A SIMPLE SYNTHESIS OF NOVEL 3-ARYL-5 HYDROXY-5-(α-HYDROXYIMINO-β-PHENYLETHYL)-4, 5-DIHYDROISOXAZOLES, 3-ARYL-6-BENZYLIDENE-4, 5-DIHYDRO-2H-1, 2-OXAZIN-5-ONE OXIMES AND 5-ARYL-2-BENZYLIDENE-1-HYDROXYPYRROL-4-IN-3 ONES FROM 3(2H)-FURANONES

MOHAMED G. MAREI*

SUMMARY: The reaction of 5-aryl-2-benzylidene-3(2H)-furanones with excess hydroxylamine in refluxing ethanol led to the formation of the title compounds which were separated by chromatography. The above intermediate isoxazolines could be converted into the corresponding isoxazole derivatives either by refluxing with concentrated hydrochloric acid in ethanol or on prolonged heating in xylene. The structures of the all products were established from their IR, ^1H nmr and mass spectral data. Pathways for their formation were suggested.

Key Words: Isoxazoline, isoxazole derivatives, furanones.

INTRODUCTION

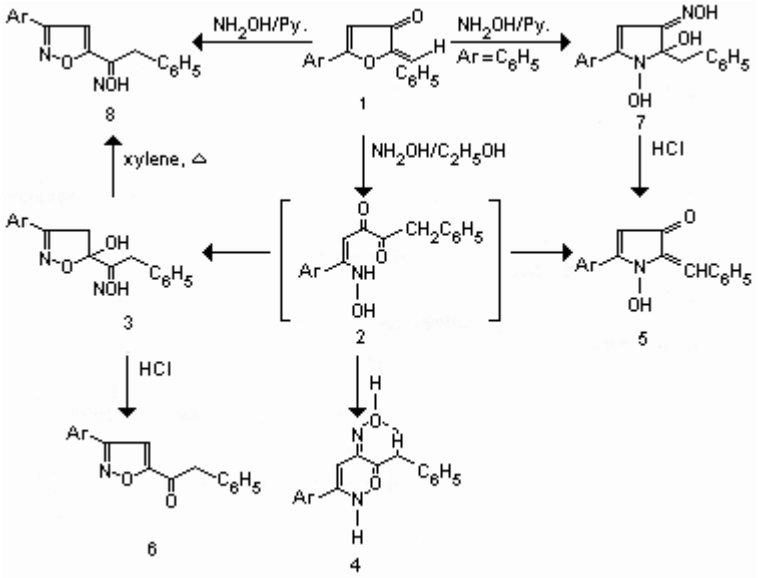
There have been several reports concerning reaction of 2-arylidene-5-methyl-3(*2H*)-furanones with a variety of nucleophilic reagents (1). As yet, only two examples have been published on the reaction of 5-aryl-2-benzylidene-3(2*H*)-furanones with some of these reagents.

In an earlier publication, I and others reported the preparation of 5-aryl-2-benzylidene-3(2*H*)-furanones 1 and their reaction with hydrazine hydrate to form the 5(3)-aryl-3(5)-(α-hydrazonophenylethyl) pyrazoles (2). Recently, I have described the reaction of these furanones with hydroxylamine hydrochloride in pyridine (3). As a result of such a study, it was found that the only product obtained, with very high yield was the 2-benzyl-1,2-dihydroxy-5-phenylpyrrol-4-in-3-one oxime 7 or 5-(α-hydroxyimino-ß-phenylethyl)-3-arylisoxazoles 8 (Figure 1). This reaction proceeds with a complete regiospecificity since only one isomer (product) was detected.

