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Synthesis of novel 3,4-fused pyrazolidinone γ-lactam bicyclic moieties from 2,3-dioxo-4-carboxy-5-(substituted)pyrrolidines

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Abstract: A new pathway for the synthesis of novel 3,4-fused pyrazolidinone γ-lactam (**4**) starting from 2,3-dioxo-4-carboxy-5-(substituted)pyrrolidines (**1**) was developed. The key synthetic strategy involved hydrazonation of the precursor **1** followed by subsequent reduction reaction of the enamino ester **2** and intramolecular cyclization reaction to furnish the unprecedented 3,4-fused pyrazolidinone γ-lactam (**4**) in reasonable yield. The structures were confirmed by spectroscopic methods and chemical transformation.

Keywords: Pyrazolidinone γ-lactam; pyrazolidinone; pyrrolidinone; bicyclic γ-lactam.

1. Introduction

The importance of pyrrolidinone ring system has increased over the last decade due to their varied reactivity, physiological and biological significance.[1-5] They also have emerged as useful building block for many natural products and bioactive molecules. For the past few years, our research interest has been devoted to the chemistry of this class of molecules.[6-9] Owing to their dense functionality and interesting structure diversity, these molecules might be further manipulated towards polysubstituted pyrrolidinones such as fused pyrazole-lactam, lactam-lactam, lactone-lactam and oxazolidine-lactam ring system.[9-11]

Meanwhile, heterocycles containing pyrazole ring also display wide applicability in industrial processes and biological activities.[12-14] Despite their rare occurrence in natural compounds, they have been used numerously in various applications and their chemistry is still continuing studied by many researchers.[15] Chemically, the reduced state of pyrazole is coined as pyrazoline or pyrazolidine. Pyrazolidinone which consist of pyrazolidine moiety are often generate from hydrazine hydrate with α,β-unsaturated carboxylic acid derivatives.

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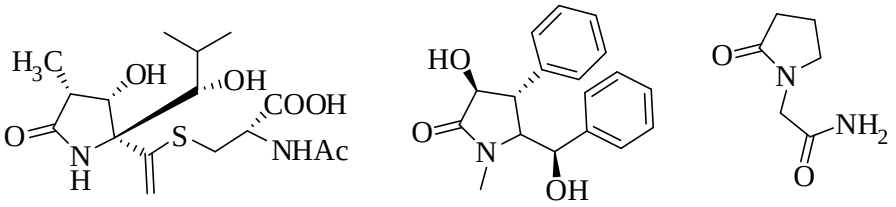
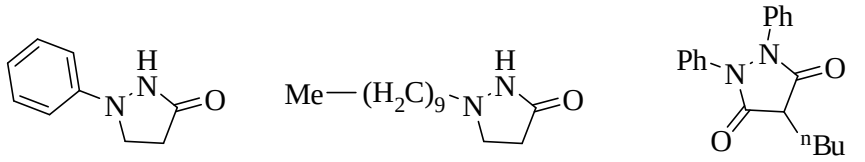
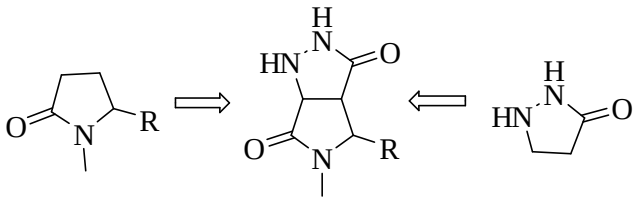
Prompted by their diverse biological properties, we were encouraged to develop synthetic strategies to synthesize molecule **C** having γ-lactam **A** and pyrazolidinone **B** functionality (Figure 1). Interestingly, there is very little attention has been reported on 3,4-fused pyrazolidinone γ-lactam.[16] Moreover, the combination of two different heterocylic rings on the same scaffold can lead to the hybrid molecules with more potent biologically activities compare to the individual molecules.[17] In connection with this, 3,4-fused pyrazolidinone γ-lactam which are fusion of two active pharmachores, are expected to be pharmacological interest.



Biologically active γ-lactam (pyrrolidinone)



Biologically active pyrazolidinone



Hybrid molecules comprising of pyrrolidinone and pyrazolidinone

Figure 1. Some example of biologically important pyrrolidinone and pyrazolidinone

2. Experimental

2.1 Chemical Material and Apparatus

All the reagents were supplied byMerck Chemical Co., Sigma-Aldrich Co. and Acros Organics Co. Melting points were recorded using an automatic FP62 melting point apparatus from Mettler Toled and are uncorrected. Infrared spectra (4000-400 cm^{-1}) were recorded on Varian 3100 Excalibur Series FT/IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Joel-400 (^{1}H400 MHz, ^{13}C 100 MHz) spectrometer. X-ray analysis was performed on APEXII Duo CCD area-detector diffractometer. The progress of the reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F254 and the spots were visualized with UV lamp (254 and365 nm).

2.2. Chemistry

*2.2.1. Synthesis of 2,3-dioxo-4-carboethoxy-5-(substituted)pyrrolidines (**1a-e**)*

This was carried out according to the literature.[6,7] Chemical analytical data are available in Supporting Information.

