The [3 + 2] Annulation of Allylsilanes and Chlorosulfonyl Isocyanate: Stereoselective Synthesis of 2-Pyrrolidinones

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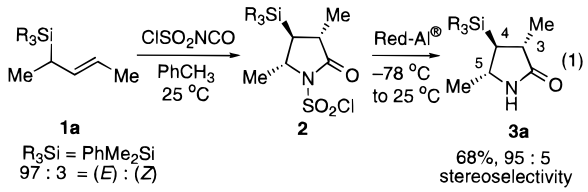
The [3 + 2] annulation reactions of allylsilanes and electrophiles represent powerful methods for the synthesis of both carbocyclic and heterocyclic five-membered rings.[1,2] An early example of heterocycle synthesis by a [3 + 2] annulation reaction was reported by Colvin and co-workers, who were studying reactions of allylsilanes with chlorosulfonyl isocyanate (CSI).[3] In addition to the expected β-lactam products arising from formal [2 + 2] annulation, 2-pyrrolidinones were obtained as side products. This synthesis of heterocycles was not pursued further, although pyrrolidinones are useful intermediates in organic synthesis.[4] We report here that the [3 + 2] annulation of a substituted allylsilane with CSI is an efficient, stereospecific, and stereoselective method for the synthesis of highly substituted 2-pyrrolidinones. The ability to oxidize a silyl group to a hydroxyl group[5] renders this annulation reaction a rapid, stereoselective synthesis of 4-hydroxy-2-pyrrolidinones.

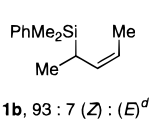
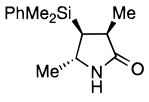
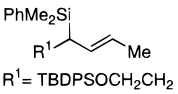
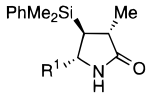
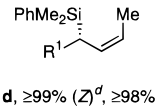
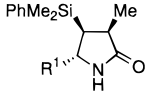
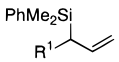
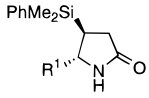
Chlorosulfonyl isocyanate,[6] which has been used most commonly to synthesize β-lactams from unactivated alkenes, reacted with the α-substituted allylsilane **1a**[7] at room temperature in toluene to give pyrrolidinone **2**, the product of a formal [3 + 2] annulation (eq 1). The annulation with



chlorosulfonyl isocyanate, unlike the reactions of allylsilanes with most electrophiles,[1,2] required no Lewis acid activation. Although the unstable *N*-chlorosulfonyl amide **2** was isolable, reduction provided the stable lactam **3a**. Of the methods known to perform this reduction,[8] an in situ Red-Al reduction[9] proved to be the most reliably high-yielding method. This two-step, one-pot protocol provided 2-pyrrolidinone **3a** in 68% overall yield and with high stereoselectivity.

Both the flexibility of alkene substitution and the consistently high levels of diastereocontrol possible in the synthesis of the 2-pyrrolidinones **3**[10] are illustrated by the annulations[11] of allylsilanes **1b**−**e** (Table 1). The alkene geometry of **1a**−**d** determined the stereochemistry at C-3 with respect to the silyl group at C-4: (*E*)-allylsilanes **1a** (eq 1) and **1c** (Table 1) yield the 3,4-*trans*-2-pyrrolidinones **3a** and **3c**, whereas the (*Z*)-allylsilanes **1b**[12] and **1d** yield the 3,4-*cis* products **3b** and **3d**. Both (*Z*)- and (*E*)-crotylsilanes undergo the CSI annulation to yield the respective 2-pyrrolidinone diastereomers with high diastereoselectivity. A comparable level of diastereocontrol in the annulations of (*E*)-crotylsilanes with various electrophiles has been observed.[2,13] (*Z*)-Crotylsilanes, however, have not been successfully employed (as far as conversion or diastereocontrol) as nucleophiles in other [3 + 2] annulations.[13] In all examples given in Table 1, a 4,5-trans relationship was observed for the annulation products **3**, including the annulation product **3e**.[14]

Table 1. [3 + 2] Annulation of Allylsilanes 1 with Chlorosulfonyl Isocyanate and in Situ Reduction To Yield 2-Pyrrolidinones 3[a]

Allylsilane **1**	Product **3**	Yield (%)[b]	Diastereomer ratio[c]
 **1b**, 93 : 7 (*Z*) : (*E*)[d]	 **3b**	63	92 : 8[e]
 **1c**, ≥99% (*E*)[d]	 **3c**	75	98 : 2
 **1d**, ≥99% (*Z*)[d], ≥98% ee[f]	 **3d**	64	≥95 : 5 ≥98% ee[g]
 **1e**	 **3e**	54	95 : 5

[a] See ref 11. [b] Isolated yield of pure material. [c] Diastereomer ratios determined by GC analyses of the unpurified product mixtures. [d] Alkene ratios of the allylsilanes **1** determined by GC analyses. [e] Minor diastereomer was **3a**. [f] Enantiomeric excess determined by GC analysis of a precursor (with a chiral auxiliary) to **1d**. [g] Enantiomeric excess determined by chiral HPLC on a Chiracel OD-H column.

