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Article

Synthesis of the ω-Brominated α-Trifluoroacetylcycloalkanones and their Isoxazole Derivatives

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Este trabalho mostra as reações entre 2-trifluoracetil-1-metoxi-1-cicloalquenos (**1a**-**1e**) ou 2-trifluoracetilcicloalcanonas e bromo molecular, para produção de ω-bromo-2-trifluoracetilcicloalcanonas (**3a**-**3e**, **4a**). Ficou demonstrado que o grupo 2-trifluoracetil determina o sítio de bromação no C-*omega*, carbono vizinho à carbonila endocíclica. Os produtos 2-trifluoracetilcicloalcanonas e ω-bromo-α-trifluoracetilcicloalcanonas foram ciclocondensados com cloridrato de hidroxilamina, formando os respectivos 5-trifluormetil-5-hidroxido-3,4-polimetileno-4,5-diidroisoxazóis (**5c**-**5e** e **6c**-**6e**).

The reactions of a serie of the 2-trifluoroacetyl-1-methoxy-1-cycloalkenes (**1a**-**1e**) and 2-trifluoroacetylcycloalkanones (**2a**-**2e**) with molecular bromine to obtain ω-bromo-α-trifluoroacetylcycloalkanones (**3a**-**3e, 4a**) is reported. Was determined that 2-trifluoroacetyl group have established the C-*omega* as reactive site. The 2-trifluoroacetylcycloalkanones and ω-bromo-α-trifluoroacetylcycloalkanones were reacted with hydroxylamine hydrochloride leading to respective 5-trifluoromethyl-5-hydroxy-4,5-dihydro-3,4-polimethyleneisoxazole derivatives (**5c**-**5e** and **6c**-**6e**).

Keywords: ω-bromo-α-trifluoroacetylcycloalkanones, 2-trifluoroacetylcycloalkanones, bromination reactions, cyclocondensation, isoxazoles

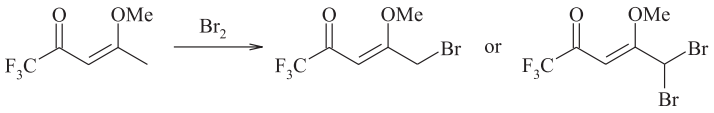
Introduction

The perfluorinated 1,3-dicarbonyl compounds, over the years, have been of constant interest to inorganic, organic, and physical chemistry.[1-6] The keto-enol and enol-enol tautomerism has been extensively studied in the perfluoroalkyl substituted 1,3-dicarbonyl compounds.[7,8] Thus 2-perfluoroacylcycloalkanones are important molecules, which offer a variety of pathways in inorganic and organic synthesis, as all the perfluoroalkyl substituted 1,3-dicarbonyl compounds these are versatiles building blocks for regiospecific heterocyclic synthesis and have high affinity for diverse metallic cations in coordination chemistry.[9-15]

The most employed method to obtain 2-perfluoroacylcycloalkanones is using alkaline acylation of enolates with perfluoroalkanoates.[1,3] As a part of our research program, we have developed general acetal acylation method for synthesis of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones and demonstrated their hydrolysis to trihalomethyl-β-diketones, the procedure signify an acid acylation method.

Moreover, we have determined that the 1,1,1-trihalo-4-alkoxy-3-penten-2-ones were regiospecifically brominated on allylic position. From 1,1,1-trihalo-4-methoxy-3-penten-2-ones were obtained 5-bromo-1,1,1-trihalo-4-methoxy-3-penten-2-ones and 5,5-dibromo-1,1,1-trihalo-4-methoxy-3-penten-2-ones demonstrating that precursors are push-pull systems highly delocalized with nucleophilic C-5 as shown on Scheme 1.[16]

The present work aimed at (*i*) the investigation of the chemical behavior of a set of differing ring size 2-trifluoroacetyl-1-methoxy-1-cycloalkenes and 2-trifluoroacetylcycloalkanones in the reaction with molecular



Scheme 1. C-5 bromination of 1,1,1-trifluoro-4-methoxy-3-penten-2-one.

