JOC*Note*

Selenium-Catalyzed Halolactonization: Nucleophilic Activation of Electrophilic Halogenating Reagents

Shelli R. Mellegaard and Jon A. Tunge*

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

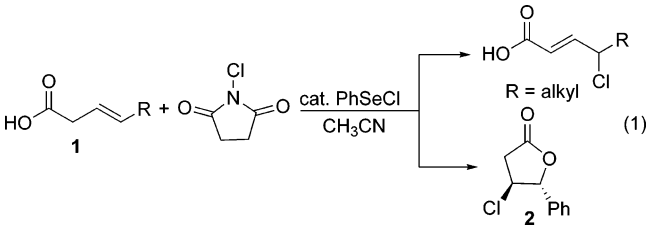
tunge@ku.edu

Received September 1, 2004

Abstract: Diphenyl diselenide catalyzes the halolactonization of unsaturated acids with *N*-halosuccinimides under mild conditions. The diselenide not only accelerates the reactions, but in some cases affords regiocontrol in favor of γ-lactone products. Experiments show that the regioselectivity in favor of γ-lactones is a result of kinetic rather than thermodynamic control.

In the years since its discovery in the early 1900s, halolactonization has proven to be a versatile reaction in organic synthesis, allowing facile formation of small or medium ring size lactones.[1] The utility of the product halolactones has been repeatedly demonstrated by their use in total syntheses.[2] The first reports of halolactonization utilized a weak base, KI, and molecular iodine[1] for the cyclofunctionalization of unsaturated acids. Similarly, reagents such as *N*-bromosuccinimide,[3] Br_2,[4] H_2O_2/NaBr,[5] $CuBr_2/Al_2O_3$,[6] Tl_2CO_3/Br_2,[7] and $ZnBr_2/Pb(OAc)_4$[8] have been shown to effect bromolactonization of unsaturated acids or carboxylates. Despite the utility of these reactions, control of the regio- and stereochemistry of the product bromolactones has not been properly addressed. With this in mind, it is particularly surprising that there are no reports of catalytic halolactonization. In this regard, it is noteworthy that Detty has developed a selenium-catalyzed protocol for halolactonization of unsaturated acids with H_2O_2/NaX;[5] however, this method is best described as a catalytic oxidation of halides. While quite useful, the catalytic oxidation produces freely diffusing electrophilic bromine species and thus leaves little hope for control of selectivity. With the goal of catalytically halogenating organic substrates through nucleophilic activation of typical electrophilic halogen sources, we have turned to the use of similar selenium catalysts with "preoxidized" halogenating agents. Herein we report that simple arylselenides catalyze the halolactonization of unsaturated acids in the presence of *N*-halosuccinimide oxidants. Furthermore, in some cases the use of selenium catalysts allows kinetic control of the regioselectivity and thus the lactone ring size.

In an effort to develop catalytic halogenation reactions, we recently investigated the selenium-catalyzed allylic halogenation of β,γ-unsaturated acids (eq 1).[9] While the



(1)

reaction was apparently general for alkyl-substituted olefins, upon switching to styrylacetic acid we discovered the ability of selenium reagents to catalyze halolactonizations. Specifically, *trans*-styrylacetic acid (R = Ph) undergoes cyclization in the presence of phenylselenyl chloride and *N*-chlorosuccinimide to afford only the β-chloro-γ-lactone product (**2***)*. In the absence of PhSeCl, <1% of **2** is formed under the same conditions. In this instance, no allylic halogenation was observed. Attempts to favor chlorolactonization of alkyl-substituted unsaturated acids by addition of bases (K_2CO_3, pyridine, Et_3N, and *i*-Pr_2NEt) invariably led to mixtures of allyl chlorides and chlorolactones. Furthermore, during the slower reactions, the base-initiated dehydrohalogenation of the chlorolactones resulted in the formation of butenolides as well.[10]

The lack of generality of the catalytic chlorolactonization led us to investigate the analogous catalytic bromolactonizations. Specifically, *trans*-styrylacetic acid was treated with 5 mol % of PhSeSePh and 1.1 equiv of *N*-bromosuccinimide (NBS) in CH_3CN at −30 °C. After 3 h, the β-bromo-γ-lactone was isolated in 90% yield. While the addition of catalytic PhSeSePh provided for an increase in yield relative to the reported 54% with NBS alone,[3] styrylacetic acid has a strong preference for formation of γ-lactones so regiochemistry was not an issue. In the interest of investigating catalyst-controlled regiochemistry, we employed *trans*-3-hexenoic acid as a substrate since it is known to react with poor regiochemical selectivity. The reaction of *trans*-3-hexenoic acid (**1b**) with NBS in acetonitrile at room temperature affords a 2:1 mixture of γ- and β-lactones (**3b** and **4b**, eq 2). Addition of 5 mol % of PhSeSePh to the reaction mixture

(1) (a) Bougault, J. *Ann. Chim. Phys.* **1908**, *14*, 145. (b) Bougault, J. *Ann. Chim. Phys.* **1908**, *15*, 296. (c) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin, Inc.: New York, 1972; p 441. (d) Dowle, M. D.; Davies, D. I.; *Chem. Soc. Rev.* **1979**, *8*, 171−197. (e) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321−3408.

