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THE SYNTHESES OF FUSED CYCLIC 5/6-MEMBERED RING LACTAMS VIA ENAMINE HYDROGENATION

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Abstract

Five- and six-membered nitrogen heterocycles are common structural units that have been studied due to their importance in natural compounds, synthetic drugs and medicines. In this study, the development of new synthetic methods towards the formation of fused nitrogen heterocyclic (γ-lactam) rings system were successfully established. The key intermediate γ-lactam ring unit which exists in the more stable enol form and also appears as racemic mixture, was successfully prepared *via* one-pot multicomponent reaction (MCR) protocol utilizing amine, aldehyde and diethyl oxalacetate sodium salt. Functional group interconversion of this highly functionalized compound into imine and enamine derivatives, in separate vessels, leads to the formation of targeted products. The enamines hydrogenation is essential towards the construction of fused bicyclic 6,5- and 5,5-ring lactams. The solvent effects on the selectivity of enamine derivative's hydrogenation of the pyrroles are also emphasized. Both fused lactams were synthesized with an overall yield of 4-21% in the five or six-steps pathway.

Keywords: Bicyclic fused, enamine hydrogenation, lactam.

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1. Introduction

The five-membered nitrogen-heterocycles are key elements that typically found in naturally occurring substances. The wide-ranging spectrum of pharmacological effects of this type of compound has attracted significant interests especially in synthetic drugs researches (Hameed & Akhtar, 2011), in agricultural industry and in organic synthesis. The pyrrolidine (also known as tetrahydropyrrole) ring structure especially γ-lactam (α-carbonyl pyrrolidine) possess significant Structure-Activity Relationship (SAR) and versatile reaction intermediates for pharmaceutical drug's productions for example doxapram, aniracetam, lactacystin and cotinine. Likely, the alkaloid cotinine that found in tobacco is verified for antipsychotic-like effects (Buccafusco & Terry, 2009), thus it was widely used biomarker to cure Alzheimer's diseases (Grizzell \7 Echeverria, 2014), schizophrenia and depression.

The synthetic approaches of α-carbonyl pyrrolidine include 1,3-dipolar cycloaddition (Li, Tong, Li, Tao, & Wang, 2011), ring-closing metathesis (Majumdar, Muhuri, Islam, & Chattopadhyay, 2009), solid-phase synthesis (Vergnon, Pottorf, Winters, & Player, 2004) and multicomponent reaction (Wei & Shaw, 2007). Moreover, Friedel- Crafts alkenylation of ionic liquids (Song, Jung, Choung, Roh, & Lee, 2004), Rhodium-catalyzed arylation-cyclisation of N-tosylarylimines (Wang, Feng, Xu, & Lin, 2007) and an intramolecular Wurtz-Fittig coupling reaction (Campbell, Dedinas, & Trumbower-Walsh, 2010) similarly have been conveyed on the formation of the respective cyclic ring system. Whereas, a classic approach to synthesize six-membered (δ)-lactam ring are involved the formation of heterocyclic ketene aminal (Huang & Liu, 1989), (3,3) sigmatropic rearrangement (Cheung & Yudin, 2006) and Huisgen (3+2) dipolar cycloaddition (Kumar & Rode, 2007).

2. Problem Statement

A review of the literature discloses that no inclusive syntheses of fused 5,5- and 6,5-bicyclic γ-lactams have been explored. Thus, the authors turn out to be concerned in the syntheses of targeted compounds utilizing the condensation of three-components comprises compound 1 (2,3-dioxo-5-(substituted) pyrroles) as the core template (Dahaen, Metten, Kostermans, Baelen, & Smet, 2006). This work may demonstrate new synthetic procedures towards fused bicyclic heterocyclic constituents that involve competent methodology, reproducible approach as well as reasonable reaction yield.

3. Research Questions

What are the simplest and approachable synthetic methodologies to transform the 2,3-pyrrolidinedione into fused bicyclic 6,5-lactam and 5,5-lactam ring systems?

4. Purpose of the Study

To design and construct the chemical conversions of highly substituted 2,3-pyrrolidinedione that serve as a core to synthesize a new fused bicyclic 5/6-nitrogen-heterocyclic-lactam ring moieties employing an amine (either enamine or imine) initial product.

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5. Research Methods

5.1. General

All chemicals and reagents were purchased from Merck and Aldrich. Column chromatography (CC) was carried out using Merck Kieselgel 60 with 70-230 mesh ASTM. Thin layer chromatography (TLC) was performed using 20x20 (cm) aluminium sheets coated with Merck Kieselgel 60 F_{254}. The TLC plates were visualized at $\lambda = 254$nm under ultraviolet light and was exposing to I_2 vapour or staining with $KMnO_4$ solution. The qualitative MS was analysed on LCMS/MS Q-TOF Agilent Technologies 6520 (for liquid sample) or MSI-High Resolution Mass Spectrometer (HRMS) Model CO-1600 Autoconcept (for solid sample). Melting points (m.p.) were determined *via* Stuart SMP30 without corrected. The analysis of ^{1}H-NMR and ^{13}C-NMR were documented on a Jeol 400 MHz with TMS as a reference. All IR spectra were analyzed using spectrometer Varian 3100 FT-IR Excalibur Series.

