Interactions of aliphatic β-amino-β-trifluoromethylvinyl ketones with ethylenediamine

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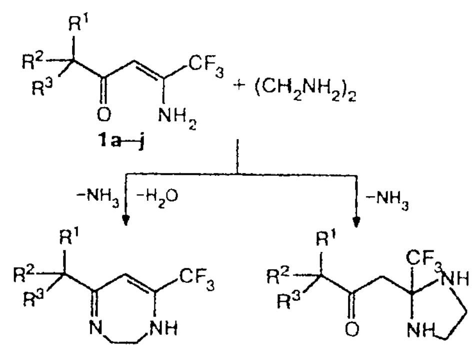
The reactions of aliphatic β-amino-β-trifluoromethylvinyl ketones with an excess of ethylenediamine at room temperature afforded the corresponding 2,3-dihydro-1*H*-1,4-diazepines or substituted 2-acetonyl-2-trifluoromethylimidazolidines (the latter were obtained when the approach to the carbonyl group was sterically hindered).

Key words: aliphatic β-amino-β-trifluoromethylvinyl ketones, ethylenediamine, 2,3-dihydro-1*H*-1,4-diazepines, substituted 2-acetonyl-2-trifluoromethylimidazolidines.

It is known[1] that the reactions of β-amino-β-polyfluoroalkylvinyl ketones with ethylenediamine (EDA) upon boiling in alcohol or benzene afforded 2,3-dihydro-1*H*-1,4-diazepines, which exist in the imine-enamine form. These compounds formed as a result of two nucleophilic attacks on the β-carbon atom and on the carbonyl group. The second possible direction of the reaction, which leads to the closure of the imidazolidine ring as a result of the double attack on the β-carbon atom accompanied by liberation of the ammonia molecule, was not observed in the case of aminoenones although the formation of 2-ethoxycarbonylmethyl-2-trifluoromethylimidazolidine in the reaction of EDA with ethyl trifluoroacetoacetate has been reported previously.[2]

Recently,[3] in attempting to synthesize dihydrodiazepines containing the trifluoromethyl and hydroxyalkyl groups, we found that the reactions of EDA with 2-amino-1,1,1-trifluoro-6-hydroxy-5,5-dimethyl-2-hexen-4-one (**1a**) and the corresponding 5,5-pentamethylene-substituted compound **1b** at room temperature in the absence of a solvent proceeded differently. Thus, the reaction of **1a** with EDA afforded the expected dihydrodiazepine **2a**, while in the case of **1b**, imidazolidine (**3b**) formed. The substantial difference in the reactivity of structurally similar compounds **1a,b** gave impetus to more detailed studies of the reactions of EDA with aliphatic β-amino-β-trifluoromethylvinyl ketones with the aim of revealing the possibilities of the synthesis of *N,N'*-unsubstituted imidazolidines, which, unlike *N,N'*-diaryl-[4] and *N,N'*-dialkylimidazolidines,[5] remain virtually unknown.

A number of aminoenones **1a—j** were synthesized by condensation of trifluoroacetonitrile with the corresponding methyl ketones in the presence of *N*-ethylanilinomagnesium bromide.[6] The reactions of the resulting compounds with a fourfold excess of EDA at



2a—c,e—i **3b,e,j**

	$R^1 = R^2$	R^3		$R^1 + R^2$	R^3
a	Me	CH_2OH	b	$(CH_2)_5$	CH_2OH
d	H	CMe_2OH	f	$(CH_2)_5$	H
g	Me	OH	i	$(CH_2)_5$	OH

	$R^1 = R^2 = R^3$		R^1	R^2	R^3
c	H	h	Me	Et	OH
e	Me	j	Me	Bu^t	OH

room temperature without a solvent (the duration of the reaction was several days, procedure *A*)[3] and upon boiling in alcohol (the duration of the reaction was 3 h, procedure *B*)[1] were studied.

Previously, we have established[3] that the reactions of aminoenones **1a,b** at room temperature gave diazepine **2a** and imidazolidine **3b**, respectively, in 75% yields, whereas when boiled with EDA in alcohol, aminoenones **1a,b** remained virtually unconsumed. In the latter case, **1a** contained an admixture of diazepine **2a** (5%), while **1b** contained admixtures of diazepine **2b** and imidazolidine **3b** (7% and 18%, respectively; the ^1H NMR spectral data). We succeeded in preparing diazepine **2b**

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2305—2308, November, 1998.
1066-5285/98/4711-2234$20.00

Table 1. Physicochemical characteristics of 2,3-dihydro-1*H*-1,4-diazepines **2a—c,e—i**

