Reaction of 2-Phenyl-4-methyl-Δ^2-oxazolin-5-one with Imines. A Convenient Synthesis of 3-Amido-β-lactams

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Azlactone **3a** reacted with furan-2-aldehyde and thiophene-2-aldehyde imines to give corresponding 3-amido-β-lactams in good yields.

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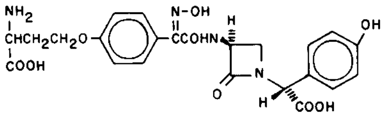
Because of several β-lactam antibiotics in clinical practice, extensive efforts have been made to further modify these molecules and have better understanding of structure and activity relationship [1-4]. Over the past several years various groups have been engaged in the synthesis of simple β-lactams [1,3]. These syntheses had been of preparative interest only, until the discovery of the non-classical β-lactam antibiotic nocardicin (**1**) [5]. The isolation of broad spectrum antibiotic thienamycin (**2**) demonstrated that the presence of the thiazole ring and the 6-amido side chain is not absolutely essential for optimal biological activity [6].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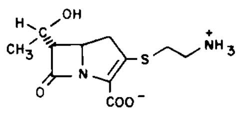
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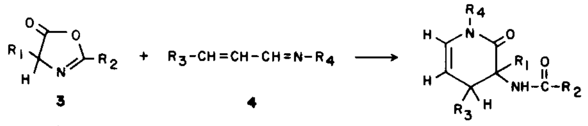
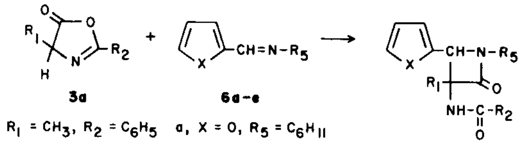
Münchone (3-methyl-2,4-diphenyl-oxazolium-5-olat) a mesoionic oxazolone which participates in 1,3-dipolar cycloaddition reactions with a variety of multiplet bonds gave β-lactams when reacted with imines, the formation of these products was explained *via* a ketene intermediate [7]. This mesoionic oxazolone also gave β-lactams when reacted with conjugated imines [8]. In contrast, azlactones (Δ^2-oxazolin-5-ones) **3** reacted with conjugated imines **4** to yield α-pyridones **5** and there was no evidence for the formation of β-lactams or 1,3 dipolar cycloadducts [8-11].


3 **4** **5**

R_1 = Alkyl, Aryl
R_2 = Aryl, Alkyl
R_3 = Aryl, Alkyl, Heterocyclic
R_4 = Aryl, Alkyl

Now we report the reaction of azlactone **3a** with imines derived from furan-2-aldehyde and thiophene-2-aldehyde where corresponding β-lactams **7a-e** were obtained in good yields. The choice of furan as well as thiophene unit annulation with the β-lactam unit was made because of their already established biological importance.


3a **6a-e** **7a-e**

$R_1 = CH_3$, $R_2 = C_6H_5$
a, X = O, $R_5 = C_6H_{11}$
b, X = O, $R_5 = CH_3$
c, X = O, $R_5 = C_2H_5$
d, X = S, $R_5 = CH_3$
e, X = S, $R_5 = C_2H_5$

Equimolar quantities of azlactone **3a** [10] and imine **6a** dissolved in dry toluene when stirred at 0° for 1 hour, then allowed to stand overnight at room temperature on working up gave white crystalline solid mp 165° in 80% yield. The ir (potassium bromide) spectrum showed strong band at 1750 cm^{-1} indicating the presence of β-lactam, the other bands at 1655 cm^{-1} and 3225 cm^{-1} correspond to amido CO and NH respectively. The nmr spectrum (270 MHz, deuteriochloroform): δ 1.05-2.17 (13H, m), 3.50 (1H, m), 5.17 (1H, s), 6.42 (2H, m), 6.52 (1H, broad s), 7.27-7.50 (4H, m), 7.80 (2H, m) was consistent with the structure **7a**. The mass spectrum showed molecular ion at m/e 352 (0.2%) and major fragments at 306 (5%), 277 (7%), 227 (80%), 226 (85%), 175 (20%), 149 (25%), 105 (100%).

Similar β-lactams **7b-e** were prepared and their characteristics are recorded in Tables 1 and 2. In the case of imines where the *N*-aryl group was present the reaction was found to be very slow and no significant amount of β-lactam could be observed. This suggests that the possible mechanistic pathway for this reaction could be the addition of oxazolone in its carbanion form on to C=N bond followed by attack of nucleophilic nitrogen. The reaction appears to be quite general and provides a convenient method for the synthesis of differently substituted 3-amido-β-lactams.