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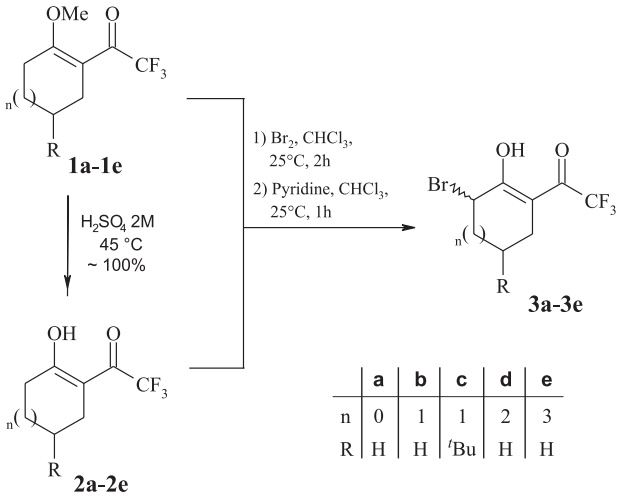
bromine, and (*ii*) the study of the cyclocondensation reactions of the brominated 2-trifluoroacetylcycloalkanones and 2-trifluoroacetylcycloalkanones with hydroxylamine hydrochloride for synthesis of the respective isoxazole derivatives. Hence, we report the synthetic approach for a series of novel w-bromo-2-trifluoroacetylcycloalkanones (**3a**-**3e**) and for the 5,5-dibromo-2-trifluoroacetylcyclopentanone (**4a**).

Results and Discussion

The 2-trifluoroacetyl-1-methoxy-1-cycloalkenes **1a**-**1e** were synthesized from the acylation reaction of cycloalkanones dimethoxyacetals compounds with trifluoroacetic anhydride in pyridine and chloroform as solvent. To obtain the 2-trifluoroacetylcycloalkanones after the acylation time was added a 2 mol L^{-1} sulfuric acid solution for 2-trifluoroacetyl-1-methoxy-1-cycloalkenes. The diketones **2a**-**2c** were obtained in good yields 90-95 % as pure slighting red liquids according to ^{1}H, ^{19}F and GC-MS data (Scheme 2). We are able to isolate the 1-methoxy-2-trifluoroacetyl-cycloalkenes washing the chloroform solution during work up only with water. However, for cyclohexanone and cycloheptanone derivatives were obtained mixtures with 1-methoxy-2-trifluoroacetylcycloalkenes and 2-trifluoroacetyl-cycloalkanones. It is worth it emphasized this method has demonstrated to be an efficient alternative to classical Claisen method for obtain of the trifluoroacetylketones and trichloroacetylketones in acid medium.[15]

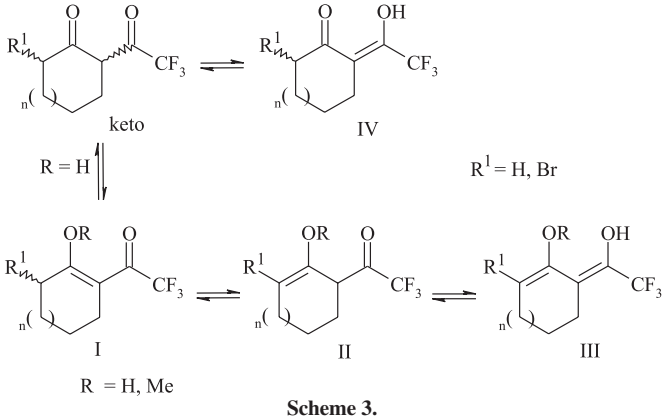
The bromination reactions were carried out in $CHCl_3$ at room temperature with an equimolar amount of the bromine and substrates **1a**-**1e** or **2a**-**2e**. The monobromination was instantaneous without acid catalyzes, as soon as the bromine was dropwise added the red coloration was lost and the HBr released. The $CHCl_3$ solution was stirred for 30 minutes and was dropwise added a solution of pyridine in $CHCl_3$. The ω-brominated-α-trifluoroacetylcycloalkanones were regio-



	a	b	c	d	e
n	0	1	1	2	3
R	H	H	^{t}Bu	H	H

Scheme 2.

