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COPPER TRIFLATE CATALYZED REGIOSELECTIVE ALKYLATION OF PYRROLE: CONVERSION OF 2-ALKYLATED PYRROLES TO NOVEL PYRROLIZINE DERIVATIVES BY SELF-CYCLIZATION

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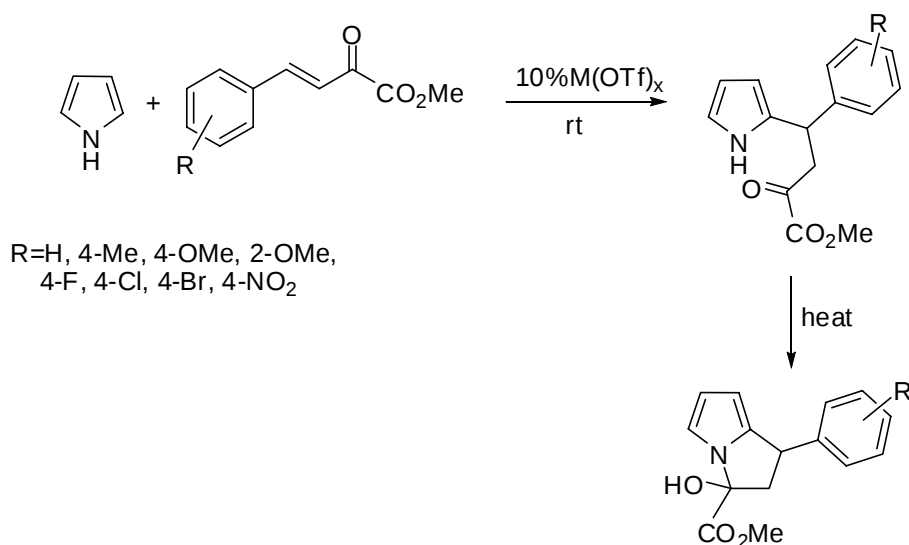
Abstract – Metal triflate catalyzed addition reaction of pyrrole to methyl 2-oxo-4-phenylbut-3-enoate and substituted derivatives generated the related novel alkylated pyrroles regioselectively at C(2) of pyrrole. Among the studied metal triflates, Cu(OTf)₂ was found to be more effective in the addition reaction. The synthesized methyl 2-oxo-4-phenyl-4-(1*H*-pyrrole-2-yl)butanoate esters underwent self-cyclization by heating and yielded the corresponding methyl 3-hydroxy-1-phenyl-2,3-dihydro-1*H*-pyrrolizine-3-carboxylate and substituted derivatives. This reaction procedure allowed easy access to pyrrolizine structure in mild reaction conditions.

INTRODUCTION

Pyrrole and many of its derivatives are very important units in many naturally occurring compounds, because of a wide variety of their pharmaceutical and biological properties.¹ Therefore, many synthetic methods have been reported in the literature for the preparation of pyrrole derivatives.² 2- and *N*-substituted pyrroles have been used as a synthon for the synthesis of pyrrolizines³ and indolizines⁴ that constitute a very large family of natural products having a wide range of biological activities.⁵ Synthesis of these heterocycles is an important area of heterocyclic chemistry.

The Michael addition reaction is a fundamental C-C bond forming reaction in organic synthesis. In recent years, metal triflates have been used in the Michael addition of pyrrole and indole to various enones.⁶ In

our previous work, we reported the addition reaction of pyrrole to *N*-tosyl imines⁷ and *N*-substituted pyrroles⁸ by using metal triflates providing the alkylated pyrrole with good to high yields. In this work, we have chosen methyl 2-oxo-4-phenylbut-3-enoate, as a suitable polyfunctional substituent, for the alkylation of pyrrole to obtain the intramolecular cyclization product from the alkylated pyrrole. We present here the regioselective, Cu(OTf)₂ catalyzed Michael addition of pyrrole to substituted methyl 2-oxo-4-phenylbut-3-enoate esters and their self-cyclization reactions (Scheme 1).

