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NOVEL SYNTHESIS OF THIANONANAM USING SULFUR DICHLORIDE AS A SULFUR TRANSFER REAGENT

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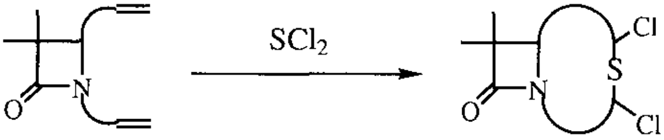
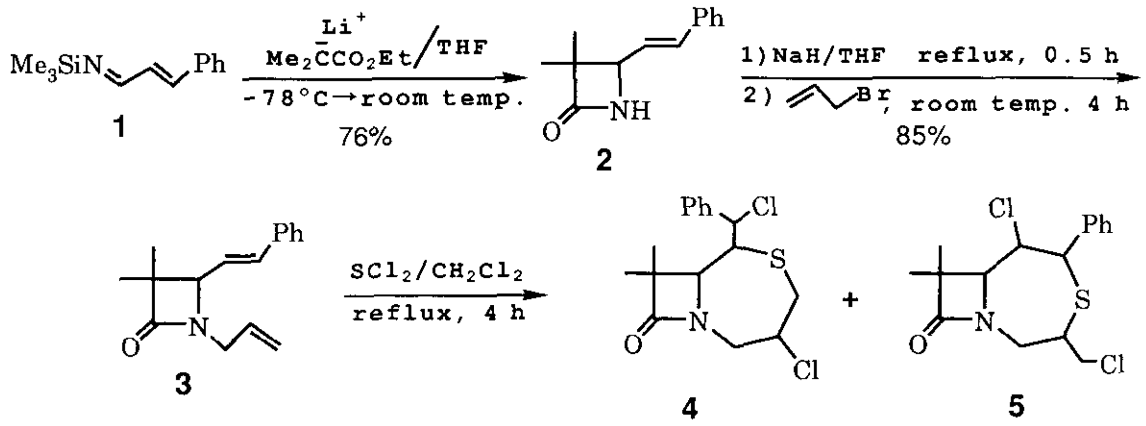
Abstract——Hitherto unknown or rarely reported sulfur-containing bicyclic β-lactams, 6-and 7-thianonanams, were synthesized by addition of sulfur dichloride to *N*-allyl-β-styryl-β-lactam.

β-Lactams condensed with a sulfur-containing ring (thiaalkanams and thiaisoalkanams) are of great interest in terms of antibiotics.[1] Since sulfur dichloride has high reactivity toward unsaturated bonds,[2] it is 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. In the preceding paper[3] we reported the synthesis of new ring systems, 6- and 7-thiaisoheptanams, utilizing sulfur dichloride as a sulfur transfer reagent. One of the features of the method is the introduction of chloro substituent which is available for further functionalization of the products. It is more desirable that this strategy is applicable to formation of thiaalkanam rings. We wish to report here new synthesis of 6- and 7-thianonanams, which are novel or rarely seen ring systems,[4] from a diolefinic β-lactam and sulfur dichloride.



The starting diolefinic β-lactam (**3**), 1-allyl-4-styrylazetidin-2-one, was prepared by usual allylation of the *N*-unsubstituted β-styryl-β-lactam (**2**) obtained by addition-cyclization of 1-



