On the Oximation of Diaryl-β-diketones

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The reaction of asymmetrically substituted β-diketones with hydroxylamine to give 3,5-diarylisoxazoles has been re-investigated, and has been found to occur with a low degree of site-selectivity unless steric effects are operating. The isoxazole that has the more electron-deficient aryl group in position 3 is formed preferentially when the reactions are run with hydroxylamine hydrochloride. When the reactions are performed in a neutral medium, a reversed site-selectivity is observed. Steric effects have a much stronger influence on the selectivity of the reaction: when a substituent is present in the *ortho* position(s) of the phenyl ring, the heterocycle bearing the *ortho*-substituted phenyl group in position 5 is obtained as the sole product both in acidic and in neutral medium.

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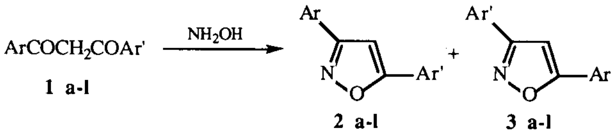
The oximation of β-diketones is the longest known method of preparation of isoxazoles [1]. This method is still widely used for the synthesis of 3,5-dialkyl (or diaryl)-isoxazoles from symmetrical β-diketones. The oximation of asymmetrically substituted β-diketones can *a priori* yield one or another of two regioisomeric 3,5-disubstituted isoxazoles. The reaction with alkyl aryl β-diketones is site-selective, and in all cases so far known the 3-alkyl-5-arylisoxazole is the only product obtained [2].

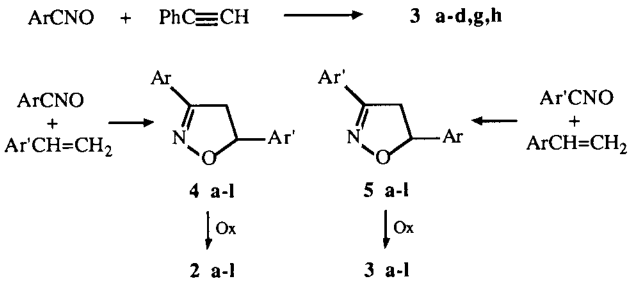
The oximation of asymmetrically disubstituted diaryl β-diketones **1** is less straightforward and can *a priori* lead to two isomeric 3,5-diarylisoxazoles **2** and **3**. Literature data are scanty and somewhat controversial. Several terms have been examined by Barnes and co-workers [3] and the structures of the isoxazoles thus obtained relied on the assumption that the precursor 2-isoxazolines were formed by 1,4-addition of hydroxylamine to the appropriate chalcones. This assumption has been demonstrated erroneous both by spectroscopic [4] and chemical methods [5], and some of the assigned structures have thus been revised. The oximations of some 1-aryl-3-phenylpropane-1,3-diones have subsequently been demonstrated to give rise either to one of the two possible isoxazoles or to a mixture of both isomers [6-9]. Nevertheless, the results were not always consistent, and the structural assignments were partly based on non-unequivocal syntheses (*e.g.* base promoted oximation of chalcone dibromides). Furthermore, the site-selectivity of the reaction might be *p*H-dependent, by analogy to what has been ascertained in the oximation of β-substituted α,β-enones [10].

In the present paper we report a re-investigation of the reaction of hydroxylamine with asymmetrical diaryl β-diketones **1a-l**, whose substituents were chosen so as to evidence both electronic and steric effects. In order to assure structural assignments to the reaction products, both series of isoxazoles **2a-l** and **3a-l** were synthesized by the nitrile oxide route, which allows to establish the nature of the substituent in isoxazole 3-position unequivocally.



