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STRUCTURAL STUDIES BY ^1H AND ^{13}C DNMR—II†

ALTERNATIVE PROTONATION SITES IN CARBONYL CONJUGATED CHAIN ENAMINES OF THE TYPE R_1–C_1O–C_2H=C_3H–NR_2R_3. A METHOD OF SYNTHESIS OF DISUBSTITUTED PYRIDINIUM SALTS

LECH KOZERSKI* and E. CZERWIŃSKA
Institute of Organic Chemistry, Polish Academy of Sciences, 00-961 Warsaw, Kasprzaka 44, Poland

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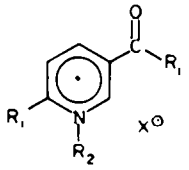
Abstract—O-Protonation of secondary enamino ketones in TFA or concentrated mineral acids in various solvents is the kinetically favoured course of reaction leading ultimately to stable 2,5- or 3,4-disubstituted pyridinium salts. The mechanism of formation of the salts involves electrophilic attack by the C-3 carbon atom on C-2 or N-nucleophilic centres of the O-protonated molecule.

The enamino ketone moiety O=C^{1}R^1–C^{2}H=C^{3}H–NHR^2, **1**, represents a set of five atoms, exhibiting alternantly nucleophilic (O, C-2, N) and electrophilic properties (C-1, C-3). The chemical reactivity[1] and intramolecular dynamics[2] determine the scope of our systematic studies in this field.

Following our earlier report,[3] we have currently carried out protonation studies on tertiary and secondary[4] enamino ketones using ^1H and ^{13}C technique. In this paper we report a simple, novel method of synthesis of pyridinium salts of the type **2**, where R_1 = alkyl or phenyl, R_2 = hydrogen atom or alkyl, $X^{\ominus}$ = anion of carboxylic or mineral acid. We found that compounds **2** are in-



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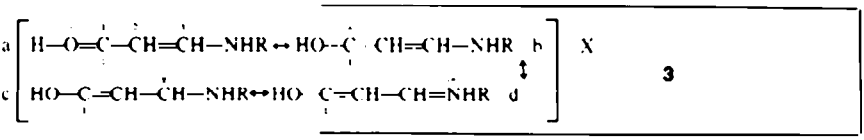
stantaneously obtained in high yields upon dissolving **1** in TFA, also, when gaseous HCl is passed through, or equivalent amount of other acid is added to a solution of **1** in ether or methyl cyanide.

This simple method gives 3-substituted pyridinium salts in one process, yielding derivatives which are close precursors of compounds having pharmacological importance in indispositions of the blood circulation system.

The formation of salt **2** is explained in terms of increased charge alternation and the reactivity of the olefinic carbons in a kinetically favored[4] (see also review 5 and references therein) O-protonated form **3**:



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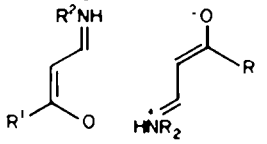
^1H and ^{13}C spectra of compounds **1** taken in kinetic conditions‡ indicate only the presence of O-protonated species, while after several hours in a sample warmed to a room temperature, signals corresponding to **2** and methylammonium salts are discernible.

A consideration of charge distribution in the ion **3** suggests the above conclusion which finds support in quantum-mechanical calculations.[6] It acknowledges the fact, that of the three nucleophilic sites, C-2 in cation **3** is the only centre susceptible to electrophilic attack. Simultaneously, electrophilicity of C-1 and C-3§ atoms should be enhanced due to acquiring some of the positive charge introduced upon protonation. We therefore propose salt **2** to be the product of thermodynamic protonation of **1**,[7] formed during the reaction of **3** with a like molecule. Consequently, the electrophilic attack of C-3 carbon on C-2 position of same molecule yields the intermediate **4**,



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which stabilizes via elimination of $CH_3\overset{\oplus}{N}H_2X^{\ominus}$ and cyclodehydratation. One of the interacting molecules enters the intermediate **4** in a *cis*-configuration, which according to Meyers *et al.*[8] exhibits stronger nucleophilicity on C-2 than in the *trans* isomer. Accordingly, we have found that cyclic secondary enaminoketones and tertiary analogues in a *trans*-configuration, do not yield salts **2** but simply O-protonated salts HO–C=CH–CH=$\overset{\oplus}{N}R_2X^{\ominus}$. This is shown by the isolation of stable salt **3** (exp. No. 14 in Table 1) in one case of a tertiary enamino ketone and its ^{13}C NMR spectrum.[4]

Quantum-mechanical calculations[6] and the contribution of form **3d** to the structure of O-protonated enamino ketone indicate the substantial loss of nucleophilic

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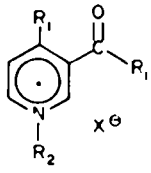
‡The enamino ketone diluted with CD_3CN was added slowly to an excess of TFA in the dry ice-acetone bath temperature and the spectra recorded at −40°.

