Haloacetylated Enol Ethers. 6 [5]. Synthesis of 4,5-Trimethylene-4,5-dihydroisoxazoles

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The investigation of the effect of the cyclopentane ring on the regiochemistry of the reactions of 2-acetylcyclopentanones **1a-d** and β-methoxyvinyl trifluoromethyl ketone derivative **2a** with hydroxylamine hydrochloride is reported. The reactions give regiospecifically the 4,5-trimethylene-4,5-dihydroisoxazoles **3a-d** in good yields.

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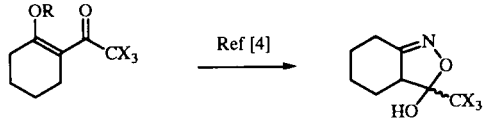
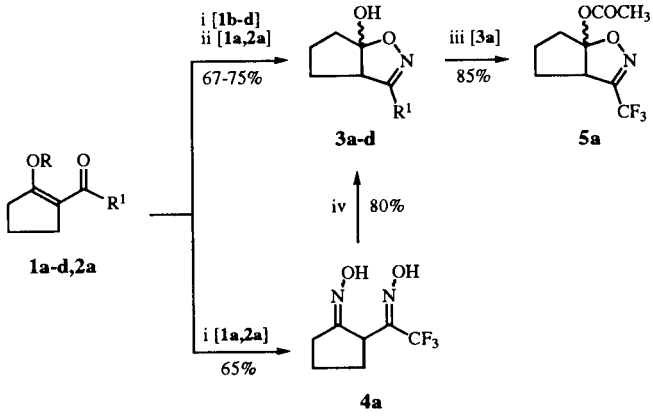
For a long time, fused isoxazole ring systems have been recognized as highly useful components in medicinal chemistry [1]. Among the available methods for the preparation of substituted isoxazoles, oximation of 1,3-dicarbonyl compounds (mainly β-keto aldehydes and β-diketones) and cyclocondensation of nitrile oxides to unsaturated compounds are by far the most widely utilized [2]. However, with non-symmetrical starting materials, neither of these methods is completely unequivocal with respect to control of site- and regioselectivities. On the other hand, we have reported a methodology which provides the regiospecific synthesis of halomethylisoxazoles in high yield when β-alkoxyvinyl halomethyl ketones, or β-diketone derivative, were employed as starting materials [3-5]. In those works we described a general procedure to synthesize β-haloacetylated enol ethers with functionalized acyl groups of the type CX_3CO [3], CHX_2CO [4,5]. These compounds have been employed as precursors for a variety of substituted five- and six-membered heterocyclic compounds, *e.g.*, isoxazoles and dihydroisoxazoles [3-5], pyrazoles [6,7], pyrimidinones and pyrimidines [8,9]. In a previous work [4] we also described the investigation of the effect of the halomethyl group on the regiochemistry of the reactions of 2-acetylcyclohexanones with hydroxylamine hydrochloride in pyridine or in hydrochloric acid which leads to cyclohexane fused isoxazole rings. It was possible to demonstrate that the presence of CX_3 group linked to the precursor was a determining factor on the regiochemistry of the reaction, to give 100% of 5-trihalomethyl- derivative (Scheme 1).

As a part of a series of cyclocondensation reactions with nitrogen dinucleophiles [3-7], the aim of this work is the investigation of the effect of the cyclopentane ring on the regiochemistry of the reactions of 2-acetylcyclopentanones **1a-d** and β-methoxyvinyl trifluoromethyl ketone derivative **2a** (R = Me, $R^1 = CF_3$) with hydroxylamine hydrochloride (Scheme 2). A systematic study using precursors with different substituents (R^1) was carried out to examine the scope of these cyclocondensation reactions.