5.2. Preparation of Compound (4)

A NH_4CO_2H ($5.0x10^{-3}$ mol) was poured into **1a** ($1.0x10^{-3}$ mol) in 100 mL CH_3OH and set up under Dean-Stark apparatus for 24 hr. After all the starting materials were consumed, the solution was cooled and later the solid formed was filtered out and washed with Et_2O to afford compound ethyl 4-amino-1-methyl-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **4** as a white solid. Yield: 94%. m.p. 133-135°C. ^{1}H-NMR ($CDCl_3$): 7.17-7.32 (m, 5H, Ar H), 6.32 (br, 2H, N*H*$_2$), 5.03 (s, 1H, Ar C*H*), 3.93-4.02 (m, 2H, C*H*$_2$O), 1.01-1.04 (t, 3H, C*H*$_3$, *J*=7.6 Hz). ^{13}C NMR ($CDCl_3$): 165.5 (CO), 164.9 (CO), 146.2 (quaternary C), 136.7 (quaternary C), 128.6 (Ar-C), 128.4 (Ar-C), 127.7 (Ar-C), 104.2 (quaternary C), 64.3 (CH_2O), 59.7 (Ar*CH*), 27.7 (NCH_3), 14.2 (CH_3). IR ν cm^{-1}: 3297, 3438 (2 x NH), 1700 (CO), 1679 (CO), 1633 (C=C). MS *m/z*: 260 $[M]^+$ (calculated for $C_{14}H_{16}N_2O_3$).

5.3. Preparation of Compound (5)

In a flask, a reaction mixture of **4** ($1.0x10^{-3}$ mol), CH_3OCOCH_2COCl ($1.2x10^{-3}$ mol) and dried C_6H_6 (20 mL) was refluxed for 9 hr. Upon completion, the solution was leave at ambient temperature. The solvent was evaporated at 40°C under pressure and later the crude product was triturated with Et_2O and washed with saturated $NaHCO_3$ and brine solution. The organic layers were combined and was dried over $MgSO_4$ and concentrated to afford product ethyl 4-(3-methoxy-3-oxopropanamido)-1-methyl-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **5** as a yellowish oil. Yield: 92%. ^{1}H-NMR ($CDCl_3$): 9.42 (br, 1H, NH), 7.19-7.36 (m, 5H, Ar H), 5.28 (s, 1H, ArC*H*NCH_3), 3.93-3.97 (m, 2H, CH_2O), 3.70 (d, 1H, CH*H*, *J*=17.6 Hz), 3.68 (s, 3H, OCH_3), 3.63 (d, 1H, C*H*H, *J*=17.6 Hz), 2.74 (s, 3H, NCH_3), 1.00-1.04 (t, 3H, CH_3, *J*=7.6 Hz). ^{13}C-NMR ($CDCl_3$): 168.0 (CO), 156.3 (CO), 163.4 (CO), 162.8 (CO), 135.0 (quaternary C), 130.9 (quaternary C), 129.9 (Ar-C), 128.8 (Ar-C), 127.9 (Ar-C), 65.3 (Ar*CH*NCH_3), 60.1 (CH_2O), 51.7 (OCH_3), 42.1 (CH_2), 26.8 (NCH_3), 13.5 (CH_3). IR ν cm^{-1}: 3260 (NH), 1725 (CO), 1682 (CO). MS *m/z*: 360 $[M^+]$ (calculated for $C_{18}H_{20}N_2O_6$).

5.4. Preparation of Compound (6)

The 10% Pd-C ($1.3x10^{-3}$ mol) was added into the solution of **5** ($1.0x10^{-3}$ mol) in CH_3COOH (150 mL), and hydrogenated at 4 atm for 12 hr. After all the starting materials were consumed, the mixture was

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filtered over celite and concentrated to afford a crude product that was chromatographed using PE/EtOAc:50/50 solvent system. The product ethyl 4-(3-methoxy-3-oxopropanamido)-1-methyl-5-oxo-2-phenylpyrrolidine-3-carboxylate **6** was collected as a brownish oil. Yield: 65%. ^{1}H-NMR (CD_3OD): 7.27-7.41 (m, 5H, Ar-C), 5.47 (s, 1H, NH), 4.85 (d, 1H, C*H*NH, *J*=5.2 Hz), 4.11-4.15 (q, 2H, CH_2O, *J*=7.2 Hz), 3.69 (s, 3H, OCH_3), 3.36-3.40 (q, 1H, C*H*CO, *J*=5.2 Hz), 2.69 (s, 3H, NCH_3), 1.87 (s, 2H, CH_2), 1.19-1.23 (t, 3H, CH_3, *J*=7.2 Hz). ^{13}C-NMR (CD_3OD): 184.3 (CO), 171.9 (CO), 171.1 (CO), 169.5 (CO), 138.3 (quaternary C), 129.0 (Ar-C), 128.5 (Ar-C), 126.7 (Ar-C), 64.9 (CH_2O), 61.2 (OCH_3), 53.49 (*CH*NH), 51.6 (*CH*Ar), 51.4 (*CH*CO), 47.7 (CH_2), 27.8 (NCH_3), 13.1 (CH_3). IR ν cm^{-1}: 3127 (OH), 1684 (CO). MS *m/z*: 362 [M^+] (calculated for $C_{18}H_{22}N_2O_6$).

