

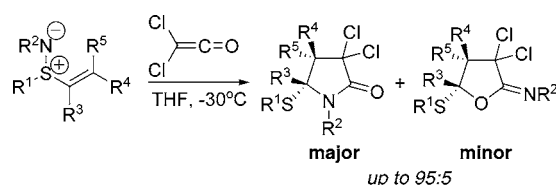
Chemoselective Syntheses of  
 $\gamma$ -Butyrolactams Using Vinyl Sulfilimines  
and Dichloroketene

Joseph P. Marino\* and Nanfei Zou

*Department of Chemistry and Biochemistry, University of Notre Dame,  
Notre Dame, Indiana 46556  
marino.12@nd.edu*

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## ABSTRACT



Reactions between vinyl sulfilimines and dichloroketene generated in situ from trichloroacetyl chloride in the presence of zinc–copper couple give mixtures of  $\alpha$ -dichloro- $\gamma$ -butyrolactams and  $\alpha$ -dichloro- $\gamma$ -butyrolactone imines. Fine-tuning of substituents within vinyl sulfilimines results in reactions with good chemoselectivity and yield for lactams.

The  $\gamma$ -butyrolactam moiety is a very important component of many natural products.<sup>1</sup> It serves not only as an important pharmacophore in the drug discovery process<sup>2</sup> but also as a key intermediate in the synthesis of biologically and pharmaceutically relevant molecules.<sup>3</sup>

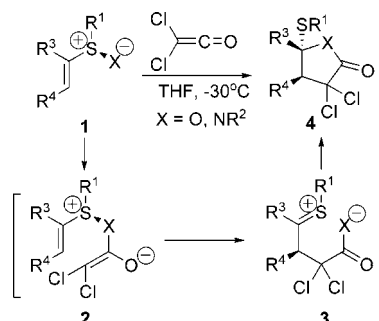
Over the past decade, our group has been interested in developing and utilizing a  $\gamma$ -lactonization reaction involving chiral vinyl sulfoxides with dichloroketene (Scheme 1, X = O).<sup>4</sup> This reaction can transfer the chirality of sulfur to as many as three contiguous carbon centers through a novel [3,3]-sigmatropic rearrangement of an intermediate vinyl oxsulfonium enolate **2**. The  $\gamma$ -lactonization reaction was later applied by our group and others to the total syntheses of natural products and medicinally useful compounds.<sup>5</sup> It had been recently demonstrated as a powerful tool for the

construction of quaternary carbon centers in a stereoselective formation of a functionalized  $\gamma$ -lactone key intermediate toward enantioselective synthesis of (+)-aspidospermidine.<sup>6</sup>

While sulfilimines are generally treated as the nitrogen analogues of sulfoxides, they have received less attention than sulfoxides.<sup>7</sup> Herein, by applying our knowledge of  $\gamma$ -lactonization reaction, we report a novel chemoselective synthesis of  $\gamma$ -butyrolactams based on the reaction between vinyl sulfilimine and dichloroketene.<sup>8</sup>

When *p*-tolyl styryl *N*-*p*-toluenesulfonyl (tosyl or Ts) sulfilimine **5f** was treated with trichloroacetyl chloride in

**Scheme 1.** Lactonization Reaction and Proposed Lactamization Reaction



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the presence of zinc–copper couple in THF at  $-30\text{ }^{\circ}\text{C}$ , the sulfilimine reacted with dichloroketene generated in situ and converted to two products as observed on thin-layer chromatography. Upon purification, these two products were identified as *N*-tosyl dichlorolactam **6f** and dichlorolactone *N*-tosylimine **7f** in a ratio of 62:38 according to  $^1\text{H}$  NMR analysis on the crude reaction mixture. Even though these two compounds behaved similarly on  $^1\text{H}$  and  $^{13}\text{C}$  NMR, their IR spectra showed quite different characteristic absorption bands. While the  $\text{C}=\text{O}$  stretching frequency of the *N*-tosyl lactam occurred at  $1765\text{ cm}^{-1}$ ,  $1665\text{ cm}^{-1}$  was assigned to that of  $\text{C}=\text{N}$  in the lactone *N*-tosylimine.<sup>9</sup> Given the poor nucleophilicity property of *N*-tosyl-stabilized amido anion, it is not surprising that both *N*-alkylation and *O*-alkylation<sup>10</sup> occurred competitively at the stage of the sulfonium intermediate **3** (Scheme 1,  $\text{X} = \text{NR}^2$ ), leading to *N*-tosyl lactam and lactone *N*-tosylimine, respectively.

It was found that the ratio of lactam to lactone imine showed no response to temperature variation ( $-30$ ,  $0$ , and  $25\text{ }^{\circ}\text{C}$ ). Suspecting that *N*-tosyl group further diminished the nucleophilicity of the amido anion within sulfonium intermediate **3**, we changed the substituents on nitrogen of sulfilimine and synthesized a series of *N*-arylsulfonyl sulfilimines (Table 1, entries a–d) with either an electron-donating group (EDG) or an electron-withdrawing group (EWG) on benzene to adjust the electronic character of the sulfonyl group.<sup>11</sup> *N*-Benzyloxycarbonyl (Cbz) sulfilimine **5e** was also synthesized in hope that the desired product *N*-Cbz lactam would allow simple deprotection to give the free lactam. First, only a 4% improvement in the lactam/lactone ratio was observed as the *N*-sulfonyl substituent was changed from electron-withdrawing to electron-donating group. To our delight, the overall conversion and combined yield of lactam and lactone imine improved, which may indicate favorable lactamization and lactonization with electron-rich sulfilimines. Therefore, it is not surprising that strong EWGs such as *p*-nitrobenzenesulfonyl in sulfilimine **5d** shut down the reaction completely. On the other hand, *N*-Cbz sulfilimine

