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REACTIONS OF C_α,O-DILITHIOXIMES WITH FUNCTIONALIZED CARBONYL COMPOUNDS. PART 1. REACTION WITH 1,2-DIKETONES[1]

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Abstract — C_α,O-Dilithioximes 2 add to symmetrical 1,2-diketones to give the 5,6-dihydroxy-1,2-oxazine derivatives 5. Under acidic conditions,the latter heterocycles undergo dehydration accompanied by ring contraction to 5-acyl-Δ^2-isoxazolines 6.

INTRODUCTION

Oxime dianions 2 have found application in organic synthesis[2-6]. These intermediates are generated in situ from the corresponding oximes by the action of a strong base. They react with a wide variety of organic substrates having electrophilic centers, such as alkyl halides[3], nitriles[4], esters[5], aldehydes and ketones[6] to yield acyclic or heterocyclic products. The reaction of 2 with bifunctional organic compounds, such as 1,2-diketones, α-haloketones and α,β-unsaturated carbonyl compounds remains, however, unexplored.

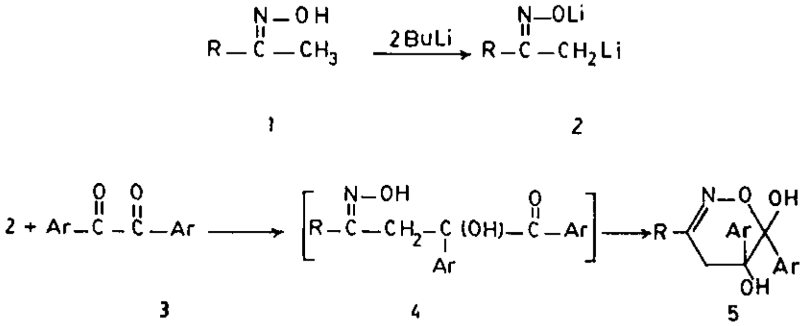
We here report on the reaction of C_α,O-dilithioximes with symmetrical 1,2-diketones. The reaction with α-chloroketones and α,β -unsaturated carbonyl compounds will be reported later.

RESULTS AND DISCUSSION

The reaction between oxime dianions 2 and symmetrical 1,2-diketones 3 (1:1 molar ratio) was carried out in dry THF at −78°C. The reaction products were isolated after careful neutralization of the resulting mixtures.

We anticipated that the reaction would afford the acyclic adducts **4**. The ir spectra of the isolated products showed, however, no carbonyl absorption bands, indicating that both carbonyl groups of the diketone have been involved in the reaction with the dianion. Under the reaction conditions employed, the presumed acyclic primary adducts **4**, which exist in the (Z)-configuration^7, readily cyclize to the final products **5** (Scheme 1).

Scheme 1:



Compounds **5a–e** were characterized by their elemental analysis (Table 1) and spectral data (Table 2). The ir spectra of these compounds showed a sharp O–H in the region 3565 – 3420 cm^{-1} (free O–H) and a broad ν(O–H) in the range 3380 – 3120 cm^{-1} (bonded O–H), but no carbonyl absorptions. The pmr spectra of compounds **5a–d** show two exchangeable singlets in the range 3.75 – 6.60 (1H) and 9.50–12.00 ppm (1H) attributed to the O–H protons at C-6 and C-5, respectively. The two distinct doublets in the region 2.00–4.00 ppm are attributed to the diastereotopic methylene protons at C-4. The mass spectra of compounds **5a–e** showed correct molecular ions $[M]^{+}$ as well as fragment ions corresponding to $[M-H_2O]^{+}$, $[M-OH]^{+}$, $[M-ArCO]^{+}$, and base peaks corresponding to $[ArCO]^{+}$ ion. These compounds were assumed to have a trans-arrangement of groups at C-5 and C-6, with the hydroxyl groups occupying axial, and the bulky Ar groups occupying equatorial positions. Such geometry would fulfill the requirements imposed both by the anomeric effect^8 and by steric factors, and would place the ring oxygen and the hydroxyl group at C-5 in close proximity for intramolecular hydrogen bonding, which seems responsible for the remarkable downfield shift experienced by this proton in the ^{1}H-nmr spectra (Table 2).

Table 1. Physical and Analytical Data for Compounds **5** and **6**.

