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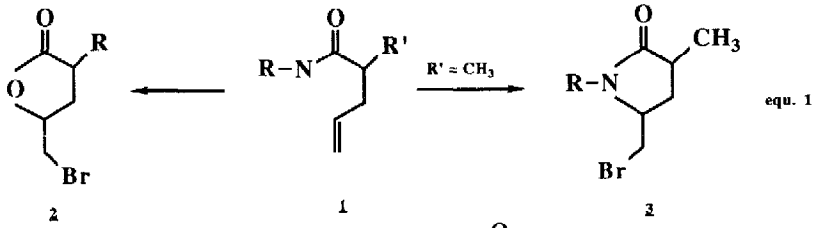
HALOCYCLIZATIONS: THE CYCLIZATION OF HETEROCYCLIC OLEFINIC AMIDES AND UREAS

T. W. Balko, R. S. Brinkmeyer*, and N. H. Terando
Lilly Research Laboratories
A Division of Eli Lilly and Company
Greenfield, IN 46140

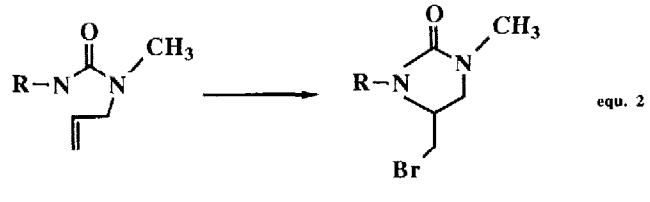
Abstract: The halocyclization of N-heterocyclicpentenamides and allylureas with N-bromosuccinimide yields the pyrrolidinones 3 and imidazolidinones 5, respectively. The thiazolylpentenamide also yields the 6-membered ring lactam.

The halocyclizations of olefinic compounds leading to heterocycles has been well documented.[1-3] For example, halocyclizations to lactams,[1] lactones[2] and cyclic carbonates[3] have been studied. Of particular interest to us was the cyclization of olefinic amides to lactams, 3, and the heretofore unreported cyclization of olefinic ureas to imidazolidinones, 5.

The cyclization of olefinic amides promoted by a halonium ion has produced, in only a few cases we are aware of, the lactam, 3. In the cases reported, the predominant product from these halocyclizations is not the lactam, but instead the imino ether which subsequently hydrolyses to the lactone, 2 (eq. 1). Two exceptions are: 1) halocyclization (using e.g. N-bromosuccinimide) of N-sulfonylolefinic amides[1] to the 4-halomethyl β-lactams, however, attempts to form the corresponding 5-membered ring lactams failed yielding instead the lactone 2 (eq. 1); and 2) the cyclization of a bis-silylated imidate with I_2. Since our interest was to form the 5-membered ring lactams, we searched for groups which would facilitate nitrogen cyclization.



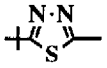
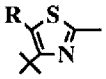
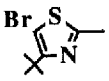
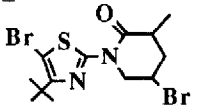
2 1 3 equ. 1



4 5 equ. 2

Our first attempt was treatment of N-aryl pentenamides[4] 1a and 1b (Table 1) with a halonium ion source such as NBS (CCl_4, 23°C) which gave after work up only the corresponding lactone 2[4] in good yield. This corresponded to what had previously been described above. Next, we looked at compounds where R is a heterocycle (see Table 1). In these cases, halocyclization gave the pyrrolidinone 3 exclusively, no lactone 2 was detected.

Table 1: Halocyclization of pentenamides 1 to 3

Entry	R	Product[5]	% Yield 3[5]	mp, °C
a	3-$CF_3C_6H_4$	2	75	oil
b	3-$OMeC_6H_4$	2	63	oil
c		3 c + t	30	oil
d		3 c + t	73	85-7
e		1 (R=Br)	63	175-6
		+ 3 (R=Br) c + t	10	oil
f			43	oil

Product 3 was a mixture of diastereomers, the ratio for pyrrolidinones 3c - e being approximately 1:1. In the case of 3d, the cis and trans isomers were separated by low-pressure liquid chromatography. By proton NMR, the relative stereochemistry of each isomer (isomer A, mp 135-136°C and isomer B, mp 81-82°C) was uncertain. By single crystal x-ray crystallography isomer B was assigned the trans configuration (Figure 1), as well as confirming cyclization on nitrogen.