trimethylsilyl-4-phenyl-1-aza-1,3-butadiene (**1**) with ethyl α-lithioisobutyrate[5] in 65% overall yield. Solutions of 965 mg (4.0 mmol) of the β-lactam (**3**) in CH_2Cl_2 (50 ml) and 412 mg (4.0 mmol) of SCl_2 in CH_2Cl_2 (50 ml) were added dropwise to 500 ml of refluxing CH_2Cl_2 by the same rate over 3 hours under nitrogen atmosphere to maintain high dilution condition. The mixture was refluxed for two hours and the solvent was removed under reduced pressure. Upon chromatography of the residue on a SiO_2 column, 96 mg (7%) of 8-chloro-3,3-dimethyl-5-(α-chlorobenzyl)-6-thianonanam (**4**: mp 163-164 °C, colorless solids from benzene/hexane) and 565 mg (41%) of two isomers of 5-chloro-8-chloromethyl-3,3-dimethyl-6-phenyl-7-thianonanam (**5**: after separation and recrystallization; major isomer: mp 74-75 °C, colorless solids from benzene/hexane, yield 21%; minor isomer: mp 154-155 °C, colorless solids from benzene/hexane, yield 5%) were isolated.

The structures of the new thiaalkanam (**4**) and the 7-thia derivatives (**5**) were determined by spectral and analytical data. The ir spectrum of **4** showed absorption band at 1740 cm^{-1} (β-lactam C=O) and a molecular ion peak in the mass spectrum was observed at *m/z* 343 along with a base peak at *m/z* 218 (M^+ - PhCHCl). The latter fragment ion peak strongly suggested the addition of SCl_2 to styryl group proceeded to form exocyclic PhCHCl moiety as in the case with thiaisoalkanams.[3] Assignments of the ^1H and ^{13}C nmr spectra[6] were supported by shifts of signals upon oxidation to its sulfone with MCPBA,[7] which was effective in assignments of nmr signals of thiaisoalkanams in the preceding paper.[3] For example, a triplet carbon showed large down field shift upon oxidation and, hence, addition of SCl_2 to allyl substituent occurred to form $-SCH_2CHCl-$ linkage.

While ir and nmr spectra of the two isomers of **5** showed some extent of differences,[6] they gave the same mass spectra [M^+: *m/z* 343, base peak: *m/z* 240 (M^+ - $ClCH=C=CMe_2$ - H)] suggesting that they are stereoisomers. Observation of a very weak peak at *m/z* 218 in clear contrast to the spectra of **4** implies that SCl_2 added to styryl group in an opposite manner to that with **4**. That addition of SCl_2 across allyl group gave $-SCH(CH_2Cl)-$ is supported by lower field shift of a doublet carbon and a higher field shift of a triplet carbon upon oxidation. The other assignments of the nmr spectra were successfully done also by means of the oxidation method to clarify their 7-thianonanam structure,[8] though the stereochemistry of them has not been decided yet.

Thus application of sulfur dichloride can be expected in syntheses of various new types of thiaalkanams by changing alkenyl substituents of the starting β-lactams.

ACKNOWLEDGEMENT

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6. All the compounds (**2**, **3**, **4**, and **5**) were isolated and gave reasonable spectral data. Key spectral data of the bicyclic β-lactams (**4**) and (**5**) are given below.

   4: **ir** (Nujol, ν, cm^{-1}) 1740 (C=O); **^{1}H nmr** (90 MHz, CDCl$_3$) δ 1.21 (s, 3H, Me), 1.29 (s, 3H, Me), 2.7-3.3 (m, 3H, SCH$_2$, NC$\underline{H}$H), 3.52 (dd, *J*=8.9, 6.0 Hz, 1H, SCH), 3.78 (d, *J*=6.0 Hz, 1H, NCH), 3.9-4.3 (m, 1H, ClCH), 4.29 (dd, *J*=11.4, 5.6 Hz, 1H, NCH$\underline{H}$), 4.95 (d, *J*=8.9 Hz, 1H, PhC$\underline{H}$Cl), 7.3-7.4 (5H, Ph); **^{13}C nmr** (22.5 MHz, CDCl$_3$) δ 17.6 (q, Me), 21.8 (q, Me), 37.7 (t, SCH$_2$), 48.4 (t, NCH$_2$), 53.3 (d, SCH), 55.3 (s, Me$_2\underline{C}$), 55.9 (d, ClCH), 65.0 (d, NCH), 68.4 (d, Ph$\underline{C}$HCl), 173.3 (s, CO); **ms** (EI) *m/z* 343 (M$^+$, 3.2), 345 (M$^+$ + 2, 2.3), 218 (M$^+$ - PhCHCl, 100). Anal. Calcd for C$_{16}$H$_{19}$NOCl$_2$S: C, 55.82, H, 5.56, N, 4.07. Found: C, 55.96, H, 5.64, N, 3.97.

