[Chem. Pharm. Bull. 21(5)1090—1095(1973)]

UDC 547.718.057 : 547.491.3.04

Syntheses of 2-Azetidinone (β-Lactam) Ring by Chlorosulfonyl Isocyanate (CSI)[1]

Koichi Hirai, Hidebumi Matsuda, and Yukichi Kishida

Central Research Laboratories, Sankyo Co., Ltd.[2]

(Received November 14, 1972)

Attempts were made to prepare sulfur substituted 2-azetidinones by the reaction of vinylsulfide with chlorosulfonyl isocyanate (CSI). The main product of the reaction of β-methylthiostyrene (I) with CSI was pyridone derivative (II), but in the case of 1-phenylthio-1-propene (V) the main products were dihydrouracil derivatives (VI and VII) and acrylic acid derivatives (VIII and IX). Reaction of 1-*p*-chloro- or *p*-methylphenylthio-1-propene (Xa and b) with CSI in dry ether at −30° gave the desired 2-azetidinone (β-lactam) derivatives (XIa and b) in 63 and 66.4% isolated yield respectively.

The cycloaddition reaction of chlorosulfonyl isocyanate ($ClSO_2NCO$, CSI)[3] with olefines has provided the most facile and direct route to β-lactams (2-azetidinones). R. Graf who discovered the extraordinary propensity of CSI to add to carbon-carbon multiple bonds, reported the addition of CSI to styrene to give 4-phenylazetidinone N-sulfonyl chloride in high yield but sulfur substituted olefins, *i.e.* thiophene to give thiophenecarboxamide-N-sulfonylchloride.[4]

In connection with the synthetic approach to the sulfur substituted 2-azetidinone (found in penicillins and cephalosporins) we investigated the reactivities of CSI with various sulfur-substituted double bonds, and have now succeeded in the syntheses of arylthio-substituted azetidinone rings together with some other products.

Addition of *cis*-β-methylthiostyrene (I)[5] to freshly distilled CSI in dry ether at −40°, followed by the hydrolysis of the mixture with thiophenol-pyridine in acetone gave mainly three products (II, III and IV) Chart 1. The first product (II) was formed in 12% yield and

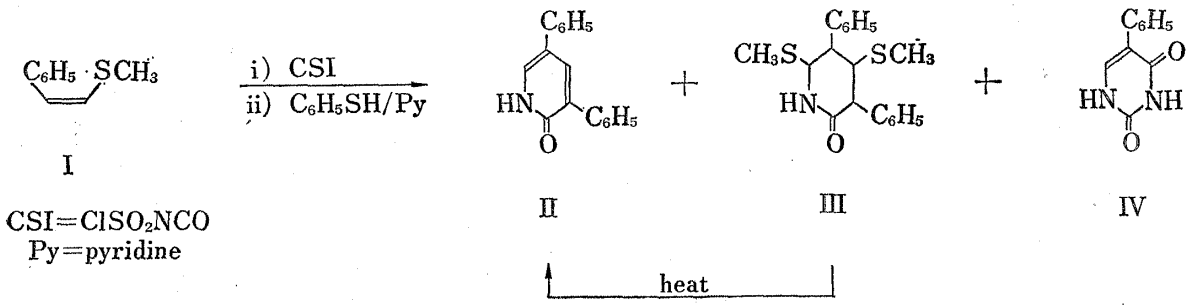


Chart 1

had a molecular formula of $C_{17}H_{13}ON$ from the elemental analysis and the mass spectrum (M^+ at *m/e* 247). The IR spectrum showed broad absorption in the region of 3200 to 2400 cm^{-1} and C=O stretching absorption at 1648 cm^{-1} due to 2-pyridone. The nuclear magnetic re-

