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Chemoselective Syntheses of γ-Butyrolactams Using Vinyl Sulfilimines and Dichloroketene

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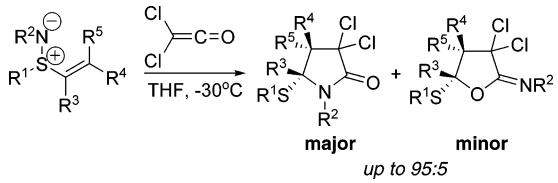
ABSTRACT



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

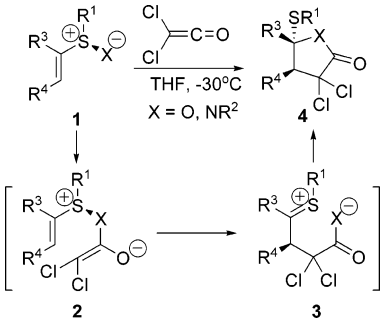
The γ-butyrolactam moiety is a very important component of many natural products.[1] It serves not only as an important pharmacophore in the drug discovery process[2] but also as a key intermediate in the synthesis of biologically and pharmaceutically relevant molecules.[3]

Over the past decade, our group has been interested in developing and utilizing a γ-lactonization reaction involving chiral vinyl sulfoxides with dichloroketene (Scheme 1, X = O).[4] 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 γ-lactonization reaction was later applied by our group and others to the total syntheses of natural products and medicinally useful compounds.[5] It had been recently demonstrated as a powerful tool for the construction of quarternary carbon centers in a stereoselective formation of a functionalized γ-lactone key intermediate toward enantioselective synthesis of (+)-aspidospermidine.[6]

While sulfilimines are generally treated as the nitrogen analogues of sulfoxides, they have received less attention than sulfoxides.[7] Herein, by applying our knowledge of γ-lactonization reaction, we report a novel chemoselective synthesis of γ-butyrolactams based on the reaction between vinyl sulfilimine and dichoroketene.[8]

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



(1) (a) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355. (b) Masse, C. E.; Morgan, A. J.; Adams, J.; Panek, J. S. *Eur. J. Org. Chem.* **2000**, 2513. (c) Corey, E. J.; Li, W.-D. *Chem. Pharm. Bull.* **1999**, *47*, 1.

(2) (a) Schreiber, S. L.; Standaert, R. F.; Fenteany, G.; Jamison, T. F. U.S. Patent 6 645 999, 2003. (b) Baldwin, J. E.; Lynch, G. P.; Pitlik, J. *J. Antibiotics* **1991**, *44*, 1.

(3) Zhang, J.; Blazecka, P. G.; Davidson, J. G. *Org. Lett.* **2003**, *5*, 553 and references therein.

(4) (a) Marino, J. P.; Neisser, M. *J. Am. Chem. Soc.* **1981**, *103*, 7687. (b) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643. (c) Marino, J. P.; Laborde, E.; Paley, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 966. (d) Marino, J. P. *Pure Appl. Chem.* **1993**, *65*, 667.

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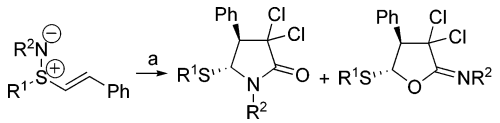
the presence of zinc−copper couple in THF at −30 °C, the sulfilimine reacted with dichloroketene generated in situ and converted to two products as observed on thin-layer chromatography. Upon purification, these two products were identified as *N*-tosyl dichlorolactam **6f** and dichlorolactone *N*-tosylimine **7f** in a ratio of 62:38 according to ^{1}H NMR analysis on the crude reaction mixture. Even though these two compounds behaved similarly on ^{1}H and ^{13}C NMR, their IR spectra showed quite different characteristic absorption bands. While the C═O stretching frequency of the *N*-tosyl lactam occurred at 1765 cm^{-1}, 1665 cm^{-1} was assigned to that of C═N in the lactone *N*-tosylimine.[9] Given the poor nucleophilicity property of *N*-tosyl-stabilized amido anion, it is not surprising that both N-alkylation and O-alkylation[10] occurred competitively at the stage of the sulfonium intermediate **3** (Scheme 1, X = 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 °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.[11] *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 **5e** denitrogenated to give 92% yield of phenyl styryl sulfide.[8] When R^1 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^1 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.[12]

Table 1. Lactam Reaction of Styryl Sulfilimines with Dichloroketene



5a-l lactam 6a-l lactone imine 7a-l

entry	R^1	R^2	lactam:lactone imine[b]	yield (%)[c]
a	Ph	Ts	59:41	71
b	Ph	*p*-ClC$_6$H$_4$SO$_2$	57:43	65
c	Ph	*p*-MeOC$_6$H$_4$SO$_2$	61:39	78
d	Ph	*p*-NO$_2$C$_6$H$_4$SO$_2$	N/A	NR[d]
e	Ph	Cbz	N/A	N/A[e]
f	Tol	Ts	62:38	74
g	*p*-ClC$_6$H$_4$	Ts	57:43	55
h	*p*-MeOC$_6$H$_4$	Ts	66:34	84
i	*n*-C$_6$H$_{13}$	Ts	90:10	81
j	*c*-C$_6$H$_{11}$	Ts	95:5	82
k	*t*-Bu	Ts	88:12	70[f]
l	Bn	Ts	95:5	80

