A CONVENIENT SYNTHESIS OF 1-BENZHYDRYL-*N*-ARYLSULFONYL-3-OXO-1,2-DIAZETIDINE-2-CARBOXAMIDES

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(Received for publication October 26, 1985)

In a search for novel compounds possessing potent antibiotic activity, a synthetic program was initiated aimed at the preparation of 1,2-diazetidin-3-ones (monocyclic aza-β-lactams). The pioneering work of TAYLOR and coworkers[1,2] provided a paradigm for this study as well as facile entry into this fascinating class of compounds.

One aspect of the present study focused on the incorporation of an arylsulfonamidocarbonyl unit at N-2 in the diazetidinone nucleus which might increase the lability of the N-2, C-3 bond. Activation of the amide bond in classical β-lactam derivatives is critical for good antibacterial action. In addition, the arylsulfonamidocarbonyl moiety should be sufficiently acidic to provide a properly positioned anionic charge which is also consonant with good activity.[3] Herein is described a convenient one step procedure for the preparation of the most accessible members of this series.

The synthesis of the starting 1-benzhydryl-1,2-diazetidin-3-ones (**1a**~**c**) was readily accomplished in three steps by the literature procedure.[1] Treatment of **1a** with *p*-toluenesulfonylisocyanate or *p*-chlorophenylsulfonylisocyanate in CH_2Cl_2 at ambient temperature afforded acylated diazetidinone derivatives **2a** (90%) and **3a** (73%), respectively.† Analogously, compounds **2b,c** and **3b,c** were prepared utilizing diazetidinones **1b,c** and the appropriate arylsulfonylisocyanate.

When evaluated *in vitro* against representative strains of Gram-positive and Gram-negative bacteria, the title compounds of this limited study were ineffective at the concentrations tested (MIC$\geq$128 μg/ml). Unexpectedly, these acylated diazetidinone derivatives displayed slight activity against a variety of pathogenic fungi, including: *Cryptococcus neoformans* (ATCC 14115), *Trichophyton mentagrophytes* (ATCC 9533), *Histoplasma capsulatum* (ATCC 11407), *Blastomyces dermatitidis* (ATCC 28839).

General Procedure for the Synthesis of 1-Benzhydryl-*N*-arylsulfonyl-3-oxo-1,2-diazetidine-2-carboxamides

To a solution of 4 mmol of the requisite 1-benzhydryl-1,2-diazetidin-3-one (**1**)[1] and 20 ml of CH_2Cl_2 at ambient temperature under a nitrogen atmosphere was added in one portion a solution of 4 mmol of the appropriate arylsulfonylisocyanate and 5 ml of CH_2Cl_2. The reaction mixture was stirred at ambient temperature for 24~72 hours. Removal of the solvent under reduced pressure followed by trituration with Et_2O furnished the title compounds.

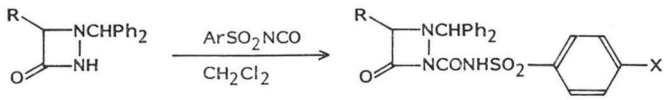
1-Benzhydryl-*N*-[(4-methylphenyl)sulfonyl]-3-oxo-1,2-diazetidine-2-carboxamide (2a)

90% yield; IR (KBr) 3310, 1810, 1740, 1430, 1350, 1170 cm^{-1}; NMR ($CDCl_3$) δ 8.0~7.2 (m, 15H, aromatic and NH), 5.05 (s, 1H, $CHPh_2$), 4.57, 3.95 (ABq, 2H, C-4 H's, J=15 Hz), and 2.47 (s, 3H, CH_3).

Anal Calcd for $C_{23}H_{21}N_3O_4S\cdot\frac{1}{2}H_2O$: C 62.14, H 4.99, N 9.45.
Found: C 61.79, H 5.07, N 9.46.

1-Benzhydryl-4-methyl-*N*-[(4-methylphenyl)-sulfonyl]-3-oxo-1,2-diazetidine-2-carboxamide (2b)

94% yield; IR (KBr) 3300, 1810, 1740, 1440,



1

2 X=Me
3 X=Cl

Series: **a** R=H
b R=Me
c R=Ph

† After the completion of this work, a definitive study examining N-2 acylation has appeared.[4]

1360, 1170 cm^{-1}; NMR ($CDCl_3$) δ 8.35~7.15 (m, 15H, aromatic and NH), 4.9 (s, 1H, C*H*Ph_2), 4.1 (q, 1H, C-4 H, J=7 Hz), 2.45 (s, 3H, CH_3), and 1.42 (d, 2H, CH_3, J=7 Hz).