   5: major isomer; **ir** (Nujol, ν, cm^{-1}) 1745 (C=O); **^{1}H nmr** (90MHz, CDCl$_3$) δ 1.40 (s, 6H, 2 Me), 3.11 (dd, *J*=13.6, 11.0 Hz, 1H, NC$\underline{H}$H), 3.37-4.03 (m, 3H, ClCH$_2$, SCH), 4.25 (d, *J*=3.6Hz, 1H, NCH), 4.48 (dd, *J*=13.6, 2.5Hz, 1H, NCH$\underline{H}$), 4.7-5.0 (m, 2H, ClCH, PhCHS), 7.1-7.6 (m, 5H, Ph); **^{13}C nmr** (22.5 MHz, CDCl$_3$) δ 17.7 (q, Me), 24.5 (q, Me), 44.8 (t, ClCH$_2$), 45.7 (t, NCH$_2$), 47.5 (d, SCH), 54.6 (d, Ph$\underline{C}$HS), 55.7 (s, Me$_2\underline{C}$), 65.1 (d, NCH), 65.5 (CHCl), 178.0 (s, CO); **ms** (EI) *m/z* 343 (M+, 1), 345 (M$^+$ + 2, 0.7), 240 (M$^+$ - Me$_2$C=C=CHCl - H, 100). minor isomer; **ir** (Nujol, ν, cm^{-1}) 1755 (C=O); **^{1}H nmr** (90 MHz, CDCl$_3$) δ 1.37 (s, 3H, Me), 1.49 (s, 3H, Me), 2.8-3.2 (m, 1H, SCH), 3.39 (dd, *J*=15.9, 3.2 Hz, 1H, NC$\underline{H}$H), 3.81 (d, *J*=8.7 Hz, 2H, ClCH$_2$), 3.96 (d, *J*=6.3 Hz, 1H, NCH), 4.36 (dd, *J*=15.9, 4.8 Hz, 1H, NCH$\underline{H}$), 4.46 (d, *J*=9.9 Hz, 1H, PhCHS), 4.99 (dd, *J*=9.9, 6.3 Hz, 1H, ClCH), 7.4-7.6 (m, 5H, Ph); **^{13}C nmr** (22.5 MHz, CDCl$_3$) δ 18.7 (q, Me), 23.8 (q, Me), 45.1 (t, ClCH$_2$), 45.5 (t, NCH$_2$), 46.3 (d, SCH), 48.8 (d, Ph$\underline{C}$HS), 56.6 (s, Me$_2\underline{C}$), 64.1 (d, NCH), 64.9 (d, CHCl), 173.6 (s, CO); **ms** (EI) *m/z* 343 (M$^+$, 1.1), 345 (M$^+$ + 2, 0.8), 240 (M$^+$ - Me$_2$C=C=CHCl - H, 100).

7. Oxidation of tetrahydrothiophene to its sulfone causes lower field shift of the α-carbon (from δ 31.2 to δ 51.5) and higher field shift of the β-carbon (from δ 31.4 to δ 22.8) in ^{13}C nmr spectra.[9] Hence, assignments of carbons α and β to sulfur atom were done without difficulty by oxidation, which also helped assignments of proton signals.

8. The reason why 7-membered ring fused to β-lactam was obtained predominantly over 6-membered ring is not clear at the moment. Molecular models show, however, that the 7-membered ring fused to β-lactam in *trans* manner seems to be less strained than 6-membered isomers.

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