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

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 β-disubstituted vinyl sulfilimine **20** reacted slowly even when 20% more trichloroacetyl chloride was added to the reaction and the reaction was held at −30 °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

(5) (a) Marino, J. P.; Bogdan, S.; Kimura, K.*J. Am. Chem. Soc.* **1992**, *114*, 5566. (b) Kosugi, H.; Mirura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1409. (c) Burke, S. D.; Shankaran, K.; Helber, M. J. *Tetrahedron Lett.* **1991**, *32*, 4655. (d) Bravo, P.; Arnone, A.; Bandiera, P.; Bruche, L.; Ohashi, Y.; Ono, T.; Sekine, A.; Zanda, M. *Eur. J. Org. Chem.* **1999**, 111.

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(8) For a report on *N*-acyl sulfilimine reacting with diphenylketene to give oxazolinone and sulfide, see: Abou-Gharbia, M.; Ketcha, D. M.; Zacharias, D. E.; Swern, D. *J. Org. Chem.* **1985**, *50*, 2224.

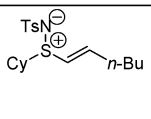
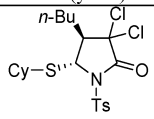
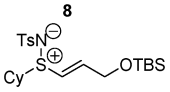
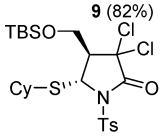
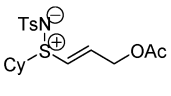
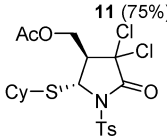
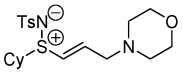
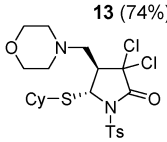
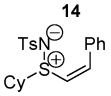
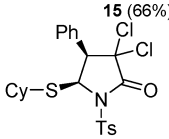
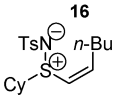
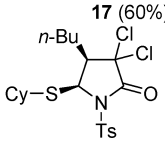
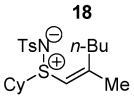
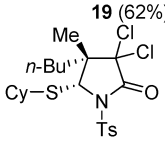
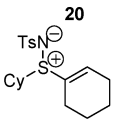
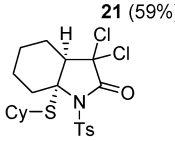
(9) Fretschi, S.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2024.

(10) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.

(11) (a) *N*-Arylsulfonyl sulfilimines **5b**−**d** (Table 1) and *N*-Cbz sulfilimines **5e** (Table 1) were prepared according to methods in ref 11b. Sodium *N*-chloro-*N*-arylsulfonamides and sodium *N*-chloro-*N*-carbamate were made by procedures adapted from refs 11c,d. (b) Marzinzik, A. L.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 594. (c) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810. (d) Campbell, M. M.; Johnson, G. *Chem. Rev.* **1978**, *78*, 65.

(12) Mukaiyama, T.; Matsuo, J.-I.; Kitagawa, H. *Chem. Lett.* **2000**, 1250.

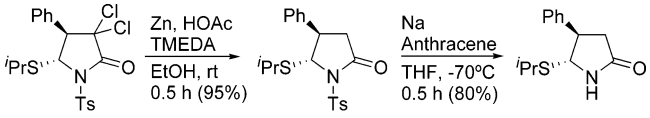
Table 2. Lactam Reaction of Functionalized Vinyl Sulfilmines[a]

entry	sulfilimine	lactam (yield)[b]
1		 **9** (82%)
2	**8** 	 **11** (75%)
3	**10** 	 **13** (74%)
4	**12** 	 **15** (66%)
5	**14** 	 **17** (60%)
6	**16** 	 **19** (62%)
7	**18** 	 **21** (59%)
8	**20**  **22**	 **23** (79%)

[a] Abbreviation: Cy = cyclohexyl. [b] Isolated yield.

proposed mechanism of γ-lactonization,[4] it is suggested that (1) the highly eletrophilic dichloroketene acylates the sulfilimine nitrogen atom to generate the vinyl aminosulfonium enolate; (2) a [3,3]-sigmatropic rearrangement gives a Pummerer-type intermediate;[13] 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.

Scheme 2



24 **25** **26**

Dechlorination of dichlorolactam **24** with zinc, HOAc, and TMEDA proceeded in excellent yield (Scheme 2).[14] Selective detosylation was obtained when *N*-tosyl lactam **25** was treated with sodium anthrathene[10] in THF at −70 °C to give lactam **26** with a labile γ-alkylthio group. This lactam would be a useful precursor for acyliminium ion chemistry.[15]

In conclusion, we have disclosed a γ-lactamization reaction between vinyl sulfilimines and dichloroketene. Upon judicious selection of substituents within the sulfilimine, good selectivity of γ-lactam over γ-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.

Acknowledgment. We thank University of Notre Dame for its generous support of this program. We also thank Mr. Anthony Turpoff for making compound **6a**. During our preparation of this manuscript, we were informed by Prof. Albert Padwa of Emory University of their recent work on similar systems of this reaction.[16]

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

OL050245M

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(14) Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299.
(15) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.
(16) Wang, Q.; Nara, S.; Padwa, A. *Org. Lett.* **2005**, *7*, 839.