Anal Calcd for $C_{24}H_{23}N_3O_4S \cdot \frac{1}{2}H_2O$: C 62.86, H 5.27, N 9.16.
Found: C 62.88, H 5.24, N 9.18.

1-Benzhydryl-*N*-[(4-methylphenyl)sulfonyl]-3-oxo-4-phenyl-1,2-diazetidine-2-carboxamide (**2c**)

68% yield; IR (KBr) 3250, 1805, 1750, 1410, 1350, 1160 cm^{-1}; NMR ($CDCl_3$) δ 8.2~6.9 (m, 20H, aromatic and NH), 5.15 (s, 1H, C-4 H), 4.98 (s, 1H, C*H*Ph_2), and 2.45 (s, 3H, CH_3).

Anal Calcd for $C_{28}H_{25}N_3O_4S \cdot H_2O$: C 65.77, H 5.14, N 7.93.
Found: C 66.09, H 5.07, N 7.98.

1-Benzhydryl-*N*-[(4-chlorophenyl)sulfonyl]-3-oxo-1,2-diazetidine-2-carboxamide (**3a**)

73% yield; IR (KBr) 3280, 1800, 1745, 1420, 1360, 1160 cm^{-1}; NMR ($CDCl_3$) δ 7.95~7.15 (m, 15H, aromatic and NH), 4.95 (s, 1H, C*H*Ph_2), and 4.57, 3.90 (ABq, 2H, C-4 H's, J= 15 Hz).

Anal Calcd for $C_{22}H_{18}N_3O_4ClS \cdot \frac{1}{2}H_2O$: C 56.84, H 4.12, N 9.04.
Found: C 57.15, H 4.35, N 9.23.

1-Benzhydryl-*N*-[(4-chlorophenyl)sulfonyl]-4-methyl-3-oxo-1,2-diazetidine-2-carboxamide (**3b**)

88% yield; IR (KBr) 3300, 1810, 1740, 1430, 1370, 1170 cm^{-1}; NMR ($CDCl_3$) δ 8.05~7.2 (m, 15H, aromatic and NH), 4.85 (s, 1H, C*H*Ph_2), 4.07 (q, 1H, C-4 H, J=7 Hz), and 1.4 (d, 3H, CH_3, J=7 Hz).

Anal Calcd for $C_{23}H_{20}N_3O_4ClS \cdot \frac{1}{2}H_2O$: C 57.68, H 4.41, N 8.77.
Found: C 57.60, H 4.66, N 8.95.

1-Benzhydryl-*N*-[(4-chlorophenyl)sulfonyl]-3-oxo-4-phenyl-1,2-diazetidine-2-carboxamide (**3c**)

53% yield; IR (KBr) 3220, 1800, 1750, 1430, 1340, 1230, 1160 cm^{-1}; NMR ($CDCl_3$) δ 8.08~7.1 (m, 20H, aromatic and NH), 5.14 (s, 1H, C-4 H), and 5.0 (s, 1H, C*H*Ph_2).

Anal Calcd for $C_{28}H_{22}N_3O_4ClS \cdot \frac{1}{2}H_2O$: C 62.15, H 4.29, N 7.77.
Found: C 62.51, H 4.31, N 7.82.

Acknowledgments

The author is grateful to the Analytical Section of these laboratories for providing spectral and microanalytical data and to Dr. JOHN L. SPETH and staff for the microbiological testing. Helpful discussions with Drs. D. P. STRIKE and T. J. COMMONS is appreciated.

References

1) TAYLOR, E. C.; N. F. HALEY & R. J. CLEMENS: Synthesis and properties of 3-oxo-1,2-diazetidium ylides. J. Am. Chem. Soc. 103: 7743~7752, 1981
2) TAYLOR, E.C.; R.J. CLEMENS, H.M.L. DAVIES & N. F. HALEY: Formation of monocyclic and bicyclic aza-β-lactams and other novel heterocycles from 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium inner salt. J. Am. Chem. Soc. 103: 7659~7660, 1981
3) SLUSARCHYK, W. A.; H. E. APPLEGATE, D. P. BONNER, H. BREUER, T. DEJNEKA & W. H. KOSTER: Monocarbams: Monocyclic β-lactam antibiotics activated by N-1 carbonyl substituents. Program and Abstracts of the 22nd Intersci. Conf. Antimicrob. Agents Chemother., No. 670, Miami Beach, Oct. 4~6, 1982
4) TAYLOR, E. C.; H. M. L. DAVIES, W. T. LAVELL & N. D. JONES: *N*- vs. *O*-Acylation of 1,2-diazetidin-3-one: 4,5-Dihydro-1,3-oxadiazin-6-ones by ring enlargement. J. Org. Chem. 49: 2204~2208, 1984