Diastereoselective Sulfenylation Reactions Employing *N*-(Phenylthio)lactams under Nonbasic Conditions

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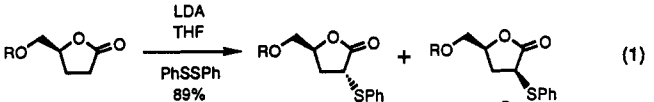
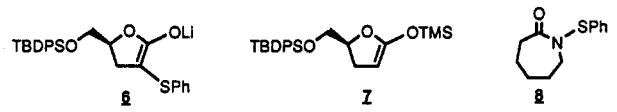
Summary: Silyl enol ethers and silyl ketene acetals react with sulfenamides in the presence of trimethylsilyl triflate to give the corresponding trans-sulfenylated ketones and lactones.

We have recently demonstrated the utility of the 2-phenylthio group for controlling the stereoselectivity of nitrogen glycosylation reactions used in the synthesis of the anti-HIV nucleoside, D4T (3, Scheme I).[1] In order for this overall approach to be successful, we required a reagent that would efficiently effect a trans-sulfenylation on various derivatives of 4-(hydroxymethyl)butyrolactone (i.e., formation of 1). Our initial attempts made use of the enolate of (*S*)-lactone 4[2] under the conditions developed by Trost and Salzmann (2 equiv of LDA, PhSSPh)[3] and resulted in a disappointing 4:3 mixture of the trans and cis products 1 and 5 (eq 1).[1,4] We determined that this



(1)



low selectivity was the result of product epimerization; i.e., the reaction of sulfenylated lactones 1 and 5 with the enolate of 4 produces the more stable enolate 6 which, upon quenching, protonates with low diastereofacial selectivity.[3,5]

In order to avoid product equilibration, we examined the reaction of phenylsulfenyl chloride (PhSCl) with the silyl ketene acetal 7 and observed a trans/cis ratio of 3:1 (83% yield).[6] We considered this level of selectivity to be unacceptable for our purposes and reasoned that by varying the size of both the aryl substituent and the leaving group on the sulfur atom, higher levels of diastereofacial selectivity could be achieved. To test this hypothesis, we examined the reaction of *N*-(phenylthio)-ε-caprolactam (8) and TMSOTf with 7 at −78 °C and found that this combination provided a 9:1 ratio of sulfenylated product favoring the trans isomer 1 (eq 2 and Table I, entry 2).[7,8]

Scheme I

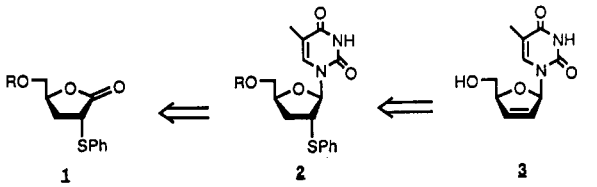
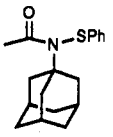
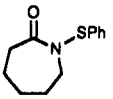
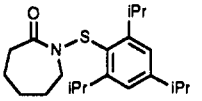
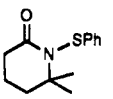
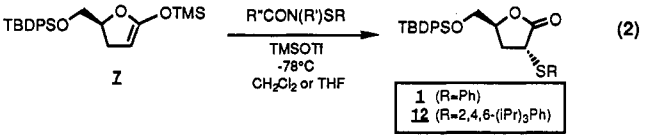


Table I. Reaction of 7 with Various Sulfenamides (eq 2)

entry	R″CON(R′)SR[a]	product ratio (trans:cis)[b,d,e]	yield (%)
1	 9	10:1	99[c]
2	 8	9:1	92 (98)[c]
3	 10	30:1[d]	73
4	 11	22:1	88 (99)[c]

[a] Sulfenamides 9–11 were synthesized by deprotonation of the corresponding amide with *n*-BuLi, followed by quenching with the appropriate sulfenyl chloride. [b] For 1:5, ratio determined by HPLC. [c] % conversion determined by HPLC. [d] For 12, ratio determined by ^{1}H NMR. [e] For entries 1, 3, and 4, 7 was generated in situ (see method A, Table II). For entry 2, both Methods A and B were employed.



