A NEW SYNTHESIS OF 5-HYDROXY-2-ISOXAZOLINES AND THEIR CONVERSION INTO ISOXAZOLES

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SUMMARY: The reaction of 1,5-diarylpent-1-yne-3, 5-diones or 2,6-diaryl-4H-pyran-4-ones with hydroxylamine in ethanol led to the formation of 5-hydroxyisoxazolines as well as isoxazoles as minor products. The isoxazolines could be converted into the latter isoxazoles on prolonged heating in xylene. The structure of the intermediate 5-hydroxyisoxazolines was established from their I. R., UV. ^{1}H-N.M.R. and mass spectral data.

Key Words: 5-hydroxy-2-isoxazolines, isoxazoles.

INTRODUCTION

2-Isoxazoline derivatives are useful as intermediates in the organic synthesis (2), polymers (2, 3), pharmacologically active materials (4), dyes and pesticides (5). They possessing fungicidal (6), antimicrobial (7), bactericidal (8, 9) and mutagenic (10) activities.

Relatively few examples of 5-hydroxy-2-isoxazolines are reported in literature. The synthesis of these isoxazolines involves the reaction of hydroxylamine with chalcone expoxides (11), certain β-diketones (12), diacetylenic ketones (13) or benzyl and subsequent addition to dimethylsulfonium methylide (14). They were also formed from heating of some 3a. 6a-dihydro [1. 3] dioxolo [4. 5-d] isoxazoles (15).

In the present study, a new route to 5-hydroxy-2-isoxazolines is described. A series of 5-aryl-5-hydroxy-3-(β-hydroxy-imino-β-phenylethyl)-2-isoxazolines (6b-e) or 5-hydroxy-5-(β-hydroxy-imino-β-phenylethyl)-3-phenyl-isoxazoline (3a) were prepared from the reaction of the respective 1, 5-diarylpent-1-yne-3, 5-diones (1a-e) or 2, 6-diaryl-4H-pyran-4-ones (2a-e) with hydroxylamine in ethanol. The isoxazole oximes 7a or 8b-e were also formed as minor products in the above reaction (Scheme 1). In earlier publications (16, 17), the reaction of the 2, 6-diaryl-4H-pyran-4-ones (2a-c) with hydroxylamine in ethanol was reported to give 2, 6-diaryl-1-hydroxy-4-pyrid-ones. Two other products were also isolated with 2a which were considered to be 2, 6-diphenyl-4H-pyran-4-one and 2, 6-diphenyl-4H-pyran-4-one oxime (17), reinvestigation of the structure of the products obtained alongside the 4H-pyran-4-one oximes from the above reaction, indicated that they are mixture of 5-hydroxylisoxazolines 3a or 6b, c and isoxazole oximes 7a or 8b, c due to the spectral characteristics of these products were not consistent with the previously assignment. Due to the presence of more than one site of attack for nucleophilic reagents, the isoxazoline oxime obtained from the substrate 1 or 2 (R≠Ph) can assume either structure 3 or 4. Moreover for the isoxazoline oximes obtained from substrates having two different aryl residue 1 or 2 (R≠Ph), two further structures 5 and 6 are possible. Based on their spectral characteristics and conversion into the corresponding isoxazoles, structure 3 was assigned to the isoxazoline oxime with two phenyl residues, while the other oximes (R≠Ph) were shown to have the isomeric structure 6. Consequently, the corresponding isoxazole oximes, ketones, hydrazones and azines have the structures 7, 8, 9, 10, 11, 12 and 13, 14 respectively (Scheme 1).

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The infrared spectra of the isoxazoline oximes 3a and 6b-e (Table 1) were characterized by the presence of C=N (ring), C=N (oxime) and OH stretching vibration bands (18). An appreciable deshielding for the methylene protons is observed in the ^{1}H-N.M.R. spectra of these compounds (Table 1) compared with that reported for 5-(β-hydroxyiminoethyl)-2-isoxazolines (18).

