

Cycloaddition Reactions of Mesoionic Oxazolones.

Reactions of Δ^2 -Oxazolin-5-one with Cinnamaldehyde Anils

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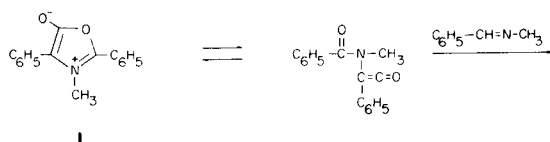
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Cinnamaldehyde anils have been reacted with several mesoionic oxazolones. The products thus obtained are α -pyridones and structures of these compounds have been fully established.

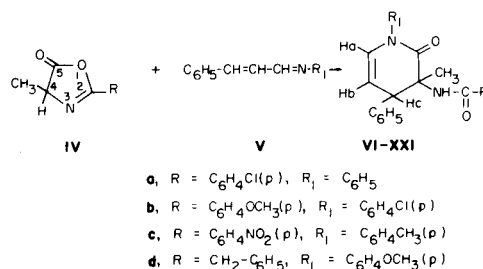
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1,3-Dipolar cycloaddition reactions of mesoionic Δ^2 -oxazolin-5-ones with various multiple bonds have been reported (1-8). In these cycloadditions 1:1 adducts initially formed lose a molecule of carbon dioxide to give stable, interesting heterocycles. The mesoionic oxazolone I when reacted with the benzylidene methylamine β -lactam structure II was obtained. The formation of II was interpreted as involving valence tautomeric ketene intermediate (9).



In the case of cinnamaldehyde anils the azlactone III gave only α -pyridones (10). In cycloaddition reactions of azlactones it has been observed that the substituents on the Δ^2 -oxazolin-5-one ring greatly influence the course of the reaction. No reaction could occur when an azlactone

derived from α -benzoylamidoisobutyric acid was reacted with dimethylacetylene dicarboxylate (1). In this investigation we report our findings, when we used azlactones IV derived from DL- α -alanine and substituted aryl chlorides and cinnamaldehyde anils V.



Equimolar quantities of oxazolone IVa and anil Va were dissolved in dry benzene and allowed to stand overnight at room temperature. On removal of the solvent under vacuum a pasty material which could be purified by thin layer chromatography was obtained as a white crystalline solid in 74% yield, mp 198-199°. The structural assignment of VI is supported by elemental as well as spectral data, nmr (deuteriochloroform): 270 MHz δ 1.38 (3H, s, CH₃), 5.32 (1H, unresolved t, Hc), 5.38 (1H, dd, J = 8 Hz, 2.5 Hz, Hb), 5.89 (1H, broad s, NH), 6.42 (1H, dd, J = 8 Hz, 2.5 Hz, Ha), 7.23-7.45 (12H, m), 7.68 (2H, m); ir (nujol):

Table 1
Spectral Data of Oxazolones IV

Compound No.	ν max cm ⁻¹	PMR (deuteriochloroform) δ	Mass Spectra m/e (%)
IVa	1820, 1800, 1650	1.60 (3H, d, J = 7 Hz), 4.42 (1H, q, J = 7 Hz) 7.52 (2H, m), 7.91 (2H, m)	209 (20), 181 (15), 165 (18), 139 (100)
IVb	1823, 1795, 1645	1.57 (3H, d, J = 7 Hz), 3.85 (3H, s), 4.40 (1H, q, J = 7 Hz), 7.08 (2H, m), 7.88 (2H, m)	205 (35), 177 (28), 161 (30), 135 (100)
IVc	1820, 1795, 1640, 1550	1.61 (3H, d, J = 7 Hz), 4.46 (1H, q, J = 7 Hz) 7.82-8.25 (4H, m)	220 (65), 192 (45), 176 (60), 150 (100)
IVd	1830, 1804, 1650	1.48 (3H, d, J = 7 Hz) 3.78 (2H, d), 4.22 (1H, m), 7.34 (5H, m)	189 (45), 161 (12), 145 (10), 119 (15), 91 (100)

