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THE SYNTHESIS AND REACTIONS OF 4-CARBOMETHOXY β-SULTAMS

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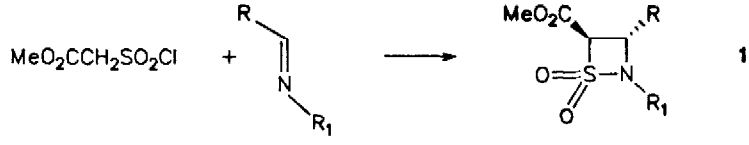
Abstract: *The preparation of 4-carbomethoxy-1,2-thiazetidine-1,1-dioxides from carbomethoxymethanesulfonyl chloride and imines is described.*

The ability of β-lactam antibiotics to acylate bacterial cell wall enzymes provides the biochemical basis for their bactericidal action. Although structural analogs of β-lactam antibiotics have been intensively investigated for more than forty years, until quite recently scant attention has been focused on replacement of the azetidinone ring by more reactive entities.[1] The 1,2-thiazetidine-1,1-dioxides are attractive candidates for such a substitution because the pi bond overlap which enhances the stability of β-lactams is unavailable to the analogous β-sultams. The greater chemical reactivity anticipated of the latter has been demonstrated,[2] thus encouraging the preparation of β-sultam analogs of β-lactam antibiotics. Previous effort in this area employed synthetic schemes which afforded a very limited range of substituents on the β-sultam nucleus.[3] We wish to report that carbomethoxymethanesulfonyl chloride, readily available *via* chlorination of methyl thioglycolate,[4] reacts with a wide variety of alkyl and aryl imines to afford β-sultams **1** in fair to excellent yield. The ester functionality thus introduced provides access to a number of interesting derivatives, and can, for example, be reduced to the hydroxymethyl sidechain found to be biologically acceptable in the carbapenem series.



A representative array of β-sultams is presented in Table 1. In general, yields are better when the R substituent is aryl rather than alkyl, presumably because isomerization of the imine to an enamine is not possible. In fact, the structure of the imine is a key determinant in the choice of reaction conditions. With non-enolizable imines, the reaction is relatively insensitive to the order of addition and reaction temperature. However, with enolizable imines, the addition of sulfonyl chloride to imine at -78° should precede the addition of base. Tables 2 and 3 outline the effect of base and solvent on yield. The substantially lower yields using ethyl ether as solvent may be attributed to the precipitation of the initial addition complex. A representative procedure is reported below.

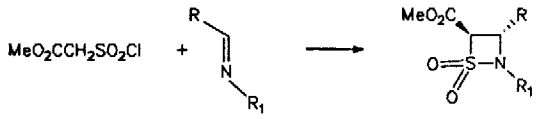


Table 1

Compound	R	R_1	%Yield
1	phenyl	benzyl	93
2	phenyl	2,4-dimethoxybenzyl	82
3	phenyl	phenylselenylethyl	87
4	phenyl	4-methoxyphenyl	16
5	4-nitrophenyl	benzyl	71
6	2-furyl	4-methoxyphenyl	17
7	2-furyl	2,4-dimethoxybenzyl	49
8	cinnamyl	4-methoxyphenyl	9
9	methyl	phenylselenylethyl	35
10	ethyl	benzyl	55
11	tBu$\varnothing_2$SiOCH$_2$CH$_2$	phenylselenylethyl	61
12	tBu(CH$_3$)$_2$SiOCH$_2$CH$_2$	phenylselenylethyl	21

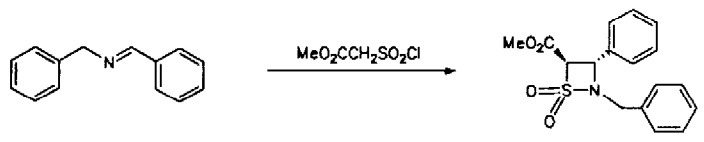


TABLE 2

Tertiary amine base	Relative yield
pyridine	1.00
N-methyl imidazole	0.94
iPr_2NEt	0.67

THF as solvent

TABLE 3

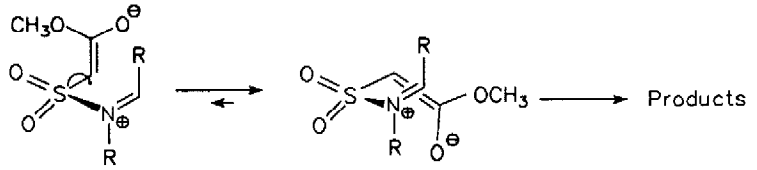
Solvent	Relative yield
THF	1.00
CH_2Cl_2	0.95
Et_2O	0.60