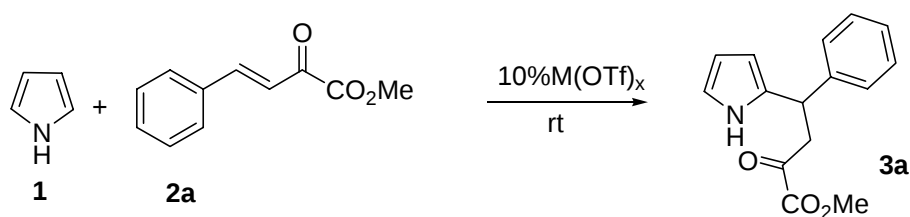


Scheme 1

2-Oxo-4-phenylbut-3-enoate esters have been used in catalytic enantioselective Friedel-Crafts alkylation reactions of indole and furan by using various metal complexes. These heteroaromatic compounds are known to give the Friedel-Crafts alkylation products with 2-oxo-4-phenylbut-3-enoate esters in very high yields.^{6c, 6d} We previously indicated that methyl 2-oxo-4-phenylbut-3-enoate (**2a**) is also a good acceptor for the 1,4-addition reaction of *N*- and C(2)-substituted pyrroles.⁸

RESULTS AND DISCUSSION

We used the electron deficient **2a-h** in the 1,4-addition of pyrrole (**1**) to obtain **3a-h** as precursors to synthesize the bicyclic systems with nitrogen at bridgehead position. Addition reaction was tested with **2a** in order to optimize the reaction conditions (Scheme 2). We first performed the addition reactions of pyrrole to **2a** in THF at rt by using various metal triflates (Table 1). The addition product, methyl 2-oxo-4-phenyl-4-(1*H*-pyrrole-2-yl)butanoate (**3a**), formed regioselectively at C(2) of pyrrole. The results in Table 1 show that Y(OTf)₃, Yb(OTf)₃, Gd(OTf)₃, Zn(OTf)₂, La(OTf)₃ and Nd(OTf)₃ furnished the product with 50-67% yields (Entries 2-7, Table 1). Cu(OTf)₂ provided **3a** with the highest yield (83%) in THF at rt (Entry 1, Table 1).



Scheme 2

Table 1. The effect of metal triflates on the addition of pyrrole to methyl 2-oxo-4-phenylbut-3-enoate at rt

Entry	M(OTf) _x	Solvent	Yield (%) ^a
1	Cu(OTf) ₂	THF	83
2	Y(OTf) ₃	THF	67
3	Yb(OTf) ₃	THF	65
4	Gd(OTf) ₃	THF	60
5	Zn(OTf) ₂	THF	50
6	La(OTf) ₃	THF	58
7	Nd(OTf) ₃	THF	56

^a isolated yield after purification.

We continued to examine the effect of the solvent and temperature on the reaction. The solvents, CH₂Cl₂, toluene, Et₂O, acetone, MeCN and THF:H₂O (1:1), all gave the product with lower yields (15-36%) in the presence of 10 mol % Cu(OTf)₂ (Entries 4-9, Table 2). The best chemical yield (83%) was obtained with 10 mol % Cu(OTf)₂ in THF at rt (Entry 3, Table 2). To examine the effect of temperature on the addition reaction, the reactions were repeated using THF and 10% Cu(OTf)₂ at 0 °C and -20 °C. The reaction was monitored with TLC. 50% and 20% chemical yields were obtained at 0 °C and -20 °C, respectively (Entries 1 and 2, Table 2). Lowering the reaction temperature increased the reaction time and decreased the chemical yield.

Substituted derivatives of methyl 2-oxo-4-phenylbut-3-enoate, **2b-h**, gave the addition product with 45-70 % yield (Entries 2-8, Table 3). 2-OMe substituted **2d** gave the lowest yield (45%) while 4-OMe substituted **2c** yielded the product with 65%. **2f** with 4-Cl gave the product with lower yield (49%) than halogen substituted **2e** and **2g**. The structures of **3a-h** were identified by ¹H NMR, ¹³C NMR and elemental analysis. The position of the substituent was assigned by COSY spectra.

Table 2. The effect of solvent and temperature on the addition reaction of pyrrole to methyl 2-oxo-4-phenylbut-3-enoate

Entry	M(OTf) _x	Solvent	Temperature (°C)	Time(h) ^a	Yield (%) ^b
1	Cu(OTf) ₂	THF	-20	12	20
2	Cu(OTf) ₂	THF	0	12	50
3	Cu(OTf) ₂	THF	rt	0.25	83
4	Cu(OTf) ₂	CH ₂ Cl ₂	rt	0.25	36
5	Cu(OTf) ₂	toluene	rt	0.25	30
6	Cu(OTf) ₂	Et ₂ O	rt	0.25	28
7	Cu(OTf) ₂	acetone	rt	0.25	20
8	Cu(OTf) ₂	MeCN	rt	0.25	15
9	Cu(OTf) ₂	THF:H ₂ O (1:1)	rt	0.25	30

^a all reactions were monitored by TLC.

^b Isolated yield after purification.