Table 2

Physical and Analytical Data for Pyridones

Compound No.	R	R ₁	Yield %	Mp °C	Molecular Formula	C	Analyses %			Halogen
							Calcd.	(Found)		
IV	<i>p</i> -C ₆ H ₄ Cl	C ₆ H ₄	74	198-199	C ₂₅ H ₂₁ ClN ₂ O ₂	72.11 (72.01)	5.10 (5.17)	6.73 (6.53)	8.41 (8.38)	
VII	<i>p</i> -C ₆ H ₄ Cl	<i>p</i> -C ₆ H ₄ Cl	72	215-216	C ₂₅ H ₂₀ Cl ₂ N ₂ O ₂	66.67 (66.82)	4.44 (4.39)	6.22 (6.15)	15.55 (15.65)	
VIII	<i>p</i> -C ₆ H ₄ Cl	<i>p</i> -C ₆ H ₄ CH ₃	78	183-184	C ₂₆ H ₂₃ ClN ₂ O ₂	72.56 (72.72)	5.35 (5.40)	6.51 (6.35)	8.14 (8.24)	
IX	<i>p</i> -C ₆ H ₄ Cl	<i>p</i> -C ₆ H ₄ OCH ₃	80	188-189	C ₂₆ H ₂₃ ClN ₂ O ₃	69.95 (70.07)	5.16 (5.10)	6.28 (6.25)	7.85 (7.65)	
X	<i>p</i> -C ₆ H ₄ OCH ₃	C ₆ H ₅	80	177-178	C ₂₆ H ₂₄ N ₂ O ₃	75.73 (75.58)	5.82 (5.85)	6.79 (6.85)	—	
XI	<i>p</i> -C ₆ H ₄ OCH ₃	<i>p</i> -C ₆ H ₄ Cl	82	150-151	C ₂₆ H ₂₃ N ₂ O ₃	69.96 (69.81)	5.16 (5.17)	6.28 (6.30)	7.84 (7.79)	
XII	<i>p</i> -C ₆ H ₄ OCH ₃	<i>p</i> -C ₆ H ₄ CH ₃	85	155-156	C ₂₇ H ₂₆ N ₂ O ₃	76.06 (76.05)	6.10 (6.15)	6.57 (6.60)	—	
XIII	<i>p</i> -C ₆ H ₄ OCH ₃	<i>p</i> -C ₆ H ₄ OCH ₃	90	175-176	C ₂₇ H ₂₆ N ₂ O ₄	73.30 (73.40)	5.88 (5.78)	6.34 (6.44)	—	
XIV	<i>p</i> -C ₆ H ₄ NO ₂	C ₆ H ₅	70	163-164	C ₂₅ H ₂₁ N ₃ O ₄	70.26 (70.30)	4.92 (4.85)	9.83 (9.75)	—	
XV	<i>p</i> -C ₆ H ₄ NO ₂	<i>p</i> -C ₆ H ₄ Cl	68	210-211	C ₂₅ H ₂₀ ClN ₃ O ₄	65.07 (75.01)	4.34 (4.44)	9.11 (9.10)	7.59 (7.49)	
XVI	<i>p</i> -C ₆ H ₄ NO ₂	<i>p</i> -C ₆ H ₄ CH ₃	72	204-205	C ₂₆ H ₂₃ N ₃ O ₄	70.75 (70.73)	5.22 (5.20)	9.52 (9.54)	—	
XVII	<i>p</i> -C ₆ H ₄ NO ₂	<i>p</i> -C ₆ H ₄ OCH ₃	75	160-161	C ₂₆ H ₂₃ N ₃ O ₅	68.27 (68.21)	5.03 (5.01)	9.19 (9.21)	—	
XVIII	CH ₂ C ₆ H ₅	C ₆ H ₅	75	156-157	C ₂₆ H ₂₄ N ₂ O ₂	78.79 (78.65)	6.06 (6.03)	7.07 (7.05)	—	
XIX	CH ₂ C ₆ H ₅	<i>p</i> -C ₆ H ₄ Cl	72	186-187	C ₂₆ H ₂₃ ClN ₂ O ₂	72.56 (72.43)	5.35 (5.32)	6.51 (6.57)	8.14 (8.09)	
XX	CH ₂ C ₆ H ₅	<i>p</i> -C ₆ H ₄ CH ₃	77	207-208	C ₂₇ H ₂₆ N ₂ O ₂	79.02 (78.99)	6.34 (6.37)	6.83 (6.80)	—	
XXI	CH ₂ C ₆ H ₅	<i>p</i> -C ₆ H ₄ OCH ₃	80	184-185	C ₂₇ H ₂₆ N ₂ O ₃	76.06 (76.01)	6.10 (6.08)	6.57 (6.67)	—	

ν max 1640, 1675, 1700, 3350 cm⁻¹. When the mass spectra was recorded under electron impact conditions the compound did not show a molecular ion peak but by chemical ionization, using methane gas, the molecular ion peak was observed (M + 1)⁺ at m/e 417 (27.96%) and major fragments at 262 (50.21%), 261 (13.99%), 209 (14.66%), 208 (75.43%), 158 (33.51%), 156 (100%). The mass spectrum confirms the following fragmentation pattern.

