Haloacetylated Enol Ethers: 3 [3]. Synthesis of 3,3a,4,5,6,7-Hexahydro-3-halomethyl[2,1]benzoisoxazoles

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The investigation of the halomethyl group effect on the regiochemistry of the reaction of 2-acetylcyclohexanones **1a-d** and β-methoxyvinyl trifluoro methyl ketone derivative **2a** with hydroxylamine to afford 3,3a,4,5,6,7-hexahydro-3-halomethyl-3-hydroxy[2,1]benzoisoxazoles **3a-c**, and the respective dehydrated compounds **4a-c**, is reported. Compounds **1a-c**, **2a** proved to be versatile building blocks for the regiospecific synthesis of isoxazole derivatives having a 3-halomethyl substituent, in good yields.

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In previous work, we described a general procedure to synthesize β-haloacetylated enol ethers, with functionalized acyl groups of the type CX_3CO [1], CHX_2CO [2]. These compounds are of general interest as precursor for a variety of substituted five- and six-membered heterocyclic compounds, *e.g.* isoxazoles [1], dihydroisoxazoles [1], pyrazoles [3] and pyrimidinones [4].

The synthesis of isoxazoles is relatively well explored using the so-called [3+2] atom fragments, where β-diketones or derivatives thereof are used as 3-atom building blocks, and hydroxylamine is the 2-atom fragment. However, the main limitation in these cyclocondensation reactions is the non selective regiochemistry of the products obtained [5,6]. For example, the reaction of 2-acylcyclohexanones with hydroxylamine yields a mixture of 4,5,6,7-tetrahydro[1,2]- and 4,5,6,7-tetrahydro[2,1]-benzoisoxazole isomers [6]. On the other hand, we have reported that β-alkoxyvinyl trihalomethyl ketones react with hydroxylamine to give regiospecifically 5-halomethyl-4,5-dihydroisoxazoles [1].

The aim of this work is the investigation of the halomethyl group effect on the regiochemistry of the reactions of 2-acetylcyclohexanones **1a-d** or β-methoxyvinyl trifluoromethyl ketone derivative **2a** with hydroxylamine hydrochloride (Scheme). A systematic study using precursors with different substituents was carried out to examine the scope of these cyclocondensation reactions.

The 2-acetylcyclohexanones **1a-d** and β-methoxyvinyl trifluoromethyl ketone derivative **2a** were synthesized from the reaction of enol ethers (or acetals) or enamine with the corresponding haloacetyl chloride or anhydride [2].

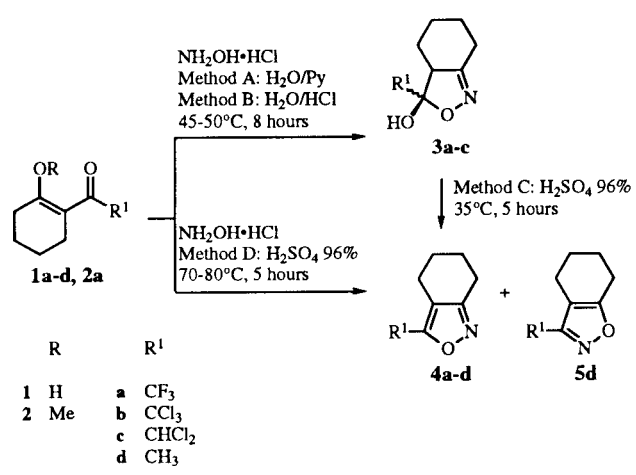
The cyclization of **1a-c, 2a** with hydroxylamine hydrochloride was carried out in pyridine (Method A) or HCl (Method B) in the molar relation of 1:1.1:1, respectively. The mixture was stirred for 8 hours at 45-50° to afford 3,3a,4,5,6,7-hexahydro-3-halomethyl-3-hydroxy-[2,1]benzoisoxazoles **3a-c**, in good yields (see Table 1). The cyclization of **1d** with hydroxylamine hydrochloride was carried out in the same conditions to afford a 1:1 mixture of 3,3a,4,5,6,7-hexahydro-3-methyl-[2,1]-benzoisoxazoles **4d** and -[1,2]benzoisoxazole **5d**.

