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ATTACHMENT OF A STYRYL GROUP TO THE 6-POSITION OF A PROTECTED PENICILLANIC ACID VIA COBALOXIME-MEDIATED RADICAL ALKYL-ALKENYL CROSS COUPLING

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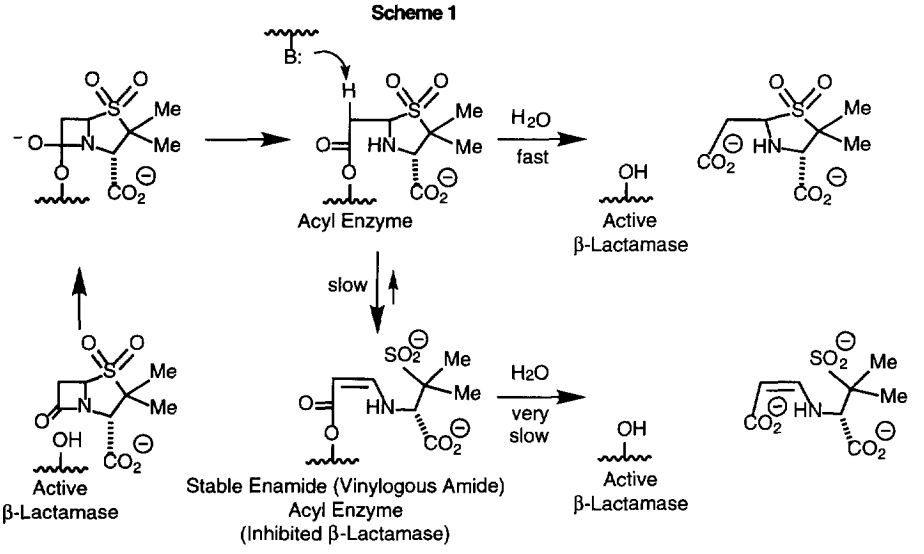
Abstract. Cobaloxime-catalyzed cross coupling of styrene with 6α-bromopenicillanic acid pivalolyl-oxymethyl ester (**4**) introduces a styryl group into the 6 position of the penicillanic acid nucleus. The method should be capable of introducing a variety of aryl-substituted alkenes into the 6 position. Such compounds may be useful as novel β-lactam antibiotics/β-lactamase inhibitors. Copyright © 1996 Elsevier Science Ltd

From 1978 to 1985 Knowles and coworkers reported a series of studies on the mechanisms of β-lactamase inhibition.[1] They showed that, in many cases, β-lactamase inhibition is the result of rearrangement of the covalent acyl enzyme complex to form a more conjugated and more stable enamide acyl enzyme (Scheme 1).

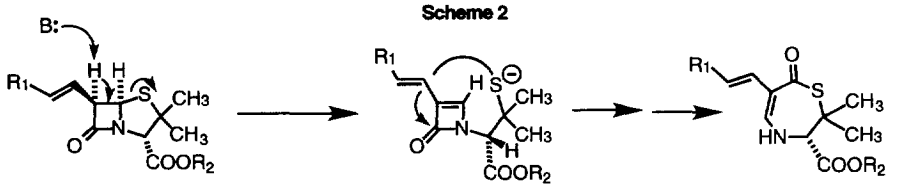
Scheme 1



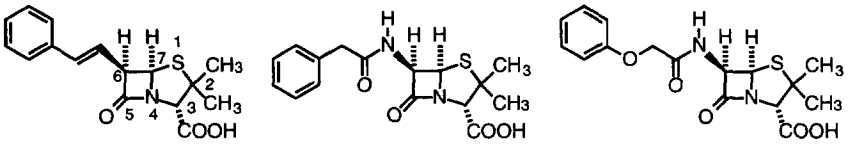
Introduction of an alkene group into the 6 position could enhance enzyme inhibition in two ways. First, the additional substituent should make the C-6 H more acidic, facilitating the formation of the enamide acyl enzyme. Second, the alkene would provide additional conjugation and stabilization to the enamide acyl enzyme, making it longer-lived and thus more effective at inhibiting enzyme activity. A few 6-alkenyl penicillin derivatives have been prepared, either by addition of penicillin 6-enolates (Grignard reagents) to vinyl sulfoxides[2] or by the rhodium-catalyzed addition of benzyhydryl 6-diazopenicillanate to furan followed by reduction of the resulting dienals and further transformations.[3] Compounds in which the substituent on