5.5. Preparation of Compound (2)

(Approach 1) A drop wise solution of **6** (1.0x10^{-3} mol) in dried toluene (5.0 mL) was added into a stirred suspension of 60% NaH in mineral oil (2.0x10^{-3} mol) in anhydrous toluene (40 mL) at ambient temperature. The reaction mixture was heated to 65°C for 4 hr until all starting material complete consumed. Next, the solution was leave at room temperature. The toluene was evaporated in vacuo and the remaining solution was partitioned with EtOAc and H_2O. The aqueous extract was acidified with acid and diluted with CH_2Cl_2. The aqueous residue was concentrated in *vacuo* and resulting solid was dissolved in CH_3OH. The methanol-dissolved portion was subjected to dryness in *vacuo* to afford compound methyl 4-hydroxy-6-methyl-2,7-dioxo-5-phenyl-2,4a,5,6,7,7a-hexahydro-1*H*-pyrrolo[3,4-b] pyridine-3-carboxylate **2** as a brownish liquid. Yield: 64%. ^{1}H and ^{13}C NMR Data refer **Table 01**. IR ν cm^{-1}: 3420, 1718, 1689. QTOF-MS *m/z*: 313 [M-3] $^+$ (calculated for $C_{16}H_{16}N_2O_5$).

(Approach 2) A solution of $NaOCH_3$ (*in-situ* synthesis from sodium (2.0x10^{-3} mol) in dry CH_3OH) was added into a compound **6** (1.0x10^{-3} mol) in dry toluene (2.0 mL). The reaction mixture was stirred for 0.5 hr under N_2 atmosphere and refluxed at 90°C for 6 hr, after which it was leave at ambient temperature. The solution was diluted with water and the aqueous extract was acidified using acid. The residue was concentrated and respective solid formed was dissolved in CH_3OH. The methanol-dissolved portion was concentrated in *vacuo* to afford compound **2**. Yield: 85%.

5.6. Preparation of Compound (7)

Compound **1b** (0.8x10^{-3} mol) was disseminated in 10% HCl (aq) (10 mL) and heated under reflux for 7 hr which is progressively dissolved to give a dark-brownish acidic-aqueous. The solution was then cooled and concentrated to dryness. The crude product was triturated with Et_2O and extracted with CH_2Cl_2 and H_2O. The organic extract was dried over $MgSO_4$, filtered and concentrated on vacuo to yield the pure product 5-(4-methoxyphenyl)-1-methylpyrrolidine-2,3-dione **7** as a yellowish solid. Yield: 75%. m.p. 140-143°C. ^{1}H-NMR ($CDCl_3$): 7.09-7.11 (d, 2H, Ar-C, *J*=8.8 Hz), 6.89-6.93 (d, 2H, Ar-C, *J*=8.8 Hz), 4.74-4.76 (dd, 1H, ArC*H*NCH_3, *J*= 3.2 Hz, 7.4 Hz), 3.79 (s, 3H, OCH_3), 3.10-3.17 (dd, 1H, CH*H*, *J*= 20.4 Hz, 7.4 Hz), 2.53-2.58 (dd, 1H, *CH*H, *J*=20.4 Hz, 3.2 Hz). ^{13}C-NMR ($CDCl_3$): 198.1 (CO), 160.0 (quaternary C), 159.3 (CO), 130.0 (quaternary C), 127.6 (Ar-C), 114.8 (Ar-C), 57.8 (ArC*H*NCH_3), 55.3 (OCH_3), 40.9 (CH_2), 29.6 (NCH_3). IR ν cm^{-1}: 1750 (CO), 1703 (CO). Elemental analysis: C=65.74, O= 21.89, N= 6.39, H=5.98; Found: C=65.13, N= 6.12, H=5.82 (calculated for $C_{12}H_{13}NO_3$).

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5.7. Preparation of Compound (8)

(Approach 1) At -78°C under N_2 atmosphere, to the solution of 1.6 M LDA in hexane ($1.2x10^{-3}$ mol) in 13 mL THF was added a solution of compound **7** ($1.0x10^{-3}$ mol) and HMPA (0.25 mL) in ahydrous THF (3 mL) over a period of 5 minute. The reaction mixture was stirred for 0.5 hr after which ethyl iodoacetate ($0.75x10^{-3}$ mol) was then added. The mixture was continued stirred for 0.5 hr and the temperature was gradually rise to ambient temperature and quenched with saturated ammonium chloride solution. The solvent was removed in *vacuo* and the residual was extracted with Et_2O (3x20 mL). All organic layers were combined and was dried and concentrated. Purification using PE/EtOAc:40/60 as a solvent system by CC afforded Ethyl 2-(4-hydroxy-2-(4-methoxyphenyl)-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) acetate **8** as a brownish liquid. Yield: 7%. ^{1}H-NMR ($CDCl_3$) 8.50 (br, 1H, OH), 7.06-7.08 (d, 2H, Ar-C, *J*=9.0 Hz), 6.91-6.94 (d, 2H, Ar-C, *J*=9.0 Hz), 4.93 (s, 1H, ArC*H*NCH_3), 3.99-4.05 (q, 2H, CH_2O, *J*=7.2 Hz), 3.78 (s, 3H, OCH_3), 3.35-3.39 (d, 1H, CH*H*CO, *J*=16.0 Hz), 2.88 (s, 3H, NCH_3), 2.66-2.70 (d, 1H, C*H*HCO, *J*=16.0 Hz), 1.14-1.18 (t, 3H, CH_3, *J*=7.2 Hz).^{13}C-NMR ($CDCl_3$) 170.6 (CO), 167.3 (quaternary C), 160.0 (CO), 143.6 (quaternary C), 129.0 (Ar-C), 126.7 (quaternary C), 117.6 (quaternary C), 114.6 (Ar-C), 65.1 (Ar*CH*NCH_3), 61.6 (CH_2O), 55.4 (OCH_3), 32.7 (CH_2CO), 29.8 (NCH_3), 14.21 (CH_3). IR ν cm^{-1}: 1729 (CO), 1684 (CO), 1601 (C=C). MS *m/z*: 305 [M^+] (calculated for $C_{16}H_{19}NO_5$).