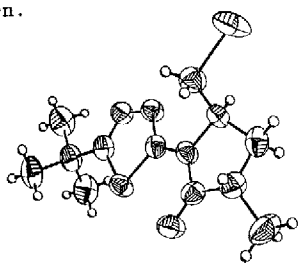
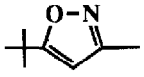


Figure 1: ORTEP drawing of the trans isomer of 3d

Treatment of amide 1e with NBS gave both ring bromination and bromocyclization. An unexpected cyclization with 1f gave the 6-membered lactam (Table 1) exclusively in 43% yield. Although reproducible, we cannot as of yet explain why the 6-membered ring is formed as opposed to the 5-membered ring.

In the case of the olefinic ureas,[6] treatment with NBS (CCL_4, 23°C) gave the bromomethylimidazolidinones in good yield (Table 2). Only in the example where R was p-tolyl did we observe overbromination to give a second product, N-[2-bromo-4-methyl]phenyl-N'-methyl-5'-bromomethylimidazolidinone.

Table 2: Halocyclization of olefinic urea 4 to 5

Entry	R	R'	X	%Yield 5[5]	mp°C
a	4-ClC_6H_4	Me	Br	68	oil
b	3-ClC_6H_4	Me	Br	67	oil
c	4-MeC_6H_4	Me	Br	40	oil
d	2,6-diMeC_6H_4	Me	Br	65	80-5
e	3-$CF_3C_6H_4$	Me	Br	36	oil
f	3-$CF_3C_6H_4$	Me	I	30	oil
g	3-$CF_3C_6H_4$	Ph	Br	95	92-4
h	2-ClC_6H_4-CO-	Me	Br	63	88-91
i	EtO_2CCH_2	Me	Br	20	oil
j	EtO_2CCH_2	Ph	Br	93	oil
k	EtO_2CCH_2	H	Br	7	oil
l		Me	Br	47	115-21

In summary, our experience is that the 5-membered ring lactams can be formed at least when R is isoxazole, thiadiazole or thiazole, but fails when R is aryl, as do the reported cases where R is tosyl[1], tert-butyldimethylsilyl,[1] and H.[2] The halocyclization of olefinic ureas 1 to bromomethylimidazolidinones 2 provided an efficient route to these compounds allowing for further elaboration of these novel intermediates. This cyclization is interesting in that the halocyclization of the corresponding N-aryl pyrrolidinone systems[1] (nitrogen replaced by carbon) did not cyclize in this manner, instead yielding lactone 2.

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References

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2. Corey, E. J.; Fleet, W. J.; Kato, M. Tetrahedron Lett. 1973, 3963. Rengevitch, E. N.; Staninets, V. L.; Shilov, E. A. Proc. Acad. Sci. USSR 1962, 146, 787. It is of note that phenylselenylchloride cyclizations of pentenamides also fail, see Clive, D.L.J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. J. Chem. Soc., Chem. Commun. 1978, 379. Toshimitsu, A.; Terao, K.; Uemura, S. Tetrahedron Lett. 1984, 5917.

3. For the synthesis of halomethyl carbonates, see Lipshutz, B. H.; Kozlowski, J. A. J. Org. Chem. 1984, 49, 1147; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S.; Tomasini, C. J. Org. Chem. 1984, 49 701 and references therein. For iodolactonizations, see Bartlett, P. A.; Richardson, D. P.; Myerson, J. Tetrahedron 1984, 40, 2317 and references therein.

4. The N-substituted pentenamides were made by condensation of the anilines or heterocyclic amines with 2-methyl-4-pentenoate ethyl ester (sodium methoxide, THF, reflux, 50-75% purified). The 3-methyl-4-pentenoate ethyl ester was made by an orthoester Claisen reaction with allyl alcohol and triethyl orthopropionate (propionic acid catalyst, reflux, 90% yield).

5. All new compounds have satisfactory spectra ir, proton NMR (IBM - 80 MHz or Bruker 250 MHz), and mass spectra consistent with assigned structures. Composition was determined by elemental analysis.

6. The olefinic ureas, 1, were prepared in high yields by standard procedures with readily available starting materials by reaction of an isocyanate with N-substituted (R=H, Me, Ph) allylamines. Where the isocyanates are not available, the amine was reacted with 1,1'-carbonyldiimidazole (Staab, H. A.; Benz, W. Ann. 1961, 648, 72) then the N-substituted allylamine to give the ureas in high yield.

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