On the Synthesis of Geometric Isomers of 2-Methyl (or Phenyl)-4-[α-arylethylidene]-5(4*H*)-oxazolones

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Several *Z*-2-methyl(or phenyl)-4-[α-arylethylidene]-5(4*H*)-oxazolones **3Z, 4Z** were prepared. The results obtained were compared by diazomethane insertion and condensation procedure. In order to synthesize *E*-2-phenyl-4-[α-arylethylidene]-5(4*H*)-oxazolones **4E** hydrogen bromide isomerization in dry benzene was used.

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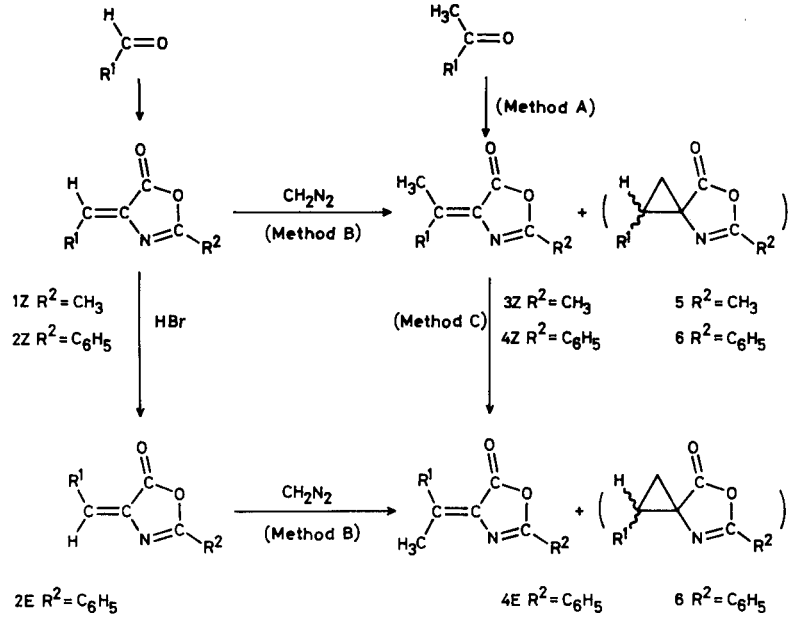
Unsaturated oxazolones are known to be useful intermediates in the synthesis of *N*-acyl-2,3-dehydroamino acids [1]. These latter compounds are precursors of 2,3-dehydroamino acids which have been found in natural products and which posess antimicrobial activity [2]. They are also precursors of chiral amino acids by homogeneous asymmetric hydrogenation [3]. With regard to our interest in synthesizing prochiral enamides containing tetrasubstituted alkene moieties with a view to hydrogenating them [4] we studied the synthesis and isomerism of *(Z/E)*-2-methyl(or phenyl)-4-[α-arylethylidene]-5(4*H*)-oxazolones **3, 4**.

Although earlier authors [5] had reported that acetophenones and hippuric acid could not be condensed under Erlenmeyer conditions, we have previously reported [6] that 2-phenyl derivatives **4** can be prepared by condensing acetophenones and hippuric acid in acetic anhydride and lead acetate with moderate yields as geometric mixtures with the *Z*-isomer predominating. As acetophenones and aceturic acid could not be condensed under the same conditions we tested [7] the action of diazomethane on *(Z/E)*-2-methyl(or phenyl)-4-arylidene-5(4*H*)-oxazolones **1** and **2** and we wish to report that the titled compounds **3Z, 4Z, 4E** can be obtained by homologation from the easily accessible **1** and **2**, the stereochemistry of which was unambiguously determined [8] on the basis of the coupling constants $^{1}H\text{-}C{=}C\text{-}^{13}CO$-. This reaction gave a three-compound mixture, two isomeric spiroazlactones **5, 6**, with the isomer with the departure configuration predominating, and the corresponding *(Z/E)*-2-methyl(or phenyl)-4-[α-arylethylidene]-5(4*H*)-oxazolone **3, 4** which retained the initial oxazolinone geometry. From this mixture *(Z/E)*-2-methyl-(or phenyl)-4-[α-arylethylidene]-5(4*H*)-oxazolones **3Z, 4Z, 4E** can be isolated by column chromatography over silica eluting with benzene as we have recently reported [7] in a detailed study of this procedure for *(Z/E)*-2-methyl(or phenyl)-4-[α-phenylethylidene]-5(4*H*)-oxazolones **3Za, 4Za** and **4Ea**.



