Isoxazolium Enolates Derived from α,β-Unsaturated and 1,3-Dicarbonyl Compounds.
## The Through-Space Effect of The Enolate Moiety on the Chemical Shift of α-Protons

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Received October 25, 1993

The reaction of 4-phenyl-3,5-dihydroxyisoxazole with α,β-unsaturated cyclic ketones and 1,3-cyclic diketones was studied. β-Substituted α,β-unsaturated ketones give pairs of isomeric isoxazolium enolates. The remarkable influence of the heterocyclic betaine on the proton chemical shifts is discussed. 1,3-Cyclic diketones reacted spontaneously with 4-phenyl-3,5-dihydroxyisoxazole yielding isoxazolium enolate enols and enol ethers.

The spontaneous condensation of aromatic aldehydes with 3,5-dihydroxyisoxazole derivatives (disic acids **1**) to produce solid red isoxazolium enolates **2** was reported in earlier publications [1-3]. Aromatic ketones fail to give even the slightest coloration. Straight chain aliphatic carbonyl compounds yield with **1** unstable derivatives. Acetone gives with **1** the mesityl oxide addition products **3**. In the presence of primary and secondary alcohols these addition products yield the isoxazolooxazines **4** [4].
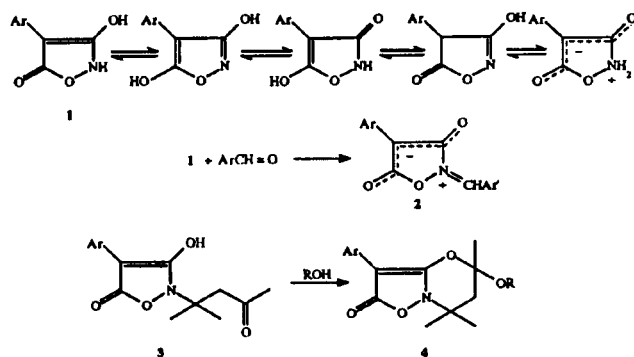
Open chain α,β-unsaturated ketones reacts with **1** to give C and N Michael addition products (**5** and **6**). Aliphatic α,β-unsaturated aldehydes like acrolein and crotonaldehyde yield polymers **7**, which are the result of both condensation and Michael addition [4].
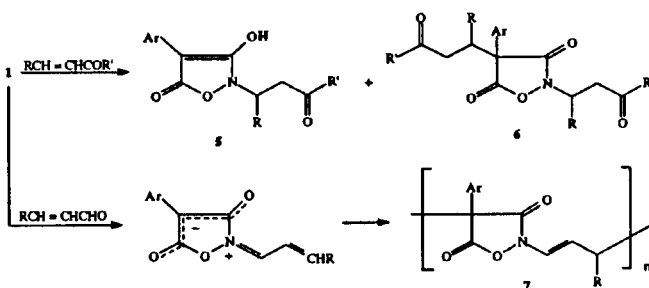

Single X-ray analysis of the dimethoxy phenyl derivative of **2** (Ar = Ph; Ar, = 2,4-diCH₃OC₆H₃) revealed that it had the Z configuration *i.e.* the aldehydic hydrogen was on the same side of the N-C-O⁻ bond rather than that of the N-O bond, probably because of sterical reasons but also possibly due to a positive interaction of the proton with the charged oxygen [5]. The X-ray analysis also showed extremely long bonds around the nitrogen within the heterocyclic ring, suggesting lack of conjugation between the cationic and anionic moieties. Such features were termed earlier as «paraionic», suggesting that of the anion and cation exist parallel to one another [6]. The pronounced through-space effect of the proximity of the resonating charge on the chemical shift of protons was reported in the case of the colorless diethyl betaines **8** [7] and the immonium enolate derived from cyclopentanone **9** [5].
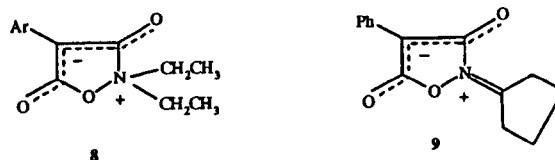
Geometric isomers were identified in nitrones which are the open chain analogs of the betaines [8-9]. Therefore it was expected that asymmetric cyclic ketones, including unsaturated cyclic ketones, will give with **1** two geometric isomers which could be distinguished by the difference in the nmr chemical shift, exerted by the proximity of the charged oxygen.