Scheme 1



Scheme 2



R = H (1), Me (2) R1 = CF_3 (a), CH_2Cl (b), CH_3 (c), Ph (d)

i: $NH_2OH{\cdot}HCl/H_2O$, Py, *p*H = 5.5, 50°C, 12 hours
ii: $NH_2OH{\cdot}HCl/H_2O$, HCl 12*N*, *p*H <1.0, 50°C, 12 hours
iii: Ac_2O, CH_2Cl_2, 50°C, 6 hours
iv: HCl 0.1 *N*, 50°C, 8 hours

The 2-acetylcyclohexanones **1a-d** and β-methoxyvinyl trifluoromethyl ketone derivative **2a** were synthesized from the reaction of an acetal or an enamine with the corresponding haloacetyl chloride or anhydride [10].

The cyclization of **1a-d**, **2a** with hydroxylamine hydrochloride was carried out in pyridine (i) or hydrochloric acid (ii) in the molar relation of 1.0:1.1:1.0, respectively (Scheme 2). In the case of pyridine medium (i), the mixture was stirred for 12 hours at 50° to afford 4,5-trimethylene-5-hydroxy-4,5-dihydroisoxazoles **3b-d**, in good yields (see Table 1). The cyclization of **1a** or **2a** with hydroxylamine hydrochloride in pyridine (i) yields the double oxime **4a**. Compound **3a** was obtained when the cyclization of **1a** or **2a** was carried out in hydrochloric

Table 1

Selected Physical and Spectral Data of Compounds **3-5**

No.	Yield [a] (%)	Bp/mbar (°C)	Molecular Formula	Analysis (%) [b] Calcd./Found C	H	N	^{1}H-NMR [c] δ, (J, Hz)	^{13}C-NMR [c] δ, (J, Hz)
3a	71	82-84/20	$C_7H_8F_3NO_2$ 195.14	43.08 43.09	4.13 4.23	7.18 7.24	1.5-2.4 [m, 6H, $(CH_2)_3$] 3.46 [dd, 1H, H4, J_{HH} = 8.8, 2.5]	151.9 [C3, J_{CF} = 35.8], 53.6 [C4], 122.9 [C5], 119.6 [C6, J_{CF} = 270]
3b	75	oil [d]	$C_7H_{10}ClNO_2$ 175.61	47.88 [d]	5.74	7.97	1.4-2.4 [m, 6H, $(CH_2)_3$] 3.23 [dd, 1H, H4], 4.13 [2H, CH_2Cl]	158.0 [C3], 55.5 [C4], 120.2 [C5], 36.9 [C6]
3c	67	120-123/20	$C_7H_{11}NO_2$ 141.17	59.55 60.01	7.85 7.89	9.92 9.93	1.4-2.5 [m, 6H, $(CH_2)_3$] 3.16 [dd, 1H, H4, J_{HH} = 9.5], 1.96 [s, 3H, CH_3]	159 [C3], 59.11 [C4], 118.3 [C5], 12.3 [C6]
3d	53	oil [d]	$C_{12}H_{13}NO_2$ 203.24	70.92 [d]	6.45	6.89	1.8-3.1 [m, 6H, $(CH_2)_3$], 3.92 [dd, 1H, H4]	160 [C3], 52.5 [C4], 112.4 [C5] 125.0, 127.2, 127.9, 128.4 [Arom]
4a	65	145-147	$C_7H_9F_3N_2O_2$ 210.15	40.00 39.70	4.31 4.21	13.32 13.00	1.4-2.7 [m, 6H, $(CH_2)_3$] 3.63 [t, 1H, H2]	164.9 (163.7) [C1], 52.2 [C2] 148.7 (148.8) [C7, J_{CF} = 35] 121.7 (122.9) [C8, J_{CF} = 280]
5a	85	oil [e]	$C_9H_{10}F_3NO_3$ 237.18	45.58 45.90	4.25 4.23	5.91 5.94	1.2-2.8 [m, 6H, $(CH_2)_3$] 2.1 [s, 3H, CH_3], 3.85 [dd, 1H, H4]	152.1 [C3, J_{CF} = 36], 52.9 [C4], 121.4 [C5], 119.6 [C6, J_{CF} = 182], 168.4 [C=O], 20.8 [CH_3]