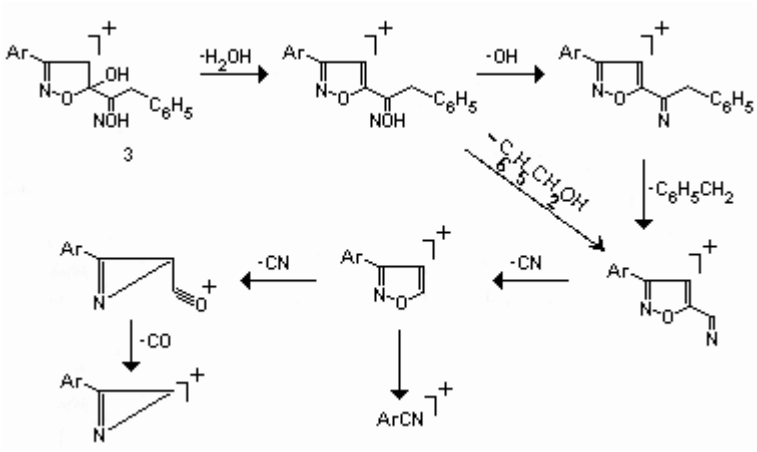
The versatility of these furanones for the synthesis of the above heterocyclic rings which have a great variety of useful properties prompted me to study the behavior of hydroxylamine towards these substrates in ethanol. In the present work, reaction of the furanones *1a-e* with excess hydroxylamine in ethanol was performed with refluxing for 6-8 hours. Upon chromatography of the reaction products on silica gel and/or tlc, were isolated the three products that proved 3-aryl-5-hydroxy-5-(α-hydroxyimino-β-phenylethyl)-4,5-dihydroisoxazoles (*3a-e,* 35-49%), 3-aryl-6-benzylidene-4,5-dihydro-*2H*-1,2-oxazin-5-one oximes (4a-e, 20-28%) and 5-aryl-2-benzylidene-1-hydroxypyrrol-4-in-3-ones (*5a-e,* 14-19%) (Figure 1). However, under similar conditions, the 2-arylidene-5-methyl-3(2H)-turanones gave only 3-methyisoxazole derivatives (1).

The reaction of hydroxylamine with 2-benzylidene-3(*2H*)-furanones 1 is assumed to proceed by intermediate

* From Department of Chemistry, Faculty of Science, Alexandria University, Ibrahimia P.O. Box 426, Alexandria, 21321, Egypt.



Schema 1



Schema 2

formation of the open chain 2 which is susceptible to cyclization to the corresponding 2-isoxazoline *3*, 1,2-oxazine *4* or N-hydro-xypyrrolinone *5* under the reaction conditions. The regiospecificity of the reaction may be rationalized by the nucleophilic addition of the N-atom of hydroxylamine to the 5-position of the furan ring (1,4) leading to the formation of the open chain intermediate 2 due to the electophilic character of the C-5 in 3(2*H*)-furanones is enhanced by the conjugated with the carbonyl group at C-3.

On the other hand, I have found that the reaction results in the exclusive or predominant formation of products *3*, a moderate products *4* and a small amount of the products *5*. This due to the formal (+) charge on the carbonyl carbon atom (C-3) is much larger than that on the carbon taking part in the keto-enol tautomerism (C-2) of the intermediate 2 : No difference in products was noticed when the phenyl group on C-5 was substituted by a p-substituted phenyl group, since there is no conjugation between C-5 and C-2.

The dipole character of the carbonyl group on C-2 (to which suffers a keto-enol tautomerism) is better pronounced in ethanol than in pyridine since the former solvent is more polar than the latter. Thus there exists the chance of a nucleophilic attack of oxygen or nitrogen atom of the -NHOH group on C-2 to form compounds 4 and 5, respectively.

The formulation of the products *3* as the 3-aryl-5-hydroxy-5-(α-hydroxyimino-β-phenylethyl)-4,5-dihydroisoxazoles resulted from their dehydrated with concentrated hydrochloric acid in glacial acetic acid which yielded the known isoxazole ketones *6* reported by me (3). Also, the heating of *3* in xylene afforded the reported 5-(α-hydroxyimino-β-phenylethyl)-3-arylisoxazoles *8* (3) (Scheme 1). Moreover, the observed characteristic fragments for isoxazole ring in the mass spectra of *3a, b* which are proposed in Scheme 2, are entirely similar to my reported mass spectra of isoxazoles *6,8* (3) and 5-hydroxy-2-isoxazolines (5). In particular the positions of the nitrogen and oxygen in the ring are unambiguously established and this result is in agreement with a primary