(a-l: see Table 1)

The 1,3-cycloaddition of an appropriate nitrile oxide either to a 1-alkyne or to a 1-alkene led to the 3,5-disubstituted isoxazole or 2-isoxazoline, respectively. This latter compound was easily oxidized to the corresponding isoxazole. Very small amounts of the 3,4-disubstituted heterocycle were sometimes evidenced as minor cycloadduct [11]. The exchange of the substituent between the dipole and the dipolarophile allowed to synthesize the couples of isomeric isoxazoles, whose structure were thus assigned in an unambiguous way.



Reaction of the β-diketones **1a-g** with hydroxylamine hydrochloride in boiling methanol yielded a mixture of the two isoxazoles, whereas aryl mesityl β-diketones **1h-l** yielded the 3-aryl-5-mesitylisoxazoles **2h-l** site-specifically. The structures of the products were assigned by comparison of the pmr data with authentic specimens prepared as above indicated. The isomer ratios, calculated by pmr spectroscopy on the crude mixture, are reported in Table 1.

In some cases, results at variance with previous literature data were observed. Indeed, diketone **1a** reacts with

Table 1

Isoxazoles **2** and **3** Obtained by Oximation of Diaryl β-Diketones **1**

2 **3**

			Acidic medium [a]			Neutral medium [b]	
Compound **1**	Ar	Ar'	Reflux hours	Yield %	Ratio **2**:**3**	Yield %	Ratio **2**:**3**
a	Ph	4-MeOC$_6$H$_4$	24	71	60:40	67	60:40
b	Ph	4-MeC$_6$H$_4$	24	76	52:48	65	45:55
c	Ph	4-ClC$_6$H$_4$	24	74	40:60	66	60:40
d	Ph	4-NO$_2$C$_6$H$_4$	24	76	27:73	74	70:30
e	3-NO$_2$C$_6$H$_4$	4-MeOC$_6$H$_4$	24	73	63:37	67	38:62
f	4-NO$_2$C$_6$H$_4$	4-MeOC$_6$H$_4$	48	85	77:23	66	40:60
g	Ph	2-NO$_2$C$_6$H$_4$	24	80	96:4	68	98:2
h	Ph	Mesityl	48	44	100:0	64	100:0
i	4-MeOC$_6$H$_4$	Mesityl	48	48	100:0	35	100:0
j	4-NO$_2$C$_6$H$_4$	Mesityl	48	65	100:0	71	100:0
k	3-NO$_2$C$_6$H$_4$	Mesityl	48	65	100:0	30	100:0
l	2-NO$_2$C$_6$H$_4$	Mesityl	72	8	100:0		

[a] Hydroxylamine hydrochloride in refluxing methanol. [b] Free hydroxylamine in refluxing methanol, followed by treatment with hot concentrated aqueous hydrochloric acid.

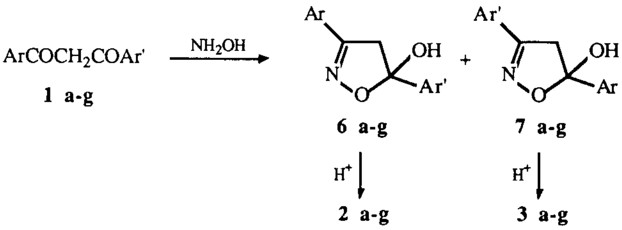
hydroxylamine hydrochloride giving a mixture of the isomeric isoxazoles **2a** and **3a** in a 60:40 ratio, in accordance with the finding of Rao *et al.* [8]. Conversely, other authors report the formation of **2a** only [12,13] or of **3a** [3b,7] as the sole or the predominant product respectively. A 1:1 mixture of isoxazoles was obtained from the diketone **1b**, whereas according to previous authors [7,14] the isoxazole **2b** was reported as the sole product. Surprisingly, already in 1927 Weygand [6] reported **1b** to react with hydroxylamine giving a mixture of isoxazoles. The 73:27 ratio between isoxazoles **3d** and **2d** is in good agreement with the 80:20 value reported by Jerzmanowska [9] (reaction run in acetic acid) and definitively invalidates the result of Nonhebel, who claimed **2d** to be the sole product of the reaction [7]. Compound **1e** gave isoxazoles **2e** and **3e** in a 63:37 ratio, while Barnes [3f] indicates **2c** as the only product. Moreover, the same authors [3g] assigned the wrong structure **3l** to the product derived from the diketone **1l**.

