ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 6, pp. 1082–1088. © Pleiades Publishing, Ltd., 2020.

Facile Reduction of β-Enamino Oxopyrrolidine Carboxylates Mediated by Heterogeneous Palladium Catalyst

F. N. A. Abdul Rashid[a], M. F. Mohammat[b,*], F. E. Bouchamma[a], Z. Shaameri[b], and A. S. Hamzah[b]

[a] *Faculty of Applied Sciences, Universiti Teknologi MARA, Shah Alam, 40450 Selangor, Malaysia*

[b] *Organic Synthesis Research Laboratory, Institute of Science, Universiti Teknologi MARA, Bandar Puncak Alam, 42300 Selangor, Malaysia*

**e-mail: mohdfazli@uitm.edu.my*

Received December 16, 2019; revised March 21, 2020; accepted March 23, 2020

Abstract—The synthesis of diastereoisomers via diastereoselective hydrogenation of unreactive endocyclic enamine system of ethyl 4-hydrazinyl- and 4-(2-hydroxyethylamino)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylates using palladium-based catalyst was developed. The steric and electronic properties of substituents, especially of the C^2 substituent, influenced both the yield and diastereoselectivity. Despite the reaction generated three chiral centers, the reduced compounds had either *cis–trans* or all-*trans* configuration which was successfully determined by means of 1D and 2D NMR experiments.

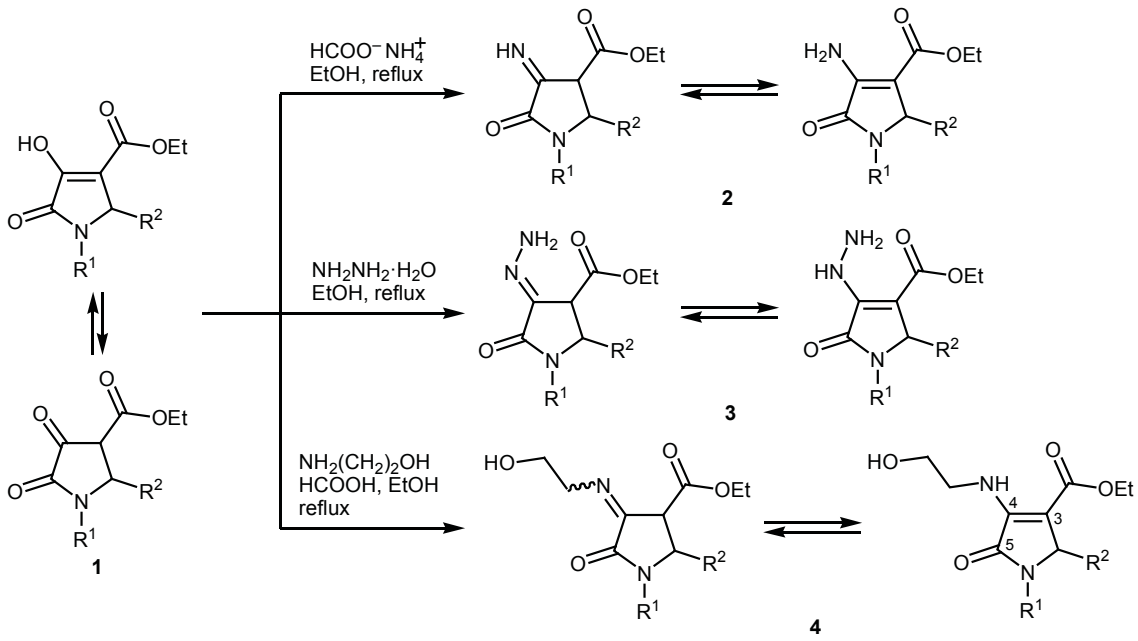
Keywords: enamino ester, hydrogenation, palladium catalysis, chiral amine

DOI: 10.1134/S1070428020060184

Chiral amines represent an important functionality for the synthesis of many bioactive molecules [1]. To date, one of the most efficient synthetic protocols toward chiral amines involves metal-catalyzed hydrogenation of prochiral imines, enamines, and *N*-heteroaromatic compounds [2]. Common noble-metal catalysts based on palladium, platinum, ruthenium, rhodium, and iridium are known as effective reagents for these chiral amine syntheses [3]. Among varieties of heterocycle compounds, pyrrolidines are of great pharmaceutical and medicinal interest as they are substructures of a number of bioactive compounds [4]. Pyrrolidine derivatives are known to display considerable medicinal properties such as antimicrobial, analgesic, anti-inflammatory, and anticancer activities [5]. In conjunction with our research endeavors on synthesizing different classes of bioactive polyhydroxy pyrrolidine alkaloids, we have successfully demonstrated diastereoselective reduction of 5-substituted 2,3-dioxopyrrolidine esters using $NaBH_4$/AcOH and heterogeneous Pd-hydrogenation reactions [6]. It was concurred that steric properties of the C^5 substituent have significant effect on both the yield and diastereoselectivity. Interestingly, a bulky C^5-substituent favored formation of more thermodynamically stable *trans*-isomeric products in this metal-assisted hydrogenation reaction. Consequently, as further extension for synthetic exploration of similar pyrrolidine ester systems, herein we report our attempts to reduce unsaturated β-enamino esters and β-hydrazino (enamino) esters of the pyrrolidone series. These protocols employed simple and diastereoselective heterogeneous catalytic reaction using Pd/C, $Pd(OH)_2$/C (Pearlman's catalyst) and PtO_2 (Adam's catalyst).