Scheme 1

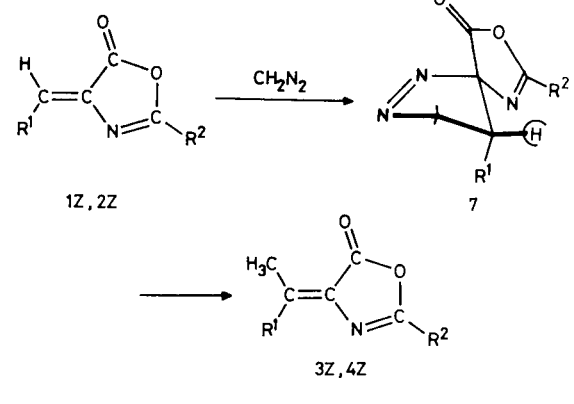
Table 1

Physical Data for 2-Methyl(or Phenyl)-4-[α-arylethylidene]-5(4*H*)-oxazolones

Compound No.	Yields (%) A	B	C	Mp (°C) lit Mp (ref)	Formula	Analyses (%) Calcd./(Found) C	H	N
3Za	—	42	—	116-117 (116-117) [7]	$C_{12}H_{11}NO_2$	71.64 (71.73)	5.47 (5.36)	6.97 (6.95)
3Zb	—	33	—	77-78	$C_{13}H_{13}NO_3$	67.63 (67.48)	5.62 (5.76)	6.06 (5.87)
3Zc	—	28	—	80-81	$C_{13}H_{13}NO_2$	72.55 (72.51)	6.04 (5.93)	6.51 (6.46)
3Zd	—	31	—	61-62	$C_{12}H_{10}ClNO_2$	61.14 (60.98)	4.24 (4.35)	5.94 (5.83)
3Ze	—	28	—	143-144	$C_{12}H_{10}N_2O_4$	58.53 (58.76)	4.06 (3.94)	11.38 (11.07)
4Za	46	48	—	101-103 (104) [6]	$C_{17}H_{13}NO_2$	77.56 (77.84)	4.94 (4.92)	5.32 (5.26)
4Zb	16	50	—	114-116 (104) [6]	$C_{18}H_{15}NO_3$	73.72 (73.58)	5.12 (5.19)	4.78 (4.71)
4Zc	38	30	—	118-119 (118) [6]	$C_{18}H_{15}NO_2$	77.98 (77.75)	5.41 (5.37)	5.05 (5.01)
4Zd	40	20	—	148-150 (144) [6]	$C_{17}H_{12}ClNO_2$	68.57 (68.52)	4.03 (4.01)	4.71 (4.68)
4Ze	40	30	—	167-169 (170) [6]	$C_{17}H_{12}N_2O_4$	66.23 (66.52)	3.89 (3.89)	9.09 (9.06)
4Ea	—	17	90	108-110 (110) [6]	$C_{17}H_{13}NO_2$	77.56 (77.78)	4.94 (4.91)	5.32 (5.28)
4Eb	—	10	90	136-137 (169) [5]	$C_{18}H_{15}NO_3$	73.72 (73.89)	5.12 (4.96)	4.78 (4.63)
4Ec	—	—	92	159-160 (150) [6]	$C_{18}H_{15}NO_2$	77.98 (78.06)	5.41 (5.42)	5.05 (4.98)
4Ed	—	—	89	167-168 (185) [5]	$C_{17}H_{12}ClNO_2$	68.57 (68.65)	4.03 (3.89)	4.71 (4.63)
4Ee	—	—	85	180-181 (180) [6]	$C_{17}H_{12}N_2O_4$	66.23 (66.38)	3.89 (3.92)	9.09 (9.05)

The formation of unsaturated compounds is stereospecific and the configuration of isomeric pairs can be established on the basis of their ^1H nmr spectral data as due to its being in a "*cis*" position with respect to the carbonyl group, the methyl signal of the *Z*-isomers gives rise to a low-field signal. The yield of 5(4*H*)-oxazolone **3, 4** depended on the initial oxazolinone structure and whereas *Z*-isomers were obtained in moderate yields, *E*-isomers were obtained in very low yields (Table 1).

