Halogenolactamization of 2-(3-Butenyl)-1,3-oxazolines to Bifunctional γ- and δ-Lactams

Keiji Terao,* Yumiko Takechi,† Munetaka Kunishima,*† Shohei Tani,† Akiko Ito,†† Chisa Yamasaki,†† and Shin-ichi Fukuzawa††
Wacker Chemicals East Asia Ltd., 2-14-1 Nishi-Waseda, Shinjuku-ku, Tokyo 169-0051
†*Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Nishi-ku, Kobe 651-2180*
††*Department of Applied Chemistry, Chuo University, Bunkyo-ku, Tokyo 112-8551*

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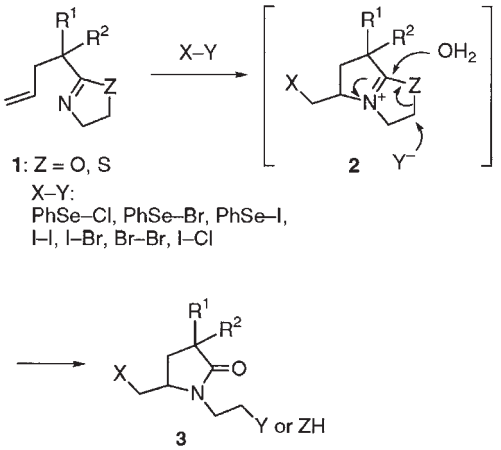
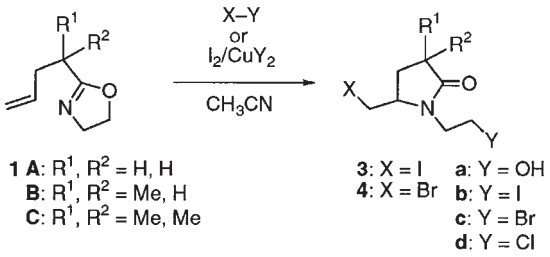
Under new conditions described herein, halogenolactamization of 2-(3-butenyl)-1,3-oxazolines (**1**) proves to be a successful approach for producing 1,5-bis(halogenoalkyl)-γ-lactams (**3**). A variety of halogens can be introduced by using reagents such as I_2, $I_2/CuCl_2$, $I_2/CuBr_2$, and Br_2 under dry conditions.

It has been reported that the intramolecular amidoselenation of 1,3-oxazolines (**1**: Z = O) or 1,3-thiazolines (**1**: Z = S) possessing an olefinic moiety at the 2-position with benzeneselenenyl halides gives γ-lactams (**3**) bearing both halogenoethyl and (phenylseleno)methyl substituents.[1,2] The interesting bifunctional structure of **3** stimulated us to transform it into bicyclic γ-lactams, which occur naturally as biologically active compounds.[3] However, all attempts at the second ring closure between halogenoalkyl and selenomethyl groups were unsuccessful because chemoselective activation of (phenylseleno)-methyl group without decomposition of other functional groups was difficult. Another promising approach for transformation of **1** to bicyclic lactams could be nucleophilic substitution or intramolecular reductive coupling of bis(halogenoalkyl)-γ-lactams (**3**: X = Y = halogen) that can be prepared by halogenolactamizaion of **1**. This approach is favorable because the use of highly toxic organoseleniums can be avoided. Although Kurth and Bloom reported iodolactamization of γ,δ–unsaturated oxazolines using iodine in THF/aqueous $NaHCO_3$, they failed to obtain such diiodides (**3**: X = Y = I).[4] Herein we report the preliminary study of halogenolactamization of 2-(3-butenyl)-1,3-oxazolines, in which bifunctional 1,5-bis(halogenoalkyl)-γ-lactams are successfully produced.



Scheme 1.

Kurth and Bloom obtained 1-hydroxyethyl-γ–lactams **3a**, which presumably arose from hydrolysis of an intermediary oxazolinium salt **2**, despite the fact that the reaction was conducted under dry conditions in THF followed by quenching with aqueous Na_2SO_3. They concluded that **2** was stable to iodide and exclusively underwent hydrolysis.[4]



Scheme 2.

By contrast, we found that the diiodo-γ-lactam **3a** was formed by elongation of the reaction time in CH_3CN. Treatment of **1A** with iodine in commercial CH_3CN at room temperature for 3 days gave diiodo-γ-lactam **3Ab**, albeit in a low yield (26%), along with 10% of a hydrolyzed product **3Aa** (Table 1, Run 1). Encouraged by this result indicating that iodide anion can attack at the C_5 position of the oxazolinium intermediate, we then explored the reaction under a variety of conditions; the results are summarized in Table 1.

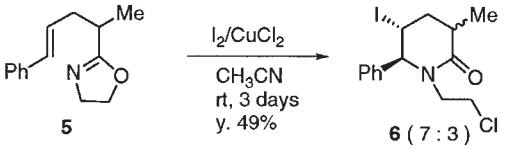
By use of a combination of I_2 and $CuCl_2$, which is known to promote iodination of alkenes and believed to generate iodine monochloride,[5] the oxazoline **1B** was converted into a γ-lactam bearing a chloroethyl substituent **3Bd** and the hydrolyzed hydoxyl compound **3Ba** in yields of 40% and 35%, respectively (Run 2). Conducting the reaction under dry conditions to depress hydrolysis of the oxazolium intermediate not only increased the yield of **3Bd** (68%) but also considerably reduced the reaction time (Run 5).[6–8] Similarly, reactions using $I_2/CuBr_2$ or I_2 proceeded to give iodobromolactam **3Bc** and diiodolactam **3Bb**, respectively, within one day (Runs 7 and 9). Low diastereoselectivities observed in the reactions of **1B** bearing a methyl group on the connecting carbon chain agree well with reported results.[4] Introduction of *gem*-dimethyl groups to the carbon chain was found to promote the cyclization; the reactions of **1C** were completed in 40 min (Runs 6, 8, 10). When bromine was used instead of I_2 or I_2/CuX_2, bromolactamization to give **4Bc** proceeded in an excellent yield (Run 11). It is not clear why chloride and bromide attack the oxazolium salt in preference to iodide in I_2/CuX_2 and I_2/Br_2 systems.

