123267-38-9; (±)-47, 123267-48-1; 49, 66323-03-3; 50, 123267-31-2; 50 bis(benzenesulfonate), 123267-30-1; 51, 123267-32-3; 52, 123267-33-4; 53, 123267-34-5; 54, 123267-35-6; (±)-55, 123267-36-7; (±)-56, 123267-37-8; (±)-57, 123289-28-1; (±)-60, 123267-39-0; (±)-*cis*-61, 123267-41-4; (±)-*trans*-61, 123267-40-3; (±)-62, 123267-43-6; (±)-*cis*-64, 123267-44-7; (±)-*trans*-64, 123267-45-8; (±)-*cis*-65, 123267-46-9; (±)-*trans*-65, 123267-47-0; (±)-66, 123267-49-2; (±)-67, 123267-50-5; (±)-68, 123267-51-6; (±)-69, 123267-52-7; (±)-70, 123267-53-8; (±)-71, 123267-54-9; (±)-72, 123267-56-1; (±)-73, 123267-56-1; (±)-73 methyl ester, 123267-57-2; (±)-74, 123267-58-3; (±)-75, 123267-59-4; (±)-76, 123267-60-7; ClC(S)OPh, 1005-56-7; $Ph_3PCH_2CH_3I$, 4736-60-1; H_2NCO_2Et, 51-79-6; $Br(CH_2)_3CH{=}CH_2$, 1119-51-3; potassium phthalimide, 1074-82-4; 4,5-dimethoxyphthalimide, 4764-20-9.

Synthesis of Azetidine-2,3-diones (α-Keto β-Lactams) via 3-(Phenylthio)-2-azetidinones[1]

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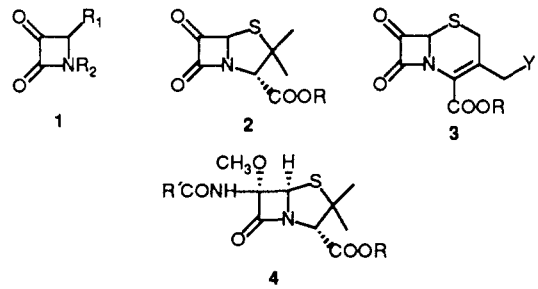
Received May 24, 1989

Stereospecific syntheses of tras and cis 3-(phenylthio)-2-azetidinones have been devised. Treatment of these β-lactams with sulfuryl chloride leads in high yield to single isomers of 3-chloro-3-(phenylthio)-2-azetidinones via a Pummerer type reaction. The structure of one of these compounds was confirmed by single-crystal X-ray diffraction analysis. The chloro group in these β-lactams is very active chemically; stereospecific replacement in high yield was used for preparing 3-methoxy-3-(phenylthio)-2-azetidinones. Hydrolysis of 3-chloro-3-(phenylthio)-2-azetidinones with moist silica gel and catalytic amounts of zinc chloride led to azetidine-2,3-diones in excellent yield.

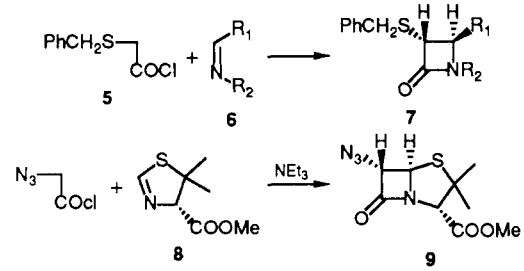
Azetidine-2,3-diones or α-keto β-lactams (**1**) are potentially very useful intermediates by virtue of the high concentration of functional groups in a small ring. In 1972 Lo and Sheehan[2] described the preparation of 6-oxopenicillanic acid (**2**) derivatives froim penicilin G and showed that the keto group adjacent to the β-lactam carbonyl was chemically very active. The same compound was also reported by Jen et al.[3] Later 7-oxocepham (**3**) derivatives were described by Applegate and co-workers[4] and also by Rapoport et al.[5] Sheehan and Lo[6] developed a Wittig type reaction involving 6-oxopenicillanic esters that led to **4**, a penicillin nucleus with the cephamycin type of side chain. Recently, Tufariello et al.[7] have reported a synthesis of azetidine-2,3-diones from α-ethylidene β-lactams.



1 **2** **3** **4**

We have prepared monocyclic α-keto β-lactams by several different methods.[8a] In a brief communication[8b] we have described the synthesis of this family of β-lactam derivatives via a Pummerer type reaction of α-phenylthio β-lactams. We describe now some highly functionalized β-lactams prepared by this general approach as well as details of our earlier work.[8b]

Steric Course of α-Phenylthio β-Lactam Formation. Previously[9] we have reported that the reaction between *S*-benzylthioglycolyl chloride (**5**), a Schiff base (**6**), and triethylamine produced a single isomer of β-lactam (**7**). On the basis of ^1H NMR spectral evidence, the trans configuration was assigned to this compound. The reaction of azidoacetyl chloride and triethylamine with a thioimidate (**8**) leads to a trans β-lactam (**9**).[10] Phenoxyacetyl chloride, triethylamine, and a Schiff base, however, generate mostly a cis β-lactam if the acid chloride is added slowly to the rest of the reactants.[11] The reason for this stereospecific formation of trans β-lactams with a thio group at C-3 or C-4 is not understood.



