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Stereoselective Synthesis of Highly Substituted γ-Lactams by the [3+2] Annulation of α-Siloxy Allylic Silanes with Chlorosulfonyl Isocyanate

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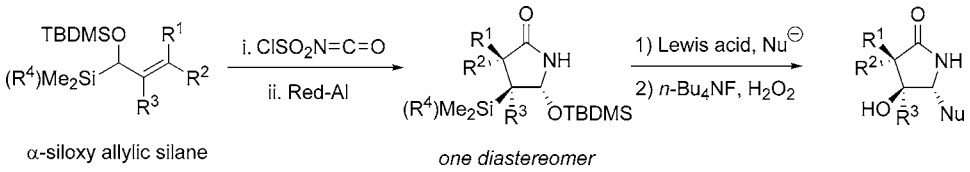
ABSTRACT



A stereoselective synthesis of γ-lactams by the [3+2] annulation of α-siloxy allylic silanes with *N*-chlorosulfonyl isocyanate ($ClSO_2NCO$) was developed. The use of these allylic silanes allowed for further diastereoselective substitution of the resultant *N,O*-acetal to give highly substituted γ-lactams. Oxidation of the silyl group afforded access to complex β-hydroxy-γ-lactams.

The γ-lactam functionality represents an important core structure in numerous biologically active compounds.[1,2] Functionalized chiral γ-lactams have also proven to be valuable intermediates for the synthesis of γ-amino acids.[3] In this letter, we report the stereoselective construction of γ-lactams by the [3+2] annulation reaction of α-siloxy allylic silanes with *N*-chlorosulfonyl isocyanate ($ClSO_2NCO$). The resultant γ-lactam could be elaborated by diastereoselective nucleophilic substitution via an *N*-acyliminium ion[4] to afford highly substituted β-hydroxy-γ-lactams after oxidation of the carbon−silicon bond.[5]

The [3+2] annulation reaction of allylic silanes has proven to be a powerful transformation for the preparation of highly substituted five-membered rings.[6] For example, the [3+2] annulation of allylic silanes with $ClSO_2NCO$[7] provides the key ring systems for the syntheses of (+)-blastmycinone[8] and (±)-peduncularine.[9] These two syntheses illustrate the two reaction pathways through which $ClSO_2NCO$ can proceed.[8] Annulation across the C═O bond yields the *N*-chlorosulfonyl iminolactone, which was utilized in the synthesis of (+)-blastmycinone.[8] The more common annulation involves addition across the C═N bond to afford the *N*-chlorosulfonyl lactam, the intermediate required for the synthesis of (±)-peduncularine.[9] The general preference for annulation across the C═N bond can be overridden by steric effects, as shown in the (+)-blastmycinone synthesis.[8,9] In the absence of any steric or electronic preference, a mixture of both products is observed.[8]

(1) Corey, E. J.; Li, W.-D. Z. *Chem. Pharm. Bull.* **1999**, *47*, 1−10.
(2) Gouliaev, A. H.; Senning, A. *Brain Res. Rev.* **1994**, *19*, 180−222.
(3) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119−125.
(4) For reviews of *N*-acyliminium ion chemistry, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628.
(5) (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694−1696. (b) Tamao, K. In *Advances in Silicon Chemistry*; JAI: Greenwich, CT, 1996; Vol. 3, pp 1−62. (c) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317−337. (d) Fleming, I. *Chemtracts-Org. Chem.* **1996**, *9*, 1−64.
(6) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094−6097.
(7) (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434−1435. (b) Isaka, M.; Williard, P. G.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2115−2116. (c) Colvin, E. W.; Loreto, M. A.; Monteith, M.; Tommasini, I. In *Frontiers in Organosilicon Chemistry*; Bassindale, A. R., Gaspar, P. P., Eds; The Royal Society of Chemistry: Cambridge, U.K., 1991; pp 356−365. (d) Colvin, E. W.; Monteith, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1230−1232.
(8) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675−678.
(9) Roberson, C. W.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 621−623.

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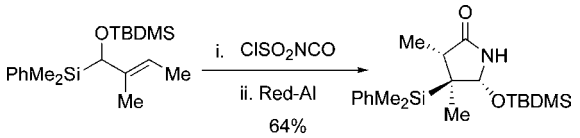
In our efforts to expand the scope of [3+2] annulations, we investigated annulation reactions of α-siloxy allylic silanes. Although the reactions of α-siloxy allylic silanes have been reported,[10] these silanes have not been utilized in [3+2] annulations. Application of α-siloxy allylic silanes in [3+2] annulations was desired because of their expedient syntheses,[11] the facile preparation of asymmetric variants,[12] and the functionality available in the annulation products.