**Table 1.** Lactam Reaction of Styryl Sulfilimines with Dichloroketene

entry	R <sup>1</sup>	R <sup>2</sup>	lactam:lactone imine <sup>b</sup>	yield (%) <sup>c</sup>
a	Ph	Ts	59:41	71
b	Ph	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	57:43	65
c	Ph	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	61:39	78
d	Ph	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	N/A	NR <sup>d</sup>
e	Ph	Cbz	N/A	N/A <sup>e</sup>
f	Tol	Ts	62:38	74
g	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ts	57:43	55
h	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ts	66:34	84
i	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	Ts	90:10	81
j	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	Ts	95:5	82
k	<i>t</i> -Bu	Ts	88:12	70 <sup>f</sup>
l	Bn	Ts	95:5	80

<sup>a</sup> Reaction conditions: trichloroacetyl chloride 5 equiv, zinc 20 equiv, copper(I) chloride 20 equiv, THF,  $-30\text{ }^{\circ}\text{C}$ , 0.5 h. <sup>b</sup> Determined by  $^1\text{H}$  NMR analysis. <sup>c</sup> Combined, isolated yield of lactam and lactone imine and isolated yield of lactams **7i–l**. <sup>d</sup> No reaction. <sup>e</sup> Phenyl styryl sulfide was isolated in 90%. <sup>f</sup> *N*-Tosylstyryl sulfenamide was isolated in 20%.

**5e** denitrogenated to give 92% yield of phenyl styryl sulfide.<sup>8</sup> When R<sup>1</sup> was varied from an EWG (*p*-chlorobenzene) to an EDG (*p*-methoxybenzene) within *N*-tosyl sulfilimines **5g** and **5h**, the lactam/lactone ratio increased only a marginal 9% but the overall yield increased 29%. Better selectivity for the lactam was reached when R<sup>1</sup> was switched to alkyl groups (Table 1, entries i–l). Both primary and secondary alkyl groups worked well in terms of chemoselectivity and yields for lactams. As for *tert*-butyl *N*-tosyl sulfilimine **5k**, about 20% *N*-*p*-tolylstyryl sulfenamide was obtained in addition to an 88:12 ratio of lactam and lactone imine in 70% yield. This sulfenamide was likely generated from the sulfilimine **5k** with nitrogen abstracting a proton from the *tert*-butyl group and eliminating it as isobutene.<sup>12</sup>

Functionalized vinyl sulfilimines were tested for compatibility with lactamization conditions (Table 2, entries 2–4). High selectivity for lactams was found in crude reaction mixtures, and good isolated yields were obtained. Cyclohexenyl sulfilimine **22** also reacted smoothly to give 79% yield of ring-fused lactam **23**.

However, it was found that  $\beta$ -disubstituted vinyl sulfilimine **20** reacted slowly even when 20% more trichloroacetyl chloride was added to the reaction and the reaction was held at  $-30\text{ }^{\circ}\text{C}$  for extended time. Similarly, *cis*-vinyl sulfilimines **16** and **18** reacted slower than their *trans* counterparts **5j** and **8**, respectively. This may indicate that the approach by dichloroketene to the *N*-tosyl nitrogen was hindered by the *cis* substituents.

The relative stereochemistry of *N*-tosyl dichlorolactam was confirmed by an NOE study. Analogous to the previously

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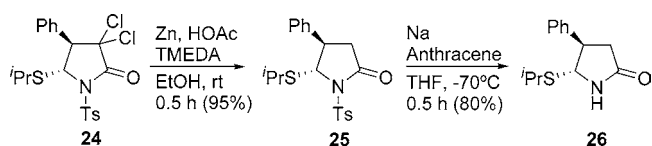
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**Table 2.** Lactam Reaction of Functionalized Vinyl Sulfilmines<sup>a</sup>

entry	sulfilimine	lactam (yield) <sup>b</sup>
1		
2		
3		
4		
5		
6		
7		
8		

<sup>a</sup> Abbreviation: Cy = cyclohexyl. <sup>b</sup> Isolated yield.

proposed mechanism of  $\gamma$ -lactonization,<sup>4</sup> it is suggested that (1) the highly electrophilic dichloroketene acylates the sulfilimine nitrogen atom to generate the vinyl aminosulfonium enolate; (2) a [3,3]-sigmatropic rearrangement gives a

**Scheme 2**

Pummerer-type intermediate;<sup>13</sup> and (3) *N*-tosylamido anion and *N*-tosylimino oxyanion intramolecularly trap this intermediate to produce the observed *N*-tosyl lactam and lactone *N*-tosylimine, respectively.

Dechlorination of dichlorolactam **24** with zinc, HOAc, and TMEDA proceeded in excellent yield (Scheme 2).<sup>14</sup> Selective detosylation was obtained when *N*-tosyl lactam **25** was treated with sodium anthracene<sup>10</sup> in THF at  $-70\text{ }^{\circ}\text{C}$  to give lactam **26** with a labile  $\gamma$ -alkylthio group. This lactam would be a useful precursor for acyliminium ion chemistry.<sup>15</sup>

In conclusion, we have disclosed a  $\gamma$ -lactamization reaction between vinyl sulfilmines and dichloroketene. Upon judicious selection of substituents within the sulfilimine, good selectivity of  $\gamma$ -lactam over  $\gamma$ -lactone imine has been established. We are currently exploring an asymmetric entry to this reaction and its applications to natural products synthesis, and our results will be reported in due course.

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**Supporting Information Available:** Experimental procedures and characterization of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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