[a] Yield of isolated compound. [b] Elemental analysis were performed on a Vario EL Foss apparatus. [c] The nmr spectra were recorded on a Bruker AC 80 (^{1}H at 80 MHz and ^{13}C at 20 MHz) in deuteriochloroform/TMS. [d] The compound degrade during the purification procedure. [e] Purified by flash chromatography, see Experimental.

acid (ii, Scheme 2). The oxime **4a** was cyclized to compound **3a** by addition of 0.1 *N* hydrochloric acid and stirring for 8 hours at 50° (iv, Scheme 2). Confirmation of the chemical structure of compound **3a** was carried out by acetylation of the free 5-hydroxyl group with acetic anhydride in trichloromethane, yielding the acetate **5a** (iii, Scheme 2).

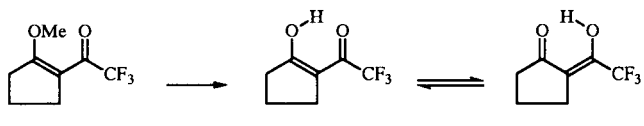
In comparison to the cyclohexanone derived dihydroisoxazoles (Scheme 1) [4] the cyclopentanone derived compounds **3a-d** show an inverted regiochemistry with oxygen directly attached to the carbocycle (Schemes 1 and 2). This suggests that in the case of the formation of two condensed five-membered ring under thermodynamic conditions formation of an sp^2-carbon at a ring junction seems to be unfavorable, *i.e.*, the thermodynamic product is one with the C=N double bond is not shared by the bridging carbons. This statement is enforced by the observation that the substrates **1a** and **2a** furnished similar results when reacted with hydroxylamine hydrochloride in water/pyridine solution (*p*H = 5.5), as well as in water/hydrochloric acid solution (*p*H< 1.0).

The β-diketone **1a**, when in acidic medium, has the possibility of equilibrium between the two tautomers **I** and **II** (Scheme 3). From the previous results [3-5] it is possible to affirm that the tautomer **I** is more reactive due to the electron withdrawing effect of the halomethyl group. However, this structure leads to the least stable heterocyclic ring as already mentioned above. Actually, in the case of the reaction of the compound **2a** (similar to **I**, Scheme 3), in water/pyridine solution, an oxime was the product obtained **4a**, resulting from the reaction of two hydroxylamine molecules, without ring closure. Finally, the isolation of the cyclic compound **3a** from the oxime **4a** proves the larger stability of the heterocycle formed.

The second factor is related to the reaction medium used. When pyridine is utilized in stoichiometric quantities the equilibrium between pyridine/hydroxylamine hydrochloride and pyridine hydrochloride/hydroxylamine should be shifted towards the formation of free hydroxylamine. This medium does not favor the hydrolysis of β-alkoxyvinyl halomethyl ketone **2a** which remains trapped (*cf.* structure **I**, Scheme 3).

The mechanism proposed for the formation of compound **3** involves conjugate addition of the nucleophilic nitrogen (Michael type) followed by 5-exo cyclic ring closure to form the dihydroisoxazole-derivatives. Considering the first step of this mechanism the obtained product of **2a** is to be expected, independent of the failure to close the heterocyclic ring in the next step.

Scheme 3



2a **I** **1a** **II**

However, in this less acidic medium, compound **1a** might be in any one of the tautomeric forms **I** or **II**. Although, previous results [4] had shown that tautomer **I** is more reactive, the product obtained shows that tautomer **II** is the one which reacted. Although, in acidic medium, a larger part of hydroxylamine is in the protoned form, this is the ideal media for the hydrolysis of the 1-methoxy-2-trifluoroacetyl-1-cyclopentene (**2a**) leading to the 2-trifluoroacetylcyclopentanone (**1a**). Thus, independent of the initial substrate, the isolation of the heterocycle can be explained by the equilibrium reaction condition used which lead to the thermodynamically more stable product. Accounting for the isomeric products makes reasonable to assign more thermodynamic stability to the isolated isoxazole.

The most relevant factor is related to the C=N double bond. In the isolated isoxazole **3a** it is not part of the cyclopentane moiety, compared to the other isomer where the double bond would be part of the junction of the two five-membered rings.