It has been shown previously that 6-endo cyclization leading to the formation of a δ-lactam becomes the predominant pathway when an oxazoline having 4-phenyl-3-butenyl substituent is used as a substrate for selenoamidation.[1c] A similar result was observed in the present reaction; δ-lactam **6** was formed exclusively when phenyl-substituted compound **5** was treated

Table 1. Formation of bifunctional γ-lactams from 2-(3-butenyl)-1,3-oxazolines **1**

Run	Substrate	Reagents[a]	Conditions	Products	(Yield)
1[b]	**1A**	I_2	r.t., 3 days	**3Ab** (26%),	**3Aa** (10%)
2[b]	**1B**	$I_2/CuCl_2$	r.t., 3 days	**3Bd** (40%),[d]	**3Ba** (35%)[d]
3[b]	**1B**	I_2/Br_2	r.t., 3 days	**3Bc** (57%),[d]	**3Ba** (11%)[d]
4[c]	**1A**	$I_2/CuCl_2$	r.t., 1 day	**3Ad** (44%)	
5[c]	**1B**	$I_2/CuCl_2$	r.t., 1 day	**3Bd** (68%)[d]	
6[c]	**1C**	$I_2/CuCl_2$	r.t., 40 min	**3Cd** (85%)	
7[c]	**1B**	$I_2/CuBr_2$	r.t., 1 day	**3Bc** (57%)[d]	
8[c]	**1C**	$I_2/CuBr_2$	r.t., 40 min	**3Cc** (62%)	
9[c]	**1B**	I_2	r.t., 1 day	**3Bb** (52%)[d]	
10[c]	**1C**	I_2	r.t., 40 min	**3Cb** (57%)	
11[c]	**1B**	Br_2	0 °C to 5 °C, 3 days	**4Bc** (97%)[d]	

[a]The ratio of the reagents to the substrate was 1.2 : 1. [b]Conducted under atmospheric conditions using commercially available CH_3CN as solvent. [c]Conducted under dry conditions using anhydrous CH_3CN dried over $CaCl_2$. Although trace amounts of hydroxy derivatives, **3Aa**, **3Ba**, **3Ca**, were always generated even under dry conditions, their yields were not determined. [d]A mixture of diasteromers ranging in a ratio from 1 : 1 to 7 : 3, whose stereochemistries were not determined.



Scheme 3.

with $I_2/CuCl_2$ (Scheme 3). The iodolactamization of γ,δ–unsaturated oxazolines was reported to proceed in a kinetically controlled process.[4] If a similar mechanism is applicable to our reaction, the observed 6-endo cyclization can be attributed to the stability of carbocation arising from the electrophilic addition of iodine to the C-C double bond of the stylyl moiety.

In summary, various bis(halogenoalkyl)lactams were successfully synthesized in fairly good yields by use of I_2, $I_2/CuCl_2$, $I_2/CuBr_2$, and Br_2 in CH_3CN under dry conditions. We are currently exploring further transformation of bifunctional lactams into bicyclic compounds.

References and Notes

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6 Starting material **1A** was synthesized from 1-methyl-1,3-oxazoline by allylation with *n*-BuLi/allyl bromide. Similarly, **1B**, **1C**, and **5** were prepared from 1-ethyl-1,3-oxazoline, 1-isopropyl-1,3-oxazoline, and 1-methyl-1,3-oxazoline, respectively.

7 The structures of **3**, **4** and **6** were confirmed on the basis of their spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) and elemental analysis.

8 For a typical procedure: iodine (152 mg, 0.6 mmol) and $CuCl_2$ (162 mg, 1.2 mmol) were added to a stirred solution of **1B** (139 mg, 1.0 mmol) in 10 mL CH_3CN at room temperature. After 24 h of stirring at room temperature, 10% aqueous $Na_2S_2O_3$ was added until the color of iodine disappeared. The reaction mixture was diluted, and extracted with AcOEt. The resulting residue was purified by Al_2O_3 column chromatography (hexane : AcOEt = 4 : 1) to give **3Bd** (204 mg, 68% yield) as a mixture of diastereoisomers: pale yellow oil, IR (neat) 2965, 1689, 1415, 1254 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ 1.17 (d, J = 7.2, 3 H for minor isomer), 1.22 (d, J = 6.9, 3 H for major isomer), 2.48–2.73 (m, 2 H), 3.22–3.54 (m, 4 H), 3.62–4.90 (m, 3 H), 3.94–4.06 (m, 1 H), ^{13}C-NMR (400 MHz $CDCl_3$) for major isomer: δ 11.20, 16.05, 34.56, 35.50, 41.67, 42.23, 55.69, 177.86; for minor isomer: δ 9.42, 16.71, 33.76, 34.78, 41.46, 42.63, 56.78, 178.00; Anal. Calcd for $C_8H_{13}NOClI$: C, 31.86; H, 4.35; N, 4.64%. Found: C, 32.13, H, 4.23; N, 4.52%.