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Efficient synthesis of pyrroles and 4,5,6,7-tetrahydroindoles via palladium-catalyzed oxidation of hydroxy-enamines

Yutaka Aoyagi, Toshihiko Mizusaki, Masahiro Shishikura, Takashi Komine, Tokuji Yoshinaga, Haruko Inaba, Akihiro Ohta* and Koichi Takeya*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

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Abstract—Facile and one-pot synthetic route of poly-substituted pyrroles and 4-oxo-4,5,6,7-tetrahydroindoles is established, which consists of three steps: (1) palladium-catalyzed oxidation of hydroxy-enamines by using tetrakis(triphenylphosphine)palladium and mesityl bromide oxidation system, (2) intramolecular cyclization, and (3) dehydration.

1. Introduction

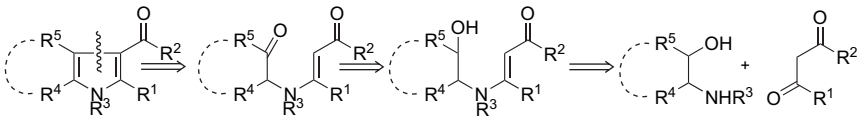
Highly functionalized pyrroles are subunits of considerable importance in heme, chlorophyll, bile pigments, vitamin B_{12}, and marine source-derived pyrrole alkaloids.[1] Since Knorr reported the first synthesis of pyrroles,[2] a series of papers have been published on the syntheses of substituted pyrroles.[3] For example, the pyrrole synthesis by the Lewis acid-mediated reaction of readily available 2-acetoxypropanal *N*,*N*-dimethylhydrazone with cyclic and open chain silyl enol ethers was reported by Enders et al.,[1] low valent titanium-mediated approach to pyrroles by Fürstner et al.,[4] pyrrole synthesis via [2+3] cycloaddition reactions of *S*-methyl *N*-(benzotriazol-1-ylmethyl)thioamide with α,β-unsaturated esters, ketones, nitriles, and vinylpyridines by Pindur and Adam,[5] and convenient synthesis of 2-cyanopyrroles from isocyanoacetonitrile by Adamczyk and Reddy.[6] 4-Substituted indole nucleus is also an important subunit in a wide range of biologically active natural products, whose construction has been a topic of interest for many years.[7]

There are a few reports on the palladium-catalyzed oxidation of hydroxyl groups such as efficient oxidation of alcohols with CCl_4 in the presence of bases by using palladium acetate or palladium chloride,[8] palladium-catalyzed oxidation of secondary alcohols by the use of bromobenzene as an oxidant,[9–11] and palladium-catalyzed oxidation of primary and secondary alcohols to carbonyl compounds under phase transfer catalyst conditions.[12] In the present paper, we describe an efficient synthetic procedure of poly-substituted pyrroles and 4-oxo-4,5,6,7-tetrahydroindoles, by the palladium-catalyzed oxidation of hydroxy-enamines to the corresponding pyrroles and indoles, part of which has been previously reported in our communication.[13]

2. Results and discussion

Our synthetic strategy to prepare pyrroles and indoles via the palladium-catalyzed oxidation is shown in Scheme 1. Poly-substituted pyrroles and 4-oxo-4,5,6,7-tetrahydroindoles are to be synthesized by the oxidation of β-hydroxy-enamines, which can be obtained by the condensation of amino alcohols and carbonyl compounds.

First, β-hydroxy-enamines **3** were prepared by condensation of amino alcohol **2** with β-ketoester or β-diketone **1** in the presence of 4 Å molecular sieves, in moderate to good yields.



Scheme 1.