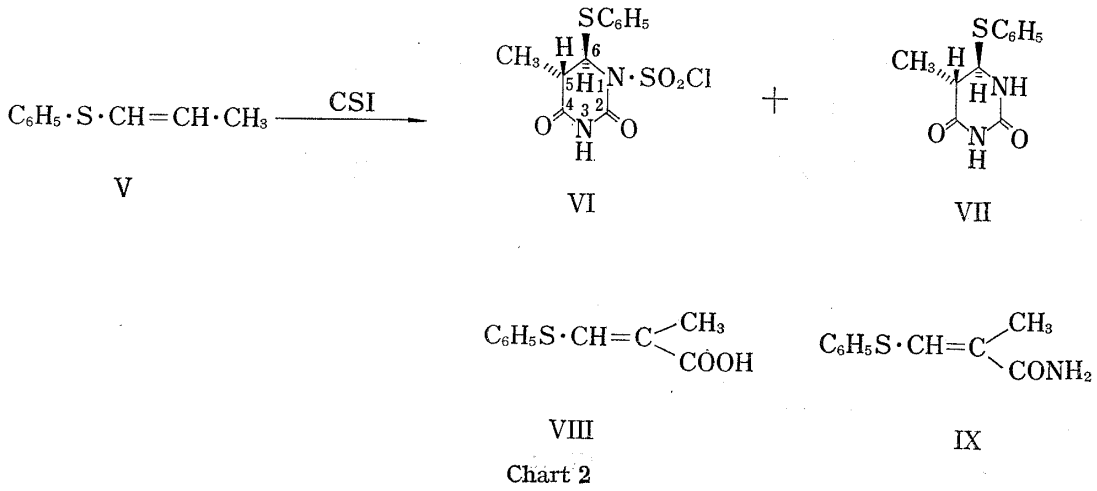
1) This work was presented at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April, 1972. Abstr. (Part II), p. 89.
2) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo.*
3) R. Graf, *Org. Syn.*, **46**, 23 (1966).
4) R. Graf, *Ann. Chem.*, **661**, 111 (1963).
5) W.E. Truce, *J. Am. Chem. Soc.*, **78**, 2756 (1956).

sonance (NMR) spectrum showed only complex signals at δ 7.0—8.0 in the aromatic region. From these data and considering the mechanism we rationally assigned the structure of the product as 3,5-diphenyl-2-pyridone (II).

The second product (III) was formed in 2% yield. This product was very unstable and showed mass spectra at *m/e* 343 (M^+), 295 (M^+-CH_3SH) and 247 (base peak: $M^+-CH_3SH\times 2$). On heating this material was converted into the third product (IV) with evolution of methyl mercaptan, and therefore was considered to be precursor of the third product (IV).

The third product (IV), mp>300° was formed only in 1% yield. The molecular formula ($C_{10}H_8O_2N_2$) was determined from the elemental analysis and mass spectrum (M^+ at *m/e* 188). The infrared (IR) spectrum showed CO absorption at 1766 and 1680 cm^{-1}, and NH stretching absorption at 3000—3250 cm^{-1}. The ultraviolet (UV) spectrum showed λ_{max} at 239.5 and 279 nm in ethanol, which was clearly different from that of 6-phenyluracil (λ_{max} at 286 nm).[6] The NMR spectrum in DMSO-d_6 showed δ 7.2—7.7 (5H) and 11.1 (1H) which coincided with the proposed structure, 5-phenyluracil (IV).

Next we studied the reaction of CSI with 3-phenylthio-2-propene (V).[7] In this case the products (VI—IX) were isolated in relatively high yield.



V VI VII

VIII IX

Chart 2

From the ether soluble part three products (VI, VII and VIII) were isolated. Product VI, mp 176° was obtained in12% isolated yield and has a molecular formula of $C_{11}H_{11}O_4N_2S_2Cl$ which was provided from the elemental analysis and the mass spectrum with the molecular ion peak at *m/e* 334.

