium acetate ((1–2) $\times 10^{-4}$ M), potassium dihydrogen phosphate ((2–5) $\times 10^{-4}$ M), borax ((2–5) $\times 10^{-4}$ M) tris ((2–5) $\times 10^{-4}$ M), sodium bicarbonate ((2–5) $\times 10^{-4}$ M), or sodium hydroxide. A constant check was maintained to detect any drift in the pH of the solutions.

General acid catalysis was studied in buffer solutions at different buffer concentrations with the ionic strength maintained constants at 1 M with potassium chloride. Reactions in mixtures of dimethyl sulfoxide and water were carried out at various solvent compositions. A series of runs were carried out at different acid concentrations for each solvent composition. Second-order constants were obtained from plots of the experimentally determined first-order constants against acid concentration.

Registry No. **3a** (L = D), 125519-61-1; **3a** (L = H), 39778-05-7; **3a** (L = Me), 25076-84-0; **3b** (L = D), 125519-62-2; **3b** (L = H), 39778-06-8; **3b** (L = Me), 125519-92-8; **3c** (L = D), 125519-63-3; **3c** (L = H), 125519-66-6; **3c** (L = MeO), 125519-94-0; **3d** (L = D), 125519-64-4; **3d** (L = H), 32117-47-8; **3d** (L = Me), 125519-93-9; **3e** (L = D), 125519-65-5; **3e** (L = H), 125519-67-7; **3e** (L = Me), 125519-95-1; **3f** (L = H), 125519-77-9; **3f** (L = Me), 125519-96-2; **4a** (L = D), 125519-73-5; **4a** (L = H), 10592-26-4; **4b** (L = D), 125519-74-6; **4b** (L = H), 22303-86-2; **4e** (L = D), 125519-75-7; **4f** (L = D), 125519-76-8; **5a** (L = D), 65514-31-0; **5b** (L = D), 125519-82-6; **6a** (L = D), 125519-83-7; **6b** (L = D), 125519-84-8; **7a** (L = H), 125519-78-0; **7b** (L = H), 125519-79-1; **7e** (L = H), 125519-80-4; **7f** (L = H), 125519-81-5; $Me_2CHCH{=}NPh$, 7020-77-1; $Me_2CHCH{=}N$-*p*-C_6H_4Cl, 33611-51-7; $Me_2CHCH{=}N$-*p*-C_6H_4OMe, 18169-40-9; $Me_2CHCH{=}$-N-*p*-C_6H_4Me, 18169-42-1; $Me_2CHCH{=}N$-*m*-$C_6H_4NO_2$, 125519-56-4; $Me_2C{=}CHN(SiMe_3)Ph$, 52164-25-7; $Me_2C{=}CHN(SiMe_3)$-*p*-C_6H_4Cl, 125519-57-5; $Me_23C{=}CHN(SiMe_3)$-*p*-C_6H_4OMe, 125519-58-6; $Me_2C{=}CHN(SiMe_3)$-*p*-C_6H_4Me, 125519-59-7; $Me_2C{=}CHN(SiMe_3)$-*m*-$C_6H_4NO_2$, 125519-60-0; $PhNH_2$, 62-53-3; *p*-$ClC_6H_4NH_2$, 106-47-8; *m*-$NO_2C_6H_4NH_2$, 99-09-2; *p*-$NO_2C_6H_4NH_2$, 100-01-6; $MeNH_2$, 74-89-5; $EtNH_2$, 75-04-7; $Me_2C{=}CHN(Me)SiMe_3$, 41003-47-8; $Me_2C{=}CHN(Et)SiMe_3$, 41003-48-9; $MeCH{=}CHN(Me)SiMe_3$, 70113-29-0; $MeCH{=}CHN(t\text{-}Bu)SiMe_3$, 75272-58-1; PhNHMe, 100-61-8; *p*-ClC_6H_4NHMe, 932-96-7; *m*-$NO_2C_6H_4NHMe$, 619-26-1; *p*-$NO_2C_6H_4NHMe$, 100-15-2; *p*-MeC_6H_4NHMe, 623-08-5; *p*-$MeOC_6H_4NHMe$, 5961-59-1; *t*-$BuNH_2$, 75-64-9; D_2, 7782-39-0; cyclohexanone, 108-94-1; 2-methylcyclohexanone, 583-60-8; *N*-cyclohexylideneaniline, 1132-38-3; *N*-cyclohexylidene-4-chloroaniline, 36132-64-6; *N*-cyclohexylidene-3-nitroaniline, 125519-68-8; *N*-cyclohexylidene-4-nitroaniline, 73655-27-3; *N*-(2-methylcyclohexylidene)aniline, 13280-22-3; *N*-(2-methylcyclohexylidene)-4-chloroaniline, 125519-69-9; *N*-(2-methylcyclohexylidene)-3-nitroaniline, 125519-70-2; *N*-(2-methylcyclohexylidene)-4-nitroaniline, 125519-71-3; *N*-(1-cyclohexen-1-yl)-*N*-(trimethylsilyl)-aniline, 75784-84-8; *N*-(1-cyclohexen-1-yl)-*N*-(trimethylsilyl)-4-chloroaniline, 125519-72-4; isobutyraldehyde, 78-84-2; *N*-phenyl-*N*-methylcyclohex-1-en-1-amine, 10468-26-5; *N*-(4-chlorophenyl)-*N*-methylcyclohex-1-en-1-amine, 125519-85-9; *N*-(*m*-nitrophenyl)-*N*-methylcyclohex-1-en-1-amine, 125519-86-0; *N*-(*p*-nitrophenyl)-*N*-methylcyclohex-1-en-1-amine, 125519-87-1; *N*-phenyl-*N*,2-dimethylcyclohex-1-en-1-amine, 13815-57-1; *N*-(4-chlorophenyl)-*N*,2-dimethylcyclohex-1-en-1-amine, 125519-88-2; *N*-(3-nitrophenyl)-*N*,2-dimethylcyclohex-1-en-1-amine, 125519-89-3; *N*-(4-nitrophenyl)-*N*,2-dimethylcyclohex-1-en-1-amine, 125519-90-6; *N*-(4-mehylphenyl)-*N*,2-dimethylcyclohex-1-en-1-amine, 125519-91-7; *N*-(4-methoxyphenyl)-*N*,2-dimethylcyclohex-1-en-1-amine, 64495-95-0; propionaldehyde, 123-38-6.

Supplementary Material Available: Tables listing properties of ring substituted isobutylideneanilines (S1), ^{1}H NMR spectroscopic data of *N*-aryl-*N*-(trimethylsilyl)-2-methylprop-1-en-1-amines (S2), accurate mass determination of precursors of secondary enamines (S3), properties of substituted cyclohexylidene- and (2-methylcyclohexylidene)anilines (S4), and ^{1}H NMR spectroscopic data on *N*-aryl-*N*-methylcyclohex-1-en-1-amines and *N*-Aryl-*N*-methyl-2-methylcyclohex-1-en-1-amines (S5) (5 pages). Ordering information is given on any current masthead page.

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