The reaction was generalized by varying the substituents on position 2 of the oxazolone IV and reacting them with differently substituted anils V. It was observed that change of the substituent at position 2 of the oxazolone IV does not change the course of reaction and in all the cases we obtain only α -pyridones, without any evidence for the formation of the β -lactam or 1,3-dipolar cycloadduct. The characteristics of these pyridones are recorded in Tables 2 and 3. However, it was observed that when an aryl group at position 2 of the oxazolone IV contains an electron withdrawing group in the *para* position the reaction is slower and in the case of electron donating group it is faster than when an unsubstituted aryl group is present.

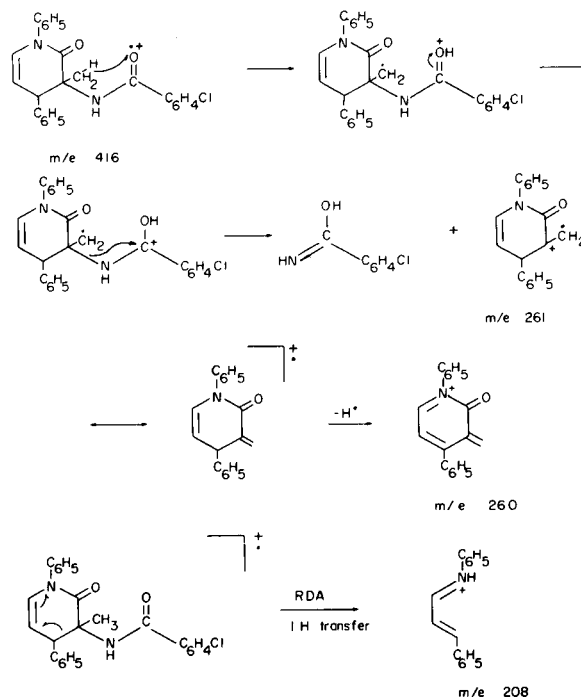


Table 3
Spectral Data of Pyridones

Compound No.	IR ν max cm^{-1}	PMR (deuteriochloroform) δ	Mass Spectra m/e (%)
VI	3350, 1700, 1670, 1640	1.38 (3H, s), 5.32 (1H, unresolved t), 5.38 (1H, dd, J = 8 Hz, 2.5 Hz), 5.89 (1H, broad s), 6.42 (1H, dd, J = 8 Hz, 2.5 Hz), 7.23-7.45 (12H, m), 7.68 (2H, m)	417 (28), 262 (50), 261 (14), 209 (15), 208 (75), 158 (33.5), 156 (100)
VII	3350, 1690, 1675, 1640	1.38 (3H, s), 5.32 (1H, unresolved t), 5.38 (1H, dd, J = 8 Hz, 2.5 Hz), 5.91 (1H, broad s), 6.43 (1H, dd, J = 8 Hz, 2.5 Hz), 7.20-7.46 (11H, m), 7.68 (2H, m)	451 (30), 296 (50), 295 (15), 243 (15), 242 (75), 158 (33.5), 156 (100)
VIII	3350, 1700, 1680, 1635	1.38 (3H, s), 2.36 (3H, s), 5.31 (1H, unresolved t), 5.38 (1H, dd, J = 8 Hz, 2.5 Hz), 5.90 (1H, broad s), 6.40 (1H, dd, J = 8 Hz, 2.5 Hz), 7.11-7.45 (11H, m), 7.67 (2H, m)	431 (28), 276 (50), 275 (15), 223 (15), 222 (75), 158 (33.5), 156 (100)
IX	3350, 1695, 1675, 1635	1.38 (3H, s), 3.83 (3H, s), 5.31 (1H, unresolved t), 5.39 (1H, dd, J = 8 Hz, 2.5 Hz), 5.90 (1H, broad s), 6.39 (1H, dd, J = 8 Hz, 2.5 Hz), 6.86-7.60 (11H, m), 7.67 (2H, m)	447 (25), 292 (50), 291 (15), 239 (15), 238 (70), 158 (33.5), 156 (100)
X	3355, 1695, 1670, 1635	1.36 (3H, s), 3.88 (3H, s), 5.31 (1H, unresolved t), 5.41 (1H, dd, J = 8 Hz, 2.5 Hz), 5.96 (1H, broad s), 6.40 (1H, dd, J = 8 Hz, 2.5 Hz), 6.86-7.68 (12H, m), 8.03 (2H, m)	413 (35), 262 (25), 208 (25), 206 (26), 153 (100), 152 (36)
XI	3355, 1690, 1675, 1640	1.36 (3H, s), 3.88 (3H, s), 5.32 (1H, unresolved t), 5.40 (1H, dd, J = 8 Hz, 2.5 Hz), 5.97 (1H, broad s), 6.40 (1H, dd, J = 8 Hz, 2.5 Hz), 6.85-7.68 (11H, m), 8.03 (2H, m)	447 (32), 296 (22), 242 (22), 206 (26), 153 (100), 152 (36)
