MESOIONIC OXAZOLONES IN HETEROCYCLIC SYNTHESIS : A FACILE SYNTHESIS OF UNCONVENTIONAL β-LACTAMS

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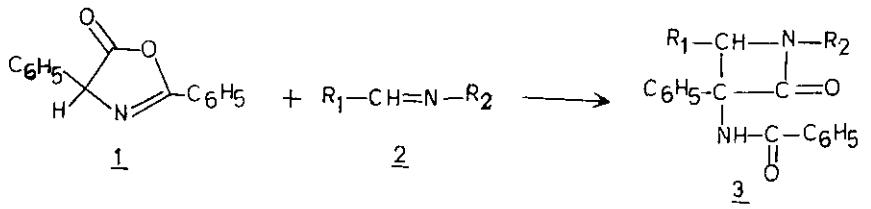
Abstract - Reaction of 2,4-diphenyl-2-oxazolin-5-one 1 with imines 2 gave novel 3-amido-β-lactams 3 in good yields.

Typical reactions and spectroscopic properties of 2,4-diphenyl-2-oxazolin-5-one 1 have confirmed its classification as a mesoionic compound[1-5]. Its reactions with a variety of multiple bonds such as alkenes[5-7], alkynes[8-10] and heteromultiple bonds[11] have been reported to afford an interesting range of heterocycles. In all these reactions it was assumed that an initially unstable 1:1 adduct is formed which loses carbondioxide to yield stable heterocycles. Recently Rodriquez et al. reported an interesting reaction of 2,4-diphenyl-2-oxazolin-5-one with nitrosobenzene, where these authors have been able to isolate 1:1 adduct thus confirming Huisgen's original postulate in these cycloaddition reactions[12]. However, reaction of 2,4-diphenyl-2-oxazolin-5-one 1 with imines does not appear to have been systematically investigated. In this communication we reported our preliminary results of the reaction of oxazolin 1 with differently substituted imines 2, where unconventional 3-amido-β-lactams 3 were obtained in good yields[13,14] (Scheme 1).

Reaction between 2,4-diphenyl-2-oxazolin-5-one[5] 1 and imine 2a was carried out by dissolving their equimolar quantities in dry benzene and refluxing the mixture under nitrogen for 2 h, followed by allowing this reaction mixture to stand overnight at room temperature. During this time a white crystalline solid separated out which was crystallized from ethyl acetate to obtain 3a, mp 171-172°C in 75% yield. The structural assignment 3a; Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.19;

H, 5.35; N, 7.44; Found : C, 70.45; H, 5.21; N, 7.38 to this product rests on elemental as well as spectral data. The IR (KBr) spectrum showed a strong band at 1750 cm^{-1} indicating the presence of β-lactam ring, other bands at 1660, 3040 and 3320 cm^{-1} correspond to amidocarbonyl, alkene C-H stretching and NH groups respectively. The ^1H NMR (60 MHz, $CDCl_3$) δ: 1.06(3H,t), 3.22(2H,q), 5.67(1H,m), 7.16-7.60(12H,m), 7.90(2H,m) was consistent with the structure 3a. Mass spectrum showed molecular ion at m/e 376 (0.5%) and other major fragments at 305 (80), 304 (85), 237 (25), 138 (38), 112 (29), 105 (100).



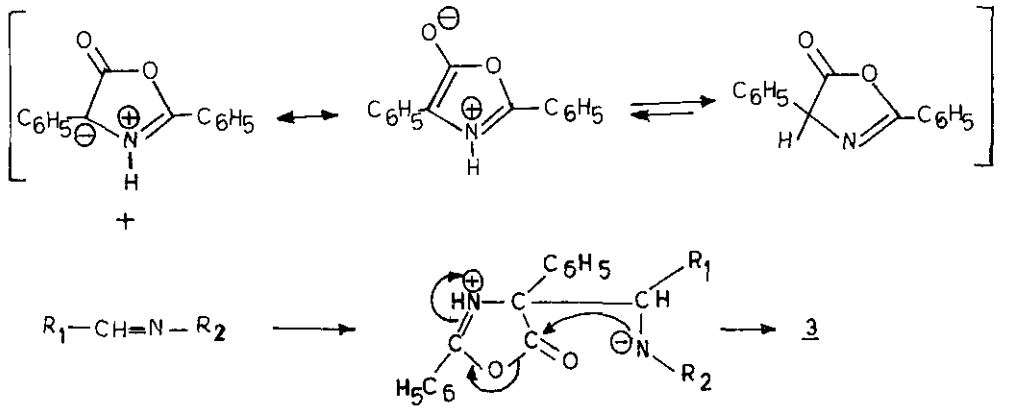
1 + 2 → 3

3		R_1	R_2	Yield (%)	Mp (°C)
a	=		C_2H_5	75	171-172
b	=		CH_3	70	154-155
c	=		C_6H_{11}	80	160-161
d	=		C_2H_5	65	Oil
e	=		CH_3	60	Oil
f	=	C_6H_5	CH_3	78	165-166

Scheme 1

Similarly β-lactams 3b,c and 3f were prepared. In the case of 3d and 3e, the products were separated through preparative tlc on silica gel using chloroform-methanol 9:1 as developing solvent system. Microanalytical and spectral data of the β-lactams 3 are recorded in the Table. In case of imines with N-aryl groups the reaction did not proceed (vide tlc). This suggests the plausible mechanism for this reaction could be the addition of oxazolone in its carbanion form on to C=N bond followed by the attack of nucleophilic nitrogen (Scheme 2). As in case of N-aryl imines anion formed at nitrogen would be further delocalized into

the aromatic ring and therefore nucleophilic attack by nitrogen may have been precluded. Reaction appears to be quite general in case of N-alkyl imines and provides a convenient method for the synthesis of novel unconventional β-lactams.



