1,3-Dipolar Cycloaddition of 1,2-*O*-Isopropylidene-α-D-xylopentadialdo-1,4-furanosenitrile Oxide to some Alkenes

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The synthesis of five 3-(1,2-*O*-isopropylidene-α-D-xylofuranosyl)-5-substituted-2-isoxazolines obtained by 1,3-dipolar cycloaddition are described, as well as the intermediate products from the synthetic route. The physical and spectroscopic characterization of these compounds are reported.

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The 1,3-dipolar cycloaddition of nitrile oxides to alkenes provides a valuable tool for the synthesis of 2-isoxazolines possessing biological activity [1].

In literature there are some references in which the carbohydrate molecule is used as dipolarophile. De Amici *et al.* [2] performed a systematic study of the diasteromeric ratio of isoxazolines obtained when 1,2-*O*-isopropylidene-α-D-xylohex-5-enofuranose, with different protective group on C-3, reacted with mesitonitrile oxide, benzonitrile oxide or etoxicarboniformylnitrile oxide, while Al-Timari and Fisera [3] worked on the same dipolarophile without protection on the C-3 hydroxyl group. Paton *et al.* [4] applied 1,3-dipolar cycloaddition at carbohydrate dipolarophiles (D-ribo or D-xylo configuration) using benzonitrile oxide or etoxicarboniformylnitrile oxide as dipole and determined the absolute configuration by crystallographic data.

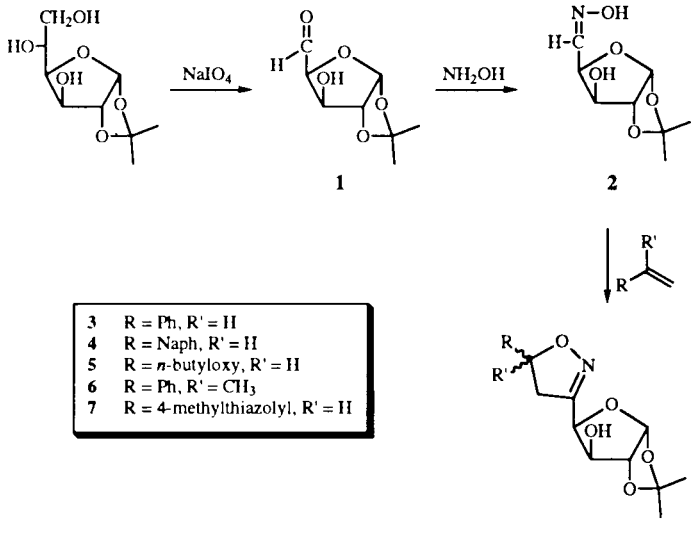
Tronchet *et al.* [5] reported the synthesis of 2-isoxazolines and 2-isoxazole from the carbohydrate molecule as dipole, where all the hydroxyl groups were protected. The author carried out the 1,3-dipolar cycloadddition from 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranosenitrile oxide with styrene and obtained a mixture of two epimeric isoxazolines. In a previous paper [6] we applied the 1,3-dipolar cycloaddition technique to 2-deoxy-sugar oximes (D-gluco and D-ribo configuration) without protection of the hydroxyl groups, with some dipolarophiles, to obtain the corresponding 2-isoxazolines as an epimeric mixture.

In this paper we report the synthesis of 3-(1,2-*O*-isopropylidene-α-D-xylofuranosyl)-5-substituted-2-isoxazolines from sugar oximes using Chloramine-T [7]. In Scheme 1, we show the synthetic route.

The 2-isoxazolines were obtained with moderate yields. The 3-(1,2-*O*-isopropylidene-α-D-xylofuranosyl)-5-substituted-2-isoxazolines synthesized are presented in Figure 1.