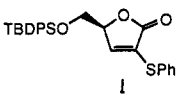
(2)

(1) (a) Wilson, L. J.; Liotta, D. C. *Tetrahedron Lett.* **1990**, *31*, 1815–1818. For approaches that utilize similar strategies, see: (b) Kawakami, H.; Ebata, T.; Koseki, K.; Matushita, H.; Naoi, Y.; Itoh, K. *Chem. Lett.* **1990**, 1459. (c) Chu, C. K.; Babu, J. R.; Beach, J. W.; Ahn, S. K.; Huang, H.; Jeong, L. S.; Lee, S. J. *J. Org. Chem.* **1990**, *55*, 1418.

(2) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449–1452. (*S*)-Lactone 4 is available in three steps from (L)-glutamic acid.

(3) Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1975**, *98*, 487–492. In this article, the low facial selectivity is the result of product equilibration because of the use of 2 equiv of base in these reactions. However, it should be noted that for many applications the facial selectivity of sulfenylation reactions is not important.

(4) The enolate of lactone 4 reacts with methyl iodide with >10:1 trans selectivity. For this and other uses of this lactone, see: Hanessian, S. *Aldrichimica Acta* **1989**, *22*, 3–14. The stereochemistries of 1 and 5 were determined from the following observations: (i) conversion of 1 to D4T, 3; (ii) ^{1}H NOE experiments show that irradiation of the 4-α-H of compound 5 results in a 7% enhancement of the 2-α-H signal; (iii) hydrogenation of 2-thiophenylbutenolide i results in a 7:1 mixture of 5 to 1.



i

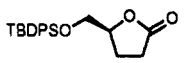
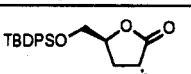
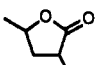
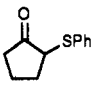
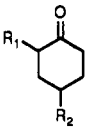
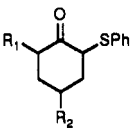
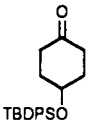
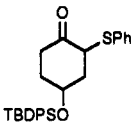
(5) This type of result has been observed previously with lactams. See: Zoretic, P. A.; Soja, P. *J. Org. Chem.* **1976**, *41*, 3587–3589.

(6) Seebach, D.; Teschner, M. *Chem. Ber.* **1976**, *109*, 1601–1616. Reaction performed with TMSOTf at −78 °C in CH_2Cl_2. In the absence of this Lewis acid, the reaction needed to be warmed to 0 °C. The observed ratio of 1 to 5 was 2:1.

(7) This reagent is available from Aldrich Chemical Co. For the synthesis of 8 and subsequent uses in the N-sulfenylation of amines, see: Sosnovsky, G.; Krogh, J. A. *Synthesis* **1979**, *3*, 228–230.

0022-3263/92/1957-1948$03.00/0

Table II. Reaction of Various Carbonyl Compounds with Caprolactam 8

entry	carbonyl or enol silane	condns[a]	product	yield[b] (%) (ratio trans:cis)
1		A		92 (9:1)[c]
2	**4**	B	**1**	76
3		A		99 (3.7:1)[d]
	13		**14**	
4		B		84[f]
	15[e]		**16**	
5		B		60 (1:1)[d,g]
6		B		68 (1:1)[d,h]
	17 (R_1 = Me, R_2 = H) **19** (R_1 = H, R_2 = tBu)		**18** (R_1 = Me, R_2 = H) **20** (R_1 = H, R_2 = tBu)	
7		B		77 (5.5:1)[d]
	21		**22**	

[a] Method A (in situ): (i) $LiN(TMS)_2$, −78 °C, THF; (ii) TMSCl, −78 °C to rt; (iii) 8 (1.25 equiv), TMSOTf (1.25 equiv), −78 °C (3 h) to rt (1 h). Method B (from enol silane): silyl enol ether, CH_2Cl_2, 8 (1.25 equiv), TMSOTf (0.25 equiv), −78 °C (3 h) to rt (1 h). [b] Isolated yield after flash chromatography. [c] Ratio determined by HPLC. [d] Ratio determined by ^1H NMR. [e] Available from Aldrich Chemical Co. [f] With PhSCl, 77% yield, ref 6. [g] With LDA/$PhSSO_2Ph$, 85% yield, 2:1 trans/cis ratio, ref 3. [h] With LDA/PhSSPh, 78% yield, 2:1 trans/cis ratio, ref 3.