5 **6** **7** **8** **9**

For the preparation of 3-(phenylthio)-2-azetidinones (**13**)

† Deceased.

(1) Studies on Lactams Part 83. For Part 82, see: Wagle, D. R.; Monteleone, M. G.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Chem. Soc., Chem. Commun.* **1989**, 915.
(2) Lo, Y. S.; Sheehan, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 8253.
(3) Jen, T.; Frazee, J.; Hoover, J. R. E. *J. Org. Chem.* **1973**, *38*, 2857.
(4) Applegate, H. E.; Cimarusti, C. M.; Slusarchyk, W. A. *Tetrahedron Lett.* **1979**, 1637.
(5) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 4446.
(6) Sheehan, J. C.; Lo, Y. S. *J. Org. Chem.* **1973**, *38*, 3227.
(7) Tufariello, J. J.; Pinto, D. J. P.; Milowsky, A. S.; Reinhardt, D. V. *Tetrahedron Lett.* **1987**, *28*, 5481.
(8) (a) Bose, A. K. et al., manuscript in preparation. (b) Manhas, M. S.; Bari, S. S.; Bhawal, B. M.; Bose, A. K. *Tetrahedron Lett.* **1984**, *25*, 4733.
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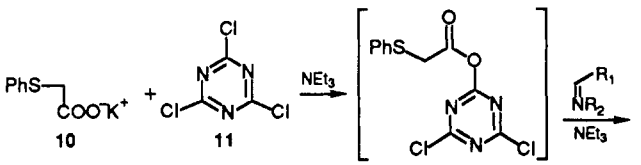
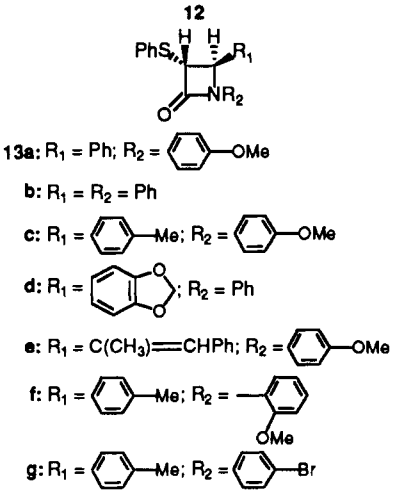
0022-3263/89/1954-5758$01.50/0

we have found it convenient to replace the acid chloride with a mixture of the potassium salt of (phenylthio)glycolic acid (**10**), triethylamine, and cyanuric chloride (**11**).[12] Apparently, an active ester (**12**) formed from the potassium salt and cyanuric chloride plays the same role as an acid chloride.[12]



10 **11** **12**



13a: R_1 = Ph; R_2 =

b: $R_1 = R_2$ = Ph

c: R_1 = ; R_2 =

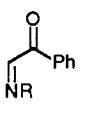
d: R_1 = ; R_2 = Ph

e: R_1 = $C(CH_3)$=CHPh; R_2 =

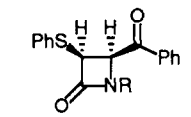
f: R_1 = ; R_2 =

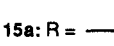
g: R_1 = ; R_2 =

When the imino components (**14**) in the β-lactam-forming reaction were prepared from phenylglyoxal and *p*-anisidine or phenethylamine, the α-phenylthio β-lactams (**15**) had the cis stereochemistry at C-3 and C-4 as indicated by their NMR spectral data. It has been found by us and others[13] that imino compounds derived from phenylglyoxal produce cis β-lactams on reaction with some other acid chlorides, too (or their equivalents).



14



15a: R = 

b: R = CH_2CH_2Ph

The benzoyl substituent in **14** obviously exerts a pronounced stereodirecting influence on β-lactam formation. In the case of (phenylthio)acetyl chlorides (and phthalimidoacetyl chloride), it is thus possible to achieve the stereospecific formation of cis or trans β-lactams by selecting the type of imino compounds that are used. The cis β-lactams of type **15** have an additional useful feature: they can be converted to the thermodynamically more stable trans β-lactams by C-4 epimerization under the influence of a strong base.