The 1,2-*O*-isopropylidene-α-D-xylopentadialdo-1,4-furanose (**1**) was first reported as a monomer [8]. However, Shaffer and Isbell [9] concluded that the molecule has a dimmer cyclic acetal-hemiacetal structure,

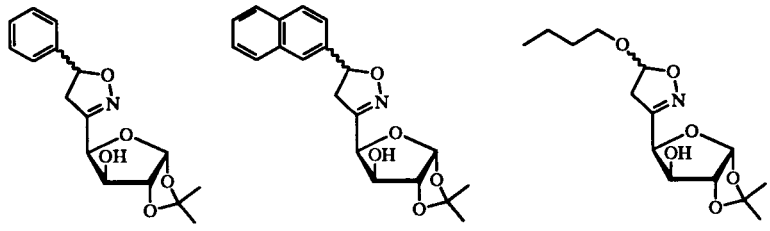
Scheme 1



formed by self aldol condensation of two monomers; each consists of a furanose ring in the D-xylo configuration, sharing C-1 and C-2 with a 1,2-dioxolane ring. The definitive proof of its structure was provided by Shalaby *et al.* [10] using X-ray crystallography. We observed in the ^{13}C nmr spectrum the signals which justified that structure in solution.

The oxime derivative of the 1,2-*O*-isopropylidene-α-D-xylopentadialdo-1,4-furanose (**2**) was synthesized from the aldehyde using hydroxylamine as described in literature [11]. We obtained a mixture of two isomers: *syn* and *anti*, as we observed in the nmr spectra. The ^1H nmr spectrum shows two signals for the hydrogen of the oxime group, as well as the duplication of the other signals of the carbohydrate protons. In the ^{13}C nmr spectrum, we observe similarly two signals for each carbon, except for C-2 (see Experimental). Our ^1H nmr assignation for *syn* and *anti* conformation are in accordance with *Tronchet et al.* [12], who worked with several sugar oximes and methyl oximes. They concluded that the difference between the chemical shifts of the H_{oxime} (*syn* and *anti*) in

Figure 1



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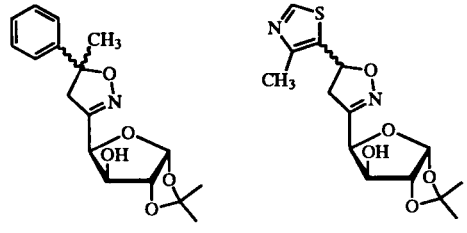

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dimethyl sulfoxide and deuteriochloroform are mostly due to the magnetic anisotropy effects, caused by associations between solvent and solute, than to change in the conformational equilibrium in the rest of the structure. This effect decreases through the distance where conformational effects are more important.

In the mass spectrum by electron impact, compound **2** shows the molecular ion with appreciable relative abundance (*m/z* 203, 12.7%) and characteristic fragments of the 1,2-*O*-isopropylidene-α-D-furanose sugar (see Experimental).

The treatment of **2** with Chloramine-T in presence of some dipolarophiles affords 2-isoxazolines derivatives **3-7**. As we expected the cycloaddition was regioselective but not stereoselective. In most of the cases, we obtained the diasteromeric pair in aproximately a 1:1 mixtures of epimers.

The ^{1}H nmr spectra of the compounds **3-7** were measured at 200 MHz. The analysis of the ^{1}H nmr data allowed us to observe the duplication of the signals near the new chiral center (C-5), due to the attack on both faces. Because of the coupling constants between furanose protons have similar values, we made a 2D-homonuclear spectrum for compound **3** to confirm the first order analysis. The chemical shifts and coupling constants are presented in Tables 1 and 2.

The analysis of the ^{13}C nmr spectra permitted the observation of the epimeric pair. Several signals appear duplicated (Table 3).

Table 1

^{1}H NMR Chemical Shifts (δ) of Compounds **3-7**

Compound	H - 5	H - 4a	H - 4b	H - 1'	H - 2'	H - 3'	H - 4'	H - Me
3 [a]	5.59	3.23	3.51	6.00	4.60	4.50	4.91	
		3.10	3.62	6.01			4.88	
4 [b]	5.76	3.23	3.58	5.99	4.52	4.25	4.94	1.44-1.28
	5.71	3.07	3.67	5.97		4.24		
5 [a]	5.53	2.96	3.23	6.01	4.59	4.47	4.93	1.50-1.33
	5.54			5.99				
6 [a]	-	3.29	-	5.99	4.60	4.47	4.78	1.48-1.32
7 [a]	5.83	3.22	3.58	6.01	4.60	4.49	4.97	1.51-1.33
		3.10	3.66		4.59		4.96	

[a] Recorded in deuteriochloroform. [b] Recorded in dimethyl-d_6 sulfoxide.

