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NOVEL SYNTHESIS OF SULFUR-CONTAINING BICYCLIC β-LACTAMS (THIAISOALKANAMS) USING SULFUR DICHLORIDE AS A SULFUR TRANSFER REAGENT

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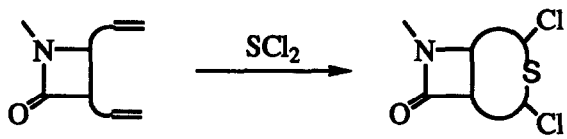
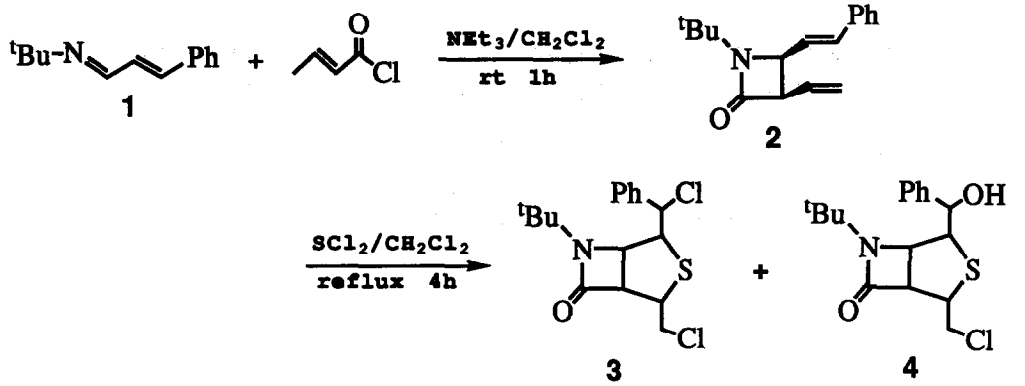
Summary: Sulfur-containing bicyclic β-lactams having new ring systems, 6- and 7-thiaisoheptanams, were synthesized by addition of sulfur dichloride to β-lactams having two olefinic substituents, which were prepared by cycloaddition of ketenes and a 1-azadiene.

β-Lactams fused to a sulfur-containing ring (thiaalkanams and thiaisoalkanams) are of great interest in terms of antibiotics. In the course of the study on sulfur dichloride which is highly reactive toward unsaturated bonds, we found that the compound is a facile sulfur transfer reagent in heterocyclic synthesis.[1] Thus it was expected that addition of sulfur dichloride to a β-lactam having two exocyclic alkenyl (or alkylidene) substituents will give rise to a sulfur containing bicyclic β-lactam.



This procedure would make it possible to design size of the fused ring and position of sulfur atom in the ring by changing the exocyclic alkenyl groups attached to the β-lactam ring, and chloro substituents will be available for functionalization of the products. In this paper we wish to report new synthesis of 6-thiaisoheptanams and a 7-thiaisoheptanam, which are novel ring systems, from diolefinic-β-lactams.

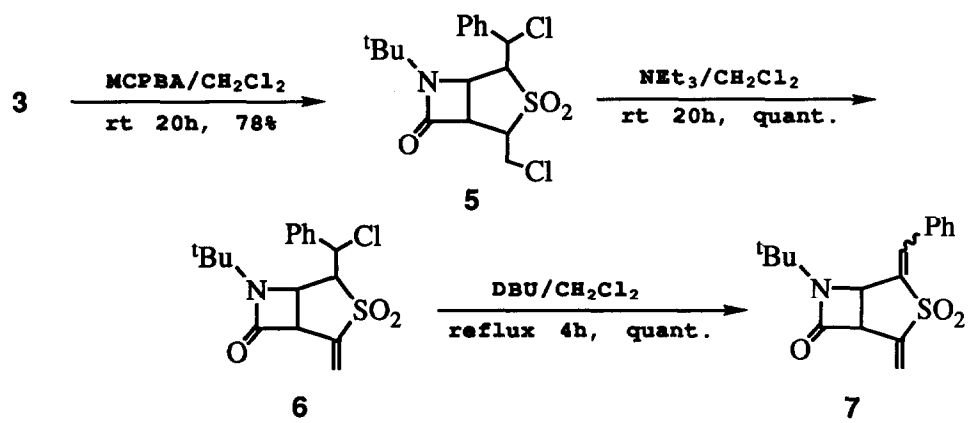
The starting diolefinic β-lactam **2**, *cis*-3-vinyl-4-styrylazetidin-2-one,[2] was prepared stereoselectively by cycloaddition of 1-*tert*-butyl-4-phenyl-1-aza-1,3-butadiene (**1**) with *in situ*-generated vinylketene in 50% yield.[3] Solutions of 511 mg (2.0 mmol) of the β-lactam **2** in CH_2Cl_2 (100 ml) and 210 mg (2.0 mmol) of SCl_2 in CH_2Cl_2 (100 ml) were added dropwise to 500 ml of refluxing CH_2Cl_2 by the same rate over 3 h under nitrogen atmosphere. The mixture was refluxed for another hour and the solvent was removed under reduced pressure. Addition of a mixture of ether/hexane to the residue gave 493 mg (71%) of 1-*tert*-butyl-5-(α-chlorobenzyl)-7-chloromethyl-6-thiaisoheptanam (**3**) as colorless plates (mp 135-137 °C, recrystallized from ether/hexane) after standing overnight. Upon chromatography of the mother liquor on a SiO_2 column, 136 mg (20%) of the 5-(α-hydroxybenzyl) derivative **4** (mp 148-150 °C, colorless plates from ether/hexane) was isolated.