Compd	R	Ar	mp	Yield	Found / Calcd (%)		
			(°C)	(%)	C	H	N
5a	C_6H_5	C_6H_5	218	63[a]	76.50	5.55	4.06
					76.45	5.55	4.09
5b	p-Me-C_6H_4	C_6H_5	181	55[a]	76.86	5.89	3.90
					76.50	5.89	3.95
5c	p-Me-C_6H_4	p-Me-C_6H_4	144	60[b]	77.50	6.50	3.62
					77.24	6.51	3.66
5d	p-Me-C_6H_4	p-MeO-C_6H_4	173(d)	68[b]	71.58	6.01	3.34
					71.92	6.03	3.31
5e	H	C_6H_5	208	50[a]	71.36	5.61	5.20
					71.19	5.70	5.22
6a	C_6H_5	C_6H_5	174	93[c]	80.71	5.23	4.28
					80.29	5.30	4.32
6b	p-Me-C_6H_4	C_6H_5	148	89[c]	80.92	5.61	4.10
					80.93	5.62	4.02
6c	p-Me-C_6H_4	p-Me-C_6H_4	104	85[c]	81.27	6.28	3.79
					80.99	6.30	3.74
6d	p-Me-C_6H_4	p-MeO-C_6H_4	oil	82	74.80	5.78	3.49
					74.95	5.81	3.43

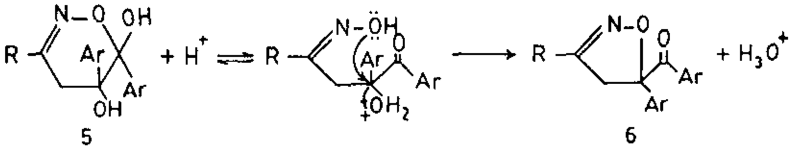
[a] Crystallized from tetrahydrofuran / petroleum ether.

[b] Crystallized from ethanol / water.

[c] Crystallized from carbon tetrachloride / pentane.

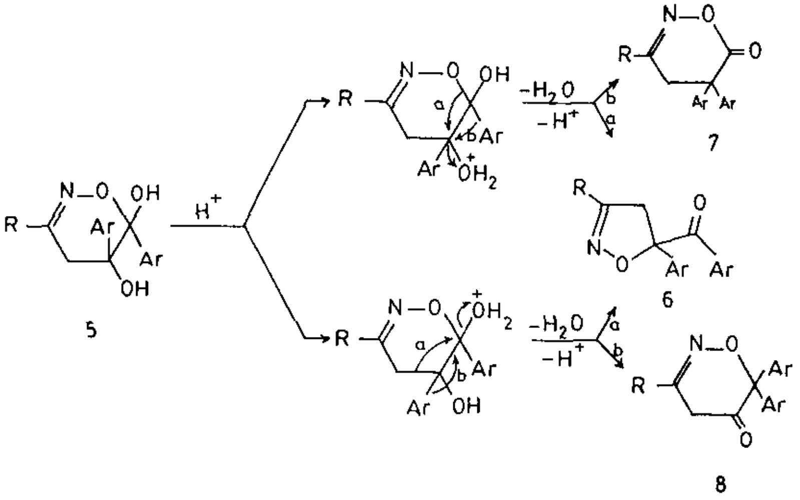
Upon treatment with cold concentrated sulfuric acid, compounds 5 were found to undergo dehydration, accompanied by ring contraction, to the corresponding 5-acylisoxazoles 6. A plausible reaction mechanism for this transformation would involve ring-opening of the oxazine 5 at the anomeric C-6 carbon, followed by acid-catalyzed dehydrative cyclization of the resulting acyclic β-hydroxyketoxime derivatives to the final products 6 (Scheme 2). Cyclization of these intermediates to compounds 6 in this manner is reminiscent of the transformation of β-hydroxyketoximes, obtained from the reaction of oxime dianions with simple aldehydes and ketones, to isoxazoles[6].

Scheme 2:



Alternatively, the transformation of 5 to 6 might involve pinacol-pinacolone type rearrangement, via ring contraction as demonstrated in Scheme 3. Rearrangements via aryl group migration (path b) to compounds 7 or 8 do not seem to take place, as no such products were formed in the reaction.

Scheme 3:



Compounds 6 were characterized by their elemental analysis (Table 1) and spectral data (Table 2). The ir spectra of these compounds exhibit a carbonyl

Table 2. Pmr and ir Spectral Data for Compounds 5 and 6.