Table 2

Vicinal Proton-Proton Coupling Constants (Hz) of Compound **3-7**

Compound	$J_{5,4a}$	$J_{5,4b}$	$J_{4a,4b}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$
3 [a]	8.6	10.9	17.7	3.6	2.4	2.6
4 [a]	8.4	11.0	17.6	3.5		2.5
5 [a]	1.8	6.7	18.2	3.7	0	2.5
6 [a]	-	-	-	3.6	0	2.3
7 [a]	8.7	10.8	17.6	3.5	0	2.7

[a] Recorded in deuteriochloroform. [b] Recorded in dimethyl-d_6 sulfoxide.

Table 3

^{13}C NMR Chemical Shifts (δ) of Compound **3-7**

Compound	C - 3	C - 4	C - 5	C - 1'	C- 2'	C - 3'	C - 4'	$C(Me)_2$	Me
3 [a]	156.4	44.0	82.1	105.1	84.8	76.3	76.7	112.1	26.8-26.2
		44.3	81.9						
4 [b]	156.7	43.1	81.1	104.5	84.8	76.2	76.5	110.9	26.6-26.0
	156.5	43.2	80.9			76.0	76.4		
5 [a]	157.4	43.2	103.0	105.4	85.0	76.3	78.0	112.3	27.1-26.4
	157.7	42.8	103.1	105.5		76.8	77.0		
6 [a]	156.2	49.8	87.7	105.1	84.6	75.9	76.6	111.9	26.7-26.1
7 [a]	156.9	44.2	75.3	105.1	84.8	76.4	76.6	112.1	26.7-26.1

[a] Recorded in deuteriochloroform. [b] Recorded in dimethyl-d_6 sulfoxide.

The total and unequivocated assignment of the ^{13}C nmr spectra was performed by 2D-heteronuclear spectra (XHCORRDC) for compounds **3** and **7**. The other compounds were assigned using them as models.

The mass spectra of all the 3-(1,2-*O*-isopropylidene-α-D-xylofuranosyl)-5-substituted-2-isoxazolines were analyzed. The molecular ion peak was found with variable intensities, except for compound **5**. In Scheme 2 we show their principal routes of fragmentation which justified the 1,3-dipolar cycloaddition. The principal ions for compounds **3-7** are listed in Table 4.

We conclude therefore that, although the 1,3-dipolar cycloaddition of 1,2-*O*-isopropylidene-α-D-xylopentadialdo-1,4-furanosenitrile oxide to some alkenes is regioselective, the carbohydrate does not induce a preferential approach between the dipole and one of the faces of the dipolarophile, so that, the diastereomeric mixture is obtained. Therefore, the reaction is not stereoselective.

Scheme 2

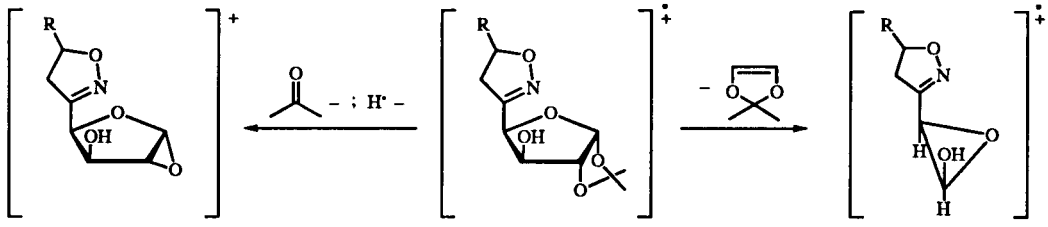

Table 4

Characteristic Fragments Resulting from Electron Impact Ionization of Compounds **3-7**