*2.2.2. Synthesis of 2-oxo-4-carboethoxy-5-substituted-3-hydrazinepyrrolines (**2**)*

2,3-Dioxo-4-carboxy-5-(substituted)pyrrolidine (1.0 equiv) was dissolved in 15 ml of ethanol and 35% hydrazine hydrate (1.1 equiv) was added. After heating under refluxed for 3 hours, the solvent was concentrated by rotary evaporator and the crude was dissolved in dichloromethane. The organic phase was then extracted with water and finally dried with $MgSO_4$. The solvents was concentrated *in vacuo* and the crude was chromatographed on silica gel (ethyl acetate/hexane) to furnish the product **2**.

*Ethyl 4-hydrazinyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**2a**)*: White solid; Yield: 0.42 g, 78%; m.p. 134-135°C; IR (KBr) 3343, 1760, 1698, 1192, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 2H, CH_2), 4.23 (q, *J*=7.2 Hz, 2H, OCH_2), 1.27 (t, *J*=7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.86, 163.58, 139.85, 114.12, 68.01, 61.30, 13.85 ppm.

*Ethyl 4-hydrazinyl-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**2b**):* White solid; Yield: 0.40 g, 74%; m.p. 138-139°C; IR (KBr) 3347, 1692, 1547, 1171, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, *J*=7.2 Hz, 2H, OCH_2), 3.94 (s, 2H, CH_2), 3.01 (s, 3H, NCH_3), 1.25 (t, *J*=7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.32, 164.00, 151.38, 100.08, 59.93, 49.03, 29.71, 14.47 ppm; CHN: Found C, 48.35; H, 6.97; N, 20.45 requires C, 48.23; H, 6.58; N, 21.09 %.

*Ethyl 4-hydrazinyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**2c**):* Yellow oil; Yield: 0.37 g, 70%; IR (KBr) 3405, 1691, 1624, 1078, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, *J*=7.0 Hz, 2H, OCH_2), 3.99 (q, *J*=6.4 Hz, 1H, CH-5), 2.90 (s, 3H, NCH_3), 1.30 (d, *J*=6.4 Hz, 3H, CH_3), 1.24 (t, *J*=7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.83, 163.57, 157.18, 112.96, 59.63, 55.39, 27.26, 18.01, 14.53 ppm.

*Ethyl 2-ethyl-4-hydrazinyl-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**2d**):* Dark yellow solid; Yield: 0.48 g, 91%; m.p. 147-148°C; IR (KBr) 3316, 1682, 1581, 1149, 760 cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ 4.21-4.09 (m, 2H, OCH_2), 4.15 (t, *J*=7.2 Hz, 1H, CH-5) 2.91 (s, 3H, NCH_3), 2.12-2.08 (m, 1H, CH_2), 1.87-1.84 (m, 1H, CH_2), 1.26 (t, *J*=7.1 Hz, 3H, CH_3), 0.47 (t, *J*=7.3 Hz, 3H, $CH_2C\underline{H}_3$) ppm; ^{13}C NMR (100 MHz, MeOD) δ 171.65, 164.23, 163.87, 109.74, 58.53, 58.27, 26.33, 21.03, 13.64, 4.16 ppm; CHN: Found C, 50.57; H, 7.83; N, 17.30 requires C, 52.85; H, 7.54; N, 18.49 %.

*Ethyl 4-hydrazinyl-2-(4-methoxyphenyl)-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**2e**):* Yellow oil; Yield: 0.45 g, 86%; IR (KBr) 3337, 1683, 1609, 1088, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J*=8.5 Hz, 2H, CHAr), 6.81 (d, *J*=8.2 Hz, 2H, CHAr), 4.93 (s, 1H, CH-5), 4.07 (q, *J*=7.0 Hz, 2H, OCH_2), 3.74 (s, 3H,OCH_3), 2.74 (s, 3H, NCH_3), 1.08 (t, *J*=7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.90, 164.08, 159.89, 157.03, 128.82, 126.13, 114.22, 112.92, 62.29, 60.92, 55.34, 27.64, 14.03 ppm.

*2.2.3. Synthesis of 2-oxo-4-carboethoxy-5-substituted-3-hydrazinepyrrolidines (**3**)*

Pd/C (10% wt) (0.1 equiv) was added to a suspension of 2-oxo-4-carboethoxy-5-substituted-3-hydrazinepyrroline (**2**) (1.0 eqiuv) in acetic acid. The reaction mixture was stirred vigorously under hydrogen atmosphere for 12 hours. The catalyst was filtered out and the filtrate was dried under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane) to furnish the target product **3**.

*Ethyl 4-hydrazinyl-5-oxopyrrolidine-3-carboxylate (**3a**):* Light yellow oil; Yield: 0.38 g; 95%; IR (KBr) 3289, 1721, 1685, 1190, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (d, *J*=7.8 Hz, 1H, CH-3), 4.48 (dd, *J*=9.6, 2.3 Hz, 1H, CH-5), 4.34 (dd, *J*=9.8, 6.2 Hz, 1H, CH-5), 4.17 (q, *J*=7.2 Hz, 2H, OCH_2), 3.54-3.50 (m, 1H, CH-4), 1.22 (t, *J*=7.1 Hz, 3H, CH_3) ppm; ^{13}CNMR (100 MHz, $CDCl_3$) δ 175.71, 170.12, 68.25, 66.60, 61.88, 45.92, 14.09 ppm.