the alkene made the C-6 H too acidic (R_1 = COPh, COOEt, and $CONMe_2$) were unstable, undergoing the rearrangement shown in Scheme 2.

Scheme 2



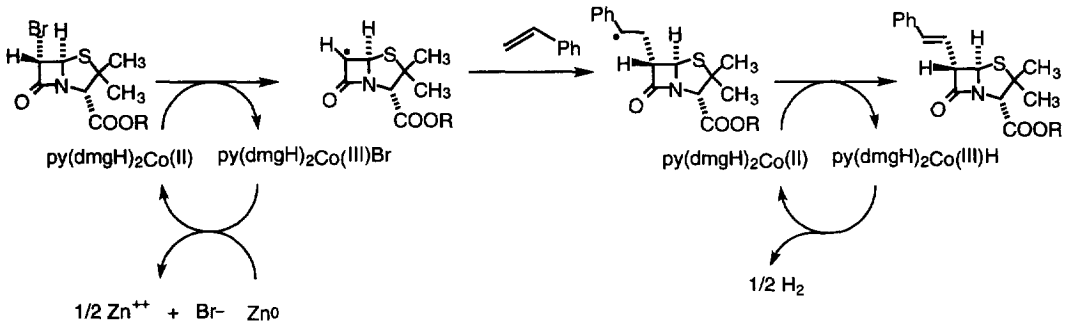
Compounds such as **1** should be good analogs of standard penicillins. The *trans* alkene is an isostere to a *trans* secondary amide and the aryl group mimics the aryl-containing side chains found in many penicillins.



