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FACTORS AFFECTING O, C AND N ACETYLATION OF ENAMINES OF THE TYPE R_1—CO—C_αH=C_βH—NHR_2

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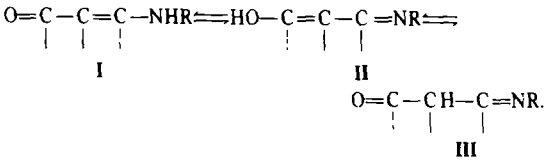
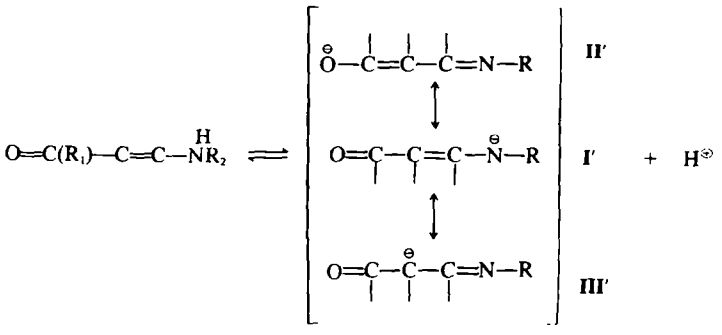
Abstract—Acetylation of the title enamino ketones with acetyl chloride was carried out in pyridine or ether with and without base. N-acetyl derivatives were obtained in pure ether, but activation of O and C nucleophilic centers was promoted by the presence of base. Electronic and structural factors governing regioselectivity of reaction are discussed.

During recent years a great deal of evidence has been collected[1] showing that the ground state of enamino ketones is best characterized by form I in the equilibrium



Nevertheless, this problem still attracts a great deal of attention.[2,3]

We recently investigated the exchange barriers of N-H protons in the secondary amino group of enamino ketones with respect to the mechanism of *cis–trans* isomerization.[4] It appeared that the barrier to N-H exchange of *ca.* 20 kcal/mole is almost equal to the barrier to *cis–trans* isomerization, indicating that both processes may go through a common transition state. The transition state may be represented by polar forms leading ultimately to the equilibrium shown below, in agreement with the fact that enamino ketones exhibit three centers susceptible to electrophilic attack.



In the present work we acetylated several enamino ketones of type I (**1–5**, $R_1 = CH_3$, C_2H_5, i-C_3H_7, t-C_4H_9, C_6H_5; $R_2 = CH_3$; **6**, $R_1 = CH_3$, $R_2 = t$-C_4H_9) in an attempt to obtain data characterizing the stability of the N-H bond and/or completing our recent spectroscopic results describing its dynamic properties.

RESULTS AND DISCUSSION

The great variety of forms in which the enamino ketone can appear in a reaction with electrophiles makes the composition of the products very sensitive to reaction conditions. Thus the results of alkylation and acetylation reactions are inconsistent.[5b] Additional complications arises from the possibility of *cis–trans* isomerization.[1b,d,e,2a,6] A systematic study of the alkylation of *cis*- and *trans*-cyclic enamino ketones[7] revealed that the *trans*-forms are O-alkylated while the *cis*-isomers undergo both C- and O-alkylation in various solvents, with considerable amounts of the O-protonated form observed in protic media. It was suggested that the *trans*-form exhibits strongest nucleophilicity on oxygen, while in the *cis* forms, structures like II′ and III′ are of comparable significance to I′ during electrophilic attack.

Data concerning acetylation are less clear with regard to the electronic structure of the compounds. Studies of N,N-disubstituted enamino ketones show the formation of O^8- or C^9-acetylated products under various conditions.[5a,b] Formation of C-acetylated products was attributed to the reversible nature of the O-acetylated form.[9] The usual course of reaction is the formation of the O-acetylated ammonium salt which is easily hydrolized to the dicarbonyl compound. Our systematic study on acetylation of secondary enamino ketones indicates that three centers of electrophilic attack are exposed under different conditions. The results of three types of experiments are collected in Table 1. The spectral and elemental analysis data of the products are gathered in Table 2.

Three types of products are formed during the reaction, viz. in Table 2.

In the absence of amines only N-acetylation occurs, in this case a molar excess of enamine is used to remove HCl generated during the reaction. In ethereal solution, in the

Table 1. Results of acetylation of secondary enamino ketones in various conditions

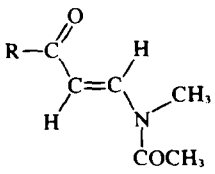
Compound	Method†	% of *trans*-isomer in solution	Product ratios % N-Ac	α-Ac	O,N-Diac.
	A	35	80‡	—	—
1	B	60	80	—	20
	C	35	60	28	12
2	B	48	72	—	28
3	B	45	73	—	27
	A	10	80‡	—	—
4	B	40	65	—	—
	C	20	45	55	—
5	B	20	50	—	—
6	B	0	19	45	—
	C	0	—	48	—

†For details of Methods A, B and C see Experimental.
‡Some unidentified saturated material formed during these reactions.