The NMR spectrum ($CDCl_3$) showed C_6-H signal at δ 6.15 as doublet (J=5 Hz) which was coupled with the C_5-H signal at δ 3.73 (d of q, J=7 and 5 Hz). The relative stereochemistry of C_5-H and C_6-H would be *trans* from the coupling constant (J_{5-6}=5 Hz). The methyl signal was detected at δ 1.45 as doublet (J=7 Hz). The IR spectrum showed NH absorption at 3200 cm^{-1}, CO absorption at 1755 and 1725 cm^{-1}, and SO_2 absorption at 1373 and 1190 cm^{-1}. Based on the above mentioned data, this product was designated as 5-methyl-6-phenylthio-5,6-dihydrouracil-1-sulfonyl chloride (VI). The second product (VII) was isolated in 10% yield from the ether-soluble part of the reaction mixture, and was also prepared by the removal of the electronegative SO_2Cl substituent of VI with thiophenol-pyridine in acetone,[4] in which all NMR signals were now shifted upfield [C_5-H at δ 3.14 (d of q, J=7 and 5 Hz, C_6-H at δ 5.02, and new N_1-H signal appeared at δ 8.36 (broad d, J=4.7 Hz)]. From these phenomena of shifts of the NMR and other physico-chemical data (see Experimental) this product was

6) J. Evans, *J. Am. Chem. Soc.*, **54**, 641 (1932).
7) C.D. Hurd, *J. Am. Chem. Soc.*, **52**, 3357 (1930). *cis* and *trans* mixture (V) was used.

assigned as 5-methyl-6-phenylthio-5,6-dihydrouracil (VII). The third product VIII, mp 132° was formed in 25% yield. The structure was deduced from the usual criteria. The molecular formula, $C_{10}H_{10}O_2S$ was determined by its mass spectrum [M^+ at *m/e* 194] and elemental analysis. The broad IR absorption at about 2500 cm^{-1} suggested that this product was carboxylic acid derivative and further strong absorption at 1670 and 1580 cm^{-1} indicated α,β-unsaturated character of the acid. The NMR spectra showed the peaks at δ 10.9 (-COOH), 7.84 (1H), 7.4 (5H, $-SC_6H_5$) and 1.96 (CH_3). These data coincided well with the proposed structure, β-phenylthiomethacrylic acid (VIII).[8]