selectively obtained as red oils in good yields (Scheme 2, Table 1). We probably do have not detected the bromo-2-trifluoroacetyl-1-methoxy-1-cycloalkene derivatives after bromination process because the strong hydrolytic acid medium at work-up. The ^{1}H NMR data have demonstrated that the 6-bromo-2-trifluoroacetyl-cyclohexanone, 7-bromo-2-trifluoroacetylcycloheptanone and 8-bromo-2-trifluoroacetylcyclooctanone are mixtures of the equilibrium tautomers (Table 1). The 2-trifluoroacetylcycloalkanones, 2,5-bis(trifluoroacetyl)cyclopentanone and 2,6-bis(trifluoroacetyl)cyclohexanone often exist in solutions as enol tautomers.[3,4] The doublet of doublets observed in ^{1}H NMR spectra of **3b**-**3e** at δ 4.00 – 5.50 range attributed to hydrogen at brominated *omega* carbon and the chemical shift for C2 at δ 104 -110 have suggested that predominant tautomers are monoenolic forms as I and IV as shown in Scheme 3. According the ^{1}H and ^{13}C NMR data the ω-bromo-α-trifluoroacetylcycloalkanones exist in chloroform as monoenolic (I and IV). However, the bromination results for **2a**-**2e** and dibromination for **3a** suggest that the mono-enolic form II or the bis-enolic form III (Scheme 3) are present and they are the reactive ones in bromine presence.



Scheme 3.

Table 1. Yields, MS and ^{1}H, ^{13}C and ^{19}F NMR data for ω-bromo-α-trifluoroacetylcycloalkanones **3a**-**3e** and 5,5-dibromo-2-trifluoroacetylcyclopentanone **4a**

Product	Yield (%)[a]	MS (%, *m/z*)[c]	^{1}H and ^{13}C NMR δ[d]	^{19}F NMR δ[e]
3a	87[90]	260 (6.5, M+ 2),258 (6.5, M^+), 189 (15.5, M^+- CF_3), 191 (15.0, M^++ 2 - CF_3), 179 (100, M^+-Br), 109 (72), 81 (38.5)	2.32 (m, 1H, H4), 2.47 (m, 1H, H4), 2.75 (m, 1H, H3), 2.88 (m, 1H, H3), 4.67 (dd, 1H, J_{HH} 7.0, 2.7 Hz, H5), 10.99 (OH); 195.5 (C1), 108.2 (C2), 23.6 (C3, $^4J_{CF}$ 2.0 Hz), 31.9 (C4), 47.6 (C5), 167.0 (COCF$_3$, $^2J_{CF}$ 37 Hz), 117.5 (CF$_3$, J_{CF} 280 Hz).	-75.10[f]
3b	90[95]	274 (17, M^+ + 2), 272 (14, M^+), 206 (100, M^+ + 2 - CF_3), 204 (98, M^+- CF_3), 195 (49, M^+ - Br), 124 (75), 95 (55)	1.77 – 2.72 (m, -(CH_2)-), 4.76 (t, 1H, *J* 3.5, H6), 5.39 (dd, 1H, J_{HH} 5.6, 10.7 Hz, H6), 5.45 (dd, 1H, *J* 6.0, 12.6, H6), 14.2 (OH), 14.6 (OH)	-75.80 -75.10
3b	45[b]	—	1.57 – 2.85 (m, -(CH_2)-), 4.35 (t, 1H, *J* 5.12, H6), 4.60 (dd, 1H, *J* 5.8, 12.5, H6), 4.91 (dd, 1H, *J* 4.92, 10.3, H6), 14.2 (OH), 14.97 (OH); 188.9 (C1), 104.3 (C2), 21.1 (C3, $^4J_{CF}$ 3.0 Hz), 20.3 (C4), 36.3 (C5), 50.5 (C6), 179.0 (COCF$_3$, $^2J_{CF}$ 35 Hz), 116.8 (CF$_3$, J_{CF} 285 Hz).	-76.50 -75.82 -81.50
3c	90[92]	330 (15, M^+ + 2), 328 (17, M^+), 261 (30, M^+ + 2 - CF_3), 259 (34, M^+- CF_3), 193 (53), 57 (100)	0.95 (s, 9H, ^{t}Bu), 1.78 – 1.95 (m, 2H), 2.32 (m, 2H), 2.70 (m, 2H), 4.85 (t, 1H, *J* 2.0), 14.07 (OH); 178.5 (C1), 104.0 (C2), 22.6 (C3, $^4J_{CF}$ 3.0 Hz), 31.6 (C4), 38.3 (C5), 45.6 (C6), 182.0 (COCF$_3$, $^2J_{CF}$ 36 Hz), 116.4 (CF$_3$, J_{CF} 286 Hz).	-73.90 -73.50
3d	78[85]	290 (10, M^+ + 2), 288 (15, M^+), 219 (85, M^+ + 2 - CF_3), 217 (100, M^+- CF_3), 137 (21), 109 (18), 81 (42)	1.20 – 2.85 (m, -(CH_2)-), 4.37 (dd, 1H, *J* 5.4, 10.0, H7), 4.54 (dd, 1H, *J* 4.5, 9.6, H7), 4.72 (dd, 1H, J_{HH} 4.5, 10.4 Hz, H7), 4.78 (dd, 1H, J_{HH} 3.95, 8.9 Hz, H7), 15.53 (OH), 15.89 (OH); 196.2 (C1), 110.7 (C2), 23.1 ($^4J_{CF}$ 2.5 Hz, C3), 32.7 (C4), 25.8 (C5), 27.7 (C6), 53.7 (C7), 187.3 (COCF$_3$, $^2J_{CF}$ 36 Hz), 118.2 (CF$_3$, J_{CF} 280 Hz).	-74.12 -73.60
3e	80[80]	302 (<5, M^+ + 2), 300 (<5, M^+), 222 (26, M^+ + 2 - Br), 153 (100, 222 - CF_3), 124 (17), 97 (60), 69 (87)	1.25 – 2.89 (m, -(CH_2)-), 4.40 (dd, 1H, *J* 5.0, 9.7, H8), 4.67 (dd, 1H, J_{HH} 4.5, 8.8 Hz), 4.73 (dd, 1H, J_{HH} 4.9, 10.6 Hz), 15.42 (OH), 15.52 (OH); 197.2 (C1), 110.5 (C2), 24.8 (C3, $^4J_{CF}$ 2.5 Hz), 34.5 (C4), 25.2 (C5), 24.3 (C6), 35.1 (C7), 51.4 (C8), 182.5 (COCF$_3$, $^2J_{CF}$ 38 Hz), 115.4 (CF$_3$, J_{CF} 290 Hz).	-73.20 -71.85
4a	82[80]	338 (< 5, M^+), 340 (< 5, M^++ 2), 259 (98, M^+ + 2 - Br), 257 (100 M^+- Br), 190 (25, $C_7H_5BrO_2$ -CF_3), 188 (20), 81 (42)	2.77 (m, 2H, H4), 2.92 (m, 2H, H3), 11.45 (OH); 192.6 (C1), 104.3 (C2), 23.4 (C3, J_{CF} 2.2), 45.6 (C4), 58.0 (C5), 164.5 (COCF$_3$, J_{CF} 38.0), 117.7 (CF$_3$, J_{CF} 290).	-74.20[f]