* Corresponding authors. Tel.: +81 42 676 3007; fax: +81 42 677 1436 (K.T.); e-mail: takeyak@ps.toyaku.ac.jp

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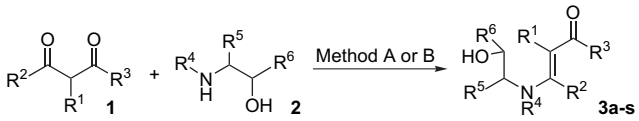
Table 1. Preparation of β-hydroxy-enamines



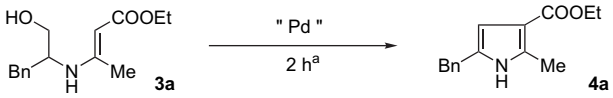
Entry	Ketones (**1**)			β-Amino alcohols (**2**)			Methods[a]	Products (**3**) (yields %)[b]
	R^1	R^2	R^3	R^4	R^5	R^6		
1	H	Me	OEt	H	Bn	H	A	**3a** (96)
2	H	Me	OEt	H	Ph	H	A	**3b** (97)
3	H	Me	OEt	H	^{i}Pr	H	A	**3c** (93)
4	H	Me	OEt	H	H	H	A	**3d**[15] (73)
5	H	Me	OEt	H	H	Me	A	**3e** (84)
6	H	Me	OEt	H	H	Ph	A	**3f** (99)
7	H	Me	Me	H	Me	H	A	**3g** (77)
8	H	Ph	OEt	H	Bn	H	B[c]	**3h** (50)
9	H	Me	OEt	Me	H	H	B	**3i** (52)
10	H	Me	OEt	–(CH$_2$)$_3$–		H	A	**3j** (97)
11	–(CH$_2$)$_3$–		OEt	H	Bn	H	A	**3k** (54)
12	–(CH$_2$)$_4$–		OEt	H	Bn	H	B	**3l** (97)
13	H	Me	OEt	H		–(CH$_2$)$_4$–	A	**3m** (93)
14	H	–(CH$_2$)$_3$–		H	H	H	B[d,e]	**3n** (60)
15	H	–(CH$_2$)$_3$–		H	Ph	H	A[f]	**3o**[16] (80)
16	H	–(CH$_2$)$_3$–		H	H	Ph	B[d,g]	**3p**[17] (78)
17	H	–(CH$_2$)$_3$–		H	Me	H	B[d,h]	**3q** (91)
18	H	–(CH$_2$)$_3$–		H	H	Me	B[d,i]	**3r** (84)
19	H	–(CH$_2$)$_3$–		H		–(CH$_2$)$_4$–	B[d,j]	**3s** (89)

[a] Method A: a THF solution (20 mL) of ketone (7.9 mmol), β-amino alcohol (9.4 mmol), and 4 Å molecular sieves (5.0 g) was stirred at room temperature for 7 days under argon. Method B: a benzene solution (30 mL) of ketone (11.7 mmol), β-amino alcohol (14.9 mmol), and 4 Å molecular sieves (15.0 g) was refluxed for 12 h under argon.
[b] Isolated yields.
[c] *p*-TsOH·H$_2$O was employed.
[d] THF was used as the solvent instead of benzene.
[e] Reaction time: 6 h.
[f] Reaction time: 144 h.
[g] Reaction time: 6.5 h.
[h] Reaction time: 2 h.
[i] Reaction time: 4 h.
[j] Reaction time: 7 h.

Amino alcohol **2** was obtained commercially or easily synthesized by lithium aluminum hydride reduction of amino acids.[14] Preparation of various β-hydroxy-enamines **3a–s** under several different reaction conditions are summarized in Table 1. Then, **3a** was converted to **4a**. Different reaction conditions examined were as summarized in Table 2. Palladium catalyst, aryl halide, and base were all shown to be indispensable components for the reaction (entries 8, 18, and 24 in Table 2). Entries 1–3 in Table 2 demonstrated that better results were to be obtained, when the reaction temperature was at 150 °C. Entries 5–7 may also support the conclusion; so all the reactions were performed at about 150 °C. As regards the solvent, DMF was found to be more efficient (entries 1 vs 4). As regards base component, potassium carbonate at the ratio between the base and β-hydroxy-enamines of 2:1 was found to give generally better results. Potassium hydroxide, potassium acetate, triethylamine, and silver carbonate were found to be less efficient (entries 1 vs 11–14 in Table 2). As regards the aryl halide component, bromobenzene gave better results than iodobenzene or chlorobenzene (entries 1 vs 15 and 16 in Table 2). According to Tamaru et al.,[9–11] mesityl bromide is an efficient oxidant in the reaction of this type. In our experiment, mesityl bromide was also shown to be the aryl halide component giving the highest yield (entry 17 in Table 2). As regards the amount of aryl halide to be used, in the case of bromobenzene, its ratio to β-hydroxy-enamine was shown to be above 1:1 (entries 1 vs 19–22 in Table 2). As regards palladium catalyst, palladium(II) acetate and palladium(II) chloride were also effective (entries 25–28 in Table 2). The Swern, PCC, and PDC oxidation of β-hydroxy-enamine **3a** led to the decomposition of **3a**. In the series of experiments presently performed, the optimum reaction conditions for the preparation of **4a** are given in entry 17 of Table 2.