Thus, we concluded that by using appropriate sulfenamide/Lewis acid combinations, it might be possible to fine tune both the reactivity and selectivity of sulfur electrophiles towards various substrates.

The initial phase of our study focused on the consequences of varying the amide portion of the sulfur electrophiles. Various *N*-(phenylthio)amides were synthesized and studied in the sulfenylation of the silyl ketene acetal **7** (Table I, eq 2). Increasing the size of the alkyl group on the nitrogen atom (entry 1) resulted in selectivities that were no better than those observed with caprolactam **8**. However, site-selective modifications of the alkyl substituent that imposed additional conformational restrictions on the system (vide infra) produced a significant increase in the selectivity. Specifically, inclusion of geminal methyl groups adjacent to the nitrogen (entry 4) resulted in trans selectivity of greater than 20:1. Not surprisingly, we found that increasing the size of the aryl group on sulfur (entry 3) further increased the facial selectivity of the process and resulted in an impressive 30:1 selectivity ratio.[11] Taken in aggregate, these results suggest that the selectivity exhibited by these reagents is governed primarily by steric factors.

The use of facially-discriminating sulfenamides can not result in high trans/cis selectivity ratios when the substrate in question lacks a significant facial bias. Thus, cyclic substrates with substituents that prefer to exist in a pseudoequatorial arrangement (e.g., the silyl enol ethers of 2-methylcyclohexanone (**17**, entry 5) and 4-*tert*-butylcyclohexanone (**19**, entry 6)) react with **8** and TMSOTf with no selectivity (1:1 for both examples). However, as the substituent on average protrudes further from the mean plane of the ring, it should exert a larger steric bias and result in higher selectivity. This pattern is illustrated by the reactions of **8** and TMSOTf with the ketene acetal of γ-valerolactone **13** and the silyl enol ether of 4-[(*tert*-butyldiphenylsilyl)oxy]cyclohexanone (**21**) which produce the sulfenylated adducts in 3.7:1 (Table II, entry 3)[12a] and 5.5:1 selectivity (Table II, entry 7),[12b] respectively.

The optimum reaction conditions vary depending on whether or not the silylated intermediate in question is isolated. When the silyl derivative is isolated, the reaction is best performed with 0.25 equiv of TMSOTf in dichloromethane (method B). However, sulfenylations carried out with silyl derivatives which have been generated in situ require 1.25 equiv of TMSOTf (method A).

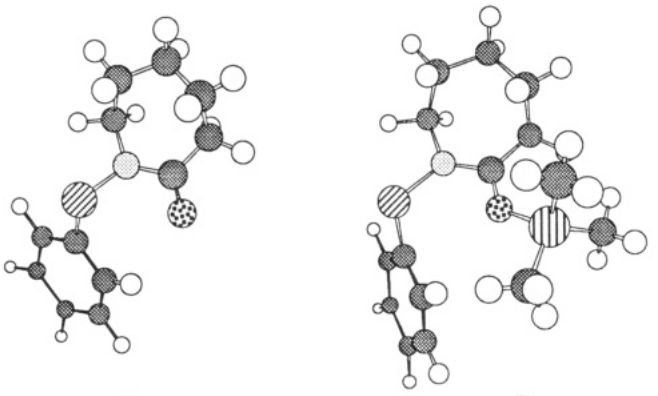
(8) Sulfenylations of active methylene compounds using *N*-sulfenylamines have been previously reported. However, under the conditions used the corresponding amine was generated as a byproduct.[9,10] Since we have determined that both **1** and **5** are equilibrated in the presence of amines, these reagents were of little use to us. Under a variety of reaction conditions (including those employed for **8**), the use of other reagents, such as *N*-(phenylthio)phthalimide (which sulfenylates enamines)[9] and phenylthio phenylsulfonate ($PhSSO_2Ph$),[3] gave no sulfenylation products.

(9) Kumamoto, T.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 866–870.

(10) For an example of a enantioselective sulfenylation of 4-*tert*-butylcyclohexanone using secondary and tertiary *N*-(phenylthio)amines that produced products with optical purities ranging from 10 to 50%, see: Hiroi, K.; Nishida, M.; Nakayama, A.; Nakazawa, K.; Fujji, E.; Sato, S. *Chem. Lett.* **1979**, 969–972. Note, however, that in this report the issue of facial selectivity in the sulfenylation reactions is not treated.

