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A STEREOCONTROLLED SYNTHESIS OF CEFPROZIL AND RELATED CEPHEMS *VIA* ALLENYLAZETIDINONES [1]

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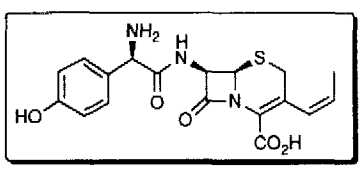
Summary: *A new method for the preparation of cephalosporins bearing carbon substituents of choice at C-3 is described. The approach involves 1,4-conjugate addition of an organocuprate to an allenylazetidinone to form a carbon-carbon bond followed by ring closure via intramolecular sulfenylation reaction.*

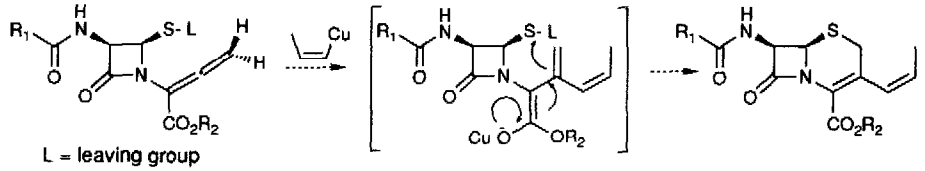
The recent discovery of Cefprozil **1**, an orally active cephalosporin, has provided impetus for considerable synthetic activity due to both the novel chemical structure and the unprecedented desirable antibiotic properties.[2] Earlier synthetic efforts in this area, mainly by the Bristol-Myers group, have relied on the stereocontrolled introduction of (Z)-propenyl moiety by the Wittig chemistry [3] ; coupling reaction between 3-trifloxycephem or 3-fluorosulfonyl-oxycephem with (Z)-1-propenyl-tri-*n*-butylstannane in the presence of palladium(0)[4] ; and by organocuprate chemistry on 3-trifloxycephems [5]



CEFPROZIL

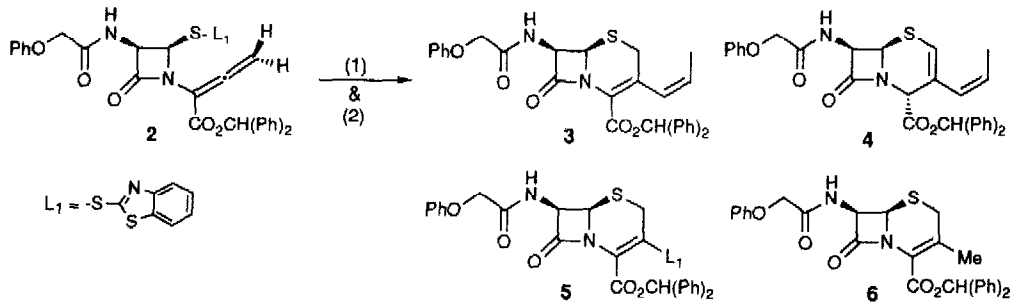
The search continued for a cost-effective and concise approach We now wish to report a stereocontrolled synthesis of Cefprozil, which is complementary to the existing methodologies with a distinct advantage. The starting intermediates are readily derived from penicillin, an inexpensive starting material available from the natural chiral pool. Recently, we have demonstrated the conversion of penicillin sulfoxides to the cephalosporins *via* allenylazetidinones.[6] The initial studies on allenenylazetidinones, especially intramolecular ring closure, suggested the possibility of employing an exogenous carbon nucleophile in conjunction with the ring closure. We envisioned the possibility of adding an organocuprate which after undergoing 1,4-conjugate addition at the central allenic carbon, might undergo ring closure *via* copper dienolate, to provide the desired cephalosporin (Scheme 1).[7] The allenylazetidinone **2** bearing mercaptobenzothiazole group at position-4 was chosen as our starting synthon.[6] Treatment of the azetidinone **2** with the lower-order (Z)-1-propenylcuprate derived from the

transmetallation reaction[8] between (Z)-1-propenyl-tri-*n*-butylstannane and dimethylcuprate at -78 °C afforded the desired cephem **3** in 55% (>98% of Z-isomer) yield along with 5 - 10 % of 3-mercaptocephem **5** and 3-methylcephem **6** (Scheme 2).