§Lech Kozerski, in Ref. 4; this primarily concerns the C-3 carbon atom as supported by theoretical calculations[6] and observed downfield shift in ^{13}C NMR.

properties of the nitrogen atom. In certain conditions, however, specifically with compound **1** (R_1 = t-C_4H_9, R_2=CH_3) we observed (compare exp. Nos. 9–12) the formation of the salt of the type **5**:



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and its precursor (t-C_4H_9–CO–CH=CH)$_2$$NCH_3$, **6**. In this case electrophilic attack of C-3 carbon atom of the O-protonated species **1** on a nitrogen of a neutral molecule yields the intermediate which affords **6** after loosing $\overset{\oplus}{C}H_3X^{\ominus}$. Consecutive mono-O-protonation of **6** (see Exp. No. 13) and dehydratation gives the salt **5**.

Our experiments confirm that electrophilic attack of C-3 on a nitrogen atom is highly sensitive to reaction conditions and electronic and structural properties of the enamino ketone. It proceeds more slowly and requires stronger acid that in the case of the reaction on C-2 carbon atom. The relevant protonation experiments are listed in Table 1.

CONCLUSION

This study reveals that in the presence of strong acids the secondary and tertiary enamino ketones undergo preferential O-protonation.

N-protonation in these conditions is not observed in any of compounds studied, in contrast to established[1] mono-N- and O,N-diacetylation by CH_3–$\overset{\oplus}{C}$=O, in neutral conditions, and in the presence of base, respectively.

The present results parallels our previous[1] acetylation studies in that the O-acetylated or O-protonated forms are kinetic intermediates of differing stabilities in basic and acidic media, yielding products not easily accessible by other means.

We have demonstrated that the ambident enamino ketone group is a highly versatile synthetic intermediate. Attempts to uncover further synthetic uses by the title method are in progress.

EXPERIMENTAL

The protonation of the enamino ketones was carried out according to procedures described below. All reagents and solvents were freshly dried. Reactions yields and product ratios were determined from the NMR spectra of the crude materials in CD_3OD using EM-360 Varian spectrometer. All chemical shifts are given in ppm from internal TMS. All TLC was performed using Merck silica gel GF_{254}.

Experiment No. 3. Through the stirred solution of 2 g (0.017 mole) of 5-methylamino-penten-4-one-3 in 10 ml of methyl cyanide, dry HCl was passed during several minutes at room temperature. The solution was allowed to stand overnight, whereafter the precipitated methylamine hydrochloride was filtered off. The filtrate was diluted twice with a solvent and the solid was separated again. The solvent was partly removed on a rotary evaporator and the solution left for crystallization. Recrystallization was repeated several times with a methyl cyanide or methanol–ether (1:9) mixture. The yield before recrystallization was greater than 95%. Complete separation of methylamine hydrochloride was achieved with the use of Ambertite IRC-50 (H form). Thirty fold excess (compared to the weight of the crude product) of the resin in a 15 md o.d. column was equilibrated with an amount of 1N HCl equal to threefold volume of the resin suspended in water. The column was washed with deionized water until pH 7. The crude material was resolved using usually 250 ml of 0.1N HCl to displace the pyridinium salt from the column. The eluate was neutralized with aq NAOH, evaporated and the salt extracted from the solid with methyl cyanide and methanol. The analytical sample, melting at 176°C was obtained by chromatography on silica with a mixture of methyl cyanide–methanol (9:1), R_f 0.3–0.5. NMR (TFA), 1.4 (3H, t, J = 7.8 Hz, –CO–$CH_2\underline{CH_3}$), 1.6 (3H, t, J = 7.8 Hz, 2-$CH_2\underline{CH_3}$), 2.9 (2H, q, J = 7.8 Hz, –CO–$\underline{CH_2}CH_3$), 3.4 (2H, q, J = 7.8 Hz, 2-$\underline{CH_2}CH_3$) 4.6 (3H, s, N–CH_3), 8.3 (1H, d, J = 8.6 Hz, 3-H), 9.2 (1H, m, J = 8.6 Hz, J = 1.0 Hz, 4-H), 9.6 (1H, d, J = 1.0 Hz, 6-H) (Calc for $C_{11}H_{14}NOCl$; C, 61.97, H, 7.51, N, 6.57. Found: C, 61.77, H, 7.45, N, 6.45%).

