Synthesis of fluorine-containing functionalized isoxazolines

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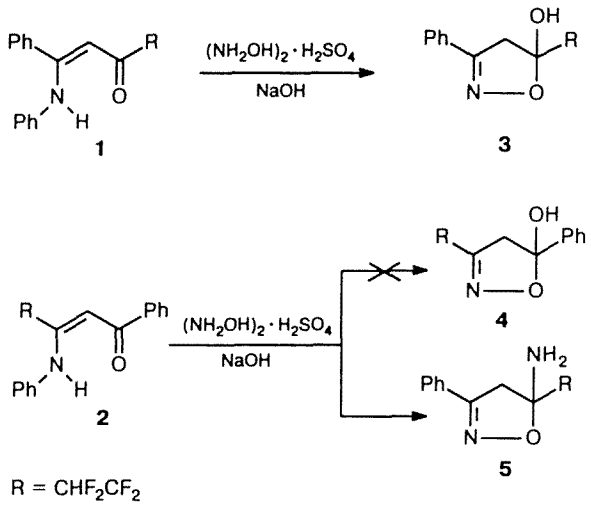
The reaction of regioisomeric fluoroalkyl-containing β-aminovinylketones with hydroxylamine generated *in situ* from hydroxylamine sulfate, afforded 5-hydroxy- or 5-amino-5-fluoroalkyl-Δ^2-isoxazolines.

Key words: fluorine-containing β-aminovinylketones, regioisomers; functionalized Δ^2-isoxazolines.

Isoxazole derivatives are widely used in syntheses of natural compounds and their analogs because it is possible to stereocontrol the formation and opening of the isoxazole cycle.[1,2] The reaction of β-diketones with hydroxylamines is one of the main methods for the synthesis of isoxazoles. However, in the case of fluorine-containing β-diketones, 5-fluoroalkyl-5-hydroxy-Δ^2-isoxazolines are formed due to the stabilizing effect of the fluorinated substituent[3] on the C—O bond.[4,5] One might expect that the application of regioisomeric β-aminovinylketones (AVK) **1** and **2** as aza-analogs of the two enol forms of β-diketones would permit us to carry out the directed synthesis of isomeric fluoroalkyl-containing isoxazolines.

In this work it has been shown that the reaction of AVK **1** with hydroxylamine generated *in situ* from hydroxylamine sulfate, affords the target 5-fluoroalkyl-5-hydroxy-3-phenyl-Δ^2-isoxazoline **3**. The formation of compound **3** can be explained by transamination, which is typical of AVK **1**, followed by ring closure. Under similar conditions, AVK **2** unexpectedly forms not the regioisomeric 3-fluoroalkyl-5-hydroxy-5-phenyl-Δ^2-isoxazoline **4**, but the previously unavailable 5-amino-5-fluoroalkyl-3-phenyl-Δ^2-isoxazoline **5**.

Compounds **3** and **5** are promising polyfunctional synthons. On the basis of the literature data,[1,2,7] one might assume their participation not only in transformations that involve ring opening, but also in nucleophilic substitutions of OH and NH_2 groups.



Experimental

IR spectra were recorded on a Specord-75IR spectrometer in vaseline oil. ^{1}H NMR spectra were obtained on a Tesla BS-567A spectrometer (100 MHz) with $SiMe_4$ as the internal standard. AVK **1** and **2** were synthesized by previously described procedures.[6,8]

5-Amino-5-tetrafluoroethyl-3-phenyl-Δ^2-isoxazoline (5). Hydroxyalmine sulfate (0.05 g, 1.2 mmol) was added to an ethanolic solution of AVK **2** (0.3 g, 1.2 mmol). Then an aqueous solution of NaOH (0.04 g, 0.6 mmol) was added dropwise to the solution. The mixture was refluxed for 5 h, then 5 mL of water was added. The precipitate that formed was filtered and crystallized from *n*-hexane to afford 0.2 g (64 %) of **5**, m.p. 105—107 °C. Found (%): C, 50.68; H, 3.16; N, 10.72. $C_{11}H_{10}F_4N_2O$. Calculated (%): C, 50.58; H, 3.47; N, 10.72. IR, ν/cm^{-1}: 3355, 3285 (NH). ^{1}H NMR ($CDCl_3$), δ: 2.41 (s, 2 H, NH_2)*; 3.05 (d, 1 H, H_A, J_{AB} = 18.31 Hz); 3.90 (d, 1 H, H_B, J_{AB} = 18.31 Hz); 6.17 (tm, 1 H, HCF_2, $^2J_{H,F}$ = 53 Hz)**; 6.75—7.68 (m, 5 H, Ph).