On the whole, the results obtained in acidic medium show some degree of site-selectivity in the oximation of **1a-f**. The major product is the isoxazole bearing in position 3 the more electron-deficient aryl group (in comparison with the other one), by either the presence of an electron-attracting substituent or the absence of an electron-repelling substituent. The extent of this effect, already observed in some previous examples [8,9,15], is quite moderate. The strongly electron-attracting nitro group in **1d** is not sufficient to make the amount of 3-*p*-nitrophenyl-5-phenylisoxazole higher than 73 percent. In close analogy, the presence of the electron-poor pyridyl group in the β-diketone moiety gave a similar result [2d]. Neither with 2-pyridyl- nor with 1-(4-pyridyl)-3-phenyl-1,3-propanedione was the ratio between the 3-pyridyl-5-phenylisoxazole and the 3-phenyl-5-pyridylisoxazole higher than 75:25.

The complete site-selectivity in the reactions of mesityl aryl β-diketones **1h-l** can be ascribed to steric effects: when a substituent is present in the *ortho* position of the ring, the attack of the nucleophile on the carbon atom bearing the *ortho*-substituted aryl is hindered, and only one isoxazole is formed. The same explanation can account for the selectivity observed with the compound **1g**. The very low yield (8%) in isoxazole starting from the diketone **1l**, where both carbonyl carbon atoms bear *ortho*-substituted aryl groups, supports the proposed explanation.

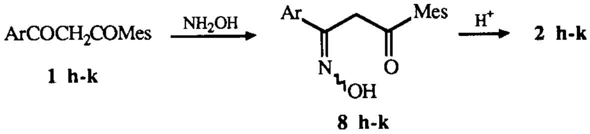
Since the product distribution in the oximation of β-diketones is known to be *p*H-dependent, the β-diketones **1a-k** were reacted with hydroxylamine hydrochloride in the presence of sodium methoxide. When a 1:1 molar ratio between hydroxylamine hydrochloride and sodium methoxide was used (neutral conditions), mixtures of isomeric 3,5-diaryl-5-hydroxy-2-isoxazolines **6a-g** and **7a-g** were obtained from compounds **1a-g**.

The ir and pmr spectral data of the isolated products support their cyclic structure. In particular, the ir spectra show no carbonyl stretching band in region 1650-1800



cm^{-1}, while the pmr spectra are characterized by the presence of an AB system at 3.3-3.9 δ with coupling constants of 17-18 Hz. The data are in accordance with those reported in the literature for 5-hydroxy-2-isoxazolines [16]. The relative position of the two aryl substituents in the 2-isoxazoline ring was determined after transformation into the corresponding isoxazole by acidic treatment. The isomer ratios of the 3,5-diarylisoxazoles thus obtained were measured by pmr spectroscopy and were found to differ from those registered in the absence of sodium methoxide, as shown in Table 1.

When β-diketones **1h-k** were analogously reacted with hydroxylamine under neutral conditions, the β-hydroximino ketones **8h-k** were formed:



According to the open structure, the ir spectra of these compounds show an intense carbonyl band near 1700 cm^{-1} and a broad band at around 3200 cm^{-1} due to the OH stretching. The pmr spectra show a singlet at 4.3-4.5 δ, whose integral corresponds to two protons, and a broad OH signal at 10.45-11.26 δ. β-Oximino ketones **8h-k** are easily converted into the corresponding isoxazoles by treatment with acids [17].

