Haloacetylated Enol Ethers. 5 [5]. Heterocyclic Ring Closure Reactions of β-Alkoxyvinyl Dichloromethyl Ketones with Hydroxylamine

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The β-alkoxyvinyl dichloromethyl ketones **1a-d** are cyclocondensed with hydroxylamine hydrochloride in pyridine to afford the 5-hydroxy-5-dichloromethyl-4,5-dihydroisoxazoles **2a-d** in good yield. The cyclocondensation of compound **1c** gave, together with **2c**, 3-cyano-2-hydroxy-2-dichloromethyltetrahydrofuran **5c**. The dehydratation of compounds **2a,b**, derived from acyclic enol ethers, with concentrated sulfuric acid at 30°, led the corresponding 5-dichloromethylisoxazoles **3a,b**. The dehydratation of compounds **2c,d**, derived from cyclic enol ethers, with concentrated sulfuric acid at 30°, led the bicyclic 4,5-dihydroisoxazoles **4c,d**, and at 55°, a competitive rearrangement reaction gives the 3-cyano-2-hydroxy-2-dichloromethyl-2*H*-pyran **5d**.

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In previous work, we described a general procedure to synthesize β-haloacetylated enol ethers (or β-alkoxyvinyl halomethyl ketones), with functionalized acyl groups of the type CX_3CO [1]. These compounds are of general interest as precursor for a variety of substituted five- and six-membered heterocyclic compounds, *e.g.*, isoxazoles [1,2], dihydroisoxazoles [1,2], pyrazoles [3], pyrimidinones [4], and thiopyrimidines [5].

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 [6]. However, with non-symmetrical starting materials, neither of these methods is completely unequivocal with respect to control of site- and regioselectivities [7]. Only a few methods affording 3,5-disubstituted isoxazoles in a regioselective are known [8].

On the other hand, we have reported a methodology which provides the regiospecific synthesis of isoxazoles, in high yield, when β-alkoxyvinyl trihalomethyl ketones were employed as starting materials [1].

As a part of a series of cyclocondensation reactions with nitrogen nucleophiles [1-5], the aim of this work is the investigation of the effect of the dichloromethyl group on the regiochemistry of the reactions of β-alkoxyvinyl dichloromethyl ketones **1a-d** with hydroxylamine hydrochloride (Scheme). A systematic study using precursors derived from acyclic and cyclic enol ethers was carried out to examine the scope of these cyclocondensation reactions.

The β-alkoxyvinyl dichloromethyl ketones **1a-d** were synthesized from the reaction of enol ethers with dichlroacetyl chloride, under similar conditions developed in our laboratories for the acylation with trichloroacetyl chloride [1].

The β-alkoxyvinyl dichloromethyl ketones **1a-d** were reacted with a highly concentrated aqueous solution of hydroxylamine hydrochloride in pyridine, at 45-50°, to afford 5-hydroxy-5-dichloromethyl-4,5-dihydroisoxazoles **2a-d** in good yield (see Table). The crude products were purified by either recrystallization, column chromatography, or bulb-tube distillation. Compound **1c**, derived from dihydrofuran, provide a 9:1 mixture of 4,5-dihydroisoxazole **2c** and 3-cyano-2-dichloromethyl-2-hydroxytetrahydrofuran **5c**. This fact was reported in a previous publication [1], where it was observed that the product ratio was mainly governed by the reaction temperature. However, different from the previous paper [1], now we have not observed the formation of the cyano-compound **5d** obtained from the pyran derivative, and increasing the temperature (40-50°) led to an equilibrium mixture where the ratio of products **2c:5c** stands at 1:1.

The isolated intermediate compounds **2a,b**, were converted into the respective isoxazoles **3a,b** by dehydration with sulfuric acid 96% (Scheme). The most efficient conditions for the dehydration employs a 2:1 molar ratio of sulfuric acid and **2a,b**, at 35°, with stirring the mixture for 5-6 hours. The dehydratation of compounds **2c,d** yields the unexpected products: the bicyclic 4,5-dihydroisoxazoles **4c,d**. On the other hand, the dehydratation of compound **2d** at 55° led to the respective cyano-compound **5d** (Scheme).