Then, poly-substituted pyrroles and 4-oxo-4,5,6,7-tetrahydroindoles were prepared via palladium-catalyzed oxidation of various β-hydroxy-enamines as shown in Tables 3 and 4, and Scheme 2. Palladium-catalyzed oxidation of β-hydroxy-enamines **3a–h** gave the corresponding poly-substituted pyrroles (**4a–h**) in moderate to good yields (entries 1–8 in Table 3), except in the case of **3i**, in which R^1 is not a hydrogen but a methyl group and the nucleophilic activity of *N*-substituted β-hydroxy-enamine **3i** is considered to be lower (entry 9 in Table 3). As shown in Table 4, these β-hydroxy-enamines **3n–q** gave 4-oxo-4,5,6,7-tetrahydroindoles (**4n–q**) in 52–85% yields, which are important intermediates for the synthesis of 4-substituted indoles such as ergot alkaloids. Palladium-catalyzed oxidation of β-hydroxy-enamines **3j**, **3m**, and **3s** gave **4j** (27%), **4m** (85%), and **4s** (99%), respectively (Scheme 2). Analogous oxidation of **3k–l** were shown to produce a number of products, as demonstrated in TLC.

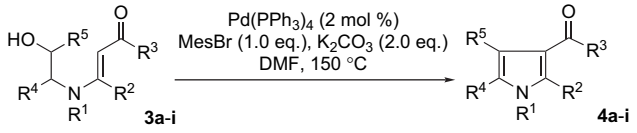
Table 2. Preparation of **4a** via palladium-catalyzed oxidation under several reaction conditions



Entry	Pd catalyst (mol %)	ArX (equiv)	Base (equiv)	Solvent	Reaction temperature (°C)	Yield (%)[b]
1	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	K_2CO_3 (2.0)	DMF	150	55
2	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	K_2CO_3 (2.0)	DMF	120	46
3	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	K_2CO_3 (2.0)	DMF	100	10
4	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	K_2CO_3 (2.0)	DMSO	150	18
5	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	K_2CO_3 (2.0)	Toluene	Reflux	38
6	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	K_2CO_3 (2.0)	1,4-Dioxane	Reflux	14
7	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	K_2CO_3 (2.0)	THF	Reflux	None
8	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	None	DMF	150	None
9	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	K_2CO_3 (1.0)	DMF	150	37
10	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	$KHCO_3$ (2.0)	DMF	150	44
11	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	KOH (2.0)	DMF	150	8
12	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	AcOK (2.0)	DMF	150	22
13	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	Et_3N (2.0)	DMF	150	None
14	$Pd(PPh_3)_4$ (2.0)	PhBr (1.0)	Ag_2CO_3	DMF	150	None
15	$Pd(PPh_3)_4$ (2.0)	PhCl (1.0)	K_2CO_3 (2.0)	DMF	150	22
16	$Pd(PPh_3)_4$ (2.0)	PhI (1.0)	K_2CO_3 (2.0)	DMF	150	17
17	$Pd(PPh_3)_4$ (2.0)	MesBr (1.0)	K_2CO_3 (2.0)	DMF	150	82
18	$Pd(PPh_3)_4$ (2.0)	None	K_2CO_3 (2.0)	DMF	150	None
19	$Pd(PPh_3)_4$ (2.0)	PhBr (0.25)	K_2CO_3 (2.0)	DMF	150	19
20	$Pd(PPh_3)_4$ (2.0)	PhBr (0.5)	K_2CO_3 (2.0)	DMF	150	28
21	$Pd(PPh_3)_4$ (2.0)	PhBr (2.0)	K_2CO_3 (2.0)	DMF	150	58
22	$Pd(PPh_3)_4$ (2.0)	PhBr (4.0)	K_2CO_3 (2.0)	DMF	150	59
23	$Pd(PPh_3)_4$ (0.8)	MesBr (1.0)	K_2CO_3 (2.0)	DMF	150	78
24	None	PhBr (1.0)	K_2CO_3 (2.0)	DMF	150	None
25	$Pd(OAc)_2$ (3.0)	MesBr (1.0)	K_2CO_3 (2.0)	DMF	150	63
26	$Pd(OAc)_2$ (3.0)	MesBr (1.0)	K_2CO_3 (2.0)	DMF	150	72
27	$Pd(OAc)_2$ (5.0)	MesBr (1.0)	K_2CO_3 (2.0)	DMF	150	74
28	$PdCl_2$ (3.0)	MesBr (1.0)	K_2CO_3 (2.0)	DMF	150	76

