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[3.3.0] PYRAZOLODINONES: AN EFFICIENT SYNTHESIS OF A NEW CLASS OF SYNTHETIC ANTIBACTERIAL AGENTS.

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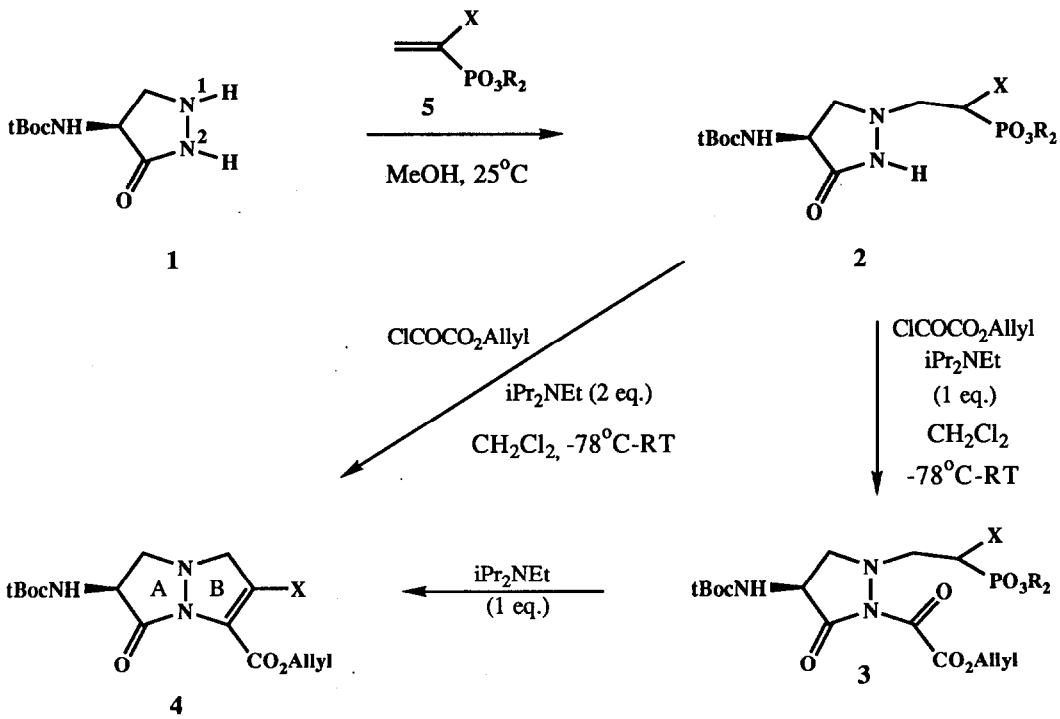
SUMMARY: A novel synthesis of [3.3.0] fused pyrazolidinones is described. The methodology relies on selective stepwise functionalization of the ring nitrogens of a known pyrazolidinone monocycle. Intramolecular Wadsworth-Horner-Emmons condensation gives rise to the desired bicyclic structure. The compounds prepared from this route have demonstrated potent antibacterial activity *in vitro*.

The widespread clinical utilization of antibacterial agents, especially those of the penicillin and cephalosporin class, is indicative of their significant role in the management of infectious disease. Although the physician's armamentarium of antimicrobial drugs is quite large, the search continues for new agents having improved activities especially against organisms resistant to current therapies. These investigations have led to the discovery of a new, totally synthetic class of antibacterial agents structurally characterized by the presence of a pyrazolidinone ring within a [3.3.0] bicyclic framework[1]. Mechanistically, it has been demonstrated that the cell wall synthesizing enzymes of gram-negative organisms (PBP proteins) are inhibited by these novel agents[2]. In this regard, the aza-gamma lactam moiety serves as a viable biological surrogate of the beta-lactam functionality common to the penicillins, cephalosporins and monobactams.

Following the initial discovery of measurable activity within this structural class[1], we set out to develop synthetic methodology which would make available a large number of variously substituted derivatives[1b]. We herein report a new and efficient synthetic approach to [3.3.0] pyrazolidinones which has led to the discovery of compounds possessing *in vitro* activity comparable to many clinically utilized cephalosporins and penicillins. Significantly, some of these new compounds have demonstrated activity against organisms known to be resistant to beta-lactam-containing drugs.