A study of the equilibrium between β-oxime ketones and 2-isoxazolin-5-ols, done by Escale *et. al.* [11], demonstrated that the presence of electron-withdrawing substituents at the 5-position of the ring strongly shift the equilibrium to the cyclic form. In case of the β-diketones **1b-d**, in water/pyridine 4,5-trimethylene-5-hydroxy-4,5-dihydroisoxazoles were obtained, **3b-d**. In these substrates the presence of the enolic forms **I** and **II** (*cf.* Scheme 3), the absence of the electronic effects of a trihalomethyl group and the large concentration of free hydroxylamine are sufficient for the thermodynamically favorable formation of compounds **3b-d**.

The isolated compounds were identified by $^{1}H/^{13}C$-nmr, gc-ms, and confirmed by elemental analysis (Yields and physical constants are reported in Table 1).

EXPERIMENTAL

Reaction of 2-Acetylcyclopentanones **1a-d** and **2a** with Hydroxylamine Hydrochloride in Pyridine. General Procedure.

To a solution of **1a-d,2a** (10 mmoles) in absolute pyridine (0.6 ml, 10 mmoles) was added a aqueous solution of hydroxylamine hydrochloride (0.75 g, 11 mmoles in 10 ml of deionized water). The mixture was stirred for 12 hours at 50°. The product was diluted in dichloromethane (100 ml) and washed with 0.1 *N* hydrochloric acid (3 x 30 ml) and with water (1 x 50 ml), dried with anhydrous sodium carbonate, evaporated in a rotavapor and the residue was dried under vacuum. Compound **4a** is crystalline and was purified by recrystallization from chloroform/hexane (3:2). Compound **3c** was obtained as an oil and was purified by distillation. Compound **3b** was obtained as an oil and needed no further purification. Compound **3d** was purified by flash chromatography in silica with chloroform/ethyl acetate (4:1), (Table 1).

Synthesis of 4,5-Trimethylene-3-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole (**3a**).

A mixture of 2-trifluoroacetylcyclopentanone (**1a**, 1.8 g, 10 mmoles) or 1-methoxy-2-trifluoroacetyl-1-cyclopentene (**2a**, 1.95 g, 10 mmoles) and hydroxylamine hydrochloride (0.7 g, 10 mmoles) in 5 ml of hydrochloric acid 20% was stirred for 12 hours. The mixture was poured into 50 ml of water and extracted with dichloromethane (3 x 50 ml). The organic layer was washed with 5% sodium hydrogencarbonate solution and dried with anhydrous sodium sulfate. The solvent was evaporated in a rotavapor and the residue was dried under vacuum. Compound **3a** is liquid and was purified by distillation (Table 1).

Synthesis of 4,5-Trimethylene-3-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole (**3a**) from the Oxime **4a**.

In a 50 ml flask oxime **4a** (5 mmoles) in 3 ml of 0.1 *N* hydrochloric acid was stirred for 8 hours at 50°. The aqueous solution was extracted with dichloromethane (3 x 50 ml), the organic layer was washed with 5% sodium hydrogencarbonate solution and dried with anhydrous sodium sulfate. The solvent was removed in a rotavapor. The residue was purified by distillation to yield compound **3a** (Table 1).

Synthesis of 4,5-Trimethylene-3-trifluoromethyl-5-acetoxy-4,5-dihydroisoxazole (**5a**).

To compound **3a** (5 mmoles, 0.95 g) in absolute pyridine (5 mmoles, 0.4 ml) acetic anhydride (5.1 mmoles, 0.55 ml) in dichloromethane (10 ml) was added. The mixture was stirred for 6 hours at room temperature (25°). The mixture then was washed with 5% sodium hydrogencarbonate solution (2 x 50 ml) and water (1 x 50 ml), dried with anhydrous sodium sulfate and the solvent was removed in a rotavapor. The residue, an oil, was purified by flash chromatography in silica with chloroform-petroleum ether (4:1), to yield compound **5a** (Table 1).

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