Assignment	m/z (AR%) **3**	m/z (AR%) **4**	m/z (AR%) **5**	m/z (AR%) **6**	m/z (AR%) **7**
R; R'	Ph, H	Naph, H	*n*-butyloxy, H	Ph, CH_3	4-methylthiazolyl, H
$M^{+\cdot}$	305 (10.3)	355 (38.7)	-	319 (21.3)	326 (6.7)
A	246 (26.5)	296 (6.8)	242 (1.9)	260 (37.2)	267 (8.8)
A - CO	218 (3.5)	268 (2.8)	-	232 (4.1)	239 (1.5)
A - CO - H_2O	200 (2.9)	250 (2.8)	-	214 (1.5)	221 (0.6)
A - CO_2	202 (7.2)	252 (2.8)	198 (2.3)	216 (6.9)	223 (2.3)
A - CO_2 - H_2O	184 (5.6)	234 (3.2)	-	198 (5.4)	205 (2.3)
B	205 (5.5)	255 (1.3)	201 (1.9)	219 (6.2)	226 (1.0)
B - CO	177 (74.6)	227 (44.3)	173 (39.5)	191 (100.0)	198 (53.5)
B - CO - H·	176 (72.3)	226 (12.4)	172 (18.9)	190 (78.8)	197 (20.0)
B - CO - H_2O	159 (5.4)	209 (3.7)	155 (89.1)	-	180 (1.1)
B - CO - OH·	160 (22.5)	210 (38.3)	156 (35.9)	174 (66.7)	181 (23.6)
B - CO - NO - OH·	130 (17.2)	180 (15.0)	126 (3.1)	144 (29.5)	151 (9.6)
RR'C=CH_2	104 (93.6)	154 (100.0)	100 (29.6)	118 (57.6)	125 (81.9)
R^+	77 (51.5)	127 (36.2)	73 (29.6)	77 (42.0)	98 (13.7)
$M^{+\cdot}$ - CH_3·	290 (15.3)	340 (11.6)	286 (12.0)	304 (49.0)	311 (9.8)
$M^{+\cdot}$ - CH_3· - CH_3CO_2H	230 (8.6)	280 (5.7)	226 (5.0)	244 (12.3)	251 (5.2)
base peak	59	154	59	191	43

EXPERIMENTAL

General Methods.

Melting points were measured on a Unimelt apparatus and are uncorrected. Optical rotations were determined at 20° with a Perkin-Elmer 141 Polarimeter. The ^1H nmr spectra were recorded with a Bruker AC 200 instrument at 200 or Bruker AM 500 at 500 MHz and the ^{13}C nmr spectra were recorded at 50 MHz for solutions in perdeuteriopyridine or dimethyl-d_6 sulfoxide with tetramethylsilane as the internal standard. Mass spectra were performed by electron impact ionization. Analysis (tlc) was performed on plates coated with silica gel G (Merck, Darmstadt) and reversed phase using appropriated eluents each time and warm sulfuric acid for detection.

1,2-*O*-Isopropylidene-α-D-xylopentadialdo-1,4-furanose (**1**).

1,2-*O*-Isopropylidene-α-D-xylofuranose [13] (2 g, 9.1 mmoles) was treated with the technique described in literature [14] and 1.5 g (8 mmoles) of 1,2-*O*-isopropylidene-α-D-xylopentadialdo-1,4-furanose (**1**) (88%) was obtained.

1,2-*O*-Isopropylidene-α-D-xylopentadialdo-1,4-furanose Oxime (**2**).