Pummerer Reaction. The Pummerer reaction[14] which permits a (phenylthio)methylene group to serve as an aldehyde equivalent has found recent use in several laboratories.[15] We attempted an analogous reaction on our 3-(phenylthio)-2-azetidinones. Under the action of sulfuryl

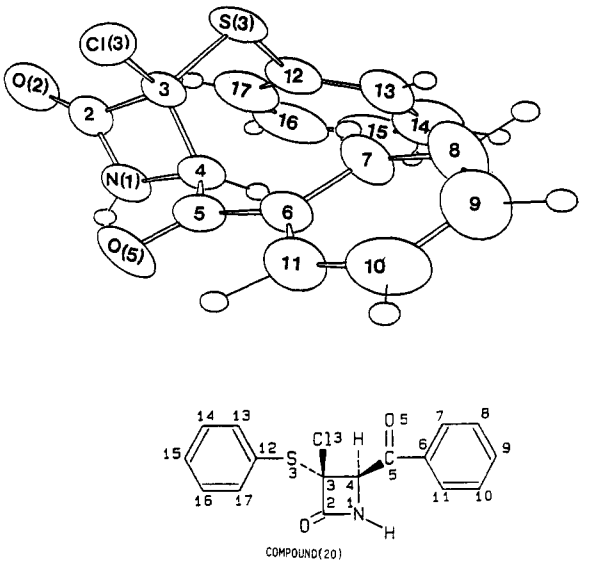
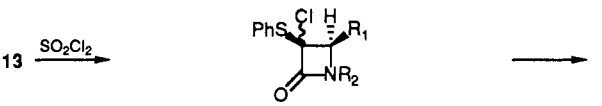
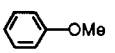


Figure 1.

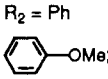
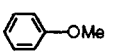
chloride on the phenylthio β-lactam **13** a chloro compound **16** was obtained in better than 90% yield from **13**. Although two isomers are possible, we observed the formation of a single 3-chloro-3-(phenylthio)-2-azetidinone.



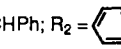
13

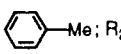
16a: R_1 = Ph; R_2 = 

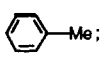
b: $R_1 = R_2$ = Ph

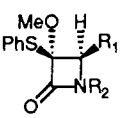
c: R_1 =  ; R_2 = 

d: R_1 =  ; R_2 = Ph

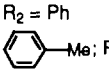
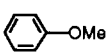
e: R_1 = $C(CH_3)$=CHPh; R_2 = 

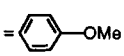
f: R_1 =  ; R_2 = 

g: R_1 =  ; R_2 = 



17a: $R_1 = R_2$ = Ph

b: R_1 =  ; R_2 = 

c: R_1 = $C(CH_3)$=CHPh; R_2 = 

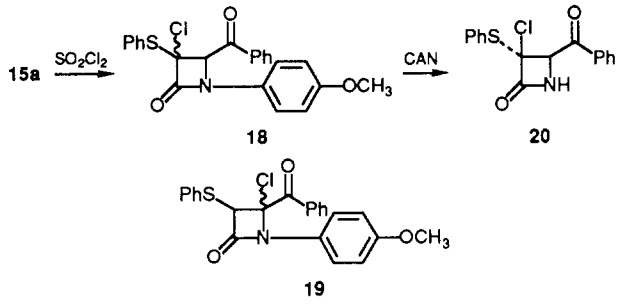
In the case of **15a** also we obtained a single isomer (**18**) of a chloro compound upon reaction with sulfuryl chloride. In this instance the possibility of the chloro substitution occurring at C-4 leading to **19** could not be ruled out, especially as hydrolysis of **18** did not lead to an azetidine-2,3-dione. Cerium(IV) ammonium nitrate oxidation[16] of **18** led to **20** in 44% yield. Since **20** was highly crystalline, X-ray diffraction studies were undertaken for determining its structure. The ORTEP projection of **20** along with its numbering scheme is illustrated in Figure 1. The X-ray crystal structure determination clearly eliminated structure **19**; the stereochemistry and the position of the chlorine atom in the molecule are described by the

(12) (a) Manhas, M. S.; Bose, A. K.; Khajavi, M. S. *Synthesis* **1981**, *209*. (b) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, 3037.
(13) Bose, A. K. et al., unpublished results. (b) Alcaide, B.; Dominguez, G.; Escobar, G.; Parreno, U.; Plumet, J. *Heterocycles* **1986**, *24*, 1579.
(14) Pummerer, R. *Chem. Ber.* **1910**, *43*, 1403.
(15) Chu, D. T. W.; Hengeveld, J. E.; Lester, D. *Tetrahedron Lett.* **1983**, *24*, 139 and references cited therein.
(16) Kronenthal, D. R.; Han, C. V.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

Table I. Crystal Parameters

a, Å	7.878 (1)	crystal form	monoclinic
b, Å	13.242 (4)	space group	$P2_1/C$
c, Å	14.833 (5)	MW	317.5
β, deg	97.45 (0.02)	density (calc)	1.375 g/cm^3
V, Å	1534.17	density (obs)	1.38 g/cm^3
Z	4		

structure **20**. It is worth noting that in **15a** the phenylthio and the benzoyl groups are cis to each other but they change to the trans disposition in **20** after chlorination. Whether similar inversion takes place in case of the trans β-lactam **13** is under study.



