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SYNTHESIS AND REACTIVITY OF SULFUR AND SILYL SUBSTITUTED α-ALKYLIDENE-β-LACTAMS

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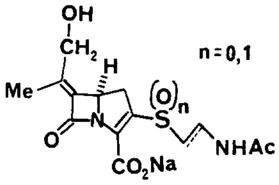
SUMMARY: Synthetically valuable α-alkylidene-β-lactams are produced from the addition of chlorosulfonyl isocyanate to allenyl sulfides.

Recently, several α-alkylidene-β-lactams have been shown to be potent β-lactamase inhibitors. Included are the asparenomycins[1] (**1**), Ro 15-1903[2] (**2**), and 6-[(*Z*)-methoxymethylene]penicillanic acid[3] (**3**). We recently initiated a program to explore the addition of chlorosulfonyl isocyanate to functionalized allenes with the goal of producing α-alkylidene-β-lactams with synthetic potential.[4] While CSI is a valuable reagent for the one step conversion of olefins to β-lactams,[5] the high reactivity of this reagent often precludes addition to olefins which contain other functionality. Yields in most cases are modest (ex. the synthetically important 4-acetoxyazetidin-2-one is prepared from vinyl acetate in 40% yield[6]).



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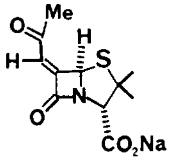

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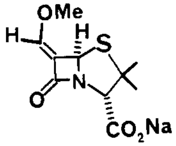

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We would now like to report that CSI can be successfully added to a variety of allenyl sulfides, in yields which are highly dependent on the structure of the allene. Allenyl sulfoxides are easily formed from reaction of propargylic alcohols with sulfenyl chlorides.[7] While these sulfoxides were unstable toward a number of different reducing agents, we found that treatment with NaI and TFAA in the presence of Et_3N produced allenyl sulfides in yields of better than 90%.[8] We were able to alkylate not only α to sulfur[9] but also at the γ position, allowing us to prepare a wide range of substituted allenyl sulfides.

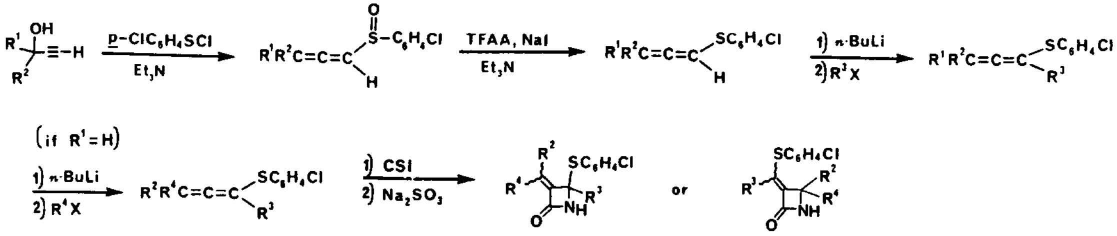


Table I shows the allenes prepared and their addition products with CSI.[10] Allenes in which none of the allenyl substituents is hydrogen react best. With the exception of 7, CSI adds regiospecifically to the vinyl sulfide portion of the allene. The unanticipated production of 7 was confirmed by x-ray diffraction[11] of the N-methyl derivative (CH_3I/KOH) as shown in figure I.

Table I

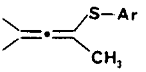
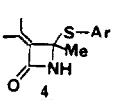
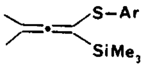
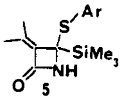
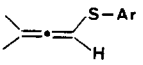
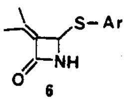
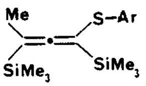
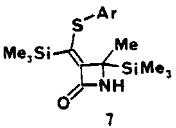
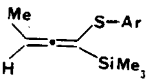
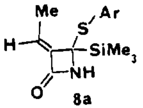
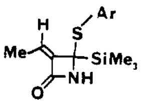
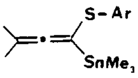
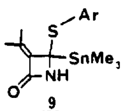
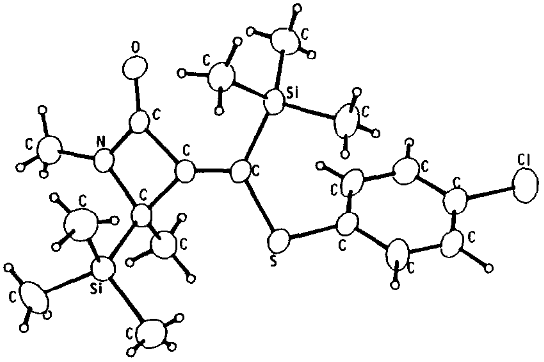
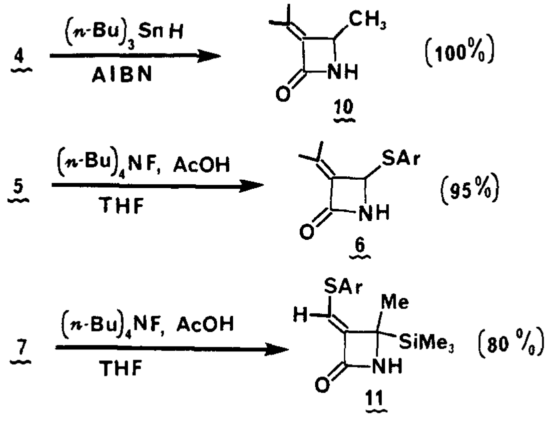
Allene	Product	Yield
	 4	55%
	 5	87%
	 6	20%
	 7	54%
	 8a  8b	10% (8a : 8b = 1:2)
	 9	22%

