1-Azadienes in Heterocyclic Synthesis. Reaction of 1-*N*-Alkyl-1-azapenta-1,3-dienes with Mesoionic Oxazolones

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1-*N*-Alkyl-1-azapenta-1,3-dienes **2** smoothly reacted with various mesoionic oxazolones **1** to afford 3,4-dihydro-2-pyridones **3** in excellent yields and there was no evidence for the formation of any products arising from the cycloaddition on the carbon-carbon double bond or on the azomethine function.

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Imines with their well explored chemistry are of great importance as synthons for building up three, four, five and six membered heterocycles [1-4]. The chemistry of 1-azabutadienes is relatively less explored for their potential utilization in various heterocyclic synthesis [5-8]. During our investigation on 1-azabutadiens, which contain two potential sites of attack, 1,3-dipoles like benzonitrile oxide [9,10], nitrile imines [11] and aziridines [12,13], reacted at the carbon-nitrogen double bond only and the carbon-carbon double bond remained intact. In contrast Ohshiro *et al.* recently reported the reaction of cinnamylidene-*N*-butylamine with *N*-phenylbenzonitrile imine and observed cycloaddition onto both carbon-nitrogen and carbon-carbon double bonds [14]. Further, these authors when reacted cinnamylidene-*N*-butylamine with benzonitrile-*p*-nitrobenzylide, addition occurred at the carbon-carbon double bond, without any addition products arising from the carbon-nitrogen double bond. Recently Moskal reported an interesting cycloaddition reactions of 1,4-diazabutadienes with heterocumulenes [15]. 1-Azadienes are also known to undergo 1,4-cycloaddition reactions but the nature of the product is very much dependent on the nature of the azadiene [16]. Azlactones are well known mesoionic compounds [17] and react with a variety of multiple bonds with the elimination of carbon dioxide to provide novel heterocycles [18-22].

While studying the cycloaddition reactions of mesoionic oxazolones we observed the formation of β-lactams with imines [23]. However, reactions of 1-azadienes with mesoionic oxazolones gave two sets of products, 2-pyridones and acetylated products depending upon the nature of the azadienes [24]. Now we describe the reaction of 1-*N*-alkyl-1-azapenta-1,3-dienes with mesoionic oxazolones where we observed exclusively the formation of 3,4-dihydro-2-pyridones [25].

Results and Discussion.

Our investigations [24] coupled with the literature

Table 1

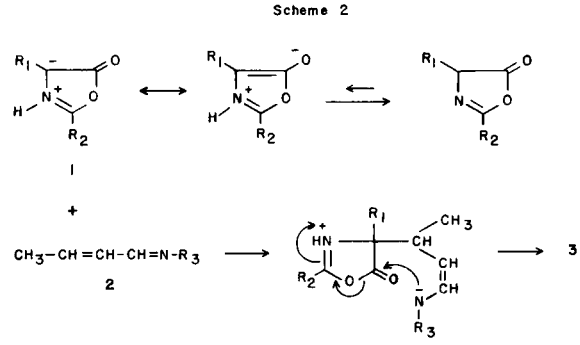
Characteristics of 3,4-Dihydro-2-pyridones **3a-i**