(Approach 2) (Step 1) To the solution of compound **7** ($1.0x10^{-3}$ mol) in C_6H_6 (50 mL), pyrrolidine ($1.2x10^{-3}$ mol) was added. The mixture was refluxed for 20 minutes and after all starting material was consumed, the solution was leave at ambient temperature. The solvent was removed to give the crude product of enamine. (Step 2). A dried K_2CO_3 ($1.9x10^{-3}$ mol) was added into a stirred solution of crude product ($1.0x10^{-3}$ mol) in Step 1 in dry acetonitrile (150 mL). Next, ethyl iodoacetate ($1.5x10^{-3}$ mol) was added into a reaction mixture under N_2 atmosphere. After reflux for 18 hr, the mixture was cooled. The solid formed was filtered off and remaining solvent was evaporated to yield a slurry crude extract. The crude was dissolved in $CHCl_3$ (20 mL) and quenched with hydrochloric acid. The biphasic mixture was stirred at 35-40°C for 5 hr and later was extracted using organic solvent. The organic layer was washed using saturated $NaHCO_3$ solution, dried over magnesium sulphate, concentrated and undergo purification using CC using *n*-hex/EtOAc:50/50 solvent system. Title compound was obtained as a brownish liquid. Yield: 43%.

5.8. Preparation of Compound (9)

Benzylamine ($2.0x10^{-3}$ mol) was added into a solution of **8** ($1.0x10^{-3}$ mol) in ethanol (10 mL) at room temperature and refluxed for 3 hr. After cooling, the reaction mixture was concentrated and afforded crude product which then was subjected to CC using EtOAc: 100 solvent system. Ethyl 2-(4-(benzylamino)-2-(4-methoxyphenyl)-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl) acetate **9** was yielded as a brownish liquid. Yield: 99%. ^{1}H-NMR ($CDCl_3$): 7.38-7.58 (m, 5H, Ar-H), 7.23-7.30 (d, 2H, Ar-H, *J*=7.2 Hz), 6.85-6.88 (d, 2H, Ar-H, *J*=7.2 Hz), 5.07 (br t, 1H, NH), 4.76 (s, 1H, ArC*H*NCH_3), 4.53-4.62 (m, 2H, CH_2Ph), 3.90-3.95 (q, 2H, CH_2O, *J*=7.2 Hz), 3.75 (s, 3H, OCH_3), 2.67 (s, 3H, NCH_3), 3.12-3.16 (d, 1H, CH*H*CO, *J*=16.0 Hz), 2.50-2.54 (d, 1H, C*H*HCO, *J*=16.0 Hz), 1.09-1.13 (t, 3H, CH_3, *J*=7.2 Hz). ^{13}C-NMR ($CDCl_3$): 174.1 (CO), 171.3 (CO), 159.9 (quaternary C), 141.2 (quaternary C), 131.1 (quaternary C), 129.1 (Ar-C), 128.2 (Ar-C), 128.2 (Ar-C), 126.7 (Ar-C), 114.1 (Ar-C), 65.6 (C*H*OH), 62.6 (ArC*H*NCH_3), 60.0 (CH_2O),

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54.8 (OCH_3), 51.0 (CH_2Ph), 46.5 (C*H*CH_2), 35.4 (CH_2), 27.3 (NCH_3), 13.6 (CH_3). IR ν cm^{-1}: 3449 (NH), 1707 (CO), 1584 (C=C). MS *m/z*: 395 $[M+1]^+$ (calculated for $C_{23}H_{26}N_2O_4$).