Therefore, as mentioned above, 5-dichloromethylisoxazoles **3a,b** are obtained when we started from acyclic enol ethers derivatives, *i.e.*, compounds that after being cyclocondensed cannot form another hydroxyl group in the molecule. Therefore, the precursors **2c,d**, which contains a hydroxyalkyl group in position-4 of the ring, when in the presence of acidic media, have two possibilities: (ii) at 30°, yield bicyclic 4,5-dihydroisoxazoles **4c,d** or, (iii) at 55°, in the case of a pyran derivative, yields cyano-compound **5d** (Scheme). Case (ii), could be explained by the mechanism of dehydratation of two molecules of alco-

Table

Selected Physical and Spectral [a] Data of **2a-d**, **3a,b**, **4c,d**, **5c,d**

	Yield [%]	Mp [Bp] (°C) [b]	Molecular Formula	Analysis (%) Calcd./Found C	H	N	GC/MS m/z	^{1}H NMR δ, J (Hz)	^{13}C NMR δ
2a	67	82-85	$C_4H_5Cl_2NO_2$ 170.00	28.26 28.24	2.96 2.93	8.24 8.03	170 (MH^+), 152, 116, 86, 70 (100%)	7.3 (dd, 1H, J = 1.5/1.8, CH), 3.1 (dd, 1H, 18.7/1.8, CH_2), 3.4 (dd, 1H, J = 18.7/1.5, CH_2), 5.9 (s, 1H, $CHCl_2$), 4.6 (s, 1H, OH)	147.6 (C-3), 44.1 (C-4), 106.5 (C-5), 73.0 ($CHCl_2$)
2b	70	83-86	$C_5H_7Cl_2NO_2$ 184.02	32.63 32.70	3.83 3.90	7.91 7.63	184 (MH^+), 166, 100, 84, 56 (100%)	3.0 (dq, 1H, J = 18.5/0.9, CH_2), 3.4 (dq, 1H, J = 18.5/1.0, CH_2), 5.9 (s, 1H, $CHCl_2$), 2.0 (dd, 3H, J = 0.9/1.0, CH_2), 5.3 (s, 1H, OH)	157.3 (C-3), 46.1 (C-4), 107.6 (C-5), 72.9 ($CHCl_2$), 12.9 (CH_3)
2c	54	oil	$C_6H_9Cl_2NO_3$ 214.00	33.66 34.68	4.24 4.36	6.54 7.31	214 (MH^+), 196, 181, 62, 112, 84, 68 (100%)	7.4 (d, 1H, J = 1.5, CH), 3.7 (td, 1H, J = 1.5/6.4, CH), 6.0 (s, 1H, $CHCl_2$), 2.0 (m, 2H, CH_2), 3.8 (t, 2H, J = 5.5, CH_2), 5.1 (s, 1H, OH)	151.0 (C-3), 50.1 (C-4), 106.8 (C-5), 74.4 ($CHCl_2$), 28.3 (CH_2), 59.3 (CH_2-O)
2d	51	109-111	$C_7H_{11}Cl_2NO_3$ 228.00	36.86 36.98	4.86 4.83	6.14 6.14	228(MH^+), 210, 195, 174, 126, 55 (100%)	7.4 (d, 1H, J = 1.5, CH), 3.6 (m, 1H, CH), 6.1 (s, 1H, $CHCl_2$), 1.7 (m, 2H, CH_2), 1.7 (m, 2H, CH_2), 3.5 (m, 2H, CH_2)	151.8 (C-3), 53.2 (C-4), 107.1 (C-5), 75.5 ($CHCl_2$), 23.8 (CH_2), 31.7 (CH_2), 62.1 (CH_2-O)
3a	71	[90/5]	$C_4H_3Cl_2NO$ 152.00	3.61 -	1.98 -	9.22 -	151(M^+), 116 (100%), 83, 68	8.2 (d, 1H, J = 1.8, CH), 6.5 (dd, 1H, J = 1.8/0.6, CH), 6.8 (dd, 1H, J = 0.6/0.5, $CHCl_2$)	150.2 (C-3), 102.9 (C-4), 166.7 (C-5), 59.6 ($CHCl_2$)
3b	76	[67/6.5]	$C_5H_5Cl_2NO$ 166.00	36.18 36.29	3.04 2.94	8.44 8.25	166 (MH^+), 130 (100%), 84	6.4 (d, 1H, J = 0.7, CH), 6.7 (s, 1H, $CHCl_2$), 2.3 (d, 3H, J = 0.4, CH_3)	159.8 (C-3), 104.1 (C-4), 167.0 (C-5), 59.6 ($CHCl_2$), 11.0 (CH_3)
4c	63	oil	$C_6H_7Cl_2NO_2$ 196.00	36.76 -	3.55 -	7.15 -	196 (MH^+), 152, 130, 117, 84, 68, 41 (100%)	7.3 (d, 1H, J = 1.6, CH), 4.1 (dt, 1H, J = 1.6/6.7, CH), 6.3 (s, 1H, $CHCl_2$), 2.3 (m, 2H, CH_2), 3.7/4.2 (2 dt, 2H, J = 8.9/8.6, CH_2)	150.3 (C-3), 55.4 (C-4), 117.9 (C-5), 71.7 ($CHCl_2$), 30.4 (CH_2), 69.4 (CH_2-O)
4d	68	oil	$C_7H_9Cl_2NO_2$ 210.00	40.03 40.23	4.32 4.27	6.67 6.42	210 (MH^+, 100%), 196, 126, 84, 67	7.1 (d, 1H, J = 1.5, CH), 3.7 (m, 1H, CH), 6.1 (s, 1H, $CHCl_2$), 1.8 (m, 2H, CH_2), 1.8 (m, 2H, CH_2), 3.7 (m, 2H, CH_2)	151.0 (C-3), 45.8 (C-4), 107.9 (C-5), 18.5 (CH_2), 72.8 (CH_2), 18.9 (CH_2), 60.5 (CH_2-O)
5c [c] [d]	-	-	$C_6H_7Cl_2NO_2$ 196.00	36.76 -	3.60 -	7.15 -	196 (MH^+), 178, 162, 112, 69 (100%)	2.5 (m, 2H, CH_2), 3.7 (dd, 1H, J = 8.4/8.4, CH), 4.1 (m, 2H, CH_2-O) 5.8 (s, 1H, $CHCl_2$)	106.1/105.7 (C-2), 36.3/39.6 (C-3), 30.7/30.6 (C-4), 68.9/68.7 (C-5), 75.3/74.9 ($CHCl_2$), 118.2/118.6 (CN)
5d [d]	54	104-110	$C_7H_9Cl_2NO_2$ 210.10	40.03 40.16	4.32 4.36	6.67 6.64	210 (MH+), 192, 108, 80, 54 (100%)	3.0-3.4/1.9-2.3 (m, 1H, CH), 1.9-2.3/1.4-1.8 (m, 2H, CH_2), 1.9-2.3/1.4-1.8 (m, 2H, CH_2), 3.8-4.0 (m, 2H, CH_2-O), 5.8/6.0 (s, 1H, $CHCl_2$)	94.7/94.8 (C-2), 32.9/32.8 (C-3), 20.4/22.4 (C-4), 23.2/23.5 (C-5), 61.4/62.1 (C-6), 75.2/76.0 ($CHCl_2$), 117.6 (CN)