EXPERIMENTAL

Melting points were taken in open capillary on a Büchi apparatus and are uncorrected. The nmr spectra were recorded on Bruker 270 MHz or Varian A-60T instrument and chemical shift values are recorded in δ parts per million relative to internal standard (tetramethylsilane). Mass spectra were recorded on AEI MS 30 instrument. The ir spectra were recorded on Perkin Elmer 237B ir spectrometer in potassium bromide discs or chloroform solutions.

Table 1

Physical and Analytical Data for β-Lactams

Compound No.	R_1	R_2	X	R_5	Yield %	Mp (°C)	Molecular Formula	Analyses (%) Calcd. (Found) C	H	N
7a	CH_3	C_6H_5	O	C_6H_{11}	80	165	$C_{21}H_{24}N_2O_3$	71.59 (71.42)	6.82 (6.79)	7.95 (7.82)
7b	CH_3	C_6H_5	O	CH_3	75	35	$C_{16}H_{16}N_2O_3$	67.60 (67.85)	5.63 (5.71)	9.86 (9.89)
7c	CH_3	C_6H_5	O	C_2H_5	65	Oil	$C_{17}H_{18}N_2O_3$	68.46 (68.62)	6.04 (6.15)	9.39 (9.21)
7d	CH_3	C_6H_5	S	CH_3	62	Oil	$C_{16}H_{16}N_2O_2S$	64.00 (64.18)	5.33 (5.12)	9.33 (9.45)
7e	CH_3	C_6H_5	S	C_2H_5	60	Oil	$C_{17}H_{18}N_2O_2S$	64.97 (64.81)	5.73 (5.81)	8.92 (8.73)

Table 2

Spectral Data of β-Lactams

Compound No.	IR ν maz cm^{-1}	PMR (deuteriochloroform) δ ppm	Mass Spectra m/e (%)
7a	3225, 1750, 1655	1.05-2.17 (13H, m), 3.50 (1H, m), 5.17 (1H, s), 6.42 (2H, m), 6.52 (1H, broad s), 7.27-7.50 (4H, m), 7.80 (2H, m)	352 (0.2), 306 (5), 277 (7), 277 (80), 226 (85), 175 (20), 149 (25), 105 (100)
7b	3250, 1750, 1660	1.45 (3H, s), 2.60 (3H, s), 5.16 (1H, s), 6.45 (2H, m), 6.53 (1H, broad s), 7.28-7.51 (4H, m), 7.80 (2H, m)	284 (0.5), 238 (80), 209 (50), 175 (20), 171 (40), 149 (20), 148 (70), 105 (100)
7c	3255, 1750, 1660	1.10 (3H, m), 1.42 (3H, s), 2.83 (2H, m), 5.15 (1H, s), 6.45 (2H, m), 6.52 (1H, broad s), 7.25-7.52 (4H, m), 7.82 (2H, m)	298 (0.6), 252 (100), 227 (10), 223 (70), 175 (15), 171 (8), 149 (70), 148 (75), 105 (85)
7d	3300, 1750, 1660	1.45 (3H, s), 2.60 (3H, s), 5.18 (1H, s), 6.80-7.50 (7H, m), 7.80 (2H, m)	300 (0.2), 254 (100), 225 (50), 191 (7), 175 (25), 151 (30), 105 (80)
7e	3300, 1750, 1662	1.10 (3H, m), 1.45 (3H, s), 2.85 (2H, m), 5.18 (1H, s), 6.80-7.50 (7H, m), 7.80 (2H, m)	314 (0.4), 268 (100), 243 (7), 239 (60), 175 (20), 165 (40), 105 (90)

Imines **6a-e** were prepared by known methods and their bp values agreed with those recorded in the literature.

Preparation of 3-Amido-β-lactams **7a-e**. General Procedure.

To a stirred solution of imine **6** (0.01 mole) in dry toluene (10 ml) at 0° was added dropwise a cooled solution azlactone **3a** (0.01 mole) in dry toluene (5 ml). The mixture was stirred at 0° for 1 hour and then allowed to stand overnight at room temperature, which resulted in the separation of gummy material. On removal of toluene under vacuum and washing the residue left with benzene-petroleum ether mixture compounds **7a,b** were obtained as white crystalline solids. Compounds **7c-e** were obtained by purifying the residue left after removal of toluene, on thin layer chromatography using silica gel as adsorbent and chloroform methanol 9:1 as developing solvent system.

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