[a] The starting material **3a** was consumed after 2 h.
[b] Isolated yields.

Table 3. Preparation of pyrroles (**4a–i**)

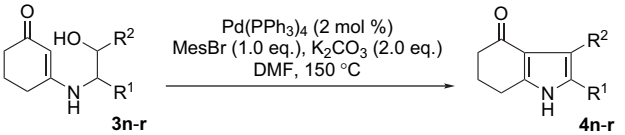


Entry	β-Hydroxy-enamine **3**	R^1	R^2	R^3	R^4	R^5	Reaction time (h)	Pyrroles **4** (yield %)[a]
1	**3a**	H	Me	OEt	Bn	H	2	**4a** (82)
2	**3b**	H	Me	OEt	Ph	H	5	**4b**[18] (67)
3	**3c**	H	Me	OEt	^{i}Pr	H	4	**4c** (83)
4	**3d**	H	Me	OEt	H	H	1	**4d**[19] (74)
5	**3e**	H	Me	OEt	H	Me	3	**4e**[20] (76)
6	**3f**	H	Me	OEt	H	Ph	5	**4f**[21] (80)
7	**3g**	H	Me	OMe	Me	H	3.5	**4g**[22] (57)
8	**3h**	H	Ph	OEt	Bn	H	4	**4h** (84)
9	**3i**	Me	Me	OEt	H	H	2	**4i**[23] (36)

[a] Isolated yields.

A plausible mechanism involved in this series of reaction is schematically shown in Figure 1. Oxidative addition of palladium(0) catalyst to aryl bromide produces palladium(II) adduct, which with β-hydroxy-enamine gives an alkoxy palladium(II). Finally, β-elimination of the palladium catalyst proceeded to give a carbonyl compound. Intramolecular cyclization of the carbonyl compound thus obtained, the subsequent dehydration, and isomerization of the protons provide pyrroles and indoles. Palladium(0) catalyst is then reproduced via reductive elimination of palladium species.

Table 4. Preparation of 4-oxo-4,5,6,7-tetrahydroindoles

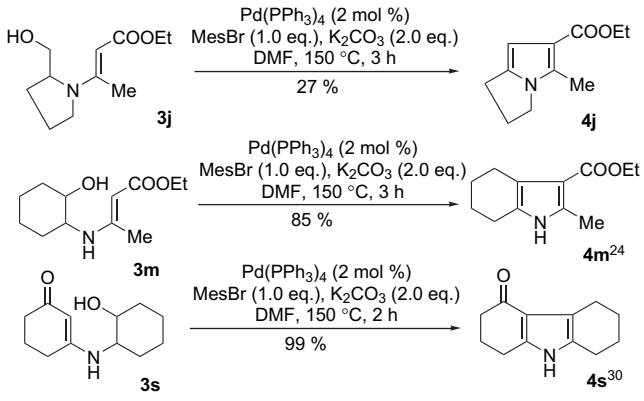


Entry	β-Hydroxy-enamine **3**	R^1	R^2	Reaction time (h)	4-Oxo-4,5,6,7-tetrahydro-indoles **4** (yield %)[a]
1	**3n**	H	H	4	**4n**[25] (63)
2	**3o**	Ph	H	2.5	**4o**[26] (65)
3	**3p**	H	Ph	7	**4p**[27] (52)
4	**3q**	Me	H	2	**4q**[28] (85)
5	**3r**	H	Me	1	**4r**[29] (60)

[a] Isolated yields.