The starting materials, ethyl 2-R-4,5-dioxopyrrolidine-3-carboxylates **1** were prepared according to the reported procedure [7, 8]. Nitrogen nucleophiles are known to react with 2,3-dioxopyrrolidines at the 3-position to afford a variety of β-enamino esters via a typical 1,2-nucleophilic addition reaction. It was anticipated that the enol tautomer of **1** could be converted to more stable keto form in a polar solvent such as ethanol during the reaction. Thus, by refluxing in ethanol with ammonium formate or hydrazine, compounds **1** afforded *N*-unprotected enamines **2** and hydrazine derivatives **3** in good to excellent yield (70–91%; Scheme 1; Table 1, entry nos. 1–10) [9]. The condensation of **1** with 2-aminoethanol in boiling ethanol in the presence of formic acid gave hydroxyethylamino derivatives **4** as different *N*-alkyl enamines in a reasonable yield (60–92%; Table 1, entry nos. 11–15) [10]. Apparently, compounds **2**–**4** exist predominantly in the enamine form due to resonance stabi-

Scheme 1.



lization via intramolecular hydrogen bonding. Similar imine–enamine tautomerism of β-enamino esters of the pyrrolidinone series was reported previously [11].

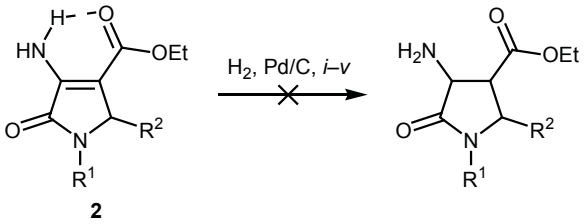
Initially, attempts towards hydrogenation of enamine **2** using 10% Pd/C in ethanol failed to give any product, and only the starting material was recovered (Scheme 2, *i*). Further attempts by prolonging the reaction time, even under pressure (8 atm), also led to negative results (Scheme 2, *ii*–*v*). It was reasoned that the nucleophilicity of the endocyclic double bond of the enamine was reduced due to its very high resonance stability resulting from hydrogen bonding between the amino group and ester functionality. It is also known that the amino group has strong electron-donor properties and is capable of competing for coordination to Pd metal, which could lead to poisoning of the catalyst [12, 13]. For that reason, an acid was added to the reaction system to prevent the catalyst from being

Table 1. Yields of ompounds **2**–**4**

Entry no.	Compound no.	R^1	R^2	Yield,[a] %
1	**2a**	Me	H	77
2	**2b**	Me	Me	76
3	**2c**	Me	Et	80
4	**2d**	Me	4-$MeOC_6H_4$	83
5	**2e**	Me	4-NCC_6H_4	86
6	**3a**	H	H	78
7	**3b**	Me	H	74
8	**3c**	Me	Me	70
9	**3d**	Me	Et	91
10	**3e**	Me	4-$MeOC_6H_4$	85
11	**4a**	Me	H	92
12	**4b**	Me	Me	62
13	**4c**	Me	Et	67
14	**4d**	Me	4-$MeOC_6H_4$	60
15	**4e**	Me	4-MeC_6H_4	62

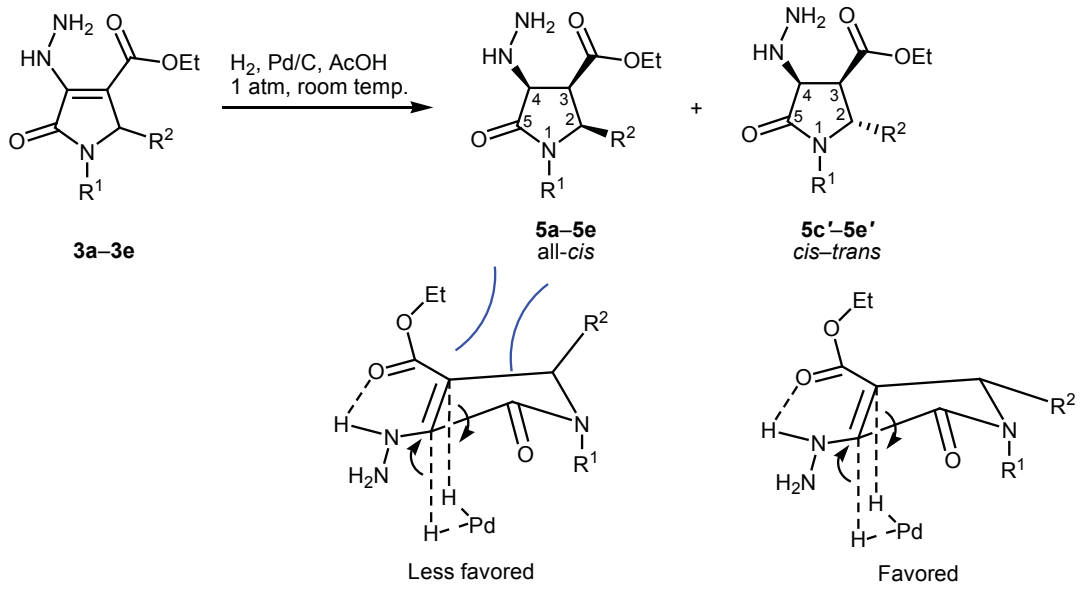
[a] Isolated by column chromatography.