X-ray Structure Determination and Refinement. Single crystals of **20** in the form of thin needles were obtained by slow evaporation from a solution of hexane–ethyl acetate. A crystal of dimensions 0.009 × 0.40 × 0.09 mm was mounted on a Syntex P2 automated diffractometer. Cell constants were derived from the setting angles of 25 reflections. The space group was found to be $P2_1/C$ ($h0l$: $l = 2n + 1$ absent, $0k0$: $k = 2n + 1$ absent). Intensity data were collected using the $\omega - 2\theta$ scan technique with monochromatized Cu Kα radiation at a scan rate of 2°/min. Three standard reflections were checked periodically for alignment and crystal stability. Data were collected for the range $2 < 2\theta < 114°$. Of 2220 unique reflections collected, 1038 had intensities $I > 2\sigma(I)$ and were classified as observed reflections. The cell data of compound **20** are summarized in Table I.

The structure was solved by the direct-methods program MULTAN 80.[17] Phases for the largest E values were calculated, and the phase set with the highest combined figure of merit produced an E map which revealed the positions of all non-hydrogen atoms. After three cycles of isotropic full-matrix least-squares refinement, the function minimized being $\sum w(|F_o| - |F_c|)^2$ converged within the discrepancy index $R = 0.19$. Anisotropic full-matrix refinement for four cycles reduced R further to 0.084. Five hydrogen atoms could be located in a different map at this point, and the other hydrogen atom positions were calculated. Full-matrix anisotropic refinement of non-hydrogen atoms and isotropic refinement of hydrogen atoms positions reduced R further to 0.079. It was necessary to use fixed positions for atoms H(4), H(7), H(8), H(9), H(10), H(13), H(14), and H(15) as they tended to wander on refinement. Most of these atoms are attached to carbon atoms which show relatively high thermal motion.

The β-lactam ring in **20** is planar, as evidenced by low deviations of its atoms from their least-squares plane (±0.004 Å). The sum of valence angles around the β-lactam nitrogen (N1) atom is 359.4°, clearly indicating its trigonal configuration. Neither of the phenyl rings are coplanar with the β-lactam moiety; the dihedral angles between least-squares planes of the β-lactam ring and phenyl rings from benzoyl and phenylthio substituents are 52° and 57°, respectively.

The crystal lattice consists of centrosymmetric dimers formed due to intermolecular hydrogen bonding between the β-lactam ring nitrogen and the carbonyl oxygen of the benzoyl group transformed by 1-X, 1-Y, 2-Z symmetry: N1–H1···O5 = 2.759 (8) Å, H1···O5 = 1.98 (8) Å, and N1–H1···O5 angle = 164 (1)°.

3-Methoxy-2-azetidinone. 6-Halopenam derivatives are not very reactive toward nucleophilic displacement reactions.[18] There is one report by the Merck group where the bromine at C-6 of a penam has been substituted by an azido group.[19] Kemp et al.[19b] have shown, however, that the very reactive trifluoromethyl sulfonate group at C-3 does undergo S_N2 displacement with halide ions. More recently the Roche group[19c] has successfully replaced bromine at C-3 of a monocyclic β-lactam with an azide functionality in 62% yield. Following the work of Lohaus[20] we have recently used α-mesyloxy β-lactams for S_N2 inversion to cis as well as trans β-lactams.[20b,c]

We have observed that the chlorine in 3-chloro-3-(phenylthio)-2-azetidinones (**16**) is reactive and undergoes displacement in excellent yield when a chloroform solution of **16** is heated under reflux with methanol, silica gel, and a trace amount of anhydrous zinc chloride. Interestingly, a single isomer **17** of 3-(phenylthio)-3-methoxy-2-azetidinone was obtained in each case. The methoxy signal in the ^{1}H NMR spectrum of these compounds appears at about 3.75 ppm.

Previous work[9] has shown that when the methoxy group is cis to the phenyl group in a 3-methoxy-4-phenyl-2-azetidinone, the methoxy signal in the ^{1}H NMR spectrum is shifted to higher field by about 0.5 ppm as compared to its resonance in α-methoxycephalosporins[9b] and α-methoxypenicillins.[19a] This upfield shift is due to the shielding effect of the *cis*-4-phenyl group on the 3-methoxy protons.

Since the replacement of the aryl group at C-4 by the styryl group in compound **17** does not alter significantly the chemical shift (3.74 ppm) of the methoxy signal, it would appear that the 4-substituent must be trans to the 3-methoxy group in **17**. Support for this configurational assignment is provided by the observation that methoxy groups in β-lactams such as **23** and **24** in which they are cis to the phenyl group resonate at a higher field (3.05–3.25 ppm) than the methoxy group in **17**.

Reduction desulfurization of penicillin derivatives has been reported to proceed with retention of configuration.[21] Earlier[9] we came to the same conclusion when we obtained cis β-lactams by the Ra-Ni desulfurization of **24** and analogous β-lactams. If the desulfurization of **17** would

(17) MULTAN 80, A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data. Peter Main; Department of Physics, University of York, England. Jan 1980. (b) X-ray Program System, Technical Report, TR-446, Computer Science Center, University of Maryland, March 1976.

