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Isomerisation and ring closing metathesis reactions towards benzo-fused heterocyclic compounds

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ABSTRACT

The aim of the project described in this dissertation is to explore the application of ring closing metathesis (RCM) to the synthesis of 6-, 7-, 8- and 9-membered *N*,*N*-, *N*,*O*- and *O*,*O*-benzo-fused heterocyclic compounds which are interesting structural motifs in medicinal chemistry. In recent times, their structures have been widely used as molecular scaffolds. Some of these heterocycles have been identified as antitumour agents, antibiotics and anti-HIV agents.

In our laboratories, a variety of 6-, 7- and 8-membered nitrogen- and oxygen- containing benzo-fused rings have been synthesized through ruthenium-mediated isomerisation and RCM in moderate to good yields. The first step in the present project was *N*-protection of suitable 2-aminophenols or *o*-phenylenediamines followed by allylation. Ruthenium-mediated isomerisation followed by RCM was then used for the synthesis of the 6-membered ring system *tert*-butyl 4*H*-1,4-benzoxazine-4-carboxylate **91** and the 7-membered ring system *tert*-butyl 1,5-benzoxazepine-5(4*H*)-carboxylate **103** while only RCM was used for the 8-membered ring systems, di(*tert*-butyl) 2,3,4,5-tetrahydro-1,6-benzodiazocine-1,6-carboxylate **130**, di(*tert*-butyl) 2,5-dihydro-1,6-benzodiazocine-1,6-dicarboxylate **129**, 1,6-dibenzoyl-1,2,5,6-tetrahydro-1,6-benzodiazocine **132**, 7-methoxy-2,5-dihydro-1,6-benzodioxocine **137** and the 9-membered ring system 1,6-*bis*[(4-methylphenyl)sulfonyl]-2,5,6,7-tetrahydro-1*H*-1,6-benzodiazonine **159**.

In the synthesis of the 7-membered ring systems, based on established methodology, we encountered problems with the RCM from suitable benzylamine or benzyl alcohol precursors. The reasons for this are not clear but we suspect this could be as a result of electronic and kinetic factors. Nevertheless, we were able to synthesize a 7-membered ring system, *tert*-butyl 1,5-benzoxazepine-5(4*H*)-carboxylate **103**, from a readily available precursor using a different methodology.

Approaches to the synthesis of the 8-membered ring systems, di(*tert*-butyl) 2,3,4,5-tetrahydro-1,6-benzodiazocine-1,6-carboxylate **130**, di(*tert*-butyl) 2,5-dihydro-1,6-benzodiazocine-1,6-dicarboxylate **129**, 1,6-dibenzoyl-1,2,5,6-tetrahydro-1,6-benzodiazocine **132** and 7-methoxy-2,5-dihydro-1,6-benzodioxocine **137**, as described in this dissertation, made extensive use of RCM in moderate to good yields, but the deprotection of the Boc group after hydrogenation proved to be a problem.

The synthesis of the 9-membered nitrogen containing benzo-fused compounds**,** 1,6-*bis*[(4-methylphenyl)sulfonyl]-2,5,6,7-tetrahydro-1*H*-1,6-benzodiazonine **159** by RCM was successful but in the synthesis of the *N*,*O*-benzo-fused compound by RCM, we suspect that polymerization, which is a side reaction in RCM reactions that are slow, occurred. In the synthesis of the 9-membered *O*,*O*-benzo-fused compounds, we only isolated the starting material.

The final approach in this dissertation involved the use of ruthenium-mediated isomerisation to afford internal isomerisation of the double bond within the heterocyclic rings of the 8-membered and 9-membered benzo-fused compounds previously prepared in our laboratory. This gave a mixture of regioisomers of 10-methoxy-2,3-dihydro-1,6-benzodioxocine **163** and 7-methoxy-2,3-dihydro-1,6-benzodiazocine **164**, 1,6-*bis*[(4-Methylphenyl)sulfonyl]-1,2,3,6-tetrahydro-1,6-benzodiazocine **166**, a regioisomeric mixture of 6-[(4-methylphenyl)sulfonyl]-3,6-dihydro-2*H*-1,6,-benzoxazocine **161** and 6-[(4-methylphenyl)sulfonyl]-5,6-dihydro-4*H*-1,6,-benzoxazocine **162**, and the 9-membered benzo-fused ring system, 1,6-*bis*[(4-methylphenyl)sulfonyl]-2,3,6,7-tetrahydro-1*H*-1,6-benzodiazonine **170**. The yields were good and the solid state structures of these isomerised compounds were examined by X-ray crystallography. X-ray diffraction was also performed on the solid state 8- and 9-membered benzo-fused ring systems. We also compared the crystal structures of the 8- and 9-membered benzo-fused compounds with their isomerised compounds.