3. Conclusion

The present study describes an efficient and facile synthesis of pyrroles and 4,5,6,7-tetrahydroindoles from hydroxy-enamines. In this procedure, the starting materials, i.e., hydroxy-enamines, are prepared easily from commercially available amino alcohols, and the final products are produced in a fewer steps in moderate to good yields. Of the compounds produced in the present method, 4-oxo-4,5,6,7-tetrahydroindoles are quite useful intermediates for the synthesis of biologically active natural products such as ergot alkaloids.



Scheme 2.

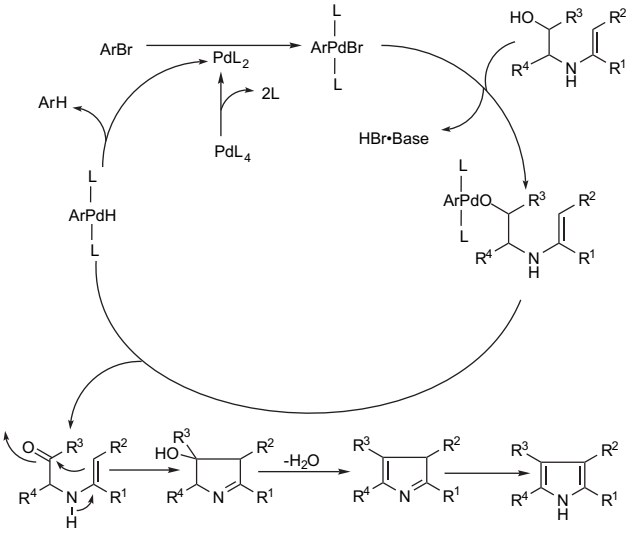


Figure 1. Plausible reaction mechanism.

4. Experimental

4.1. General methods

Melting points were measured in Yanagimoto micro melting point apparatus and are recorded uncorrected. Infrared spectra (cm^{-1}) were recorded on a Japan Spectroscopic Co. A-100 and Mass spectra were recorded on a Hitachi M-80B or Fisons VG Auto Spec instrument. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained on a Varian Gemini A-300 and the chemical shifts are given in parts per million downfield from the internal standard (TMS). Flash chromatography and MPLC were performed by using Merck silica gel Kieselgel 60® (230–400 mesh) or Merck Aluminum oxide 90® (70–230 mesh) column and preparative thin layer chromatography (PTLC) with Merck Kieselgel 60 F_{254} precoated glass plates (thickness 0.25 or 0.50 mm). All solvents were of commercial grade, which were distilled and dried with sodium benzophenone ketyl (tetrahydrofuran (THF), 1,4-dioxane, toluene, and benzene) or with CaH_2 (DMF, DMSO, and CH_2Cl_2). Lithium bases (^{n}BuLi, ^{s}BuLi, and ^{t}BuLi) were purchased from Aldrich Chemical Co., Ltd. All other reagents were of the highest available grade and used as purchased.

4.2. General procedure for the preparation of β-hydroxy-enamines

Method A: 4 Å MS (5 g) and THF solution (10 mL) of β-dicarbonyl compound (7.9 mmol, 1.0 equiv) were added to a dry THF solution (20 mL) of β-amino alcohol (9.4 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 7 day under an argon atmosphere. After filtration through a short pad of Celite® 545, the solvent was evaporated in vacuo to give a residue, which was purified by aluminum oxide flash chromatography (eluting with EtOAc) to give a β-amino alcohol (**3a–g**, **3j–k**, **3m**, and **3o**).

Method B: 4 Å MS (5 g) and THF solution (10 mL) of β-dicarbonyl compound (11.7 mmol, 1.0 equiv) were added to a dry benzene solution (30 mL) of β-amino alcohol (14.9 mmol, 1.2 equiv). The reaction mixture was refluxed for 12 h under an argon atmosphere. After filtration through a short pad of Celite® 545, the solvent was evaporated in vacuo to give a residue, which was purified by aluminum oxide flash chromatography eluting with EtOAc to give a β-amino alcohol (**3h–i**, **3l**, **3n**, and **3p–s**).