In the present work the reaction of 4-phenyl-3,5-dihydroxyisoxazole (**1**, Ar = Ph) with α,β-unsaturated cyclic ketones and 1,3-diketones were studied. Cyclic α,β-unsaturated ketones, those without any substituent at the β-position like 2-cyclohexanone reacted spontaneously with
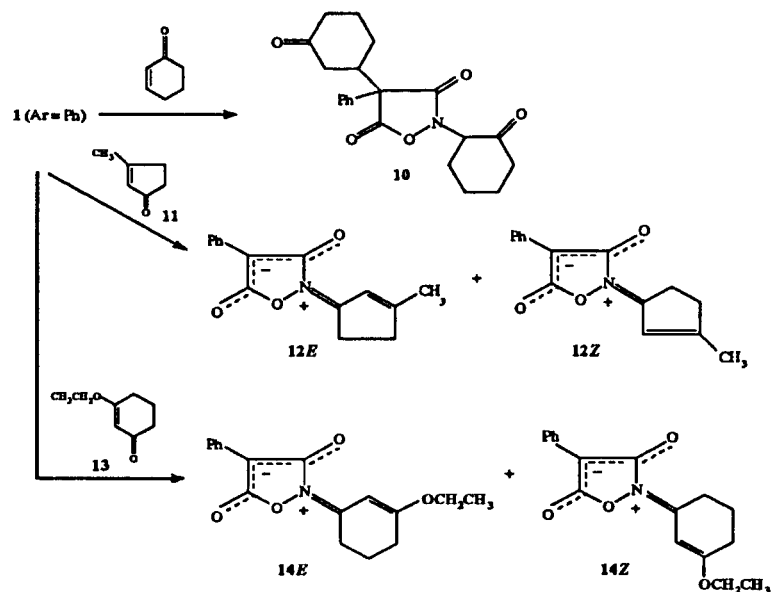
1 (Ar = Ph) to yield a mixture of stereoisomers of a double Michael addition product **10**. β-Substituted unsaturated ketones like **11** and **13** gave pairs of geometric isomers **12** and **14** in the ratio *E:Z* of 3:2 and 6:1 respectively. The ratio *E:Z* was determined by ^{1}H nmr of the resulting mixtures of isomers. The products are orange red (λ max 420-450 nm) and are sensitive to light. 1,3-Diketones bearing two substituents at position 2, like 2,2-dimethyl-1,3-cyclohexanedione, fail to react with **1**. This is probably

due to the lack of possibility of enolization. It does not lead even to the slightest coloration.

The remarkable influence of the heterocyclic betaine on the chemical shifts of the α-hydrogens, as compared to those in the parent ketones are shown in Table 1. Structure of one of these isomer pairs, as calculated by PC-model MM-2 is shown in Figure 1.

The close proximity of the α-hydrogens to the C $=$ O group, as shown in Figure 1 is probably the explanation

Table 1

Chemical Shifts of α-Protons and The Through Space Effect ($\Delta\delta_{EZ}$) [a] of The Anionic Ring
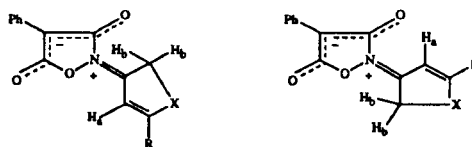
R	X	Isomer	Solvent	δH_a	δH_b	$\Delta\delta_a$ [b]	$\Delta_{EZ}\delta a$	$\Delta\delta_b$ [b]	$\Delta_{EZ}\delta_b$
CH$_3$	CH$_2$	Z	CDCl$_3$	6.70	3.70	0.75		1.09	
							0.94		0.44
CH$_3$	CH$_2$	E	CDCl$_3$	7.64	3.26	1.69		0.65	
CH$_3$CH$_2$O	CH$_2$	Z	CDCl$_3$	6.00	3.65	0.74		1.07	
							1.00		0.39
CH$_3$CH$_2$O	CH$_2$	E	CDCl$_3$	7.00	3.26	1.74		0.68	
OH	CH$_2$	Z	DMSO-d$_6$	5.68	3.15	0.55		0.65	
CH$_3$CH$_2$O	CH$_2$	Z	CDCl$_3$	6.09	3.55	0.76		1.22	
							1.63		0.56
CH$_3$CH$_2$O	(CH$_2$)$_2$	E	CDCl$_3$	7.72	2.99	2.39		0.66	
OH	(CH$_2$)$_2$	Z	DMSO-d$_6$	6.08	3.12	0.78		0.90	
CH$_3$O	(CH$_2$)$_2$	Z	CDCl$_3$	6.08	3.61	0.75		1.28	
							1.64		0.61
CH$_3$O	(CH$_2$)$_2$	E	CDCl$_3$	7.72	3.00	2.39		0.67	
OH	C(CH$_3$)$_2$CH$_2$		DMSO-d$_6$	6.00	3.01	1.30		0.79	

[a] The difference in chemical shift between the two geometric isomers, in ppm. [b] The difference of chemical shift compared to the starting ketone, in ppm.

