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ORGANIC REACTIONS IN AQUEOUS SOLUTION SYNTHESES OF 4-ARYLIDENE-3-METHYLISOXAZOL-5-ONES

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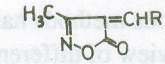
The syntheses of various 4-substituted arylidene-3-methyl-isoxazol-5-ones, have been described in the aqueous medium and their structures established using combustion analysis and spectroscopic techniques. The comparison of previous methods on the subject reveals that the present method offers simple route for the syntheses of arylidene isoxazolones and this widens the scope of reactions in the aqueous medium.



(I)

R = C_6H_4OH-2; C_6H_4OH-3; C_6H_4OH-4; $C_6H_4OCH_3$-2; $C_6H_4OCH_3$-4; C_6H_5-CH = CH

Key words: Arylidene, Isoxazolones, Syntheses in water.

INTRODUCTION

Isoxazolones and related compounds find various industrial uses. Substituted methylisoxazolones have proved to be effective agricultural fungicides for protection against foliage and seedborne diseases. They have demonstrated marked fungicidal activity on a wide range of micro-organisms [1, 2]. The antimicrobial activity of the isoxazolone and its derivatives have been determined by Matolcsy and co-workers [3]. 4-Substituted methylisoxazolones, when converted to their anils, have been found to inhibit the growth of *Staphylococcus aureus* [4]. A large number of 3-substituted (other than methyl) isoxazolones showed varying degree of anti-tuberculosis activity [5]. 2-Aryl-isoxazolones have recently been tested for their activity for the central nervous system [6]. In addition 4',4-acetylidene-*bis*-3-methylisoxazol-5-one gave a colour reaction, which became the basis of colorimetric determination of palladium and uranium [7] Colorimetric determination of gold (III) using 3-methyl-4-vanillidene-isoxazol-5-one has also been reported [8]. In view of the importance of substituted isoxazolones we were interested in the syntheses of these compounds by using simple technique under mild conditions in the aqueous medium. Robinson [9] in 1917, initiated the field of organic syntheses in aqueous solution and demonstrated its applicability in the syntheses of tropinone at room temperature, and later, made many outstanding theoretical contributions in this field. Schöpf [10] made many striking advances in the field of alkaloid syntheses in aqueous solution under varying pH conditions which effect the yield, as well as, the nature of the product. Extensive investigations made by Haley and Maitland [11] at room or below room temperature have shown that water is an effective medium for simple condensations involving substances containing naturally occurring groups (CHO, CO, NH_2, $CO.NH_2$, $CH_2.CN$, $CH_2.CO$, $CO.CH_2CO$ etc.) leading to Schiff bases and quinoxaline, diazepine, pyrimidine, pyridine derivatives. In our earlier communications we have already reported that pyrimidine [12], dihydropyridine [13] and even 3-methyl-4-arylidene isoxazolone [14] can be prepared in the aqueous medium. The present work describes the syntheses of various substituted isoxazolones (I) (R = C_6H_4-OH-2; C_6H_4OH-3; C_6H_4OH-4; $C_6H_4OCH_3$-2; $C_6H_4OCH_3$-4; C_6H_5-CH = CH) in the aqueous medium and further illustrates the potential of this system.

EXPERIMENTAL

Melting points were determined on a Kofler microscope hot stage and are uncorrected. Infrared absorption spectra were recorded on Beckman-IR 5A and Beckman Acculab-10 spectrophotometers. The H-n.m.r. spectra were recorded for CF_3 COOH solutions contain in TMS as external reference using varian T60 and Hitachi Perkin Elmer R-24 60 MMz spectrometers.

All the chemicals used were of analytical grade. The solvents required were distilled before use. Distilled water was used for all experiments. No attempt was made to control the pH developed ($\simeq$ 3.5) in various reaction mixtures.

Method. Ethyl acetoacetate (0.1 mole; 13.0 g) and hydroxylamine hydrochloride (0.1 mole; 6.95 g) were dissolved in water (50 ml) by shaking vigorously and were kept at 10 ± 3°0 for one day. To the above solution, aldehyde (0.1 mole), was added and shaken thoroughly. The formation of isoxazol-5-one commenced a few minutes after the addition of the aldehyde. The mixture was allowed to stand at room temperature for two days and the isoxazol-5-one formed was filtered at the pump, washed several times with small lots of water and dried in a vacuum desiccator for one day. It was purified by recrystallization from ethanol/acetone. Different componds synthesised were:

(i) *4-Salicylidene-3-methylisoxazol-5-one.* Pale yellow needless, (17.6 g; 87%) m.p. 190-191° (lit[2], m.p. 190°). (Found: C, 65.14; H, 4.38; N, 6.78%; $C_{11}H_9NO_3$ requires, C, 65.02; H, 4.43; N, 6.90%). The molecular mass of the product was also confirmed by the molecular ion absorption corresponing to m/z 203.