The structure of the new thiaisoalkanam **3** was determined by spectral and analytical data. The ir spectrum of **3** showed absorption band at 1730 cm^{-1} (β-lactam C=O) and a molecular ion peak in the mass spectrum was observed at *m/z* 357. Assignments of ^{1}H- and ^{13}C-nmr[4] were supported by further chemical transformations.[5,6] Taking into account of addition mode of sulfur dichloride to C=C bonds, alternative structures having a six- or seven-membered fused ring were also conceivable in place of **3**. However, formation of such types of bicyclic β-lactams was not detected at all.

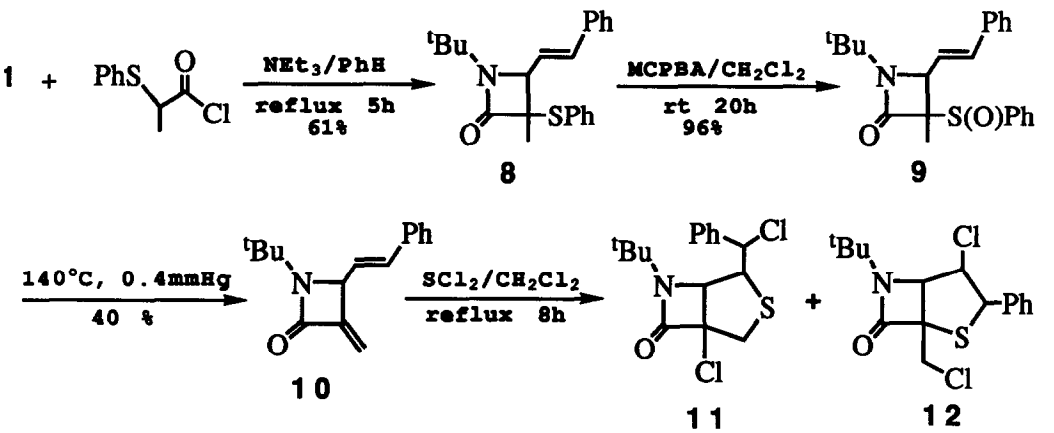
The structure of the compound **4** was similarly determined by spectral analyses, one of whose features is a very intense fragment ion peak at *m/z* 107 ($PhCH=OH^{+}$) in the mass spectrum. It is clear that the hydroxy derivative **4** was formed by hydrolysis during chromatography since it was obtained quantitatively by treatment of the isolated dichloride **3** on a SiO_2 column (eluent: benzene). Hence, it suggests that the present reaction gave the thiaisoheptanam **3** with high selectivity (> 91%). Ready displacement of the chloro substituent by hydroxy group seems to be promoted by neighboring group assistance via a thiiranium ion, which is wellknown for β-halosulfides. Thus various types of nucleophiles can be introduced to the β-lactam **3**.

