Haloacetylated Enol Ethers. 14 [6]. Reaction of β-Alkoxyvinyl Trifluoromethyl Ketones with *N*-Methylhydroxylamine

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The reaction of a series of β-methoxyvinyl trifluoromethyl ketones [$CF_3COC(R^2)=C(OMe)R^1$, where R^1 = Me, -$(CH_2)_3$-*C*3, -$(CH_2)_4$-*C*3, Ph and R^2 = H, Me, -$(CH_2)_3$-*C*4, -$(CH_2)_4$-*C*4] with *N*-methylhydroxylamine is reported. The regiochemistry of the reaction are explained by MO calculation data.

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The haloacetylation of acyclic enol ethers described elsewhere [1,2] and by our research group [3], affords β-alkoxyvinyl halomethyl ketones or β-diketones, which have been used as precursors for the synthesis of 5-, 6- and 7-membered heterocycles [4-6]. Although through the past few years we have reported extensively the synthesis and isolation of 5-hydroxy-2-isoxazolines (or 5-hydroxy-4,5-dihydroisoxazoles) [3,4], there is still a lack in the literature on 5-hydroxy-3-isoxazolines (or 5-hydroxy-2,5-dihydroisoxazoles). Practically unknown until the late 1960's, 3-isoxazolines have received little attention and have not yet been systematically studied. A limited number of polysubstituted derivatives have been obtained by one of the three methods of preparation with general applicability, explored until the present time [7]. All these methods start from quaternary salts: oximation of flavylium salts [8], nucleophilic addition to isoxazolinium salts [9], and basic treatment of 2-isoxazolinium salts [10].

The purpose of this work is to investigate the regiochemistry of the reaction of β-methoxyvinyl trifluoromethyl ketones **1a-e** with *N*-methylhydroxylamine to obtain the 3-isoxazoline derivatives (the cyclic compounds) and the enaminone derivatives (the open-chain compounds), Scheme. The equilibrium open-chain/cyclic compounds is studied by MO calculations.

The β-alkoxyvinyl trifluoromethyl ketones **1a-e** were synthesized from the reaction of the respective enol ether or acetal with trifluoroacetyl anhydride [3].

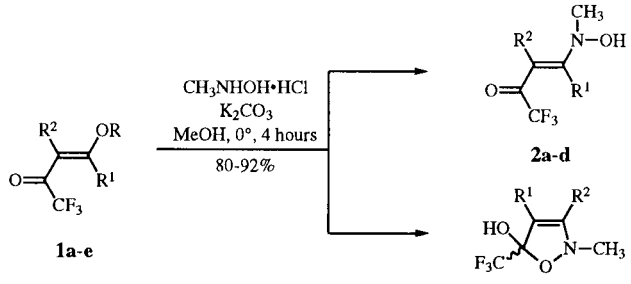
The reactions of compounds **1a-e** with *N*-methylhydroxylamine hydrochloride were carried out in a molar ratio of 1:1.2 using methanol as the solvent. The use of a small excess of *N*-methylhydroxylamine hydrochloride was essential to obtain a saturated solution during the reaction resulting in an improvement of the yield. Pyridine and triethylamine were also used as organic bases, but the most satisfactory yields were obtained in the presence of potassium hydroxide or potassium carbonate. It was not possible to perform the reaction of compound **1** with *N*-methylhydroxylamine at *p*H <5.0 because when a low *p*H was used [11], only the hydrolysis product of β-alkoxyvinyltrifluoromethyl ketones was obtained.

The reaction times were estimated by monitoring the disappearance of **1a** by hplc. The disappearance of **1a** occurred after 3 hours, thus the reaction time was established to be 4 hours for all reactions. The reaction mixtures were stirred under reflux for 4 hours, then the excess of *N*-methylhydroxylamine hydrochloride was filtered and the solvent was evaporated under reduced pressure. The product was taken up in dichloromethane and then purified by column chromatography.

The reaction of compounds **1a-c** with *N*-methylhydroxylamine lead to the enaminone derivatives **2a-c**, while the compounds **1d,e** furnished the 3-isoxazoline derivatives **3d,e**. The products **2**, **3** were obtained in 80-92% yield (Scheme, Table 1). A mixture of products **2** and **3** was not observed, except in the reaction of compound **1d**, where the presence of products **2d** and **3d** in a 30:70% ratio was detected.