(ii) *4-(3-Hydroxy benzylidene)-3-methylisoxazol-5-one.* Pale yellow granular crystals, (17.4 g; 86%) m.p. 221.222° with decomposition (lit[15] m.p. 220°) (Found: C, 64.98; H, 4.40; N, 6.83%; $C_{11}H_9NO_3$ requires: C, 65.2; H, 4.43; N, 6.90%. Its I.R. spectrum was superimposable on the corresponding spectrum of an authentic sample.

(iii) *4-(4-Hydroxybenzylidene)-3-methylisoxazole-5-one.* Yellow needles with sligh treddish lustre, (14.6 g; 72%) m.p. 214-215° (decomp) (lit[15] m.p. 215°). (Found: C, 65.08; H, 4.45; N, 6.82%; $C_{11}H_9NO_3$ requires: C, 65.02; H, 4.43; N, 6.90%). Mixed m.p. of the product with an authentic sample did not show any depression an dtheir I.R. spectra were superimposable.

(iv) *4-(2-Methoxybenzylidene)-3-methylisoxazol-5-one.* Pale yellow needles, (16.6 g; 77%) m.p. 157-158°. (Found: C, 66.40; H, 4.97; N, 6.38%; $C_{12}H_{11}NO_3$ requires: C, 66.36; H, 5.07; N, 6.45%). Its n.m.r. in trifluoroacetic acid solution using TMS as external reference gave signals at 8.0 (singlet, 3H, methyl protons), 5.57 (singlet, 3H, OCH_3 protons), 3.5-1.77 τ (multiplet, 5 H, aromatic and olefinic protons).

(v) *4-Anisalidene-3-methylisoxazol-5-one.* Bright yellow needles, (17.5 g; 80%), m.p. 179-180° (lit[16] m.p. 180-181°). (Found: C, 66.29 H, 4.96 N, 6.38% $C_{12}H_{11}NO_3$ required: C, 66.36; H, 5.07; N, 6.65%). Its mixed m.p. with an authentic sample did not show any depression and their I.R. spectra were superimposable. Its n.m.r. spectrum in trifluoroacetic acid using TMS as external reference showed signals at 8.0 (singlet, 3H, methyl protons), 5.47 (singlet, 3H, methoxy protons), 3.34 (doublet, 2H, ortho to OCH_3, J ≃ 9Hz), 2.54 (singlet, 1H olefinic and 1.92 τ (doublet, 2H, meta to OCH_3, J ≃ 9Hz).

(vi) *4-Cinnamylidene-3-methylisoxazol-5-one.* Reddish yellow fluffy crystals, (15.6 g; 73%) m.p. 184-185°. Its I.R. (KBr disc) spectrum gave expected absorption. Its molecular ion (m/z 213) agreed with its molecular formula. (Found: C, 73.18; H, 4.98; N, 6-48%; $C_{13}H_{11}NO_2$ requires: C, 73.24; H, 5.16; N, 6.57%). Its n.m.r. spectrum in trifluoroacetic acid solution (TMS as external reference) gave signals at 8.30 (singlet, 3Hm methyl protons) and 2.5 τ (unresolved multiplets, 8H, aromatic and olefinic protons).

DISCUSSION

The synthesis of 4-arylidene-3-methylisoxazol-5-ones has been the subject of various researchers [2, 16-28]. Comparison of various methods has been briefly outlined in Table 1. A cursory view of different routes (labelled as a, b, c, d, e) for the syntheses of various arylidene isoxazolones has been presented in the reaction schemes.