5.9. Preparation of Compound (10)

To a solution of **8** ($1.0x10^{-3}$ mol) in EtOH (30 mL), $NH_2OH.HCl$ ($1.2x10^{-3}$ mol), sodium sulphate ($1.0x10^{-3}$ mol) and $NaHCO_3$ ($1.2x10^{-3}$ mol) were added. The reaction mixture was stirred at room temperature for 48 hr and once completed, the white solid was filtered off. The filtrate was concentrated in vacuo and oxime, ethyl 2-(4-(hydroxyimino)-2-(4-methoxyphenyl)-1-methyl-5-oxopyrrolidin-3-yl) acetate **10** was collected as a brownish liquid. Yield: 94%. ^{1}H-NMR ($CDCl_3$) 7.04-7.06 (d, 2H, Ar-H, *J*=8.6 Hz), 6.83-6.86 (d, 2H, Ar-H, *J*=8.6 Hz), 4.30-4.31 (d, 1H, ArC*H*NCH_3, *J*=2.4 Hz), 4.06-4.11 (q, 2H, CH_2O, *J*=7.2 Hz), 3.76 (s, 3H, OCH_3), 3.25-3.37 (d, 1H, C*H*CH_2, *J*=17.2 Hz, 8.8 Hz), 3.00-3.05 (d, 1H, CH*H*CO, *J*=3.2 Hz, 17.2 Hz), 2.77 (s, 3H, NCH_3), 2.68-2.75 (d, 1H, C*H*HCO, *J*=8.8 Hz, 16.4 Hz), 1.15-1.19 (t, 3H, CH_3, *J*=7.2 Hz). ^{13}C-NMR ($CDCl_3$) 179.1 (CO), 173.6 (CO), 159.4 (C=N), 154.5 (quaternary C), 146.6 (quaternary C), 127.7 (Ar-C), 114.7 (Ar-C), 66.5 (ArC*H*NCH_3), 64.7 (CH_2O), 56.0 (OCH_3), 49.3 (CH_2), 29.5 (NCH_3), 23.5 (CH), 14.2 (CH_3). IR ν cm^{-1}: 3376 (OH), 1700 (CO). MS *m/z*: 321 $[M+1]^+$ (calculated for $C_{16}H_{20}N_2O_5$).

5.10. Preparation of Compound (3)

A catalytic amount of 10% Pd-C ($1.0x10^{-3}$ mol) was added into a solution of **10** ($1.0x10^{-3}$ mol) in CH_3OH (70 mL), and undergo hydrogenation at 150°C and 4 atm. The mixture was stirred for 10 hr then leave at ambient temperature and the metal catalyst was removed through celite filtration. After dryness, without purification, the crude product was used for the consecutive cyclisation reaction using xylene and refluxed for 20 hr. Upon completion, the solution was cooled and concentrated, later washed with *n*-C_5H_{12}. The filtrate was concentrated in which the resulting oily crude was chromatographed using 100% EtOAc as a solvent system to afford the 4-(4-Methoxyphenyl)-1,5-Dimethylhexahydropyrrolo[3,4-b] Pyrrole-2,6-Dione **3** as a brownish liquid. Yield 23%. ^{1}H and ^{13}C NMR Data refer **Table 01**. IR ν cm^{-1}: 1692, 1613. QTOF-MS *m/z*: 275 $[M+1]^+$ (calculated for $C_{15}H_{18}N_2O_3$).

6. Findings

Among a list of the produced reaction products of our prior work (Mohammat et al., 2012), compound **1a** and **1b** were nominated. After an effort to reductive amination (Hosseini et al., 2007) of **1a** unsuccessful, a substitute chemical transformation was then engaged *via* two-steps approaches: (1) nucleophilic addition and (2) reduction of amine intermediate. A 94% yield of enamine **4** was effectively synthesized *via* nucleophilic addition of **1a** using $NH_4^+HCOO^-$ in EtOH (Philip & George, 1963). The formation of enamine is predominant due to similar chemical environment of the enolic form of **1** that allowed the tautomerization to take place. On the subsequent step, a reduction of C_3=C_4 to C_3-C_4 bond either *via syn* hydrogenation or common metal hydrides however still failed to afford the targeted amine.

The coupling reaction between **4** with methyl malonyl chloride effectively afforded compound **5** in 92% yield. Dieckmann cyclisation of compound **5** using strong (NaH) and moderate (NaOEt) bases in different attempts was then attempted. An α proton will be removed by the base to produce the stable

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enolate in which later attacks the opposite-end-carbonyl of ester group which eventually form cyclisation product. Unfortunately, the targeted *δ*-lactam ring moiety failed to be formed because of the trigonal planar molecular geometry (the atoms are as far apart as possible) between C_3=C_4 bond and the CO ester of *γ*-lactam ring. Besides, a competition between available acidic protons to be abstracted by a base also matter. Consequently, heterogeneous hydrogenation of **5** was then applied to give an intermediate unsaturated amine **6**. The effect of solvents (ethanol and acetic acid) on the selectivity of *syn* hydrogenation of **5** was considered. Supplying a H_2 to compound **5** in EtOH failed to reduce the C_3=C_4 bond even with the assistance of external circumstances such as higher pressure or temperature. However, by using CH_3COOH as the solvent, the desired secondary amine-ester **6** was effectively materialized in 65% yield. In the latter effort, CH_3COOH was expected to stimulate the process of hydrogenolysis (Rylander, 1985) *via* NH protonation (Wen & Lei, 2012). The finishing step via Dieckmann cyclization of **6** using appropriate freshly prepared bases, NaH and NaOEt provided the essential bicyclic fused 6,5-lactam **2** in 64% and 85% yields, respectively. Its ^{1}H-NMR spectrum reveals the absence of ethyl ester group in compound **2** that originally present in amine **6**.

