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ACID-CATALYZED [4+2]CYCLOADDITION BETWEEN ENAMINES AND BENZYLIDENEANILINES. SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINE DERIVATIVES[1)]

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The enamines having an α-hydrogen, $R^1R^2N\text{-}\overset{\alpha}{C}H=\overset{\beta}{C}R^3CH_3$, reacted with a variety of benzylideneanilines to provide the [4+2] cycloadducts, 1,2,3,4-tetrahydroquinoline derivatives, in acetic acid or in methanol containing a catalytic amount of p-toluenesulfonic acid in considerable yield.

Among numerous examples of [4+2] cycloadditions of the enamines as the dienophile,[2)] those involving conjugated imines as the heterodiene counterpart have not hitherto been accomplished presumably because of inertness of the latter under the neutral conditions.

In our previous communication, it was reported that enamines derived from cyclic ketones react rapidly with benzylideneanilines in glacial acetic acid at ambient temperature to provide acridine derivatives as a result of initial [2+2]cycloaddition between these.[3)] We now wish to report that under analogous acidic conditions enamines having an α-hydrogen undergo facile [4+2] cycloaddition with benzylideneanilines to give 1,2,3,4-tetrahydroquinoline derivatives in moderate to high yields.

An exothermic reaction occurred when a solution of benzylideneaniline (4a) (6.41 g, 0.035 mol) in glacial acetic acid(100 ml) was added with stirring at room temperature over 30 min to 4-(2-methyl-1-propenyl)morpholine (1) (5.22 g, 0.037 mol). Additional stirring at room temperature for 30 min provided white precipitates. Stirring was continued further for 5 h to complete the reaction and the resulting precipitates, 4-acetoxy-3,3-dimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline (5a), were collected by filtration(8.33 g: 81% yield). The pertinent data of the products (5) obtained from the reaction in acetic acid using enamines (1, 2) and Schiff bases (4a-f) are collected in TABLE 1.

$R^1R^2N\text{-}\overset{\alpha}{C}H=\overset{\beta}{C}R^3CH_3$

1 R^1R^2N = morpholino, $R^3 = CH_3$

2 $R^1=R^2=R^3= CH_3$

3 R^1R^2N = morpholino, $R^3 = H$

p-X-C_6H_4-N=CH-C_6H_4-Y-p

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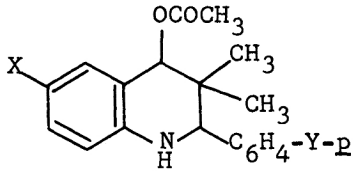

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4, 5	a	b	c	d	e	f
X	H	H	H	H	CH_3O	CH_3O
Y	H	Cl	NO_2	CH_3O	Cl	NO_2

TABLE 1. Data of 4-acetoxy-2-aryl-3,3-dimethyl-1,2,3,4-tetrahydroquinoline (5) obtained from the reaction between enamine (1 or 2) and Schiff base(4) in acetic acid

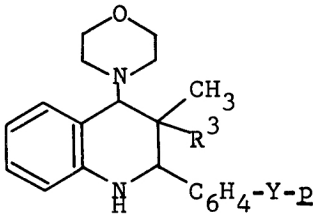
Compound	Mp(°C)	Yield(%)	Mol. Formula		Elemental Analysis C	H	N	Cl
5a[a)]	153	81	$C_{19}H_{21}NO_2$	Found	77.12	7.12	4.73	
				Calcd	77.26	7.17	4.74	
5b[a)]	212	90	$C_{19}H_{20}NO_2Cl$	Found	69.09	6.38	4.16	10.71
				Calcd	69.19	6.11	4.25	10.75
5c[a)]	225	91	$C_{19}H_{20}N_2O_4$	Found	67.25	6.00	8.08	
				Calcd	67.04	5.92	8.23	
5d[b)]	163	49	$C_{20}H_{23}NO_3$	Found	73.98	7.07	4.10	
				Calcd	73.82	7.11	4.30	
5e[b)]	186	56	$C_{20}H_{22}NO_3Cl$	Found	66.72	6.07	4.05	
				Calcd	66.76	6.16	3.89	
5f[b)]	199	70	$C_{20}H_{22}N_2O_5$	Found	64.69	5.82	7.52	
				Calcd	64.85	5.99	7.56	

a) Using 1. b) Using 2.

The structure of these compounds 5 was identified chiefly by their NMR spectral data as well as their physicochemical properties. Thus the mass spectral molecular weight and elemental analysis of 5a, for example, established the molecular formula as $C_{19}H_{21}NO_2$. The nine protons at δ=7.7-6.5 ppm in its ^{1}H-NMR spectrum were unambiguously assigned as aromatic protons suggesting the disappearance of only one aromatic proton in the final product. Three protons each of which shows up as a singlet at δ=4.1, 4.5 and 5.7 ppm were assigned as H-1, H-2 and H-4, respectively, with some broadening observed for H-1. The observation that these protons are all singlets precluded the possibility of 1,2,3,4-tetrahydroisoquinoline structure.

