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

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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 coworkers1,2) 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 arylsulfonamidecarbonyl 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 arylsulfonamidecarbonyl 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-toluenesulfonyl isocyanate or p-chlorophenylsulfonyl isocyanate in CH₂Cl₂ at ambient temperature afforded acylated diazetidinone derivatives 2a (90%) and 3a (73%), respectively. Treatment of 1a with p-toluenesulfonyl isocyanate or p-chlorophenylsulfonyl isocyanate in CH₂Cl₂ at ambient temperature afforded acylated diazetidinone derivatives 2a (90%) and 3a (73%), respectively.1 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 ≥ 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 CH₂Cl₂ at ambient temperature under a nitrogen atmosphere was added a solution of 4 mmol of the appropriate arylsulfonyl isocyanate and 5 ml of CH₂Cl₂. The reaction mixture was stirred at ambient temperature for 24–72 hours. Removal of the solvent under reduced pressure followed by trituration with Et₂O 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 (CDCl₃) δ 8.0–7.2 (m, 15H, aromatic and NH), 5.05 (s, 1H, CHPh₂), 4.57, 3.95 (ABq, 2H, C-4 H's, J=15 Hz), and 2.47 (s, 3H, CH₃).

Anal Calcd for C₂₃H₂₁N₃O₄S • ½H₂O:
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, 1350, 1170 cm⁻¹; NMR (CDCl₃) δ 8.0–7.2 (m, 15H, aromatic and NH), 5.05 (s, 1H, CHPh₃), 4.57, 3.95 (ABq, 2H, C-4 H's, J=15 Hz), and 2.47 (s, 3H, CH₃).

Anal Calcd for C₃₁H₂₆N₃O₄S • ½H₂O:
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,
1360, 1170 cm⁻¹; NMR (CDCl₃) δ 8.35~7.15 (m, 15H, aromatic and NH), 4.9 (s, 1H, CHₒPh₂), 4.1 (q, 1H, C-4 H, J=7 Hz), 2.45 (s, 3H, CH₃), and 1.42 (d, 2H, CH₃, J=7 Hz).

Anal Calcd for C₂₄H₂₃N₃O₄S • ½H₂O:
C 62.86, H 5.27, N 9.16.

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 (CDCl₃) δ 8.2-6.9 (m, 20H, aromatic and NH), 5.15 (s, 1H, C-4 H), 4.98 (s, 1H, CH₂Ph₂), and 2.45 (s, 3H, CH₃).

Anal Calcd for C₂₈H₂₅N₃O₄S • H₂O:
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) 3250, 1800, 1745, 1410, 1360, 1160 cm⁻¹; NMR (CDCl₃) δ 7.95~7.15 (m, 15H, aromatic and NH), 4.95 (s, 1H, CH₂Ph₂), and 4.57, 3.90 (ABq, 2H, C-4 H's, J=15 Hz).

Anal Calcd for C₂₈H₂₁N₃O₄ClS • ½H₂O:
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 (CDCl₃) δ 8.05~7.2 (m, 15H, aromatic and NH), 4.85 (s, 1H, CH₂Ph₂), 4.07 (q, 1H, C-4 H, J=7 Hz), and 1.4 (d, 3H, CH₃, J=7 Hz).

Anal Calcd for C₂₃H₂₀N₃O₄ClS • ½H₂O:
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 (CDCl₃) δ 8.08~7.1 (m, 20H, aromatic and NH), 5.14 (s, 1H, C-4 H), and 5.0 (s, 1H, CH₂Ph₂).

Anal Calcd for C₂₈H₂₃N₃O₄S • ½H₂O:
C 62.15, H 4.29, N 7.77.
Found: C 62.51, H 4.31, N 7.82.

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