While the electronic spectra of isoxazoline oximes (Table 2) in both neutral and 0.1 M sulfuric acid media were similar, a blue shift was observed for the high wave length maximum with an appreciable increase in its intensity in the presence of 0.1 M $NaOCH_3$. A different pattern was observed on increasing the acidity (1 M H_2SO_4) or basicity (1 M $NaOCH_3$). In non-polar solvents (cyclohexane), the low wave length band suffered from a red shift (about 26 nm). However, in chloroform solution, the spectra of 3a showed a new band at 264 nm and a red shift was observed for the low wave length maximum with an appreciable decrease in its intensity.

Moreover, the mass spectrometry has proved useful in the structure elucidation of isoxazolines (18) and in the differentiation between 3- and 5-arylisomers.

5-hydroxy-2-isoxazolines can be converted into isoxazoles on heating in xylene (13). In the present work, the refluxing of 5-hydroxyisoxazolines 3a or 6b-e in xylene afforded the respective 3-phenyl-5-(β-hydroxyiminophenylethyl) isoxazole (7a) or 5-aryl -3-(β-hydroxyiminophenylethyl isoxazoles (8b-e). Moreover, dehydration of the above isoxazolines 3a or 6b-e with sulfuric acid led to the formation of the corresponding isoxazole ketones 9a or 10b-e (Scheme 1).

It is worthy to mention that the isolation of the intermediate isoxazolines 6b-e excludes the earlier assignment for isoxazole derivatives which were formed from the reaction of the substrates 1b-e or 2b, c with hydroxylamine hydrochloride in pyridine (19).

MATERIALS AND METHODS

Melting points were determined with a Kofler-block apparatus and are uncorrected. Infrared spectra were recorded with a Unicom SP 1025 spectrophotometer for potassium bromide pellets and electronic spectra were measured for solutions in methanol with a Unicam SP 800 spectrophotometer. The ^{1}H-N. M. R. spectra were measured with an EM-390 90 MHz spectrometer for solutions in DMSo-d_6 using TMS as internal standard. Chemical shifts are given on the δ scale. TLC was performed on 'Bakerflex' silica gel 1B-F (2.7-7.5 cm^{-1}) plates. Microanalyses were performed in the Faculty of Science, Cairo University, Cairo, Egypt.

5-Hydroxy-5-(β-hydroxyimino-b-phenylethyl) -3-phenyl-2-isoxazoline (3a) and 5-aryl-5-hydroxy-3-(β-hydroxyimino-β-phenylethyl)-2- isoxazolines (6b-e) (Tables 1 and 2)

a. From acetylenic β-diketones

A solution of the acetylenic β-diketone 1a-e (20 mmol) in ethanol (20 ml) was stirred at room temperature overnight or refluxed with hydroxylamine hydrochloride (70 mmol) and sodium acetate (70 mmol) in water (2 ml) for 5-8 hours. After removal of most of the solvent under reduced pressure and then dilution with water, the separated solid was subjected to fractional crystallization from ethanol or methanol. The isoxazoline oximes (55-70% yield) separated first, and from the mother liquors. 5-(β-hydroxyimino- β-phenylethyl)-3-phenylisoxazole 7a or 5-aryl-3-(β-hydroxyimino-β-phenylethyl) isoxazoles 8b-e were obtained (20-25% yield). MS for 3a: 296 (M^+). 278 (M^+-H_2O). 176 (M^+-C (NOHPh). 175 (M^+-H_2O-PhCN). 162 (M^+-CH_2C (NOH) Ph). 145 (M^+-CHC (NOH) Ph-H_2O). 158 (M^+-C (NOH) Ph-H_2O). 135 (CH_2C (NOH) Ph+H. 134 (CH_2C (NOH) Ph). 103 (PhCN). 77 (base peak): MS for 6b: 310 (M^+). 292 (M^+-H_2O). 190 (M^+-C (=NOH) Ph). 189 (M^+-H_2O-PhCN). 176 (M^+-CH_2C (=NOH) Ph). 173 (M^+-H_2O-p-MeC_2H_2CO). 158 (M^+-CH_2C (=NOH) Ph-H_2O). 135 (CH_2C (=NOH) Ph+H). 134 (CH_2C (=NOH) Ph). 133 (CH-C (=NOH) Ph). 120 (PhCNOH). 119 (p-Me-C_6H_4-CO). 91 (p-Me-C_6H_4). 77 (C_6H_5).

