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Reaction between Enamines and Schiff Basess.[1] Evidence for the Thermal [2+2] Cycloaddition Reaction

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Synopsis. Reaction between 4-(1-phenyl-1-propenyl)morpholine and *N*-benzylideneanilines provided *N*-(3-aryl-2-methyl-1-phenylallylidene)anilines in 60—65% yields, which unequivocally established the initial [2+2] cycloaddition reaction between enamines and Schiff bases.

Thermal [2+2] cycloaddition reactions are generally prohibited by the Woodward-Hoffmann rule.[2] Several exceptions involving Schiff bases include reactions with electron-deficient double bonds, such as heterocumulenes, N=O bond, and C=C bond carrying highly electronegative substituents.[3] More recently, titanium-(IV) chloride-mediated [2+2] cycloadditions between Schiff bases and ketene acetals, representative electron-rich olefins, have been reported.[4]

In our previous communications, we postulated thermal [2+2] cycloaddition reaction between *N*-benzylideneanilines and enamines, another class of highly nucleophilic olefins, as the most reasonable explanation for the formation of decahydroacridines[5] and hexahydro-4-azaindacenes[6] in acetic acid as the solvent. We wish to present herein direct evidence for the intermediacy of the [2+2] cycloadduct in the reaction between the enamine (**1**) and the Schiff bases (**2**) in acetic acid.

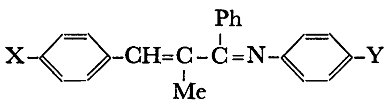
The reactions between *N*-benzylideneanilines (**2**) and 4-(1-phenyl-1-propenyl)morpholine (**1**) were performed at room temperature under nitrogen using acetic acid as the solvent. The products, *N*-(3-aryl-2-methyl-1-phenylallylidene)anilines (**3**), were obtained in 60—65% yield after recrystallization from methanol (Table 1).

Structural assignments of these products were based on elemental analysis, spectroscopic methods and independent synthesis of their hydrolyzed products. For example, **3a**, which had a sharp melting point (mp 108—109 °C), showed strong IR absorption bands at 1605 and 1590 cm^{-1}, one of which can be assigned to the conjugated imine moiety. On the other hand, the ^1H NMR spectrum, obtained as a solution in deuteriochloroform, exhibited two methyl doublets (in each case, $J=1$ Hz; assigned to allylic coupling with the olefinic proton) due to *syn-anti* isomerism about the C=N double bond (Table 2). The relatively large difference in the chemical shifts of the methyl group between the *syn* and *anti* isomers of **3a** ($\Delta\delta=0.58$) can be attributed to the strong shielding effect of the *N*-aryl ring (Ar^2) on the methyl protons in the *syn* isomer[7] which may most probably exist as the *s-trans* conformational isomer by steric reasons.

Since these spectral and analytical informations alone may not be sufficient to prove the structure **3a**, we hydrolyzed it with MeOH–HCl to obtain the *α,β*-unsaturated ketone (**4a**) virtually quantitatively (98% yield). The ^1H NMR spectrum of **4a** indicated one methyl doublet ($J=1$ Hz) in accord with nearly complete stereospecificity of the reaction leading to **3a**. This was also in agreement with the experimental observation that the stereoisomerism observed for **3** by ^1H NMR is due to *syn-anti* isomerism rather than *cis-trans* isomerism involving the olefinic C=C double bond. The structure of **4a** was confirmed by spectral (IR and ^1H NMR) comparison with an authentic sample prepared by the aldol condensation between *p*-chlorobenzaldehyde and propiophenone.[8]

The present reaction can be rationalized by the mechanism illustrated in Scheme 1. Reaction between **1** and **2** would produce the azetidine intermediate (**5**) either by concerted [2+2] cycloaddition or by stepwise cycloaddition *via* zwitterionic intermediate as **6**. The azetidine intermediate **5** would rapidly undergo deamination in the acid medium to afford 2-azetine derivative

TABLE 1. SYNTHESIS AND PROPERTIES OF **3**



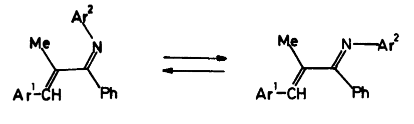
$X\text{-}C_6H_4\text{-}CH{=}C(Me)\text{-}C(Ph){=}N\text{-}C_6H_4\text{-}Y$