[a] Yields from **1** of isolated after CC with hexane:$CHCl_3$ (4:1) as eluent. Represented in bracket, yields from **2** of isolated after CC with hexane:$CHCl_3$ (4:1) as eluent; [b] Yield from **1** after distillation, with intense HBr releasing; [c] Values represent M + 2 due to appearance of isotopic peak; [d] 10^{-2} mol L^{-1} $CDCl_3$ solutions with TMS internal standard. Predominant tautomer data; [e] 10^{-2} mol L^{-1} $CDCl_3$ solutions with external C_6H_5F at δ -113.1 from $CFCl_3$ δ = 0.0 ppm, reference 20; [f] Resolved as triplet, **3a** $^5J_{FH}$ = 2.4 Hz, **4a** $^5J_{FH}$ = 1.8 Hz.

The monobrominated 2-trifluoroacetylcycloalkanones were isolated by column chromatography using hexane: $CHCl_3$ (4:1) as eluent. Was unsuccessful the distilling purification of the 6-bromo-2-trifluoroacetylcyclo-hexanone, was released HBr with heating decreasing yield leading to resinous by-products. The 5-bromo-2-trifluoroacetyl-cyclopentanone was a simple tautomer in enol form characterized by a broad hydrogen signal at δ 11.0 in ^{1}H NMR spectrum. The ^{13}C NMR spectrum of the **3a** show only one set of signals, and have confirmed the enol form with C-2 at 108.2 ppm. A triplet with $^4J_{CF}$ 2.0 Hz in the high field rage of the spectrum attributed to C-3 suggest an exocyclic enol tautomer (form IV, Scheme 3) by analogy with literature data.[4] The compounds **1a** or **2a** reacting with two molar-equivalent of bromine have furnished only one product identified as 5,5-dibromo-2-trifluoroacetylcyclopentanone (**4a**). The ^{1}H NMR spectrum of **4a** showed a large signal at δ 10.8 ppm from

enol hydrogen, too. The ^{13}C NMR spectrum had showed only one set of signals with the C-2 at 104.3 ppm, confirming the enol attribution. Was observed the triplet with $^{3}J_{CF}$ 2.2 Hz at 23.4 ppm attributed to C-3 and suggesting the exocyclic enol as only measured tautomer. The C-5 chemical shift 58.0 ppm and ^{13}C NMR DEPT 135 experiment have confirmed the dibrominated product.