Experiment No. 8. 1 g (0.007 mole) of 2,2-dimethyl-5-methylaminopent-4-en-3-one was added to 10 ml of TFA and left for several hours. 30 ml of methanol was added and mixture was boiled until it was neutral. Solvents were evaporated and the residue subjected to the usual work up with ion exchange resin and TLC on silica. The reaction yielded over 90% of salt **2**.

Table 1. Protonation of enamino-ketones

Exp. No.	Structure **1**	Reaction conditions* Solvent	Acid	Product composition % **2**	**5**	**6**
1	CH_3, CH_3	$(C_2H_5)_2O$	HCl g.	>90		
2		CH_3CN	HI aq.	>90		
3	C_2H_5, CH_3	CH_3CN	HCl g.	95		
4		CH_3CN	TFA	>90		
5	C_6H_5, CH_3	CH_3CN	HCl g.	90		
6	CH_3, H	$(C_2H_5)_2O$	HCl g.	85		
7		$(C_2H_5)_2O$	HCl g.	>90		
8		TFA	TFA	>90		
9	t-C_4H_9, CH_3	CH_3CN	TFA	56		36
10		$(C_2H_5)_2O$	HI aq.		26	42
11		CH_3OH	HI aq.†			60
12		CH_3CN	HI aq.		10	70
13	**6**	CH_3CN	HI aq.		70	
14	CH_3CO–CH=CH–$N(CH_3)_2$	$(C_2H_5)_2O$	HCl g.	90% of **3**		

*Usually molar equivalent of acid was used, reactions were carried out at room temperature and the reaction mixture was allowed to stay several hours before work up.

†0.5 equivalent of acid was used with respect to the enamine.

Experiment No. 9. To a stirred solution of 2 g (0.014 m) of 2,2-dimethyl-5-methylaminopent-4-en-3-one in 10 ml of methyl cyanide was slowly added in portions 0.5 ml (0.014 mole) of TFA in 5 ml of ether. The solvents were evaporated and residue dissolved in 20 ml of hot mixture of petroleum ether–carbon tetrachloride (3:2). Undissolved oil contained 1.4 g (56% yield) of crude product **2** (R_1 = t-C_4H_9, R_2 = CH_3, X = CF_3COO). Work up on ion exchange resin and chromatography on silica yielded oil of **2** (X = Cl). NMR (CD_3CN), 1.35 (9H, s, –CO–C(CH_3)$_3$), 1.6 (9H, s, 2-C(CH_3)$_3$), 4.7 (3H, s, N–CH_3), 8.3 (1H, d, J = 9.0 Hz, 3-H), 8.8 (1H, m, J = 9 Hz, J = 2 Hz, 4-H), 9.2 (1H, d, J = 2.0 Hz, 6-H) (Calc. for $C_{13}H_{24}NOCl$: C, 66.91, H, 8.92, N, 5.2. Found: C, 66.80, H, 8.81, N, 5.1%). The solution decanted from the oil above yielded on recrystallization 0.65 g (36% yield) of side product **6**, mp 175°. NMR (CCl_4), 1.1 (18H, s, –CO–C(CH_3)$_3$), 3.1 (3H, s, N–CH_3), 5.8 (2H, d, J = 13 Hz, CO–CH=), 7.7 (2H, d, J = 13 Hz, =CH–N) (Calc. for $C_{13}H_{23}NO_2$: C, 70.59, H, 9.80, N, 5.49. Found: C, 70.61, H, 9.85, N, 5.40%).

Experiment No. 10. To the stirred solution of 2 g (0.014 m) of 2,2-dimethyl-5-methylaminopent-4-en-3-one in 10 ml of ether was added slowly in portions equimolar amount of 67% aqueous solutions of hydroiodide in 5 ml of methanol–ether mixture (1:1) at room temperature. The mixture was left overnight whereafter deposited crystals were filtered off. TLC of the solid from the evaporated solution, on silica in a mixture of methyl cyanide–benzene (2:3) afforded 0.75 g (42% yield) of **6** and 0.63 g (26% yield) of **5** (R_1 = C_4H_9, R_2 = CH_3, X = I) as yellow crystals melting at 231°. NMR in DMSO-d_6, 1.3 (18H, s, –CO–C(CH_3)$_3$), 4-C(CH_3)), 4.4 (3H, s, N-CH_3), 8.7 (1H, s, 2-H), 9.2 (2H, broad s, 5-H, 6-H). (Calc. for $C_{13}H_{24}NOI$: C, 49.86, H, 6.65, N, 3.88. Found: C, 49.25, H, 6.55, N, 3.65%).

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