(11) The reaction of **7** with 2,4,6-triisopropylbenzenesulfenyl chloride results in a 14:1 trans:cis mixture of **12** in 96% yield. *Trans*-**12** can also be converted to D4T (**3**) using a procedure similar to that described in ref 1. Details of this process will be reported in a future publication.

(12) (a) The methyl group on the nearly planar, five-membered ring of γ-valerolactone protrudes further out of plane than a pseudoequatorial substituent on a six-membered ring. (b) Siloxy substituents are reported to exhibit an axial preference in a variety of six membered rings. See: Nagao, Y.; Goto, M.; Ochiai, M.; Shiro, M. *Chem. Lett.* **1990**, 1503–1506.



A B

Figure 1.

The yields are usually better using the latter approach, presumably because it minimizes losses due to the moisture sensitivity of the silylated intermediates. Thus, the silyl ketene acetal of lactone **4** gives 92% isolated yield in the one-pot procedure (entry 1) and 76% yield when **7** is isolated first (entry 2, 83% based on recovered **4**).

Previous studies on the conformations of *N*-sulfenamides[13] indicate that this class of compounds exhibits distinct conformational preferences resulting from both $n-\pi^*$ stabilizations and lone pair–lone pair repulsions between the orbitals on the sulfur and nitrogen atoms. Since it seemed that the results obtained here might be related to this observation, we performed a series of molecular orbital calculations (MOPAC 5.0, PM3) on both the caprolactam **8** as well as its O-silylated derivative. This study indicated that the global minimum of **8** is the conformer in which the aryl carbon–sulfur bond is perpendicular to the plane defined by the amide and that the calculated barrier to rotation around the S–N bond is 6.5 kcal/mol between the degenerate minima (Figure 1A).[13,14] When a trimethylsilyl group is added to the lactam oxygen, the global minimum shifts slightly to 63° and the bond rotation barrier drops to 3.8 kcal/mol (Figure 1B).[15] We believe that this preference for twisted structures plays a significant role in determining the diastereoselectivity which is observed. In the energetically-favored conformer, one face of the sulfur is significantly more hindered than the other. Therefore, an incoming nucleophile must select an approach trajectory that minimizes destabilizing interactions with both the aryl and lactam substituents. As the relative facial bias of the incoming nucleophile increases, so too does the observed product selectivity. Using this model, it is also apparent why reagents which possess geminal methyl substituents at the carbon adjacent to nitrogen (**11**) and/or the triisopropylphenyl substituent (**10**) exhibit higher facial selectivities.[16,17]

The results obtained here with *N*-(phenylthio)-ϵ-caprolactam (**8**) provide a new method for sulfenylating active methylene compounds under nonbasic conditions via their silyl enol derivatives. These reagents possess an inherent source of steric bias that can be tailored to increase the diastereoselectivity, if needed. This method thus complements our earlier efforts at developing efficient methods for producing antiviral nucleosides. Further studies on this new type of reaction will be reported in due course.

Acknowledgment. We thank the National Institutes of Health for funding this research and Kathy Durkin for performing the MOPAC calculations on **8**.

Supplementary Material Available: Experimental procedures for **1** and **5** (conditions A and B, Table II) and **11**, as well as spectral and analytical data for **1**, **5**, **9**–**11**, **12**, **14**, and **22** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689–712.
(14) Kost, D.; Egozy, H. *J. Org. Chem.* **1989**, *54*, 4909–4913.
(15) Although the global minimum is calculated to be 63°, the 87° conformer is only 0.29 kcal/mol higher in energy.
(16) This stereoselectivity dependence on the amide portion rules out formation of a "common" sulfenylating reagent, such as PhSOTf (resulting from N–S bond cleavage by triflate anion), since this would be expected to give the same selectivity for any lactam example. See ref 13 for examples of this occurrence in other sulfenylation reactions.
(17) For an example of another sulfur electrophile/Lewis acid combination (PhSOMe/TMSOTf), see: Edstrom, E. D.; Livinghouse, T. *J. Am. Chem. Soc.* **1986**, *108*, 1334–1336.