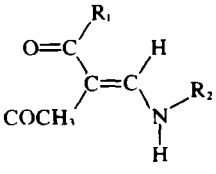
Table 2. ^{1}H NMR spectra and elemental analyses of the acetylated compounds

Compound	Chemical shifts δ(ppm)† and coupling constants J(Hz) CO–R, OAc	C_α–R	H_β	$J_{H_\alpha H_\beta}$	N–R	N-Ac	Molecular formula	Elemental analyses Calc. C%	H%	Found N%
7	2.25 —	5.65	8.08	13.75	3.12	2.4	$C_7H_{11}O_2N$	59.55	7.85	9.92
								59.60	7.9	10.0
8	CH_3 1.05 CH_2 2.39	5.52	7.95	13.75	3.07	2.32	$C_8H_{13}O_2N$	61.91	8.44	9.03
								61.3	8.21	8.85
9	CH_3 1.16 CH 2.7	5.67	8.10	13.9	3.15	2.35	$C_9H_{15}O_2N$	63.8	8.94	8.28
								64.0	8.96	7.52
10	1.13	5.73	7.92	13.31	3.07	2.32	$C_{10}H_{17}O_2N$	65.54	9.35	7.64
								65.9	9.5	7.3
11	7.5 and 7.9	6.35	8.24	13.75	3.02	2.36	$C_{12}H_{13}O_2N$	70.91	6.45	6.89
								70.85	6.41	6.46
12	CH_2 4.73 and 4.85, J = 1.8 OAc 2.2	5.5	6.9 7.6	14.5	3.11	2.20	$C_9H_{13}O_3N$	59.0	7.15	7.65
								57.5	7.13	7.45
13	CH_3 1.75 H 5.07 J = 7.5 OAc 2.2	5.58	6.81 7.45	14.0	3.11	2.18	$C_{10}H_{15}O_3N$	60.89	7.67	7.10
								59.02	7.62	6.65
14	CH_3 1.62, 1.8 OAc 2.2	5.75	6.8 7.45	15.0	3.37	2.25	$C_{11}H_{17}O_3N$	62.54	8.11	6.63
								61.85	8.07	6.32
	2.42	2.22	7.67	—	CH_3 3.15 NH 10.7 $J_{NH-C_\beta H}$ 15.0	—	$C_7H_{11}O_2N$	59.55	7.85	9.92
								59.98	7.93	9.30
16	*t*-C_4H_9 1.25	2.22	7.45	—	CH_3 3.1 NH 10.7 $J_{NH-C_\beta H}$ 12.5	—	$C_9H_{17}O_2N$	63.13	10.0	8.18
								63.52	9.82	8.52
17	2.46	2.26	8.03	—	*t*-Bu 1.4 NH 11.5 $J_{NH-C_\beta H}$ 14.0	—	$C_{10}H_{14}O_2N$	66.6	7.78	7.78
								66.41	7.82	7.85

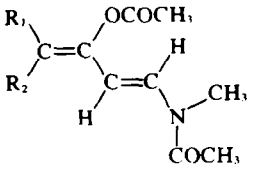
†Spectra were obtained on 10% (by wt) solutions in $CDCl_3$ and calibrated against internal TMS.



N-Acetyl-
7–11: R = CH_3, C_2H_5, *i*-C_3H_7, *t*-C_4H_9, C_6H_5.



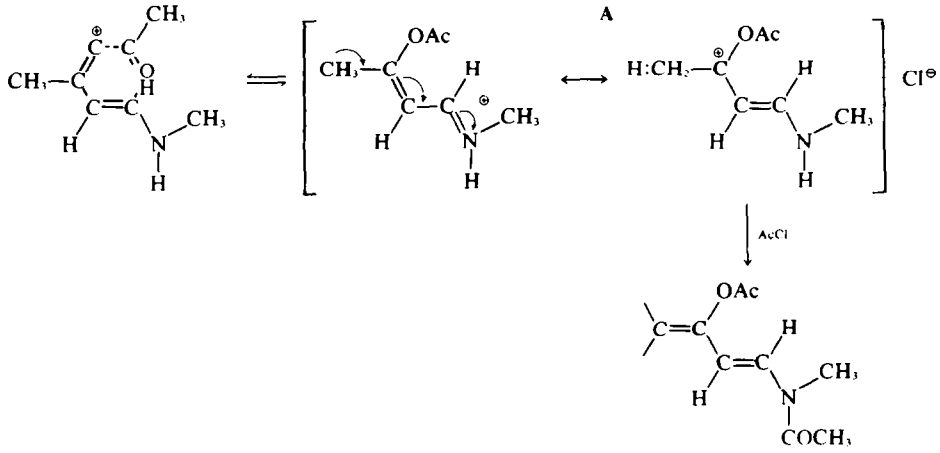
α-Acetyl-
15: $R_1 = R_2 = CH_3$
16: R_1 = *t*-C_4H_9, $R_2 = CH_3$
17: $R_1 = CH_3$, R_2 = *t*-C_4H_9