Compound	Yield[a] (%)	M.p. /°C	Molecular formula	Found/Calculated (%) C	H	N
2a	75	130—131	$C_{10}H_{15}F_3N_2O$	50.87 50.84	6.53 6.40	11.73 11.86
2b	40	180—181	$C_{13}H_{19}F_3N_2O$	56.40 56.51	7.07 6.93	10.06 10.14
2c	66	115—116[b]	$C_7H_9F_3N_2$	47.27 47.19	5.15 5.09	15.56 15.72
2e	73	104—105[c]	$C_{10}H_{15}F_3N_2$	54.42 54.54	6.98 6.87	12.77 12.72
2f	73	126—127	$C_{12}H_{17}F_3N_2 \cdot 0.25\ NH_3$	57.56 57.53	7.35 7.14	12.31 12.58
2g	60	133—134	$C_9H_{13}F_3N_2O$	48.52 48.65	5.86 5.90	12.62 12.61
2h	65	156—157	$C_{10}H_{15}F_3N_2O$	50.93 50.84	6.28 6.40	11.81 11.86
2i	59	152—153	$C_{12}H_{17}F_3N_2O \cdot H_2O$	51.63 51.42	6.64 6.83	9.97 9.99

[a] Procedure *A*. [b] Ref. 1: 116—117 °C. [c] Ref. 1: 105—105.5 °C.

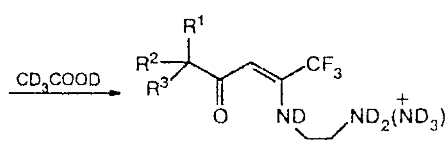
according to procedure *A* with the use of a 20-fold excess of EDA. Under these conditions, imidazolidine **3b** and diazepine **2b** were obtained in approximately equal amounts. The latter was isolated in 40% yield (Table 1).

Compounds **1c,d**, which were prepared from acetone and diacetone alcohol, respectively, gave the same diazepine **2c** described previously[1] regardless of the reaction conditions. Aminoenone **1e** bearing the *tert*-butyl substituent slowly reacted with EDA at room temperature to give imidazolidine **3e** in 52% yield (after four weeks), whereas when boiled in alcohol, **1e** gave diazepine **2e** reported previously[1] in the approximately identical yield. Compounds **1f—i** containing the cyclohexyl and dialkylhydroxymethyl substituents at the carbonyl group gave only diazepines **2f—i**. The reaction of EDA with aminoenone **1j** proceeded at room temperature during 7 days to give imidazolidine **3j** in 48% yield. This reaction did not occur upon boiling in alcohol.

Therefore, of the ten studied β-amino-β-trifluoromethylvinyl ketones containing alkyl and α(or β)-hydroxyalkyl substituents, only aminoenones **1b,e,j** that bear the most sterically hindered carbonyl groups reacted with EDA to form imidazolidines **3b,e,j** (procedure *A*). In the remaining cases, diazepines **2a,c,f—i** were obtained under these reaction conditions. Diazepine **2b** was prepared according to procedure *A* with the use of a large excess of EDA. Diazepine **2e** was obtained according to procedure *B*. An attempt to prepare diazepine **2j** failed.

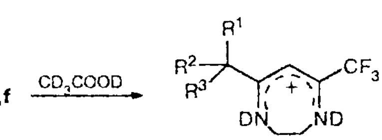
The ^1H NMR spectra of imidazolidines **3b,e** have two singlets for the protons of the exocyclic methylene group and of the ethylene fragment of the imidazolidine ring in the region of δ 2.90—3.08 and a broadened singlet for the protons of the NH group (and of the OH group in the case of **3b**) at δ 3.4 and δ 2.7 for **3b** and **3e**, respectively. Because of the presence of the second chiral center in imidazolidine **3j**, its exocyclic methylene group gives an AB system with the center at δ 3.08 (Δδ = 1.48) and the protons of the two methylene groups of the ring give a multiplet in the region of δ 2.6—3.3, which masks the signals of the NH and OH groups. When CD_3COOD was added to a solution of imidazolidine **3e** in $CDCl_3$, the broadened singlet for the protons of the NH group at δ 2.7 disappeared and the signals of the CH_2 and $(CH_2)_2$ groups were shifted downfield (δ 3.02 and 3.13, respectively). In addition, a new set of signals consisting of two singlets at δ 1.17 and 5.75 and two multiplets with the centers at δ 3.2 and 3.7 appeared. These signals were assigned to the *tert*-butyl group, the vinyl proton, and the two nonequivalent methylene groups of aminoenone **4e**, which formed as a result of cleavage of the imidazolidine ring of compound **3e** and which was present in the *N*-deuterated form (probably, as a monocation) in ~30% yield. The available data did not allow us to make an unambiguous conclusion about the configuration of the double bond of aminoenone **4e**. However, based on the comparison of the values of the chemical shifts of the vinyl protons of compounds **1e** and **4e** (δ 5.69 and 5.75, respectively), it is believed that the *Z* configuration is more probable. An analogous conversion in the presence of CD_3COOD was observed in the case of imidazolidines **3b,j**. The ^1H NMR spectra of these compounds, which were recorded immediately after addition of CD_3COOD, have singlets of the vinyl protons of aminoenone **4b** at δ 5.84 and of aminoenone **4j** at δ 5.77. The concentrations of **4b** and **4j** were ~10% and ~35%, respectively.