We further studied chemical transformations of the new β-lactams utilizing sulfur and chloro functions to have better knowledge on chemical properties and to provide wider range of derivatives for biological activity screening. Oxidation of the thiaisoheptanam **3** with *m*-chloro-



perbenzoic acid (MCPBA) led to its sulfone derivative **5** quantitatively. Treatment of **5** with triethylamine in CH_2Cl_2 at room temperature caused selective dehydrochlorination leading to the exo-methylene compound **6**. The dehydro- chlorinated sulfone **6** showed two new olefinic carbon signals, as one singlet at 144.6 ppm and one triplet at 119.6 ppm, in ^{13}C-nmr and a pair of exocyclic methylene protons (at δ 5.92 and 6.20) in ^{1}H-nmr. Successive dehydrochlorination of **6** to **7** was performed by treatment with DBU. A new olefinic proton (-CH=) of **7** was observed at δ 7.57 as a singlet, implyingformation of only one isomer whose structure (*E* or *Z*) is not decided at the moment. Other spectral data of the β-lactams **5**, **6** and **7** are also in good agreement with this 6-thiaisoheptanam structure. *cis*-Configuration of the sulfur-containing fused ring was confirmed by the coupling constant between 3-H and 4-H of each azetidinone ring.[4]

Then cyclization of a diolefinic-β-lactam having one carbon less than the β-lactam **2** was studied. Starting with the same azadiene **1**, the sulfenyl β-lactam **8** was prepared by cycloaddition with an *in situ*-generated sulfenylketene[7] and was purified on a SiO_2 column (mp 131-133 °C, colorless crystals from benzene). Oxidation of **8** with MCPBA to sulfoxide **9** (mp 173-175 °C, colorless plates from hexane) and successive thermal desulfenylation of **9** led to 1-*tert*-butyl-3-methylene-4-styrylazetidin-2-one (**10**)[8] (mp 105-107 °C, colorless plates from benzene-hexane) which was isolated by SiO_2 column chromatography. The reaction of the β-lactam **10** with sulfur dichloride was performed by the similar high dilution method as that for **2** to give 1-*tert*-butyl-3-chloro-5-(α-chlorobenzyl)-6-thiaisoheptanam (**11**: 23%) as well as 1-*tert*-butyl-5-chloro-3-chloromethyl-6-phenyl-7-thiaisoheptanam (**12**: 18%).



These new thiaisoheptanam isomers were isolated on SiO_2 column (eluent: hexane/ethyl acetate) and their structures were established by spectral data and elemental analysis which clarified addition pattern of sulfur dichloride to the olefinic bonds leading to five membered ring. No six-membered ring-fused β-lactam (thiaisooctanam) was detected.[9]

Synthesis of bicyclic β-lactam having a bridgehead nitrogen (thiaalkanam) from another type of diolefinic-β-lactam and sulfur dichloride is under investigation.

References and Notes

1) M. Komatsu, J-i. Shibata, Y. Ohshiro, T. Agawa, *Bull. Chem. Soc. Jpn.*, **56**, 180 (1983); M. Komatsu, N. Harada, H. Kashiwagi, Y. Ohshiro, T. Agawa, *Phosphorus and Sulfur*, **16**, 119 (1983); Y. Ohshiro and M. Komatsu, *Kagaku Zokan*, **115**, 33 (1988) and references cited therein.

2) Y. Ohshiro, M. Komatsu, M. Uesaka, T. Agawa, *Heterocycles*, **22**, 549 (1984).

3) The *cis*-structure was determined by ^{1}H nmr; $J_{3H\text{-}4H}$ = 5.6 Hz. See ref. 2).