4.2.1. Compound 3a. Pale yellow oil; IR (film) 3420 (OH), 3290 (NH), 1610 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (1H, br d, 9.6), 7.31–7.15 (5H, m), 4.37 (1H, s), 4.08 (2H, q, 7.1), 3.76–3.56 (3H, m), 2.86 (1H, dd, 13.5, 5.2), 2.69 (1H, dd, 13.5, 7.9), 2.24 (1H, br s), 1.62 (3H, s), 1.24 (3H, t, 7.1); MS (EI, *m/z*) 263 (M^+). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.49; H, 8.09; N, 5.31.

4.2.2. Compound 3b. Pale yellow oil; IR (film) 3420 (OH), 3300 (NH), 1650 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (1H, br d, 8.4), 7.40–7.25 (5H, m), 4.70–4.60 (1H, m), 4.55 (1H, s), 4.13 (2H, q, 7.1), 3.86 (1H, dd, 11.3, 4.5), 3.77 (1H, dd, 11.3, 7.0), 1.82 (3H, s), 1.28 (3H, t, 7.1); MS (EI, *m/z*) 249 (M^+). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.40; H, 7.75; N, 5.62.

4.2.3. Compound 3c. Pale yellow oil; IR (film) 3420 (OH), 3300 (NH), 1650 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, br d, 9.4), 4.47 (1H, s), 4.10 (2H, qd, 7 0.9), 3.65–3.76 (1H, m), 3.50–3.60 (1H, m), 3.30–3.42 (1H, m), 1.95 (3H, s), 1.67 (1H, br s), 1.26 (3H, t, 7.1), 0.96 (6H, d, 6.9); HRMS (EI, *m/z*) Calcd for $C_{11}H_{21}NO_3$ (M^+): 215.1521. Found: 215.1532.

4.2.4. Compound 3e. Colorless prisms, mp 63–65 °C (hexane); IR (KBr) 3420 (OH), 3300 (NH), 1620 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (1H, br s), 4.49 (1H, s), 4.09 (2H, q, 7.1), 3.92 (1H, m), 3.27 (1H, ddd, 13.5, 6.2, 4.0), 3.16 (1H, ddd, 13.5, 7.3, 6.4), 1.99 (1H, br d), 1.93 (3H, s), 1.25 (3H, t, 7.1), 1.23 (3H, t, 7.1); MS (EI, *m/z*) 187 (M^+). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.77; H, 9.15; N, 7.59.

4.2.5. Compound 3f. Colorless needles, mp 91–93 °C (hexane); IR (KBr) 3450 (OH), 3300 (NH), 1640 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (1H, br s), 7.40–7.27 (5H, m), 4.85–4.79 (1H, m), 4.48 (1H, s), 4.09 (2H, q, 7.1), 3.43 (1H, dd, 6.4, 4.7), 3.42 (1H, dd, 7.5, 6.2), 2.38 (1H, br d), 1.86 (3H, s), 1.24 (3H, t, 7.1); MS (EI, *m/z*)

249 (M^+). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.34; H, 7.70; N, 5.77.

4.2.6. Compound 3g. Pale yellow oil; IR (KBr) 3320 (NH), 1615 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.8 (1H, br s), 4.96 (1H, s), 3.73 (1H, m), 3.66 (1H, m), 3.53 (1H, dd, 11.1, 7.4), 2.42 (1H, br s), 1.99 (3H, s), 1.98 (3H, s), 1.19 (3H, d, 6.6); MS (EI, *m/z*) 249 (M^+). HRMS (EI, *m/z*) Calcd for $C_8H_{15}NO_2$ (M^+): 157.1103. Found: 157.1095.

4.2.7. Compound 3h. Pale yellow oil; IR (KBr) 3450 (OH), 3300 (NH), 1735 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (1H, br d, 10.2), 7.37–7.20 (6H, m), 7.04–6.92 (4H, m), 4.57 (1H, s), 4.16 (2H, q, 7.1), 3.64–3.44 (3H, m), 2.79 (1H, dd, 13.5, 5.5), 2.51 (1H, dd, 13.5, 7.8), 2.30 (1H, br s), 1.29 (3H, t, 7.1); MS (EI, *m/z*) 325 (M^+). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.53; H, 7.31; N, 4.25.