A preliminary investigation of α-siloxy allylic silanes with $ClSO_2NCO$ provided promising results. Allylic silane **1** was treated with $ClSO_2NCO$ to provide γ-lactam **2**, after reductive removal of the chlorosulfonyl moiety, as the only annulation product (Scheme 1). Lactam **2** was formed as a single

Scheme 1. [3+2] Annulation of α-Siloxy Allylic Silanes **1** with $ClSO_2NCO$



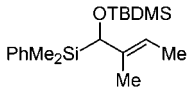
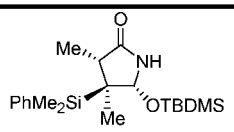
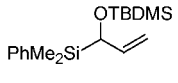
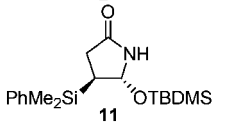
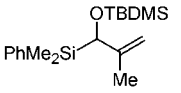
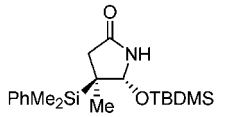
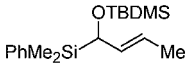
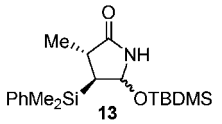
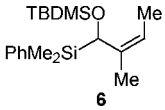
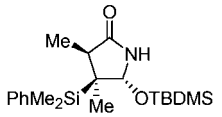
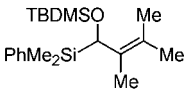
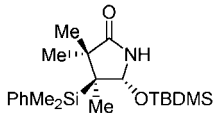
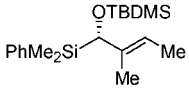
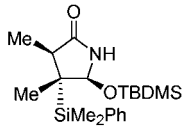
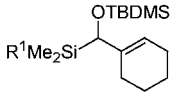
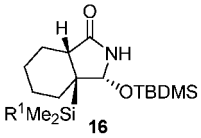
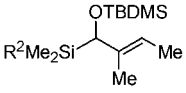
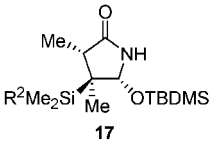
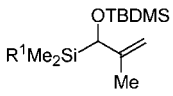
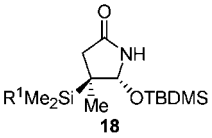
1 **2**
> 97 : 3 *ds*

diastereomer as determined by ^1H NMR spectroscopic analysis, and its relative stereochemistry, which is consistent with other annulations,[7−9] was proven by X-ray crystallography. No formation of the *N*-chlorosulfonyl iminolactone was observed, a marked difference from previous annulation studies involving $ClSO_2NCO$.[8]

The [3+2] annulation to form γ-lactams was general for a wide range of α-siloxy allylic silanes (**3**−**10**). In all cases, γ-lactams were formed exclusively. The stereospecificity of this reaction was illustrated by the annulation reactions of the isomeric allylic silanes **1** and **6**, which provided diastereomeric lactams **2** and **14** (Table 1). Compounds bearing tetrasubstituted carbon stereocenters[13] and bicyclic structures were accessed through this methodology with the appropriate allylic silanes (**7** and **8**). The annulation was also shown to proceed with retention of stereochemical integrity. Enantioenriched allylic silanes (*S*)-**1** afforded γ-lactam (+)-**2** with no loss of optical purity, thus providing a route to chiral, nonracemic γ-lactams.[14]

A study of various silyl moieties demonstrated that more electron-donating[15] and more sterically encumbering silyl groups[16] led to improved yields for the [3+2] annulation. Replacing the phenyl group of the silicon with benzhydryl or cumyl functionalities (allylic silanes **9** and **10**) resulted

Table 1. Annulation Reactions of α-Siloxy Allylic Silanes[a] with $ClSO_2NCO$[b]

α-siloxy allylic silane	product[c]	yield[d]
 **1**	 **2**	64%
 **3**	 **11**	59%
 **4**	 **12**	53%
 **5**	 **13**	51%[e]
 **6**	 **14**	52%
 **7**	 **15**	60%[f]
 **(*S*)-1** ≥ 94% ee	 **(+)-2** ≥ 94% ee	57%[g]
 **8**	 **16**	79%
 **9**	 **17**	84%
 **10**	 **18**	80%

[a] $R^1 = Ph_2CH$. $R^2 = PhCMe_2$. [b] All transformations were performed in CH_2Cl_2 at 0 °C unless otherwise stated. [c] Analysis of unpurified mixtures by ^1H NMR spectroscopy revealed only lactam products. [d] Isolated yields. [e] A 5:1 mixture of diastereomers was observed by ^1H NMR spectroscopy of the unpurified annulation products. [f] Annulation was performed at −78 °C. [g] As determined by chiral HPLC.