*Ethyl 4-hydrazinyl-1-methyl-5-oxopyrrolidine-3-carboxylate (**3b**):* Light yellow oil; Yield: 0.61 g, 60%; IR (KBr) 3265, 1729, 1692, 1194, 732 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 4.44 (d, *J*=7.3 Hz, 1H, CH-3), 4.18-4.12 (q, *J*=6.8 Hz, 2H, OCH_2), 3.65 (dd, *J*=9.4, 3.4 Hz, 1H, CH_2), 3.44 (dd, *J*=17.2, 7.6 Hz, 1H, CH_2), 3.45-3.39 (m, 1H, CH-4), 2.85 (s, 3H, NCH_3), 1.24 (t, *J*=7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 172.92, 170.67, 70.26, 60.68, 48.10, 43.44, 28.69, 13.16 ppm.

*Ethyl 4-hydrazinyl-1,2-dimethyl-5-oxopyrrolidine-3-carboxylate (all-cis **3c**) and (cis-trans **3c'**). all-cis* (**3c**): Light yellow oil; Yield: 0.11 g, 16%; IR (KBr) 3339, 1686, 1690, 1096, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (dd, *J*=6.4, 5.5 Hz, 1H, CH-3), 4.22-4.16 (m, 2H, OCH_2), 3.74 (p, *J*=6.8 Hz,1H, CH-5), 3.55 (d, *J*=5.5 Hz, 1H, NH), 3.38 (t, *J*=6.9 Hz, 1H, CH-4), 2.82 (s, 3H, NCH_3), 1.82 (s, 1H, NH), 1.30 (d, *J*=6.9 Hz, 3H, CH_3), 1.26 (t, *J*=7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ172.73, 169.60, 70.82, 61.12, 53.04, 49.20, 27.27, 15.20, 14.32 ppm; *cis-trans* (**3c'**): Yield: 0.16 g, 23%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 1H, NH), 4.55 (dd, *J*=8.7, 2.7 Hz, 1H, CH-3), 4.22-4.17 (m, 2H, OCH_2),3.58 (p, *J*=6.9 Hz, 1H, CH-5), 2.78 (s, 3H, NCH_3), 2.64 (t, *J*=8.5 Hz, 1H, H-4), 2.28 (s, 1H, NH), 1.34 (d, *J*=6.6 Hz, 3H, CH_3), 1.26 (t, *J*=7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.09, 171.57, 72.23, 61.60, 54.46, 54.44, 27.40, 19.23, 14.25 ppm; CHN: Found C, 51.92; H, 7.50 requires C, 50.22; H, 7.96 %.

*Ethyl 2-ethyl-4-hydrazinyl-1-methyl-5-oxopyrrolidine-3-carboxylate (all-cis **3d**) and (cis-trans**3d'**). all-cis* (**3d**): Light yellow oil; Yield: 0.10 g, 10%; IR (KBr) 2978, 1729, 1691, 1183, 800 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (d, *J*=6.9 Hz, 1H, CH-3), 4.23-4.14 (m, 2H, OCH_2), 3.53-3.50 (m, 1H, CH-5), 3.49-3.47 (m, 1H, CH-4), 2.84 (s, 3H, NCH_3), 2.00-1.90(m, 1H, CH_2), 1.65 (s, 2H, NH_2), 1.54-1.46 (m, 1H CH_2), 1.25 (t, *J*=7.1 Hz, 3H, CH_3), 1.00 (t, *J*=7.5 Hz, 3H, $CH_2C\underline{H_3}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.26, 169.47, 70.97, 61.24, 58.92, 48.44, 27.81, 22.24, 14.27, 9.95 ppm; *cis-trans* (**3d'**): Yield: 0.23 g, 23%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (br s, 1H, NH), 4.52 (d, *J*=8.2 Hz, 1H, CH-3), 4.24-4.15 (m, 2H, OCH_2), 3.61 (td, *J*=7.5, 3.2 Hz, 1H, CH-5), 2.79 (s, 3H, NCH_3), 2.77 (t, *J*=8.0 Hz, 1H, CH-4), 2.19 (br s, 2H, NH_2), 1.89-1.79 (m,1H, CH_2), 1.66-1.56 (m, 1H, CH_2), 1.26 (t, *J*=7.1 Hz, 3H, CH_3), 0.87 (t, *J*=7.3 Hz, 3H, $CH_2C\underline{H_3}$); ppm; ^{13}CNMR (100 MHz, $CDCl_3$) δ 172.80, 172.20, 72.82, 61.67, 59.40, 50.72, 27.82, 24.53, 14.23, 7.58 ppm.

*Ethyl 4-hydrazinyl-2-(4-methoxyphenyl)-1-methyl-5-oxopyrrolidine-3-carboxylate (all-cis **3e**) and (cis-trans **3e'**). all-cis* (**3e**): White solid; Yield: 0.12 g, 12%; m.p. 109-111°C; IR (KBr) 3258, 1736, 1692, 1184, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J*=8.7 Hz, 2H, CHAr), 6.84 (d, *J*=8.7 Hz, 2H, CHAr), 4.69 (d, *J*=7.8 Hz, 1H, CH-3), 4.54 (dd, *J*=3.4 Hz, 1H, CH-5), 3.86-3.70 (m, 2H, OCH_2), 3.77 (s, 3H, OCH_3), 3.58 (t, *J*=7.5 Hz, 1H, CH-4), 2.71 (s, 3H, NCH_3), 0.89 (t, *J*=7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.40, 169.67, 159.97, 129.25, 126.88, 114.03, 70.48, 62.82, 61.11, 55.40, 49.29, 28.87, 13.76 ppm; *cis-trans* (**3e'**): Yield: 0.26 g, 26%;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J*=8.7 Hz, 2H, CHAr), 6.87 (d, *J*=8.7 Hz, 2H, CHAr), 4.65 (d, *J*= 8.2 Hz, 1H, CH-3), 4.53 (d, *J*=7.8 Hz, 1H, CH-5), 4.14- 4.12 (m, 2H, OCH_2), 3.77 (s, 3H, OCH_3), 3.01 (t, *J*=8.2 Hz, 1H, CH-4), 2.58 (s, 3H, NCH_3), 1.17 (t, *J*=7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ173.57, 171.52, 160.03, 129.68, 128.77, 114.54, 72.58, 62.92, 61.57, 56.16, 55.38, 28.40, 14.21ppm.