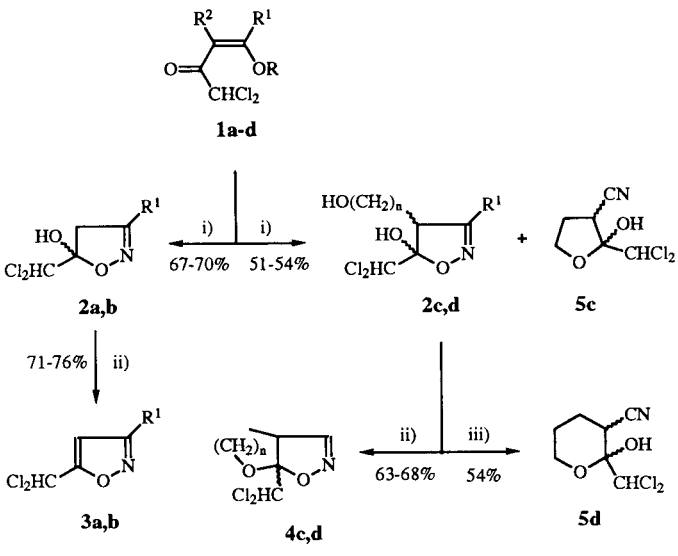
[a] NMR-Spectra were recorded on a Bruker AC 80 (^{1}H at 80 MHz and ^{13}C at 20 MHz) in deuteriochloroform/TMS. The mass spectra were recorded on a Varian 3400 GC equipped with a Finigan-Mat ITD 80A. Elemental analysis were performed on a Vario EL Foss-Heraeus apparatus. [b] Melting points determined with a Reichert Thermovar apparatus. [c] The nmr data refers to the non isolated product. [d] Data refers to the mixture of diastereoisomers.

hol to obtain an ether, with concentrated acid. Case (iii), could originate from the protonation of the oxygen atom of the isoxazole ring leading to the rupture of the C-O bond, to afford a β-dichloromethyl ketone oxime. The carbonyl group of this β-oxime can undergo an attack from the hydroxyl group of the hydroxyalkyl side chain, resulting in the closure of an ether ring (pyran ring), where the oxime group is easily dehydrated forming the cyano group, yielding **5d**.

