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A Convenient *trans*-Stereoselective Synthesis of Phenanthridine Derived 2-Azetidinones Using the Staudinger Ketene-Imine Cycloaddition

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Abstract: Staudinger reactions between acid chlorides having electron-withdrawing substituents at the α-position and phenanthridine, provide new fused tetracyclic 2-azetidinones in good yields with exclusive *trans*-stereoselectivity, both in racemic and enantiopure forms.

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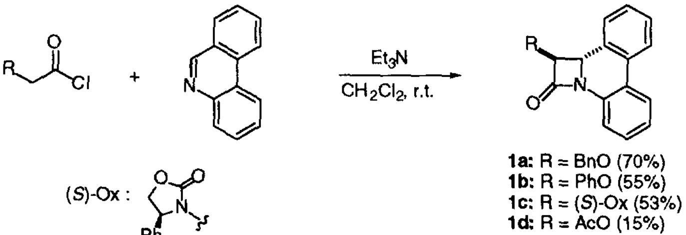
The increased resistance of bacteria to the commonly used β-lactam antibiotics[1] and the ever-growing new applications of these products in fields ranging from enzyme inhibition[2] to the use of 2-azetidinones as starting materials to develop new synthetic methodologies,[3] has triggered a renewed interest in the building of new systems having the 2-azetidinone ring as common feature. Very recently we have reported the preparation of new polycyclic 2-azetidinones by intramolecular aryl-aryl tin-mediated radical cyclisation of readily available aryl substituted 2-azetidinones.[4] In the previous paper, we anticipated an alternative synthesis of some of the phenanthridine derived 2-azetidinones (type **1**) through Staudinger ketene-imine cycloaddition using phenanthridine as the imine component of the reaction.[5] The recent report of Afonso *et al.*[6] on the preparation, in very low yields, of some tetracyclic 2-azetidinones derived from phenanthridines and 5-phenyl valeryl chloride, in connection with their synthesis of rigid analogs of the cholesterol absorption inhibitor Sch 48461, prompted us to describe our results on this topic. These authors state that the low yield obtained (5-7.2% as *trans/cis* mixtures) is not surprising due to the energetically less favourable cyclisation step and the high strain of the products. We report here that phenanthridine reacts smoothly with acid chlorides having electron-withdrawing substituents at the α-position, in the presence of Et_3N, in dichloromethane at room temperature, to give the corresponding fused tetracyclic 2-azetidinones **1** in good yields (Scheme 1).[7] All products were obtained as single *trans* isomers. Enantiopure compound **1c** was obtained using the ketene derived from the Evans and Sjögren chiral 2-oxazolidinone.[8, 9] However, reactions with alkanoyl chlorides (i.e. propanoyl-



1a: R = BnO (70%)
1b: R = PhO (55%)
1c: R = (*S*)-Ox (53%)
1d: R = AcO (15%)

Scheme 1

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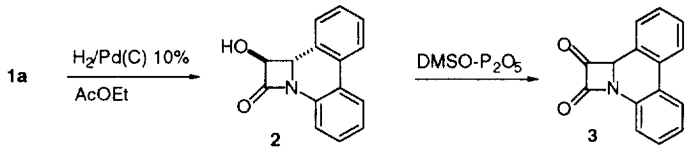
and isovaleryl chlorides), fail to give the corresponding β-lactam. Therefore, more electrophilic ketenes seem to provide the driving force for the reaction to occur. Moreover, the exclusive *trans*-selectivity observed must be due to the cyclic imine structure and not a consequence of the nature of the ketene and the reaction conditions used.[10]



Scheme 2

The β-lactams 1 were very labile towards different reagents and conditions [AlH_2Cl, MeONa/MeOH, $NH_4^+HCOO^-$/methanol/Pd(C)], cycloreversion to phenanthridine being an important process in all cases. However, compound **1a** undergoes facile hydrogenolysis with H_2/Pd (C) affording the corresponding 3-hydroxy-2-azetidinone derivative **2**, which by oxidation with P_2O_5 in DMSO[11] was easily transformed into the 3-oxo derivative **3** in 60% overall yield (Scheme 2). 3-Oxo-2-azetidinones are valuable substrates for the synthesis of biologically important compounds, such as cephamycin, nocardicin-A,[12] and more recently α-amino-acid derived N-carboxy anhydrides (NCAs).[13] In summary, we report a convenient *trans*-stereoselective synthesis of phenanthridine derived 2-azetidinones using phenanthridine as the imine component in the Staudinger reaction. We also demonstrate that the efficiency of the process is dependent on the reactivity of the ketene used.

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5. See note 9 in Ref. 4.
6. Afonso, A.; Rosenblum, S. B.; Puar, M. S.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 7431.
7. Experimental procedure: Et_3N (3 mmol) and the corresponding acid chloride (1.5 mmol) were added in this order to a solution of phenanthridine (1 mmol) in CH_2Cl_2 (15 ml) under argon and at room temperature, and the reaction mixture was stirred at room temperature for 16 h. Then, the reaction mixture was washed with brine (2x10 ml) and water (1x10 ml), and extracted with CH_2Cl_2. After drying with $MgSO_4$ the product was purified by column chromatography to afford the tetracyclic 2-azetidinone **1**.
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9. Dichlorophenylphosphate was used as the condensating agent in this case. See: Arrieta, A.; Lecea, B.; Cossío, F. P.; Palomo, C. *J. Org. Chem.* **1988**, *53*, 3784-3791.
10. The stereochemistry observed for these reactions was expected according to the current model for the Staudinger reaction. See, for example: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers Inc., New York, 1993; Ch. 6, p 295.
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