Table 1: Infrared and ^{1}H-N.M.R. spectral data of 2-Isoxazolines.

	I.R. (cm^{-1}) C=N	OH	^{1}H-N.M.R. CH_2 (s)	Chemical Ar-H (m)	Shift (d/ppm) (a) Others (s)
3a	1560. 1697	3437	3.76.3.84	7.55	
6a	1562. 1605	3440	3.66.3.75	7.55	2.20 (3H.CH_3)
6c	1562. 1607	3496	3.80.3.90	7.37	3.76 (3H.OCH_3)
6d	1567. 1591	3498	3.84.3.93	7.56	
6e	1569. 1593	3191	3.83.3.91	7.60	

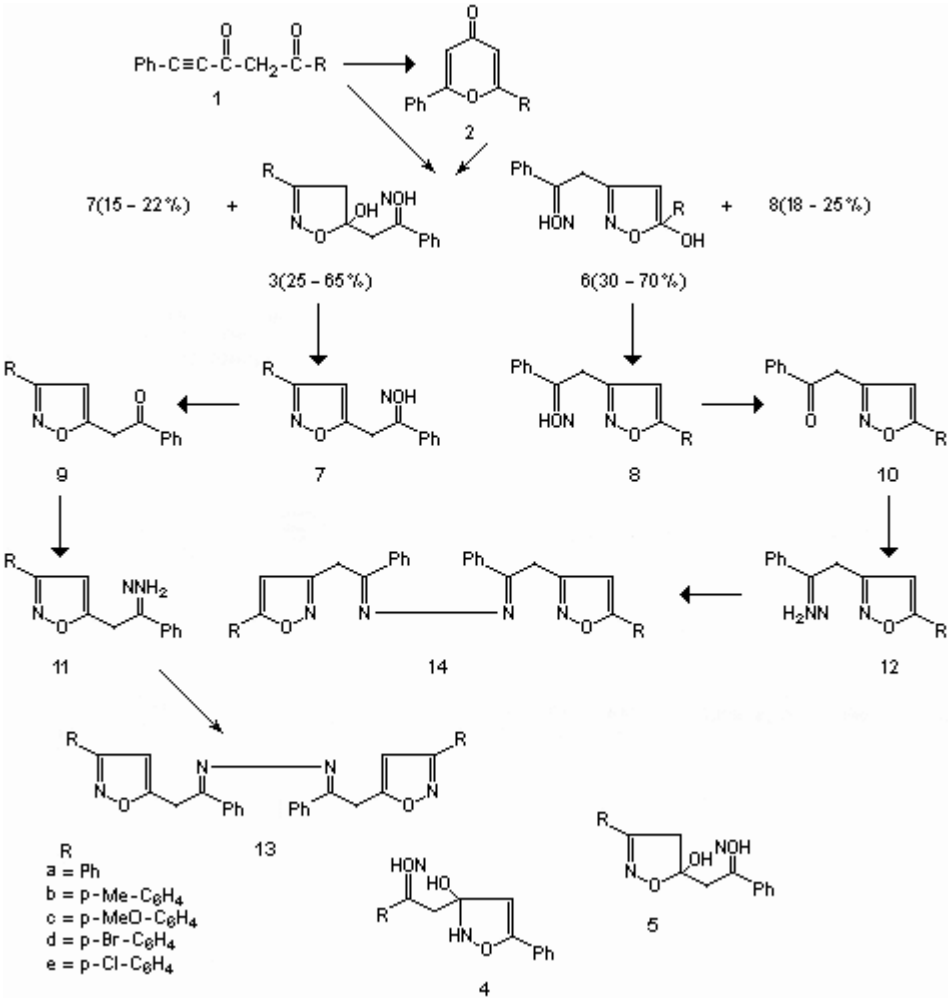
(a) s: Singlet m: multiplet

Table 2: Analytical and electronic data of 2-isoxazolines.