*2.2.4. Synthesis of 2-oxo-5-substitutedpyrrolidines fused pyrazolidin-3-ones (**4**)*

2-Oxo-4-carboethoxy-5-substituted-3-hydrazinepyrrolidine (**3**) (1.0 equiv) in dry THF was treated with 60% NaH (3.5 equiv). The mixture was refluxed for 3 hours, cooled to room temperature and quenched with 0.1 M of HCl. The solid form was filtered out and the filtrate was rotavaped. The

crude product was purified by column chromatography on silica gel (EtOAc/MeOH 4:1) to give the final products as oil.

*Tetrahydropyrrolo[3,4-c]pyrazole-3,6-dione (**4a**):* Yield: 0.11 g, 58%; IR (KBr) 3397, 1718, 1136, 818 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 4.69 (d, *J*=7.8 Hz, 1H, CH-3), 4.48 (dd, *J*=9.6, 2.3 Hz, 1H, CH-5), 4.34 (dd, *J*=9.8, 6.2 Hz, 1H, CH-5), 3.50-3.54 (m, 1H, CH-4) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 178.74, 170.13, 68.25, 61.88, 45.92 ppm.

*5-Methyltetrahydropyrrolo[3,4-c]pyrazole-3,6-dione (**4b**):* Yield: 0.05 g, 60%; IR (KBr) 3347, 1694, 1635, 1078, 739 cm^{-1}; 1H NMR (400 MHz, CD_3OD) δ 4.45 (d, *J*=8.2 Hz, 1H, CH-3), 3.67-3.56 (m, 1H, CH_2), 3.49-3.3 (m, 1H, CH_2), 3.04 (q, *J*=8.7 Hz, 1H, CH-4), 2.84 (s, 3H, NCH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 173.45, 172.27, 72.14, 47.23, 46.53, 28.80 ppm.

*4,5-Dimethyltetrahydropyrrolo[3,4-c]pyrazole-3,6-dione (all-cis **4c**) and (cis-trans **4c'**). all-cis* (**4c**): Yield: 0.03 g, 34%; IR (KBr) 3435, 1678, 1578, 1078, 655 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 4.45 (d, *J*=9.65 Hz, 1H, CH-3), 3.77 (p, *J*=6.4 Hz,1H, CH-5), 3.33 (t, *J*=6.6 Hz, 1H, CH-4), 2.80 (s, 3H, NCH_3), 1.32 (d, J = 6.9 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 174.07, 173.22, 70.26, 52.46, 49.60, 25.86, 13.65 ppm; *cis-trans* (**4c'**): Yield: 0.03 g, 32%; ^{1}H NMR (400 MHz, CD_3OD) δ 4.45 (d, *J*=8.7 Hz, 1H, CH-3), 3.57-3.62 (m, 1H, CH-5), 2.80 (s, 3H, NCH_3), 2.54 (t, *J*=8.2 Hz, 1H, CH-4), 1.37 (d, *J*=6.4 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 173.36, 173.21, 72.17, 54.90, 54.44, 26.30, 18.17 ppm.

*4-Ethyl-5-methyltetrahydropyrrolo[3,4-c]pyrazole-3,6-dione (all-cis **4d**) and (cis-trans **4d'**). all-cis* **(4d)**: Yield: 0.04 g, 45%; IR (KBr) 2919, 1620, 1596, 1103, 674 cm^{-1};^{1}H NMR (400 MHz, CD_3OD) δ 4.43 (d, *J*=7.8 Hz, 1H, CH-3), 3.63 (td, *J*=7.2, 2.9 Hz, 1H, CH-4), 2.79 (s, 3H, NCH_3), 2.67 (t, *J*=7.5 Hz, 1H, CH-5), 1.94-1.84 (m, 1H, CH_2), 1.72-1.61 (m, 1H, CH_2), 0.89 (t, *J*=7.3 Hz, 3H, $CH_2C\underline{H_3}$) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 174.03, 173.52, 72.74, 59.73, 51.11, 26.83, 24.07, 6.46 ppm; *cis-trans* **(4d')**: Yield: 0.04 g, 46%; ^{1}H NMR (400 MHz, CD_3OD) δ 4.43 (d, *J*=7.8 Hz, 1H, CH-3), 3.63 (td, *J*=7.3, 3.2 Hz, 1H, CH-4), 2.79 (s, 3H, NCH_3), 2.68 (t, *J*=7.8 Hz, 1H, CH-5), 1.94-1.84 (m, 1H, CH_2), 1.61-1.72 (m, 1H, CH_2), 0.89 (t, *J*=7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 174.06, 173.53, 72.73, 59.53, 51.09, 26.86, 24.08, 6.48 ppm.