R = CH₃, CH₃CH₂; X = CH₂, (CH₂)₂, C(CH₃)₂CH₂

α-hydrogens. The influence of the through space effect is very well demonstrated in the large difference in the chemical shifts between the two geometric positions.

Cyclic β-diketones like 1,3-cyclopentadione, 1,3-cyclo-hexadione and dimedone react with **1** (Ar = Ph) in THF and AcOH to yield betaines **15**. The Z geometry is assumed as the vinylic protons absorb at about 5.7-6.0 ppm, as compared to 7.0-7.7 ppm in the E series, described above. The latter difference (*e.g.* 1-1.6 ppm) was shown to be much larger than the effect of solvent alone. In the presence of alcohols these β-diketones yield the enol ethers **16**. The same as in the case of the unsaturated cyclic ketones these enol ethers are formed in pairs of isomers, **16E** and **16Z**. The ratios between **16E** and **16Z**

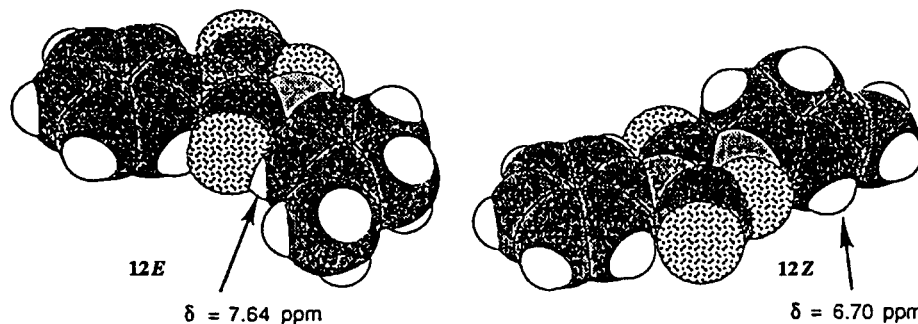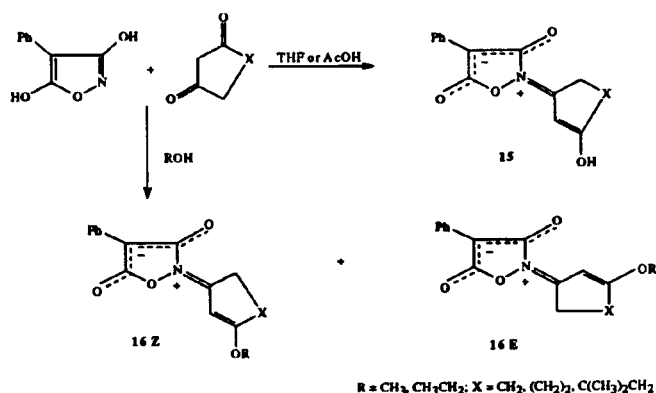δ = 7.64 ppm   δ = 6.70 ppm

Figure 1. Space filling models of **12E** and **12Z**, made by the MM-2 energy minimalization technique.

for the large change in the chemical shift as compared to the parent ketone. In the E form it is the vinylic proton which is shifted Δ β_E 2.39 ppm down field, whereas in the Z form the methylenic protons are affected (Δ β_Z = 1.22 ppm). However there is an overall deshilding effect on the

range from 6:1 to 1:20, as observed in the nmr spectra of the mixture of products. The ratio in the case of R = CH_3CH_2O and X = $(CH_2)_2$ was found to be identical with that obtained from the reaction of **1** (Ar = Ph) with 3-ethoxy-2-cyclohexanone. This fact suggests that the enol