Comparing these results with that obtained from bromination reactions of the 2-acetylcyclopentanone and 2-acetylcyclohexanone or 2-ethylcarboxycyclopentanone and 2-ethylcarboxycyclohexanone was possible to display the differentiate behavior of the 2-trifluoroacetylcycloalkanones which do not support the C-2 bromination.[17] Then, favored reaction site was the C-*omega*, vicinal to the endocyclic carbonyl group. The 4,4,4-trifluoro-1-phenylbutan-1,3-dione react with N-bromosuccinimide furnishing the product from α-bromination 2-bromo-4,4,4-trifluoro-1-phenylbutan-1,3-dione. The *alfa* carbon is the only enolization site to react with electrophilic bromine.[18]

The cyclization reactions of the compounds **3a**-**3e** with hydroxylamine hydrochloride were carried out under similar conditions as that described in the literature and are presented in the experimental part.[9,16] The cyclocondensation reactions were performed with the tautomers mixture of the ω-bromo-α-trifluoroacetylcycloalkanones **3a**-**e**. The cyclocondensation reactions of **3a** and **3b** with hydroxylamine hydrochloride under HCl or pyridine catalyzes were unsuccessful leading to problematical tar material. Though, the hydroxylamine cyclocondensation reactions with substrates **3c**-**3e** have furnished only one isoxazole derivative as show in Scheme 5. The intermediate **3c** was a simple tautomer and have furnished the isoxazole derivative **6c** in good yield as only product. However, from complex mixture of **3d** and **3e** tautomers were obtained

Table 2. Yields, MS and ^{1}H, ^{13}C and ^{19}F NMR data for 5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazoles **5c**-**5e** and **6c**-**6e**