*4-(4-Methoxyphenyl)-5-methyltetrahydropyrrolo[3,4-c]pyrazole-3,6-dione (all-cis **4e**) and (cis-trans **4e'**). all-cis* (**4e**): Yield: 0.03 g, 29%; IR (KBr) 3447, 1682, 1645, 1197, 699 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (d, *J*=8.2 Hz, 2H, CHAr), 6.94 (d, *J*=8.2 Hz, 2H, CHAr), 4.55 (d, *J*=8.8 Hz, 1H, CH-3), 4.54 (t, *J*=8.8 Hz, 1H, CH-5), 3.78 (s, 3H, OCH_3), 2.88 (t, *J*=8.5 Hz, 1H, CH-4), 2.55 (s, 3H, NCH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 173.60, 173.05, 160.24, 129.92, 128.57, 114.16, 72.54, 62.66, 56.82, 54.46, 27.27 ppm; *cis-trans* (**4e'**): Yield: 0.03 g, 32%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (d, *J*=8.2 Hz, 2H), 6.94 (d, *J*=8.2 Hz, 2H), 4.55 (d, *J*=8.0 Hz, 1H, CH-3), 4.54 (d, *J*=8.8 Hz, 1H, CH-5), 3.78 (s, 3H, OCH_3), 2.88 (t, *J*=8.5 Hz, 1H, CH-4), 2.55 (s, 3H, NCH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 173.58, 173.06, 160.25, 129.94, 128.55, 114.15, 72.54, 62.67, 56.82, 54.45, 27.24 ppm.

*2.2.5. Synthesis of ethyl 3-substituted-5-methylcarbamoyl-1H-pyrazole-4-carboxylate (**5**)*[19]

35% Hydrazine hydrate (1.1 equiv) was added to a solution of 2,3-dioxo-4-carboxy-5-(subtituted)pyrrolidines (**1**) (1.0 equiv) and 15 ml of acetic acid. The mixture was heated under reflux for 3 hours. The solvent was evaporated and the crude product was chromatographed to afford compound **5** and **6**.

*Ethyl 3-ethyl-5-(methylcarbamoyl)-1H-pyrazole-4-carboxylate (**5d**):* Light yellow oil; Yield: 0.05 g, 10%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (q, *J*=7.0 Hz, 2H, OCH_2), 3.17 (s, 3H, NCH_3), 2.97 (q, *J*=7.6 Hz, 2H, CH_2), 1.33 (t, *J*=7.1 Hz, 3H, CH_3), 1.23 (t, *J*=7.5 Hz, 3H, $CH_2C\underline{H_3}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.49, 162.60, 159.73, 132.82, 101.45, 60.20, 25.91, 19.87, 14.32, 12.26 ppm.

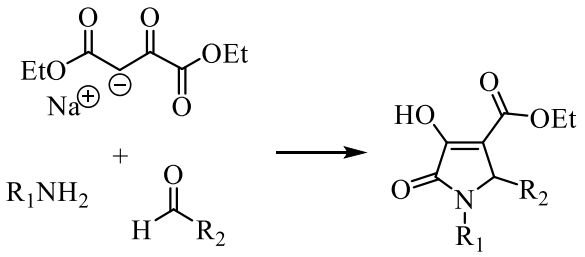
*Ethyl 4-amino-2-ethyl-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**6d**):* Light yellow solid; Yield: 0.05 g, 10%; m.p. 92-94°C;IR (KBr) 3438, 3284, 1708, 1674, 1628, 1262, 1092 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17-4.28 (m, 3H, OCH_2+CH-5), 2.95 (s, 3H, NCH_3), 2.13 (m, 1H, CH_2), 1.83 (m, 1H, CH_2), 1.30 (t, *J*=7.1 Hz, 3H, CH_3), 0.50 (t, *J*=7.3 Hz, $CH_2C\underline{H}_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.56, 165.20, 147.11, 101.03, 59.88, 59.77, 27.32, 21.42, 14.60, 5.59 ppm.CHN: Found C, 56.57; H, 7.48; N, 12.59 requires C, 56.59; H, 7.60; N, 13.20 %.

*Ethyl 3-(4-methoxyphenyl)-5-methylcarbamoyl-1H-pyrazole-4-carboxylate (**5e**):* Orange solid; Yield: 0.03 g, 5%; IR (KBr) 3304, 1196 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (br s, 1H, NH), 7.43 (d, *J*=8.7 Hz, 2H, CHAr), 6.91 (d, *J*=9.1 Hz, 2H, CHAr), 4.18 (q, *J*=7.2 Hz, 2H, OCH_2), 3.84 (s, 3H, OCH_3), 3.04 (d, *J*=4.6 Hz, 3H, NCH_3), 1.10 (t, *J*=7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.03, 159.96, 158.80, 154.84, 140.45, 130.94, 125.51, 113.19, 108.65, 61.54, 55.41, 26.43, 13.76 ppm.

*Ethyl 4-amino-2-(4-methoxyphenyl)-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**6e**):* Colourless solid; Yield: 0.04 g, 8%; m.p. 151-153°C;IR (KBr) 3409, 3310, 1678, 1643, 1238, 1093 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J*=8.7 Hz, 2H, CHAr), 6.83 (d, *J*=8.7 Hz, 2H, CHAr), 4.92 (s, 1H, CH-5), 4.01-4.09 (m, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 2.76 (s, 3H, NCH_3), 1.11 (t, *J*=7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.43, 164.93, 159.58, 146.08, 128.82, 128.51, 113.98, 104.25, 63.81, 59.71, 55.33, 27.59, 14.31 ppm.CHN: Found C, 61.17; H, 6.24; N, 9.48 requires C, 62.06; H, 6.25; N, 9.65 %.