Comp.	M.P. (°C)	Molecular Formula	Analysis (Calcd./Found %)				Uv λ max.		nm. (ε)
			C	H	N	X			
3a	260	$C_{17}H_{16}N_2O_3$	68.9	5.4	9.5		237		398
			(68.7	5.2	9.7)		(110947		642)
							237		397 (a)
							(115988		1433)
							238	252	258 (b)
							(59200	57505	56514)
							263	266	268
							(53945	56375	55799)
							274		344
							(51658		771)
							236		344 (c)
							(118400		3490)
							209	251	341 (d)
							(84594	118400	65978)
							263		397 (e)
							243	264	397 (f)
							(23656	29762	1418)
6b	225	$C_{18}H_{18}N_2O_3$	69.7	5.8	9.0		236		397
			(69.9	5.9	9.2)		(225054		2683)
							236		397 (a)
							(38462		2200)
							237		344 (f)
							(38462		7994)
6c	257	$C_{18}H_{18}N_2O_4$	66.3	5.5	8.6		235	278	398
			66.5	5.7	8.7		(116429	32344	5821)
							236		397 (a)
							(465644		5123)
							237		396 (c)
							(465714		11934)
6d	280	$C_{17}H_{15}BrN_2O_3$	54.4	4.0	7.5	21.3	236		397
			(54.3	4.1	7.4	21.5)	(205141		2099)
							238		396 (a)
							(208333		2151)
							236		396 (c)
							(208333		5635
6e	240	$C_{17}H_{15}ClN_2O_3$	61.7	4.5	8.5	10.8	244	279	397
			(61.9	4.7	8.8	10.4	(10328	163	1815)
							238		397 (a)
							(110167		2597)
							237		396 (c)
							(110167		2597)

(a) Spectra carried out in methanolic 0.1 M sulfuric acid. (b) Spectra carried out in methanolic 1 M sulfuric acid. (c) Spectra carried out in methanolic 0.1 M sodium methoxide. (d) Spectra carried out in methanolic 1 M sodium methoxid. (e) Saturated solution in cyclohexane. (f) Spectra carried out in chloroform.

Scheme 1



b. From 2-aryl-6-phenyl-4H-pyran-4-one

A solution of 2a-e (50 mmol) in ethanol (25 ml) was refluxed with hydroxylamine hydrochloride (200 mmol) and sodium acetate (200 mmol) in water (3 ml) for 10-12 hours. The solvent was then removed under reduced pressure, water (20 ml) added and the separated solid was filtered and washed several times with water. On treatment of an ethanolic solution of the above product with hot saturated solution of picric acid in ethanol (10 ml). 2-aryl-6-phenyl-4H-pyran-4-one oxime picrates separated out and were removed by filtration. The residual ethanol solution was mixed with 25% aqueous ammonia and extracted with chloroform. The residue after removal of most of the solvent afforded the isoxazoline oximes (25-35% yield) on treatment with benzene-petroleum ether (b. p. 60-80°). From the mother liquors, the isoxazole oximes 7a or 8b-e were obtained (15-20% yield). These isoxazoles were found to be completely identical (m.p. and mixed m. p.) I. R. and ^{1}H-N. M. R. spectra with authentic samples prepared from 1 or 2 and hydroxylamine hydrochloride in pyridine (19).

Conversion of 5-hydroxyisoxazolines into isoxazole oximes

A solution of 3a or 6b-e (200 mmol) in dry xylene (10 ml) was refluxed for 5-7 hours. On concentration, the isoxazole oximes (19) 7a or 8b-e (70-80% yield) separated out and were crystallized from methanol.

Conversion of 5-hydroxyisoxazolines into isoxazole ketones 9a and 10b-e

A solution of the above isoxazolines 3a or 6b-e (10 mmol) in glacial acetic acid (10 ml) was refluxed in presence of few drops of concentrated sulfuric acid for 3-6 hours. On concentration, the isoxazole ketones (85-90% yield) separated out and were crystallized from methanol. These ketones were found to be completely identical with authentic samples synthesized from isoxazole oximes and hydrochloric acid (19).

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