Organoselenium-Induced Cyclization of 2-Alkenylthiazolines to Functionalized γ-Lactams

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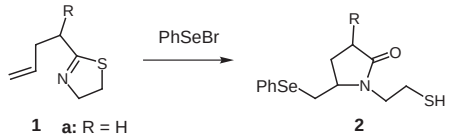
Abstract: The reaction of alkenylthiazolines with benzeneselenenyl bromide in a mixed solvent of acetonitrile and water saturated with sodium bicarbonate gives lactams bearing both mercaptoethyl and phenylselenenyl groups in moderated to good yields. Intramolecular amidoselenation and subsequent hydrolysis will be involved.

Key words: amidoselenation, thiazolines, γ-lactams, selenides, thiols

An enormous number of mono- and bicyclic lactam ring systems are well adapted as biologically active compounds so that findings of new synthetic ways of versatile functionalized lactams are of great interest.[1] In this connection much attention has been paid to the methodology for the lactam ring formation by selenium-induced or iodonium-induced cyclization of alkenyl imidates,[2] alkenyl cyclic imidates,[3] alkenyl bis(trimethylsilyl) amides,[4] alkenylurethanes,[5] alkenyl imines,[6] and alkenyl thioimidates.[7] Among them, in particular, the reaction of alkenyloxazolines with benzeneselenenyl halides is highly useful because two functional groups, halogeno and phenylselenenyl groups, of resulting lactams allow further transformation of them into various bicyclic lactams possessing nitrogen atom at a bridgehead.[3] Herein, we report our preliminary studies on a new direct approach to γ-lactams bearing both mercaptoethyl and (phenylselenenyl)methyl substituents by use of alkenylthiazolines.



1 **a:** R = H
b: R = Bn
c: R = Me

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Results are summarized in Table 1. Our first attempt to obtain a γ-lactam by the reaction of 2-(3-butenyl)-1,3-thiazoline **1a**[8] with benzeneselenenyl bromide in acetonitrile was unsuccessful giving various non-cyclic materials that could not be identified (Run 1). Desired selenium-induced cyclization took place by addition of 10% water, and *N*-mercaptoethyl 5-[(phenylselenenyl)methyl] γ-lactam **2a** was obtained albeit in low yield (21%, Run 2). The yield of **2a** was improved to 66% by replacement of water with a saturated sodium bicarbonate solution.[9] The use of another solvent system (chloroform, THF, and diethyl ether) under similar conditions resulted in somewhat low yields. The immiscible property of chloroform or ether with water might be responsible for a low yield observed in those solvents. The reaction with thiazolines, having an alkyl group like benzyl **1b** or methyl group **1c** at the 1-position of 3-butenyl group, were found to proceed in a good yield to afford **2b** (7:3 mixture of diastereoisomers) and **2c** (57:43), respectively (Runs 8 and 10).[9-12] The observed substituent effect on the yield of amidoselenation is in agreement with the result reported by Toshimitsu et al.[3]

Table 1 Formation of γ-lactams (2) *via* amidoselenation.

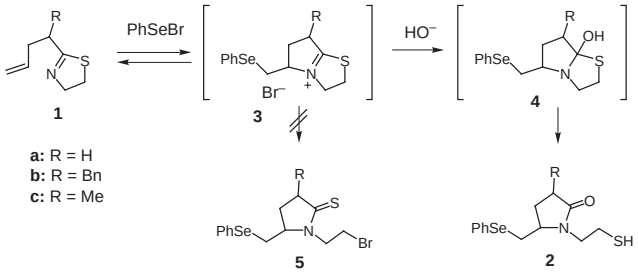
Run	Substrate	Solvent	Conditions	Yield **2** (%)[a]
1	**1a**	MeCN	rt, 24hr	0
2	**1a**	MeCN–H_2O (10 : 1)	rt, 24hr	21
3	**1a**	MeCN–sat.$NaHCO_3$ (10 : 1)	rt, 24hr	66
4	**1a**	MeCN–sat.Na_2CO_3 (10 : 1)	rt, 24hr	56
5	**1a**	$CHCl_3$–sat.$NaHCO_3$ (10 : 1)	rt, 24hr	35
6	**1a**	THF–sat.$NaHCO_3$ (10 : 1)	rt, 24hr	54
7	**1a**	Et_2O–sat.$NaHCO_3$ (10 : 1)	rt, 24hr	46
8	**1b**	MeCN–sat.$NaHCO_3$ (10 : 1)	rt, 24hr	92
9	**1b**	MeCN–sat.$NaHCO_3$ (10 : 1)	reflux, 5hr	15
10	**1c**	MeCN–sat.$NaHCO_3$ (1 : 1)	rt, 24hr	90
11[b]	**1c**	MeCN–sat.$NaHCO_3$ (1 : 1)	rt, 4days	57

[a] Isolated yield. [b] Performed in a large scale (0.1 mol).