Scheme 2.



i: EtOH, 1 atm, r.t., 12 h; *ii*: AcOH, 1 atm, r.t., 24 h; *iii*: EtOH, 8 atm, r.t., 12 h; *iv*: AcOH, 8 atm, r.t., 12 h; *v*: EtOH, AcOH, 8 atm, r.t., 12 h.

Scheme 3.



poisoned via protonation of the amino group. Unfortunately, this attempt also failed to furnish the desired reduction products despite similar synthetic approach was successfully demonstrated by Wang et al. before [14].

Interestingly, further reduction study with more electronegative substrates, β-enehydrazino esters **3a** and **3b**, resulted in successful synthesis of hydrazinylpyrrolidines **5a** and **5b** in good yield (88–89%; Scheme 3, Table 2, entry nos. 1, 2) [15]. This reduction was achieved by employing a heterogeneous Pd/C catalytic system. It should be noted that all the reduction products of **3** and **4** have three chiral centers, so that the formation of eight different diastereoisomers is possible. However, regardless the absolute configuration, only two diastereoisomers, all-*cis* and *cis–trans* were present in the racemic mixture. Therefore, complete diastereoselectivity (*dr* = 100:0) was observed for compounds **3a** and **3b** which lack a substituent on C^2. If a substituent was present at the 2-position, the yield

Table 2. Reduction of dihydropyrrolecarboxylates **3a**–**3e** to pyrrolidines **5a**–**5e**

Entry no.	Compound no.	R^1	R^2	Yield, %		*dr*[a]
				all-*cis*	*cis–trans*	
1	**3a**	H	H	**5a**, 88	–	100:0
2	**3b**	Me	H	**5b**, 89	–	100:0
3	**3c**	Me	Me	**5c**, 16	**5c′**, 23	41:59
4	**3d**	Me	Et	**5d**, 10	**5d′**, 23	30:70
5	**3e**	Me	4-$MeOC_6H_4$	**5e**, 12	**5e′**, 26	32:68

[a] Diastereoisomer ratio was based on the isolated yield after column chromatography.

Scheme 4.

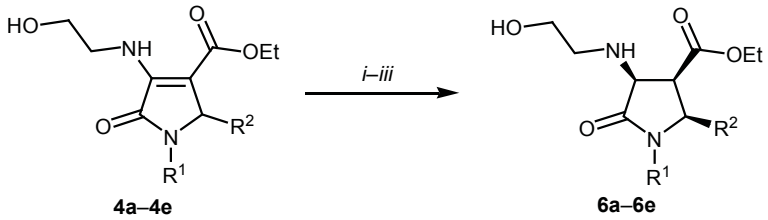


Table 3. Hydrogenation of ethyl 4-(2-hydroxyethylamino)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylates **4a**–**4e**

Entry no.	Compound no.	R^1	R^2	Reaction conditions	Yield, %
1	**4a**	Me	H	*i*: H_2, Pd/C, AcOH, 1 atm, room temp., 12 h	35
2	**4a**	Me	H	*ii*: H_2, PtO_2, AcOH, MeOH, 1 atm, room temp., 12 h	Traces
3	**4a**	Me	H	*iii*: H_2, $Pd(OH)_2$, AcOH, EtOH, 1 atm, room temp., 12 h	83
4	**4b**	Me	Me	*iii*: H_2, $Pd(OH)_2$, AcOH, EtOH, 1 atm, room temp., 12 h	25
5	**4c**	Me	Et	*iii*: H_2, $Pd(OH)_2$, AcOH, EtOH, 1 atm, room temp., 12 h	23
6	**4d**	Me	4-$MeOC_6H_4$	*iii*: H_2, $Pd(OH)_2$, AcOH, EtOH, 1 atm, room temp., 12 h	34
7	**4e**	Me	4-MeC_6H_4	*iii*: H_2, $Pd(OH)_2$, AcOH, EtOH, 1 atm, room temp., 12 h	33

and diastereoselectivity were lower (Table 2, entry nos. 3–5), and mixtures of diastereoisomers **5c**–**5e** (all-*cis*) and **5c′**–**5e′** (*cis*–*trans*) were isolated in the reduction of compounds **3c**–**3e**. Both column chromatography and 2D NMR spectroscopy revealed that the major diastereoisomers had *cis*–*trans* configuration (**5c′**–**5e′**), and the ratio *cis*–*trans*/all-*cis* increased in parallel with the size of C^2-substituent (Table 2). This observation contradicted our previous results obtained in the Pd-assisted enolic reduction which favored the *all-cis* configuration [6].