(2) (a) Murata, Y.; Kamino, T.; Aoki, T.; Hosokawa, S.; Kobayashi, S. Angew. *Chem., Int. Ed.* **2004**, *43*, 3175−3177. (b) Bodkin, J. A.; Humphries, E. J.; McLeod, M. D. *Tetrahedron Lett.* **2003**, *44*, 2869−2872. (c) Jung, M.; Ham, J.; Song, J. *Org. Lett* **2002**, *4*, 2763−2765. (d) Schultz, A. G.; Kirincich, S. J. *J. Org. Chem.* **1996**, *61*, 5626−5630. (e) Corey, E. J.; Trybulski, E. J.; Melvin, L. S., Jr.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, D. F.; Kim, S.; Yoo, S.-e. *J. Am. Chem. Soc.* **1978**, *100*, 4618−4620.

(3) (a) Terashima, S.; Jew, S. *Tetrahedron Lett*. **1977**, *11*, 1005−1008. (b) Jew, S. *Arch. Pharm. Res.* **1982**, *5*, 97−101. (c) Cook, C.; Cho, Y.; Jew, S.; Suh, Y.; Kang, E. *Arch. Pharm. Res.* **1983**, *6*, 45−53.

(4) Berti, B. *Tetrahedron* **1958**, *4*, 393−402.

(5) (a) Drake, M. D.; Bateman, M. A.; Detty, M. R. *Organometallics* **2003**, *22*, 4158−4162. (b) Goodman, M. A.; Detty, M. R. *Organometallics* **2004**, *23*, 3016−3020.

(6) Rood, G. A.; DeHaan, J. M.; Zibuck, R. *Tetrahedron Lett.* **1996**, *37*, 157−158.

(7) Cambie, R. C.; Rutledge, P. S.; Somerville, R. F.; Woodgate, P. D. *Synthesis* **1988**, 1009−1011.

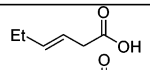
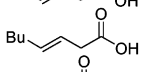
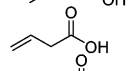
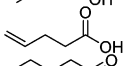
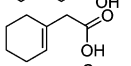
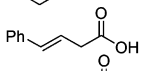
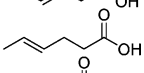
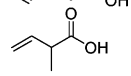
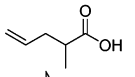
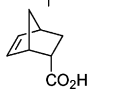
(8) Motohashi, S.; Satomi, M. *Heterocycles* **1985**, *23*, 2035−2039.

(9) Tunge, J. A.; Mellegaard, S. R. *Org. Lett.* **2004**, *6*, 1205−1207.

(10) Direct selenium-catalyzed formation of butenolides is also possible: Tiecco, M. *Top. Curr. Chem*. **2000**, *208*, 7−54.

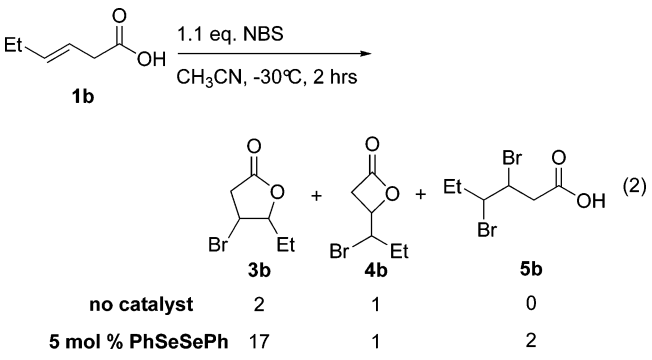
10.1021/jo048460o CCC: $27.50
Published on Web 11/11/2004

TABLE 1. Yields and Selectivities of Selenium-Catalyzed Bromolactonizations

Substrate	Time (h)	Selectivity[a]	Yield[b]
	2	94:6	52%
	1	75:25	61%[c]
	6	0:100	48%
	2	100:0	55%
	1	60:40	41%[c]
	4	100:0	90%
	2	66:34	33%[c,d]
	5	0:100	34%[e]
	3.5	100:0	89%[f]
	2	100:0	78%

[a] γ vs β or γ vs δ. [b] Reactions were run with 5 mol % of PhSeSePh, 1.1 equiv of NBS, CH_3CN, −30 °C. [c] Combined yield. [d] Mixture of diastereomers reflecting the *E*/*Z* ratio of starting material. [e] 5:1 mixture of diastereomers. [f] 3:1 mixture of diastereomers.

significantly improved the selectivity, yielding a 17:1 mixture of γ- and β-lactones. The selenium-catalyzed reaction also afforded a small amount (7%) of dibrominated acid (**5b**), which was not present in the uncatalyzed product mixture.