Although it is known that the variation of the *p*H influences the equilibrium among the free hydroxylamine with their protonated and deprotonated forms [7], leading, in this way, to a control upon which nucleophilic center, O or N, would be the most reactive. Our studies showed that there is a little influence of the *p*H on the regiochemistry of these cyclocondensations, because the reaction carried out in the presence of pyridine, where must exist a large concentration of the free hydroxylamine [7], as well as in acidic media, where must exist a large concentration of hydroxylamonium cation led, regiospecifically, to the 3,3a,4,5,6,7-hexahydro-3-halomethyl-3-hydroxy[2,1]-benzoisoxazoles **3a-c**.

The regiochemistry observed on the reaction of the β-diketone substract **1a-c**, which can be in equilibrium with two enolic forms, suggests a large difference of reactivity of these enolic forms due to electronic effects of the halogenated group.

Considering that the rate determining step of the reaction is the Michael type conjugated addition, the nucle-

Scheme



ophilic nitrogen of hydroxylamine attacks exclusively the β-carbon forming an enaminone or oxime intermediate [7,8]. The regiochemistry of the products shows that the enolic form, similar of the compound **2a**, is the most reactive in the tested conditions.

Table 1

Yields of Compounds **3, 4a-d, 5d** Prepared

Product	Method [a]	Product	Yield [b]
1a	A	**3a**	63
	B		80
1b	A	**3b**	60
	B		82
1c	A	**3c**	76
	B		51
1d	A	**4,5d**	63
	B		50
2a	A	**3a**	63
	B		80
3a	C	**4a**	90
3b	C	**4b**	82
3c	C	**4c**	78
1a	D	**4a**	89
1b	D	**4b**	82
1c	D	**4c**	80
2a	D	**4a**	90

[a] See Experimental. [b] Yields of isolated compounds.

that determines the large stability of the 2-isoxazolin-5-ol type intermediate [9,10], on the case of 3,3a,4,5,6,7-hexahydro-3-halomethyl-3-hydroxy[2,1]benzoisoxazoles. A clear evidence of these facts is given by the reaction of 2-acetylcyclohexanone (**1d**) with hydroxylamine, in identical reaction conditions of those used for the halogenated substracts, where the absence of the halogenated group causes the lack of the reaction selectivity, leading to a mixture (1:1) of two isomers of isoxazole, the 4,5,6,7-tetrahydro-3-methyl[2,1]benzoisoxazole (**4d**) and the 4,5,6,7-tetrahydro-3-methyl[1,2]benzoisoxazole (**5d**), without the possibility of isolating the intermediate compounds, 3,3a,4,5,6,7-hexahydro-3-methyl-3-hydroxy[2,1]benzoisoxazole (**3d**) or -[1,2]benzoisoxazole.

As formerly reported [1], the isolated intermediate compounds **3a-c**, can be converted on the respective isoxazoles **4a-c** by dehydration with sulfuric acid 96% (Scheme). The most efficient condition for the dehydration employs an excess of the acid (10:1) relative to the substrates **3a-c**, at 35° (Method C).

As we have shown, the regiochemistry of the cyclization reaction has not been changed with the use of an acidic media (HCl) stead of pyridine. However, the use of an excess of sulfuric acid (5:1) and, mainly, by increasing