Table 01 confirms the presence of enol tautomer of compound **2** by the signals of C_8 and C_9 quaternary carbons. An intramolecular cyclisation of targeted fused ring lactam was indicated by the multiplicity pattern of methane (-CH) protons at H-3 and H-4 positions.

Table 01. ^{1}H and ^{13}C NMR analysis for compounds 2 and 3

Position	**^{13}C (ppm)**		**^{1}H (*mult*., Σ**H**))**	
	2 ($CDCl_3$)	**3** (MeOD)	**2 (**$CDCl_3$)	**3** (MeOD)
1-N	27.70	28.24	2.57 (*s*, 3H)	2.52 (*s*, 3H)
2	171.99	170.89	-	-
3	54.96	65.65	3.78-3.79 (*d*, 1H)	3.35-3.37 (*d*, 1H)
4	52.37	41.86	3.32-3.36 (*m*, 1H)	2.52-2.54 (*m*, 1H)
5	65.06	69.35	4.66-4.68 (*d*, 1H)	4.02-4.04 (*d*, 1H)
6-N	-	51.65	-	3.47 (*s*, 3H)
7	172.01	173.16	-	-
8	168.53	35.79	-	2.37-2.45 (*m*, 2H)
9	171.28	-	-	-
10	167.50	-	-	-
OCH_3	51.29	55.42	3.69 (*s*, 3H)	3.80 (*s*, 3H)
1’	138.40	130.53	-	-
2’	128.60	114.43	7.35-7.42 (*m*, 5H)	6.88-6.91 (*d*, 2H)
3’	128.44	128.62		7.10-7.12 (*d*, 2H)
4’	127.67	159.81		-
5’	128.44	128.62		7.10-7.12 (*d*, 2H)
6’	128.60	114.43		6.88-6.91 (*d*, 2H)

In short, the five-steps pathway successfully synthesize the targeted fused lactam **2** from **1a** with an overall yield of 21% (**Figure 01**).

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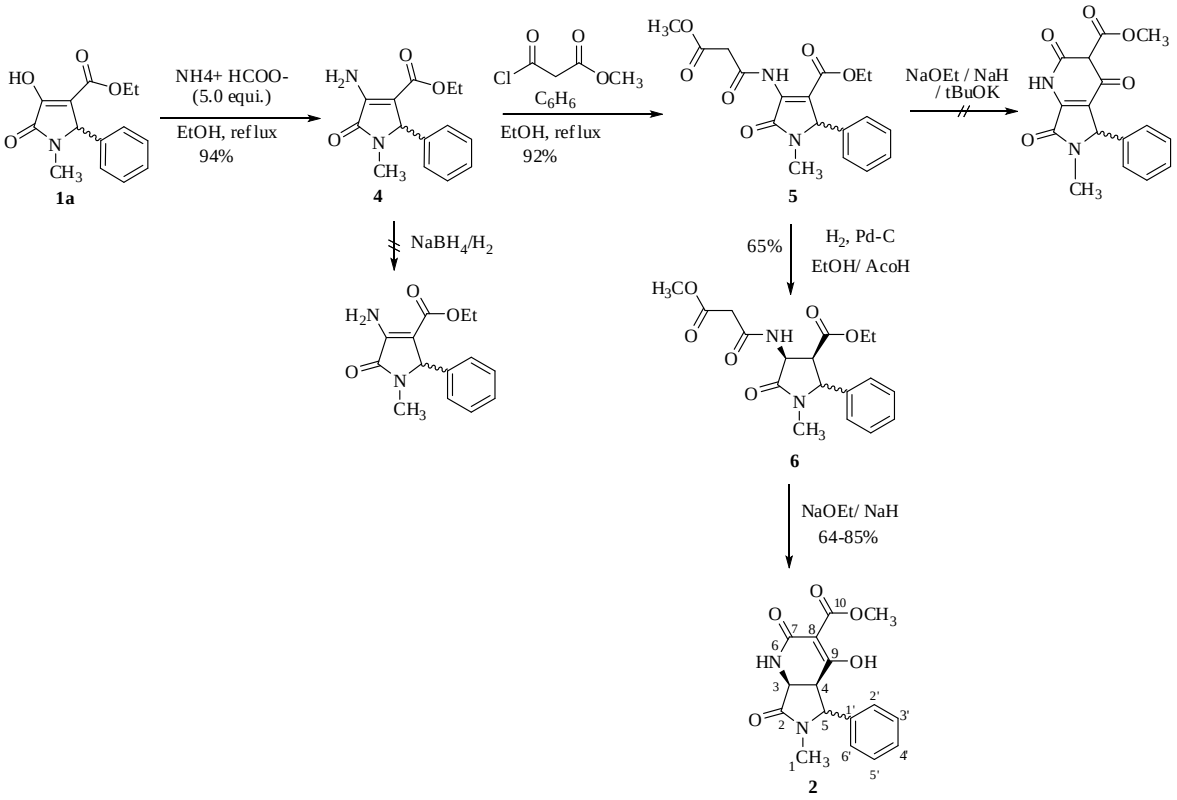