Other substrates were treated under our established conditions and in most cases the bromolactones were afforded in moderate to good yields (Table 1). For substrates that generally favor formation of γ-lactones, the addition of PhSeSePh only affects the time and/or conditions required for cyclization. However, for substrates where regiochemistry is an issue, catalytic quantities of PhSeSePh also favor formation of γ-lactones. For example, cyclohexenylacetic acid provides β-lactone exclusively when treated with NBS alone, but with 5 mol % of PhSeSePh γ-lactone is favored. Attempts to lower the catalyst loading to 1 mol % resulted in total loss of regiocontrol. Furthermore, PhSeSePh did not provide any regiocontrol in the catalytic bromolactonization of terminal β,γ-unsaturated acids, which are known to strongly favor formation of β-lactones.[11]

In an effort to establish the nature of the regiocontrol by PhSeSePh, we tested whether the product ratio was the result of kinetic or thermodynamic control. We thought it was possible that PhSeSePh/NBS simply catalyzed the equilibration of β-lactone to the thermodynamically favored γ-lactone. To address this issue a 2:1 mixture of γ- and β-lactones was generated by uncatalyzed bromolactonization of *trans*-3-hexenoic acid followed by treatment with either 5 mol % of PhSeSePh or with the combination of PhSeSePh and 1 equiv of NBS. After 2 h at room temperature, no equilibration of β-lactone to the γ-lactone was observed in either case. Similarly, treatment of dibrominated product **5b** under the conditions of catalysis does not result in formation of γ-lactone **3b**. Collectively, these reactions demonstrate that the product selectivity is a result of kinetic rather than thermodynamic control.

Next, we felt it was necessary to substantiate the catalytic effect of diphenyl diselenide despite the causal evidence in the change of kinetic product ratios. Toward this end, variable-temperature NMR spectroscopy allowed us to directly observe the reaction under the conditions of the reaction. Two reactions, one without PhSeSePh and one with PhSeSePh, were run with *trans*-3-hexenoic acid under otherwise identical conditions. Specifically, a 0.32 M *trans*-3-hexenoic acid solution in CD_3CN was treated with 5 mol % of PhSeSePh then cooled to −30 °C. NBS (1.1 equiv) was added, and the reaction mixture was placed in a precooled NMR probe at −30 °C. While the reaction mixture containing PhSeSePh had completely consumed the soluble NBS before the first spectrum was obtained, the control reaction had consumed <5% of the dissolved NBS. Although the soluble NBS was rapidly consumed to give halolactone when PhSeSePh was present, the hexenoic acid was not completely converted to product (30% conversion). Further reaction was more sluggish as evidenced by the low conversion (6%) of the remaining hexenoic acid over the following 10 min. This is a consequence of the low solubility of NBS in CD_3CN at −30 °C. From this information, it was surmised that the catalyzed reaction rate is limited by the rate of dissolution of NBS at low temperature.[12] To test this idea, the reaction mixture was warmed to −15 °C. At this temperature, product lactone began to form rapidly in the mixture containing PhSeSePh. Once again, free NBS was not observed, indicating mass transport limited kinetics. In contrast, the uncatalyzed reaction did not ensue despite the observable increase in NBS concentration. These experiments unequivocally establish that PhSeSePh is a catalyst for bromolactonization.

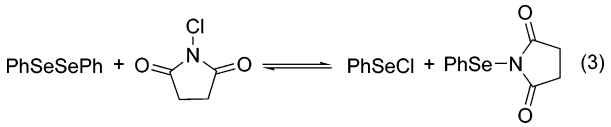
The observation of small amounts of dibrominated product **5b** indicated that it was possible that molecular bromine was being formed and was responsible for the observed bromolactonization as well. Thus, *trans*-3-hexenoic acid was treated with Br_2 at −30 °C in CH_3CN in both the presence and absence of PhSeSePh. In both

(11) Shibata, I.; Toyota, M.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1990**, *55*, 2487−2491.