Analysis of the isomer ratios obtained in neutral conditions shows that compounds **1a,g-k** react with the same selectivity as found in acidic conditions, while a reversed site-selectivity is observed with the diketones **1b-e**. The results of the mesityl diketones **1h-k** are remarkable: since they give the same isoxazoles both in acidic and neutral medium, it is reasonable to assume that the free hydroxylamine is the attacking species also in acidic medium [18].

In order to explain the site-selectivity reversal with the diketones **1b-e**, we should recall the multistep mechanism proposed for the oximation of acetylacetone [19]. The rate-determining step depends on the *p*H, and changes from hydroxylamine addition to the substrate (at *p*H <3) to monodehydration of the cyclic intermediate, *i.e.* 3,5-dimethylisoxazolidine-3,5-diol (at *p*H 7-8). If the same mechanism is assumed in our case, with hydroxylamine hydrochloride the attack of the nucleophile is the rate-determining step, thus favouring oximation of the electron-poorer carbonyl. In neutral medium, the dehydration of the intermediate 3,5-diarylisoxazolidine-3,5-diol to the 3,5-diaryl-2-isoxazolin-5-ol is the rate-determining step. When nitrogen nucleophiles attack aryl-substituted carbonyl compounds, the dehydration of the intermediate carbinolamine is known to be accelerated by electron-donating substituents on the aryl group [20]. The isoxazolidine-3,5-diol bearing the more electron-rich group in position 3 should therefore eliminate water more readily than the isomeric one. As a consequence, the isoxazoline bearing the more electron-deficient aryl group in position 5 will preferably be formed, and a reversal of site-selectivity should be expected, in line with the experimental results.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were made on a Carlo Erba CHN analyzer mod.1106. The ir spectra were measured as nujol suspensions on Perkin-Elmer 197 and 983 spectrophotometers; pmr spectra were recorded on a Bruker WP80SY spectrometer equipped with an Aspect 2000 computer and with TMS as internal standard.

Diaryl-β-diketones **1a-l**.

Compounds **1a-l** were prepared according to literature methods [3,6,21-25].

3,5-Diaryl-2-isoxazolines **4** and **5**.

General Procedure.

To an ether solution of arylhydroximic acid chloride (20 mmoles) and of the appropriate styrene (25 mmoles) an ether solution of triethylamine (20 mmoles) was added dropwise under ice cooling. After 2 days at rt the triethylammonium chloride was filtered, and the solution was evaporated under reduced pressure. The residue was purified by crystallization or column chromatography. The known adducts showed physical properties in accordance with literature data; following novel compounds have been characterized.

3-(4'-Methoxy)phenyl-5-(3'-nitro)phenyl-2-isoxazoline (**5e**).

Colorless crystals were obtained from methanol, mp 117-118°, yield 65%.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.27; H, 4.58; N, 9.55.

3-(4'-Nitro)phenyl-5-(4'-methoxy)phenyl-2-isoxazoline (**4f**).

Colorless crystals were obtained from ethanol-isopropyl ether, mp 132-133°, yield 95%.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.63; H, 4.58; N, 9.45.

3-(4'-Methoxy)phenyl-5-mesityl-2-isoxazoline (**4i**).

Colorless crystals were obtained from ethanol-isopropyl ether, mp 130-131°, yield 41%.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.02; H, 7.24; N, 4.85.

3-(4'-Nitro)phenyl-5-mesityl-2-isoxazoline (**4j**).

Colorless crystals were obtained from ethyl acetate, mp 129-130°, yield 78%.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.48; H, 5.74; N, 9.18.

3-(3'-Nitro)phenyl-5-mesityl-2-isoxazoline (**4k**).

Colorless crystals were obtained from ethyl acetate-cyclohexane, mp 141-142°, yield 47%.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.84; H, 5.93; N, 8.95.

3-Mesityl-5-(3'-nitro)phenyl-2-isoxazoline (**5k**).

Colorless crystals were obtained from isopropyl ether, mp 89-91°, yield 94%.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.58; H, 5.69; N, 9.31.