From the mechanistic viewpoint, it was proposed that the hydrazine group would form a stable six-membered transition ring system via hydrogen bonding with the ester carbonyl functionality and subsequently force them away from the C^2 substituent due to steric congestion. Thus, the two hydrogen atoms are transferred via the concerted *syn* addition from the opposite side of the 2-H proton, leading to the *cis*–*trans* configuration of the major product (Scheme 3). A similar observation was also disclosed by Wang et al. during hydrogenation of various aminopyrrolidinecarboxylates [14]. In addition, it was reasoned that bulkier substituent on C^2 markedly contributes to lower yield by blocking off hydrogen from the active site of the Pd-ene complex.

For further mechanistic study on the effect of steric or electronic factors on the reduction process, 4-(2-hydroxyethylamino)pyrrolidinecarboxylate **4a** containing an alcohol functionality was subjected to similar Pd/C-catalyzed heterogeneous reduction. Fortunately, this reaction successfully gave compound **6a** (Scheme 4) but in a poor yield (35%; Table 3, entry no. 1). Nevertheless, replacement of the catalyst by $Pd(OH)_2$/C resulted in a superior yield (83%; Table 3, entry no. 3). However, the use of PtO_2 as catalyst led to the poorest yield (Table 3, entry no. 2).

It should be noted that high diastereoselectivity was observed with $Pd(OH)_2$/C, as only all-*cis* isomers were obtained. The all-*cis* configuration of the products was confirmed by ^{1}H NMR and 2D NMR experiments. Proton correlations observed in the 2D NMR spectra resembled those reported by us previously [15]. Likewise, the presence of a bulky substituent on C^2 significantly reduced the yield. A different mechanism was proposed for the reduction of 2-hydroxyethylamino derivatives **4**. Due to the presence of a terminal hydroxy group, the transition state has a structure different from that shown in Scheme 3. Here, the concerted *syn* addition becomes less significant, and all-*cis* diastereoisomers are formed as the sole product (Table 3, entry nos. 4–7). Thus, chelation effect of the terminal hydroxy group significantly contributes to the observed diastereoselectivity.

In conclusion, we have discovered a simple method for the synthesis of chiral amines via palladium-catalyzed *syn*-hydrogenation of ethyl 4-(2-hydroxyethylamino)- and 4-hydrazinyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylates with high diastereoselectivity. However, hydrogenation of unprotected β-enamino esters is still challenging, and further optimization of this hydrogenation process is currently in progress in our laboratory.

EXPERIMENTAL

All reagents were supplied by Merck, Sigma–Aldrich, and Acros Organics. The melting points were measured using a Mettler Toledo FP62 automatic melting point apparatus and are uncorrected. The IR spectra (4000–400 cm^{-1}) were recorded on a Varian 3100 Excalibur Series FT/IR spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Joel 400 spectrometer at 400 and 100 MHz, respectively. The progress of reactions was monitored by thin layer chromatography (TLC) on silica gel 60 F254, and spots were visualized with a UV lamp (λ 254 and 365 nm).

Ethyl 3-amino-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylates 2a–2e (*general procedure***).** Ammonium formate (21.60 mmol) was added to a solution of pyrrolidine **1a**–**1e** (10.80 mmol) in ethanol (54 mL), and the mixture was refluxed for 24 h. After completion of the reaction, the mixture was concentrated under reduced pressure, the residue was extracted with ethyl acetate, the extract was dried over $MgSO_4$ and evaporated, and the residue was purified by chromatography using ethyl acetate as eluent.

Ethyl 4-amino-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2a). Yield: 77%, white solid, mp 153–155°C. IR spectrum, ν, cm^{-1}: 3454, 3302, 1702, 1675, 1626, 1278, 1097. ^1H NMR spectrum (acetone-d_6), δ, ppm: 1.24 t (3H, J = 7.1 Hz, CH_3), 2.99 s (3H, NCH_3), 3.89 s (2H, CH_2), 4.17 q (2H, J = 7.2 Hz, OCH_2). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 14.02, 28.83, 48.82, 59.15, 103.66, 144.59, 164.45, 165.18. Found, %: C 52.66; H 6.61; N 16.35. $C_8H_{12}N_2O_3$. Calculated, %: C 52.17; H 6.57; N 15.21.