XII	3360, 1700, 1680, 1640	1.36 (3H, s), 2.36 (3H, s), 3.88 (3H, s), 5.31 (1H, unresolved t), 5.41 (1H, dd, J = 8 Hz, 2.5 Hz), 5.96 (1H, broad s), 6.38 (1H, dd, J = 8 Hz, 2.5 Hz), 6.86-7.70 (11H, m), 8.03 (2H, m)	427 (34), 276 (25), 222 (25), 206 (27), 153 (100), 152 (35)
XIII	3350, 1705, 1685, 1645	1.36 (3H, s), 3.83 (3H, s), 3.88 (3H, s), 5.31 (1H, unresolved t), 5.41 (1H, dd, J = 8 Hz, 2.5 Hz), 5.96 (1H, broad s), 6.37 (1H, dd, J = 8 Hz, 2.5 Hz), 6.86-7.70 (11H, m), 8.03 (2H, m)	443 (30), 292 (25), 238 (25), 206 (28), 153 (100), 152 (34)
XIV	3330, 1695, 1660, 1645, 1525	1.39 (3H, s), 5.30 (1H, unresolved t), 5.38 (1H, dd, J = 8 Hz, 2.5 Hz), 6.05 (1H, broad s), 6.40 (1H, dd, J = 8 Hz, 2.5 Hz), 7.23-7.89 (12H, m), 8.22 (2H, m)	428 (48), 262 (100), 261 (60), 260 (25), 208 (60), 167 (20)
XV	3335, 1700, 1660, 1640, 1535	1.39 (3H, s), 5.30 (1H, unresolved t), 5.39 (1H, dd, J = 8 Hz, 2.5 Hz), 6.05 (1H, broad s), 6.41 (1H, dd, J = 8 Hz, 2.5 Hz), 7.25-7.90 (11H, m), 8.22 (2H, m)	462 (45), 296 (100), 295 (60), 294 (25), 242 (59), 167 (25)
XVI	3330, 1695, 1660, 1645, 1525	1.39 (3H, s), 2.36 (3H, s), 5.30 (1H, unresolved t), 5.38 (1H, dd, J = 8 Hz, 2.5 Hz), 6.05 (1H, broad s), 6.39 (1H, dd, J = 8 Hz, 2.5 Hz), 7.22-7.89 (11H, m), 8.22 (2H, m)	442 (46), 276 (100), 275 (58), 274 (22), 222 (59), 167 (21)
XVII	3335, 1798, 1655, 1640, 1535	1.39 (3H, s), 3.82 (3H, s), 5.30 (1H, unresolved t), 5.38 (1H, dd, J = 8 Hz, 2.5 Hz), 6.05 (1H, broad s), 6.39 (1H, dd, J = 8 Hz, 2.5 Hz), 6.86-7.89 (11H, m), 8.22 (2H, m)	458 (45), 292 (100), 291 (60), 290 (25), 238 (58), 167 (22)
XVIII	3310, 1700, 1665, 1648	1.14 (3H, s), 3.60 (2H, d, J = 4.7 Hz), 5.10 (1H, unresolved t), 5.24 (2H, m), 6.30 (1H, dd, J = 9.2 Hz, 3.1 Hz), 7.20-7.42 (15H, m)	397 (100), 262 (30), 261 (25), 208 (48), 136 (15)
XIX	3315, 1699, 1667, 1645	1.14 (3H, s), 3.60 (2H, d, J = 4.7 Hz), 5.10 (1H, unresolved t), 5.24 (2H, m), 6.31 (1H, dd, J = 9.2 Hz, 3.1 Hz), 7.22-7.45 (14H, m)	431 (100), 296 (30), 295 (26), 242 (47), 136 (16)
XX	3315, 1700, 1667, 1645	1.14 (3H, s), 2.36 (3H, s), 3.60 (2H, d, J = 4.7 Hz), 5.10 (1H, unresolved t), 5.24 (2H, m), 6.28 (1H, dd, J = 9.2 Hz, 3.1 Hz), 7.10-7.38 (14H, m)	411 (100), 276 (30), 275 (28), 222 (50), 136 (17)
XXI	3312, 1698, 1666, 1642	1.14 (3H, s), 3.60 (2H, d, J = 4.7 Hz), 3.81 (3H, s), 5.10 (1H, unresolved t), 5.24 (2H, m), 6.28 (1H, dd, J = 9.2 Hz, 3.1 Hz), 6.90-7.36 (14H, m)	427 (100), 292 (29), 291 (24), 238 (45), 136 (14)