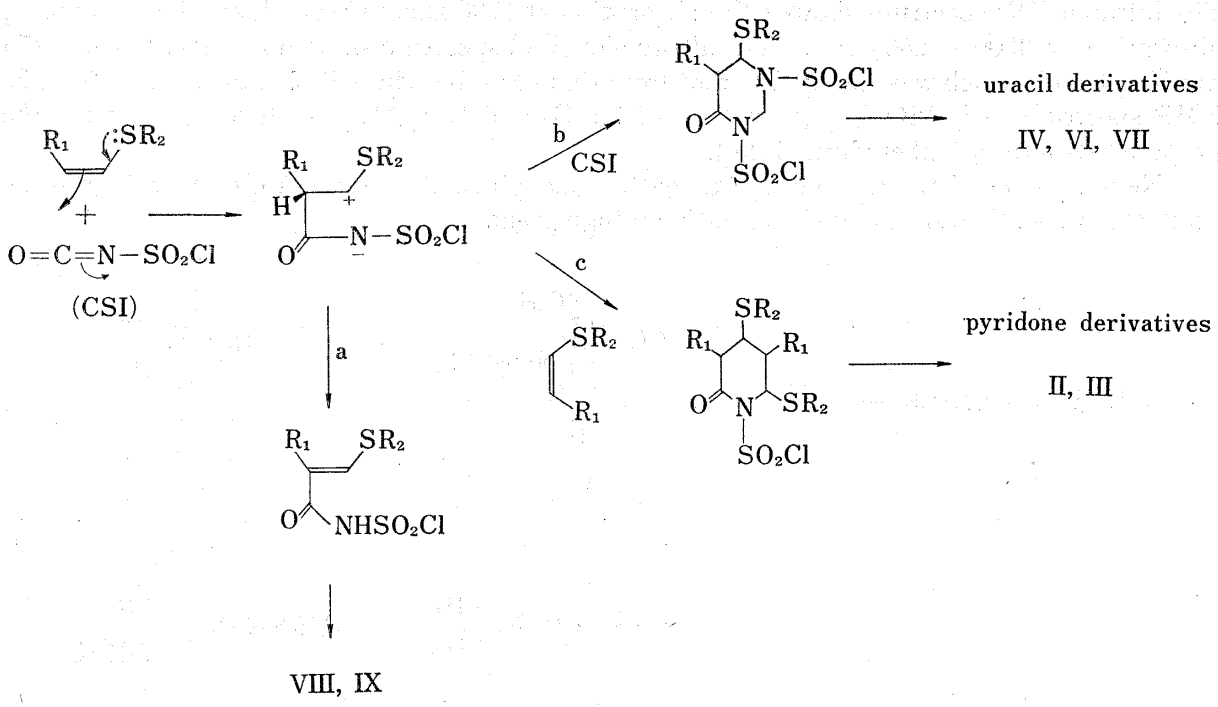


Chart 3

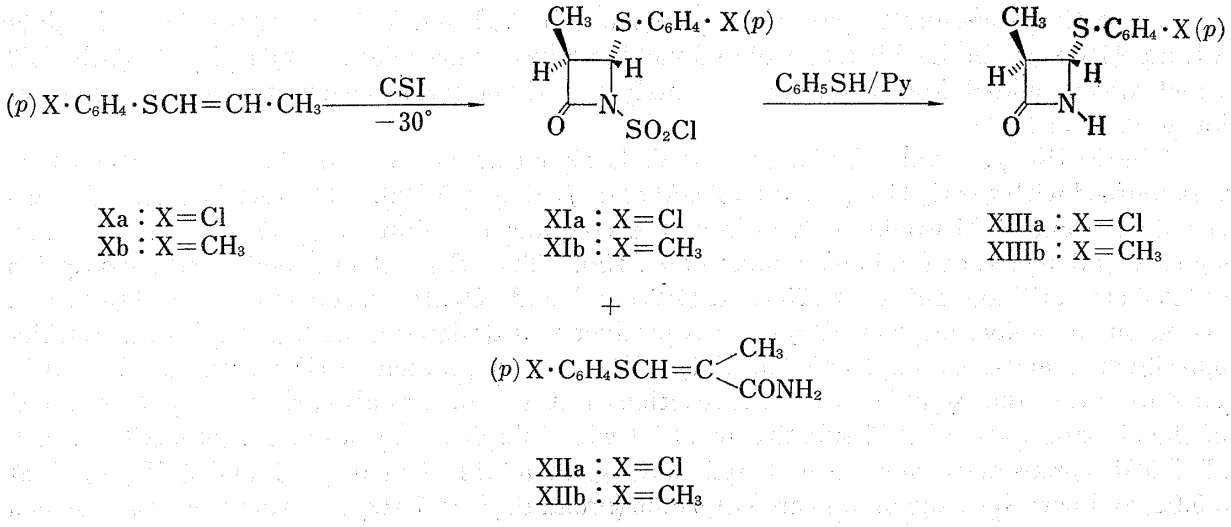


Chart 4

8) Although the stereochemistry about the double bond in VIII and IX could not be determined conclusively from the available data, it is probably *trans*.

The fourth product (IX) was obtained in 40% yield from the ether-insoluble part of the reaction mixture. Hydrolysis of this product gave VIII and therefore the structure of the fourth product was determined as β-phenylthiomethacrylamide (IX).[8]

Probable mechanistic pathways for the formation of the products (II—IX) are shown in Chart 3. Path a and b are the main paths for the reaction with the vinylsulfide (V) (R_1=CH_3 and R_2=C_6H_5), whereas c is the path with I (R_1=C_6H_5 and R_2=CH_3).