Table 2

Experimental Data for The Preparation of Isoxazolium Enolate Derivatives

Carbonyl compounds	Solvent	Mps.	Yield, % (Number of isomers)	Formula	Calcd.			Found		
					% C	% H	%N	%C	%H	%N
3-Methyl-2-cyclo-pentenone	THF	165-168	65 (2)	$C_{15}H_{13}NO_3$	70.58	5.13	5.49	70.77	5.02	5.62
3-Ethoxycyclohexenone	EtOH	180	90 (2)	$C_{17}H_{17}NO_4$	68.22	5.72	4.68	68.09	5.61	4.77
1,3-Cyclopentandione	THF	225 dec	55 (1)	$C_{14}H_{11}NO_4$	65.37	4.31	5.44	65.35	4.55	5.12
4,4-Dimethyl-1,3-cyclohexadione (dimedone)	AcOH	191	90 (1)	$C_{17}H_{17}NO_4$	68.22	5.72	4.68	68.46	5.55	4.51
1,3-Cyclohexanedione	EtOH	180	80 (2)	$C_{17}H_{17}NO_4$	68.22	5.72	4.68	68.33	5.61	4.78
	AcOH	182	81 (1)	$C_{15}H_{13}NO_4$	66.41	4.83	5.16	66.22	4.68	4.84
	MeOH	165	55 (2)	$C_{16}H_{15}NO_4$	67.36	5.30	4.91	67.27	4.99	5.02
	PrOH	175	30 (1)	$C_{18}H_{19}NO_4$	69.00	6.11	4.47	68.70	5.83	4.51
1,3-Cyclopentanedione	EtOH	205 dec	45 (2)	$C_{16}H_{15}NO_4$	67.36	5.30	4.91	67.39	5.22	5.11
3-Oxobutyladehyde	AcOH[a]	170	75 (1)	$C_{13}H_{11}NO_4$	63.67	4.52	5.71	63.68	4.79	5.81
(as dimethylacetal)	MeOH[b]	150	65 (1)	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	64.66	4.96	5.59
Malonaldehyde	THF	230 dec	30 (1)	$C_{12}H_9NO_4$	62.34	3.92	6.06	62.06	4.19	5.97
(as tetramethylacetal)	AcOH	215	90 (1)	$C_{13}H_{11}NO_4$	63.67	4.52	5.71	63.39	4.66	5.58

[a] The same product was obtained in THF. [b] The same product was obtained in acetic acid at room temperature.

Table 3

NMR Data for The Condensation Products of Phenyl Disic Acid With Oxobutylaldehyde
and Malonaldehyde in CDCl₃

17a R = CH₃, R' = CH₃   **17c** R = H, R' = CH₃
17b R = CH₃, R' = H   **17d** R = H, R' = H
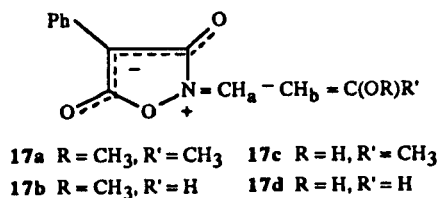
Compound	Solvent	δH_a	δH_b	δH_c	δH_d	δH_e	δH_R	$\delta H_{R'}$
17a	CDCl₃	8.50 d	6.00 d	8.11 d	7.33 t	7.14 t	4.05 s	2.39 s
17b	CDCl₃	8.35	6.21 dd	8.07 d	7.35 t	7.14 t	4.05 s	7.85 d
17c	DMSO-d₆	7.95 d	5.55 d	8.09 d	7.19 t	6.96 t	13.24 bs	2.16 s
17d	DMSO-d₆	9.31	5.49 dd	8.12 d	7.25 t	7.00 t	11.20 bs	8.02 d

ether formation takes place before the condensation.

Compounds **15** tend to undergo partial hydrolysis in wet DMSO. The formation of both the enol **17c** and **17d** and enol ethers **17a** and **17b** could be observed in the reaction of malonaldehyde and 3-oxobutylaldehyde with phenyl-disic acid (**1**, Ar = Ph). The nmr spectra show that only compound **17d** is in the Z configuration (see Table 3).

EXPERIMENTAL

The nmr spectra were taken with nmr spectrometer Bruker WP-200SY, mps are uncorrected. 4-Phenyldisic acid (**1**, Ar = Ph) was prepared as described earlier [2].

4-Phenyl-2,4-bis(3'-oxocyclohexyl)-3,5-isoxazolidinedione (**10**).

4-Phenyldisic acid (**1**, Ar = Ph, 0.186 g) was dissolved by gentle heating in ethyl acetate (3 ml). 2-Cyclohexenone (0.3 ml) was added. The red color which appeared faded gradually. The mixture was allowed to stand at room temperature for 24 hours. A small fraction of crystals (0.06 g), probably of an insoluble diastereoisomer, precipitated (mp 170°). The remaining product was precipitated as colorless gum by the addition of hexane. The gum gave very similar nmr spectrum; ¹H nmr (deuteriochloroform): δ 7.48 (dd, 2 H, Ph, *ortho*), 7.3 (m, 3 H, Ph, *meta, para*), 4.68 (m, 1 H, N-CH), 2.85-1.45 (m, 17 H, CH and CH₂); ir (Nujol): ν max 1800 (strong), 1710 (very strong),

1600 (medium), 1060 (strong), 755 (strong) cm⁻¹.

Anal. Calcd. for C₂₁H₂₃NO₅: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.99; H, 6.15; N, 3.68.

General Procedure for Isoxazolium Enolate Derivatives.

4-Phenyldisic acid hemihydrate (**1**, Ar = Ph), 0.186 g, was dissolved in 3 ml of either neat or 1 M solution of the diketone heated to boiling and allowed to stand overnight at room temperature wrapped with aluminium foil. The orange or red precipitate was collected, washed with ether and dried *in vacuo*. Experimental results are summarized in Table 2.

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