

UNIVERSITI TEKNOLOGI MARA

**DESIGN AND CHEMICAL
SYNTHESIS OF FUSED 5-, 6-
OXYGEN AND/OR NITROGEN-
CONTAINING HETEROCYCLES- γ -
LACTAM UTILIZING 2,3-DIOXO-4-
CARBOXY-5-(SUBSTITUTED)
PYRROLIDINE AS THE KEY
PRECURSOR**

NURUL SYAFIQAH BINTI REZALI

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ABSTRACT

In this study, the development of synthetic strategy towards the formation of fused heterocyclic- γ -lactam rings system containing oxygen and/or nitrogen atom were successfully established. The key intermediate γ -lactam or 2,3-pyrrolidinedione ring template was effectively constructed using a multicomponent reaction (MCR) approach utilizing primary amine, aldehyde and diethyl oxalacetate sodium salt in ethanolic medium. The γ -lactam ring compound formed exists in the more stable enol form and also appears as racemic mixture. Following this, functional group interconversion of this highly functionalized compound leads to the formation of seven new fused heterocyclic- γ -lactam rings system. The fused δ -lactam- γ -lactam was effectively constructed *via* Leuckart reaction, condensation, hydrogenation and Dieckmann cyclisation. The synthesis of fused γ -lactam- γ -lactam however, involves decarboxylation, insertion of ethyl acetyl group *via* enamine-chemistry, imine formation and hydrogenation followed by an intramolecular cyclisation. The stereoselective reduction of the ethyl acetylic product followed by ester hydrolysis and lactonization *via* acid activation protocol was successfully carried out to furnish the fused γ -lactone- γ -lactam compound. The *syn* hydrogenation product of key intermediate 2,3-pyrrolidinedione was further reacted with hydrazine to afford the hydrazide. Intramolecular cyclisation *via* Curtius rearrangement of the hydrazide gave the new product fused oxazolidinone- γ -lactam. In another synthetic strategy, decarboxylation followed by Friedlander condensation productively gave fused quinoline- γ -lactam (pyrroloquinoline) in moderate yields. Meanwhile the synthesis of fused quinolone- γ -lactam (pyrroloquinolone) was obtained from a nucleophilic addition and Conrad-Limpach cyclisation. The *O*-alkylated product of 2,3-pyrrolidinedione was further elaborated through Dieckmann cyclisation reaction to give fused furan- γ -lactam ring compound. Supplementary synthetic attempts toward the synthesis of other bicyclic compounds such as oxadiazole- γ -lactam and triazole- γ -lactam using key intermediate 2,3-pyrrolidinedione however, failed to give the targeted products.

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CHAPTER ONE

INTRODUCTION

1.1 Oxygen and Nitrogen Heterocycles

Heterocyclic compound is a cyclic compound that has atoms of at least two different elements as members such as nitrogen, oxygen or sulphur, replacing the carbon atom. Table 1.1 and Figure 1.1 show some examples of five and six-membered rings containing one or two oxygen and nitrogen heteroatoms, which are assigned as either aromatic or non-aromatic.

Table 1.1
Five- and Six-Membered *O*- and *N*-Heterocycles

Type of Ring	Heteroatom	No of Heteroatom	IUPAC Name
5-membered	Nitrogen	1	Pyrrolidine
	Oxygen	1	Tetrahydrofuran
	Nitrogen / Nitrogen	2	Imidazolidine
	Nitrogen / Oxygen	2	Oxazolidine
	Nitrogen	3	Triazole
	2 Nitrogen / 1 Oxygen	3	Oxadiazole
6-membered	Nitrogen	1	Piperidine
	Nitrogen	1	Pyridine
	Oxygen	1	Tetrahydropyran

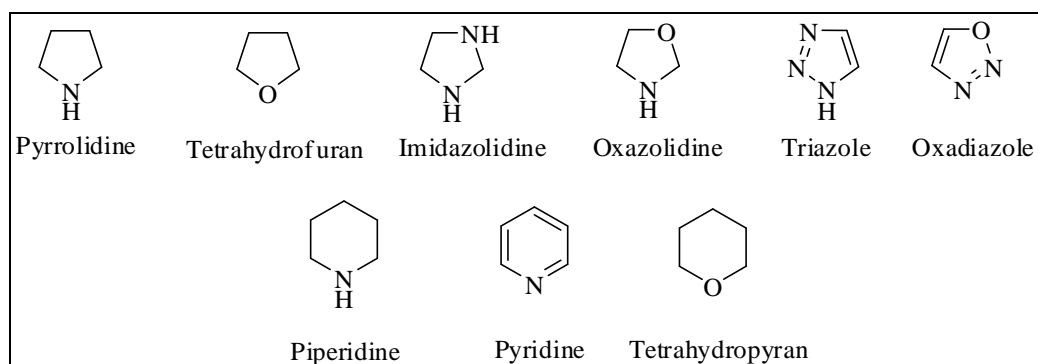


Figure 1.1 Five- and Six-Membered *O*- and *N*-Heterocycles