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NOVEL PALLADIUM (II) MEDIATED REACTIONS OF N-HYDROXY-β-LACTAMS

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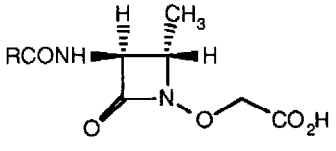
Summary: The attempted cyclization of an N-hydroxy-β-lactam onto an olefin activated with palladium (II) resulted in the formation of two interesting products, both of which suggest that the palladium acted as a Lewis acid.

One of the more recent advances in the area of β-lactam antibiotics was the synthesis of oxamazin **1**.[1] Oxamazin, an antibiotic which possesses significant Gram-negative antibacterial activity, has attracted considerable interest because of its unusual structure. Oxamazin is a monocyclic member of the β-lactam antibiotic family, whose carboxylate is one bond length further removed from the β-lactam ring than that which is normally observed in this family of antibiotics. The activity of oxamazin has been attributed to the activation of the β-lactam ring by the heteroatom directly attached to the β-lactam nitrogen.

Since most β-lactam antibiotics are bicyclic in nature, the combination of heteroatom activation and a bicyclic structure would be expected to provide a β-lactam which is an active acylating agent. Researchers at Squibb reported the successful racemic synthesis of the biologically active [4.2.0] bicyclic system **2**,[2] however no report



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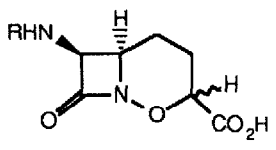

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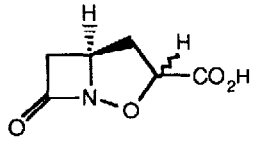


3

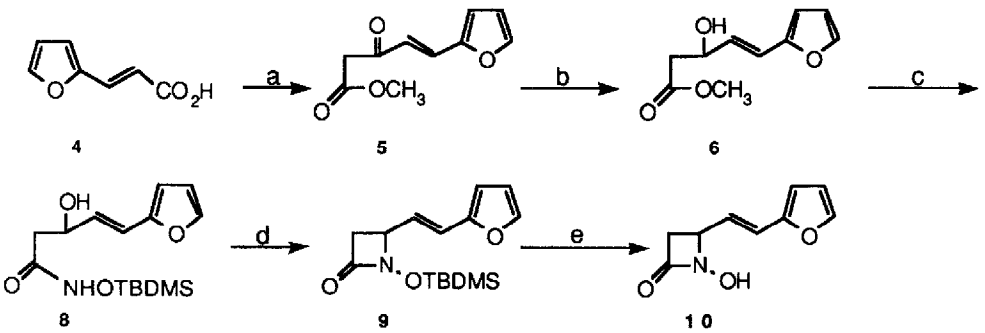
of the corresponding [3.2.0] system was made. In order to simplify the initial synthetic target, we proposed the synthesis of the compound **3** which did not possess substitution at the C-3 position of the azetidinone. Herein, we report an approach to the [3.2.0] bicyclic β-lactam, in which we attempted to utilize palladium (II) in the cyclization of the second ring.

Since ozonolysis of a furan system yields a carboxylic acid,[3] it was decided to mask the carboxylic acid as a furan ring. The strategy for the formation of cyclo-oxamazin **3** was designed to utilize a nucleophilic attack of an N-hydroxy-β-lactam on

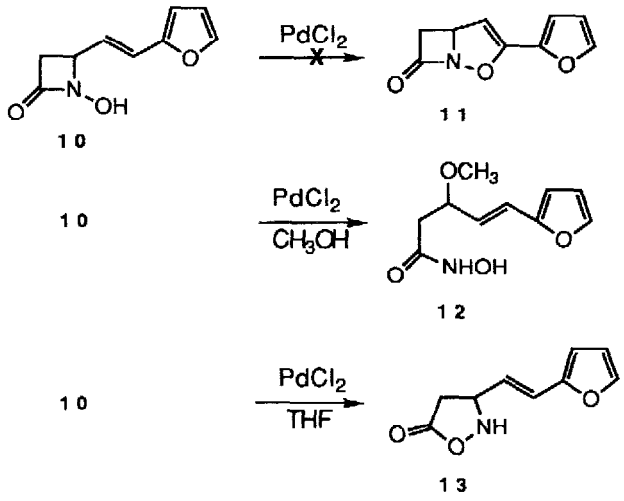
the benzylic-like carbon next to the furan ring to form the five-membered ring. There were many options for the choice of the functional group α to the furan, but an olefin in conjugation with the furan was a very accessable functionality. Presumably, the treatment of this olefin with an electrophile would induce electrophilic character at the α carbon and render itself to attack by the N-hydroxy-β-lactam. While a great number of electrophiles could facilitate this reaction, the multitude of palladium (II)[4] promoted cyclizations encouraged its exploration.