Table 2

Selected Physical and Spectral [a] Data of **3,4a-d**

	Mp [Bp] [b] (°C)	Molecular Formula	Analysis (%) [c] Calcd./Found C	H	N	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J_{C-F} (Hz)
3a	104-106	$C_8H_{10}F_3NO_2$	45.94	4.82	6.70	1.32-2.87 (m, 8H, H4, H5, H6, H7),	102.0 (C3, J = 33.2), 51.4 (C3a),
		209.17	45.84	4.76	6.53	3.15 (dd, 1H, J = 5.7, J = 6.7, H3a)	160.9 (C7a), 122.4 (C8, J = 285)
3b	148-151	$C_8H_{10}Cl_3NO_2$	37.17	3.90	5.42	1.24-2.85 (m, 8H, H4, H5, H6, H7),	109.5 (C3), 52.1 (C3a), 160.9
		258.53	37.00	3.87	5.20	3.41 (dd, 1H, J = 5.7, J = 6.7, H3a)	(C7a), 102.9 (C8)
3c	oil	$C_8H_{11}Cl_2NO_2$	42.88	4.95	6.25	1.25-2.85 (m, 8H, H4, H5, H6, H7),	106.3 (C3), 51.9 (C3a),
		224.09	42.73	4.92	6.37	3.19 (dd, 1H, J = 5.7, J = 6.7, H3a)	161.4 (C7a), 74.2 (C8)
						5.87 (s, 1H, $CHCl_2$)	
4a	[126-128/20]	$C_8H_8F_3NO$	50.27	4.22	7.33	1.60-1.92 (m, 4H, H4, H7),	151.5 (C3, J = 41.5), 116.4 (C3a,
		191.15	50.32	4.40	7.50	2.55-2.85 (m, 4H, H5, H6)	J = 2.0), 161.3 (C7a), 118.8 (C8, J = 270)
4b	[174-177/20]	$C_8H_8Cl_3NO$	39.95	3.35	5.82	1.70-1.95 (m, 4H, H4, H7),	159.9 (C3), 112.8 (C3a), 161.8
		250.52	40.10	3.49	6.16	2.65-2.96 (m, 4H, H5, H6)	(C7a), 85.9 (C8)
4c	oil	$C_8H_9Cl_2NO$	46.63	4.40	6.80	1.65-1.90 (m, 4H, H4, H7),	158.9 (C3), 112.7 (C3a), 160.9
		206.07	46.52	4.35	6.76	2.64-2.96 (m, 4H, H5, H6)	(C7a), 59.6 (C8)
4d	[87-89/20]	$C_8H_{11}NO$	70.04	8.08	10.21	1.65-1.82 (m, 4H, H4, H7),	159.7 (C3), 109.8 (C3a), 162.4
	[d]	137.18	69.80	8.14	9.94	2.45-2.75 (m, 4H, H5, H6)	(C7a), 10.1 (C8)
5d						1.65-1.82 (m, 4H, H4, H7),	157.3 (C3), 111.6 (C3a), 166.7
						2.45-1.82 (m, 4H, H5, H6)	(C7a), 9.1 (C8)

[a] The nmr-spectra were recorded on a Bruker AC 80 (^{1}H at 80 MHz and ^{13}C at 20 MHz) in $CDCl_3$/TMS. [b] Melting points determined with a Reichert Thermovar apparatus, and are uncorrected. [c] Elemental analysis performed on a Vario EL Foss Heraeus apparatus. [d] Data refers of the 1:1 mixture of **4d** and **5d** isomers.

Remembering that the reaction conditions for the closure of a 5-membered ring are of equilibrium, the formation of a semi-ketalic portion is also another extremely important step, because it is the presence of the halogenated group

the reaction temperature (70-80°) was possible to isolate, in one-pot procedure (Method D), the 3,3a,4,5,6,7-hexahydro-3-halomethyl[2,1]benzoisoxazoles **4a-c** in good yields (Scheme, Table 1).

The isolated compounds were identified by ^1H- and ^{13}C-nmr and confirmed by elemental analysis (Scheme, yields and physical constants are reported in Tables 1 and 2).

Thus, we have demonstrated that the presence of halogenated groups (-CF_3, -CCl_3, $CHCl_2$) is a determining factor on the regiochemistry of the reaction, providing a large difference of reactivity of the enolic forms of the substrate and a large thermodynamics stability to the 2-isoxazolin-5-ols **3a-c**. In the studied cases, the effect of R^1 overcomes the effect of changing the *p*H and, even that the enolic form, which gives raise the isolated products, is in lower concentration, its interaction with the hydroxylamine is more suitable in the used media, giving rise only the isolated products.

EXPERIMENTAL

Synthesis of 3,3a,4,5,6,7-Hexahydro-3-halomethyl-3-hydroxy-[2,1]benzoisoxazoles **3a-c**. General Procedure.

Method A.