3b,e,j



4b,e,j

2a—c,e,f



5a—c,e,f

The ^1H NMR spectra of diazepines **2a—c,e—i** are characterized by the presence of multiplets of the two nonequivalent CH_2 groups of the dihydrodiazepine ring at δ 3.37—3.64 and 3.75—3.98 and a singlet of the vinyl proton at δ 4.89—5.11. When CD_3COOD was added to solutions of compounds **2a—c,e,f** in $CDCl_3$, symmetrically delocalized monocations **5a—c,e,f** formed as evi-

Table 2. Spectra of 2,3-dihydro-1*H*-1,4-diazepines **2a—c,e—i**

Compound	^{1}H NMR, δ, *J*/Hz: $CDCl_3$	^{1}H NMR, δ, *J*/Hz: $CDCl_3 + CD_3COOD$	IR, ν/cm^{-1}: NH, OH	IR, ν/cm^{-1}: C=N, C=C, NH
2a	1.19 (s, 6 H, 2 CH_3); 2.9 (br.s, 2 H, OH, NH); 3.50 (m, 2 H, CH_2N); 3.57 (m, 2 H, CH_2O); 3.78 (m, 2 H, CH_2N=); 5.07 (s, 1 H, =CH)	1.31 (s, 6 H, 2 CH_3); 3.69 (s, 2 H, CH_2O); 3.82 (s, 4 H, CH_2CH_2); 5.40 (s, 1 H, =CH)	3345, 3140	1620, 1570, 1550
2b	1.2—2.0 (m, 10 H, $(CH_2)_5$), 3.52 (m, 2 H, CH_2N); 3.59 (s, 2 H, CH_2O); 3.89 (m, 2 H, CH_2N=); 5.11 (s, 1 H, =CH)	1.2—2.0 (m, 10 H, $(CH_2)_5$); 3.70 (s, 2 H, CH_2O); 3.90 (s, 4 H, CH_2CH_2); 5.45 (s, 1 H, =CH)	3340, 3100	1620, 1570, 1535
2c	2.01 (s, 3 H, CH_3); 3.38 (m, 2 H, CH_2N); 3.98 (m, 2 H, CH_2N=); 4.5 (br.s, 1 H, NH); 4.89 (s, 1 H, =CH)	2.41 (s, 3 H, CH_3); 3.78 (s, 4 H, CH_2CH_2); 5.24 (s, 1 H, =CH)	3235, 3120, 3075	1620, 1590, 1545
2e	1.23 (s, 9 H, Bu^t); 3.40 (m, 2 H, CH_2N); 3.95 (m, 2 H, CH_2N=); 4.9 (br.s, 1 H, NH); 5.06 (s, 1 H, =CH)	1.35 (s, 9 H, Bu^t); 3.82 (s, 4 H, CH_2CH_2); 5.42 (s, 1 H, =CH)	3240, 3160, 3105	1625, 1575, 1540
2f	1.0—1.5 (m, 6 H, $(CH_2)_3$); 1.6—2.1 (m, 5 H, $(CH_2)_2$CH); 3.37 (m, 2 H, CH_2N); 3.96 (m, 2 H, CH_2N=); 4.90 (s, 1 H, =CH); 5.1 (br.s, 1 H, NH)	1.1—1.5 (m, 6 H, $(CH_2)_3$); 1.6—2.1 (m, 4 H, $(\underline{CH_2})_2$CH);2.6 (m, 1 H, $(CH_2)_2\underline{CH}$); 3.79 (s, 4 H, CH_2CH_2); 5.27 (s, 1 H, =CH)	3240, 3110, 3085	1615, 1590, 1540
2g	1.47 (s, 6 H, 2 CH_3); 3.55 (m, 2 H, CH_2N); 3.82 (m, 2 H, CH_2N=); 4.9 (br.s, 2 H, OH, NH); 4.96 (s, 1 H, =CH)	1.54 (s, 6 H, 2CH_3); 3.80 (m, 2 H, CH_2); 3.89 (m, 2 H, CH_2); 5.26 (s, 1 H, =CH)	3375, 3130	1625, 1560
2h	0.87 (t, 3 H, CH_3, *J* = 7.0); 1.44 (s, 3 H, CH_3); 1.74 (q, 2 H, CH_2, *J* = 7.0); 3.3 (br.s, 2 H, OH, NH); 3.64 (m, 2 H, CH_2N); 3.80 (m, 2 H, CH_2N=); 4.97 (s, 1 H, =CH)	0.90 (t, 3 H, CH_3, *J* = 7.1); 1.52 (s, 3 H, CH_3); 1.80 (q, 2 H, CH_2, *J* = 7.1); 3.80 (m, 2 H, CH_2); 3.94 (m, 2 H, CH_2); 5.23 (s, 1 H, =CH)	3390, 3090	1620, 1555
2i	1.5—1.7 (m, 10 H, $(CH_2)_5$); 3.48 (m, 2 H, CH_2N); 3.75 (m, 2 H, CH_2N=); 4.0 (br.s, 2 H, OH, NH); 4.94 (s, 1 H, =CH)	1.5—1.7 (m, 10 H, $(CH_2)_5$); 3.71 (m, 2 H, CH_2); 3.83 (m, 2 H, CH_2); 5.25 (s, 1 H, =CH)	3390, 3090	1620, 1550