The annulation of an enantiomerically pure allylsilane occurred with retention of enantiomeric purity,[15] expanding the scope of this reaction to the synthesis of optically active 2-pyrrolidinones. The annulation of enantiopure allylsilane

(1) For a leading reference on the [3 + 2] annulation of allylsilanes, see: Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517−5522.
(2) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.
(3) 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.
(4) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825−1872.
(5) (a) Fleming, I. *Chemtracts−Org. Chem.* **1996**, *9*, 1−64. (b) Jones, G.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.
(6) Dhar, D. N.; Murthy, K. S. K. *Synthesis* **1986**, 437−449.
(7) Fleming, I.; Higgins, D.; Lawrence, N. J.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3331−3349.
(8) Malpass, J. R.; Tweddle, N. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 874−884.
(9) Furman, B.; Kaluza, Z.; Chmielewski, M. *Tetrahedron* **1996**, *52*, 6019−6024.
(10) The details are provided as Supporting Information.
(11) **Representative Procedure.** To a solution of **1c** (0.204 g, 0.431 mmol) in 9 mL of toluene was added chlorosulfonyl isocyanate (0.056 mL, 0.647 mmol). After 2 h at 25 °C, the reaction mixture was cooled to −45 °C, and Red-Al (65+ wt % solution in toluene, 2.0 mmol) was added. The reaction mixture was kept at −45 °C for 2 h. The reaction was quenched by dropwise addition of H_2O (until H_2 evolution ceased), and the mixture was warmed to 25 °C. The heterogeneous solution was filtered, and the filtrate was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes:EtOAc) provided **3c** as an oil that solidified on standing (0.166 g, 75%). Spectral and analytical data confirmed the structure of the product.
(12) Fleming, I.; Gil, S.; Sarkar, A. K.; Schmidlin, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3351−3360.
(13) Danheiser, R. L.; Takahashi, T.; Bertók, B.; Dixon, B. R. *Tetrahedron Lett.* **1993**, *34*, 3845−3848.

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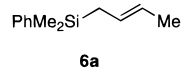
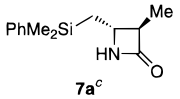
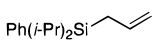
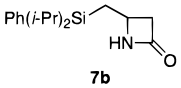
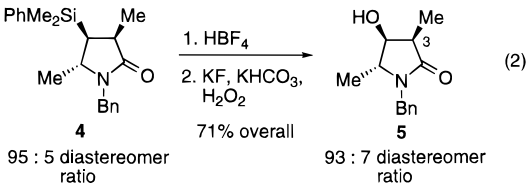
Table 2. [2 + 2] Annulation with Allylsilanes 6, Unsubstituted at the Allylic Position, Yields β-Lactams 7[a]

Allylsilane **6**	Product **7**	Yield (%)[b]
 **6a**	 **7a**[c]	60
 **6b**	 **7b**	55

[a] A solution of allylsilane **6** in toluene was treated with 1 equiv of chlorosulfonyl isocyanate at −20 °C (for **6a**) or +22 °C (for **6b**). After consumption of **6**, Red-Al was added to the cooled (−78 °C) reaction mixture, which was allowed to warm to 22 °C. [b] Isolated yield of pure material. [c] ≥95:5 diastereomer ratio by ^{1}H NMR spectroscopy.

1d (Table 1), using the protocol described earlier, provided pyrrolidinone **3d** in 64% yield, ≥95% diastereoselectivity, and ≥98% ee (as determined by chiral HPLC). X-ray crystallographic analysis of the (*S*)-α-methylbenzyl carbamate derivative of **3d** provided proof of its absolute and relative configuration.[10]

The 4-silyl-2-pyrrolidinones **3** synthesized from the [3 + 2] annulation provide access to 4-hydroxy-2-pyrrolidinones by oxidation of the silicon−carbon bond. 3,4-*cis*-2-Pyrrolidinone **3b** was alkylated with a benzyl group (81%) to aid in isolation of the oxidation product. *N*-Benzyl-2-pyrrolidinone **4** (eq 2) was exposed to Fleming/Tamao oxidation conditions[5]

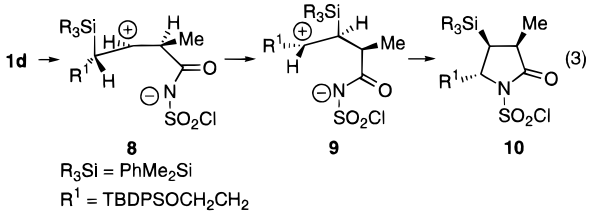


(2)

to provide **5** (71% overall) without effecting a significant change in the diastereomer ratio of the pyrrolidinones. The 3,4-*trans*-2-pyrrolidinone **3a** was treated in a similar manner (benzylation, 82%; Fleming/Tamao oxidation, 79%) to provide a 3,4-*trans*-4-hydroxy-2-pyrrolidinone, an epimer of **5** at C-3.