It seems that the thermodynamic stability of product **2** or **3** governs the formation of the open-chain compound (enaminone derivatives **2**) or the cyclic compound (3-isoxazoline derivatives **3**). In Table 2 are listed the energy dif-

Scheme



	R	R^1	R^2
a	CH_3	CH_3	H
b	CH_3	Ph	H
c	CH_3	-$(CH_2)_3$-	
d	CH_3	-$(CH_2)_4$-	
e	CH_3	Ph	CH_3

Table 1

Selected [a] Physical and Spectral Data of **2a-d, 3d,e**

Compound	Molecular Formula	Yield (%) [b]	Elemental Analysis (%) C Calcd./Found	Elemental Analysis (%) H Calcd./Found	GC-MS m/z (%)	m.p. (°C)	IR (film) ν (cm^{-1})	^{1}H NMR δ	^{13}C NMR δ (J_{CF}/Hz)
2a	$C_6H_8F_3NO_2$ (183.13)	92	39.35 / 39.59	4.40 / 4.43	184 (MH^+, 100), 166 (65), 114 (84)	55-57	3040, 2986, 1682, 1575, 1178	2.18 (CH_3), 5.33 (H), 3.62 (NCH_3)	118.8 (Cl, 281), 163.2 (C2, 33), 91.8 (C3, 2.8), 155.5 (C4), 44.6 (NCH_3)
2b	$C_{11}H_{10}F_3NO_2$ (245.20)	88	53.88 / 53.74	4.11 / 4.10	246 (MH^+, 100), 228 (70), 176 (95), 103 (80)	107-108	3050, 1641, 1564, 1180	7.3-7.8 (Ph), 5.45 (H), 3.56 (NCH_3)	118.7 (Cl, 281), 163.9 (C2, 33), 92.3 (C3, 2.7), 158.5 (C4), 46.4 (NCH_3)
2c	$C_8H_{10}F_3NO_2$ (209.17)	80	45.94 / 45.80	4.82 / 4.78	210 (MH^+, 100), 192 (55), 124 (95)	oil	2982, 2883, 1650, 1590, 1210	1.7-2.1 (CH_2), 2.4-2.9 (CH_2CH_2), 3.6 (NCH_3)	119.5 (Cl, 281), 158.4 (C2, 33), 104.6 (C3), 162.3 (C4), 45.2 (NCH_3)
2d [c]	$C_9H_{12}F_3NO_2$ (223.19)	85	48.43 / 48.33	5.42 / 5.35	224 (MH^+, 100), 206 (70), 154 (90)	oil	2940, 2860, 1698, 1262, 1181, 1094	1.6-2.5 [$(CH_2)_4$], 3.62 (NCH_3)	118.7 (Cl, 281), 164.3 (C2, 33), 102.0 (C3), 161.0 (C4), 45.5 (NCH_3)
3d [c]	$C_9H_{12}F_3NO_2$ (223.19)	85	48.43 / 48.33	5.42 / 5.35	223 (M^+, 35), 206 (100), 81 (45)	oil	2940, 2860, 1439, 1262, 1181, 1094	1.6 -2.5 [$(CH_2)_4$], 2.85 (NCH_3)	151.2 (C3), 104.0 (C4), 109.5 (C5, 34), 121.4 (CF_3, 286), 42.4 (NCH_3)
3e	$C_{12}H_{12}F_3NO_2$ (259.23)	87	55.60 / 55.69	4.67 / 4.89	259 (M^+, 20), 242 (100), 118 (40)	82-85	3068, 2985, 1681, 1442, 1255, 1178	7.32 (Ph), 1.86 (CH_3), 2.79 (NCH_3)	149.5 (C3), 107.3 (C4), 107.3 (C5, 34), 121.5 (CF_3, 286), 44.6 (NCH_3)

[a] See Experimental; [b] Yields of isolated compounds; [c] Data obtained for the mixture of **2d**:**3d** (30%:70%).

Table 2

Difference of Energy between the Open-Chain Compounds **2a-e** and the Respective Cyclic Compounds **3a-e**, obtained by MO Calculation [a]

Open-chain Compound (%) [b]	Dihedral Angle $OC_2C_3C_4$ (Degrees), **2**	Dihedral Angle C_3C_4NO (Degrees), **2**	Cyclic Compound (%) [b]	$\Delta E = (E_2-E_3)$ (kcal.mol^{-1})
2a (93)	38	26	**3a** (7)	-1.5
2b (95)	39	3	**3b** (5)	-1.7
2c (100)	14	165	**3c** (0)	-13.8
2d (30)	53	25	**3d** (70)	0.5
2e (9)	47	88	**3e** (91)	1.4

[a] The MO calculations were carried out by the AM1 semiempirical method (see Experimental); [b] Calculated for the equilibrium at 298 K, as described in the Experimental.

ference (ΔE) between the open-chain compounds **2a-e** and the cyclic compounds **3a-e** obtained by MO calculations, with molecular geometries completely optimized for each compound without fixing any parameter (see Experimental). The MO calculations were performed using the Austin Model 1 (AM1) semiempirical method [12], implemented in the HyperChem 4.5 package [13].

One may consider that the cyclocondensation reactions of β-alkoxyvinyltrifluoro methyl ketones **1** with hydroxylamine been carried out under an equilibrium between the open-chain (oxime) and cyclic (2-isoxazolin-5-ol) structures [3,4]. Normally only the 5-membered rings would be obtained due to the inductive withdrawing effect of the trifluoromethyl group stabilize the semi-acetal portion formed in the 2-isoxazolin-5-ol ring [3,4]. Thus, we believe that the *N*-methylhydroxylamine react with compounds **1a-e** leading initially to the formation of β-enamino ketones **2a-e** with possible π-orbital overlaping even higher than the normal enamines [14]. In the next step, due to the semi-acetal formation, part of the conjugation is lost, which is an unfavorable situation in the medium under thermodynamic conditions. However, when R^2 = methyl, alkyl (**1d,e**) the heterocyclic ring closure was favored and the 3-isoxazolin-5-ols **3d,e** were obtained. The ring closure can be explained by the evidence that the conjugation energy of the β-enamino ketones by the interference of the R^2 substituent in the push-pull resonance interaction between RC=O acceptor and -OR or -NRR donor group (see dihedral angles of $OC_2C_3C_4$ and C_3C_4NO, Table 2) [14].