3-(2'-Nitro)phenyl-5-mesityl-2-isoxazoline (**4l**).

Colorless crystals were obtained from methanol, mp 120-121°, yield 71%.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.48; H, 5.69; N, 9.31.

3-Mesityl-5-(2'-nitro)phenyl-2-isoxazoline (**5l**).

Colorless crystals were obtained from ethanol, mp 131-132°, yield 96%.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.48; H, 5.91; N, 9.27.

3,5-Diarylisoxazoles **2** and **3**.

Three general procedures have been employed.

(A) To a mixture of the appropriately substituted benzohydroximic chloride (10 mmoles) and of phenylacetylene (12 mmoles) dissolved in ether an ether solution of triethylamine (10 mmoles) was added dropwise and under ice cooling. After 2 days at rt the crystals are filtered, washed with water, and recrystallized.

(B) The appropriate 3,5-diaryl-2-isoxazoline (3 mmoles) was suspended in glacial acetic acid (50 ml) and heated to reflux. Chromic anhydride (3 equivalents) was added, the mixture was refluxed 4 hours, poured in water and extracted with chloroform. The organic phase was washed with 5% sodium bicarbonate, water, and dried over anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, the isoxazole was purified by column chromatography (Kieselgel 60, 400-230 mesh, eluant benzene).

Table 2

Physical Data of Isoxazoles **2** and **3**

2 **3**

Compound [b]	Preparation method	Yield %	Recrystallization solvent	Mp (°C)	Ref	PMR [a] δ_{H-4} (ppm)	Anal. Formula	Calcd.			Found		
								C	H	N	C	H	N
2a	B	50	MeOH	127-128	13	6.73							
3a	A	65	MeOH	119-120	13	6.80							
2b	C	57	EtOH	137-138	13	6.77							
3b	A	64	MeOH	130-131	13	6.80							
2c	C	77	MeOH	178-180	26	6.81							
3c	A	72	EtOH	176-177	27	6.82							
2d	B	60	$MeOH/CHCl_3$	227-228	28	7.03							
3d	A	22	MeCN	221-223	23	6.92							
2e	B	8	$MeOH/CHCl_3$	178-180	–	6.10 [c]	$C_{16}H_{12}N_2O_4$	64.86	4.08	9.46	64.92	3.95	9.86
3e	B	5	$MeOH/CHCl_3$	186-187	–	6.18 [c]	$C_{16}H_{12}N_2O_4$	64.86	4.08	9.46	64.54	4.03	9.74
2f	C	60	EtOH	206-207	–	6.77	$C_{16}H_{12}N_2O_4$	64.86	4.08	9.46	64.85	4.03	9.33
3f	C	50	EtOH	191-192	–	6.97	$C_{16}H_{12}N_2O_4$	64.86	4.08	9.46	64.73	3.96	9.54
2g	C	88	*iso*-Pr_2O	83-84	28	6.82							
3g	A	63	EtOH	90-91	29	6.65							
2h	C	31	MeOH	65-66	30	6.56							
3h	A	78	MeOH	90-91	31	6.50							
2i	B	29	MeOH	150-151	–	6.50	$C_{19}H_{19}NO_2$	77.79	6.53	4.77	77.68	6.53	4.78
3i	B	40	MeOH	146	–	6.36	$C_{19}H_{19}NO_2$	77.79	6.53	4.77	77.55	6.62	4.64
2j	B	6	MeOH	137-138	–	6.65	$C_{18}H_{16}N_2O_3$	70.11	5.23	9.09	69.88	5.17	9.10
3j	B	10	MeOH	158-159	–	6.70	$C_{18}H_{16}N_2O_3$	70.11	5.23	9.09	70.09	5.30	9.10
2k	B	6	MeOH	120-121	–	6.67	$C_{18}H_{16}N_2O_3$	70.11	5.23	9.09	69.94	5.10	8.97
3k	B	13	MeOH	119-120	–	6.68	$C_{18}H_{16}N_2O_3$	70.11	5.23	9.09	69.98	5.21	9.07
2l	B	5	MeOH	123-124	–	6.35	$C_{18}H_{16}N_2O_3$	70.11	5.23	9.09	69.72	5.22	9.13
3l	C	10	MeOH	119	–	6.48	$C_{18}H_{16}N_2O_3$	70.11	5.23	9.09	70.33	5.24	9.12

[a] Solvent deuteriochloroform [b] For Ar and Ar' see Table 1 [c] Solvent perdeuteriobenzene.