Figure 01. Five-steps preparation of 6,5-lactam 2

Compared to 6,5-lactam ring system that need the CO functionality at C_4 position, the synthesis of 5,5-lactam ring system is likely contrariwise. The elimination of ethyl ester group at C_4 position and the replacement by ethyl acetyl group are essential prior to intramolecular cyclisation step. A *C*-alkylation using weak, moderate and strong bases were unsuccessful; instead the *O*-alkylation reaction product was dominated. Thus, the deethoxycarbonylation is critically needed with the aim of removing the present ethyl ester group prior introduction of new ethyl acetyl substituent at that C_4 carbon. Compound **7** was obtained in 75% yield and used directly in second tries of *C*-alkylation using LiHMDS/HMPA as a base. However, very low yield of targeted compound was collected. Since there is an insufficient amount of compound **8** for the subsequent synthesis step, the *C*-alkylation of **7** was withdrawn and the enamine chemistry was then proceed. The conversion of **7** to its corresponding enamine gave the quantitative yield of product. This enamine crude was later subjected to alkylation reaction followed by hydrolysis to reform the keto functionality of compound **8** in 43% yield.

The nucleophilic addition reaction was designed for a next step by treating **8** with $NH_2OH{\cdot}HCl$ and $BnNH_2$ to give hydroxyl-imine **10** and *N*-benzylated enamine **9** in 94% and 99% yields, respectively. The reduction of enamine **9** into its amine were definitely unsuccessful, instead recovery of starting material and cleavage of Bn group were obtained. In the meantime, the heterogeneous hydrogenation of **10** in CH_3OH followed by subsequent cyclisation (Zhang *et al.*, 2015) under reflux successfully yielded targeted fused 5,5-lactam **3** in 23% yield. Similar multiplicity pattern was also detected in NMR spectra of compound **3** (**Table 01**).

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In brief, fused lactam **3** was well synthesized with an overall yield of 4% in the six-steps pathway (**Figure 02**).

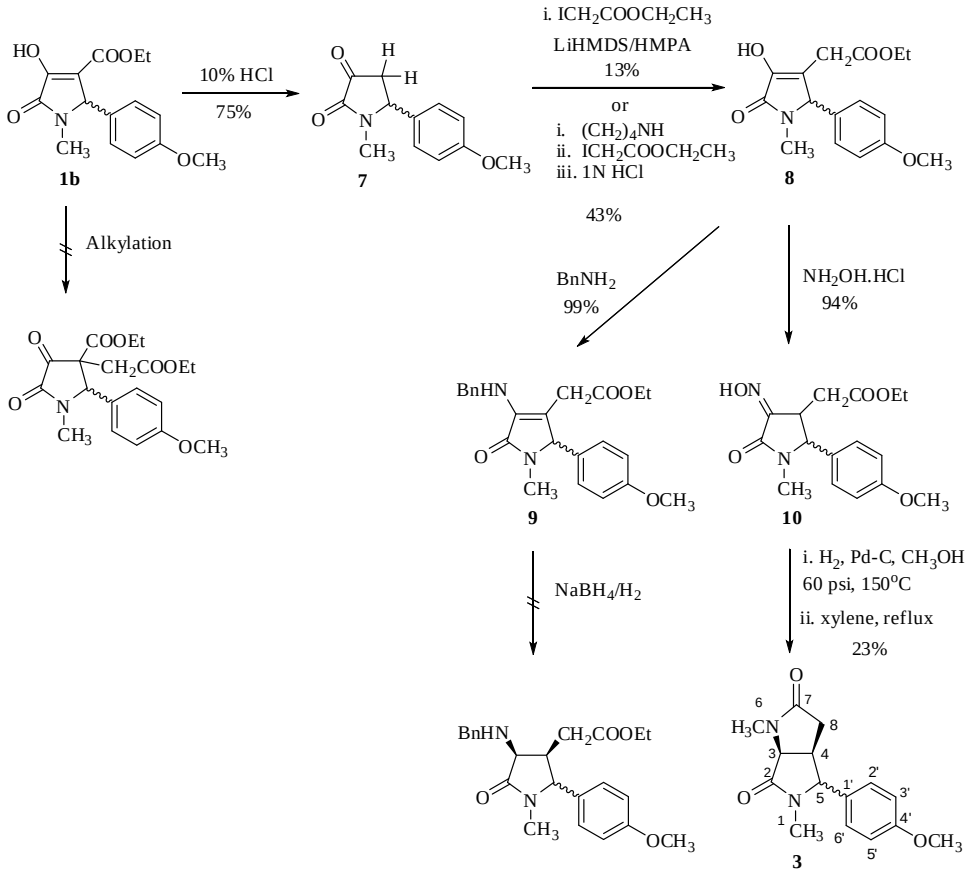

Figure 02. Six-steps preparation of 6,5-lactam 3

7. Conclusion

Both bicyclic fused 6,5- and 5,5-lactams were successfully produced and reported for the first time from highly substituted and accessible 2,3-dioxo-5-(substituted)arylpyrroles. Both synthetic methodologies require *syn* hydrogenation of imine/enamine analogue.

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References

Buccafusco, J. J., & Terry, A. V. (2009). A Reversible Model of the Cognitive Impairment Associated with Schizophrenia in Monkeys: Potential Therapeutic Effects of Two Nicotinic Acetylcholine Receptor Agonists. *Biochemical Pharmacology*, *78*(7), 852-662.