From the experimental results and the MO calculations it is possible to conclude that the structure of the substituents R^1 and R^2 are the main factor to obtain either compound **2** or compound **3**. When R^2 = H (**1a,b**) the open-chain compounds **2a,b** were obtained (ΔE favors to the open-chain compounds, 1.5-1.7 kcal.mol^{-1}, Table 2). On the other hand, for R^2 = methyl or alkyl (**1d,e**) the cyclic compounds **3d,e** were obtained (ΔE favors to the cyclic compounds, 0.8-1.4 kcal.mol^{-1}, Table 2). For the reaction of compound **1c** (R^2 = alkyl) the cyclic compound was not obtained because its stability is much lower (ΔE is highly favorable to the open-chain compound, 13.8 kcal.mol^{-1}, Table 2). This was attributed to the strain of the distortion angle necessary to close a five-membered ring condensed to another five-membered ring with a double bond at the ring junction. This effect already has been observed in the cyclocondensation of compound **1c** with hydroxylamine [4]. The mixture of compounds **2d**:**3d** (30:70%) was attributed to the small difference in energy between the two compounds (0.5 kcal.mol^{-1}). The relative abundance of each species in equilibrium (**2** and **3**) calculated for the equilibrium at 298 K are in agreement with the pecentage obtained experimentally (Table 2).

Both the open chain and cyclic structures were easily assign by the ^{13}C chemical shift of the α-carbon to the trifluoromethyl group, which appear as a quartet by the coupling with fluorine atoms ($^2J_{CF}$ = 33 Hz, Table 1). These structures were also confirmed by infrared and gc-ms data.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Elemental analysis was carried out on a Vario EL Elemental Analysensysteme apparatus. The ^1H and ^{13}C nmr spectra were acquired on a Bruker AC-80 spectrometer (^1H at 80 MHz and ^{13}C at 20 MHz) in chloroform-d_1/tetramethylsilane. The infrared spectra were recorded on a Bruker IFS 28 spectrometer. The mass spectra were recorded on a ion trapp detector Finnigan Mat ITD 80A connected to a Varian 3400 GC equipped with SE-30 fused silica capillary column, 50 m, 0.32 mm ID. The progress of the reactions was monitored with a LKJB Broma HPLC equipped with a LKB2241 pump, rheodyne manual injector, LKB2151 UV detector and a two channel LKB 2210 plotter. The hplc runs were performed on a C-18 analytical column (250 x 4.6 mm, 5 μ) and methanol/water 70:30 as mobile phase.

Synthesis of 5-Hydroxy-5-trifluoromethyl-2,5-dihydroisoxazoles **3d,e** and Enaminones Derivatives **2a-c**.

General Procedure.

A solution of *N*-methylhydroxylamine (0.011 mole) and potassium hydroxide (0.01 mole) in 5 ml of methanol was prepared in a 50 ml flask and cooled (0° to 10°). To this solution was added β-alkoxyvinyl trifluoromethyl ketone **1** (0.01 mole) in methanol (3 ml). The mixture was stirred for 2-3 hours, the precipitated potassium chloride was filtered and the solvent was evaporated in a rotavapor. The residue obtained showed high purity of products **2**, **3**. When necessary, the products **2**, **3** were purified by column chromatographic with silica gel 60 (0.004-0.063 mm) and eluted with mixtures of dichloromethane/-ethyl acetate (yields 80-92%, Table 1).

Calculations.

The MO calculations were carried out by the Austin Model 1 (AM1) semiempirical method [12], implemented in the HyperChem 4.5 package (1995) [13]. Geometries were completely optimized without fixing any parameter, thus bringing all geometric variables to their equilibrium values. The energy minimization protocol employs the Polak-Ribiere algorithm, a conjugated gradient method [13]. Convergence to a local minimum is achieved when the energy gradient is <0.01 kcal.mol^{-1}. The relative abundance of each species in equilibrium is calculated from the minimum energy associated with each compound employing the relationships: (i) $\Delta E = -RT \ln K$ (where ΔE stands for the standard energy difference between two given species, R is the molar gas constant expressed in units of kcal.mol^{-1}.K^{-1}, T is the absolute temperature in K, *K* is the corresponding equilibrium constant) and (ii) [A] + [B] = 100, where [A] and [B] represent the percentage molar ratio of each conformer in equilib-

rium. The calculations were performed on a PC Pentium II 400 MHz computer equipped with a DeskJet HP 720C printer.

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