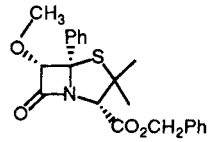
(18) Manhas, M. S.; Bose, A. K. In *Beta Lactams: Natural and Synthetic*; Wiley Interscience: New York, 1971; p 96. (b) McMillan, I.; Stoodley, R. J. *J. Chem. Soc. C* **1968**, 2533. (c) Morin, R. B.; Jackson, B. G.; Flynn, E. H.; Roeske, R. W.; Andrews, S. L. *J. Am. Chem. Soc.* **1969**, *91*, 1396.

(19) Cama, L. D.; Leanza, W. J.; Beattie, T. R.; Christensen, B. G. *J. Am. Chem. Soc.* **1972**, *94*, 1408. (b) Kemp, J. E. G. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Gregory, G. I., Ed.; Special Publication No. 38; The Royal Society of Chemistry: London, **1980**; Chapter 26, p 320. (c) Isenring, H. P.; Hofheinz, W. *Tetrahedron* **1983**, *39*, 2591.

(20) (a) Lattrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 901. (b) Monteleone, M. G. Ph.D. Thesis, Stevens Institute of Technology, 1989. (c) Hollinger, F. P. M.S. Thesis, Stevens Institute of Technology, 1989.

(21) (a) Wolfe, S.; Hasan, S. K. *Chem. Commun.* **1970**, 833. (b) Bose, A. K.; Manhas, M. S.; Chib, J. S.; Chawla, H. P. S.; Dayal, B. *J. Org. Chem.* **1974**, *39*, 2877.

also proceed with retention of configuration, *trans*-3-methoxy-4-aryl-2-azetidinones (**25**) would become available. This is of practical interest since the reaction of methoxyacetyl chloride with Schiff bases and triethylamine produces mostly or exclusively cis β-lactams.



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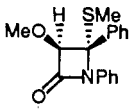

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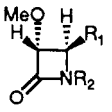

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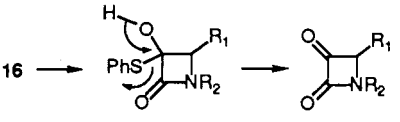
In the conversion of **16** to **17** the stereospecific replacement of the chloro group with retention of configuration of the phenylthio group is worthy of note. In the absence of the 3-phenylthio group, S_N2 reaction with inversion is the observed mode of reaction for a good leaving group at C-3 (such as a triflate or a mesylate group).[19] If an S_N2 mechanism is operative for **16**, the formation of **17** would indicate that the chlorine group at C_3 in **16** is trans to aryl group at C_4. On the other hand, the replacement of the chloro group in **16** could involve an S_N1 type reaction. The bulky group at C-4 would direct the incoming group to a position trans to it irrespective of the configuration of **16**. Thus, without definitive knowledge about the reaction mechanism, the stereochemistry of **16** cannot be deduced from that of **17**.

Azetidine-2,3-diones. 3-Chloro-3-(phenylthio)-2-azetidinones (**16**) could be conveniently hydrolyzed to azetidine-2,3-diones (**22**) in about 85–90% yield in a one-step reaction. This conversion was achieved by refluxing **16** in chloroform solution with moist silica gel and a catalytic amount of zinc chloride. It may be surmized that the keto β-lactams **22** are generated via the intermediate formation of the hydroxy derivatives **21**, which are transformed to **22** through the loss of thiophenol.



21 **22**

In summary, a convenient method has been developed for the synthesis of azetidine-2,3-diones and the stereospecific formation of 2-azetidinones with a 3-alkoxy group trans to the substituent at C-4. Also, strategies have been devised for the stereospecific preparation of a variety of cis and trans β-lactams.

Experimental Section

Melting points were taken for samples in open capillary tubes (Mel. Temp. apparatus) and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1310 IR spectrophotometer. NMR spectra were recorded on a Bruker WP200 SY spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectra were recorded on a CIMS Biospect. instrument. Elemental analyses were determined by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY.

General Method for the Synthesis of α-Phenylthio β-Lactams. *trans*-1-(*p*-Anisyl)-3-(phenylthio)-4-phenyl-2-azetidinone (13a). To a refluxing suspension of potassium thiophenoxyacetate (1.54 g, 7.5 mmol), *N*-benzylidene-*p*-methoxyaniline (1.12 g, 5 mmol), and triethylamine (3.5 mL, 20 mmol) in CCl_4 (100 mL) was added dropwise, under nitrogen atmosphere, a solution of cyanuric chloride (1.38 g, 5.5 mmol) in CCl_4 (40 mL) with constant stirring. The reactants were stirred overnight at room temperature, washed successively with 1 N HCl (30 mL), water (3 × 3 mL), 5% $NaHCO_3$ solution (30 mL), and brine (30 mL), and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the residue was chromatographed using silica gel (200–400 mesh) and $CHCl_3$–EtOAc–petroleum ether (10:0.3:0.8) solvent system. The title compound was obtained in 55% yield (1.04 g): mp 142 °C (ether–petroleum ether); IR (KBr) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.7 (s, 3 H), 4.2 (d, 1 H, J = 2.25 Hz), 4.73 (d, 1 H, J = 2.25 Hz), 6.65–7.9 (m, 14 H); CIMS (CH_4 reagent gas) m/z 362 $(M + H)^+$. Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.12; H, 5.30; N, 3.88. Found: C, 72.94; H, 5.18; N, 3.72.