The overall strategy for the synthesis of the desired N-hydroxy-β-lactam used the hydroxamate mediated β-lactam synthesis method developed previously in our group.[5] Furacrylic acid **4**[6] was activated with carbonyldiimidazole and subjected to reaction with the magnesium salt of the monomethylester of malonic acid.[7] The resultant β-keto ester **5** was isolated in 83% yield. The β-keto ester **5** was reduced with one equivalent of sodium borohydride in methanol to afford the racemic β-hydroxy ester **6** in 95% yield. Adaptation of the method of Bottaro[8] provided easy access to the desired O-(*tert*-butyldimethylsilyl)hydroxylamine **7**.[9] The saponification of **6**, followed by coupling with **7** in dichloromethane with DCC successfully afforded the hydroxamate **8** in 47% yield. Cyclization to the β-lactam **9** proceeded in a 75% yield using dimethylazodicarboxylate[10] and triphenylphosphine. It is interesting to note that no six-membered ring resulting from allylic migration of the olefin was formed in the Mitsunobu reaction, indicating very little carbocationic character was present in the reaction. The desired N-hydroxy-β-lactam **10**[11] was formed in 39% yield by deprotection of **9** with a THF solution of tetra-n-butylammonium fluoride.

If palladium (II) induced cyclization of **10** took place, a reductive β-elimination might result in the formation of **11**. Interestingly, when **10** was subjected to one equivalent of $PdCl_2$ in methanol, the ring-opened allylic methyl ether **12**[11] was isolated in 24% yield.



a) 1) carbonyldiimidazole, THF, rt, 2) $(CH_3O_2CCH_2CO_2^-)_2\ Mg^{2+}$, THF, rt; b) $NaBH_4$, CH_3OH, 0°C;
c) 1) NaOH, THF/H_2O, rt, 2) O-(*tert*-butyldimethylsilyl)hydroxylamine **7**, DCC, CH_2Cl_2, 0°C;
d) dimethylazodicarboxylate, triphenylphosphine, THF, rt; e) $(n\text{-}Bu)_4N^+\ F^-$, THF, 0°C;



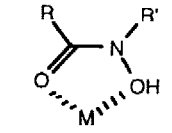
While β-lactones have been opened nucleophilically at the C-4 position,[12] *the opening of a β-lactam ring by nucleophilic attack at the C-4 position is unprecedented.* This unexpected result suggests that the palladium acted as a Lewis acid, to promote nucleophilic attack at the C-4 position of the β-lactam, with no allylic transposition of the olefin.[13]

In order to prevent ring opening by solvent attack at the C-4 position, compound **10** was stirred with one equivalent of $PdCl_2$ in THF at room temperature. No discernable reaction took place. Upon heating the solution to reflux for 24 hours, the starting material disappeared with the production of the isoxazolidin-5-one **13**[11] in 64% yield. This rearrangement of N-hydroxy-β-lactams has been observed under thermal conditions,[14] under basic conditions,[15] as well as under protic acid conditions.[2] But to our knowledge, this rearrangement has not been observed under Lewis acid conditions. No isoxazolidine **13** formed when **10** was heated overnight at reflux in THF alone. However, when a catalytic amount of $AlCl_3$ was added, complete conversion to the five-membered ring was observed within thirty minutes.

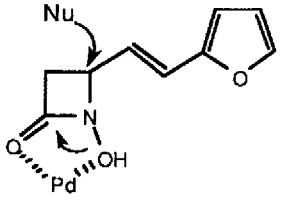
Even though the interesting side-products **12** and **13** were produced, it appears that palladium (II) is ineffective in promoting irreversible intramolecular attack on the benzylic-like position of **10**. It is possible that the desired cyclization took place, for β-elimination could account for the regeneration of the starting material which was then prone to the competitive reactions described.

Many metals have been shown to chelate with hydroxamic acids. In fact, this principle is presently being utilized in the isolation of valuable metals and radionuclides.[16] Despite the possible steric constraints of the β-lactam ring, the coordination of a transition metal with the N-hydroxy-β-lactam functionality appears similar and may be responsible for the observed reactivity. Regardless of the exact

mechanisms involved, these palladium induced reactions provide unique information on the reactivity of the N-hydroxy-β-lactams.



M = Ag, Cu, Co, Ni, Fe,



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11. Selected characterization data includes: **10**: mp 90-91° C; ^{1}HNMR (200 MHz, $CDCl_3$) δ 2.55 (dd, 1H), 2.97 (dd, 1H), 4.43 (m, 1H), 6.10 (dd, 1H), 6.30 (d, 1H), 6.37 (dd, 1H), 6.56 (d, 1H), 7.34 (d, 1H); IR (KBr) 3400, 2950, 1760 cm^{-1}; MS (EI) m/e 179 (M^+). **12**: Oil; ^{1}HNMR (90 MHz, $CDCl_3$) δ 2.48 (d, 2H), 3.3 (s, 3H), 4.10 (m, 1H), 5.95 (dd, 1H, J=15 Hz), 6.35 (dd, 1H), 6.39 (dd, 1H), 6.45 (d, 1H, J=15 Hz), 7.36 (d, 1H); IR (neat film) 3200, 2900, 1650 cm^{-1}; MS (EI) m/e 223 (M^+). **13**: Oil; ^{1}NMR (300 MHz, $CDCl_3$) δ 2.65 (dd, 1H, J=6, 16 Hz), 2.84 (dd 1H, J=8, 16 Hz), 4.47 (m, 1H), 5.97 (dd, 1H, J=9, 16 Hz), 6.26 (d, 1H, J=3 Hz), 6.33 (dd, 1H, J=1, 3 Hz), 6.47 (d, 1H, J=16 Hz), 7.32 (d, 1H, J=1Hz); IR (neat film) 3100, 1800 cm^{-1}; MS (EI) m/e 179 (M^+).
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