EXPERIMENTAL

Melting points were taken in open capillary tubes on a Büchi apparatus and are uncorrected. The nmr spectra were recorded on a Varian T-60 or Bruker 270 MHz spectrometer and chemical shift values are recorded in δ units (parts per million), relative to TMS as the internal standard. The ir spectra were recorded on a Specord 75 IR spectrometer in nujol or on a Perkin Elmer 237 B IR spectrometer in potassium bromide discs. Mass spectra were recorded in the chemical ionization mode using methane as the reagent gas and by the electron impact method on an AEI MS 30 instrument.

General Procedure for the Preparation of Oxazolone IV.

n-Acyl- α -amino acids were prepared by the usual benzylation procedure from DL- α -alanine and aroyl chlorides. *N*-Acyl- α -amino acid (0.01 mole) and acetic anhydride (10 ml) were heated on a water bath at 55-60° (bath temperature) for 20 minutes to get a clear solution and excess of acetic anhydride was removed under vacuum. Oxazolones IVa, IVb and IVc were obtained as crystalline solids and recrystallized from benzene-petroleum ether (60-80°) mixture giving melting points 107-108°, 89-90° and 127-128°, respectively. In the case of oxazolone IVd the residue remaining after acetic anhydride removal was found to be analytically pure and was used directly for reaction purposes.

Reactions of Oxazolone IVa with Cinnamaldehyde Anils V.

To a solution of cinnamaldehyde anil V (0.005 mole) in dry benzene (5 ml) was added at room temperature. The mixture was allowed to stand for 12 hours, benzene was removed under vacuum and the residue which remained was purified by thin layer chromatography using silica gel as the adsorbent and benzene-ethyl acetate 14:1 as the developing solvent system. The compounds VI-IX were recrystallized from a benzene-petroleum ether (60-80°) mixture.

Reaction of Oxazolone IVb with Cinnamaldehyde Anils V.

The oxazolone and anils were reacted as above. The residue remaining after removal of benzene was purified by thin layer chromatography using silica gel as the adsorbent and benzene-ethyl acetate 7:1 as the developing solvent system. The pyridones X-XIII were recrystallized from a benzene-petroleum ether (60-80°) mixture.

Reactions of Oxazolone IVc with Cinnamaldehyde Anils V.

The oxazolone and anils were reacted as above. The residue remaining

after removal of benzene was purified by thin layer chromatography using silica gel as adsorbent and benzene-ethyl acetate 10:1 as developing solvent system. The pyridones XIV-XVII were recrystallized from a benzene-petroleum ether (60-80°) mixture.

Reactions of Oxazolone IVd with Cinnamaldehyde Anils V.

Solutions of the oxazolone (0.005 mole) and the anils (0.005 mole) in dry benzene (10 ml) were refluxed for 30 minutes and then allowed to stand overnight at room temperature. Pyridone XXI separated as a white crystalline solid from the reaction mixture and was filtered and recrystallized from benzene. Pyridones XVIII-XX were obtained by purifying the residue remaining after benzene removal by thin layer chromatography using silica gel as the adsorbent and benzene-ethyl acetate 7:1 as the developing solvent system. The compounds were finally recrystallized from a benzene-petroleum ether (60-80°) mixture.

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