Ethyl 4-amino-1,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2b). Yield 76%, brown solid, mp 92–94°C. IR spectrum, ν, cm^{-1}: 3431, 3320, 1701, 1673, 1633, 1276, 1092. ^1H NMR spectrum (acetone-d_6), δ, ppm: 1.26 t (3H, J = 7.1 Hz, CH_3), 1.32 d (3H, J = 6.4 Hz, 2-CH_3), 2.92 s (3H, NCH_3), 4.03 q (1H, J = 6.4 Hz, 2-H), 4.12–4.26 m (2H, OCH_2). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 14.04, 17.23, 26.22, 55.33, 59.05, 102.96, 146.79, 164.34, 164.83. Found, %: C 54.88; H 7.12; N 15.13. $C_9H_{14}N_2O_3$. Calculated, %: C 54.53; H 7.12; N 14.13.

Ethyl 4-amino-2-ethyl-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2c). Yield 80%, light yellow solid, mp 92–94°C. IR spectrum, ν, cm^{-1}: 3438, 3284, 1708, 1674, 1628, 1262, 1092. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.50 t (3H, J = 7.3 Hz, CH_2CH_3), 1.30 t (3H, J = 7.1 Hz, CH_3), 1.83 m (1H, CH_2), 2.13 m (1H, CH_2), 2.95 s (3H, NCH_3), 4.17–4.28 m (3H, OCH_2, 2-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 5.59, 14.60, 21.42, 27.32, 59.77, 59.88, 101.03, 147.11, 165.20. Found, %: C 56.57; H 7.48; N 12.59. $C_{10}H_{16}N_2O_3$. Calculated, %: C 56.59; H 7.60; N 13.20.

Ethyl 4-hydroxy-2-(4-methoxyphenyl)-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2d). Yield 83%, light yellow solid, mp 151–153°C. IR spectrum, ν, cm^{-1}: 3409, 3310, 1678, 1643, 1238, 1093. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.11 t (3H, J = 7.1 Hz, CH_3), 2.76 s (3H, NCH_3), 3.78 s (3H, OCH_3), 4.01–4.09 m (2H, OCH_2), 4.92 s (1H, 2-H), 6.83 d (2H, J = 8.7 Hz, H_{arom}), 7.06 d (2H, J = 8.7 Hz, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.31, 27.59, 55.33, 59.71, 63.81, 104.25, 113.98, 128.51, 128.82, 146.08, 159.58, 164.93, 165.43. Found, %: C 61.17; H 6.24; N 9.48. $C_{15}H_{17}NO_5$. Calculated, %: C 62.06; H 6.25; N 9.65.

Ethyl 2-(4-cyanophenyl)-4-hydroxy-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2e). Yield 86%, light yellow solid. ^1H NMR spectrum (CD_3OD), δ, ppm: 1.06 t (3H, J = 7.1, CH_3), 2.74 s (3H, NCH_3), 4.05–3.97 m (2H, OCH_2), 5.14 s (2H, NH_2), 5.47 s (1H, 2-H), 7.36 d (2H, J = 8.7 Hz, H_{arom}), 7.69 d (2H, J = 8.7 Hz, H_{arom}). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 13.27, 26.60, 59.40, 63.41, 101.97, 111.73, 118.15, 128.60, 132.24, 143.33, 146.95, 164.60, 165.95.

Ethyl 4-hydrazinyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylates **3a**–**3e** were synthesized according to the reported procedure [15].

Ethyl 4-(2-hydroxyethylamino)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylates 4a–4e (*general procedure***).** 2-Aminoethanol (6.02 mmol) was added to a solution of compound **1a**–**1e** (5.02 mmol) and formic acid (8.03 mmol) in ethanol (25 mL), and the mixture was refluxed for 12 h. After completion of the reaction, the solution was evaporated under reduced pressure, the residue was extracted with ethyl acetate, and the extract was washed with water, dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography on silica gel (EtOAc–hexane, 1:1).

Ethyl 4-(2-hydroxyethylamino)-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4a). Yield 92%, yellowish solid, mp 72–74°C. IR spectrum, ν, cm^{-1}: 3346, 1662, 1623, 1215, 1096. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, J = 7.1 Hz, CH_3), 3.00 s (3H, NCH_3), 3.70 t (2H, J = 5.3 Hz, CH_2), 3.90–3.94 m (4H, 2-H, CH_2), 4.15 q (2H, J = 7.2 Hz, OCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.55, 29.90,

44.58, 49.60, 59.73, 63.20, 97.50, 147.36, 165.58, 166.27. Found, %: C 52.41; H 7.11; N 12.40. $C_{10}H_{16}N_2O_4$. Calculated, %: C 52.62; H 7.07; N 12.27. Mass spectrum (ESI): *m*/*z* 251.1 $[M + Na]^+$. $C_{10}H_{16}N_2NaO_4$. Calculated: *M* + Na 251.1.