3. Results and Discussion

Previously, our group had reported that the initial starting compound; 2,3-dioxo-4-carboxy-5-(substituted)pyrrolidines (**1**) could be synthesized by refluxing equimolar amounts of diethyl oxalacetate, aldehyde and primary amine[6,7] (Scheme 1). Although the yield was not excellent, the product could be easily isolated without the need of any purification process.

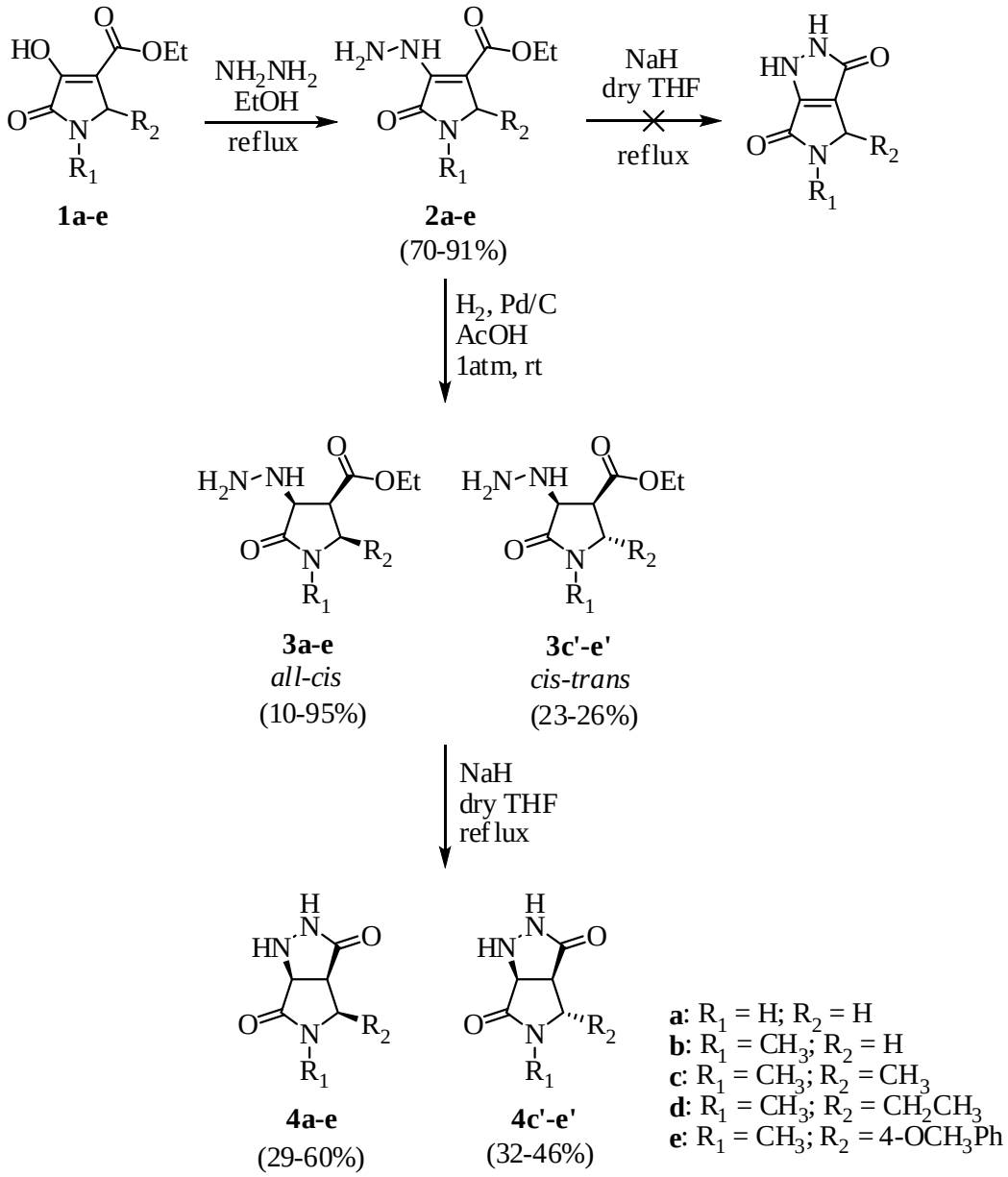


1a-e

Scheme 1. Synthesis of 2,3-dioxo-4-carboxy-5-(substituted)pyrrolidines (**1**)

Subsequently, the treatment of **1** with hydrazine in ethanol under reflux condition gave the pyrrolyl hydrazine **2** in good yields (Scheme 2). Various attempts on direct cyclization of **2** using different bases were failed probably due to the delocalization of lone pair *N*-hydrazine that deactivate keto ester function.

In parallel, the reduction of pyrrolyl hydrazine **2** is essential to subsequently carry out intramolecular cyclization. The reduction of enamino ester **2** *via syn*-hydrogenation using Pd/C as a catalyst gave chiral hydrazine γ-lactam **3** (Scheme 2). Eventually, by treatment with NaH in dry THF, the bicyclic compounds **4** were obtained in moderate yield.