	Chemical shift (ppm)				$\nu_{(O-H)}$
Compd	C-4 protons[a]	R/ Ar protons	C^6-OH	C^5-OH	(cm^{-1})
5a[b]	2.75 (1H,d); 3.69 (1H,d)	R/Ar: 6.82-7.80 (15H, m)	5.80	11.93	3510; 3380 (br)
5b[b]	2.68 (1H,d); 3.92 (1H,d)	R/Ar: 6.82-7.83 (14H, m) Me: 2.33 (3H, s)	5.95	12.15	3480; 3120 (br)
5c[b]	2.72 (1H,d); 3.55 (1H,d)	R/Ar: 6.67-7.65 (12H, m) Me: 2.27 (3H,s); 2.29 (3H, s); 3.32 (3H, s)	5.36	11.85	3565; 3260 (br)
5d[c]	2.77 (1H,d); 3.34 (1H,d)	R/Ar: 6.48-7.88 (12H, m) Me: 3.63 (3H, s); 3.73 (3H, s); 3.75 (3H, s)	5.48	11.70	3520; 3320 (br)
5e[b]	2.18 (1H,dd); 2.82 (1H,dd)[d]	R: 8.33 (1H, m) Ar: 7.12-7.53 (10H, m)	5.12	11.20	3420; 3310 (br)
6a[c]	3.35 (1H,d) 4.78 (1H,d)	R/Ar: 6.76-8.11 (15H, m)	--	--	-- --
6b[c]	3.31 (1H,d) 4.74 (1H,d)	R/Ar: 7.07-8.08 (14H, m) Me: 2.33 (3H, s)	--	--	-- --
6c[c]	3.26 (1H,d) 4.68 (1H,d)	R/Ar: 6.97-7.92 (12H, m) Me: 2.33 (3H, s); 2.28 (3H, s)	--	--	-- --
6d[c]	2.99 (1H,d) 4.45 (1H,d)	R/Ar: 6.42-7.76 (12H, m) Me: 3.59 (3H, s); 3.55 (3H, s)	--	--	-- --

[a] J(geminal C-4 protons) = 16 Hz. [b] In DMSO-d_6. [c] In $CDCl_3$ as solvent. [d] J(3,4) = 7 Hz.

absorption band at about 1680 – 1690 cm^{-1}, but no O-H absorptions. The position of this absorption is consistent with the assigned structure, in which the carbonyl group is conjugated with an aryl group, but excludes strutures 7 and 8 ,both of which would exhibit a carbonyl absorption at a much higher frequency. The pmr spectra of compounds **6a-d** show two doublets at 3.35 – 3.00 (1H) and 4.78 – 4.40 ppm (1H) assigned to the diastereotopic methylene protons at C-4. The downfield shift experienced by one of them is attributed to the anisotropic effect of the carbonyl group at the neighbouring C-5 position. In addition to the correct molecular ion peaks, the mass spectra of compounds **6a-d** exhibit prominant peaks which correspond to $[M - ArCOH]^{+\cdot}$, $[RCNO]^{+\cdot}$, $[ArCO]^{+}$ fragment ions, and base peak corresponding to $[M - ArCO]^{+}$.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were performed by Pascher Microanalytisches Labor, Bonn. Ir spectra (KBr) were recorded with a Perkin Elmer 577 spectrophotometer. Pmr spectra were obtained using a Varian T60 spectrometer with tetramethylsilane as an internal reference. Mass spectral measurements were obtained by EI ionization on a Varian MAT 112 mass spectrometer. n-Butyllithium (in hexane) was a product of Aldrich Chemical Company. Diketones were prepared from the corresponding benzoins[9] by oxidation with potassium ferricyanide[10].

General Procedure for the Preparation of Compounds 5:

To a stirred and cooled (ice bath) solution of the appropriate oxime (25 mmol) in dry tetrahydrofuran (50 ml), was added dropwise butyllithium (55 mmol) in hexane (32 ml). The reaction mixture became milky after the addition of the first equivalent of butyllithium, but aquired a yellowish color at the end of the addition. The resulting mixture was kept at 0°C under nitrogen atmosphere for 2h, during which time it became homogeneous and yellow-orange in color. It was cooled to -78°C, and the desired 1,2-diketone (25 mmol) in dry tetrahydrofuran (20 ml) was added dropwise. After 2 – 3 h of stirring, the cold mixture was neutralized carefully with 3M HCl. After warming to room temperature, the organic layer was separated, washed with water (50 ml), dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The residue was finally recrystallized from the appropriate solvent.

General Procedure for the Preparation of Compounds 6:

The appropriate 5,6-dihydroxy-1,2-oxazine **5** (4 mmol) was dissolved in cold concentrated sulfuric acid (10 ml). The resulting solution was kept for 1 h at 0°C and then poured, with stirring, over crushed ice (100 g). The solid which seperated was collected, washed with cold water, dried, and recrystallized from the suitable solvent (Table 1).

ACKNOWLEDGEMENT

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