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A NOVEL CHEMICAL TRANSFORMATION OF 3-VINYL-4-SUBSTITUTED-2-AZETIDINONES[1]

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Summary: Transformation of α-vinyl-β-lactams involving an anti-Markovnikov addition reaction is described. The action of $PdCl_2$-CuCl-O_2 on the vinyl group leads to terminal aldehydes instead of the expected methyl ketones. The intermediate prepared by the reduction of this aldehyde group followed by conversion of the primary hydroxyl group to a chloro derivative was rearranged in good yield to a 1,2-diaryl-3-carbomethoxypyrrolidine.

Earlier work[2] in our laboratory has shown that the addition of crotonyl chloride to imines in the presence of triethylamine leads to the formation of α-vinyl-β-lactams (1). The stereochemistry of the β-lactams formed in this reaction was unpredictable ranging from pure cis to pure trans and a mixture of cis and trans products in varying proportions as revealed by the ^{1}H-NMR spectra of the crude material. The isomeric β-lactams could, however, be separated by chromatography. This synthesis was used later by Zamboni and Just[3] for preparing a number of substituted 2-azetidinones. We have revived our work on α-vinyl-β-lactams in order to explore their synthetic utility and prepared several β-lactams of type (1) by the addition of crotonyl chloride to Schiff bases (see Table 1). We were initially interested in the transformation of the vinyl group to the hydroxyethyl side chain which is found in the β-lactam antibiotic thienamycin.

Facile conversion of a terminal vinyl group to an acetyl group by palladium catalysed oxidation of the double bond in the presence of cuprous chloride and oxygen is well documented in the literature.[4] This reaction of terminal olefins appears to involve Markovnikov hydration of the double bond followed by oxidation in a one step conversion to methyl ketones. In this sense olefins may be regarded as masked ketones.[5]

When β-lactam (**1a**) was subjected to oxidation with $PdCl_2$-CuCl-O_2, the major product was the aldehyde (**2a**) obtained in about 60% yield (Scheme 1). This is in marked contrast to what is normally observed when terminal olefins are subjected to the same oxidation conditions.[6] Conversion of the α-vinyl substituent of β-lactam (**1**) into an aldehyde (**2**) instead of the expected methyl ketone (**3**) would involve anti-Markovnikov hydration followed by oxidation. This reaction was found to be compatible with a variety of different substituents at positions 3 and 4 of the 2-azetidinone. Table 2 illustrates the various types of β-lactams that were obtained by this oxidation process. Methyl ketones were formed in some cases as by products - in very low yields (5-7%). The anomalous reaction of α-vinyl-β-lactams with palladium chloride could probably be explained by postulating that palladium coordinates with the carbonyl group of the β-lactam as well as the double bond of the vinyl group and thereby influences the regioselectivity of the hydration step.

In keeping with our continuing interest in the utilization of β-lactams as synthons for other heterocycles[7] we have studied chemical transformations of α-vinyl-β-lactams. The aldehyde (**2a**) was quantitatively converted to the 3-(β-chloroethyl)-2-azetidinone(**5**)[8] in two steps (1. $NaBH_4$/EtOH; 2. $SOCl_2/CH_2Cl_2$). β-Lactam (**5**) was rearranged with ring expansion to a substituted pyrrolidine (**6**) using sodium cyanide in methanol following the conditions described by Reuschling et al.[9] The structure of the rearrangement product was confirmed by the ^1H and ^{13}C-NMR spectral data. The coupling constant of 3.2 Hz between the protons at C-2 and C-3 in (**6**) is compatible with their cis stereochemistry and is in keeping with the mechanism of the rearrangement of the trans β-lactam (**5**) which does not alter the configuration of the carboxy group derived from the β-lactam carbonyl. The ^1H NMR spectrum of (**6**) was strongly pH dependent as expected for an amine[10,11]- a drop of CF_3COOH changed the ^1H NMR spectrum drastically[12] and thus provided additional support for the assigned structure. The carbonyl carbon of the pyrrolidine ester (**6**) resonates at 173.7 ppm in contrast to the β-lactam carbonyl which appears at the characterestic position of 166.5 ppm.