Ethyl 4-(2-hydroxyethylamino)-1,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4b). Yield 62%, dark brown oil. IR spectrum, ν, cm^{-1}: 3201, 1670, 1622, 1217, 1051. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, *J* = 7.1 Hz, CH_3), 1.30 d (3H, *J* = 6.4 Hz, 2-CH_3), 2.90 s (3H, NCH_3), 3.68 t (2H, *J* = 5.3 Hz, CH_2), 3.83–3.95 m (2H, CH_2), 3.99 q (1H, *J* = 6.4 Hz, 2-H), 4.09–4.23 m (2H, OCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.53, 18.01, 27.26, 44.45, 55.39, 59.63, 63.16, 103.84, 147.71, 165.31, 165.83. Mass spectrum (ESI): *m*/*z* 265.1 $[M + Na]^+$. $C_{11}H_{18}N_2NaO_4$. Calculated: *M* + Na 265.1.

Ethyl 2-ethyl-4-(2-hydroxyethylamino)-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4c). Yield 67%, yellow oil. IR spectrum, ν, cm^{-1}: 3204, 1673, 1629, 1204, 1031. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.48 t (3H, *J* = 7.5 Hz, 2-$CH_2C\mathbf{H}_3$), 1.25 t (3H, *J* = 7.1 Hz, CH_3), 1.79 m and 2.04–2.11 m (1H each, 2-$C\mathbf{H}_2CH_3$), 2.88 s (3H, NCH_3), 3.66–3.75 m (2H, CH_2), 3.82–3.89 m (1H, CH_2), 3.97–4.04 m (1H, CH_2), 4.10-4.22 m (3H, OCH_2, 2-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 5.52, 14.50, 21.64, 27.30, 44.49, 59.27, 59.58, 63.07, 100.57, 148.57, 165.73, 166.03. Mass spectrum (ESI): *m*/*z* 279.1 $[M + Na]^+$. $C_{12}H_{20}N_2NaO_4$. Calculated: *M* + $Na]^+$ 279.1.

Ethyl 4-(2-hydroxyethylamino)-2-(4-methoxyphenyl)-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4d). Yield 60%, dark yellow solid, mp 89–90°C. IR spectrum, ν, cm^{-1}: 3478, 1692, 1621, 1242, 1031. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.01 t (3H, *J* = 7.1 Hz, CH_3), 2.70 s (3H, NCH_3), 3.74–3.76 m (5H, OCH_3, CH_2), 3.90–4.10 m (4H, OCH_2, CH_2), 4.87 s (1H, 2-H), 6.80 d (2H, *J* = 8.7 Hz, H_{arom}), 7.03 d (2H, *J* = 8.7 Hz, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.19, 27.63, 44.60, 55.33, 59.53, 63.23, 63.40, 103.68, 113.87, 128.83, 129.02, 147.67, 159.46, 165.51, 165.94. Found, %: C 59.64; H 6.54; N 7.74. $C_{17}H_{22}N_2O_5$. Calculated, %: C 61.07; H 6.63; N 8.38. Mass spectrum (ESI): *m*/*z* 357.1 $[M + Na]^+$. $C_{17}H_{22}N_2NaO_5$. Calculated: *M* + Na 357.1.

Ethyl 4-(2-hydroxyethylamino)-1-methyl-2-(4-methylphenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4e). Yield: 62%, white solid, mp 123–125°C. IR spectrum, ν, cm^{-1}: 3362, 1668, 1617, 1203, 1087. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.00 t (3H, *J* = 7.1 Hz, CH_3), 2.28 s (3H, CH_3), 2.69 s (3H, NCH_3), 3.74 t (2H, *J* = 5.3 Hz, CH_2), 3.89–4.07 m (4H, OCH_2, CH_2), 4.87 s (1H, 2-H), 6.98 d (2H, *J* = 7.8 Hz, H_{arom}), 7.06 d (2H, *J* = 8.2 Hz, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.13, 21.20, 27.67, 44.67, 59.53, 63.03, 63.72, 103.46, 127.59, 129.18, 134.10, 137.88, 147.56, 165.45, 165.97. Found, %: C 63.07; H 6.79; N 7.94. $C_{17}H_{22}N_2O_4$. Calculated, %: C 64.13; H 6.97; N 8.80. Mass spectrum (ESI): *m*/*z* 341.1 $[M + Na]^+$. $C_{17}H_{22}N_2NaO_4$. Calculated: *M* + Na 341.1.

Ethyl 4-hydrazinyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylates **5a–5e** were synthesized according to the procedure reported in [15].

Ethyl 4-(2-hydroxyethylamino)-5-oxopyrrolidine-3-carboxylates 6a–6e (*general procedure*). A solution of compound **4a–4e** (2.19 mmol) in ethanol (15 mL) containing glacial acetic acid (4.38 mmol) was hydrogenated in the presence of 20 wt % of $Pd(OH)_2/C$ (0.59 mmol) under a pressure of 1 atm at room temperature for 12 h. The catalyst was removed by filtration through Celite and rinsed with methanol. The filtrate was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel (EtOAc–hexane, 4:1).