(C) To a benzene solution of the appropriate 3,5-diaryl-2-isoxazoline (2 mmoles) a 5-fold amount in weight of γ-manganese dioxide was added, and the mixture was refluxed, separating the water with a Dean-Stark apparatus. When the reaction was ended, the solvent was evaporated under reduced pressure, and the isoxazole was either directly recrystallized or purified by column chromatography as above.

Physical data of the compound thus isolated are reported in Table 2.

Oximation of Diaryl β-Diketones **1**.

(A) Under Acidic Conditions.

To a suspension of diaryl β-diketones (1 mmole) in methanol (30 ml) hydroxylamine hydrochloride (2 mmoles) was added, and the mixture was refluxed for 24 or 48 hours. The reaction mixture was poured in water and extracted with chloroform (4 x 20 ml). The organic phase was dried and evaporated under reduced pressure. The isomeric ratios were determined on the residue by measuring the relative intensities of the H-4 protons of the two isomeric isoxazoles. The results are reported in Table 1.

(B) Under Neutral Conditions.

To a solution of sodium (4 g-atoms) in methanol (25 ml) hydroxylamine hydrochloride (4 mmoles) was added, and the mixture was stirred until dissolution was complete. The appropriate β-diketone (1 mmole) was added, and the mixture was refluxed for 24-30 hours until tlc analysis showed disappearance of the diketone (with aryl mesityl ketones, the reaction was stopped after 48 hours although some diketone was still present). After cooling 0.3 ml of 37% aqueous hydrochloric acid were added. The mixture was refluxed for 1 hour, poured in water, and extracted with chloroform as above under (A). The isomer ratios were likewise determined, and are also reported in Table 1.

3,5-Diaryl-2-isoxazolin-5-ols **6** and **7**.

To a solution of free hydroxylamine in methanol (100 ml), freshly prepared from equimolar amounts (14 mmoles) of the hydrochloride and sodium methoxide, the appropriate diketone, **1a,c-e**, was added and the mixture was refluxed for 3 hours. After cooling, the precipitated inorganic salts and some unreacted diketone were filtered off. After evaporation of the filtrate under reduced pressure, the presence of the two isomeric 3,5-diaryl-2-isoxazolin-5-ols in the solid residue has been ascertained by ir and pmr spectroscopy of the crude mixture, followed by acidic treatment, which allowed to deduce the isomer ratio as above described. Attempts to isolate isomers in pure form by repeated crystallizations from ethanol were successful only in a few cases. Due to losses during the purification procedure, yields in pure product are very low (5-15%).

3-(4'-Methoxy)phenyl-5-phenyl-2-isoxazolin-5-ol (**7a**).

This compound was obtained as colorless crystals, mp 127-129°; ir (potassium bromide): 3300 (OH), 1610 cm^{-1} (C=N); pmr (deuteriochloroform): δ ppm 3.47 (H_4), 3.65 ($H_{4'}$), $J_{4,4'}$ 17 Hz.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.52; H, 5.67; N, 5.40.

3-Phenyl-5-(4'-chloro)phenyl-2-isoxazolin-5-ol (**6c**).

This compound was obtained as colorless crystals, mp 183-185°; ir (potassium bromide): 3280 (OH), 1600 cm^{-1} (C=N); pmr (deuteriochloroform): δ ppm 3.2 (OH), 3.48 (H_4), 3.69 ($H_{4'}$), $J_{4,4'}$ 18 Hz.