Table 3. Addition of the pyrrole to β,γ-unsaturated α-keto esters in the presence of Cu(OTf)₂ in THF at rt

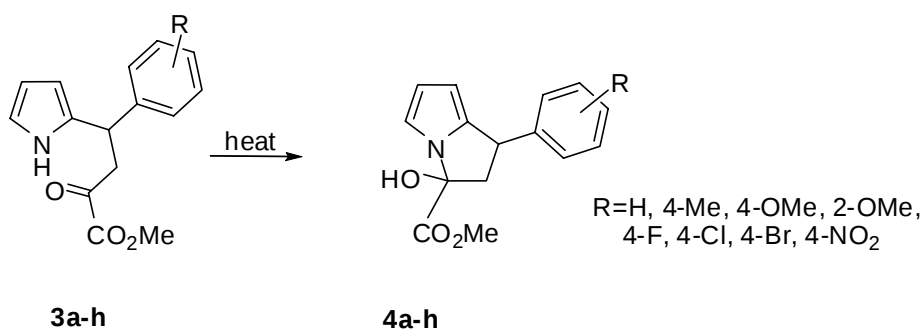
Reaction scheme: Pyrrole (1) + β,γ-unsaturated α-keto ester (2a-h) $\xrightarrow[\text{THF, rt}]{10\% \text{Cu(OTf)}_2}$ 3-oxo-2,3-dihydro-1H-pyrrolizine derivative (3a-h).

Entry	R	3	Yield (%) ^a
1	H	3a	83
2	4-Me	3b	65
3	4-OMe	3c	65
4	2-OMe	3d	45
5	4-F	3e	58
6	4-Cl	3f	49
7	4-Br	3g	63
8	4-NO ₂	3h	70

^a isolated yield after purification.

The synthesized novel alkylated pyrroles **3a-h** with α-ketoester on alkyl group are convenient precursors for investigating intramolecular cyclization reaction. We have recently synthesized the 3-oxo-2,3-dihydro-1H-pyrrolizine derivatives from intramolecular cyclization of dimethyl

2-(phenyl(1*H*-pyrrol-2-yl)methyl)malonate esters.⁹ Ester functional groups bearing diethyl 2-(1*H*-pyrrol-2-yl)butanedioate with Na₂CO₃ in toluene and dimethyl 2-(1*H*-pyrrol-2-yl)pentanedioate with K₂CO₃ in DMF also gave the corresponding bicyclic pyrroles by the intramolecular cyclization reactions.¹⁰ Such reactions proceed through the intramolecular cyclization of pyrrole nitrogen and ester functional group upon treatment with a base. **3a-h**, with α -ketoester functionalized alkyl group at C(2) of pyrrole, readily gave the intramolecular self-cyclization reaction between the keto group and pyrrole nitrogen. Alkylated pyrroles **3a-h** completely converted to the self-cyclization products **4a-h** by heating in CCl₄ at 75 °C (Scheme 3). Formation of self-cyclization products were monitored by TLC and checked by ¹H NMR after the heating process. ¹H NMR spectra of **4a-h** indicated that the cyclization products were formed as diastereoisomeric mixtures in 1:1 ratio. Diastereomers were separated by column chromatography and denoted as **4a** and **4a'** according to their R_f values. The structures of **4a-h** were identified by ¹H NMR, ¹³C NMR and elemental analysis although their stereochemistries have remained undetermined.



Scheme 3

CONCLUSION

In summary, we have developed a catalytic addition reaction of pyrrole to substituted methyl 2-oxo-4-phenylbut-3-enoate for the synthesis of novel alkylated pyrrole derivatives. Metal triflate catalyzed addition products formed regioselectively at C(2) of pyrrole. C(2) alkylated pyrrole derivatives **3a-h** gave the self-cyclization products **4a-h** by heating. Consequently, novel pyrrolizine structures have been synthesized from easily available starting materials and in mild reaction conditions.

EXPERIMENTAL

General. Solvents were of the highest commercial quality and used without further purification. β,γ -Unsaturated α -keto esters **2a-g**¹¹ and **2h**¹² were prepared according to literature procedures. Reactions were monitored by thin layer chromatography plates (Kieselgel 60, F254, E.Merck) and visualized with

UV-light or phosphomolybdic acid in methanol or anisaldehyde in methanol. Flash column chromatography was carried out using silica gel (0.05-0.63 nm. 230-400 mesh ASTM, Merck). ^1H NMR and ^{13}C NMR spectra were recorded by a Bruker DPX-400, Ultrashield, 400 MHz high performance digital FT-NMR spectrometer using CDCl_3 as the solvent and tetramethylsilane (TMS) as the internal standard. Spin multiplicities were mentioned as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet). Infrared spectra were taken by 2000 Perkin-Elmer FTIR Spectrophotometer. Melting points were measured by Gallenkamp capillary melting point apparatus and were uncorrected. Elemental analyses were performed by LECO CHNS system.