The geminal dimethyl groups appeared at δ=0.8 as a sharp singlet and the signal due to the acetoxy methyl emerged at δ =2.1 ppm also as a singlet. The presence of -NH and $OCOCH_3$ functions was indicated by the IR spectrum which showed characteristic absorptions at 3360, 1710 and 1240 cm^{-1}. All of these structural informations were only consistent with structure 5a. The location of the acetoxyl group was in agreement with transformation of 5a into the 4-ethoxy derivative 7(mp 114°C) on treatment with ethanol at 80°C in 85% yield. It is interesting that among the four conceivable stereoisomers of the tetrahydroquinoline product a single racemate, whose configurational identification at C-2 and C-4 still requires further study, was exclusively formed under the conditions employed. Thus the reaction is formally regarded as the [4+2] cycloaddition between enamine and Schiff base in which the latter component serves as the diene.

It may be noted that enamines having hydrogens both at α- and β-positions gave only polymeric materials under these conditions. The reaction was effective only with enamines having an α-hydrogen alone(without β-hydrogen) in acetic acid. Expectedly the production of the tetrahydroquinoline derivative does not necessarily require acetic acid as the reaction medium. The reaction did occur in methanol in the presence of catalytic amount of p-toluenesulfonic acid(TsOH). Thus when 1 (10.0 g, 0.071 mol) and 4a(9.2 g, 0.051 mol) were stirred overnight in methanol containing a trace amount of TsOH, 3,3-dimethyl-4-morpholino-2-phenyl-1,2,3,4-tetrahydroquinoline (6a)(4.93 g) was obtained in 30% yield as the only product. Unlike the reactions in acetic acid, when the reactions were carried out in methanol with TsOH, the enamines having an additional hydrogen in β-position (3) also gave product which corresponded to the 1,2,3,4-tetrahydroquinoline structure. The data of all these products are collected in TABLE 2.



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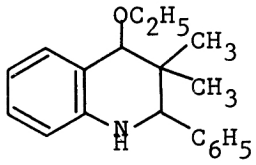

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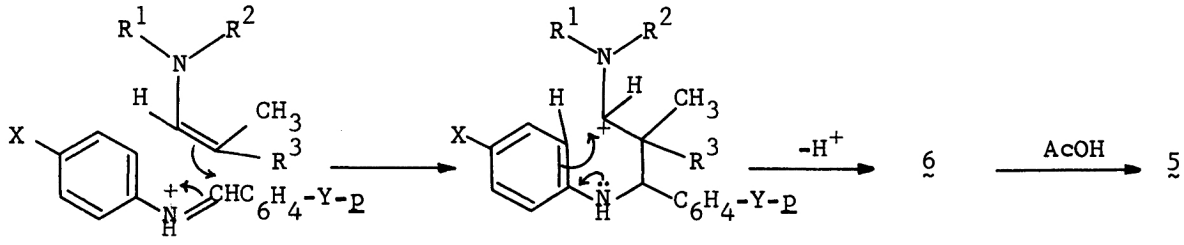
TABLE 2. Data of 2-aryl-3-methyl-4-morpholino-3-R^3-1,2,3,4-tetrahydroquinoline (6) obtained from the reaction between enamine (1 or 3) and Schiff base (4) in methanol containing catalytic amount of p-toluenesulfonic acid

Compound	R^3	Y	Mp(°C)	Yield(%)	Mol.Formula		Elemental Analysis C	H	N
6a	CH_3	H	238	30	$C_{21}H_{26}N_2Cl$	Found	78.06	8.08	8.82
						Calcd	78.22	8.13	8.69
6b	H	H	196	25	$C_{20}H_{24}N_2O$	Found	77.64	7.95	8.78
						Calcd	77.88	7.84	9.08
6c	H	Cl	184	15	$C_{20}H_{23}N_2OCl$	Found	70.07	6.84	8.13
						Calcd	70.06	6.76	8.17

As reported previously,[4] the cycloaddition between enamines and Schiff bases does not occur in methanol in the absence of TsOH. They instead gave the Michael-type adduct as the only product. The necessity of an acid for the [4+2] cycloaddition was further demonstrated by the observation that they reacted without solvent in the presence of a small amount of TsOH to give 6 in high yields. Thus the presence of an acid seems indispensable for the [4+2] cycloaddition to take place. Mechanistically the acid-catalyzed reaction can be envisaged as the initial Michael-type addition of enamines to the protonated Schiff base followed by intramolecular electrophilic aromatic substitution at the ortho position of the activated N-phenyl ring to give 6 after deprotonation as shown in the following scheme;



In acetic acid 6 should turn into 5 since 6 was in fact smoothly converted into 5 upon treatment with acetic acid in 82% yield. Whether the cycloaddition is concerted or stepwise, it is intriguing that the [4+2] cycloaddition can become the predominant route only in the presence of an acid. Explanation for why this is so must await future investigation.

REFERENCES AND NOTE

1) ENAMINES VIII of this series: ENAMINES VII, reference 3.
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3) Y. Nomura, S. Tomoda, and Y. Takeuchi, Chem. Lett., 1972, 79.
4) S. Tomoda, Y. Takeuchi, and Y. Nomura, Tetrahedron Lett., 1969, 3549.

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