Scheme 2. Synthesis of 3,4-fused pyrazolidinone γ-lactam (**4a**-**4e**)

High diastereoselectivity can be seen with compound **2a** and **2b** (free C-5 substituent), which yielded the *all-cis* **3a** and **3b** as the sole amine γ-lactam product (de= 100:0) (Table 1). However, diastereoselection decreased as the steric effect of C-5 substituent increase, which gave rise to the mixture of diastereomers with *cis-trans* configuration as a major product. This observed stereoselectivity was contradicted with what we would predict before, based on steric hindrance.[8] We assumed that, the hydrazine group repelled the ester group and influenced the *trans* configuration at C-5 position. The similar observation was also disclosed by Wang *et al*. during hydrogenation of 3-aminoesterpyrrolidine.[18]

Table 1. Stereoselective reduction **3a-e**

Compound	R_1	R_2	Yield (3a-e) (%)	Yield (3c'-e') (%)	dr*
2a	H	H	95	-	100:0
2b	CH_3	H	85	-	100:0
2c	CH_3	CH_3	16	23	41:59
2d	CH_3	CH_2CH_3	10	23	30:70
2e	CH_3	4-OCH_3Ph	12	26	32:68

*Diastereomeric ratio was based on the isolated yield after column chromatography

All the diastereomers were confirmed by ^{1}H NMR and 2D NMR experiments. For example, the NOESY spectrum of the major product **3e'** (*cis-trans*) showed that the proton at C-4 (3.01 ppm) is located at the same side of the aryl proton (7.17 ppm) (Figure 2). Besides, the proximity of this proton and the aryl proton was confirmed by the low proton signal of C-4 (3.01 ppm) in ^{1}H NMR spectrum which is due to the anisotropic effect of the ring current. The configuration of **3e'** (*cis-trans*) also supported by large $J_{4,5}$ coupling constant value compared to the *all-cis* **3e** (Table 2). Meanwhile, the NOESY spectrum of minor product **3e** (*all-cis*) showed no correlation between proton signal at C-4 (3.58 ppm) and aryl proton (7.17 ppm). It can be assumed that this proton is located on opposite side of the aryl ring and assign as all-cis structure **3e**. Moreover, the low shift values for ester function in ^{1}H NMR spectrum (in comparison with *cis-trans* **3e'**) also confirmed that the ester function and aryl ring are on the same side.

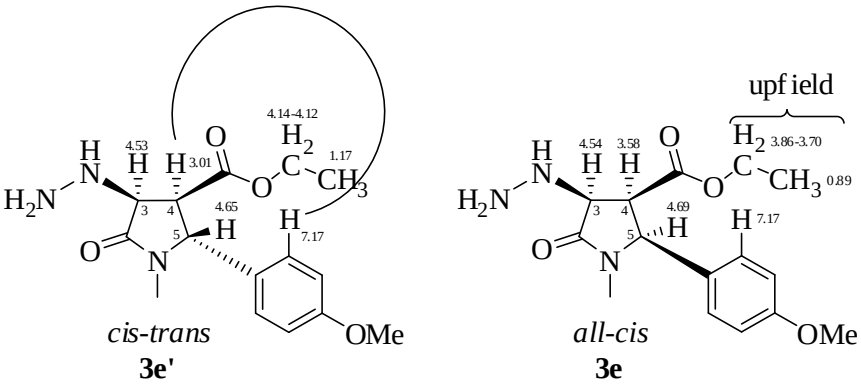


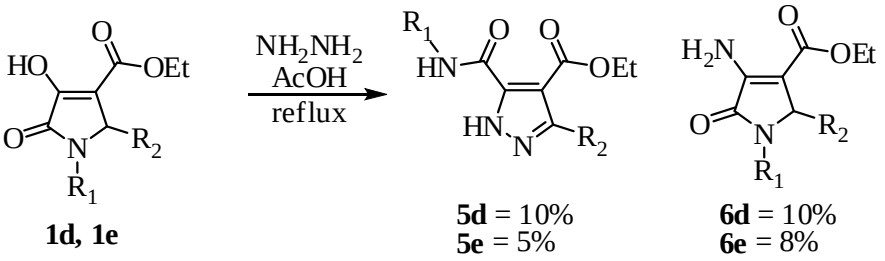
Figure 2. Diastereoisomers of **3e-3e'** obtained after hydrogenation of **2e** with H_2, Pd/C

Table 2. Selected ^{1}H NMR data for **3c-e** and **3c'-e'**

Compound	Shift value (ppm)			Coupling constant (*J* in Hz)		
	H-3	H-4	H-5	H-3	H-4	H-5
3c	4.43	3.38	3.74	6.4	6.9	6.8
3c'	4.55	2.64	3.58	8.7	8.5	6.9
3d	4.41	_*	_*	6.9	_*	_*
3d'	4.52	2.77	3.64	8.2	8.0	7.5
3e	4.69	3.58	4.54	7.8	7.5	3.4
3e'	4.65	3.01	4.53	8.2	8.2	7.8