By use of the same reaction conditions and appropriate Schiff bases the β-lactams **13b–g** were synthesized. Spectral data are summarized below.

13b: mp 100–101 °C (ether–petroleum); yield 55%; IR (KBr) 1740, 1680, 1660, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (d, 1 H, J = 2.18 Hz), 4.82 (d, 1 H, J = 2.27 Hz), 6.95–7.57 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 61.46, 62.97, 117.16, 124.15, 125.88, 127.86, 128.92, 129.06, 129.11, 129.11, 129.26, 132.16, 136.32, 137.17, 163.12; CIMS (CH_4) m/z 332 $(M + H)^+$.

13c: trans stereochemistry; mp 100–104 °C; yield 57%; IR (KBr) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.69 (s, 3 H), 4.23 (d, 1 H, J = 2.25 Hz), 6.71–7.51 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 21.28, 55.51, 61.67, 63.33, 114.51, 118.82, 126.19, 127.97, 129.28, 130.03, 130.99, 132.26, 132.35, 133.61, 138.93, 156.51, 162.85; CIMS (CH_4) m/z 376 $(M + H)^+$. Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.53; H, 5.67; N, 3.90.

13d: trans stereochemistry; mp 99–100 °C (ether–hexane); yield 41%; IR (KBr) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (d, 1 H, J = 1.9 Hz), 4.73 (d, 1 H, J = 1.9 Hz), 5.95 (s, 2 H), 6.72–7.55 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 61.64, 63.13, 101.44, 105.96, 108.82, 117.33, 120.04, 124.35, 128.02, 120.09, 129.33, 130.22, 132.28, 132.39, 137.26, 148.30, 148.68, 163.28; CIMS (CH_4) m/z 376 $(M + H)^+$. Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.39; H, 4.56; N, 3.73. Found: C, 70.10; H, 4.53; N, 3.81.

13e: cis stereochemistry; mp 144 °C (CH_2Cl_2–hexane); yield 44%; IR (KBr) 1740, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94 (d, 3 H), 3.8 (s, 3 H), 4.88 (m, 2 H, resolved into two doublets with $Pr(fod)_3$, J = 5.49 Hz), 6.63 (b s, 1 H), 6.85–7.65 (m, 14 H); CIMS (CH_4) m/z 402 $(M + H)^+$. Anal. Calcd for $C_{25}H_{23}NO_2S$: C, 74.44; H, 6.2; N, 3.47. Found: C, 74.42; H, 6.0; N, 3.33.

13f: trans stereochemistry; mp 80–81 °C; yield 56%; IR (KBr) 1743, 1610, 1580, 735, 680, cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3 H), 3.53 (s, 3 H), 4.25 (d, 1 H, J = 2.25 Hz), 5.16 (d, 1 H, J = 2.22 Hz), 6.68–7.79 (m, 13 H); CIMS (NH_3) m/z 376 $(M + H)^+$, 393 $(M + NH_4)^+$. Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.63; N, 3.72. Found: C, 73.16; H, 5.68; N, 3.52.

13g: trans stereochemistry; mp 129–130 °C (ether–*n*-hexane); IR (KBr) 1743, 1670, 1480, 1370, 820, 735, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H), 4.21 (d, 1 H, J = 2.5 Hz), 4.73 (d, 1 H), 6.6–7.8 (m, 13 H); CIMS (CH_4) m/z 441, 443 $(M + 18)^+$, in the ratio of 1:1, 362 $(M - Br + NH_4)^+$. Anal. Calcd for $C_{22}H_{18}NOS$: C, 73.79; H, 5.35; N, 3.74. Found: C, 73.76; H, 5.25; N, 3.72.

General Method for the Synthesis of α-(Phenylthio)-α-chloro β-Lactams. 1-(*p*-Anisyl)-3-chloro-3-(phenylthio)-4-phenyl-2-azetidinone (16a). A solution of sulfuryl chloride (42 mg, 11 mmol) in 2 mL of methylene chloride was added dropwise to a cooled (−10 °C) and stirred solution of β-lactam **13a** (100 mg, 100 mmol) in 20 mL of methylene chloride under anhydrous conditions. The stirring was continued, and the progress of the reaction was monitored by TLC. The disappearance of the spot corresponding to the β-lactam **7a** was considered as the completion of the reaction. The organic solvent and excess sulfuryl chloride were removed under reduced pressure, and the residue was crystallized from CH_2Cl_2/ether to provide 101 mg (91%) of the chloro compound **16a**: mp 167 °C; yield 91%; IR (KBr) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.7 (s, 3 H), 5.4 (s, 1 H), 6.7–7.5 (m, 14 H); CIMS (CH_4) m/z 395, 397 $(M + H)^+$ in the ratio of 3:1, 360 $(M - Cl)^+$.