Figure 1



The wide variety of structures which can be produced is demonstrated by the ease with which these β-lactams can be desulfurized and desilylated. Treatment of 4 with $(n\text{-Bu})_3SnH$ (cat. AIBN, 95°C) produces 10 in quantitative yield. It should be noted that since the methyl group at the 4 position was attached via alkylation of the allenyl sulfide, that this constitutes a reversal in polarity with respect to the usual nucleophilic substitution of the 4-acetate. The activating effect of sulfur on the desilylation is demonstrated by the reactions of 5 and 7 with $(n\text{-Bu})_4NF$ (2 eq of 1M soln in THF) in the presence of 2 eq AcOH to produce 6 and 11, respectively, in good yield.



The CSI addition was performed as follows: 4.45 mmol of allene was dissolved in 4.0 mL anhydrous ether and chilled to -23° C. 4.68 mmol of CSI was then added dropwise via syringe. The reaction was monitored by TLC, and if the starting material had not disappeared within one hour, it was allowed to slowly warm to 0°C. The solution was then added to a chilled and rapidly stirred two phase system consisting of 10 mL ether, 7.93 mmol Na_2SO_3, 14.35 mmol K_2HPO_4, and 10 mL water. After stirring for 1 hr at room temperature, the products were isolated and further purified by flash chromatography on silica gel using an appropriate EtOAC/CH_2Cl_2 mixture (1-10%) as elluent.

ACKNOWLEDGEMENT: This work was supported by the Robert A. Welch Foundation and the Petroleum Research Fund, administered by the American Chemical Society.

References and Notes

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9. Cookson, R. C.; Parsons, P. J. J. Chem. Soc. Chem. Commun. *1978*, 822.
10. Spectroscopic details of β-lactams: 4: ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.74 (s, 3H), 1.86 (s, 3H), 1.88 (s, 3H), 7.19, 7.24, 7.31, 7.36 (ABq, J=9 Hz, 4H), 7.71 (br s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ= 19.16, 19.71, 25.06 70.42, 128.79, 129.07, 135.58, 137.21, 137.53, 138.10, 163.67; IR ($CHCl_3$) 3420, 3000, 2920, 1745, 1090, 842 cm^{-1}; UV ($CHCl_3$) λ_{max} =242nm (ε = 11,000). 5: ^{1}H NMR ($CDCl_3$, 200MHz) δ=0.20 (s, 9H), 1.84 (s, 3H), 1.88 (s, 3H), 6.32 (br s, 1H), 7.21, 7.25, 7.30, 7.34 (Abq, J = 9 Hz, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ = -2.94, 19.68, 20.62, 65.57, 127.75, 128.49, 135.18, 135.57, 137.26, 138.27, 164.18; IR ($CHCl_3$) 3420, 2960, 1735, 1252, 840 cm^{-1}; UV ($CHCl_3$) λ_{max} = 240 nm (ε = 8500). 6: ^{1}H NMR ($CDCl_3$, 200MHz) δ = 1.91 (s, 3H), 2.01, (s, 3H), 5.35 (s, 1H), 6.50 (br s, 1H), 7.28, 7.33, 7.36, 7.40, (ABq, J = 9 Hz, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ = 19.8, 20.3, 61.7, 129.1, 129.4, 133.0, 134.7, 135.1, 140.5, 164.1; IR ($CHCl_3$) 3420, 3000, 2940, 2920, 1750, 1480, 1160, 1100, 1030, 825 cm^{-1}; UV ($CHCl_3$) λ_{max} = 240 (ε = 9100), 256 (ε = 7100). 7 ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.14 (s, 9H), 0.15 (s, 9H), 1.53 (s, 3H), 6.36 (br s, 1H), 7.12, 7.16, 7.26, 7.30 (ABq, J = 9 Hz, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz) -3.9, -0.2, 20.8, 57.6, 129.1, 129.7, 132.2, 135.4, 162.0, 163.4; IR ($CHCl_3$) 3420, 3000, 2950, 1735, 1250, 1100, 840 cm^{-1}; UV ($CHCl_3$) λ_{max} = 239 (ε = 8700), 265 (ε = 13000), 323 (ε = 6300). 8a: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.09 (s, 9H), 1.87 (d, J = 7 Hz, 3H), 6.10 (q, J = 7 Hz, 1H), 6.40 (br s, 1H), 7.24, 7.28, 7.32, 7.36 (ABq, J = 9 Hz, 4H). 8b ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.15 (s, 9H), 1.88 (d, J = 7 Hz, 3H) 5.63 (q, J = 7 Hz, 1H), 6.40 (br s, 1H) 7.26, 7.30, 7.33, 7.37 ABq, J = 9 Hz, 4H); IR (mixture of 8a and 8b, $CHCl_3$) 3420, 3000, 2960, 1745, 1475, 1250, 1095, 840, 820 cm^{-1}. 9 ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.27 (s, 9H), 1.83 (s, 3H), 1.92 (s, 3H), 7.22, 7.26, 7.30, 7.34 (ABq, J = 9 Hz, 4H), 7.55 (br s, 1H); IR ($CHCl_3$) 3420, 3000, 2960, 1735, 1360, 1090, 1015, 815 cm^{-1}; UV ($CHCl_3$) λ_{max} = 241 (ε = 11000), 260 (sh).
11. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre and are available from them.

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