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A CONVENIENT SYNTHESIS OF AZETIDINE-2,3-DIONES (α-Keto-β-Lactams)[1]

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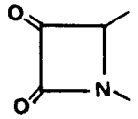
Summary: Azetidine-2,3-diones can be conveniently synthesized by mild hydrolysis of the product of the reaction between α-phenylthio-β-lactams and sulfuryl chloride.

The discovery of non-classical β-lactam antibiotics has directed the interest of medicinal chemists to the synthesis of diverse side chains in place of the amide side chain of penicillins and cephalosporins. Azetidine-2,3-diones or α-keto-β-lactams 1 have been shown by Lo and Sheehan [2] to be convenient intermediates for β-lactams with the cephamycin type side chains. They can also serve for the introduction of carbon chains which are potentially useful for the preparation of thienamycin and related compounds. We describe here a convenient method for the synthesis of azetidine-2,3-diones via easily prepared 3-thiophenoxy-2-azetidinones 2.



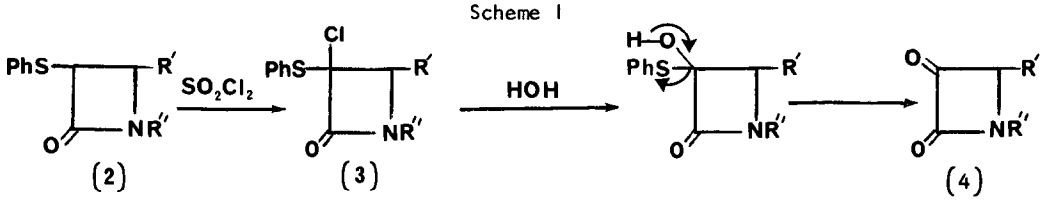
(1)

The key step in the synthesis is the reaction between an α-phenylthio-β-lactam 2 and sulfuryl chloride leading to a 3-chloro-3-phenylthio-2-azetidinone 3 as shown in Scheme I. This type of reaction has been used by earlier workers to prepare acyclic aldehydes and ketones from thio compounds[3].

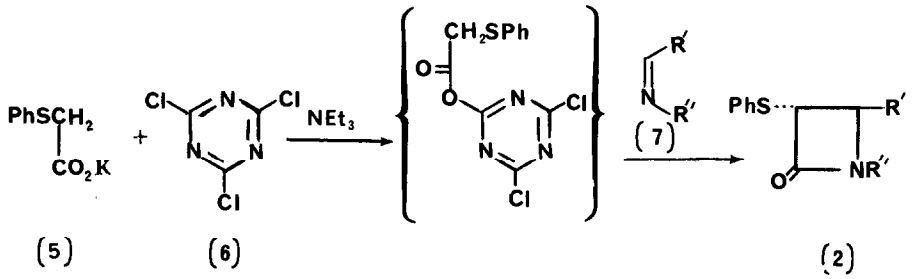
The starting β-lactams for reactions shown in Scheme I are readily obtained by a cycloaddition reaction depicted in Scheme II. Previously we[4] have prepared trans-β-lactams from S-benzylthioglycolyl chloride, a Schiff

base and triethylamine. We have found it convenient however,to use a mixture of the potassium salt of phenylthioglycolic acid 5, cyanuric chloride 6, an imino compound 7 and triethylamine for preparing β-lactams 2. For example, using the Schiff base 7 (R'=Ph, R"=p-anisyl) a single trans-β-lactam 2 (R'=Ph, R"=p-anisyl) could be obtained in 50-60% yield. Under similar reaction conditions, sodium phenoxyacetate leads to a cis-β-lactam [5]. It may be noted that when a 4-thioalkyl-2-azetidinone is prepared from a thioimidate by a cycloaddition reaction, a single trans-β-lactam is obtained [6]. The reason for such stereospecificity or exclusive trans geometry of β-lactams with a thio group at C-3 or C-4 is not clear.