The α-chloro β-lactams (**16b–g**) were synthesized from the corresponding phenylthio β-lactams by chlorination with SO_2Cl_2 using the procedure given above.

16b: mp 170–171 °C (CH_2Cl_2–ether); yield 84%; IR (KBr) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.5 (s, 1 H), 7.05–7.6 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 71.96, 80.05, 117.90, 124.90, 128.19, 128.29, 128.61, 129.20, 129.69, 131.68, 135.41, 136.62, 160.59; CIMS (CH_4) m/z 366, 368 $(M + H)^+$ in the ratio of 3:1.

16c: mp 170–171 °C; yield 95%; IR (KBr) 1740 cm^{-1}; ^2H NMR ($CDCl_3$) δ 2.37 (s, 3 H), 3.7 (s, 3 H), 5.4 (s, 1 H), 6.75–7.55 (m, 13 H); CIMS (CH_4) m/z 410, 412 $(M + H)^+$ in the ratio of 3:1 (M

- Cl)$^+$. Anal. Calcd for $C_{23}H_{20}ClNO_2S$: C, 67.39; H, 4.91; N, 3.69. Found: C, 67.54; H, 4.84; N, 3.69.

16d: mp 144–145 °C (CH_2Cl_2–hexane); yield 96%; ^1H NMR ($CDCl_3$) δ 5.38 (s, 1 H), 5.96 (d, 2 H), 6.78–7.6 (m, 13 H); CIMS (CH_4) m/z 410, 412 (M + H)$^+$ in the ratio of 3:1. Anal. Calcd for $C_{22}H_{16}ClNO_3S$: C, 64.46; H, 3.91; N, 3.41. Found: C, 64.58; H, 3.91; N, 3.58.

16e: yield 78% (mixture of 3α-chloro and 3β-chloro, 2:1); IR (neat) 1745, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ (major isomer) 2.08 (s, 3 H), 3.79 (s, 3 H), 4.96 (s, 1 H), 6.67 (b s, 1 H), 6.8–7.8 (m, 14 H); (minor isomer) 1.8 (s, 3 H), 3.79 (s, 3 H), 4.73 (s, 1 H), 6.37 (b s, 1 H), 6.78–7.8 (m, 14 H); CIMS (CH_4) m/z 436, 438 (M + H)$^+$ in the ratio of 3:1.

16f: mp 171–172 °C (CH_2Cl_2–hexane); yield 97%; IR (KBr) 1770, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.55 (s, 3 H), 5.85 (s, 1 H), 6.66–7.93 (m, 13 H); CIMS (CH_4) 410, 412 (M + H)$^+$ in the ratio of 3:1. Anal. Calcd for $C_{23}H_{20}ClNO_2S$: C, 67.39; H, 4.91; N, 3.41. Found: C, 67.28; H, 5.07; N, 3.12.

16g: mp 144–145 °C (CH_2Cl_2–hexane); yield 89%; IR (KBr) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 5.4 (s, 1 H), 6.6–7.8 (m, 13 H); CIMS (CH_4) m/z 458, 460 (M + H)$^+$ in the ratio of 3:1, 474, 476 (M + CH_4)$^+$ in the ratio 3:1.

General Method for the Synthesis of α-Keto β-Lactams. 1-(*p*-Anisyl)-3-oxo-4-phenyl-2-azetidinone (22a). A mixture containing silica gel (1.2 g, 100–200 mesh), water (0.6 mL), a solution of 1-(*p*-anisyl)-3-(phenylthio)-3-chloro-4-phenyl-2-azetidinone (**16a**, 100 mg) in 15 mL of $CHCl_3$ and a catalytic amount of zinc chloride was refluxed overnight with constant stirring. The progress of the reaction was monitored by TLC. Disappearance of the starting β-lactam was considered as completion of the reaction. The reactants were filtered, and the residue was washed with ethyl acetate. The combined filtrates were evaporated under reduced pressure, and the residue was chromatographed on a silica gel column using ethyl acetate–hexane (1:2) as the eluant to obtain the pure title compound (60 mg, 89%): mp 130–131 °C ($CHCl_3$–petroleum ether); IR (KBr) 1820, 1790, 1730, 1500, 1240, 1050, 1010, 950, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3 H), 5.5 (s, 1 H), 6.8–7.5 (m, 9 H); CIMS (CH_4) m/z 268 (M + H)$^+$, 535 (2MH)$^+$ cluster ion. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.49. Found: C, 71.68; H, 5.05; N, 5.49.

Compounds **22b–g** were prepared in an analogous manner starting with the corresponding chloro compounds.

22b: mp 135–137 °C; yield 69%; IR (KBr) 1810, 1795, 1735, 1560, 1450, 1110, 800, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.56 (s, 1 H), 7.1–7.6 (m, 10 H); CIMS (CH_4) m/z 238 (M + H)$^+$, 475 (2M + H)$^+$ cluster ion. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.64; N, 5.9. Found: C, 75.92; H, 4.60; N, 5.88.