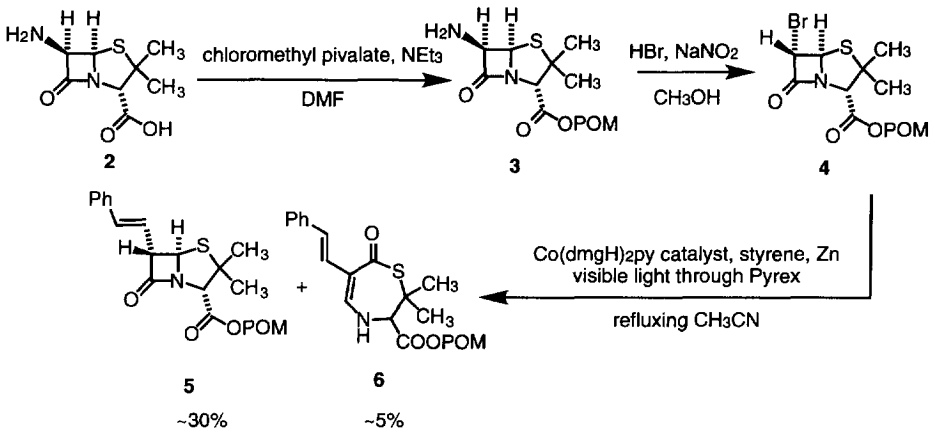
1 Penicillin G Penicillin V

In 1991, we reported the first examples of cobaloxime-catalyzed radical alkyl-alkenyl intermolecular cross coupling reactions.[4] A possible application of this method to the introduction of an aryl-substituted alkene into the 6-position of the penicillanic acid nucleus is shown in Scheme 3. Tribytyltin hydride radical chain reactions have been used to cross couple 6-α-bromo and 6,6-dibromo penicillanic acid benzyhydryl esters with acrylonitrile, methyl acrylate, vinyl acetate and allyltributyltin.[5] In those examples the new C-C bond was formed on the α face of the penicillanic acid nucleus, as shown in Scheme 3 and as found in this work (see below). The key difference with the cobaloxime-mediated reactions is that they are nonreductive and the alkene functionality in the cross coupling partner, in this case styrene, is regenerated in the final product. Facile introduction of the alkene functionality into molecules such as **1** or **5** is critical for the design of potential β-lactamase inhibitors using the concept described on the previous page. In this paper, we report the preparation of **5** to illustrate what should be a general method to introduce aryl-substituted alkenes in the 6-position of the penicillanic acid nucleus, using alkene regeneration by the cobaloxime cross coupling method as the lynchpin to this strategy.

Scheme 3



Treatment of 6-aminopenicillanic acid (**2**) with chloromethyl pivalate and triethylamine in *N,N*-dimethylformamide at room temperature according to a literature procedure[6] produced 6β-penicillanic acid pivalolyloxymethyl ester (**3**), isolated as the para-toluenesulfonate salt in 43% crystallized yield from ethyl acetate.[7] Treatment of **3** with hydrobromic acid and sodium nitrite in methanol in a modification of a standard literature procedure[8] proceeded by amine diazotization then bromide displacement to produce 6α-bromopenicillanic acid pivalolyloxymethyl ester (**4**) in 89% yield as a red-green, viscous liquid which solidified upon standing.[9] Cobaloxime-catalyzed cross coupling of **4** with styrene[10] provided chromatographically pure **5** in 29% isolated yield after gradient column chromatography. A small amount of **6** was isolated in about 5% yield from one run of this reaction.[11] In this reaction the $Co^{II}(dmgH)_2py$ catalyst is formed by in situ Zn reduction of $ClCo^{III}(dmgH)_2py$, which is added as a catalyst precursor.[12]



Our objective in this work was the development of the methodology to introduce aryl-substituted alkenes into the 6 position of the penicillanic acid nucleus. We have not examined the antibacterial or β-lactamase inhibitory properties of **5** or its derivatives. A free carboxylate is necessary for β-lactamase activity. To get such a compound our synthesis would have to be repeated with a more labile protecting group than the POM group – the POM group was chosen for this study because it was easy to introduce and could be relied upon to be quite stable under possible reaction conditions. The α stereochemistry at the 6 position in **5** is opposite that of the side chain found in penicillins. It is generally true that only compounds with a 6-β configuration have penicillin type antibacterial activity. It should be possible to invert the C-6 stereochemistry in **5** by a low temperature deprotonation at C-6 followed by low temperature kinetic protonation at C-6 from the *exo* face.[13] It is unlikely that such an intentional inversion would be necessary since compounds such as **5**, with a fairly acid H at C-6, should spontaneously epimerize under physiological-type conditions, in analogy to the facile interconversion of 6-α-bromopenicillanic acid (not active as a β-lactamase inhibitor) and 6-β-bromopenicillanic acid (potent β-lactamase inhibitor).[14] These are topics of future research in this area.