A solution of β-methoxyvinyl trifluoromethyl ketone (**2a**) or 2-haloacetylcyclohexanone, **1a-d** (10 mmoles) in pyridine (0.6 ml, 10 mmoles) was prepared in a 50 ml flask. To this solution was added a saturated aqueous solution of hydroxylamine hydrochloride (0.75 g, 11 mmoles in 5 ml of deionized water). The mixture was stirred for 8 hours at 45-50°. The product was extracted with ethyl ether (100 ml) and the organic layer was washed with distilled water (3 x 50 ml), dried with anhydrous sodium sulfate, evaporated in rotavapor, and the residue was further dried under vacuum to give the 3,3a,4,5,6,7-hexahydro-3-halomethyl-3-hydroxy[2,1]benzoisoxazoles **3a-c**. Compounds **3a** and **3b** are crystalline, and were purified by recrystallization from hexane. The 3,3a,4,5,6,7-hexahydro-3-dichloromethyl-3-hydroxy[2,1]-benzoisoxazole **3c** was obtained as an oil, and it needed no further purification (Tables 1 and 2). The reaction of **1d** with hydroxylamine hydrochloride gave directly a 1:1 mixture of 4,5,6,7-tetrahydro-3-methyl[2,1]benzoisoxazole (**4d**) and the 4,5,6,7-tetrahydro-3-methyl[1,2]benzoisoxazole (**5d**). Compounds **4,5d** are liquids, and they were purified by distillation (Tables 1 and 2).

Method B.

The procedure of the addition of the reagents was the same as the reaction in pyridine media (Method A), however, instead of pyridine was added hydrochloric acid or sulfuric acid in the same proportion (10 mmoles). The reaction mixture was stirred for 8 hours at 45-50°. The compound was extracted with ethyl ether (3 x 50 ml) and the organic layer was washed (3 x 25 ml), dried with anhydrous sodium carbonate, the solvent evaporated in rotavapor, and the residue was further dried under vacuum to obtain the 3,3a,4,5,6,7-hexahydro-3-halomethyl-3-hydroxy[2,1]benzoisoxazoles **3a,b** that were isolated as solid crystals, and were purified by recrystallization in hexane. Compound **3c** remained as an oil, and it needed no further purification (Tables 1 and 2). The reaction of **1d** with hydroxylamine hydrochloride gave directly a 1:1 mixture of 4,5,6,7-tetrahydro-3-methyl[2,1]benzoisoxazole (**4d**) and the 4,5,6,7-tetrahydro-3-methyl[1,2]benzoisoxazole (**5d**). Compounds **4,5d** are liquids, and they were purified by distillation (Tables 1 and 2).

Synthesis of 4,5,6,7-Tetrahydro-3-halomethyl[2,1]benzoisoxazoles **4a-c**. General Procedure.

Method C.

In a 25 ml flask a mixture of 3,3a,4,5,6,7-hexahydro-3-halomethyl-3-hydroxy[2,1]benzoisoxazole **3a-c** (5 mmoles) and 5 ml of concentrated sulfuric acid was stirred at 30-35° for 5 hours. The mixture was poured slowly into 50 ml of ice water and the solution was extracted with chloroform (5 x 30 ml), the combined organic fractions were washed with deionized water, dried under anhydrous sodium carbonate, and the solvent removed with rotavapor. All 4,5,6,7-tetrahydro-3-halomethyl-[2,1]benzoisoxazoles **4a-c** are liquids, and they were purified by vacuum distillation (Tables 1 and 2).

Method D.

A solution of β-methoxyvinyl trifluoromethyl ketone (**2a**) or 2-acetylcyclohexanone **1a-c** (10 mmoles) and sulfuric acid 97% (50 mmoles) in 10 ml of water was prepared in a 50 ml flask. To this solution was added a saturated aqueous solution of hydroxylamine hydrochloride (0.75 g, 11 mmoles in 5 ml of deionized water) and the mixture was stirred for 8 hours at 70-80° and, then, poured into 50 ml of ice water. The solution was extracted with chloroform (5 x 30 ml), the chloroform fractions were combined, washed with deionized water, dried under anhydrous sodium carbonate, and the solvent removed by rotavapor, yielding directly the compounds **4a-c**, which were purified by vacuum distillation (Tables 1 and 2).

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