This procedure constitutes an interesting and in some cases improved alternative to the synthesis of *Z*-2-phenyl-4-[α-arylethylidene]-5(4*H*)-oxazolones **4Z** and it is the only way in which *Z*-2-methyl-4-[α-arylethylidene]-5(4*H*)-oxazolones **3Z** can be obtained. The *E*-isomers we tested were obtained in very poor yields and although Rao claims [5] that acetophenones in PPA medium react with hippuric acid to give *E*-2-phenyl-4-[α-arylethylidene]-5(4*H*)-oxazolones **4E** in good yields we could not reproduce these results and so we studied isomerization procedures as a means of synthesizing them and found that treatment of the corresponding *Z*-isomer **4Z** suspended in 48% hydrobromic acid with hydrogen bromide afforded in some cases *E*-isomers in near quantitative yields (*e.g.* **4Ea, 4Ec**). This procedure, however, failed with some substituents (*e.g.* **4Eb, 4Ed,** and **4Ee**), but when isomerization with hydrogen bromide was carried out using dry benzene as solvent, *E*-isomers **4E** were obtained in near quantitative yields in all cases. All attempts to obtain *E*-2-methyl-4-[α-arylethylidene]-5(4*H*)-oxazolones **3E** were unsuccessful (Scheme 1, Table 1).



Scheme 2

The formation of compounds **3Z, 4Z** and **4E** from the corresponding **1Z, 2Z** and **2E** can be explained by the hydride shift in the spiropyrazoline intermediate **7** [9] which has been thought [10] to proceed on the side of the molecule *"trans"* to the leaving group (Scheme 2).

Table 2

Spectral Data for 2-Methyl (or Phenyl)-4-[α-arylethylidene]-5(4*H*)-oxazolones

Compound No.	IR ν max cm^{-1} (C=O)	NMR, δ (deuteriochloroform)
3Za	1770, 1760	2.30 (s, CH_3, 3H), 2.70 (s, CH_3C=, 3H), 7.40-7.60 (m, aromatic, 3H), 7.70-7.90 (m, aromatic, 2H)
3Zb	1750	2.31 (s, CH_3, 3H), 2.71 (s, CH_3C=, 3H), 3.84 (s, OCH_3, 3H), 7.02 (d, H-2, 2H, $J_{2,3}$ = 9 Hz), 7.90 (d, H-3, 2H, $J_{2,3}$ = 9 Hz)
3Zc	1770, 1760	2.28 (s, CH_3, 3H), 2.42 (s, CH_3-Ar, 3H), 2.71 (s, CH_3C=, 3H), 7.33 (d, H-2, 2H, $J_{2,3}$ = 8 Hz), 7.77 (d, H-3, 2H, $J_{2,3}$ = 8 Hz)
3Zd	1770	2.31 (s, CH_3, 3H), 2.70 (s, CH_3C=, 3H), 7.44 (d, H-2, 2H, $J_{2,3}$ = 9 Hz), 7.77 (d, H-3, 2H, $J_{2,3}$ = 9 Hz)
3Ze	1775	2.37 (s, CH_3, 3H), 2.76 (s, CH_3C=, 3H), 8.00 (d, H-2, 2H, $J_{2,3}$ = 9 Hz), 8.42 (d, H-3, 2H, $J_{2,3}$ = 9 Hz)
4Za	1780, 1760	2.75 (s, CH_3C=, 3H), 7.40-7.60 (m, aromatic, 6H), 7.80-8.20 (m, aromatic, 4H)
4Zb	1790, 1760	2.77 (s, CH_3C=, 3H), 3.91 (s, OCH_3, 3H), 7.08 (d, H-2, 2H, $J_{2,3}$ = 9 Hz), 7.40-7.60 (m, Ar, 3H), 8.05-8.20 (m, Ar, 4H)
4Zc	1790, 1760	2.41 (s, CH_3-Ar, 3H), 2.74 (s, CH_3C=, 3H), 7.20-7.65 (m, aromatic, 5H), 7.75-8.25 (m, aromatic, 4H)
4Zd	1790, 1755	2.74 (s, CH_3C=, 3H), 7.45-7.80 (m, aromatic, 5H), 7.75-8.25 (m, aromatic, 4H)
4Ze	1800, 1760	2.83 (s, CH_3C=, 3H), 7.55-7.75 (m, aromatic, 3H), 7.95-8.30 (m, aromatic, 4H), 8.45 (d, H-3, 2H, $J_{2,3}$ = 9 Hz)
4Ea	1795, 1765	2.56 (s, CH_3C=, 3H), 7.30-7.60 (m, aromatic, 8H), 8.00-8.20 (m, aromatic, 2H)
4Eb	1790, 1770	2.66 (s, CH_3C=, 3H), 3.86 (s, OCH_3, 3H), 6.90-7.15 (m, aromatic, 2H), 7.40-7.70 (m, aromatic, 5H), 7.90-8.20 (m, aromatic, 2H)
4Ec	1790, 1765	2,42 (s, CH_3-Ar, 3H), 2.65 (s, CH_3C=, 3H), 7.30-7.70 (m, Ar, 7H), 8.15-8.35 (m, aromatic, 2H)
4Ed	1790, 1770	2.62 (s, CH_3C=, 3H), 7.30-7.60 (m, aromatic, 7H), 7.90-8.20 (m, aromatic, 2H)
4Ee	1795, 1775	2.66 (s, CH_3C=, 3H), 7.45-7.70 (m, aromatic, 5H), 8.00-8.45 (m, aromatic, 4H)