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7. Compound **3** was characterized by melting point, ^{1}H NMR, ^{13}C NMR and IR data.
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9. Compound **4** was characterized by ^{1}H NMR, ^{13}C NMR and IR data.
10. Freshly distilled CH_3CN (10 mL) was added to a 25 mL, 3-neck, Pyrex® round-bottom flask equipped with a magnetic stirrer, a reflux condenser on the center neck, and rubber septa for all ports. N_2 was bubbled through the solvent by a stainless steel needle. The septum at the top of the condenser was vented with another needle. $ClCo(dmgH)_2py$, (0.304 g, 7.53 x 10^{-4} mol) and Zn granules (0.323 g, 4.971 x 10^{-3} mol) were charged to the bubbling flask and the flask was resealed. Visible light was applied from a 300 Watt incandescent bulb held about 10 cm from the reaction vessel and heating was provided by an oil bath. A white precipitate formed as the materials were heated to the reaction temperature of 82 °C. 6α-Bromopenicillanic acid pivalolyloxymethyl ester (**4**) (1.57 g, 3.98 x 10^{-3} mol) was dissolved in 12 mL of CH_3CN and deoxygenated by N_2 bubbling in a separate vessel. After the main reaction vessel reached 82 °C, styrene (distilled, 2.9 mL, 2.6 g, 2.5 x 10^{-2} mol) was injected. After 5 min, the N_2 bubble was removed and the apparatus was placed under low N_2 flow. The deoxygenated solution of **4** was transferred in by gas-tight syringe. As soon as the solution of **4** was added much of the precipitate disappeared. The reaction was followed by TLC on silica gel plates (9:1 hexane:ethyl acetate). The reaction normally ran for about four hours on this scale. It was important to stop the reaction as soon as it was finished to minimize the decomposition of the product **5**. When the reaction was complete, heat and light were removed and the reaction mixture was poured immediately into 150 mL of Et_2O. After stirring for several minutes to let all precipitates form, the material was filtered through silica gel (60-200 mesh), then the filter cake was washed with 50 mL of Et_2O. Most of the Et_2O was removed on a rotary evaporator and the residue was taken up in hexane. After stirring overnight a two-phase system formed, with a red layer on the bottom. The red layer was removed by pipet and discarded. The solvent was removed from the remaining upper phase on a rotary evaporator. The product was purified by gradient column chromatography on silica gel using 100 mL of ethyl acetate as the polar solvent added into 400 mL of hexane followed by addition to the column, providing 0.474 g (29%) of pure **5**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.2 (s, 9H), 1.5 (s, 3H), 1.6 (s, 3H), 4.0 (d, 1H, J = 8 Hz), 4.5 (s, 1H), 5.2 (d, 1H, J = 1 Hz), 5.8 (m, 2H), 6.3 (dd, 1H, J = 8, 16 Hz), 6.6 (d, 1H, J = 16 Hz), 7.3 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 26.7, 27.3, 33.0, 39.2, 49.7, 64.7, 67.9, 69.9, 80.2, 121.4, 126.9, 128.5, 129.1, 135.2, 136.5, 167.0, 172.6, 177.2; IR 3022, 2973, 2934, 2878, 1770, 1767, 1760, 1480, 1460, 1394, 1370, 1282, 1250, 1201, 1179, 1150, 1109, 1022, 987, 854, 767, 693 cm^{-1}; MS *m/z* 417 (M+), 402, 340, 328, 303, 274, 258, 244, 231, 163, 145, 128, 115, 105, 90; HRMS calcd for $C_{22}H_{27}NO_5S$ 417.1611, found 417.1620.
11. Characterization data for **6**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.2 (s, 9H), 1.48 (s, 3H), 1.55 (s, 3H), 4.5 (d, 1H, J = 6 Hz), 5.8 (d, 1H, J = 5 Hz), 6.0 (d, 1H, J = 5 Hz), 6.1 (t, 1H, J = 6 Hz), 6.5 (d, 1H, J = 16 Hz), 7.1 (d, 1H, J = 16 Hz), 7.2 (d, 1H, J = 7 Hz), 7.3 (m, 3H), 7.4 (d, 2H, J = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 25.6, 26.7, 26.9, 27.7, 49.0, 68.3, 80.5, 124.9, 126.2, 126.8, 127.2, 128.5, 141.6, 168.0.
12. $ClCo(dmgH)_2py$ was prepared as described in Schrauzer, G. N. in *Inorganic Synthesis, Vol. 11.* Jolly, W. L., Ed.; McGraw Hill, Inc.: NY, 1968, 61-70.
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