4.2.8. Compound 3i. Pale yellow oil; IR (KBr) 3430 (OH), 1680, 1660 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (1H, s), 4.09 (2H, q, 7.1), 3.77 (2H, q, 5.7), 3.46 (2H, t, 5.7), 2.95 (3H, s), 2.49 (3H, s), 1.51 (1H, br t), 1.25 (3H, t, 7.1); MS (EI, *m/z*) 187 (M^+). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.79; H, 9.06; N, 7.43.

4.2.9. Compound 3j. Pale yellow oil; IR (KBr) 3450 (OH), 3300 (NH), 1740 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (1H, s), 4.08 (2H, td, 7.1, 1.3), 3.98–3.88 (1H, m), 3.66 (1H, dd, 10.9, 3.9), 3.50 (1H, dd, 10.9, 3.5), 3.33–3.21 (2H, m), 2.50 (3H, s), 2.10–1.91 (4H, m), 1.78 (1H, br s), 1.25 (3H, t, 7.1); MS (EI, *m/z*) 213 (M^+). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57. Found: C, 62.15; H, 9.05; N, 6.61.

4.2.10. Compound 3k. Pale yellow oil; IR (KBr) 3425 (OH), 3320 (NH), 1650 (C=O), 1590 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, br d, 8.7), 7.30–7.10 (5H, m), 4.14 (2H, q, 7.1), 3.70–3.49 (3H, m), 2.85 (1H, dd, 13.5, 5.2), 2.71 (1H, dd, 13.5, 7.5), 2.50 (1H, br s), 2.49–2.35 (3H, m), 2.10–1.95 (1H, m), 1.80–1.50 (2H, m), 1.27 (3H, t, 7.1); MS (EI, *m/z*) 213 (M^+). HRMS (EI, *m/z*) Calcd for $C_{17}H_{23}NO_3$ (M^+): 289.1678. Found: 289.1690.

4.2.11. Compound 3l. Pale yellow oil; IR (film) 3450 (OH), 3290 (NH), 1720 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (1H, br d, 10.2), 7.32–7.14 (5H, m), 4.13 (2H, q, 7.1), 3.82–3.68 (1H, m), 3.65 (1H, dd, 11.0, 4.2), 3.53 (1H, dd, 11.0, 6.8), 2.83 (1H, dd, 13.5, 6.0), 2.70 (1H, dd, 13.5, 7.7), 2.26–2.12 (4H, m), 1.88–1.78 (2H, m), 1.56–1.32 (3H, m), 1.28 (3H, t, 7.1); MS (EI, *m/z*) 303 (M^+). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.08; H, 8.47; N, 4.52.

4.2.12. Compound 3m. Colorless oil; IR (film) 3450 (OH), 3300 (NH), 1740 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (1H, br d, 9.4), 4.48 (1H, s), 4.09 (2H, q, 7.1), 3.42–3.33 (1H, m), 3.23–3.10 (1H, m), 2.30 (1H, br s), 2.10–2.02 (1H, m), 1.98 (3H, s), 1.95–1.87 (1H, m), 1.80–1.67 (2H, m), 1.29 (4H, m), 1.26 (3H, t, 7.1); MS (EI, *m/z*) 227 (M^+). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.43; H, 9.45; N, 6.14.

4.2.13. Compound 3n. Colorless needles, mp 102–106 °C (MeCN); IR (film) 3260 (OH, NH), 1680 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (1H, br s), 5.10 (1H, s), 3.81 (2H, td, 5.3, 2.4), 3.22 (2H, td, 5.0, 5.0), 2.37 (2H, t, 6.3), 2.30 (2H, t, 6.5), 1.95 (2H, m); MS (EI, *m/z*) 155 (M^+). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.89; H, 8.42; N, 9.09.

4.2.14. Compound 3q. Pale yellow oil; IR (film) 3300 (OH, NH), 1550 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (1H, s), 3.74–3.68 (1H, m), 3.63–3.54 (2H, m), 2.37–2.28 (4H, m), 1.95 (2H, m), 1.20 (3H, d, 6.3); HRMS (EI, *m/z*) Calcd for $C_9H_{15}NO_2$ (M^+): 169.1103. Found: 169.1106.