Pyridine as base

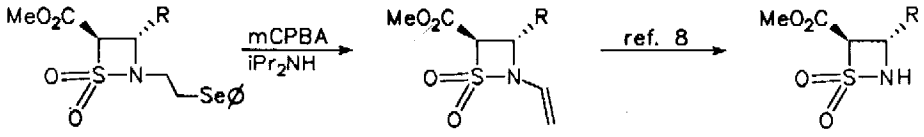
A solution of 1.5 eq. pyridine and 1.0 eq. N-benzyl benzaldimine in THF (0.3M) was chilled to -78° under an argon atmosphere and 1.5 eq. of carbomethoxymethanesulfonyl chloride (diluted with THF to prevent freezing) was added dropwise. The suspension was aged 30 minutes at -78° then allowed to warm to 0° over 30 minutes. The reaction was quenched by the addition of 0.5M pH7 phosphate buffer and extracted with ether. The combined organics were dried over Na_2SO_4, concentrated and subjected to flash chromatography using a stepwise gradient of 10→30% ether/hexanes. The product, a colorless oil, was characterized as follows: ^{1}H-NMR (δ, $CDCl_3$): 3.85 (s, 3H); 4.23 (AB Δδ=41.5Hz, J=14.3Hz); 4.62 (d, 1H, J=6.3Hz); 4.87 (d, 1H, J=6.3Hz); 7.25-7.45 (m, 10H).

The stereochemistry of all products obtained by this method has been established as exclusively *trans* by NMR analysis[5] and an X-ray crystal structure determination of sultam **5**. The exchange of the **C4** methine is very slow at room temperature with catalytic pyridine-*d5* in CD_3OD, thus eliminating from consideration the base catalyzed isomerization of the kinetic to the thermodynamic product during the course of the reaction. Similarly stereospecific production of

the *trans* isomer has been reported for the reaction of benzoylmethanesulfonyl chloride and imines[6a] but these results are in marked contrast to the reaction of benzylsulfonyl chloride and imines, which yields a mixture of *cis* and *trans* isomers.[6b] We believe that the stereochemical outcome of the present case is a reflection of the population of rotamers **A** and **B** of the probable zwitterionic intermediate.



This new methodology allows modification at **C3** and **C4**, but elaboration of these compounds into useful analogs of β-lactam antibiotics requires the exposure of the sultam nitrogen. Attempted application of the usual protecting groups developed for ketene-imine syntheses of β-lactams, 4-methoxyphenyl and 2,4-dimethoxybenzyl, was unsuccessful as the deblocking conditions proved too harsh for β-sultams to endure.[7] The N-unsubstituted β-sultams were obtained with the phenylselenylethyl protecting group previously developed in these laboratories.[8]



Summary: The 4-carbomethoxy-1,2-thiazetidine-1,1-dioxides allow synthetic access to a broad range of analogs of β-lactam antibiotics. The sidechains requisite for bioactivity may be derived from the 4-carbomethoxy group, a variety of substituents is acceptable at **C3**, and the sultam nitrogen is made accessible *via* the phenylselenylethyl protecting group.

References and Notes

1. For leading references to: 1,2-diazetidinones, see E.C. Taylor, H.M.L. Davies, *J. Org. Chem.*, **1984**, *49*, 113 and E.C. Taylor, H.M.L. Davies, *J. Org. Chem.*, **1984**, *49*, 4415; thiono-β-lactams, see C.M. Cimarusti, P. Wojtkowski, J.E. Dolfini, U.S. Patents 3,971,776, 3,971,780, and 4,010,175; γ-lactam analogs, see L.N. Jungheim, C.J. Barnett, J.E. Gray, L.H. Horcher, T.A. Shepherd, S.K. Sigmund, *Tetrahedron* **1988**, *44*, 3119.

2. W. Koller, A. Linkies, H. Rehling, D. Reuschling, *Tetrahedron Lett.*, **1983**, *24*, 2131.

3. F. Cavagna, W. Koller, A. Linkies, H. Rehling, D. Reuschling, *Angew. Chem. Int. Ed.*, **1982**, *21*, 548; W. Koller, A. Linkies, H. Rehling, D. Reuschling, *Tetrahedron Lett.*, **1983**, *24*, 2131; H.H. Otto, P. Schwenkkraus, *Tetrahedron Lett.*, **1982**, *23*, 5389; E. Meyle, H.H. Otto, *Arch. Pharm.*, **1983**, *316*, 281; E. Meyle, E. Keller, H.H. Otto, *Liebigs Ann. Chem*, **1985**, 802. For a recent review: J. Chanet-Ray, R. Vessiere, *Org. Prep. Proc. Int.*, **1986**, *18*, 159.