Further we planned constructing the sulfur-substituted β-lactam ring by introducing Cl or CH_3 group at the *p*-position of the benzene ring to stabilize the 1,4-dipolar intermediate (Chart 3). *p*-Chlorophenylsulfide (Xa) was treated with 1.1 equivalents of CSI in dry ether at −30°C to afford an unstable, white crystalline product. After rapid washing with cold ether, the product, mp 54° (decomp.) was isolated in 63% yield. From the elemental analysis, a molecular formula of $C_{10}H_{19}O_3NS_2Cl_2$ was given to this product, indicating a 1: 1 adduct of CSI and Xa. Especially in the IR spectrum (Fig. 1) the C=O stretching absorption was detected at 1825 cm^{-1} which was characteristic of 2-azetidinone N-sulfonyl chloride. Removal of the SO_2Cl group in this product was smoothly effected by thiophenol-pyridine in acetone to give the stable 3-methyl-4-*p*-chlorophenylthio-2-azetidinone (XIIIa) mp 115°.

The physico-chemical data of the final product were in good accordance with the proposed structure, XIIIa. The IR spectrum showed absorption at 3225 cm^{-1} due to NH, and 1747 cm^{-1} due to C=O. The NMR spectrum ($CDCl_3$) exhibited a doublet at δ 4.82 (J=2 Hz, C_4-H) and a quartet (J=7 Hz) with further splitting (J=2 Hz) at 3.06. The coupling constant (J=2 Hz) between C_3-H and C_4-H clearly indicates the *trans* configuration of each proton.[9]

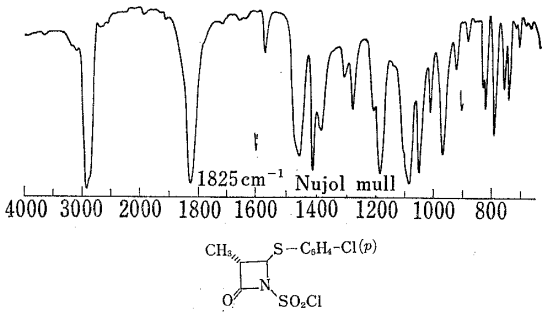


Fig. 1.

From the mother liquor was obtained the β-*p*-chlorophenylthiomethacrylamide (XIIa) in 15.8% yield, and the structure was determined analogously as with IX. This amide would be formed by the hydrolysis of the sulfonyl chloride moiety of the intermediate from the path a in Chart 3 (R_1=CH_3, R_2=*p*-Cl·C_6H_4-) in the isolation process.

Parallel results were obtained with *p*-tolylsulfide (Xb). The azetidinone N-sulfonyl chloride (XIb), mp 40° (decomp.), (ν_{max}: 1822 cm^{-1}) was obtained in 66.4% yield, and its azetidinone derivative (XIIIb), mp 86° showed the analogous physico-chemical data to those of XIIIa (*see* Experimental). The chemical reactivities of these azetidinones (XIIIa and XIIIb) will be reported in the near future.

Experimental

All melting points are uncorrected. NMR spectra were recorded on a Varian A-60 spectrometer containing 2—3% tetramethylsilane (TMS). Chemical shifts were recorded under the δ convertion in parts per million relative to TMS (0 ppm); s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a Perkin-Elmer Model 137 spectrometer. UV spectra were recorded on a Shimadzu Model IV-50 AL spectrometer. Thin-layer chromatography (TLC) were carried out on Merck TLC-plates silica gel F_{254} pre-coated.

Reaction of *cis* β-Methylthiostyrene (I) with Chlorosulfonyl Isocyanate (CSI)——To a stirred solution of CSI (850 mg) in 3.5 ml of *liq.* sulfur dioxide was added 750 mg of *cis* β-methylthiostyrene (I)[5] at −40—−50° over ten minutes. After stirring at −40——50° for thirty minutes, the temperature of the reaction mixture raised to −6° and almost all of the sulfur dioxide was removed off. Water was added and the products were extracted with methylene chloride. The organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent gave *ca.* 1.1 g of oily residue. The oily residue was dissolved in 3 ml of

9) A.K. Bose, G. Spiegelman, and M.S. Manhas, *J. Am. Chem. Soc.*, **90**, 4506 (1968).

acetone and to this solution was added 720 mg of thiophenol and 343 mg of pyridine successively. After stirring for thirty minutes water was added and the precipitated material was filtered off and recrystallized from *n*-hexane to give 20 mg of 3,5-diphenyl-4,6-dimethylthio-2-piperidone (III). mp 158° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1663 (C=O). Mass Spectrum *m/e*: 342 (M^+), 296 (M^+–CH_3SH), 247 (M^+–$CH_3SH\times 2$). This material was unstable and easily converted to 5-phenyluracil (IV) on heating at 150° for 5 minutes.