Compound No.	R_1	R_2	R_3	Yield %	Mp °C	Molecular Formula	Analyses (%) Calculated (Found) C	H	N
3a	C_6H_5	C_6H_5	C_6H_{11}	78	160-161	$C_{25}H_{28}N_2O_2$	77.32	7.21	7.21
							(77.23	7.22	7.28)
3b	CH_3	C_6H_5	C_6H_{11}	88	168-169	$C_{20}H_{26}N_2O_2$	73.62	7.97	8.59
							(73.70	7.91	8.52)
3c	CH_3	$C_6H_4NO_2(p)$	C_6H_{11}	80	180-182	$C_{20}H_{25}N_3O_4$	64.69	6.74	11.32
							(64.81	6.79	11.21)
3d	CH_3	$C_6H_4Cl(p)$	C_6H_{11}	85	190-191	$C_{20}H_{25}N_2O_2Cl$	66.57	6.93	7.76
							(66.65	6.82	7.81)
3e	CH_3	$CH_2C_6H_5$	C_6H_{11}	78	175-176	$C_{21}H_{28}N_2O_2$	74.12	8.23	8.23
							(74.25	8.31	8.18)
3f	CH_3	$C_6H_4OCH_3(p)$	C_6H_{11}	90	145-146	$C_{21}H_{28}N_2O_3$	70.78	7.86	7.86
							(70.88	7.79	8.90)
3g	CH_3	$C(CH_3)_3$	C_6H_{11}	70	184-185	$C_{19}H_{30}N_2O_2$	71.69	9.43	8.80
							(71.78	9.34	8.88)
3h	C_6H_5	C_6H_5	$CH(CH_3)_2$	65	150-152	$C_{22}H_{24}N_2O_2$	75.86	6.89	8.04
							(75.72	6.78	8.00)
3i	CH_3	C_6H_5	$CH(CH_3)_2$	72	159-160	$C_{17}H_{22}N_2O_2$	71.33	7.69	9.79
							(71.18	7.60	9.89)

reports [14,16] strongly indicate that the nature of the products obtained in cycloaddition reactions of 1-azadienes is very much dependent upon the imine employed and this prompted us to study the reaction of 1-*N*-alkyl-1-azapenta-1,3-dienes **2** with differently substituted mesoionic oxazolones **1** (Scheme 1). When equimolar quantities of the oxazolone **1a** [26] and the azadiene **2a** were stirred at room temperature for 8 hours under nitrogen removal of solvent under vacuum gave a pasty material which yielded a white crystalline solid, mp 160-161°, yield 78%, on further work up and recrystallization from benzene. The stuctural assignment **3a** to this product rests on elemental as well as spectral data. The ir (potassium bromide) showed absorptions at 3345, 1678 and 1665 cm^{-1} indicating the presence of NH and two amidocarbonyl groups respectively. Also, this clearly ruled out the formation of any β-lactam of the type **4**, anhydride of the type **5** and acetylated adduct of the type **7**, which are likely to absorb well above 1740, 1770 and 1800 cm^{-1} respectively. The nmr (360 MHz, deuteriochloroform): δ 1.09 (d, 3H), 1.38-1.89 (m, 10H), 3.78 (unresolved dd, 1H), 4.45 (m, 1H), 4.95 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.09 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.28 (s, 1H), 7.00-7.60 (m, 8H), 7.88 (m, 2H). The doublet of doublet at δ 4.95 has been assigned to Hb and is coupled with Ha (J = 8 Hz) and Hc (J = 2.5 Hz). The doublet of doublet at δ 6.09 has been assigned for Ha and coupled with Hb (J = 8 Hz) and Hc (J = 2.5 Hz). The unresolved doublet of doublet at δ 3.78 was assigned to Hc. Mass spectra when recorded in chemical ionization mode showed molecular ion $(M+1)^+$ peak at m/e 389 (6.5%) and other major fragments at 267 (100%), 185 (80.5%), 152 (14.5%), 105 (50.8%), 77 (35.8%). The observed mass spectra and nmr spectra clearly ruled out the possibility of any 1-pyrroline **6** type structure. Similarly the oxazolone **1a** reacted with the azadiene **2b** to give the 2-pyridone **3h** in 65% yield.

The reaction was generalised by varying the substituents in positions 2 and 4 of the oxazolone **1** and reacting them with differently substituted 1-azadienes **2**. The characteristics of these pyridones **3** are recorded in Tables 1 and 2. Oxazolone **1** when prepared by ethyl chloroformate triethylamine method [27] gave parallel results with that of acetic anhydride method.