4. Previous preparations of carbomethoxymethanesulfonyl chloride and related esters have been multistep processes. Typically the bisulfite addition product of a haloacetate has been reacted with PCl_5 to afford the sulfonyl chloride. We wish to report that the oxidative chlorination of methyl thioglycolate directly affords the desired product in good yield.

   Methyl thioglycolate (25 ml, 0.28 moles) was dissolved in 200 ml CH_2Cl_2 and the flask was chilled in an ice/acetone bath. Ice (100 g) was added and chlorine was bubbled into the mixture, rapidly at first but then at a rate such that the internal temperature did not exceed

30°. The solution was kept saturated with chlorine for 1 hour after the yellow color of chlorine first failed to discharge. The solution was sparged with nitrogen, the layers were separated and the organics were dried over Na_2SO_4 and concentrated in vacuo. *The crude product was vacuum distilled to afford 32.5 g colorless oil, bp 78-80°/0.5 mm. Yield: 67%. ^{1}H-NMR δ(CDCl$_3$): 3.92(s,3H); 4.64(s,2H).*

5. The coupling constants observed for the **C3** and **C4** methines range from 5.8-6.4 Hz; average values are 6.1-6.3 Hz., in accord with the coupling constants reported in reference 6b.

6. a) O. Tsuge, S. Iwanami, *Bull. Chem. Soc. Jap.*, **1970**, *43*, 3543. b) T. Hiraoka, T. Kobayashi, *Bull. Chem. Soc. Jap.*, **1975**, *48*, 480; P. Loiseau, M. Bonnafous, Y. Adam, *Eur. J. Med. Chem.*, **1984**, *19*, 569.

7. W.F. Huffman, K.G. Holden, T.F. Buckley III, J.G. Gleason, L. Wu, *J. Am. Chem. Soc.*, **1977**, *99*, 2352. D.R. Kronenthal, C.Y. Han, M.K. Taylor, *J. Org. Chem.*, **1982**, *47*, 2765.

8. J.V. Heck, B.G. Christensen, *Tetrahedron Lett.*, **1981**, *22*, 5027. A more facile method for the oxidative deblock of the enamide was subsequently employed.

The enamide (1.0 eq.) was dissolved in 10% aq. THF (0.4M) and 1.1 eq. I_2 was added in one portion. The solution was heated to 40° for 10 minutes, then cooled, and the reaction was quenched by the addition of 2 eq. (aq.) Na_2SO_3. The suspension was stirred an additional 5 minutes then partitioned between EtOAc and 0.5M pH7 phosphate buffer. The usual extractive workup was followed by purification via flash chromatography to afford the deblocked sultam in 70-90% yield.