3

Compd	X	Y	Mp θ_m/°C[a]	Yield/%[b]	M^+(*m*/*e*)	Mol. Formula	Found (Calcd) (%) C	H	N	Cl
3a	Cl	H	108—109	62	331	$C_{22}H_{18}NCl$	79.83 (79.63	5.24 5.47	4.31 4.22	10.95 10.68)
3b	Cl	Cl	112—113	60	365	$C_{22}H_{17}NCl_2$	71.86 (72.14	4.53 4.68	4.07 3.82	19.52 19.36)
3c	Cl	CH_3O	132—133	63	361	$C_{23}H_{20}NOCl$	76.26 (76.34	5.43 5.57	3.86 3.87	9.83 9.80)
3d	NO_2	H	140—141	65	342	$C_{22}H_{18}N_2O_2$	77.34 (77.17	5.24 5.30	8.04 8.18)	— —

a) Uncorrected. b) Isolated yield (recrystallized from methanol). c) Measured at 70 eV.

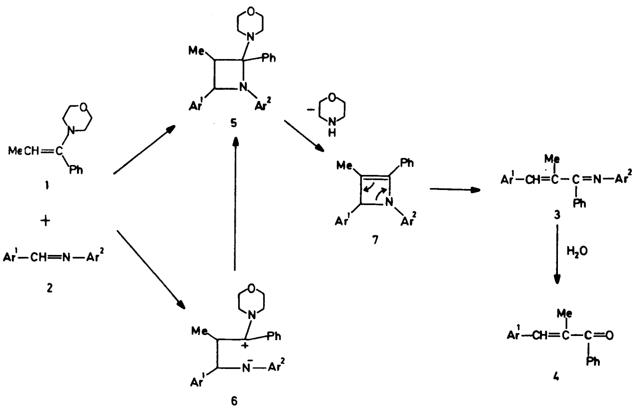
Table 2. ^{1}H NMR spectra of *syn* and *anti* isomers of **3**$^{a)}$



syn-**3** *anti*-**3**

Compd	δ (Me)$^{b)}$ *syn*	δ (Me)$^{b)}$ *anti*	δ(sp^2-protons)$^{c)}$	*syn* : *anti*$^{d)}$
3a	1.78	2.36	6.3—7.9	32 : 68
3b	1.82	2.35	6.1—8.1	34 : 66
3c	1.84	2.38	6.4—8.0	31 : 69
3d	1.88	2.40	6.4—8.1	35 : 65

a) 100 MHz NMR spectra obtained in $CDCl_3$ with tetramethylsilane as internal standard. Assignments of these isomers were based on Ref. 7. b) Each peak shows up as a finely-split doublet with a coupling constant of about 1 Hz. c) Benzylidene and aromatic protons (multiplet). d) Determined by ^{1}H NMR integration of the methyl groups.



Scheme 1. Mechanism for the formation of **3**.

7, which would then collapse into the conjugated imine **3** by ring-opening process. Whether the [2+2] cycloaddition route is concerted or stepwise, it is intriguing that this route appears to be operative only in acetic acid.[9]

Experimental

Enamine (**1**) was prepared according to the procedure previously described.[10] *N*-Benzylideneanilines (**2**) were prepared by the known method.[11] Acetic acid was distilled over phosphorus pentaoxide under nitrogen. Melting points were uncorrected. IR spectra were recorded as nujol paste with a HITACHI EPS-3T Recording Spectrometer. ^{1}H NMR spectra were obtained on a JEOL JNM-MH-100 Spectrometer operated at 100 MHz. Elemental analyses were performed by Organic Analysis Laboratory of the University of Tokyo.

*General Procedure for the Reaction between **1** and **2***: A solution of **2** (41 mmol) in anhydrous acetic acid (100 ml) was slowly added to enamine (**1**) (10.4 g, 51 mmol) with stirring at room temperature under nitrogen. The resulting yellow precipitates, obtained after 7 h stirring, were collected by filtration and recrystallized from methanol to give product **3** in 60—65% yields (see Tables 1 and 2 for pertinent data of **3**).

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