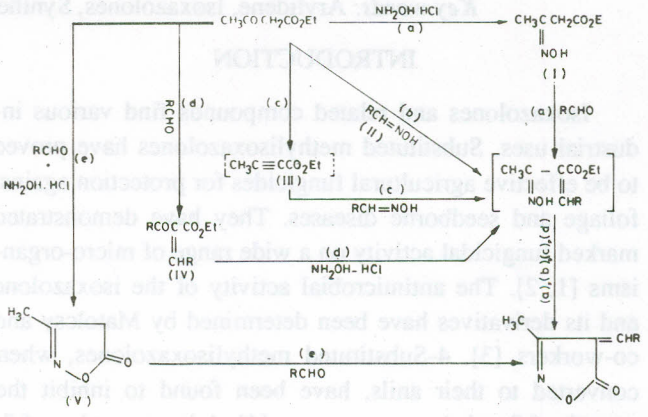


Fig. 1. Reaction schemes syntetic routes of various arylidene isoxazolones.

From the diversity of methods reported for the preparation of arylidene isoxazolones, as outlined in Table 1, it is obvious that no simple method is available for their synthesis. However, in the present work hydroxylamine hydrochloride and ethyl acetoacetate were allowed to react with the desired aromatic aldehyde in purely aqueous medium forming corresponding arylindene isoxazolones in reasonably pure form and in quite good yield ranging from 72 to 96%. The elegance of our method lies in the fact that the entire reaction has been carried out in the aqueous medium. Moreover, there is no necessity of using any external catalyst or othe reagents.

For the present mode of formation of various arylidene isoxazolones it is suggestd that initially ethyl-acetoacetate and hydroxylamine hydrochloride condense together to yield corresponding ester oxime, which very likely cyclises

Table 1. Comparison of various methods for the syntheses of arylidene isoxazolones.

Method of syntheses		Isoxazolone	Yield (%)	Melting point °C
Reactants	Medium			
1. Ethyl acetoacetate hydroxylamine hydrochloride & aldehyde. (17, 19)	Reactants in aqueous-alcoholic solutions in presence of aniline/pyridine and hydrochloric acid	C_6H_5	88	140-145
		$C_6H_5CH{:}CH$	Not reported	175
		C_6H_4OMe-4	Not reported	171-175, 178
2(a) Oxime of ethyl acetoacetate and aldehyde/ketone	Aqueous, in presence of aniline and hydrochloric acid	C_6H_5	Not reported	141
(b) Oxime of acetoacetic acid and aldehyde/ ketone				
(c) Anilide of the oxime of ethyl acetoacetate and aldehyde/ketone. (18, 25, 26)				
3. Ethyl acetoacetate and aromatic aldoxime/ketoxime (2, 16, 20, 21, 22, 27, 28)	Reactants in presence of phosphoric acid or	C_6H_5	65	146-147, 144
	Reactants in presence of zinc chloride	C_6H_4OMe-4		180
		C_6H_4OH-2	Not reported	191
		C_6H_4OH-4	Not reported	223
4. Mono-ester of aromatic aldehyde and hydroxylamine hydrochloride (15)	Absolute alcohol in presence of a few drops of sodium hydroxide (5% aqueous)	C_6H_4OH-3	Not reported	220
		C_6H_4OH-4	Not reported	215
5. 3-Methylisoxazol-5-one, and aldehyde ketone or morpholine salt of isoxazolone & aldehyde/ketone (2, 23,24)	Reactants refluxed/tetrahydrofuran	C_6H_5	40-95	Not reported
6. Ethyl acetoacetate hydroxuylamine hydrochloride and aromatic aldehyde	Aqueous	C_6H_5	73	142-144 (decomp)
		$C_6H_5CH{:}CH$	73	184-185 (")
		C_6H_4OH-2	87	190-191 (")
		C_6H_4OH-3	86	222-223 (")

(Continued .....)

(Table 1, Continue)

(present work as described in the experimental)	C_6H_4OH-4	72	214-215 (")
	C_6H_4OMe-2	77	157-158 (")
	C_6H_4OMe-4	80	179-180 (")
	C_6H_3 (Ome) (OH)-3, 4	96	230-231 (")

to yield 3-methylisoxazol-5-one. Its subsequent treatment with an aldehyde affords the respective arylidene isoxazolone. Our assumption is based on the fact the both ester oxime and 3-methylisoxazol-5-one are reddish liquid and are very soluble in water and these remain in solution. In view of the fact that the oxime of ethyl acetoacetate is quite unstable, it may cyclise to the isoxazolone or hydrolyse to corresponding acid oxime. This acid oxime is reported to have low solubility in water and should, therefore precipitate out. However, no such precipitate was obtained. Therefore, we strongly believe that the formation of arylidene isoxazol-5-ones in our method proceed through the formation of 3-methylisoxazolone.

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