After removal of the solvent from the mother liquor ether was added and the precipitated material was recrystallized from methylene chloride and benzene to give 9 mg of 5-phenyluracil (IV). mp>300°. UV λ_{max}^{EtOH} nm (ε): 239.5 (10700), 279 (8560). *Anal.* Calcd. for $C_{10}H_8O_2N_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.48; H 4.36; N, 14.74. Mass Spectrum *m/e*: 188 (M^+). After collecting of the precipitated material the ether was removed off to give long needles. Recrystallization from methanol gave pure sample of 3,5-diphenyl-2-pyridone (II), 120 mg. mp 202°. UV λ_{max}^{EtOH} nm (ε): 252 (19350), 338 (8600). *Anal.* Calcd. for $C_{17}H_{13}ON$: C, 82.57; H, 5.30; N, 5.50. Found: C, 82.17; H, 5.50; N, 5.70. Mass Spectrum *m/e*: 247 (M^+), 219 (M^+–CO), 204 (M^+–COOH).

Reaction of 1-Phenylthio-1-propene (V) and CSI——To a stirred solution of 6.24 g of CSI in 10 ml of dry ether was added 6 g of 1-phenylthio-1-propene (V) at −45——50°, over 25 minutes. After stirring at −45——50° for 2 hr, the temperature of the reaction mixture raised to room temperature and stirring was continued for 5 hr. The ether solution was washed with cold water and dried over $MgSO_4$. Removal of the ether gave viscous fluid, which was dissolved in ether again and after removal of the insoluble part (*ca.* 4 g) the ethereal layer was concentrated and was added methanol to give precipitates. Recrystallization from small amount of ether gave pure 1.6 g of 5-methyl-6-phenylthio-5,6-dihydrouracil-1-sulfonyl chloride (VI). mp 176° (decomp). UV λ_{max}^{EtOH} nm (ε): 253.5 (4000). *Anal.* Calcd. for $C_{11}H_{11}O_4N_2S_2Cl$: C, 39.49; H, 3.31; N, 8.37; S, 19.16; Cl, 10.59. Found: C, 39.75; H, 3.34; N, 8.59; S, 19.16; Cl, 10.72. Mass Spectrum *m/e*: 334 and 336 (M^+, 1:3), 225 and 227 (1:3), 126 (M^+-C_6H_5S, -SO_2Cl).

From the mother liquor were obtained 1.2 g of 3-phenylthiomethacrylic acid (VIII) and 150 mg of 5-methyl-6-phenylthio-5,6-dihydrouracil (VII) by fractional recrystallization from *n*-hexane. 3-Phenylthiomethacrylic acid (VIII). mp 132°. IR ν_{max}^{Nujol} cm^{-1}: 2700—2300 (COOH), 1670 and 1588. UV λ_{max}^{EtOH} nm (ε): 280 (16200). NMR ($CDCl_3$) δ: 10.9 (1H, s, -COO<u>H</u>), 7.84 (1H, q, J=1.3 Hz), 1.96 (3H, d, J=1.3 Hz), 7.4 ($C_6\underline{H}_5$). *Anal.* Calcd. for $C_{10}H_{11}O_2S$: C, 61.85; H, 5.19; N, 16.48. Found: C, 61.75; H, 5.23; N, 16.82. Mass Spectrum *m/e*: 194 (M^+).