EXPERIMENTAL

All melting points were taken on a Büchi 150 capillary melting point apparatus and are uncorrected. Melting point of *E*-isomers are not well reproduced as compounds isomerize thermically. The ir spectra were measured on a Perkin-Elmer Infrared Spectrophotometer Model 283. The ^1H nmr spectra were recorded at 60 MHz with a Perkin-Elmer Spectrometer Model R-12B in deuteriochloroform with tetramethylsilane as the internal standard. Microanalyses were measured on a Perkin-Elmer 240B analyzer and were in satisfactory agreement with the calculated values. Reported values are given in Table 2.

General Procedures.

Z-2-Methyl(or Phenyl)-4-arylidene-5(4*H*)-oxazolones **1Z** and **2Z**.

Z-2-Methyl(or phenyl)-4-arylidene-5(4*H*)-oxazolones were prepared by the general procedure employed by Rao [1] condensing the benzaldehydes with aceturic or hippuric acid in the presence of acetic anhydride and sodium acetate.

E-2-Phenyl-4-arylidene-5(4*H*)-oxazolones **2E**.

E-2-Phenyl-4-arylidene-5(4*H*)-oxazolones were prepared by the general procedure used by Rao [1], by isomerization of the corresponding *Z*-isomers in saturated hydrobromic acid.

Z/E-2-Methyl(or Phenyl)-4[α-arylethylidene]-5(4*H*)-oxazolones **3Z, 4Z** and **4E**.

Method A.

A mixture of the carbonyl compound (0.3 mole), hippuric acid (0.1 mole), lead acetate (0.05 mole), acetic anhydride (0.3 mole) and tetrahydrofuran (80 ml) freshly distilled over potassium hydroxide was heated under reflux for 24 hours. The contents were poured on crushed ice, the azlactone was filtered (**4Zd, 4Ze**) or extracted with carbon tetrachloride (**4Za, 4Zb, 4Zc**), the extracts washed with sodium hydrogen carbonate solution and dried over anhydrous sodium sulphate, the solution evaporated under reduced pressure and the solid filtered. The solid azlactone was washed with water, dried and then crystallized from ethanol/water to give the pure *Z*-isomer.

Method B.

The corresponding **1Z, 2Z** or **2E** (1 g) dissolved in 10 ml of tetrahydrofuran freshly distilled over potassium hydroxide was treated with an ethereal solution of diazomethane (from *N*-methyl-*N*-nitrosourea) until no initial oxazolone was noticed by thin layer chromatography, then calcium chloride was added to destroy the excess of diazomethane. The solution was filtered and concentrated *in vacuo* and the resultant yellow oil was dried. The whole yellow solid was dissolved in the minimum amount of warm benzene, and the three compounds of the mixtures were separated by column chromatography (silica gel, 70-230 mesh), using benzene as the eluting agent, to afford analytically pure samples of the oxazolones.

Method C.

A solution of the corresponding **4Z** (1 g) in benzene was saturated with hydrogen bromide gas. The reaction mixture was left overnight at 5°, the solid was filtered and washed with ethanol to afford the pure *E*-isomer **4E** in near quantitative yields.

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