Regioselectivity of the protonation of capto-dative enaminones

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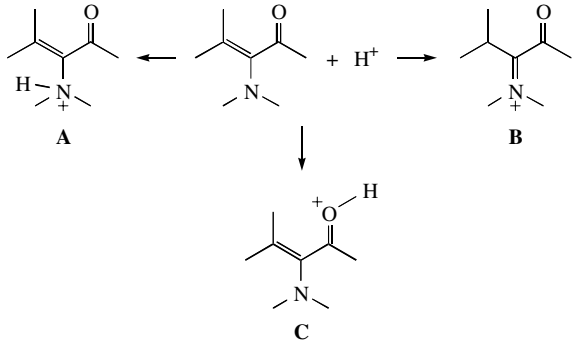
Being polydentate nucleophiles, capto-dative enaminones are regiospecifically protonated at the N or β-C atom depending on the nature of the protonating reagent.

α-Ketoenamines are of particular interest as useful synthons; however, their chemical behaviour is poorly understood.[1] Many properties of this class of compounds originate from their polydentate nucleophilic character. Protonation can provide the simplest reactivity test of these systems.

Previously, we found that N,N-disubstituted 2-amino-2-alkenals react with both mineral and strong organic acids to give very stable enammonium salts, which do not transform to the corresponding iminium salts.[2,3] In the case of azomethine derivatives of the above 2-amino-2-alkenals, the rapid formation of salts having N-protonated structures followed by slow conversion in a $CDCl_3$ solution to more stable C-protonated isomers has been described.[4] Finally, 2-amino-2-cycloalken-1-ones add a proton at the heteroatom, as well as at the β-carbon, with subsequent enolization.[5,6]

Here, we report the protonation of α-ketoenamines **1a**,**b** by both mineral and strong carboxylic acids.

The regioselectivity of proton addition is one of the most attractive aspects of the protonation of enamines.[7] *A priori* the proton attack on α-ketoenamines **1** can result in the formation of enammonium **A**, iminium **B** or oxonium **C** salts (Scheme 1).



A **B** **C**

Scheme 1

We found that the regioselectivity of protonation of α-ketoenamines **1a**,**b** dramatically depends on the nature of the protonating reagent (Scheme 2).

When 3-piperidino-3-buten-2-one **1a** was treated with a cool solution of trifluoroacetic acid in $CDCl_3$ only C-protonated derivative **2a** was detected. The formation of the iminium salt was confirmed by the NMR spectra (Table 1). Thus, the vinylic proton signals disappear and two singlets of two methyl groups appear at 2.57 and 2.60 ppm. A downfield shift by more than 1.0 ppm was observed for the α-CH_2 protons of the piperidine moiety as compared with initial base **1a**. In the ^{13}C NMR spectrum, the appearence of two resonance signals at 197.41 and 196.54 ppm was assigned to carbon of the C=N$^+$ and C=O groups, respectively.[8]

Similar results were obtained for ketoenamine **1b** possesing, in contrast to **1a**, an internal rather than terminal double bond: no enammonium salt traces were detected (Table 2).

Thus, enamines bearing a formyl group at the α-position undergo exclusively N-protonation, whereas α-ketoenamines **1a**,**b** react with trifluoroacetic acid under similar conditions to give regiospecifically alternative C-protonated derivatives **2a**,**b**. This result can be explained in terms of lowering the electron-acceptor ability of the activating group in the transition from α-formyl to

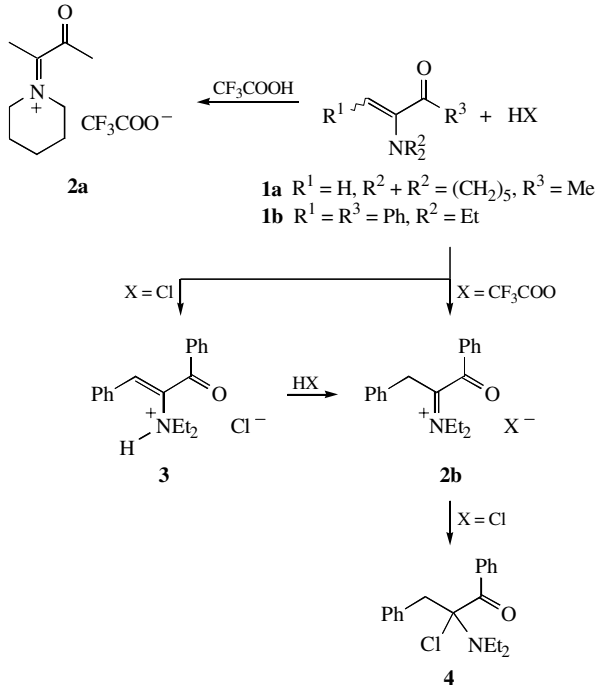
Table 1 NMR spectra of α-ketoenamine **1a** and its iminium salt **2a**.

	^1H NMR			
	CH_2=	Me	NCH_2	$(CH_2)_3$
1a	4.47 and 4.85 (2s, 2H)	2.28 (s, 3H)	2.65–2.75 (m, 4H)	1.45–1.55 (m, 2H), 1.60–1.70 (m, 4H)
2a	—	2.57 (s, 3H) 2.60 (s, 3H)	3.80–3.90 (m, 2H), 4.00–4.10 (m, 2H)	1.75–2.05 (m, 6H)

	^{13}C NMR					
	C(1)	C(2)	C(3)	C(4)	NCH_2	$(CH_2)_3$
1a	27.69	200.54	157.35	98.52	50.66	24.16 25.68
2a	27.06	196.54	197.41	18.70	54.55 54.74	22.20 22.63

α-ketoenamines **1a**,**b**. Because of this, the latter exhibit the properties of simple enamines.[7]

