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On the base-induced isomerization of cyclic propargylamides to cyclic allenamides

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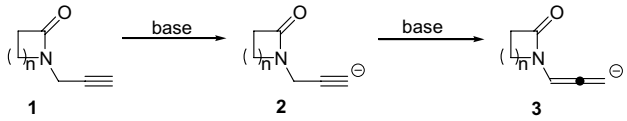
Abstract—The reaction of lactams **4** ($n = 1$–5) with propargyl bromide affords propargylamides or allenylamides depending on the ring-size. Theoretical calculations support the dependence of the extension of the isomerization on the ring-size.

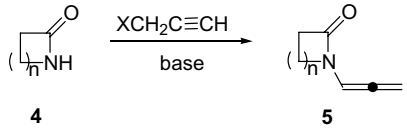
Interest in the chemistry of allenamides[1] covers the range from medicinal chemistry[2] to materials[3] including their use as building blocks in organic synthesis.[4] In the case of *N*-allenyl lactams the base-induced isomerization of propargylamides **1** constitutes the most common synthetic approach (Scheme 1).

In general, this isomerization has been achieved on the isolated propargylamides using KOH in DMSO[5] or ^{t}BuOK in THF[6] among other methods. However, the direct synthesis of allenylamides during the base-catalyzed propargylation of lactams has, to the best of our knowledge, only one precedent in the literature[7] (Scheme 2).

From the accidental discovery of the base catalyzed isomerization of acetylenes by Favorskii in 1886,[8] hundreds of reports concerning the mechanistic features of this reaction have been published. However, the influence of the ring-size which supports the functionality



Scheme 1.



Scheme 2.

attached to the propargylic carbon on the alkyne–allene equilibrium has, to the best of our knowledge, never been reported.[9]

On the basis of this consideration, we decided to explore the behavior of different cyclic amides **4** in their reactions with propargyl bromide using KOH in THF as a basic reagent. The results are gathered in Table 1.

Considering the process depicted in Scheme 2,[10] the n–π conjugation appears to be crucial in allene stabilization.[11] Thus, accessibility of the n electrons in the β- and γ-lactams are greater than in not strained six, seven, and eight membered ring systems because the inhibition of the amine resonance is more important in four and five membered rings.[12] In consequence, stabilization of the allenic form should also be more important in β- and γ-lactams, according to the experimental observations.

In order to obtain theoretical support for the above findings, computations were carried out on the anions **2** and **3** (Scheme 1). Electron correlation has been partially taken into account using the hybrid functional usually denoted as B3LYP[13] and the standard G-31++G** basis set[14] for hydrogen, carbon, oxygen, and nitrogen.

Keywords: Allenamides; Propargylamides; Base-induced isomerization; Lactams.
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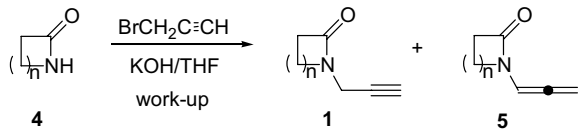
Table 1. Reaction of lactams **4** with propargyl bromide[a]



4 **1** **5**

Entry	*n*	Isolated yield[b]	Ratio **1**:**5**[c]
1	1 (**4a**)	37%	0:100[d] (**5a**)
2	2 (**4b**)	Quantitative	<1:>99 (**1b**, **5b**)
3	3 (**4c**)	Quantitative	1.5:1 (**1c**, **5c**)
4	4 (**4d**)	91%	2.4:1 (**1d**, **5d**)
5	5 (**4e**)	77%	30: 1 (**1e**, **5e**)

[a] Reaction conditions: 1.0 equiv **4**, 3.0 equiv KOH, 1.2 equiv K_2CO_3, 0.13 equiv benzyltriethylammonium chloride (TEBA).
[b] Combined isolated yields **1** + **5**.
[c] From the reaction crude, compounds **1** and **5** were isolated by column chromatography (SiO_2, eluent pentane–Et_2O, 1:2). R_f values: **5a**, 0.40; **1b**, 0.10; **5b**, 0.23; **1c**, 0.12; **5c**, 0.20; **1d**, 0.15; **5d**, 0.40; **1e**, 0.13; **5e**, 0.29. No propargyllactam–allenelactam interconversion was observed by treatment of both compounds **1** and **5** with SiO_2 under the chromatography conditions.
[d] No traces of compound **1a** were detected by ^{1}H NMR.

Table 2. Calculated ΔE (**3**–**2**, kcal/mol) (Scheme 1) in THF ($\varepsilon = 7.58$)

Entry	*n*	ΔE (**3**–**2**)
1	1	−2.34
2	2	−0.20
3	3	+1.28[a]
4	4	+1.32
5	5	+3.30

[a] Calculations have been achieved at the B3LYP/G −31 + G* + ΔZPVE.

Zero point vibrational energy (ZPVE) corrections have been computed at the B3LYP/G-31++G** level and have not been corrected. Stationary points were characterized by frequency calculations,[15] and have positive defined Hessian matrices. Nonspecific solvent effects have been taken into account by using the self-consistent reaction field (SCRF)[16] approach with sequential single-point calculations at the gas-phase optimized geometries. All the calculations were performed with the Gaussian 03 suite of programs.[17] The results are quoted in Table 2.

The relative stabilities of anions **2** and **3** depend on the ring size and the ΔE values match well with the experimental results shown in Table 1.

In summary, reaction of lactams with propargyl bromide affords *N*-propargyl or *N*-allenyl derivatives depending on the ring size of the starting material. In the case of $n = 1$, 2, and 5 this reaction has synthetic applicability.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.013. Experimental procedure including ^{1}H and ^{13}C spectra of **5a**–**e** products are available.

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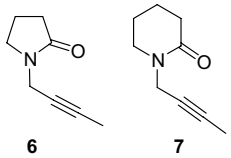

6 **7**

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