5-Tetrafluoroethyl-5-hydroxy-3-phenyl-Δ^2-isoxazoline (3). Similarly, from AVK **1** (0.5 g, 1.6 mmol), hydroxylamine sulfate (0.13 g, 1.6 mmol), and NaOH (0.032 g, 0.8 mmol) we obtained 0.27 g (66 %) of **3**, m.p. 138—140 °C (from *n*-hexane). Found

* The signal disappears when CD_3COOD is added.

** The splitting of each triplet component into a multiplet results from the location of the $H(CF_2)_2$ group at the asymmetric C atom.

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(%): C, 50.31; H, 3.16; N, 5.43. $C_{11}H_9F_4NO_2$. Calculated (%): C, 50.18; H, 3.47; N, 5.34. IR, ν/cm^{-1}: 3150 (OH). ^1H NMR ($CDCl_3$), δ: 3.36 (d, 1 H, H_A, J_{AB} = 18.07 Hz); 3.75 (d, 1 H, H_B, J_{AB} = 18.01 Hz); 3.43 (s, 1 H, OH)*; 6.13 (tt, 1 H, HCF_2, $^2J_{H,F}$ = 53 Hz, $^3J_{H,F}$ = 6.1 Hz); 7.35—7.70 (m, 5 H, Ph).

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* The signal disappears when CD_3COOD is added.

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Electrochemical oxidative ring opening of 1-methylcyclobutanol

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The manganese(III) acetate-mediated electrooxidative ring opening of 1-methylcyclobutanol (**1**) in acetic acid affords pentane-2-one (**2**) as the major product. The reaction of 1-methylcyclobutanol with $Mn(OAc)_3$—LiCl gives 5-chloropentane-2-one (**4**).

Key words: 1-methylcyclobutanol, manganese(III) acetate, electrochemical oxidation; pentane-2-one, 5-chloropentane-2-one; β-cleavage.

The oxidative ring opening of tertiary cyclic alcohols with salts and complexes of multivalent metals proceeds *via* the formation of cycloalkoxyl radicals, which isomerize to oxoalkyl radicals. These radicals transform into the final products by three pathways, thus participating in the oxidation reactions, recombination and the hydrogen transfer.

In the series of homologs differing in the ring size, 1-methylcyclobutanol (**1**) is of the highest reactivity in the oxidation processes with Ce^{IV} and Pb^{IV} compounds. Cerium(IV) sulfate oxidizes compound **1** in pentane-2-one (**2**),[1] and cerium(IV) ammonium sulfate gives a mixture of pent-4-en-2-one and decane-2,9-dione (**3**).[2] The $Mn(OAc)_3$—LiCl,[3] $Pb(OAc)_4$—LiCl,[3] and $Ca(OCl)_2$—$FeSO_4$ [4] systems selectively oxidize alcohol **1** to 5-chloropentane-2-one (**4**).

The peculiarity of 1-methylcyclobutanol with respect to oxidizers is its ability to be oxidized with $Mn(OAc)_3$, the latter does not react under similar conditions with cycloalkanols containing more than four C atoms in the cycle.[3]

A solution of $Mn(OAc)_3$ in AcOH oxidizes compound **1** affording ketones **2** and **3**. The reaction of alcohol **1** with the $Mn(OAc)_3$—LiCl system gives only chloroketone **4**. In these reactions, $Mn(OAc)_3$ was used in stoichiometric amounts.[3]

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