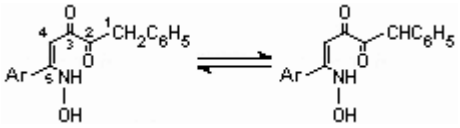


Table 1: Physical and analytical data for the products *3-6a, 8a.*

Compd.	yield (%)	MP (°C)	Molecular Formula	Analysis (%)		Cald. / Found	
				C	H	N	X
3a	35	165	$C_{17}H_{16}N_2O_3$	68.9 (68.8)	5.4 (5.5)	9.5 (9.4)	
3b	37	185	$C_{18}H_{18}N_2O_3$	69.7 (69.5)	5.8 (5.7)	9.0 (9.1)	
3c	40	187	$C_{18}H_{18}N_2O_4$	66.3 (66.2)	5.5 (5.4)	8.6 (8.7)	
3d	49	162	$C_{17}H_{15}BrN_2O_3$	54.4 (54.6)	4.0 (4.0)	7.5 (7.7)	21.3 (21.1)
3e	46	190	$C_{17}H_{15}ClN_2O_3$	61.7 (61.5)	4.5 (4.3)	8.5 (8.7)	10.8 (10.9)
4a	25	162	$C_{17}H_{14}N_2O_2$	73.4 (73.6)	5.0 (5.1)	10.1 (10.2)	
4b	23	175	$C_{18}H_{16}N_2O_2$	74.0 (74.3)	5.5 (5.2)	9.6 (9.4)	
4c	28	166	$C_{18}H_{16}N_2O_3$	70.1 (70.3)	5.2 (5.3)	9.1 (9.5)	
4d	27	150	$C_{17}H_{13}BrN_2O_2$	57.1 (57.5)	3.6 (3.2)	7.8 (7.2)	22.4 (22.0)
4e	20	187	$C_{17}H_{13}ClN_2O_2$	65.3 (65.6)	4.2 (4.6)	9.0 (9.2)	11.4 (11.6)
5b	14	210	$C_{18}H_{15}NO_2$	78.0 (77.9)	5.4 (5.7)	5.1 (5.5)	
5c	19	225	$C_{18}H_{15}NO_3$	73.8 (73.5)	5.1 (5.0)	4.8 (4.9)	
5d	16	215	$C_{17}H_{12}BrNO_2$	59.7 (60.1)	3.5 (3.7)	4.1 (4.3)	23.4 (23.0)
5e	15	235	$C_{17}H_{12}ClNO_2$	68.6 (68.8)	4.0 (4.2)	4.7 (4.9)	12.0 (12.2)
6a	90	195	$C_{17}H_{13}NO_2$	77.6 (77.8)	5.0 (5.3)	5.3 (5.1)	
8a	85	195	$C_{17}H_{14}N_2O_2$	73.4 (73.5)	5.1 (4.8)	10.1 (10.2)	

attack of the nitrogen of hydroxylamine at C-5 of the benzylidene furanones *1* as supposed in the structure of the open chain intermediate 2.

On the other hand, the structural assignments of the compounds *5* as the 5-aryl-2-benzylidene-1-hydroxypyrrol-4-in-3-ones are in agreement with that recently reported by me (3), 2-benzylidene-1-hydroxy-5-phenylpyrrol-4-in-3-one 5a. This leads to the assignment of a Z configuration for these compounds (3).

The above reaction of hydroxylamine with 3(*2H*)-furanones 1 in ethanol provides a simple synthesis of 4,5-dihydroisoxazoles, 1,2-oxazines and 2-pyrrolines. Relatively few examples of 5-hydroxy-4,5-dihydro-isoxazoles are reported in literature and they have interesting properties both in fundamental, synthetic or biological fields (5). There are many methods known in the literature for the preparation of *2H*-1,2-oxazines (6), owing to their useful applications. Some are reported as agrochemical fungicides (7) as herbicides plant growth regulators (8), as bactericides (9) and as insecticides, acricides and ectoparasiticides (10). 2-Pyrrolines represent an important class of heterocycles and interest in their chemistry contin-

Table 2: Spectral data for compounds *3-6a,8a.*

Compd.	IR (KBr) cm^{-1}				^1H NMR, DMSO-d_6, δ (ppm)*			
	C=N	C=O	OH	NH	CH_2 (s)	H-4 (s)	Ph-CH= (s)	Others (s)
3a	1569,1590		3430		3.61,4.33			5.29 (OH-5), 8.01 (=NOH),
3b	1595,1645		3415		3.45,4.20			2.2 (CH_3), 5.2 (OH-5), 8.3 (=NOH),
3c	1602,1669		3412		3.40,4.15			3.7 (OCH_3), 5.3 (OH-5), 9.1 (=NOH)
3d	1600,1660		3413		3.64,4.20			5.33 (OH-5), 8.4 (=NOH)
3e	1597,1657		3420		3.62,4.10			5.3 (OH-5), 8.4 (=NOH)
4a	1652		3250	3500		6.87	7.20	8.2 (NH), 11.2 (OH)
4b	1655		3302	3495		6.90	7.32	2.3 (CH_3), 8.1 (NH), 12.2 (OH)
4c	1640		3300	3502		6.92	7.25	3.6 (OCH_3), 10.2 (NH), 12.1 (OH)
4d	1645		3245	3518		6.69	7.15	9.3 (NH), 11.4 (OH)
4e	1650		3250	3503		6.90	7.18	11.50 (OH)
5b		1653	3449			7.00	7.46	2.2 (CH_3), 8.2 (OH)
5c		1660	3430			6.89	7.14	3.8 (OCH_3), 9.2 (OH)
5d		1677	3445			6.72	7.14	10.12 (OH)
5e		1665	3450			6.75	7.25	11.2 (OH)
6a	1610	1700			4.42	6.55		
8a	1569,1605		3462		4.32	6.42		9.91 (OH)

*s: Singlet; all the OH and NH signals are deuterium exchangeable.

ues unabated because of usefulness as synthons and only a few examples of these pyrrolinones are known (8).