4.2.15. Compound 3r. Pale yellow amorphous solid, mp 81–82 °C ($CHCl_3$); IR (film) 3300 (OH, NH), 1550 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44–5.22 (1H, br s), 5.10 (1H, s), 4.04–3.98 (1H, s), 3.17 (1H, ddd, 13.1, 6.0, 3.0), 2.96 (1H, ddd, 13.1, 8.5, 4.4), 2.36 (1H, t, 6.2), 2.30 (2H, t, 6.5), 1.95 (2H, m), 1.25 (3H, d, 6.3); HRMS (EI, *m/z*) Calcd for $C_9H_{15}NO_2$ (M^+): 169.1103. Found: 169.1107.

4.2.16. Compound 3s. Pale yellow needles, mp 198–199 °C (hexane/AcOEt); IR (film) 3300 (OH, NH), 1580 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (1H, d, 7.1), 4.86 (1H, s), 4.64 (1H, d, 4.9), 3.36–3.20 (1H, m), 3.04–2.93 (1H, m), 2.36–2.26 (2H, m), 2.08–2.02 (2H, m), 1.92–1.80 (2H, m), 1.77 (2H, m), 1.66–1.52 (2H, m), 1.30–0.98 (4H, m); MS (EI, *m/z*) 209 (M^+). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.82; H, 9.07; N, 6.59.

4.3. General procedure for the preparation of pyrrole derivatives

A mixture of $Pd(PPh_3)_4$ (0.025 g, 0.02 mmol, 2 mol %), K_2CO_3 (0.27 g, 2.0 mmol), mesityl bromide (0.20 g, 1.0 mmol), β-hydroxy-enamine (1.0 mmol), and dry DMF (5 mL) was heated at 150 °C for 2 h under an argon atmosphere. After cooling, H_2O (20 mL) was added to the mixture, which was extracted with Et_2O (3×20 mL). The extract was then dried over Na_2SO_4, filtered, and evaporated in vacuo to give a residue, which was purified by silica gel flash chromatography (eluting with hexane–EtOAc system) to give the pyrrole derivatives (**4a–j** and **4m–r**).

4.3.1. Compound 4a. Colorless prisms, mp 106–107 °C (hexane); R_f 0.16 (hexane/AcOEt=4:1); IR (KBr) 3270 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (1H, s), 7.36–7.16 (5H, m), 6.32 (1H, d, 2.9), 4.25 (2H, q, 7.1), 3.88 (2H, s), 2.45 (3H, s), 1.33 (3H, t, 7.1); MS (EI, *m/z*) 243 (M^+). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.99; H, 6.94; N, 5.72.

4.3.2. Compound 4c. Colorless prisms, mp 66–68 °C (hexane); R_f 0.17 (hexane/AcOEt=4:1); IR (KBr) 3030 (NH), 1690 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (1H, br s), 6.23 (1H, dd, 3.0, 0.9), 4.25 (2H, q, 7.1), 2.83 (1H, m), 2.50 (3H, s), 1.33 (3H, t, 7.1), 1.24 (6H, d, 6.9); MS (EI, *m/z*) 195 (M^+). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.67; H, 8.72; N, 7.21.

4.3.3. Compound 4h. Colorless prisms, mp 107–108 °C (hexane); R_f 0.37 (hexane/AcOEt=4:1); IR (KBr) 3300 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, br s), 7.57–7.51 (2H, m), 7.41–7.29 (5H, m), 7.28–7.21 (3H, m), 6.52 (1H, dd, 3.0, 0.9), 4.20 (2H, q, 7.1), 3.98 (2H, s), 1.25 (3H, t, 7.1); MS (EI, *m/z*) 305 (M^+). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.56; H, 6.27; N, 4.70.

4.3.4. Compound 4j. Colorless oil; R_f 0.24 (hexane/AcOEt=4:1); IR (film) 1695 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (1H, d, 1.1), 4.24 (2H, q, 7.1), 3.82 (2H, t, 7.1), 2.80 (2H, t, 7.4), 2.47 (2H, m), 2.46 (3H, s), 1.32 (3H, t, 7.1); MS (EI, *m/z*) 193 (M^+). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.46; H, 7.78; N, 7.05.

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