The ether insoluble part (*ca.* 4 g) was separated by 400 g of silica gel dry column (ϕ=50 mm) chromatography with elution of benzene: acetone=1:1, and a portion of *Rf*=0.2 was extracted with methylene chloride to give 2.3 g of β-phenylthiomethacrylamide (IX). This product was also isolated from the ether soluble part and totally amounted 3.065 g. mp 110°. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3180, 1662 (C=O), 1620 (C=O). UV λ_{max}^{EtOH} nm (ε): 280 (16300). NMR ($CDCl_3$) δ: 7.2—7.53 (6H, $C_6\underline{H}_5$- and vinyl H), 6.13 (2H, -$N\underline{H}_2$), 1.97 (3H, d, J=1.4 Hz). *Anal.* Calcd. for $C_{10}H_{10}ONS$: C, 62.13; H, 5.74; N, 7.24; S, 16.59. Found: C, 61.70; H, 5.86; N, 7.19; S, 16.68. Mass Spectrum *m/e*: 193 (M^+).

***trans*-3-Methyl-4-*p*-chlorophenylthio-2-azetidinone N-Sulfonyl Chloride (XIa)**——To a stirred solution of 1.62 g of CSI in 5 ml of dry ether was added 1.8 g of 1-*p*-chlorophenylthio-1-propene at −30° over 40 min. After stirring for 1.5 hr at the same temperature the appeared crystals were collected and washed with cold ether to give 2 g of *trans*-3-methyl-4-*p*-chlorophenylthio-2-azetidinone N-sulfonyl chloride (XI b). mp 54° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1825 (C=O). *Anal.* Calcd. for $C_{10}H_{19}O_3NS_2Cl_2$: C, 36.78; H, 2.78; N, 4.29; S, 19.66. Found: C, 36.58; H, 2.96; N, 4.07; S, 19.11.

From the mother liquor was obtained 350 mg of β-*p*-chlorophenylthiomethacrylamide (XIIa). mp 143—145°. IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 1663 (C=O). UV λ_{max}^{EtOH} nm (ε): 260 (sh), 283.5 (15400). NMR ($(CD_3)_2$-CO) δ: 7.6 (1H, q, J=1.1 Hz), 7.54 (4H, s, arom.), 5.67 (1H, N<u>H</u>), 2.03 (3H, d, J=1.1 Hz, C<u>H</u>$_3$). *Anal.* Calcd. for $C_{10}H_{10}ONSCl$: C, 52.74; H, 4.43; N, 6.15; S, 14.08. Found: C, 52.13; H, 4.21; N, 6.10; S, 14.53. Mass Spectrum *m/e*: 227 and 229 (M^+, 1:3), 211 and 213 (M^+-NH_2, 1:3), 183 and 185 (M^+-$CONH_2$).

***trans*-3-Methyl-4-*p*-tolylthio-2-azetidinone N-Sulfonyl Chloride (XIb)**——This compound was obtained from 1-tolylthio-1-propene (Xb) and CSI under the same conditions of the formation of IXa in 66.4% isolated yield. mp 40° (decomp). IR ν_{max}^{Nujol} cm^{-1}: 1820. *Anal.* Calcd. for $C_{11}H_{12}O_3NS_2Cl$: C, 43.29; H, 3.96; N, 4.58; S, 20.97. Found: C, 43.53; H, 3.65; N, 5.01; S, 20.46.

From the mother liquid were obtained β-*p*-tolylthiomethacrylamide (XIIIb) and β-*p*-tolylthiomethacrylic acid in 8.95% and 2.62% isolated yield respectively.