Substitution at the allylic carbon is necessary for the [3 + 2] annulation pathway to be favored over the [2 + 2] pathway[16] in the cyclization of allylsilanes with chlorosulfonyl isocyanate (Table 2). Exclusive formation of the respective *N*-chlorosulfonyl β-lactams was observed (as determined using ^{1}H NMR spectroscopy in toluene-d_8) when allylsilanes **6a**[7] and **6b**[17] were treated with chlorosulfonyl isocyanate. Upon in situ reduction with Red-Al, β-lactams **7a** and **7b** were obtained as the only cyclization products. This observation is consistent with earlier reports by Dunogues[18] and Colvin[3] in their syntheses of β-lactams from allylsilanes with CSI.

Because the [3 + 2] annulation with CSI is stereospecific and highly diastereoselective, the initial electrophilic attack must be stereoselective, the silyl migration must be stereospecific, and both β-silyl carbocation intermediates must be configurationally stable. The origin of the stereospecificity of the annulation is illustrated with the example of the reaction of (*Z*)-allylsilane **1d** with chlorosulfonyl isocyanate (eq 3). Electrophilic attack by chlorosulfonyl isocyanate



antiperiplanar to the silyl group of the allylsilane in its lowest energy conformer[19] forms the β-silyl carbocation **8**.[20] The stereochemistry at C-3 is set at this point, having been determined by the alkene geometry of **1**. A 1,2-silyl migration[21] occurs to provide intermediate **9**, which then cyclizes anti to the silyl group to give the 4,5-*trans*-*N*-chlorosulfonyl pyrrolidinone **10**. The importance of allylic substitution[22] in the [3 + 2] pathway is made clear when considering zwitterionic intermediates **8** and **9**. For the unsubstituted allylsilanes **6**, a 1,2-silyl migration of the first β-silyl carbocation would result in a higher energy primary β-silyl carbocation.[23] Therefore, silyl migration does not occur and the β-lactam is observed for these allylsilanes. In contrast, for allylsilanes such as **1d**, the 1,2-silyl migration gives a secondary β-silyl carbocation, and cyclization of **9** affords the more thermodynamically favored five-membered ring in preference to the four-membered ring.

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Supporting Information Available: Full experimental and analytical data for all new compounds; descriptions of stereochemistry proofs; X-ray data for **1a** and a derivative of **3d**; and GC or HPLC traces of **1** and **3**−**5**.

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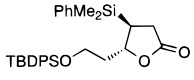
(14) The lower yield for **3e** is due to competitive cyclization by the oxygen atom of the dipolar intermediate to give an imino ether. The *N*-chlorosulfonyl pyrrolidinone and the imino ether exist in a 2:1 ratio (by ^{1}H NMR spectroscopy in toluene-d_8). Lactone **3f** has been isolated in 22% yield, using milder reducing conditions (25% aqueous Na_2SO_3).



3f

(15) Enantiopure (*E*)-crotylsilanes have been used in [3 + 2] annulations. See, for example: Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1993**, *58*, 2345−2348.

(16) For a recent example of a [2 + 2] annulation of an allylsilane, see: Knölker, H.-J.; Baum, E.; Schmitt, O. *Tetrahedron Lett.* **1998**, *39*, 7705−7708.

(17) Allylsilane **4b** has been shown to undergo [3 + 2] annulation reactions with enones: (a) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R.; Jones, P. G.; Wanzl, G. *Chem. Eur. J.* **1997**, *3*, 538−550. (b) Akiyama, T.; Hoshi, E.; Fujiyoshi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2121−2122.

(18) Déléris, G.; Dunoguès, J.; Calas, R. *J. Organomet. Chem.* **1976**, *116*, C45−C48.

(19) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650−663.

(20) Siliranium ions have also been proposed as intermediates in annulation reactions: Knölker, H.-J.; Foitzik, N.; Graf, R.; Pannek, J.-B.; Jones, P. G. *Tetrahedron* **1993**, *49*, 9955−9972.

(21) Seyferth, D.; White, D. L. *J. Am. Chem. Soc.* **1972**, *94*, 3132−3138.

(22) The importance of allylic substitution to annulation yield has been observed by other researchers: (a) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094−6097. (b) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627−630. (c) Schinzer, D.; Panke, G. *J. Org. Chem.* **1996**, *61*, 4496−4497.

(23) For an excellent discussion of the structure and stability of β-silyl carbocations, see: Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677−2689.