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

Thus, we have demonstrated that the presence of dichloromethyl group ($CHCl_2$) is a determining factor in the regiochemistry of the reaction by providing a large thermodynamic stability to the 5-hydroxy-5-dichloromethyl-4,5-dihydroisoxazoles **2a-d**. In the case of dehydratation of compounds **2c,d**, the dichloromethyl group is fundamental to obtain the bicyclic 4,5-dihydroisoxazoles **4c,d**, because these compounds are not synthesized when trichloromethyl or trifluoromethyl groups are present at the same position on the molecule [1].

Scheme



i) $NH_2OH{\cdot}HCl/H_2O$, Py, 35-52°, 20-48 hours
ii) H_2SO_4 conc., 30°, 5-6 hours
iii) H_2SO_4 conc., 50°, 5-6 hours

1-4	R_1	R_2	R	n = 2,3
a	H	H	Et	
b	Me	H	Me	
c	H	$-(CH_2)_2-$		
d	H	$-(CH_2)_3-$		

EXPERIMENTAL

Synthesis of 5-Hydroxy-5-dichloro-4,5-dihydroisoxazoles **2a-d**.

General Procedure.

A mixture of **1a-d** (5.5 mmoles), absolute pyridine (5.7 mmoles), and a highly concentrated aqueous solution of hydroxylamine hydrochloride (5.7 mmoles/1.0 ml), are stirred at 35-40° for 20 hours (50°, 48 hours for **2d**). The oily reaction mixture is washed with a mixture of petroleum ether/ethyl acetate 1:2 and dried overnight with anhydrous sodium carbonate. The solvent is evaporated in rotavapor, and the residue is recrystallized from benzene (or a mixture 2:1 ethyl acetate:petroleum ether, **2d**) to give **2a-d** (Table). Compound **2c**, that gave *ca.* 10% of 3-cyano-2-dichloromethyl-2-hydroxytetrahydrofuran (**5c**), was isolated chromatographically (silica gel 60, 30 cm column, eluent 3:1 dichloromethane/ethyl acetate), and recrystallized from benzene. Compound **5c** was identified by gc/ms and nmr spectroscopy (Table) and it has not been isolated from the mixture.

Synthesis of 5-Dichloromethylisoxazoles **3a,b**.

General Procedure.

A mixture of the 5-hydroxy-5-dichloromethyl-4,5-dihydroisoxazoles **2a,b** (5.5 mmoles) and sulfuric acid 96% (11.0 mmoles) is stirred at 30° for 5-6 hours. To the mixture is added demineralized and cooled water. The product is extracted with dichloromethane and dried overnight with anhydrous magnesium sulfate. The solvent is evaporated in rotavapor, and the residue is purified by vacuum distillation to give the 5-hydroxy-5-dichloro-4,5-dihydroisoxazoles **2a,b** (Table).

Synthesis of Bicyclic 5-Dichloromethyl-4,5-dihydroisoxazoles **4c,d**.

General Procedure.

A mixture of the **2c,d** (1.0 mmole) and sulfuric acid 96% (2.0 mmoles) is stirred at 30° for 5-6 hours. The product is extracted with dichloromethane and dried overnight with anhydrous magnesium sulfate. The solvent is evaporated in rotavapor, and the residue is purified chromatographically (silica gel 60, 30 cm column, eluent 4:1 petroleum ether/ethyl acetate for **4c** or 4:1 hexane/chloroform for **4d** to give the bicyclic 5-dichloro-4,5-dihydroisoxazoles **4c,d** (Table).

Synthesis of 3-Cyano-2-dichloromethyl-2-hydroxytetrahydro-2*H*-pyran (**5d**).

The synthetic method and purification of compound **5d** were the same as that described above for the synthesis of compounds **4c,d**, however, instead of 30°, the reaction temperature was 55° (Table).

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