Anal. Calcd. for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 66.04; H, 4.47; N, 5.12.

3-Phenyl-5-(4'-nitro)phenyl-2-isoxazolin-5-ol (**6d**).

This compound was obtained as colorless crystals, mp 149-151°; ir (potassium bromide): 3240 (OH), 1610 cm^{-1} (C=N); pmr (deuteriochloroform): δ ppm 3.3 (OH), 3.51 (H_4), 3.76 ($H_{4'}$), $J_{4,4'}$ 17 Hz.

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.24; H, 4.29; N, 9.92.

3-(4'-Methoxy)phenyl-5-(3'-nitro)phenyl-2-isoxazolin-5-ol (**7e**).

This compound was obtained as colorless crystals, mp 153-155°; ir (potassium bromide): 3340 (OH), 1610 cm^{-1} (C=N); pmr (deuteriochloroform): δ ppm 3.49 (H_4), 3.73 ($H_{4'}$), $J_{4,4'}$ 17 Hz.

Anal. Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.21; H, 4.39; N, 9.04.

3-Phenyl-5-(2'-nitro)phenyl-2-isoxazolin-5-ol (**6g**).

This compound was obtained as colorless crystals, mp 170-171°; ir (potassium bromide): 3240 (OH), 1600 cm^{-1} (C=N); pmr (acetone-d$_6$): δ ppm 3.78 (H_4), 3.97 ($H_{4'}$), $J_{4,4'}$ 18 Hz.

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.14; H, 4.35; N, 9.78.

β-Hydroximinoketones **8**.

The above procedure was repeated exactly starting from diketones **1h-k** modifying the heating time (48 hours instead of 3 hours). The following pure products have been isolated and crystallized from ethanol (yield 15-40%).

3-Hydroximino-1-mesityl-3-phenylpropan-1-one (**8h**).

This compound had mp 119-121°; ir (potassium bromide): 3200 (OH), 1696 cm^{-1} (C=O); pmr (acetone-d$_6$): δ ppm 4.35 (CH_2), 10.65 (OH).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.97; H, 6.82; N, 5.04.

3-Hydroximino-1-mesityl-3-(4'-methoxy)phenylpropan-1-one (**8i**).

This compound had mp 137-138°; ir (potassium bromide): 3230 (OH), 1700 cm^{-1} (C=O); pmr (acetone-d$_6$): δ ppm 4.31 (CH_2), 10.45 (OH).

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.25; H, 6.75; N, 4.68.

3-Hydroximino-1-mesityl-3-(4'-nitro)phenylpropan-1-one (**8j**).

This compound had mp 172-174°; ir (potassium bromide): 3240 (OH), 1693 cm^{-1} (C=O); pmr (acetone-d$_6$): δ ppm 4.47 (CH_2), 11.26 (OH).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.08; H, 5.52; N, 8.50.

3-Hydroximino-1-mesityl-3-(3'-nitro)phenylpropan-1-one (**8k**).

This compound had mp 136-138°; ir (potassium bromide): 3230 (OH), 1695 cm^{-1} (C=O); pmr (acetone-d$_6$): δ ppm 4.46 (CH_2), 11.10 (OH).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.24; H, 5.58; N, 8.56.

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[17] β-Diketones **1a-l** were also reacted using two molar equivalents of sodium methoxide per mole of hydroxylamine hydrochloride (basic conditions). Compounds **1a-g** are not stable under these conditions, giving a retro-condensation with formation of esters and ketones which, in turn, can react with hydroxylamine to yield hydroxamic acids and oximes. Conversely, diketones **1h-l** do not react. The tlc analysis of the reaction mixture shows no presence of isoxazole after 48 hours at reflux.

[18] Taking into account the time necessary for the diketones to react completely, the reactions in neutral medium proceed approximately twice as fast as the reactions in acidic medium.

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