To our surprise, the situation was completely inversed if a hard acid such as anhydrous hydrogen chloride was used as a protonating agent. When dry HCl was bubbled through a solution of ketoenamine **1b** in dry hexane at 0 °C, slightly yellow crystals precipitated. The salt was separated from the solution by filtration, washed with dry hexane and dried *in vacuo* at room temperature. The ^1H NMR spectrum supported the existence of pure hydrochloride of 2-diethylamino benzalacetophenone



2a

1a R^1 = H, $R^2 + R^2 = (CH_2)_5$, R^3 = Me
1b $R^1 = R^3$ = Ph, R^2 = Et

3 **2b** **4**

Scheme 2

3 exclusively in the enammonium form. This is evident from the absence of a CH_2 group singlet corresponding to C-protonated structure **2b**. At the same time, the olefin proton resonance was preserved but strongly downfield shifted and superimposed on the aromatic moiety multiplet. A downfield shift of the β-olefin carbon (37.6 ppm) observed in the ^{13}C NMR spectrum is in good agreement with the principal change in the conjugation of the C=C–C=O chain after protonation.[9] Finally, the presence of the absorption bands observed at 1630 (C=C), 1647 (C=O) and 2300–2600 cm^{-1} (NH^+) in the IR spectrum of **3** provides additional evidence for the enammonium structure.

In contrast, if dry HCl is bubbled through a solution of **1b** in $CDCl_3$ on cooling, an equimolar mixture of enammonium and iminium salts is formed. This difference in the behaviour of mineral and strong carboxylic acids can be attributed to the bifunctional catalytic effect of trifluoroacetic acid on the proton transfer from nitrogen to carbon.[10]

An analysis of 2D COSY and NOESY spectra allows a conclusion that the enammonuim salt obtained exhibits the *Z*-configuration. At the same time, initial base **1b** exists as a non-equimolar mixture of geometrical isomers (*E*:*Z* = 5:1). This fact suggests that the formation of the enammonium salt is accompanied by geometrical isomerization. This easy *E*,*Z*-isomerization was also observed with N,N-disubstituted α-amino-α,β-unsaturated aldehydes and their azomethine derivatives.[2–4]

Enammonium chloride **3** is quite stable: no iminium-type compounds were observed in the proton spectra on standing even for a day at ambient temperature in a $CDCl_3$ solution. In contrast, when dry hydrogen chloride was bubbled through a solution of **3** in $CDCl_3$, the signals of C-protonated form **2b** appeared in the ^1H NMR spectrum: after several minutes, the ratio between enammonium/iminium salts was 1:1. The addition of an excess of trifluoroacetic acid led to the immediate complete conversion of **3** to an isomer having the C-protonated structure of **2b**. Therefore, we may conclude that the transformation of enammonium salt **3** to iminium salt **2b** occurs by an intermolecular acid-assisted process.

Table 2 NMR spectra of α-ketoenamine **1b** and its salts.

	^1H NMR				
	Ph	CH=, CH_2	NCH_2	Me	
(*E*)-**1b**	6.80–8.00 (m, 10H)	5.64 (s, 1H)	3.11 (q, 4H, *J* 7.2 Hz)	1.13 (t, 6H, *J* 7.2 Hz)	
(*Z*)-**1b**		6.20 (s, 1H)	3.05 (q, 4H, *J* 7.2 Hz)	1.06 (t, 6H, *J* 7.2 Hz)	
2b	7.00–7.70 (m, 10H)	4.37 (s, 2H)	4.22 (q, 2H, *J* 7.2 Hz) 3.79 (q, 2H, *J* 7.2 Hz)	1.49 (t, 3H, *J* 7.2 Hz) 1.34 (t, 3H, *J* 7.2 Hz)	
3	7.00–7.85 (m, 10H)	7.18 (s, 1H) masked	3.61 (q, 4H, *J* 7.2 Hz)	1.56 (t, 3H, *J* 7.2 Hz)	
	^{13}C NMR				
	Ph	CH=, CH_2	=C–N, $C=N^+$	C=O	NCH_2	Me
(*E*)-**1b**	124.72, 127.62, 128.12, 128.61, 129.69, 133.53, 137.04, 137.49	103.4	145.75	197.02	43.93	12.58
(*Z*)-**1b**	127.78, 128.25, 128.28, 129.55, 130.07, 132.29, 136.17, 138.80	126.90	145.57	196.31	46.14	13.91
2b	128.08, 129.45, 129.70, 129.77, 130.17, 130.19, 130.93, 137.83	40.19	186.30	187.59	50.97, 54.37	12.68, 13.18
3	128.48, 128.70, 128.94, 129.80, 130.05, 130.30, 131.44, 134.41	141.03	134.86	191.35	51.86	11.16

Surprisingly, enammonium salt **3** undergoes a transformation after a month of keeping in a desiccator at ambient temperature. According to ^1H and ^{13}C NMR spectra, the new solid compound formally has the structure of Markovnikov adduct **4**. Thus, its ^1H NMR spectrum contains an AB-system that is characteristic of the resonance of benzyl group methylenic protons [4.85 (d, 1H, A-part of the AB system, *J* 23.6 Hz), 4.37 (d, 1H, B-part of the AB system, *J* 23.6 Hz)]. Furthemore, the presence of a $–CH_2–C(Cl)(NEt_2)–C(O)–$ fragment was also revealed using ^{13}C NMR spectroscopy: the signals at δ 40.95, 84.31 and 200.36 ppm were assigned to $PhCH_2$, C_{quat} and C=O, respectively (DEPT experiment). The formation of compound **4** could be explained through a sequential mechanism involving the initial rearrangement of enammonium salt **3** to corresponding iminium salt **2b** (X = Cl) followed by chloro anion addition.

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