From 1,2-*O*-isopropylidene-α-D-xylopentadialdo-1,4-furanose (0.23 g, 1.22 mmoles) and using the procedure described in the literature [11], we obtained compound **2** (0.18 g, 0.9 mmoles, 74%), as an amorphous solid, mp 133-134°, $[\alpha]_D$ -83.93 (c1, chloroform); ^1H nmr (deuterium oxide): *Syn*, δ 6.03 (d, J = 3.5 Hz, 1H, C1-H), 4.70 (d, J = 3.5 Hz, 1H, C2-H), 4.57 (d, J = 2.9 Hz, 1H, C3-H), 4.75 (dd, J = 2.9, 6.0 Hz, 1H, C4-H), 7.49 (d, J = 6.0 Hz, 1H, C5-H), 1.48-1.32 (s, 3H, CH_3); *Anti*, δ 6.05 (d, J = 3.4 Hz, 1H, C1-H), 4.72 (d, J = 3.4 Hz, 1H, C2-H), 4.33 (d, J = 2.9 Hz, 1H, C3-H), 5.17 (dd, J = 2.9, 4.0 Hz, 1H, C4-H), 6.88 (d, J = 4.0 Hz, 1H, C5-H), 1.48-1.32 (s, 3H, CH_3); ^{13}C nmr (deuterium oxide): *Syn*, δ 105.5 (C-1), 85.4 (C-2), 76.1 (C-3), 79.1 (C-4), 148.4 (C-5), 113.8 ($C(Me)_2$), 26.5-26.0 (CH_3); *Anti*, δ 105.1 (C-1), 85.4 (C-2), 75.2 (C-3), 77.2 (C-4), 149.3 (C-5), 113.7 ($C(Me)_2$), 26.5-26.0 (CH_3); ms: m/z 203 (12.7, $M^{+\bullet}$), 188 (47.5, $M^{+\bullet}$ -$CH_3^\bullet$), 170 (5.2, $M^{+\bullet}$ -H_2O -$CH_3^\bullet$), 146 (15.6, $M^{+\bullet}$ -CH_2CO -$CH_3^\bullet$), 128 (26.0, $M^{+\bullet}$ -CH_3CO_2H -$CH_3^\bullet$), 102 (3.3, $M^{+\bullet}$ -$C_5H_8O_2$ -$H^\bullet$), 100 (22.2, $C_5H_8O_2^{+\bullet}$), 86 (25.5, $C_3H_4NO_2^+$), 70 (35.4, $C_2H_4NO^+$), 59 (base peak, $M^{+\bullet}$ -$C_5H_8O_2$ -CNOH -$H^\bullet$), 43 (83.5, $CNOH^{+\bullet}$).

Anal. Calcd. for $C_8H_{13}NO_5$: C, 47.29; H, 6.40. Found: C, 47.68; H, 6.37.

3-(1,2-*O*-Isopropylidene-α-D-xylofuranosyl)-5-phenyl-2-isoxazoline (**3**).

1,2-*O*-Isopropylidene-α-D-xylopentadialdo-1,4-furanose oxime (0.20 g, 0.98 mmoles) was dissolved in 5 ml of ethanol and put into an ice bath. Styrene (0.2 ml, 1.75 mmoles) was added in excess and when the solution was homogeneous, 0.4 g of chloramine-T was added slowly. After the mixture reached room temperature, it was heated at 60° during about 3 hours. The reaction was monitored by tlc [solvent:toluene:ethyl acetate (1:1)]. The product was purified by column chromatography, on silica gel G, using toluene and toluene-ethyl acetate. Compound **3** (0.17 g, 0.56 mmole, 57%) was obtained as a crystalline solid, which was recrystallyzed from ethanol-water, mp 131-133°, $[\alpha]_D$ -58.6 (c1, methanol); ^1H nmr: see Tables 1 and 2; ^{13}C nmr: see Table 3; ms: see Scheme 2 and Table 4.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.95; H, 6.23. Found: C, 62.72; H, 6.47.

Standard Procedures for the Preparation of the Other Isoxazolines.

A solution of sodium methoxide (2.6 mmoles in 8 ml of methanol) was mixed with hydroxylamine hydrochloride (3.1 mmoles) dissolved in a minimum volume of water. This mixture was passed through a filter into an Erlenmeyer flask containing a methanolic solution of compound **1** (1.13 mmoles in 2 ml). This reaction mixture was allowed to stand at room temperature with stirring until the disappearance of the starting material (controlled by tlc, solvent ethyl acetate) and then evaporated to dryness to provide compound **2** as a solid.

3-(1,2-*O*-Isopropylidene-α-D-xylofuranosyl)-5-naphthyl-2-isoxazoline (**4**).

Compound **2** (from 4.38 mmoles of compound **1**) in dioxane was placed in an ice bath with stirring. To this was added an excess of 2-vinylnaphthalene (1.34 g, 9.46 mmoles). More dioxane may have to be added in order that the dipolarophile remain in solution because it is very important that only one phase is formed.