O,N-Diacetyl-
12: $R_1 = R_2 = H$
13: $R_1 = CH_3$, $R_2 = H$
14: $R_1 = R_2 = CH_3$

presence of Et_3N, all three centers are acylated. When the reaction is carried out in pyridine the N-acetylated product is accompanied by a considerable amount of the O,N-diacetyl derivative. In the latter case a new, interesting diene is formed, which is a derivative of the O-acetylated compound. Formation of this compound probably proceeds via oxonium[10] and ammonium salts (Scheme 1), which are stabilized by successive acetylations. A recent review[5d] of acetylation mechanisms stressed three ways in which the reaction may be completed. In this case acylium ion attack is reasonable, lack of O,N-diacetylated products in the case of compounds **6** and **7**, in pyridine. This effect may be enhanced in compound **6** due to steric hindrance of the tertiary butyl group.

In summary our results show that acetylation carried out without base yields only N-acetyl derivatives. This confirms the stability of the N–H bond in the ground state and explains the high barrier to exchange.[4] The other two nucleophilic centers are activated by the presence of base, facilitating proton abstraction during the reaction. C_α-acetylation requires the presence of a strong amine.



Scheme 1.

since the oxygen of enamino ketones is easily protonated,[11] and the presence of an amine facilitates proton abstraction. Other possibilities leading to diene formation involve consecutive acetylation of the N-acetyl derivative or the presence of considerable amounts of the enol imine **II** in solution. Although the O-acetylated salt **A** has not been isolated, as it rearranges to the O,N-diacetyl derivative, other courses of reaction may be disregarded on the basis of experimental results. Acetyl derivatives of the type R-C(OAc)=CH-CH=N-Alk were not observed in any reaction, but unchanged starting material was recovered from the attempted acetylation of compound **7** in pyridine.

In neutral conditions aliphatic secondary enamino ketones yield only N-acetyl derivatives (Table 1), supporting the view that the ground state is best described by structure **I**. Formation of the other products has been attributed to activation by bases, amines of different basicity are required to activate the O or C_α positions, the latter exhibiting the lowest nucleophilicity. The nucleophilicity of the three positions, O, N and C_α, is dependent to a great extent on the configuration of the molecule, close analogy to the above cited alkylation of cyclic enamino ketones is apparent. In the *trans* isomer oxygen is a strong nucleophilic center giving rise to the O,N-diacetyl derivative. This diene is not formed when the molecule exist mainly in the *cis* configuration (**6**), in which oxygen is internally hydrogen bonding, and of course when hydrogens are lacking on the carbon atom α to the carbonyl group (**4**, **5**). Thus the *cis* isomer preferentially gives the C_α-acetylated product. On the other hand, the basicity of the nitrogen and the extent of conjugation of its lone pair electrons with the double bonds determines the electron density on O and C_α. Decreased basicity of the nitrogen is responsible for the O-acetylation is rendered irreversible by abstraction of a proton from the saturated carbon α to the carbonyl group. O,N-diacetylation gives butadiene derivatives belonging to a group of compounds attracting considerable interest due to their utilisation in various Diels–Alder reactions.[12]

EXPERIMENTAL

Acetylation of enamino ketones was carried out with acetyl chloride according to three known procedures. All reagents and solvents were used freshly dried. Reaction yields and product ratios (Table 1) were determined from the NMR spectra of the crude materials in $CDCl_3$ using an EM-360 Varian spectrometer. The ratio of *cis-trans* isomers in a reaction mixture was checked before running the experiment. The products were separated by preparative TLC, using Merck GF_{254} silica gel.

Method A. To a solution of enamino ketone (*ca.* 0.02 mole) in ether (30 ml) was added freshly distilled acetyl chloride (0.01 mole) in ether (5 ml) and the mixture was stirred for 1.5 hr at room temperature. Precipitated solid was filtered off and the ethereal solution evaporated to give a crude product. This was chromatographed on silica gel (TLC) using acetone–CCl_4 (1:1) to give the N-acetyl derivative (~80%). A large amount of a saturated black material was formed during the reaction, however in the presence of base the reaction was much cleaner.

Method B. Acetyl chloride (0.01 mole) in toluene (5 ml) was added dropwise to a solution of enamino ketone (ca. 0.01 mole) in dry pyridine (30 ml). The mixture was stirred at room temperature for 1.5 hr, diluted with toluene (30 ml), the precipitated solid filtered off and the solution evaporated on a rotatory evaporator. After TLC, as described above, N-acetyl and O,N-diacetyl derivatives were identified by NMR and IR spectra.

Method C. As in Method A, but in the presence of Et_3N (0.01 mole). This procedure was applied to compounds **1**, **4** and **6**. The reaction mixtures worked up as before, but with three products present preparative TLC was repeated twice to achieve complete separation. Chromatographic separation of the α-acetyl derivative from the starting material was difficult because of

similar polarities, prolonged heating to complete the reaction was therefore necessary.

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