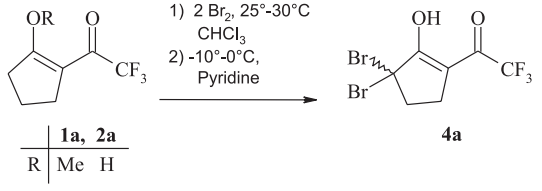
Product	Molecular Formula	Yield (%)[a]	MS (*m/z*, %)	^{1}H and ^{13}C NMR δ [b]	^{19}F NMR δ [c]
5c	$C_{12}H_{18}F_3NO_2$ 265.28	70	-	0.93 (s, 9H, ^{t}Bu), 1.41-2.45 (m, 7H, -CH_2-), 3.17 (dd, 1H, H4 ^{3}J 8.8, 2.5 Hz); 160.9 (C3), 53.0 (C4), 109.5 (C5, $^{2}J_{CF}$ 33 Hz), 122.5 (CF_3 J_{CF} 282 Hz), 46.1 (C7), 28.1, 26.2, 25.4 (-CH_2-), 26.1 (^{t}Bu), 30.3 (C(Me)$_3$).	-80.59
5d	$C_9H_{12}F_3NO_2$ 223.20	75	223 (11, M^+), 154 (18, M^+-CF_3), 136 (25), 108 (100), 69 (85), 55 (47)	1.50 -1.92 (m, 8H, -CH_2-), 2.58 (m, 1H, H10a), 2.65 (m, 1H, H10b), 3.48 (dd, 1H, H4, ^{3}J 9.7, 3.6 Hz); 164.6 (C3), 55.5 (C4), 102.7 (C5, $^{2}J_{CF}$ 32 Hz), 122.3 (CF_3 J_{CF} 282 Hz), 31.1 (C10), 28.4, 27.2, 25.9, 24.2 (-CH_2-).	-82.20
5e	$C_{10}H_{14}F_3NO_2$ 237.22	78	237 (31, M^+), 209 (20), 168 (24, M^+- CF_3), 151 (10), 122 (100), 69 (62), 55 (89)	1.35 -1.85 (m, 10H, -CH_2-), 2.20-2.55 (m, 2H, H10a, H10b), 3.38 (dd, 1H, H4, ^{3}J 8.2, 3.5 Hz); 162.8 (C3), 52.4 (C4), 103.3 (C5, $^{2}J_{CF}$ 32 Hz), 122.9 (CF_3 J_{CF} 284 Hz), 26.3 (C11), 25.3, 25.0, 24.9, 24.3, 22.4 (-CH_2-).	-82.00
6c	$C_{12}H_{17}BrF_3NO_2$ 344.17	57	-	1.10 (s, 9H, ^{t}Bu), 1.41-2.45 (m, 7H, -CH_2-), 3.67 (dd, 1H, H4 ^{3}J 7.8, 4.5); 162.5 (C3), 53.2 (C4), 106.7 (C5, $^{2}J_{CF}$ 34 Hz), 121.5 (CF_3 J_{CF} 282 Hz), 46.6 (C7), 29.5, 28.2, 24.8 (-CH_2-), 26.7 (^{t}Bu), 32.3 (C(Me)$_3$).	-81.40
6d	$C_9H_{11}BrF_3NO_2$ 302.09	63	302 (<5, M^++ 2), 300 (<5, M^+), 222 (45, M^+- CF_3), 204 (100), 107 (25), 69 (80), 55 (53)	1.81 -2.78 (m, 8H, -CH_2-), 3.85 (dd, 1H, H4, ^{3}J 7.6, 3.2), 5.26 (dd, 1H, ^{3}J 5.2, 3.0 Hz, H11); 163.0 (C3), 51.3 (C4), 104.0 (C5, $^{2}J_{CF}$ 33 Hz), 121.9 (CF_3 J_{CF} 284 Hz), 45.2 (C10), 36.7, 26.2, 25.9, 22.9 (-CH_2-).	-81.50
6e	$C_{10}H_{13}BrF_3NO_2$ 316.12	65	316 (<5, M^++ 2), 314 (<5, M^+), 236 (100, M^+- CF_3), 218 (80), 120 (20), 69 (30), 55 (32)	1.28 -2.52 (m, 10H, -CH_2-), 3.89 (dd, 1H, H4, ^{3}J 6.2, 2.5), 5.03 (dd, 1H, H11, ^{3}J 11.5, 5.9 Hz); 162.4 (C3), 48.9 (C4), 105.0 (C5, $^{2}J_{CF}$ 33 Hz), 121.9 (CF_3 J_{CF} 286 Hz), 44.3 (C11), 35.9, 27.9, 26.0, 25.2, 23.4 (-CH_2-).	-81.45

[a] Yields determinated by recristalization from hexane solutions. Satisfactory microanalyses obtained: C ± 0.20, H ± 0.19, N ± 0.10; [b] 10^{-2} mol L^{-1} $CDCl_3$ solutions with TMS internal standard; [c] 10^{-2} mol L^{-1} $CDCl_3$ solutions with external C_6H_5F at δ -113.1 from $CFCl_3$ δ = 0.0 ppm, reference 19.

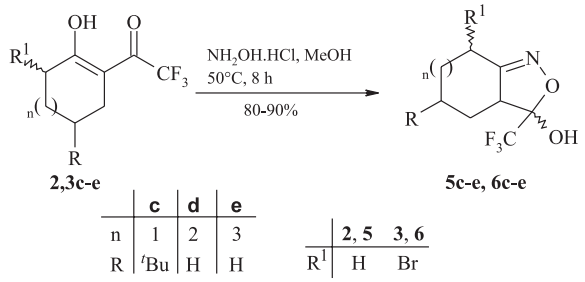
mixtures of respective isoxazole derivatives **6d** and **6e** with one highly predominant enantiomer pair (20:1) in yields 80-90 %. In the structurally fixed isoxazoles **6c**-**e** were generated chiral carbons, thus for compound **6c** are possible three enantiomers pairs and **6d**, **6e** can exist as four enantiomers. The mixtures obtained from **3d** and **3e** showed high diastereoisomeric excess demonstrating the stereoseletivity of cyclocondensation reactions, with data obtained was not possible the configuration attribution. From the reactions of 2-trifluoroacetylcycloalkanones **2c**-**2e** with hydroxylamine hydrochloride, isoxazoles **5c**-**5d** were isolated in good yields 85-90 %. These are novel isoxazoles obtained as racemic mixture which physical and spectroscopic data do not were published early (Table 2).[19]

The 2-trifluoroacetyl-1-methoxycycloalkenes (**1a**-**1e**) and 2-trifluoroacetylcycloalkanones (**2a**-**2e**) were regiospecificaly brominated at ω-carbon, that carbon alfa only to the ring carbonyl, suggesting that enolization direction as shown in Scheme 4. Moreover, that enolic forms II or/and III can be the reactive specie in bromine presence, reacting instantaneously at used conditions.