The structures of 4,5-dihydroisoxazoles 3, oxazines 4 and pyrrolinones 5 were confirmed by elemental analysis, spectroscopic data (ir, mass, ^{1}H nmr, Tables 1 and 2) and in good agreement with those earlier reported (1,3-5,11).

E and Z isomerism is possible in the case of benzylidene oxazines. The Z- configuration is tentatively assigned to the oxazines *4* since it is expected to be more favored due to intramolecular hydrogen bonding and in agreement with the steric hindrance of the phenyl group.

The results have shown that the furanones 1 are useful intermediates for the preparation of substituted heterocycles *3,4,5.* Studies involving the reactions with other nucleophiles are in progress in this laboratory.

EXPERIMENTAL

All melting points were determined on a Kofler block apparatus. The infrared spectra were measured with a Unicam, SP 1025 spectrophotometer for potassium bromide pellets. The ^{1}H nmr spectra were recorded on a Varian EM-390 90 MHz spectrometer with TMS as internal standard. Mass spectra were recorded on an AEI MS 30 spectrometer. Elemental Analysis were performed by the Microanalysis Unit, Cairo University, Cairo, Egypt.

3-Aryl-5-hydroxy-5-(α-hydroxyimino-ß-phenylethyl)-4,5-dihydroisoxazoles *3a-e*, 3-Aryl-6-benzylidene-4,5-dihydro-*2H*-1,2-oxazin-5-one oximes 4a-e and 5-aryl-2-benzylidene-1-hydroxypyrrol-4-in-3-ones *5a-e* (Tables 1 and 2). General procedure.

A mixture of 3(*2H*)-furanone *1* (18 mmoles), sodium acetate (72 mmoles), hydroxylamine hydrochloride (72 mmoles), water (3 ml) and ethanol (15 ml) was refluxed for 6-8 hours. After removal of most of the solvent under reduced pressure and then dilution with water (5 ml), the separated solid was chromatographed on silica. Elution with hexane, hexane-benzene (1:1), benzene, dichloromethane and benzene-acetone (20:1) gave 3 and a mixture of 4 and 5. Silica gel chromatography of the mixture of successive elution with hexane-dichloromethane (10:1 and 5:1) and dichloromethane gave *4* and a mixture of *4* and *5* from which *5* was isolated by tlc [Kieselgel 6OHF254 (Merck)] with dichloromethane. The compounds *3,4* and *5* were purified by re-crystallization from methanol, ethanol and benzene in needles, respectively. MS: m/e (relative abundance) 3a: M^+ 296 (13), 278 (30), 261 (12), 176 (20), 175 (22), 170 (11), 162 (8), 144 (32), 134 (15), 116 (44), 108 (19), 91 (90), 77 (100); 3b: M+ 310 (15), 292 (35), 279 (15), 184 (10), 176 (20), 162 (7), 158 (12), 135 (10), 134 (15), 133 (12), 130 (25), 108 (33), 91 (100), 77 (76). The pyrrolinone 5a was found to be completely identical (mp, mixed mp, ir and 1H nmr spectra) with authentic sample prepared from the oxime 7 and concentrated hydrochloric acid (3).

Conversion of 4,5-dihydroisoxazoles 3 into 3-aryl-5-phenylacetylisoxazoles 6

A solution of 3 (10 mmoles) in glacial acetic acid (10 ml) was refluxed in presence of few drops of concentrated hydrochloric acid for 4-7 hours. On concentration, the isoxazole ketones *6* (87-92% yield), separated out and were crystallized from methanol. These ketones were found to be completely identical with authentic samples prepared from isoxazole oximes 8 and hydrochloric acid (3).

Conversion of *3* into 3-Aryl-5-(α-hydroxyimino-ß-phenylethyl)-isoxazoles *8*

A solution of *3a-e* (40 mmoles) in dry xylene (15 ml) was refluxed for 2-3 hours. On concentration, the isoxazole oximes *8a-e* (75-90% yield), separated out and were crystallized from methanol. These oximes were found to be completely identical with authentic samples prepared from furanones 1 and hydroxylamine hydrochloride in pyridine (3).

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Correspondence:
Mohamed Gaber Marei
Chemistry Department,
Faculty of Science,
Alexandria University,
Alexandria, 21321,
EGYPT.