The functionalized γ-lactams are most likely formed by a mechanism illustrated in the Scheme. Intramolecular amidoselenation of **1** generates a bicyclic iminium salt **3**, which undergoes attack by a hydroxyl anion (or a water molecule) at the iminium carbon to give **4**. Ring opening of the thiazoline with carbonyl formation gives the lactam **2**. Since no cyclization occurs in the absence of hydroxyl anion, the first amidoselenation step can be reversible. In contrast to the result observed in a similar reaction of alkenyloxazoline,[3] where *N*-(2-bromoethyl) lactams are formed, no corresponding bromide **5** was observed.

It would be desirable to introduce sulfur functionalities into lactam systems from the viewpoint of biological activity. Introduction of such functional groups by known methods, using a reagent like hydrogen sulfides or carbon

sulfide, often suffers the disadvantage caused by toxicity and unpleasant smell of the reagent used. Thus, present reaction appears to be very useful because γ-lactams having a mercapto group can be formed directly in only one step reaction. Further experimental studies for the derivation of γ-lactams are in progress.



Scheme

References and Notes

(1) For example: Dowle, M. D.; Davis, D. J. *Chem. Soc. Rev.* **1979**, 171.
(2) Terao, K.; Toshimitsu, A.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1837.
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(8) Starting **1a** was synthesized from 1-methyl-1,3-thiazoline by allylation with nBuLi/allyl bromide. Similarly, **1b** and **1c** were prepared from **1a** (*n*-BuLi/benzyl bromide or *n*-BuLi/iodomethane).
(9) The structures of **2** were confirmed on the bases of spectroscopic data (^{1}H NMR, IR, and MS).
(10) The stereochemistries were not determined.
(11) In order to comfirm of the existence of mercapto group (not hydroxy group), further transformation of **2b** was attempted by use of methyl iodide/sodium borohydride in EtOH. The chemical shift at 2.07 or 2.08 ppm observed by ^{1}H NMR analysis of the resulting diastereoisomeric products indicates the formation of methylmercapto group.
(12) For a typical procedure: To a stirred solution of **1c** (155 mg, 1.0 mmol) in 5 mL CH_3CN was added benzeneselenenyl bromide (260 mg, 1.1 mmol) at rt. After 30 min of stirring at rt, the mixture was cooled to 0 °C, and 5mL of a saturated $NaHCO_3$ was added dropwise over a period of 30 min at 0 °C. The mixture was allowed to warm to rt and stirred for 24 h. The reaction mixture was diluted with water, and extracted with AcOEt. The resulting residue was purified by silica gel column chromatography (AcOEt) to give **2c** (295 mg, 90%, a mixture of diastereoisomers): pale yellow oil, IR (neat) 3056, 2973, 1683 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) for the major isomer: δ 1.22 (d, *J* = 6.9, 3H), 1.36-1.45 (m, 1H), 2.38-2.54 (m, 2H), 2.64-2.84 (m, 2H), 2.87-2.94 (m, 1H), 3.06-3.28 (m, 2H), 3.64-3.85 (m, 2H), 7.26-7.30 (m, 3H), 7.50-7.55 (m, 2H); for the minor isomer: δ 1.17 (d, *J* = 7.2, 3H), 1.78-1.87 (m, 1H), 2.13-2.21 (m, 1H), 2.57-2.84 (m, 3H), 2.87-2.94 (m, 1H), 3.06-3.28 (m, 2H), 3.64-3.85 (m, 2H), 7.26-7.30 (m, 3H), 7.50-7.55 (m, 2H). HRMS m/z Calcd for $C_{14}H_{19}NOSSe$: 329.0352. Found:329.0336.

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