In planning a synthetic route to the [3.3.0] fused pyrazolidinones, we sought an efficient process that would be regioselective, amenable to substituent variation in the B-ring, and non-destructive of the optical center present in the homochiral monocycle **1**[3]. Retrosynthetically, the regioselective attachment of ring B to ring A was envisioned as arising via intramolecular Wadsworth-Horner-Emmons condensation of the differentially functionalized monocycle **3**. Intermediate **3** would be available from selective stepwise functionalization of pyrazolidinone **1** via alkylation at N-1 followed by acylation at N-2 (Scheme 1).

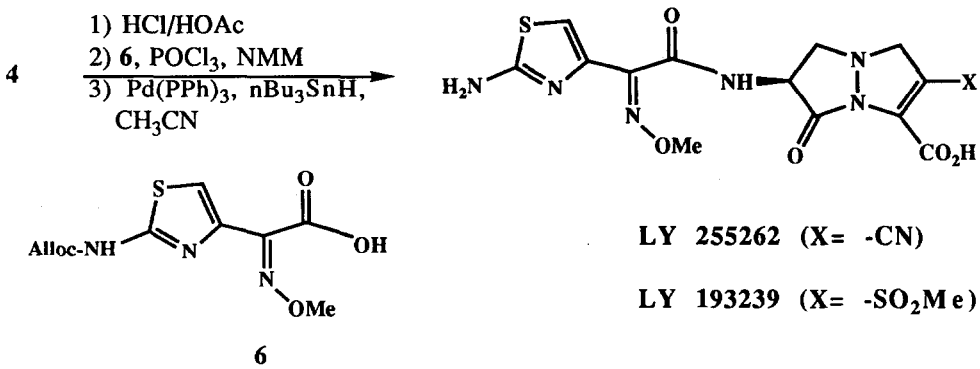


SCHEME 1

The successful reduction to practice of this proposed route is illustrated with the preparation of the cyano-substituted nucleus **4** (X= CN). Treatment of **1** (derived from L-serine)[3] with the known vinyl phosphonate **5** (X= CN; R= Et; MeOH, 25°C)[4] provided the conjugate addition product **2** (X= CN; R= Et)[5] in >95% yield. Treatment of this adduct with allyloxalyl chloride[6] and diisopropylethyl amine (one equivalent) in methylene chloride at low temperature gave rise to the cyclization precursor **3** (R= Et; X= CN). Although compound **3** could not be isolated in pure form due to the lability of the glyoxamide group, isolation was found not to be necessary as addition of a second equivalent of base (diisopropylethyl amine) instigated the desired intramolecular ring closure to **4** (X= CN). (overall yield 25%) This regioselective, two-operation process preserved the chirality present in **1**[7] ($[\alpha]_D$ -647.3° (c=0.15, DMSO)). In addition, the incorporation of alternate B-ring substituents was readily accomplished by utilization of different vinyl phosphonates (**5**) in the initial step as demonstrated with the preparation of methyl sulfone **4** (X=SO_2Me) utilizing **5** (X=SO_2Me; R=Me)[8]. Again, the final product was obtained with chirality preserved[7] ($[\alpha]_D$ -337.4° (c=1.0167, DMSO))(overall yield 18%).

The nitrogen protecting group of these two new pyrazolidinone nuclei was removed and the resulting free amine acylated with the allyloxycarbonyl-protected 2-(-2-aminothiazolc-4-yl)-2-(Z)-methoxyiminoacetic acid (**6**)[9] and deblocked as depicted in **Scheme 2** providing compounds suitable for biological evaluation.

When tested against a range of bacterial strains, both compounds (LY 255262 and LY 193239) demonstrated potent antibacterial activity with LY 193239 exhibiting somewhat greater overall activity. Significantly, LY 255262 was quite active against a strain of *Enterobacter cloacae* (265A) resistant to many beta-lactam antibiotics[10]. Further investigations into this unique class of antibacterial agents are underway and will be reported in due course.



SCHEME 2

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4. The vinyl phosphonate was prepared following the procedure described in McIntosh, J.M.; Sieler, R.A. *Can. J. Chem.* **1978**, *56*, 226 and used without purification. Attempted distillation resulted in rapid, vigorous polymerization. The compound has also been reported in the following; Pudovik, A.N.; Yastrebova, G.E.; Nikitina, V.I. *J. Gen. Chem. USSR*, **1966**, *36*, 1247. Minami, T.; Suganuma, H.; Agawa, T. *Chem. Lett.*, **1978**, 285.

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7. As determined by removal of the amine protecting group (HCl/HOAc) followed by acylation with (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid and NMR analysis as described in Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

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10. MIC (in ug/ml) against *Enterobacter cloacae* (265A): LY 255262: 1.0; LY 193239: 8.0; cefotaxime: 64.0; ceftazidime: 64.0.

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