Scheme 2



Although in all the cases 2-pyridones **3** were obtained without any evidence for the formation of β-lactam, 1,3-dipolar cycloadduct or acetylated adduct, the rate of reaction was found to be dependent on the nature of substituents present in the oxazolone **1**. In general, the presence of an aryl group with an electron donating group at the *para* position of C-2 enhanced the rate of reaction. However, the oxazolone **1** with a methyl group at C-4 was found to react faster in comparison to when a phenyl group was present.

Mechanism of 3,4-Dihydro-2-pyridone **3** Formation.

Huisgen described the reaction of 3-methyl-2,4-diphenyloxazolium-5-oxide (münchnone) with imines to give β-lactams and assumbed the involvement of a thermal equilibrating ketene tautomer [28]. As the reactions for the formations of 3,4-dihydro-2-pyridones **3**, could proceed at room temperature or below, we assume that the reaction might have been initiated by the attack of an azlactone in its carbanion form at the C=C bond of the azadiene and subsequent attack of nucleophilic nitrogen yielded the 2-pyridone as shown in Scheme 2.

The proposed mechanism is also supported by the observed fact that the oxazolone **1** with methyl group at C-4 reacted faster in comparison to when phenyl group was present, as in the latter case the anion formed would be less available at C - 4 due to its possible delocalization in to the aromatic ring.

Scheme - 1.

