UNIVERSITI TEKNOLOGI MARA

SYNTHESIS OF [5:5] PYRAZOLIDINONE AND [5:7] OXAZEPANONE γ-LACTAM RING SYSTEMS

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

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ABSTRACT

γ-Lactam is an important structural motif that features in a variety of bioactive natural products and drugs. Due to the high synthetic value, considerable efforts have been devoted to develop various synthetic strategies to diversify the structural molecule, especially towards bicyclic γ-lactam. In this study, the synthetic strategy of bicyclic moiety of 3,4-fused [5:5] pyrazolidinone and [5:7] oxazepanone γ-lactam ring systems were successfully established. The synthetic strategy was divided into three main parts in which the first part concentrated on the construction of the key intermediates, γ-lactam or 2,3-dioxopyrrolidine ring moiety *via* multicomponent reaction (MCR's) of sodium diethyl oxalacetate salt, primary amine and aldehyde in refluxing ethanol. The approach successfully gave a series of 2,3-dioxo-4-carboxy-5-(substituted)pyrrolidines **100** in moderate yield. Later, this highly functionalized intermediate **100** was subjected to various chemical transformations that lead to the formation of new bicyclic γ-lactam and also other interesting heterocyclic compounds. The second part focused on the formation of 3,4-fused [5:5] pyrazolidinone γ-lactam bicyclic ring system. The key intermediate; 2,3-dioxopyrrolidine underwent nucleophilic addition reaction at C-3 position *via* insertion of hydrazine hydrate by refluxing in ethanol solvent. Subsequently, metal-catalyzed hydrogenation was performed using Pd/C as a catalyst to afford hydrazine γ-lactam **104** with *cis-trans* configuration as a major product. Eventually, intramolecular cyclization of hydrazine γ-lactam **104** in basic condition had furnished the desired [5:5] pyrazolidinone γ-lactam **109** in 3-18% overall yields. The final part of this study emphasized on the formation of 3,4-fused [5:7] oxazepanone γ-lactam bicyclic ring systems using the same approach as pyrazolidinone γ-lactam which included of nucleophilic addition, metal-catalyzed hydrogenation and intramolecular cyclization reaction. Nucleophilic addition of ethanolamine at C-3 position was performed using catalytic amount of acid in ethanolic solvent. Accordingly, metal-catalyzed hydrogenation was carried using Pearlman's catalyst followed by intramolecular cyclization to afford [5:7] oxazepanone γ-lactam **118** in 5-29% overall yields. In conclusion, not only 10 new bicyclic γ-lactam were successfully synthesized, but other interesting pyrrolidinone type compounds and various synthetic approaches were also been explored. The structures of all synthesized and intermediate compounds were confirmed using spectroscopic technique.

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