Ethyl 4-(2-hydroxyethylamino)-1-methyl-5-oxopyrrolidine-3-carboxylate (6a). Yield 83%, light yellow oil. IR spectrum, ν, cm^{-1}: 3377, 1646, 1558, 1222, 1069. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 t (3H, *J* = 7.1 Hz, CH_3), 2.86–2.89 m (5H, $NHC\mathbf{H}_2$, NCH_3), 3.00–3.09 m (1H, 3-H), 3.43–3.52 m (2H, CH_2), 3.55–3.67 m (2H, $C\mathbf{H}_2OH$), 3.73 d (1H, *J* = 10.1 Hz, 4-H), 3.75 s (1H, NH), 4.20 q.d (2H, *J* = 7.2, 1.5 Hz, OCH_2), 4.93 br.s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.25, 30.12, 45.76, 48.35, 50.05, 61.31, 61.69, 61.78, 172.24, 173.29. Mass spectrum (ESI): *m*/*z* 253.1 $[M + Na]^+$. $C_{10}H_{18}N_2NaO_4$. Calculated: *M* + Na 253.1.

Ethyl 4-(2-hydroxyethylamino)-1,2-dimethyl-5-oxopyrrolidine-3-carboxylate (6b). Yield 25%, light yellow oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 t (3H, *J* = 7.1 Hz, CH_3), 1.35 d (3H, *J* = 5.9 Hz, 2-CH_3), 2.52 d.d (1H, *J* = 9.4, 8.5 Hz, 3-H), 2.81 s (3H, NCH_3), 2.83–2.88 m (2H, $NHC\mathbf{H}_2$), 3.54–3.66 m (3H, $C\mathbf{H}_2OH$, 2-H), 3.75 d (1H, *J* = 9.6 Hz, 4-H), 3.77 s (1H, NH), 4.22 q (2H, *J* = 7.2 Hz, OCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.29, 19.32, 27.53, 50.10, 54.48, 54.81, 61.35, 61.63, 61.88, 172.20, 173.38. Mass spectrum (ESI): *m*/*z* 267.1 $[M + Na]^+$. $C_{11}H_{20}N_2NaO_4$. Calculated: *M* + Na 267.1.

Ethyl 2-ethyl-4-(2-hydroxyethylamino)-1-methyl-5-oxopyrrolidine-3-carboxylate (6c). Yield 23%, light yellow oil. ^1H NMR spectrum (CD_3OD), δ, ppm:

0.99 t (3H, J = 7.2 Hz, 2-CH_2CH_3), 1.23 t (3H, J = 7.1 Hz, CH_3), 1.35–1.43 m (1H, 2-CH_2CH_3), 1.94 s (1H, NH), 1.97–2.03 m (1H, 2-CH_2CH_3), 2.79 s (3H, NCH_3), 2.84–2.90 m (2H, $NHCH_2$), 3.52–3.68 m (4H, CH_2OH, 2-H, 3-H), 3.70 d (1H, J = 6.4 Hz, 4-H), 4.11–4.25 m (2H, OCH_2). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 8.69, 13.21, 21.71, 26.41, 47.66, 50.21, 59.60, 60.47, 60.58, 61.07, 172.23, 173.71. Mass spectrum (ESI): m/z 281.1 $[M + Na]^+$. $C_{12}H_{22}N_2NaO_4$. Calculated: M + Na 281.1.

Ethyl 4-(2-hydroxyethylamino)-2-(4-methoxyphenyl)-1-methyl-5-oxopyrrolidine-3-carboxylate (6d). Yield 34%, light yellow oil. IR spectrum, ν, cm^{-1}: 3427, 1714, 1614, 1195, 1030. ^1H NMR spectrum (CD_3OD), δ, ppm: 0.76 t (3H, J = 7.1 Hz, CH_3), 2.70 s (3H, NCH_3), 3.27–3.31 m (2H, $NHCH_2$), 3.49–3.60 m (2H, $NHCH_2$, CH_2OH), 3.78 s (3H, OCH_3), 3.81–3.85 m (3H, OCH_2, CH_2OH), 3.95 t (1H, J = 7.3 Hz, 3-H), 4.59 d (1H, J = 7.8 Hz, 4-H), 5.05 d (1H, J = 7.3 Hz, 2-H), 6.96 d (2H, J = 8.7 Hz, H_{arom}), 7.14 d (2H, J = 8.7 Hz, H_{arom}). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 12.37, 28.31, 47.28, 50.02, 54.63, 56.35, 57.41, 61.58, 62.84, 114.01, 125.68, 128.86, 160.60, 169.20, 169.40. Mass spectrum (ESI): m/z 359.1 $[M + Na]^+$. $C_{17}H_{24}N_2NaO_5$. Calculated: M + Na 359.1.