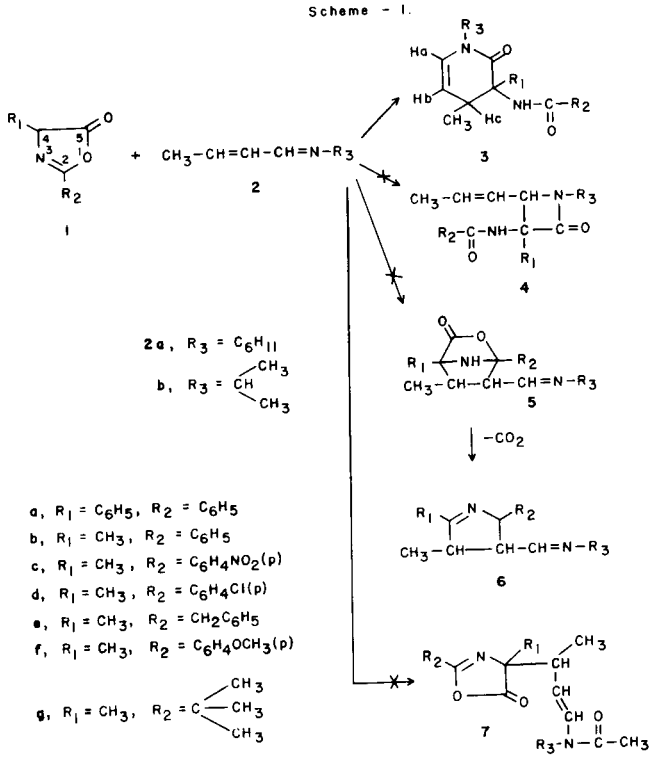


Table 2

Spectral Data of Compounds **3a-i**

Compound no.	IR ν max cm^{-1}	PMR (deuteriochloroform) δ	Mass Spectra m/e (%)
3a	3345, 1678, 1665, 1645	1.09 (d, 3H), 1.38-1.89 (m, 10H), 3.78 (unresolved, dd, 1H), 4.45 (m, 1H), 4.95 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.09 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.28 (s, 1H), 7.00-7.60 (m, 8H), 7.88 (m, 2H)	389 (6.5), 267 (100), 185 (80.5), 152 (14.5), 105 (50.8), 77 (35.8)
3b	3340, 1685 1668, 1642	1.06 (d, 3H), 1.36-1.89 (m, 13H), 3.78 (unresolved dd, 1H), 4.46 (m, 1H), 4.98 (dd, 1H), J = 8 Hz, 2.5 Hz), 6.07 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.29 (s, 1H), 7.30-7.54 (m, 3H), 7.87 (m, 2H)	327 (3.8), 205 (73.1), 152 (7.7), 123 (100), 105 (42.3), 77 (40.7)
3c	3338, 1690, 1660, 1640, 1525	1.06 (d, 3H), 1.36-1.89 (m, 13H), 3.79 (unresolved dd, 1H), 4.47 (m, 1H), 4.97 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.09 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.30 (s, 1H), 7.40-7.67 (m, 2H), 7.92 (m, 2H)	372 (5.5), 205 (100), 152 (11.5), 150 (15.8), 123 (78.5), 122 (20)
3d	3315, 1689, 1665, 1640	1.08 (d, 3H), 1.35-1.89 (m, 13H), 3.80 (unresolved dd, 1H), 4.40 (m, 1H), 4.95 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.06 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.32 (s, 1H), 7.30-7.50 (m, 2H), 7.90 (m, 2H)	361 (4.5), 205 (80.5), 152 (31.5), 139 (20.5), 123 (100), 111 (38.6)
3e	3312, 1690 1666, 1642	1.05 (d, 3H), 1.28-1.88 (m, 13H), 3.60 (d, 2H, J = 4.7 Hz), 3.80 (unresolved dd, 1H), 4.44 (m, 1H), 4.98 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.06 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.32 (s, 1H), 7.10-7.54 (m, 5H)	341 (6.5), 205 (100), 152 (18.7), 123 (93.5), 119 (40.8)
3f	3350, 1690 1670, 1635	1.06 (d, 3H), 1.36-1.88 (m, 13H), 3.78 (unresolved dd, 1H), 3.88 (s, 3H), 4.46 (m, 1H), 4.98 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.10 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.28 (s, 1H), 7.30-7.50 (m, 2H), 7.86 (m, 2H)	357 (8.2), 205 (94.5), 152 (12.5), 135 (15.8), 123 (100), 77 (31.5)
3g	3320, 1690 1665, 1640	1.00-1.98 (m, 25H), 3.80 (unresolved dd, 1H), 4.40 (m, 1H), 4.95 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.09 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.50 (s, 1H)	319 (3.1), 205 (80.5), 152 (12.5), 123 (100)
3h	3328, 1675 1660, 1642	1.06-1.48 (m, 9H), 2.20-2.60 (m, 1H), 3.78 (unresolved dd, 1H), 4.88 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.00 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.25 (s, 1H), 7.00-7.60 (m, 8H), 7.89 (m, 2H)	349 (6.4), 227 (100), 185 (94.5), 152 (10.5), 105 (42.7), 77 (28.5)
3i	3335, 1678, 1662, 1640	1.06-1.50 (m, 12H), 2.20-2.60 (m, 1H), 3.80 (unresolved dd, 1H), 4.90 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.05 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.28 (s, 1H), 7.30-7.50 (m, 3H), 7.89 (m, 2H)	287 (5.2), 165 (82.5), 123 (100), 112 (12.5), 105 (45.5), 77 (38.4)

EXPERIMENTAL

The melting points were taken in open capillary tubes on a Büchi apparatus and are uncorrected. The nmr spectra were recorded on Brucker 360 MHz or Varian 90 MHz specrometers and chemical shift values are recorded in δ units (parts per million) relative to TMS as an internal standard. The ir spectra were determined as potassium bromide discs recorded on a Perkin-Elmer 237B IR spectrometer. Mass spectra were recorded in the chemical ionization mode using methane as reagent gas or by the electron impact method on a AEI MS 30 instrument. Azadienes **2a,b** were prepared by standard methods. Activated basic alumina was prepared by activating laboratory reagent grade basic alumina at 400° for 2 hours.

Preparation of the Oxazolone **1a**.