(12) The rate of NBS dissolution is much higher in larger scale reactions where vigorous stirring is possible.

cases, the reaction cleanly afforded a 1:1 ratio of γ-lactone **3b** and dibromination product **5b**. Thus, the 17:2 ratio of **3b**:**5b** in the selenium-catalyzed reaction is inconsistent with the formation of molecular bromine. On the basis of this evidence, and the fact that selenium provides for kinetic control of the product ratio of halolactonization, we suggest that the reaction occurs through a selenium-bound electrophilic bromine species. We cannot rule out the possibility that dibrominated acid **5b** is formed from a low concentration of freely diffusing bromine.

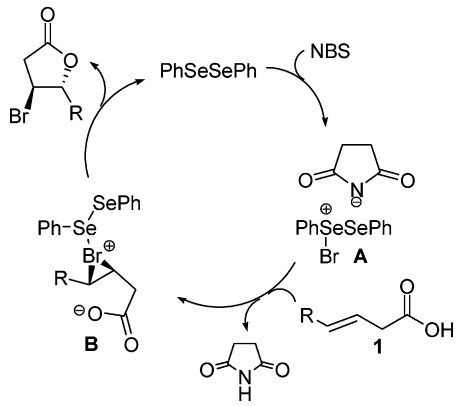
Finally, we wanted to address catalyst speciation. Sharpless has demonstrated that PhSeSePh reacts with *N*-chlorosuccinimide to give two separate selenium species, phenylselenyl chloride and phenylselenyl succinimide (eq 3).[13] In light of this precedent, we became curious



whether PhSeBr or phenylselenyl succinimide was singly responsible for the catalytic bromolactonization. In an effort to determine the active catalytic species, phenylselenyl bromide and *N*-phenylselenopthalimide[14]were separately screened as catalysts for the halolactonization of *trans*-3-hexenoic acid. While both catalysts effected halolactonization, the **3b**:**5b** product ratios (4:1 for phenylselenyl bromide, and 2:1 for *N*-phenylselenopthalimide) obtained were not consistent with that observed with PhSeSePh. The fact that neither catalyst reproduced the experimental results given by PhSeSePh suggests that the diselenide may not be oxidatively cleaved by NBS during catalysis.

Although more experiments are required to elucidate the mechanism of catalysis, we suggest the following mechanism based on the available experimental results. First, we propose that the NBS undergoes nucleophilic attack by the diselenide to produce the cationic selenium complex (**A**) with a succinimide counterion (Scheme 1). This transformation is equivalent to the first step in the well-known oxidative cleavage of diselenides with molecular bromine.[15] The resulting succinimide anion is expected to rapidly deprotonate the carboxylic acid (**1**) to form the carboxylate. To rationalize the observed

SCHEME 1



regiocontrol, we suggest that lactone formation proceeds through nucleophilic displacement of a selenium-coordinated bromonium ion (**B**). Such a cyclization is reminiscent of halocyclizations with bromopyridinium reagents, where the pyridine derivative remains coordinated to bromine during lactone ring formation.[16]

In conclusion, we have demonstrated that diphenyl diselenide is an efficient catalyst for the halolactonization of unsaturated acids. This is to our knowledge the first example of catalytic halolactonization. Moreover, selenium catalytically activates halogen oxidants toward reaction, which is a new approach to oxidative halogenation. In the future, we hope to take advantage of our ability to alter the ligand environment of selenium to achieve higher degrees of regioselectivity.

Experimental Section

General Procedure for Bromolactonization of β,γ- or γ,δ-Unsaturated Acids. Diphenyl diselenide (0.05 mmol) was dissolved in 5 mL of CH_3CN (stored over 4 Å MS), producing a yellow solution. The unsaturated acid (1.00 mmol) was added, and the resulting mixture was cooled to −30 °C. Next, *N*-bromosuccinimide (1.1 mmol) was added and the resulting reaction mixture was stirred for the reported time. The resulting solution was concentrated to <1 mL, and 10 mL of diethyl ether was added. The ether was decanted from the solid and washed with H_2O (2 × 3 mL). The resulting ether layer was dried over $MgSO_4$ and concentrated, and the residue was purified by flash chromatography (100% methylene chloride).

Acknowledgment. We thank the EPSCoR program of the National Science Foundation for funding.

Supporting Information Available: Spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048460O

(13) (a) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4208−10. (b) Chabaud, B.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4204−4208.

(14) *N*-Phenylselenophthalimide is a more thermally stable form of *N*-phenylselenosuccinimide. Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884−3893.

(15) (a) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429−430. (b) Clive, D. L. J.; Chittattu, G.; Curtis, N. J.; Kiel, W. A.; Wong, C. K. *J. Chem Soc., Chem. Commun.* **1977**, 725−727.

(16) (a) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1998**, *63*, 5977−82. (b) Neverov, A. A.; Feng, H. X.; Hamilton, K.; Brown, R. S. J. *Org. Chem.* **2003**, *68*, 3802−10.