denced by the fact that the ^{1}H NMR spectra of these compounds have a singlet of the ethylene unit at δ 3.78—3.90 and the signals of the alkyl substituent and the vinyl proton are substantially shifted downfield (by 0.12—0.40 and 0.33—0.37 ppm, respectively). It should be noted that under analogous conditions, the methylene groups of diazepines **2g—i** bearing the α-hydroxyalkyl substituents are not completely equivalent and are observed as two closely-spaced multiplets at δ 3.71—3.80 and 3.83—3.94. This is more likely associated with the presence of a rather strong intramolecular hydrogen bond between the α-hydroxyl group and the imine nitrogen atom, which hinders the formation of the symmetrically delocalized monocation (Table 1).

Therefore, the reactions of aliphatic β-amino-β-trifluoromethylvinyl ketones with ethylenediamine would be expected to give thermodynamically more stable dihydrodiazepines. However, under mild conditions and in the presence of steric hindrances at the carbonyl group, the direction of the reaction, which leads to the formation of 2,2-disubstituted imidazolidines (products of the kinetically controlled process), becomes more favorable.

Experimental

The IR spectra were recorded on an IKS-29 instrument as Nujol mulls. The ^{1}H NMR spectra were obtained on a Tesla BS-567A spectrometer in $CDCl_3$ operating at 100 MHz with Me_4Si as the internal standard.

The yields, melting points, and data of elemental analysis and ^{1}H NMR and IR spectroscopy of the synthesized compounds are given in Table 1.

Procedures *A* and *B* have been reported previously.[1,3]

2-(3-Hydroxymethyl-3,3-pentamethyleneacetonyl)-2-trifluoromethylimidazolidine (3b). The yield was 76%, m.p. 85—86 °C. Found (%): C, 53.26; H, 7.32; N, 9.59. $C_{13}H_{21}F_3N_2O_2$. Calculated (%): C, 53.05; H, 7.19; N, 9.52. IR, ν/cm^{-1}: 3360, 3315, 3195 (NH, OH), 1705 (C=O), 1645 (NH). ^{1}H NMR, δ: 1.2—2.0 (m, 10 H, cyclohexane ring); 2.90 (s, 2 H, CH_2); 3.02 (s, 4 H, CH_2CH_2); 3.4 (br.s, 3 H, OH, 2 NH); 3.72 (s, 2 H, CH_2—O).

2-Pivaloylmethyl-2-trifluoromethylimidazolidine (3e). The yield was 44%, m.p. 49—50 °C. Found (%): C, 50.43; H, 7.12; N, 11.67. $C_{10}H_{17}F_3N_2O$. Calculated (%): C, 50.41; H, 7.19; N, 11.76. IR, ν/cm^{-1}: 3410 (NH), 1700 (C=O). ^{1}H NMR, δ: 1.15 (s, 9 H, Bu^t); 2.7 (br.s, 2 H, 2 NH); 2.90 (s, 2 H, CH_2); 3.08 (s, 4 H, CH_2CH_2).

2-(3-*tert*-Butyl-3-hydroxy-3-methylacetonyl)-2-trifluoromethylimidazolidine (3j). The yield was 48%, m.p. 85—86 °C. Found (%): C, 51.12; H, 7.63; N, 10.10. $C_{12}H_{21}F_3N_2O_2$. Calculated (%): C, 51.06; H, 7.50; N, 9.92. IR, ν/cm^{-1}: 3380, 3300 (NH, OH), 1700 (C=O). ^{1}H NMR, δ: 0.96 (s, 9 H, Bu^t); 1.22 (s, 3 H, CH_3); 3.08 (AB system, 2 H, CH_2, $\Delta\delta$ = 1.48 Hz, J = 11.8 Hz); 2.6—3.3 (m, 7 H, CH_2CH_2, OH, 2 NH).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 96-03-33373).

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Received May 8, 1998