(10) Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.* **1978**, *43*, 2551−2552.

(11) Synthesis of α-siloxy allylic silanes was achieved by the protection of α-hydroxy allylic silanes. Numerous reports have been published for the synthesis of α-hydroxy allylic silanes: (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84. (b) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 5393−5396. (c) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520−2526. (d) Burke, S. D.; Saunders, J. O.; Oplinger, J. A.; Murtiashaw, C. W. *Tetrahedron Lett.* **1985**, *26*, 1131−1134. (e) Cirillo, P. F.; Panek, J. S. *J. Org. Chem.* **1994**, *59*, 3055−3063. (f) Koreeda, M.; Koo, S. *Tetrahedron Lett.* **1990**, *31*, 831−834.

(12) Asymmetric syntheses of α-hydroxy allylic silanes: (a) Takeda, K.; Ohnishi, Y.; Koizumi, T. *Org. Lett.* **1999**, *1*, 237−239. (b) Sakaguchi, K.; Higashino, M.; Ohfune, Y. *Tetrahedron* **2003**, *59*, 6647−6658.

(13) Dennisova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146.

in improved yields of the desired product as compared to analogous substrates **1** and **4**.

The exclusive formation of γ-lactam products in the [3+2] annulation of α-siloxy allylic silanes with $ClSO_2NCO$ demonstrated that α-siloxy allylic silanes do not behave like other allylic silanes. The difference in behavior may be understood by analyzing the reactivities of the zwitterionic intermediates.[7a] These intermediates possess different characteristics depending on the substitution at the α-position. In previous studies, allylic silanes without an α-heteroatom were used, resulting in β-silyl stabilized carbocation intermediate **IA**.[17] These electrophiles would be attacked along a trajectory of 90° from the carbon plane (Figure 1).[18] Allylic

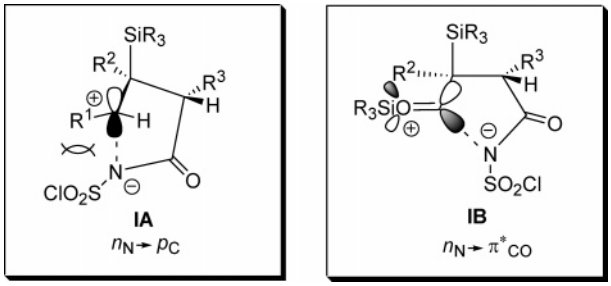
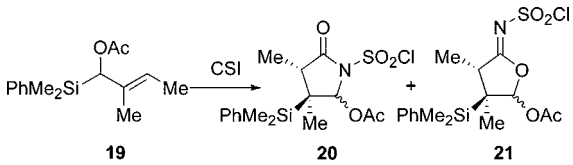


Figure 1. Ring-closing intermediates in the [3+2] annulation mechanism.

silanes possessing an α-heteroatom lead to a β-silyl oxocarbenium ion intermediate **IB**.[19] The trajectory of approach for attack onto an oxocarbenium ion is likely to be closer to the Burgi−Dunitz angle (109°).[20] The difference in trajectories diminishes any steric interactions that disfavor cyclization on the nitrogen (Figure 1).[8]

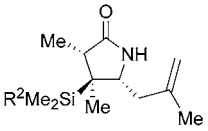
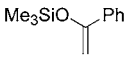
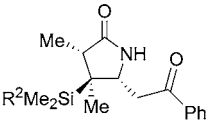
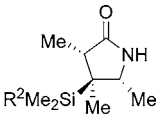
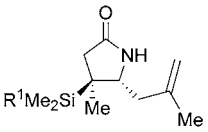
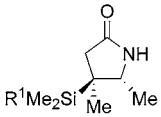
A [3+2] annulation with an α-acetoxy allylic silane demonstrates how a small perturbation in the intermediate affects product distribution. Treatment of α-acetoxy allylic silane **19** with $ClSO_2NCO$ afforded a mixture of *N*-chlorosulfonyl γ-lactam **20** and *N*-chlorosulfonyl iminolactone **21** (Scheme 2). Utilizing an α-acetoxy allylic silane would generate an intermediate possessing an α-oxygen with less electron-donating ability.[21] The diminished oxocarbe-