Ethyl 4-(2-hydroxyethylamino)-1-methyl-2-(4-methylphenyl)-5-oxopyrrolidine-3-carboxylate (6e). Yield 33%, light yellow oil. IR spectrum, ν, cm^{-1}: 3364, 1671, 1569, 1225, 1095. ^1H NMR spectrum (CD_3OD), δ, ppm: 0.73 t (3H, J = 7.1 Hz, CH_3), 2.34 s (3H, CH_3), 2.70 s (3H, NCH_3), 3.45–3.53 m (2H, $NHCH_2$, CH_2OH), 3.72–3.83 m (4H, OCH_2, CH_2OH, $NHCH_2$), 3.90 t (1H, J = 7.3 Hz, 3-H), 4.46 d (1H, J = 7.8 Hz, 4-H), 4.99 d (1H, J = 7.3 Hz, 2-H), 7.09 d (2H, J = 8.2 Hz, H_{arom}), 7.23 d (2H, J = 7.8 Hz, H_{arom}). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 13.44, 20.02, 28.58, 46.05, 49.73, 57.89, 61.52, 68.89, 77.28, 128.21, 128.82, 130.14, 138.47, 139.62, 168.23, 169.74. Mass spectrum (ESI): m/z 343.1 [M + Na]. $C_{17}H_{24}N_2NaO_4$. Calculated: M + Na 343.1.

ACKNOWLEDGMENTS

The authors thank Universiti Teknologi MARA and Ministry of Higher Education for the support and members of Organic Synthesis Research Laboratory, I.O.S., UiTM for helpful discussions.

FUNDING

This study was performed under financial support by the Ministry of Higher Education of Malaysia [600-IRMI/FRGS 5/3 (398/2019)].

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Yu, Z., Jin, W., and Jiang, Q., *Angew. Chem., Int. Ed*., 2012, vol. 51, p. 6060. https://doi.org/10.1002/anie.201200963
2. Tin, S., Fanjul, T., and Clarke, M.L., *Beilstein J. Org. Chem*., 2015, vol. 11, p. 622. https://doi.org/10.3762/bjoc.11.70
3. Mrsic, N., *Ph.D. Thesis*, Groningen: Univ. of Groningen, 2010.
4. Ahankar, H., Ramazani, A., Ślepokura, K., Lis, T., and Joo, S.W., *Green Chem*., 2016, vol. 18, p. 3582. https://doi.org/10.1039/c6gc00157b
5. Sarkar, R. and Mukhopadhyay, C., *Tetrahedron Lett*., 2013, vol. 54, p. 3706. https://doi.org/10.1016/j.tetlet.2013.05.017
6. Mohammat, M.F., Mansor, N.S., Shaameri, Z., and Hamzah, A.S., *J. Korean Chem. Soc*., 2015, vol. 59, p. 31. https://doi.org/10.5012/jkcs.2015.59.1.31
7. Mohammat, M.F., Shaameri, Z., and Hamzah, A.S., *Molecules*, 2009, vol. 14, p. 250. https://doi.org/10.3390/molecules14010250
8. Mohammat, M.F., Najim, N., Mansor, N.S., Sarman, S., Shaameri, Z., Zain, M.M., and Hamzah, A.S., *Arkivoc*, 2011, vol. 2011, no. 9, p. 429. https://doi.org/10.3998/ark.5550190.0012.932
9. Southwick, P.L. and Hofmann, G.H., *J. Org. Chem*., 1963, vol. 28, p. 1332. https://doi.org/10.1021/jo01040a044
10. Madhav, R., Dufresne, R.F., and Southwick, P.L., *J. Heterocycl. Chem*., 1973, vol. 10, p. 225. https://doi.org/10.1002/jhet.5570100218
11. Jourdan, F., Kaiser, J.T., and Lowe, D.J., *Synth. Commun*., 2005, vol. 35, p. 2453. https://doi.org/10.1080/00397910500191219
12. Marcazzan, P., Patrick, B.O., and James, B.R., *Organometallics*, 2003, vol. 22, p. 1177. https://doi.org/10.1021/om020992c
13. Albers, P., Pietsch, J., and Parker, S.F., *J. Mol. Catal. A: Chem*., 2001, vol. 173, p. 275. https://doi.org/10.1016/S1381-1169(01)00154-6
14. Wang, G.T., Chen, Y., Wang, S., Gentles, R., Sowin, T., Kati, W., Muchmore, S., Giranda, V., Stewart, K., Sham, H., Kempf, D., and Laver, W.G., *J. Med. Chem*., 2001, vol. 44, p. 1192. https://doi.org/10.1021/jm000468c
15. Abdul Rashid, F.N.A., Mohammat, M.F., Shaameri, Z., and Hamzah, A.S., *Org. Commun*., 2019, vol. 12, p. 121. https://doi.org/10.25135/acg.oc.62.19.07.1323