22c: mp 139–140 °C; yield 72%; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.78 (s, 3 H), 5.52 (s, 1 H), 6.85–7.52 (m, 8 H); CIMS (CH_4) m/z 282 (M + H)$^+$, 563 (2M + H)$^+$ cluster ion. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.22; H, 5.32; N, 4.41.

22d: yield 36%; IR (KBr) 1815, 1750, 1710, 1235, 1040, 1010, 950, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.5 (s, 1 H), 5.95 (s, 2 H), 6.70–7.5 (m, 8 H); CIMS (CH_4) m/z 282 (M + H)$^+$, 563 (2M + H)$^+$ cluster ion.

22e: yield 48%; ^1H NMR ($CDCl_3$) δ 1.88 (d, 3 H, J = 1.1 Hz), 3.79 (s, 3 H), 5.12 (s, 1 H), 6.68 (b s, 1 H), 6.89–7.67 (m, 9 H); CIMS (CH_4) m/z 308 (M + H)$^+$.

22f: mp 138–139 °C; yield 63%; ^1H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 3.7 (s, 3 H), 5.93 (s, 1 H), 6.82–8.06 (m, 8 H); CIMS (CH_4) m/z 282 (M + H)$^+$, 562 (2M + H)$^+$ cluster ion. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.28; H, 5.43; N, 5.06.

22g: mp 191–192 °C; yield 47%; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H), 5.50 (s, 1 H), 6.6–7.6 (m, 8 H); CIMS (CH_4) m/z 330, 332 (M + H)$^+$ in the ratio of 1:1, 349 (M + CH_4)$^+$ in the ratio of 1.1. Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 55.49; H, 3.46; N, 4.0. Found: C, 55.45; H, 3.42; N, 3.66.

General Method for the Synthesis of α-Methoxy-α-(phenylthio)-2-azetidinones. 1-Phenyl-3-methoxy-3-(phenylthio)-4-phenyl-2-azetidinone (17a). A mixture containing silica gel (1 g, 100–200 mesh), methanol, a solution of **16** (100 mg, 0.27 mmol) in anhydrous chloroform (10 mL), and a catalytic amount of anhydrous zinc chloride was refluxed overnight with constant stirring. After completion of reaction (TLC monitoring), the reaction mixture was worked up in the usual way to obtain 89 mg of the title compound (90%): mp 121–122 °C (CH_2Cl_2–hexane); IR (KBr) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (s, 3 H), 5.17 (s, 1 H), 7.1–7.45 (m, 15 H); CIMS (CH_4) m/z 362 (M + H)$^+$, 330 (M – OCH_3)$^+$. Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.13; H, 5.26; N, 3.88. Found: C, 73.10; H, 5.26; N, 3.84.

17b: mp 111–112 °C; yield 79%; IR (KBr) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (s, 3 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 5.1 (s, 1 H), 6.7–7.4 (m, 13 H); CIMS (CH_4) m/z 406 (M + H)$^+$, 374 (M – CH_3OH + H)$^+$. Anal. Calcd for $C_{24}H_{23}NO_3S$: C, 1.1; H, 5.68; N, 3.46. Found: C, 71.0; H, 5.70; N, 3.50.

17c: yield 40%; IR (neat) 1750, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (s, 3 H), 3.64 (s, 3 H), 3.73 (s, 3 H), 4.67 (s, 1 H), 6.57 (b s, 1 H), 6.75–7.74 (m, 14 H); CIMS (CH_4) m/z 432 (M + H)$^+$.

1-(*p*-Anisyl)-3-(phenylthio)-4-benzoyl-2-azetidinone (15a) was prepared by the general procedure described earlier starting from the Schiff base of phenylglyoxal with *p*-anisidine. The spectral and analytical data for **15a** are summarized below: yield 51%; mp 114–115 °C; IR (KBr) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (s, 3 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 5.1 (s, 1 H), 6.7–7.4 (m, 13 H); CIMS (CH_4) m/z 406 (M + H)$^+$, 374 (M – CH_3OH + H)$^+$. Anal. Calcd for $C_{23}H_{19}NO_3S$: C, 70.94; H, 4.92; N, 3.60. Found: C, 70.93; H, 4.72; N, 3.48.

3-Chloro-3-(phenylthio)-4-benzoyl-2-azetidinone (20). Ceric ammonium nitrate oxidation of the corresponding *N*-*p*-anisyl derivative **18** using the procedure reported in literature[16] gave **20** in 44% yield: mp 140–141 °C; IR (KBr) 3300, 1780, 1685, 1230, 780, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.05 (s, 1 H), 6.45 (b s, 1 H), 7.4–8.08 (m, 10 H); CIMS (CH_4) m/z 335, 337 (M + CH_4)$^+$, 318, 320 (M + H)$^+$ in the ratio of 3:1. Anal. Calcd for $C_{16}H_{12}ClNO_2S$: C, 60.18; H, 3.76; N, 4.39. Found: C, 60.47; H, 3.78; N, 4.2.

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