Scheme 2. Annulation of α-Acetoxy Allylic Silane **19** with $ClSO_2NCO$



nium ion character in this intermediate produces an intermediate that behaves more like **IA** (Figure 1). The lower

Table 2. Substitution of γ-Lactams Using *N*-Acyliminium Ion Chemistry

γ-lactam[a]	nucleophile[b]	product[c]	yield[d]
16	Me_2AlCN	 **22**	33%
17		 **23**	67%
17		 **24**	48%
17	Me_2Zn	 **25**	43%
18		 **26**	63%
18	$AlMe_3$	 **27**	75%

[a] $R^1 = Ph_2CH$. $R^2 = PhCMe_2$. [b] For reaction conditions, see Supporting Information. [c] All reactions afforded one diastereomer as determined by ^1H NMR spectroscopy of the unpurified products. [d] Isolated yield.

selectivity of the [3+2] annulation of α-acetoxy allylic silanes with $ClSO_2NCO$, as compared with α-siloxy allylic

(14) The stereochemistry of (*S*)-**1** was assigned by analogy. See ref 12a. The stereochemistry of the lactam (+)-**2** was assigned utilizing the accepted [3+2] annulation mechanism. For the mechanism of the [3+2] annulation, see ref 7a.

(15) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957.

(16) (a) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1081−1083. (b) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627−630. (c) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517−5522.

(17) (a) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677−2689. (b) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183−190.

(18) Laube, T. *Acc. Chem. Res.* **1995**, *28*, 399−405 and references therein.

(19) Stabilization of an oxocarbenium ion by a β-silyl group is consistent with IR studies that show hyperconjugation between σ_{CSi} and π^*_{CO}. Peddle, G. J. D. *J. Organomet. Chem.* **1968**, *14*, 115−121.

(20) Rakhmankulov, D. L.; Akhmatdinov, R. T.; Kantor, E. A. *Russ. Chem. Rev.* **1984**, *53*, 888−899.

(21) Begue, J.-P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207−212.

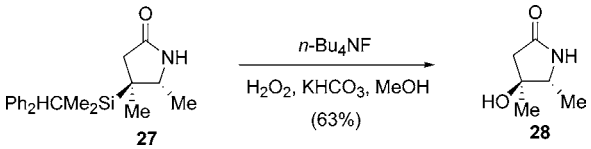
silanes, suggests that the electron-donating ability of the heteroatom is critical for selective product formation.

The [3+2] annulation of α-siloxy allylic silanes with $ClSO_2NCO$ provided γ-lactams possessing an *N*,*O*-acetal moiety, which is ideal for substitution via *N*-acyliminium ion chemistry.[4] Initial attempts to substitute γ-lactams possessing the phenyldimethylsilyl group were unsuccessful. The products obtained from these experiments had undergone desilylation. To suppress desilylation, the sterically encumbered benzhydryldimethylsilyl and cumyldimethylsilyl groups were utilized.[22]

A series of γ-lactams **16**−**18** possessing these larger silyl groups were converted to γ-substituted γ-lactams via *N*-acyliminium ion intermediates. High diastereoselectivity was observed for a range of nucleophiles, including allylic silanes, silyl enol ethers, and zinc and aluminum complexes (Table 2).[23] The products were formed by nucleophilic attack anti to the silyl group, in accord with previous studies.[24]

Oxidation of the silyl moiety afforded β-hydroxy-γ-lactams.[25] Exposing γ-lactam **27** to Tamao−Fleming oxidation conditions[5] provided β-hydroxy-γ-lactam **28** in 63% yield as a single diastereomer as determined by ^{1}H NMR spectroscopic analysis (Scheme 3).

Scheme 3. Oxidation of the Silyl Group



In summary, the [3+2] annulation reaction of α-siloxy allylic silanes with chlorosulfonyl isocyanate provides an efficient stereoselective synthesis of γ-lactams. These γ-lactams can be further substituted at the γ-position with high diastereoselectivity. Oxidative cleavage of the C−Si bond allowed access to highly substituted β-hydroxy-γ-lactams.

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

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(23) The stereochemistry of γ-lactam **25** was confirmed by X-ray crystallography and nOe studies. The stereochemistry of all other substituted γ-lactams were proven by nOe studies.

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(25) The benzhydryldimethylsilyl group led to better oxidation yields as compared to the cumyldimethylsilyl group.