*H-4 and H-5 give rise to a multiplet pattern

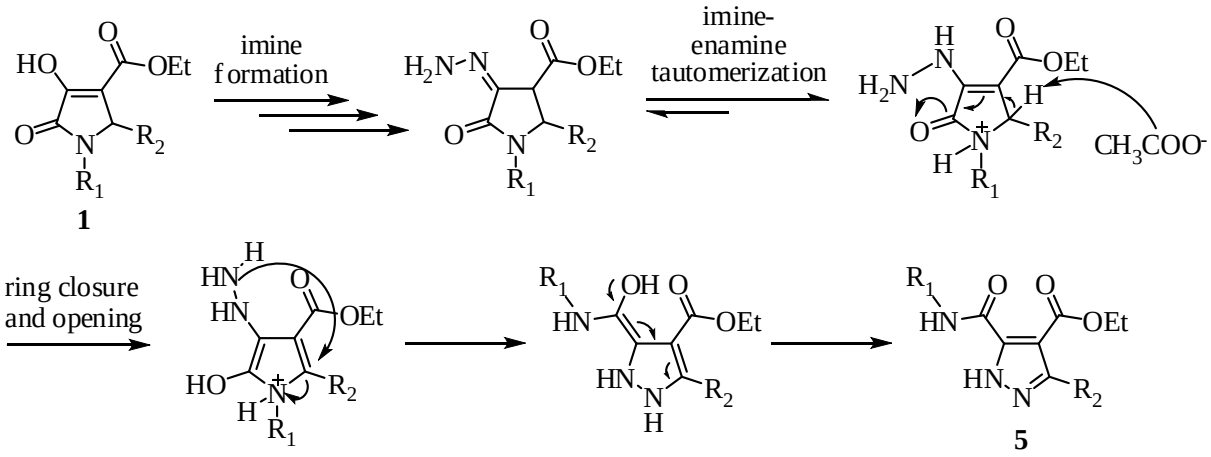
Interestingly, further optimization for the synthesis of pyrrolyl hydrazine **2** was conducted by changing the solvent to acetic acid in reflux condition[19] (Scheme 3). Unexpectedly, the reaction gave 3-(substituted)-4-carboxy-5-methylcarbamoylpyrazoles (**5**) together with 2-amino-3-oxo-4-carboxy-5-(substituted)pyrrolidines (**6**) in low yield. The by-products **6** may take place as side reaction prior to the reductive cleavage of hydrazine *N*-*N* bonds.[19,20] Besides, it was believed that in the presence of acetic acid, pyrrolidine ring undergo ring chain transformation to furnish the pyrazole type compound. To the best of our knowledge, this is the first report that synthesize substituted pyrazole from pyrrolidine ring chain transformation. Commonly, substituted pyrazole was synthesized either by condensation of hydrazines with 1,3-dicarbonyl or by intermolecular cycloaddition reaction of alkynes to 3-dipoles.[21]



d: $R_1 = CH_3$; $R_2 = CH_2CH_3$
e: $R_1 = CH_3$; R_2 = 4-OCH_3Ph

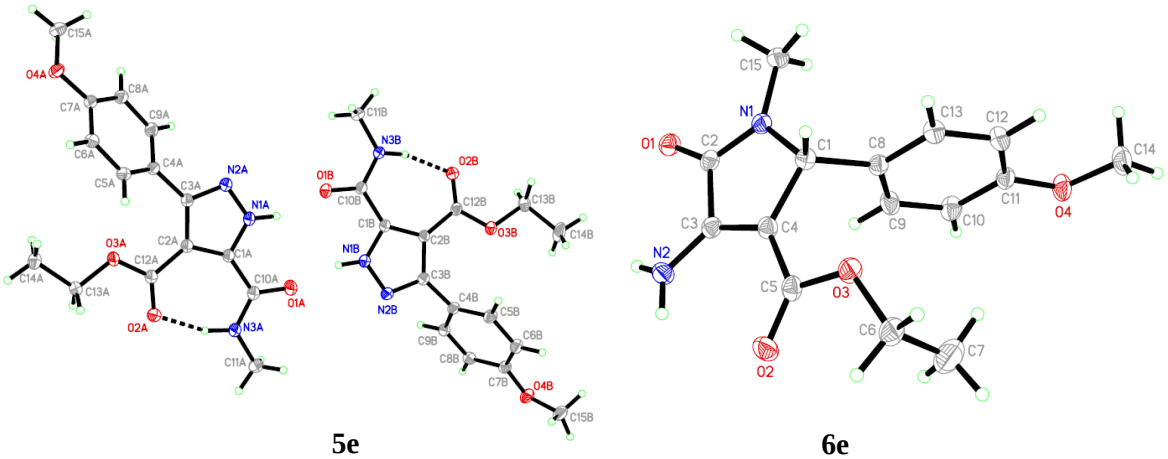
Scheme 3. Unprecedented synthesis of 3-(substituted)-4-carboxy-5-methylcarbamoylpyrazoles (**5**)

A plausible mechanism for the formation of 3-(substituted)-4-carboxy-5-methylcarbamoylpyrazoles (**5**) is proposed in Scheme 4. The processes proceed as domino reaction started from imine formation, ring closure and ring opening.



Scheme 4. A plausible mechanism for the **1**-to-**5** transformation

The product was confirmed to be 3-(substituted)-4-carboxy-5-methylcarbamoylpyrazoles (**5**) and 2-amino-3-oxo-4-carboxy-5-(substituted)pyrrolidines (**6**) by ^{1}H NMR, ^{13}C NMR and X-ray (for compounds **5e** and **6e** only) (Figure 3). Further study on this interesting finding currently in progress.



5e **6e**

Figure 3. X-ray structure of ethyl 3-(4-methoxyphenyl)-5-methylcarbamoyl-1*H*-pyrazole-4-carboxylate (**5e**) and 2-amino-3-oxo-4-carboxy-5-(4-methoxyphenyl)pyrrolidines (**6e**)

4. Conclusion

In conclusion, we have described a short and efficent method for the synthesis of novel 3,4-fused pyrazolidinone γ-lactam from 2,3-dioxo-4-carboxy-5-(substituted)pyrrolidines. Further transformation of the synthesized compounds was applied to synthesis another interesting biologically active compounds.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications.

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