4) All the compounds **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, and **12** were isolated and gave reasonable spectral data. Key spectral data of the bicyclic β-lactams **3**, **4**, **7**, **11**, and **12**, which also gave satisfactory elemental analyses, are given below. **3**: ir (Nujol, cm^{-1}) 1730 (C=O); ^{1}H-nmr ($CDCl_3$, δ) 3.3-3.8 (m, 3H, $ClCH_2$, SCH), 3.96 (d, *J*=4.1 Hz, 1H, COCH), 4.02 (d, *J*=11.6 Hz, 1H, SCH), 4.73 (d, *J*=11.6 Hz, 1H, PhC<u>H</u>), 4.86 (d, *J*=4.1 Hz, 1H, NCH); ^{13}C-nmr ($CDCl_3$, ppm) 47.6 (d, SCH), 48.7 (t, CH_2Cl), 54.7 (d, CO<u>C</u>H), 60.9 (d, S<u>C</u>HCPh), 64.6 (d, NCH), 65.5 (d, Ph<u>C</u>H), 165.3 (s, CO); MS (*m/z*) 357 (M^+). **4**: ir (Nujol, cm^{-1}) 1730 (C=O); ^{1}H-nmr ($CDCl_3$, δ) 2.3 (br, 1H, OH), 3.6-3.8 (m, 3H, SCH, CH_2Cl), 3.89 (d, *J*=4.0 Hz, 1H, COCH), 4.64 (d, *J*=4.0 Hz, 1H, NCH), 4.79 (d, *J*=6.4 Hz, 1H, PhC<u>H</u>); MS (*m/z*) 339 (M^+). **7**: ir (Nujol, cm^{-1}) 1755 (CO); ^{1}H-nmr ($CDCl_3$, δ) 4.19 (d, *J*=4.9 Hz, 1H, COCH), 5.20 (d, *J*=4.9 Hz, 1H, NCH), 5.82 (d, *J*=1.7Hz, 1H, =C<u>H</u>H), 6.16 (d, *J*=1.7Hz, 1H, =CH<u>H</u>), 7.57 (s, 1H, =C<u>H</u>Ph); ^{13}C-nmr ($CDCl_3$, ppm) 45.6 (CO<u>C</u>H), 50.9 (NCH), 118.2 (=CH_2), 124.6 (=<u>C</u>HPh), 137.1 (SO_2C=), 141.5 (SO_2C=), 161.2 (CO); MS (*m/z*) 218 (M^+ - *t*-BuNCO). **11**: ir (Nujol, cm^{-1}) 1755 (C=O); ^{1}H-nmr ($CDCl_3$, δ) 2.95 (d, *J*=13.4Hz, 1H, C<u>H</u>H), 3.23 (d, *J*=13.4 Hz, 1H, CH<u>H</u>), 3.77 (d, *J*=10.8Hz, 1H, SCH), 4.67 (s, 1H, NCH), 4.86 (d, *J*=10.8 Hz, 1H, PhC<u>H</u>); ^{13}C-nmr ($CDCl_3$, ppm) 34.8 (t, CH_2), 57.2 (d, SCH), 63.6 (d, NCH), 71.5 (d, Ph<u>C</u>H), 75.2 (s, CO<u>C</u>Cl), 162.0 (s, CO); MS (*m/z*) 343 (M^+). **12**: ir (Nujol, cm^{-1}) 1730(C=O); ^{1}H-nmr ($CDCl_3$, δ) 3.97 (s, 2H, $ClCH_2$), 4.42 (d, *J*=2.4 Hz, 1H, NCH), 4.60 (dd, *J*=2.4, 5.9 Hz, 1H, CHCl), 5.02 (d, *J*=5.9 Hz, 1H, PhC<u>H</u>); ^{13}C-nmr ($CDCl_3$, ppm) 43.4 (s, S<u>C</u>CO), 64.5 (d, Ph<u>C</u>HS), 67.0 (d, NCH), 69.1 (t, CHCl), 165.0 (s, CO); MS (*m/z*) 357 (M^+).

5) It is known that oxidation of tetrahydrothiophene to its sulfone causes lower field shift of the α-carbon (from 31.2ppm to 51.5 ppm) and higher field shift of the β-carbon (from 31.4 ppm to 22.8 ppm) in ^{13}C-nmr spectra.[6] Hence, a large higher field shift of the triplet carbon of **3** upon oxidation (from 48.7 ppm to 39.3 ppm) enabled not only its assignment as the β-carbon but also assignment of doublets which shifted to lower field as the α-carbons.

6) L. F. Johnson and W. C. Jankowski, "Carbon-13 Spectra, A Collection of Assigned, Coded and Indexed Spectra", John Wiley & Sons, New York, 1972.

7) T. Minami, M. Ishida, T. Agawa, *J. Chem. Soc. Chem. Commun.*, 12 (1978).

8) M. Ishida, T. Minami, T. Agawa, *J. Org. Chem.*, 44, 2067 (1979).

9) Comparison of *cis*-fused thiaisoheptanam and thiaisooctanam using a molecular model suggests larger steric destabilization in the latter compound, which can be one of the reasons for lack of thiaisooctanams in the both reactions.

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