The oxazolone **1a** was prepared by cyclodehydration of *N*-benzoyl-*C*-phenylglycine following the literature method reported by Huisgen [18]. This yielded a white crystalline solid which was recrystallized twice from petroleum ether (bp 60-80°) (yield 60%), mp 90-92° (lit [18] mp 103.5-105.5°). Further recrystallization from petroleum ether did not raise the mp; ir (potassium bromide): 1820, 1780 and 1635 cm^{-1}; nmr (deuteriochloroform): δ 2.33 (s, 3H), 7.20-7.98 (m, 11H); ms: M^+ at m/e (relative intensity), 237 (100), other major peaks at m/e 209 (77), 193 (41), 105 (80). To prepare acetic anhydride free oxazolone **1a**, the solution of the oxazolone **1a** (mp 90-92°) in dry benzene was passed through a short column of activated basic alumina. The eluted solution was evaporated under vacuum, the residue left was dissolved in minimum amount of warm dry benzene and diluted with warm petroleum ether (bp 60-80°) until slightly turbid. After scratching the solution was stored under nitrogen in a refrigerator for 12 hours. The separated white crystalline solid was filtered and recrystallized from petroleum ether, yield 45%, mp 103.5-105.5° (same as reported by Huisgen), spectral data same as reported [18].

General Procedure for the Preparation of Oxazolones **1b-g**.

N-Acyl-α-amino acids were prepared by the usual benzoylation procedure from DL-α-alanine and aroyl chlorides. *N*-Acyl-α-amino acid (0.02 mole) and acetic anhydride (20 ml) were heated on a water bath at 55-60° (bath temperature) for 20 minutes to get a clear solution and the excess of acetic anhydride was then removed under vacuum. The oxazolones **1c**, **1d** and **1f** were obtained as crystalline solids and recrystallized from benzene-petroleum ether (60-80°) mixture giving mps 127-128°, 107-108° and 89-90° respectively. In case of the oxazolones **1b**, **1e** and **1g** the residue remaining after acetic anhydride removal were found to be analytically pure and were used directly for reaction purposes.

Reaction of the Oxazolone **1** with Azadiene **2**. General Procedure.

To a stirred solution of the azadiene **2** (0.005 mole) in dry benzene (5 ml) was added a solution of the azlactone **1** (0.005 mole) in dry benzene (5 ml) and the mixture was further stirred at room temperature for 8 hours under nitrogen. Benzene was then removed under reduced pressure and the residue remaining was repeatedly washed with hot petroleum ether (60-80°)-benzene mixture to obtain the corresponding pyridone. All the compunds were recrystallized from benzene.

Preparation of the Oxazolone **1** by the Ethyl Chloroformate-Triethylamine Method.

The oxazolone **1** was prepared by this method following the literature procedure [27]. To a suspension of *N*-acyl-α-amino acid (0.01 mole) in dry benzene (40 ml) containing triethylamine (1.01 g, 0.01 mole) was added

ethyl chloroformate (1.08 g, 0.01 mole) and the mixture was shaken at room temperature until a clear solution was obtained and triethylamine hydrochloride separated. The precipitated hydrochloride was filtered and washed twice with benzene. Benzene was removed under vacuum and the residue left was dissolved in dry benzene (10 ml). This solution of the oxazolone **1** (0.01 mole) was used for reactions with the azadienes **2**. Oxazolones **1** prepared by this method smoothly reacted with the azadienes **2** to yield the pyridones **3** in comparable yields.

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[26] The oxazolone **1a** when prepared following the literature method reported by Huisgen [18] gave mp 90-92° (lit mp 103.5-105.5°) and its nmr spectra showed the presence of acetic anhydride presumably available in the crystal lattice. Acetic anhydride could be removed by passing the benzene solution of the oxazolone **1a**, mp 90-92°, through a short column of activated basic alumina. The oxazolone **1a** thus obtained showed mp 103.5-105.5° (same as reported by Huisgen). Both these oxazolones **1a** containing acetic anhydride (mp 90-92°) and free of acetic anhydride (mp 103.5-105.5°) reacted with azadienes **2** to give 3,4-dihydro-2-pyridones **3** only.

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