The chloramine-T (1.34 g) was slowly added and the mixture was stirred until it came to room temperature while the reaction progress was followed by tlc [toluene:ethyl acetate (1:1)]. The product precipitated from the reaction medium. It was filtered and recrystallized with ethanol-water. Compound **4** (0.81 g, 2.3 mmoles, 53%) was obtained as a crystalline solid, mp 174-176°, $[\alpha]_D$ -52.9 (c1, methanol); ^1H nmr: see Tables 1 and 2; ^{13}C nmr: see Table 3; ms: see Scheme 2 and Table 4.

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.61; H, 5.92; N, 3.94. Found: C, 67.29; H, 6.26; N, 3.84.

3-(1,2-*O*-Isopropylidene-α-D-xylofuranosyl)-5-butyloxy-2-isoxazoline (**5**).

Compound **2** (from 2.56 mmoles of compound **1**) was dissolved in ethanol:water (10:3), and placed in an ice bath. An excess of *n*-butyl vinyl ether (1 ml, 7.7 mmoles) was added. When only one phase was formed, 1.30 g of chloramine-T was added slowly. The reaction mixture was allowed to reach room temperature and the course of the reaction was followed by tlc [toluene:ethyl acetate (1:1)]. The reaction mixture was evaporated and purified by column chromatography using toluene/toluene:ethyl acetate (9:1). The fractions with the product were rechromatographed *via* RP-18 column chromatography using methanol:water (1:1) as eluent. Compound **5** (0.40 g, 1.33 mmoles, 52%) was obtained as a syrup, $[\alpha]_D$ -20.3 (c1, methanol); ^1H nmr: see Tables 1 and 2; ^{13}C nmr: see Table 3; ms: see Scheme 2 and Table 4.

Anal. Calcd. for $C_{14}H_{23}NO_6$: C, 55.81; H, 7.64. Found: C, 56.17; H, 7.33.

3-(1,2-*O*-Isopropylidene-α-D-xylofuranosyl)-5-phenyl-5-methyl-2-isoxazoline (**6**).

Compound **2** (from 1.13 mmoles of compound **1**) was dissolved in dioxane:water (10:3), and placed in an ice bath, stirred and an excess of α-methylstyrene (1 ml, 7.7 mmoles) added. When the solution was homogeneous, 0.48 g of Chloramine-T was added slowly and allowed to reach room temperature [monitored by tlc, solvent:toluene:ethyl acetate (1:1)]. The product

was purified as above, but the eluents of the first column were toluene/toluene:ethyl acetate (95:5). Compound **6** (0.14 g, 0.44 mmoles, 39%) was obtained as a crystalline solid, which was recrystallized from ethanol:water (1:1), mp 165-167°, $[\alpha]_D$ -44.6 (c1, methanol); ^1H nmr: see Tables 1 and 2; ^{13}C nmr: see Table 3; ms: see Scheme 2 and Table 4; hrms: EI, Calcd. $C_{17}H_{21}NO_5$: 319.1420. Found: 319.1416.

3-(1,2-*O*-Isopropylidene-α-D-xylofuranosyl-5-(4-methylthiazolyl)-2-isoxazoline (**7**).

Compound **2** (from 4.38 mmoles of compound **1**) was dissolved in dioxane in an ice bath, stirred and an excess of 4-methyl-5-vinylthiazole (0.1 ml, 8.7 mmoles) added processing as for the compounds described above.

Chloramine-T (1.43 g) was added slowly and the mixture was stirred until it reached room temperature and then heated at 60° for about 6 hours, while the course of the reaction was followed by tlc [toluene:ethyl acetate (1:1)]. After evaporation to dryness, the residue was column chromatographed and the product isolated. Compound **7** (0.68 g, 2.1 mmoles, 48%) was obtained as a crystalline solid and recrystallized from 2-propanol:water, mp 177-178°, $[\alpha]_D$ -224.1 (c1, methanol); ^1H nmr: see Tables 1 and 2; ^{13}C nmr: see Table 3; ms: see Scheme 2 and Table 4.

Anal. Calcd. for $C_{14}H_{18}N_2O_5S$: C, 51.53; H, 5.52; N, 8.59. Found: C, 51.93; H, 5.92; N, 8.30.

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