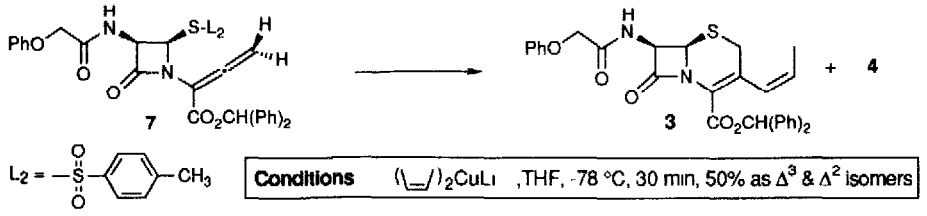
Scheme 1

The formation of **5** was probably the result of nucleophilic attack on allene by the mercaptide anion (leaving group) followed by ring closure. The presence of **6** could be attributed to the reaction of allene with dimethylcuprate, likely to be present due to incomplete transmetallation reaction A more reactive higher-order cyanocuprate, generated again *via* transmetallation reaction, afforded only 45% of the desired cephem as a mixture of Δ^2 and Δ^3 isomers **3** and **4**, along with 5-10% of the undesired cephems **5** and **6** (Scheme 2). The cephalosporins are very susceptible to the base catalyzed Δ^2/Δ^3 isomerization[9] and the result with cyanocuprate was not surprising as cuprates are known to be basic in nature.[10] To avoid the formation of 3-mercaptocephem **5** it was decided to employ a different leaving group. An ideal choice would be to have a good leaving group with a poor nucleophilic property. This would preclude any kind of participation by the leaving group during the reaction. To suppress any Δ^2/Δ^3 isomerization as well as the formation of 3-methylcephem **6**, it was decided to use the low-order cuprates from organolithium or organomagnesium prepared by the classical ways.[10] The mercaptobenzothiazole group was replaced by *p*-toluenesulfinate group and the cuprate was prepared from (Z)-1-propenyllithium[11] and copper iodide. Unfortunately, the reaction with the allene **7** afforded only 50% of the desired cephem isolated as a mixture of Δ^2 and Δ^3 isomers **3** and **4**. However, the changes eliminated the formation of cephems **5** and **6** respectively (Scheme 3).



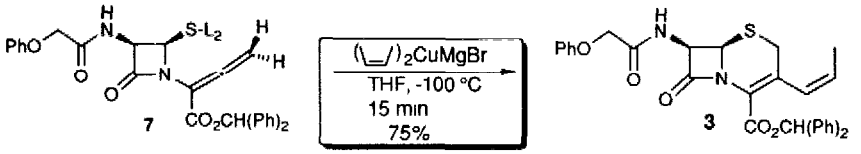
Conditions: (1) [(*Z*)-propenyl]$_2$CuLi from transmetallation reaction , THF, -78 °C, 60 min, 55%.
(2) [(*Z*)-propenyl]$_2$Cu(CN)Li$_2$ from transmetallation reaction, THF, -78 °C, 30 min, 45%

Scheme 2



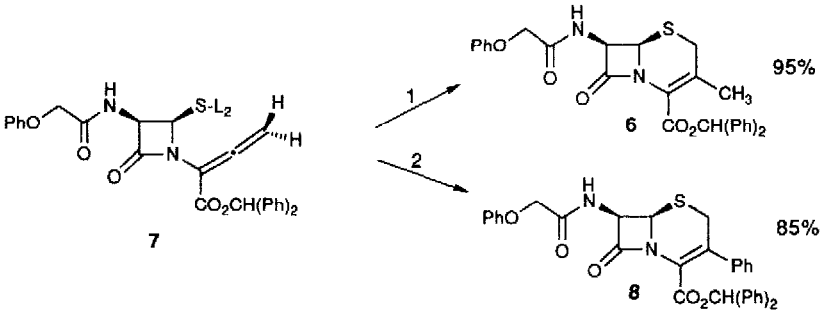
Scheme 3

Next, we evaluated the formation of the organocopper reagent from (Z)-1-propenylmagnesium bromide[12] and copper iodide. Treatment of allene with 1.5-1.8 equivalents of (Z)-1-(propenyl)$_2$CuMgBr (2.0 equiv. of Grignard and 1.0 equiv of CuI) at -100 °C for 15 min afforded 75% of the cephem 3 (>96% of Z-isomer). The reaction was very clean and the product was isolated simply by triturating the crude mixture with isopropyl alcohol.[13] (Scheme 4). The key intermediate 3 was converted to Cefprozil by following the deprotection and acylation procedures as described earlier.[3]



Scheme 4

The versatility of this novel methodology was further demonstrated by the synthesis of 3-methylcephem **6** and 3-phenylcephem **8** in high yields (Scheme 5).[13]



Scheme 5

In summary, we have presented a new methodology for the synthesis of cephalosporins from inexpensive penicillins. The methodology will enable us to introduce a variety of carbon

based substituents of our choice at position-3 of cephalosporins Further application of this chemistry is currently being explored and will be reported in due time.

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References and Notes

1. Part II in the series. For part I, see the preceding paper in the issue. The work was carried out at the Chemical Process Development Department, Bristol-Myers Company, Pharmaceutical R&D, Syracuse, NY.
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12. (Z)-1-propenylmagnesium bromide was prepared in THF. See: Rosenberg, S.D.; Gibsons, A.J.; Ramsden, H.E. *J. Am. Chem. Soc.* **1957**, *79*, 2139 The ratio of *Z* and *E* isomer present in the Grignard solution was determined (by NMR) to be ca. 96:4.
13. A typical procedure· In a two necked flask under argon atmosphere was placed copper iodide (1.83 mmol). Using a syringe, freshly distilled THF (15.0 mL) was added. The suspension was cooled to -78 °C and Grignard reagent (3.66 mmol) was added over a period of 5.0 min The cold bath was removed and the suspension was stirred for 20 min (a black homogeneous thick slurry was observed). The organocuprate solution was re-cooled to -78 °C and to it was added dropwise the solution of allenylazetidinone (1.53 mmol). After 15 min the reaction was quenched with sat NH_4Cl solution. The aqueous layer was extracted with ethyl acetate and further washed with brine, 10% $NaHCO_3$, dried ($MgSO_4$) and concentrated to give a foam. Further purification was achieved by flash chromatography or crystallization. All new compounds were fully characterized by NMR, MS and/or combustion analysis.

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