Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6133-6134, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01213-X

Facile Acid Catalyzed Ring Cleavage of N-Acylated Lactams#

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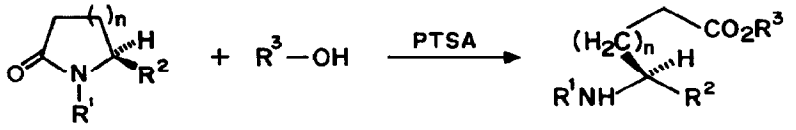
Abstract: *N-Alkoxycarbonyl and N-arylsulfonyl lactams (1a - e) were prepared and converted to the corresponding acyclic products (2a - h) by acid catalyzed cleavage of the lactam ring in good yields and excellent regioselectivity.*

The designing of a method for the hydrolysis of lactams under mild conditions has been an objective of several investigations in the last few years.[1-5] Most of the solutions to this problem have depended on the preliminary activation of the carbonyl (rendered more electrophilic) by N-alkoxycarbonylation of the lactam. In the resulting -CO-N-CO-O-R unit, attack by HO^- or MeO^- takes place preferentially at the lactam carbonyl (more electrophilic than the urethane carbonyl). However, the regioselectivity also depends to some extent on the bulk of the R group; the *tert*-butoxycarbonyl group gives the best results.[1] The scope of the reaction is therefore rather restricted. N-Tosyl derivatives of pyrrolidones (including pyroglutamic acid tert-butyl ester[6]) have been successfully cleaved by NaOH or LiOH.[6,7] We now report a versatile *acid catalyzed* ring opening of lactams in which the nitrogen atom is linked to -COOMe, -CSSMe or $-SO_2Ar$; the reaction proceeds under mild conditions and acyclic products are obtained in good to excellent yields. 2-Pyrrolidone was converted to the N-carbomethoxy derivative (**1a**) by treatment with sodium hydride followed by methyl chloroformate.[8] A solution of this (1 mmole) in methanol containing p-toluenesulfonic acid (PTSA) (0.1 mmole) was stirred at 25°C for 36 h. Evaporation of the solvent, followed by chromatographic purification (alumina, grade II; pet.ether - ethyl acetate) gave the ring opened product **2a** in 94% yield. There was thus no necessity of introducing the bulky *t*-Boc group in the first step.



	R^1	R^2	n
a:	-COOMe	H	1
b:	-COOMe	H	3
c:	-CSSMe	H	1
d:	-Ts	H	1
e:	-COOMe	-COOMe	1

	R^1	R^2	R^3	n
a:	-COOMe	H	Me	1
b:	-COOMe	H	Et	1
c:	-COOMe	H	^iPr	1
d:	-COOMe	H	C_6H_{11}	1
e:	-COOMe	H	Me	3
f:	-CSSMe	H	Me	1
g:	-Ts	H	Me	1
h:	-COOMe	-COOMe	Me	1

Acyclic compounds (**2b, c, d**) were generated in equally good yields by the use of the appropriate alcohol in the ring opening reaction. The N-acylated lactams (**1b** to **1e**) were prepared similarly and converted to the corresponding acyclic products (**2e** to **2h**) in good yields and excellent regioselectivity (***Table 1***). No cleavage of carbamate or dithiocarbamate was observed under these acid catalyzed conditions.[9]

Table 1

Conversion of Lactams (**1**) to acyclic products (**2**)

Substrate	R^3OH	Temp °C	Time (h)	Product[a]	Yield(%)
1a	MeOH	25	36	**2a**[11]	94
1a	EtOH	80	24	**2b**[10]	90
1a	i-PrOH	80	30	**2c**[10]	89
1a	$C_6H_{11}OH$	100	24	**2d**[10]	88
1b	MeOH	65	22	**2e**[11]	86
1c	MeOH	65	24	**2f**[12]	86
1d	MeOH	65	24	**2g**[13]	70
1e	MeOH	65	24	**2h**[14]	65[b]

a : All the products, except **2g** (m.p.89°C) were liquids or gums. b : $[\alpha]_D$: + 7.65 (Partial recemisation might have occurred during the preparation of **1e**.)

Acknowledgment : We are grateful to Dr.N.N.Joshi for many valuable suggestions and discussions during the course of this work. We thank UGC and CSIR for the award of Senior Research Fellowships (to SKT and AND). We also acknowledge financial assistance from CSIR (to SR) under the Emeritus Scientist Scheme.

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NCL communication No. 5988

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9. We have found that the reaction could also be carried out using sodium methoxide as the catalyst (1 mole %); however, the yield of the product in the base-catalysed reaction was only 60 %, perhaps due to partial cleavage of the N-acyl group.
10. Satisfactory analytical values were obtained for all new compounds.
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(*Received in UK* 14 *April* 1994; *revised* 20 *June* 1994; *accepted* 24 *June* 1994)