PREPARATION OF A MODEL SYSTEM FOR A CONSTRAINED ANGIOTENSIN II RECEPTOR ANTAGONIST

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Abstract - An imidazo[5,1-c][1,4]oxazin-8-one system, designed to be a fused ring analog of a potent angiotensin II receptor antagonist, was prepared.

DuP 753, also known as losartan, is a nonpeptide angiotensin II receptor antagonist currently in clinical trials for the treatment of hypertension. Several pharmaceutical companies are pursuing lead compounds that are structural modifications of DuP 753. The major metabolite of DuP 753 is Exp 3174, arising via in vivo oxidation of the primary alcohol to the corresponding carboxylic acid. We were interested in making a rigid analog of Exp 3174 by forming a ring between the imidazole and the biphenyl to provide I. In order to determine the feasibility of forming the desired imidazo [5,1-c][1,4]oxazin-8-one ring system we first examined a model system, namely II, where the biphenyl ring substituted with a tetrazole is replaced with a phenyl ring.
As depicted in Scheme I, valeronitrile was converted to the known amide oxime (1). Addition of ethyl propiolate to 1 gave intermediate (2) as a mixture of isomers. Thermolysis of 2 provided imidazole (3). Unfortunately attempts to chlorinate (3) failed. Reduction of the ester group of 3 with DIBAL resulted in formation of imidazole (4), which was readily chlorinated to provide 5 as previously reported.

Scheme 1

\[
\begin{align*}
n-\text{BuCN} & \xrightarrow{\text{a}} n-\text{BuCNH}_2 \quad & 1 \\
n-\text{BuCNH}_2 & \xrightarrow{\text{b}} n-\text{BuCNOEt} \quad & 2 \\
n-\text{BuCNOEt} & \xrightarrow{\text{c}} n-\text{BuCNOEt} \quad & 3 \\
n-\text{BuCNOEt} & \xrightarrow{\text{d}} n-\text{BuCNOEt} \quad & 4 \\
n-\text{BuCNOEt} & \xrightarrow{\text{e}} n-\text{BuCNOEt} \quad & 5
\end{align*}
\]

a) hydroxylamine hydrochloride\(^4\); b) ethyl propiolate, EtOH, reflux (75%); c) diphenyl ether, 180°C (46%); d) DIBAL, toluene (88%); e) NCS\(^7\).
The primary alcohol of imidazole (5) was converted to the corresponding methyl ester (6), via the two step oxidative protocol first utilized by DuPont. As shown in Scheme 2, alkylation of 6 with Cs₂CO₃ and bromoacetophenone gave a 11 : 1 mixture of two regioisomers. These isomers were separated by chromatography with the major isomer being the desired 7. Reduction of 7 with NaBH₄ gave 8 which was hydrolysed to key intermediate (9). Ring formation to II readily occurred upon treatment of 9 with p-toluenesulfonic acid in toluene.

Application of this methodology to the preparation of I is in progress.

Scheme 2

\[ \text{5} \xrightarrow{a} \text{6} \xrightarrow{b} \text{7} \xrightarrow{c} \text{II} \xrightarrow{e} \text{9} \xrightarrow{d} \text{8} \]

a) 1) MnO₂, THF; 2) MnO₂, NaCN, MeOH, HOAc; b) Cs₂CO₃, bromoacetophenone (79%); c) NaBH₄, MeOH (81%); d) NaOH, MeOH; e) TsOH, toluene, reflux (86% for two steps).
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REFERENCES

2. For a recent review of Angiotensin II receptor binding inhibitors see: J.C. Hodges, J. M. Hamby, and C. J. Blankley, Drugs Fut., 1992, 17, 575.


6. Substitution at this position is required to obtain the desired regiochemistry in the next (alkylation) step.

7. For details of the chlorination of 4 to 5 and also an alternate route to 4 see: Y. Furukawa, S. Kishimoto, and K. Nishikawa, U. S. Patent 4,355,040 (Chem. Abstr., 1981, 95, 132889t).


9. We thank the Parke-Davis Analytical Chemistry Department for the nOe spectra that were used to assign the structure.

10. All new compounds had satisfactory nmr, ir and mass spectra and were within +/- .4% CHN.

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