Campbell, J. B., Dedinas, R. F., & Trumbower-Walsh, S. (2010). Preparation of Isoindolones by a Lithium-Iodide Exchange-Induced Intra-molecular Wurtz-Fittig Reaction of *O*-Iodobenzoyl Chloride/Imine Adducts. *Synlett*, 3008-3010.

Cheung, L. L. W., & Yudin, A. K. (2006). Synthesis of Aminocyclobutanes through Ring Expansion of *N*-Vinyl-*β*-Lactams. *Org. Lett.*, *11*(6), 1281-1284.

Dahaen, W., Metten, B., Kostermans, M., Baelen, G. V., & Smet, M. (2006). Synthesis of 5-aryl-2-oxopyrrole Derivatives as Synthons for Highly Substituted Pyrroles. *Tetrahedron*, *62*, 6018-6028.

Grizzell, J. A., & Echeverria, A. (2014). New Insights into the Mechanisms of Action of Cotinine and Its istinctive Effects from Nicotine. *Neurochemical Research*, *40*, 2032-2046.

Hameed, S., & Akhtar, T. (2011). Recent Advances in the Synthesis of Five-Membered Heterocycles. *Current Organic Chemistry*, *15*, 694 -711.

Hosseini, M., Grau, J. S., Sorenson, K. K., Sotofte, I., Tanner, D., Murray, A., & Tonder, J. E. (2007). Short and efficient diastereoselective synthesis of pyrrolidinone-containing dipeptideanalogues. *Org. Biomol. Chem*., *5*, 2207-2210.

Huang, Z. T., & Liu, Z. R. (1989). Alkylation of Heterocyclic Ketene Aminals with Benzyl Chloride and Ethyl Bromoacetate. Synthesis of Heterobicycles Containing *γ*-Lactam-Fused Diazaheterocycles. *Eur. J. Inorg. Chem.*, *122*(1), 95-100.

Kumar, I., & Rode, C. V. (2007). Efficient Synthesis of Fused 1,2,3-Triazolo-Delta-Lactams Using Huisgen [3+2] Dipolar Cycloaddition-Click-Chemistry‖ In Water. *Chem. Lett*., *36*(5), 592-593.

Li, Q. H., Tong, M. C., Li, M. C., Tao, J. H. Y., & Wang, C. J. (2011). Asymmetric construction of trifluoromethylated pyrrolidines *via* Cu(I)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with 4,4,4-trifluorocrotonates. *Chem. Commun.*, *47*, 11110-11112.

Majumdar, K. C., Muhuri, S., Islam, R. U. and Chattopadhyay, B. (2009). Synthesis of Five- and Six-Membered Heterocyclic Compounds by the Application of the Metathesis Reactions. *Heterocycle, 78*(5), 1109-1169.

Mohammat, M. F., Najim, N., Mansor, N. S., Sarman, S., Shaameri, Z., & Hamzah, A. S. (2012). Synthesis and bioactivity of some 2-oxo-5-aryl-3-hydrazone and 2-oxo-5-aryl-4-hydrazone pyrrolidine derivatives. *ARKIVOV, IX*, 429-438.

Philip, L. S., & George, H. H. (1963). Compounds in the Pyrrolo[3,4-d] pyrimidine Series. Syntheses Based on 2,3-Dioxopyrrolidines. *J. Org. Chem.*, *28*(5), 1332-1336.

Rylander, P. N. (1985). *Hydrogenation Methods*. New York: Academic Press Inc. Ltd.

Song, C. E., Jung, D. U., Choung, S. Y., Roh, E. J., & Lee, S. G. (2004). The Employment of Hydrophobic Ionic Liquids Dramatically Enhanced the Activity of Metal Triflates in Friedel-Crafts Alkenylations of Aromatic Compounds with Various Alkyl- and Aryl-Substituted Alkynes. *Angew. Chem.*, *116*, 6309-6311.

Vergnon, A. L., Pottorf, R. S., Winters, M. P., & Player, M. R. (2004). Solid-Phase Synthesis of a 4-Substituted *γ*-Lactam Library. *J. Comb. Chem*., *6*(6), 903-910.

Wang, Z. Q., Feng, C. G., Xu, M. H., & Lin, G. Q. (2007). Design of *C2*-Symmetric Tetrahydropentalenes as New Chiral Diene Ligands for Highly Enantioselective Rh-Catalyzed Arylation of *N*-Tosylarylimines with Arylboronic Acids. *J. Am. Chem. Soc*., *129*(17), 5336-5337.

Wei, J., & Shaw, J. T. (2007). Diastereoselective Synthesis of *γ*-Lactams by a One-Pot, Four-Component Reaction. *Org. Lett*., *9*(20), 4077 – 4080.

Wen, Y., & Lei, F. (2012). Effect of Solvent Polarity Properties on the Selectivity and Activity for 3,4-Dichloronitrobenzene Hydrogenation over Pd/C Catalyst. *Advanced Materials Research, 396 – 398*, 2379 – 2383.

Zhang,L., Zhang, Y., Denga, Y., & Shi, F. (2015). Light-Promoted *N*, *N*-dimethylation of Amine and Nitro Compound with Methanol Catalyzed by Pd/TiO_2 at Room Temperature. *RSC Adv*., *5*, 14514-14521.