Scheme 2

Table. Microanalytical and spectral data of 3-amido-β-lactams (3b-f)

Compound	Molecular formula	Analysis % Calculated (Found) C	H	N	IR ν max(cm^{-1})	^{1}H nmr ($CDCl_3$/TMS) δ (ppm)	MS M$^+$ m/e
3b	$C_{21}H_{18}N_2O_2S$	69.59 (69.50	5.01 4.81	7.73 7.52)	3328,3045, 1750,1662	2.98(3H,s),5.68(1H,m), 7.15-7.58(12H,m),7.88 (2H,m)	362
3c	$C_{26}H_{26}N_2O_3$	75.34 (75.51	6.32 6.08	6.76 6.89)	3270,3050, 1750,1655	1.05-2.17(10H,m),3.50 (1H,m),5.35(1H,s), 6.42(2H,m),6.52(1H, broad s),7.20-7.55 (9H,m),7.85(2H,m)	414
3d	$C_{22}H_{20}N_2O_3$	73.32 (73.52	5.59 5.44	7.77 7.61)	3275,3040, 1750,1660	1.10(3H,t),3.25(2H,q), 5.30(1H,s),6.42(2H,m), 6.55(1H,broad s),7.21-7.56(9H,m),7.88(2H,m)	360
3e	$C_{21}H_{18}N_2O_3$	72.82 (72.61	5.24 5.12	8.09 8.21)	3280,3045, 1750,1660	2.95(3H,s),5.30(1H,s), 6.40(2H,m),6.58(1H, broad s),7.20-7.55 (9H,m),7.89(2H,m)	346
3f	$C_{23}H_{20}N_2O_2$	77.51 (77.69	5.66 5.50	7.86 7.69)	3275,3040, 1750,1657	2.96(3H,s),5.62(1H,m), 7.16-7.65(14H,m), 7.90(2H,m)	356

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REFERENCES

1. W. Baker and W.D. Ollis, Quart. Rev., 1957, 11, 15.
2. C.A. Ramsden, "Comprehensive Organic Chemistry", Ed., by D.H.R. Barton and W.D. Ollis, Volume 4, p. 1171, Pergamon Press, Oxford, 1979.
3. W.D. Ollis and C.A. Ramsden, Adv. Heterocyclic Chem., 1976, 19, 1.
4. C.G. Newton and C.A. Ramsden, Tetrahedron, 1982, 38, 2965.
5. R. Huisgen, H. Gotthardt and H.O. Bayer, Tetrahedron Letters, 1964, 481.
6. R. Huisgen, H. Gotthardt and H.O. Bayer, Chem. Ber., 1970, 103, 2368.
7. I.A. Benages and S.M. Albonico, J.Org.Chem., 1978, 43, 4273.
8. H. Gotthardt, R. Huisgen and H.O. Bayer, J.Am.Chem.Soc., 1970, 92, 4340.
9. H.O. Bayer, H. Gotthardt and R. Huisgen, Chem.Ber., 1970, 103, 2356.
10. R. Huisgen, H. Gotthardt and H.O. Bayer, Angew.Chem., 1964, 76, 185.
11. J.M. Riordan and C.H. Stammer, Tetrahedron Letters, 1976, 1247.
12. H. Rodriquez, H. Pavez, A. Marquez and P. Navarrete, Tetrahedron, 1983,39,23.
13. The discovery of monobactum, a broad spectrum antibiotics has generated a considerable interest in the synthesis of monocyclic unconventional β-lactams. H. Aoki, H. Sakai, M. Kohsaka, T. Konomi, Y. Kubochi, J. Hosoda, E. Iguchi and H. Imanaka, J. Antibiot., 1976, 29, 492.
14. a G. Albers-Schönberg, B.H. Arison, O.D. Heusens, J. Hirshfield, K. Hoogsteen, E.A. Kazcka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratclift, E.A. Walton, L.J. Ruswinble, R.B. Morin and B.G. Christensen, J.Am.Chem.Soc., 1978, 100, 6491; b R. Huisgen has described the formation of amido-β-lactams from 3-methyl-2,4-diphenyloxazolium-5-oxide (münchnone) assuming the involvement of a ketene tautomer : E. Funke and R. Huisgen, Chem. Ber., 1971, 104, 3222; R. Huisgen, E. Funke, F.C. Schaefer and R. Knorr, Angew.Chem.Int.Ed., 1967, 6, 367.

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