9. All compounds are diastereomeric; only one diastereomer is shown in the diagrams. ^{1}H-NMR data (200MHz, δ,CDCl$_3$) for all new compounds follow: **1.** 7.35 (m, φ); 4.87 (d, $J_{3,4}$=6.3 Hz, C<u>H</u>SO$_2$); 4.61 (d, $J_{3,4}$=6.3 Hz, C<u>H</u>N); 4.23 (AB, J=14.3 Hz, Δδ=41.5 Hz, C<u>H</u>$_2$φ); 3.85 (s, CO$_2$C<u>H</u>$_3$). **2.** 7.46 and 7.36 (m, φ); 7.22(d), 6.41(dd) and 6.32(d) (2,4-dimethoxy-φ); 4.79 (d, $J_{3,4}$=6.4 Hz, C<u>H</u>SO$_2$); 4.65 (d, $J_{3,4}$=6.4 Hz, C<u>H</u>N); 4.22 (AB, J=14 Hz, Δδ=49 Hz, C<u>H</u>$_2$-aryl); 3.87, 3.78 and 3.66 (s, OC<u>H</u>$_3$). **3.** 7.54, 7.44 and 7.26 (m, φ); 4.87 (d, $J_{3,4}$=6.2 Hz, C<u>H</u>SO$_2$); 4.61 (d, $J_{3,4}$=6.2 Hz, C<u>H</u>N); 3.87 (s, CO$_2$C<u>H</u>$_3$); 3.54 and 3.16 (m,NC<u>H</u>$_2$CH$_2$Seφ); 2.96 (m, C<u>H</u>$_2$Seφ). **4.** 7.56 and 7.40 (m, φ); 7.00 and 6.83 (d, J=9Hz, φ-OMe); 5.25 (d, $J_{3,4}$=6.0 Hz, C<u>H</u>SO$_2$); 4.97 (d, $J_{3,4}$=6.0 Hz, C<u>H</u>N); 3.90 (s, φ-OC<u>H</u>$_3$); 3.73 (s, CO$_2$C<u>H</u>$_3$). **5.** 8.19 and 7.60 (d, J=9Hz, φ-NO$_2$); 7.28 (s, φ); 4.87 (d, $J_{3,4}$=6.2 Hz, C<u>H</u>SO$_2$); 4.71 (d, $J_{3,4}$=6.2 Hz, C<u>H</u>N); 4.31 (AB, J=14 Hz, Δδ=61 Hz, C<u>H</u>$_2$φ); 3.92 (s, CO$_2$C<u>H</u>$_3$). **6.** 7.50(dd), 6.56(dd) and 6.40(dd) (furyl); 7.1 and 6.88 (d, J=9 Hz, φ-OMe); 5.38 (d, $J_{3,4}$=6.0 Hz, C<u>H</u>SO$_2$); 5.33 (d, $J_{3,4}$=6.0 Hz, C<u>H</u>N); 3.92 (s, φ-OMe); 3.77 (s, CO$_2$C<u>H</u>$_3$). **7.** 7.44(d) and 6.38(m) (furyl); 7.16(d) and 6.38(m) (2,4-dimethoxy-φ); 5.20 (d, $J_{3,4}$=5.9 Hz, C<u>H</u>SO$_2$); 4.73 (d, $J_{3,4}$=5.9 Hz, C<u>H</u>N); 4.19 (AB, J=14.2 Hz, Δδ=24.9 Hz, 2,4-dimethoxy-φ); 3.84, 3.76 and 3.72 (s, OC<u>H</u>$_3$). **8.** 7.36 (m, φ); 7.14 and 6.9 (d, J=9 Hz, φ-OMe); 6.88 (d, J=15.5 Hz, φC<u>H</u>=C); 6.26 (dd, J_{C3}=7.5 Hz, J_{trans}=15.5 Hz, φCH=C<u>H</u>); 5.00 (d, $J_{3,4}$=5.8 Hz, C<u>H</u>SO$_2$); 4.90 (dd, $J_{3,4}$=5.8 Hz, J_{vinyl}=7.5 Hz, C<u>H</u>N); 3.92 (s, φ-OC<u>H</u>$_3$); 3.78 (s, CO$_2$C<u>H</u>$_3$). **9.** 7.56 and 7.32 (m, Seφ); 4.66 (d, $J_{3,4}$=6.1 Hz, C<u>H</u>SO$_2$); 3.88 (s, CO$_2$C<u>H</u>$_3$); 3.68 (dq, $J_{3,4}$=6.1 Hz, J_{Me}=6.1 C<u>H</u>N); 3.48 and 3.12 (m, NC<u>H</u>$_2$CH$_2$Seφ); 3.1 (m, CH$_2$C<u>H</u>$_2$Seφ); 1.42 (d, J=6.1 Hz, C<u>H</u>$_3$). **10.** 7.40 (m, φ); 4.72 (d, $J_{3,4}$=6.0 Hz, C<u>H</u>SO$_2$); 4.28 (AB, J=14.5 Hz, Δδ=79.5 Hz, C<u>H</u>$_2$φ); 3.88 (s, CO$_2$C<u>H</u>$_3$); 3.58 (m, C<u>H</u>N); 1.6 (m, C<u>H</u>$_2$CH$_3$); 0.88 (t, J=8 Hz, CH$_2$C<u>H</u>$_3$). **11.** 7.68-7.24 (m, Seφ and Siφ); 5.12 (d, $J_{3,4}$=6.1 Hz, C<u>H</u>SO$_2$); 3.9-3.5 (m, NC<u>H</u>$_2$CH$_2$Seφ , C<u>H</u>N, C<u>H</u>$_2$O); 3.82 (s, CO$_2$C<u>H</u>$_3$); 3.2-3.0 (m, NC<u>H</u>$_2$CH$_2$Seφ, C<u>H</u>$_2$Seφ); 2.04-1.84 (m, C<u>H</u>$_2$CH$_2$O); 1.02 (s, SiC(C<u>H</u>$_3$)$_3$). **12.** 7.56 and 7.32 (m, Seφ); 5.03 (d, $J_{3,4}$=6.1 Hz, C<u>H</u>SO$_2$); 3.9-3.5 (m, NC<u>H</u>$_2$CH$_2$Seφ, C<u>H</u>N, C<u>H</u>$_2$O); 3.84 (s, CO$_2$C<u>H</u>$_3$); 3.2-3.0 (m, NC<u>H</u>$_2$CH$_2$Seφ, C<u>H</u>$_2$Seφ); 2.1-1.8 (m, C<u>H</u>$_2$CH$_2$O); 0.85 (s, SiC(C<u>H</u>$_3$)$_3$); 0.04 (s, SiC<u>H</u>$_3$).

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