β-*p*-Tolylthiomethacrylamide (XIIb). mp 130—132°. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3150 (NH), 1660 (C=O). UV λ_{max}^{EtOH} nm (ε): 253 (sh), 281 (16600). NMR ($CDCl_3$) δ: 7.02—7.47 (5H, m, arom. and vinyl-H), 5.8 (2H, br, N<u>H</u>$_2$), 2.32 (3H, s, C<u>H</u>$_3$), 1.97 (3H, d, J=1.1 Hz). *Anal.* Calcd. for $C_{11}H_{13}ONS$: C, 63.42; H, 6.73; N, 6.73; S, 15.39. Found: C, 63.42; H, 6.40; N, 6.82; S, 15.53. β-*p*-Tolylthiomethacrylic acid. mp 160—163°. IR ν_{max}^{Nujol} cm^{-1}: 2200—2600 (CO_2H), 1665. UV λ_{max}^{EtOH} nm (ε): 255 (sh), 281.5 (19600). NMR (in $CDCl_3$) δ: 11.62 (1H, s, $CO_2\underline{H}$), 7.79 (1H, d, J=1.1 Hz), 7.03—7.45 (4H, m, arom.), 2.36 (3H, s, C<u>H</u>$_3$), 1.94 (3H, d, J=1.1 Hz, C<u>H</u>$_3$). *Anal.* Calcd. for $C_{11}H_{12}O_2S$: C, 63.42; H, 5.81; S, 15.39. Found: C, 63.28; H, 5.81; S, 15.60. Mass Spectrum *m/e*: 208 (M^+), 161 (M^+-CO_2).

***trans*-3-Methyl-4-*p*-chlorophenylthio-2-azetidinone (XIIIa)**——To a suspension of 1.63 g of *trans*-3-methyl-4-*p*-chlorophenylthio-2-azetidinone N-sulfonyl chloride (XIa) in 15 ml of ether was added a solution of 1.3 g of sodium sulfite in 7 ml of water at −10°, and then 10% aqueous NaOH solution was added dropwise at 0°. The ethereal layer was separated and washed with water and dried over $MgSO_4$. Removal of the solvent and recrystallization from ether gave 0.5 g of the title compound (XIIIa). mp 115°. IR ν_{max}^{Nujol} cm^{-1}: 3225 (NH), 1747 (C=O). UV λ_{max}^{EtOH} nm (ε): 225.5 (12000), 257.5 (7580). NMR ($(CD_3)_2CO$) δ: 7.3—7.7 (4H, m, 6.7—7.0 (1H, NH), 4.82 (1H, d, J=2 Hz), 3.06 (1H, d, of q, J=7.2 and 2 Hz), 1.32 (3H, d, J=7.2 Hz, CH_3). *Anal.* Calcd. for $C_{10}H_{10}ONSCl$: C, 52.74; H, 4.43; N, 6.15; S, 14.08. Found: C, 52.76; H, 4.70; N, 6.21; S, 14.32. Mass Spectrum *m/e*: 227 and 229 (M^+, 1: 3), 184 and 186 (M^+-NHCO), 169 and 171 (M^+-CH_3, NHCO), 144 and 146 (HSC_6H_4Cl).

***trans*-3-Methyl-4-*p*-tolylthio-2-azetidinone (XIIIb)**——To a solution of 2.8 g of *trans*-3-methyl-*p*-tolylthio-2-azetidinone N-sulfonyl chloride (XIb) in 15 ml of acetone was added 2.0 g of thiophenol at −20°, and then 700 mg of pyridine was added at 0° over 30 min. Water was added and the mixture was extracted with methylene chloride. After removal of the solvent the products were separated by silica gel preparative TLC (solvent system, benzene: acetone=5: 1). Extraction of a portion of Rf=0.4 with methylene chloride gave 1.0 g of the title compound. mp 88° (recrystallized from *n*-hexane: ether). IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1745 (C=O). UV λ_{max}^{EtOH} nm (ε): 214 (11200), 254 (5300). NMR ($CDCl_3$) δ: 7.3—7.5 (4H, A_2B_2 part of *p*-tolyl), 6.6—6.9 (1H, br, NH), 4.56 (1H, d, J=2 Hz), 3.08 (1H, d, of q, J=7.5 and 2 Hz), 2.34 (3H, s, CH_3), 1.32 (3H, d, J=7.5 Hz CH_3). *Anal.* Calcd. for $C_{11}H_{13}ONS$: C, 63.42; H, 6.29; N, 6.73; S, 15.39. Found: C, 63.79; H, 6.55; N, 7.04; S, 15.51. Mass Spectrum *m/e*: 207 (M^+), 192 (M^+-CH_3), 164 (M^+-NHCO), 149 (M^+-CH_3, -CONH).