Scheme I



Scheme II

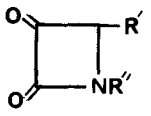


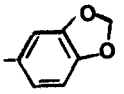
An illustrative example of the conversion of 2 to 4 is provided here. A solution of sulfuryl chloride in methylene chloride was added slowly to a stirred methylene chloride solution of 2 (R'= Ph, R" =p-anisyl) at 0 C. Nearly pure chloro- β-lactam 3 was obtained in a few hours in 91% yield by removing the excess sulfuryl chloride and solvent under reduced pressure [7]. The α-chloro-α-thiophenyl-β-lactam 3 could be hydrolyzed under very mild conditions. When a mixture of 100 mg of 3 (R'=Ph, R" =p-anisyl) in chloroform solution, silica gel (1.2g, 100-200 mesh, with 0.6 ml water) and a catalytic amount of zinc chloride was heated under reflux for a few hours, the desired compound 4, (R'=Ph, R" =p-anisyl) was obtained in 89% yield [8].

A number of α-keto-β-lactams [9] of type 4 were prepared by this method (see Table I). These compounds were characterized by a light yellow color

and strong U.V. absorption (λmax 350 nm, e 9000), the infrared absorption for the CO groups was at 1820, 1790cm^{-1} . The -CO.CO.NAr group constitutes a strong U.V. chromophore.

Table 1



	R'	R"	m.p. °C
a	Ph	$C_6H_4OCH_3$(p)	130-131
b	Ph	Ph	135-137
c	$C_6H_4CH_3$(p)	$C_6H_4OCH_3$(p)	139-140
d		Ph	139-140
e	$-C(CH_3)=CHPh$	$C_6H_4OCH_3$(p)	oily liquid
f	$C_6H_4CH_3$(p)	$C_6H_4OCH_3$(o)	138-139
g	$C_6H_4CH_3$(p)	C_6H_4Br(p)	191-192

In the light of our previous work [10] on the U.V. spectra on N-aryl-β-lactams, it would appear that the N-aryl ring lies in the plane of the β-lactam ring thus permitting the maximum overlap of the pi orbitals of the CO groups, the pi orbital of the nitrogen carrying the lone pair of electrons and the pi orbitals of the N-aryl ring.

Work is in progress in our laboratory for the use of compounds of type 4 as intermediates for various 3-substituted-2-azetidinones.

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(b) Y.S. Lo and J.C. Sheehan, J. Org. Chem., 1973, 38, 3227.

[3]. This type of reaction is known in the literature; for example, see D.T.W. Chu, J.E. Hengeveld and D. Lester, Tetrahedron Lett., 1983, 24,139 and M. Hojo, R. Masuda, T. Saeki, K. Fujimori and S. Tsutsumi, Tetrahedron Lett., 1977, 3883.

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[7]. 1-p-Anisyl-3-thiophenoxy-3-chloro-4-phenylazetidine-2-one 3, mp: 167 ; ir(KBr): 1755 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ :3.7(3H,s), 5.4(1H,s), 6.7-7.5(14H,m); CIMS(CH_4 as reagent gas) m/z:395,397 (M^++H, ratio of peak intensity 3:1), 360(M-Cl)$^+$.

[8]. 1-p-Anisyl-4-phenylazetidine-2,3-dione 4: mp. 130-131 ($CHCl_3$-pet. ether); U.V. (CH_2Cl_2)λ_{max} : 3540 nm (ϵ 9000); ir(KBr):1820,1790,1730,1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ: 3.77(3H,s), 5.5(1H,s) 6.8-7.5(9H,m); ^{13}C-NMR ($CDCl_3$)δ: 55.44, 74.89, 114.81, 119.71, 126.33, 129.00, 129.35, 129.39, 130.00, 131.89, 158.04, 160.00, 190.63; CIMS(CH_4 as reagent gas) m/z: 268(M+H)$^+$, 335(2M+H)$^+$ cluster ion; Anal. Found: C, 71.68, H, 5.05, N, 5.49, $C_{16}H_{13}NO_3$ requires: C 71.90, H, 4.90, N, 5.24%.

[9]. All compounds gave satisfactory spectroscopic data and elemental analyses.

[10]. M.S. Manhas, S. Jeng and A.K. Bose, Tetrahedron, 1968, 24, 1237.

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