Scheme 1

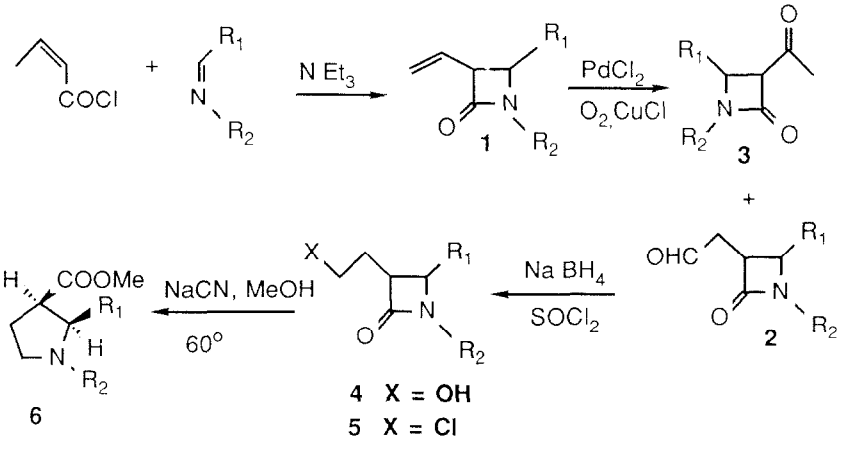
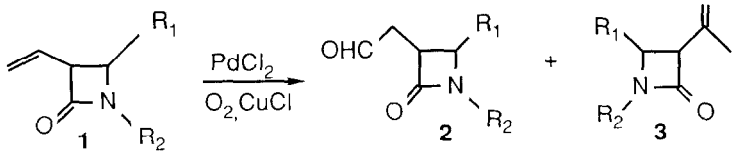


Table - 1*

No.	R_1	R_2	stereochem	m.p.(°C)	yield (%)
a	C_6H_5	C_6H_5	trans	97-99	65
b		$C_6H_4OCH_3$-p	"	101-103	52
c	-COPh	"	cis,trans (70:30)	132-135(trans) 116-118 (cis)	50 30
d	-COPh	$CH(CH_3)Ph$	cis	oil	55
e		$-CH(CO_2PNB)CH(CH_3)OH$	cis	oil	15
f	$C_6H_4OCH_3$-p	$C_6H_4OCH_3p$	trans	65-67	55
g	C_6H_5	$-C_6H_4OCH_3p$	trans	115-117	50
h	trans cinnamyl	$-CH(CO_2PNB)CHCH_3(OH)$	cis 90:10	127-129 major oil minor	60

Table - 2*



No.	R_1	R_2	Yield (%) (2)	(3)
a	Ph	Ph	65	5
b	α-methyl-cinnamyl	$C_6H_4OMe(p)$	60	4
c	C_6H_4OMe (p)	"	60	5
d	Ph	"	60	5
e	COPh	"	70	0

*All new compounds were characterized by their elemental and/or spectroscopic analysis.

The unusual oxidation reaction of α-vinyl-β-lactams[11] provides a convenient route to substituted pyrrolidine ring systems to which many alkaloids belong. Further work is in progress for gaining insight into the nature of this oxidation reaction and for utilizing its synthetic potential.

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References and Notes:

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(6) A survey of literature[5] indicates that 4-vinylcyclohexene yields minor amounts of the terminal aldehyde in addition to the corresponding methyl ketone.
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(8) β-Lactams of type (5) were synthesised earlier in our laboratory by the acid chloride - imine reaction in low yields (Unpublished results).
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(12) ^{1}H NMR ($CDCl_3$) **6** : 2.3 (m, 2H, 4-H), 3.0 (m, 1H, 3-H) 3.6 (m, 2H, 5-H), 3.75 (s, 3H, OCH_3), 5.1 (d, 1H, 2-H, J=3.2Hz), and 6.4 - 7.48 (m, arH).
^{1}H NMR ($CDCl_3$) 6 + a drop of TFA: 2.5 (m, 2H, 4-H), 3.3 (m, 1H, 3-H), 3.7 (S, 3H, OCH_3), 3.9 (m, 2H, 5-H), 5.1 (d, 1H, 2-H, J=5.3Hz) and 6.4 - 7.48 (m, arH).
(13) Typical procedure for the synthesis of 2: A suspension of CuCl (198 mg, 2mmole) and $PdCl_2$ (36mg, 0.2mmole) in 2 ml of aq. DMF (DMF: H_2O (7:1) was stirred under oxygen at room temperature. The initial green solution gradually turned black and then green again in 1 h. The α-vinyl-β-lactam 1a (500 mg. 2 mmole) in aq. DMF (4 ml) was then added dropwise. The reaction mixture was stirred overnight under oxygen at room temperature and then poured into cold 3N HCl (50 ml) and extracted with ether (5 x 20 ml). The combined ether extracts were washed with 5% sodium bicarbonate, dried (Na_2SO_4) and then stripped of solvent under reduced pressure. The residue was purified by flash column chromatography over silica gel using hexane - ethyl ecetate (3:1) as eluant and 2a was obtained as a colorless solid, m.p. 135-137° C; ^{1}H NMR 3a ($CDCl_3$): 3.3 (m,2H,CH_2), 3.4-3.5 (m, 1H,3-H), 4.7 (d, 1H,4-H), 7.0-7.4 (m, 10H, arH), and 9.8δ (s, 1H, CHO); CIMS (reagent gas,NH_3): m/e 266 $(M+1)^+$.
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