That hydroxylamine cyclocondensation using substrates **2c**-**2e** and **3c**-**3e** were regiospecific furnishing only the 5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole derivatives. Independent of ring size and *omega* substitution the 5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazoles **5a**-**5e** and **6c**-**6d** were formed exclusively as products of amino-group addition to the endocyclic carbonyl group followed by oxygen attack to trifluoroacetyl and stable hemi-acetal formation in cyclization.[9]



Scheme 4.



Scheme 5.

Experimental

General

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.32 MHz), in 0.01 mol L^{-1} in chloroform-d_1/TMS. The mass spectra were performed on a GC/MS spectrometric system (HP 6890 GC coupling to HP 5973 mass selective detector).

*Synthesis of 2-trifluoroacetyl-1-methoxycycloalkenes (**1a**-**1e**) and 2-trifluoroacetylcycloalkano-nes (**2a**-**2e**).*

The 2-trifluoroacetyl-1-methoxycycloalkenes and 2-trifluoroacetylcycloalkanones were synthesized according to the procedure reported in literature from 1,1-dimethoxy-cycloalkanes and trifluoroacetic anhydride and were purified by distillation. For complete spectroscopic characterization of 2-trifluoroacetylcycloalkanones see reference 4 and references cited therein. For **2c**: bp 76 - 78 ºC, 0.6 mmHg, ^{1}H NMR, δ 0.92 (s, 9H, *t*-butyl), 1.85 (m, 2H), 2.21 (m, 2H), 2.57 (m, 3H), 15.17 (s, OH); ^{13}C NMR $CDCl_3$, 188.6 (C1), 104.2 (C2), 22.4 (C3, $^{4}J_{CF}$ 2.9 Hz), 21.6 (C4), 43.5 (C5), 32.0 (C6), 179.2 (α-CO, $^{2}J_{CF}$ 34 Hz), 116.8 (CF_3, J_{CF} 285 Hz), 23.5 (CH_3, *t*-butyl), 33.3 (Cq, *t*-butyl); MS for $C_{12}H_{17}F_3O_2$ *m/z* (%) 250 [M^+] (40), 181 [M^+ - CF_3] (100), 153 [M^+ - $COCF_3$] (55).

General procedure for bromination reactions

A solution of bromine (22 mmol, 3.52 g) in 30 mL of anhydrous chloroform was dropwise added to stirred solution of substrates **1a**-**1e** or **2a**-**2e** (20 mmol) in 30 mL of anhydrous chloroform kept at room temperature. After the bromine solution addition (1-2 h) the mixture was stirred for 30 minutes. Then a solution of pyridine (22 mmol, 1.75 mL) in 10 mL of chloroform was added dropwise, and resultant solution was stirred for 30 minutes. The mixture was washed with water (three times 30 mL). The organic layer was dried with Na_2SO_4, the solvent was removed by rotatory evaporation and the products **3a**-**3e** were purified by CC using silica gel and hexane: chloroform (4:1) as eluent. The ω-bromo-2-trifluoro-acetylcycloalkanones were brown to red skin irritant and lachrymator oils, yields and spectroscopic data are shown in Table 1. The 5,5-dibromo-2-trifluorocetylcyclo-pentanone was obtained starting from 42 mmol of bromine and 20 mmol of 2-trifluoroacetylcyclopentanone using the procedure described.

Cyclocondensation of ω-bromo-2-trifluoroacetyl-cycloalkanones with hydroxylamine hydrochloride

Hydroxylamine hydrochloride (5.5 mmol) was added to a stirred solution of ω-bromo-2-trifluoroacetyl-cycloalkanones (**3c**-**3d**) in 10 mL of methanol at room temperature. The stirred mixture was heated at 50 ºC for 8 h. The methanol was removed by rotatory evaporation and the solid residue was dissolved in chloroform (30 mL) and washed with water (three times 20 mL). The organic layer was dried with Na_2SO_4, chloroform was evaporated and the solid products **6c**-**6e** were recrystalized from hexane solution. The previously unreported isoxazoles **5c**-**e** were synthesized from 2-trifluoroacetyl-1-methoxy-1-cycloalkenes **1c**-**1e** using the method described above.

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