General Procedure for the 1,4 -Addition Reaction of Pyrrole to β,γ -Unsaturated α -Keto Esters: A mixture of β,γ -unsaturated α -keto esters **2a-h** (1 mmol) and $\text{Cu}(\text{OTf})_2$ (36 mg, 0.1 mmol) was stirred in THF (5 mL) at rt for 30 min. The solution of pyrrole (134 mg, 2 mmol) in THF (2 mL) was added dropwise into the reaction mixture. The pale yellow colour of the mixture turned black and the reaction was monitored by TLC. After the consumption of reactants, the reaction was quenched by the addition of 2 mL of water and extracted with Et_2O (2 x 10 mL). The organic layer was dried with anhydrous MgSO_4 . The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography.

Methyl 2-oxo-4-phenyl-4-(1H-pyrrole-2-yl)butanoate (3a): Yield: 0.214g (83%); light brown solid; mp 76-77 °C ; R_f 0.44 (EtOAc:hexane, 1:3). IR (KBr): 3426, 2978, 2865, 1636, 1360, 1125 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 3.45 (dd, $J=18.4$ and $J=6.8$ Hz, 1H, CHH), 3.67 (dd, $J=18.4$ and $J=8.0$ Hz, 1H, CHH), 3.84 (s, 3H, OCH_3), 4.62 (t, $J=7.2$ Hz, 1H, CH), 5.94 (bs, 1H, $\text{C}(3)\text{H}$), 6.08 (dd, $J=6.0$ and $J=2.8$ Hz, 1H, $\text{C}(4)\text{H}$), 6.61(bs, 1H, $\text{C}(5)\text{H}$), 7.24-7.34 (m, 5H, ArH), 7.95 (bs, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 39.06, 45.56, 52.81, 105.78, 108.33, 117.41, 127.12, 127.95, 128.80, 133.02, 142.15, 161.10, 192.21. Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3$ (257.28): C 70.02, H 5.88, N 5.44. Found: C 69.87, H 5.83, N 5.43.

Methyl 2-oxo-4-(1H-pyrrol-2-yl)-4-*p*-tolylbutanoate (3b): Yield: 0.176 g (65%); orange viscous oil; R_f 0.32 (EtOAc:hexane, 1:3). IR (KBr): 3421, 3098, 3022, 2954, 2923, 1730, 1563, 1513, 1438, 1272, 1076, 1041 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.36 (s, 3H, CH_3), 3.44 (dd, $J=18.0$ and $J=6.8$ Hz, 1H, CHH), 3.65 (dd, $J=18.0$ and $J=7.6$ Hz, 1H, CHH), 3.84 (s, 3H, OCH_3), 4.58 (t, $J=7.2$ Hz, 1H, CH), 5.94 (bs, 1H, $\text{C}(3)\text{H}$), 6.08 (dd, $J=5.6$ and $J=2.8$ Hz, 1H, $\text{C}(4)\text{H}$), 6.60 (bs, 1H, $\text{C}(5)\text{H}$), 7.11-7.21 (m, 4H, ArH), 7.95 (bs, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 21.07, 38.65, 45.56, 52.76, 105.58, 108.25,

117.27, 127.82, 129.43, 133.24, 136.49, 139.10, 161.10, 192.25. Anal. Calcd for $C_{16}H_{17}NO_3$ (271.31): C 70.83, H 6.32, N 5.16. Found: C 70.67, H 6.18, N 4.77.

Methyl 4-(4-methoxyphenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (3c): Yield: 0.187 g (65%); light brown viscous oil; R_f 0.43 (EtOAc:hexane, 1:3). IR (KBr): 3442, 2977, 2863, 1636, 1505, 1451, 1381, 1250, 1123, 1012 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 3.43 (dd, $J=18.0$ and $J=7.2$ Hz, 1H, CHH), 3.62 (dd, $J=18.0$ and $J=7.6$ Hz, 1H, CHH), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.56 (t, $J=7.3$ Hz, 1H, CH), 5.93 (bs, 1H, C(3)H), 6.08 (bs, 1H, C(4)H), 6.60 (bs, 1H, C(5)H), 6.82-6.87 (m, 2H, ArH), 7.14-7.16 (m, 2H, ArH), 7.96 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 38.28, 45.68, 52.77, 55.08, 105.53, 108.26, 114.05, 117.28, 128.60, 133.41, 134.13, 158.62, 161.12, 192.30. Anal. Calcd for $C_{16}H_{17}NO_4$ (287.31): C 66.89, H 5.96, N 4.88. Found: C 66.59, H 5.83, N 4.71.

Methyl-4-(2-methoxyphenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (3d): Yield: 0.129 g (45%); white solid; mp 119-120 $^{\circ}C$; R_f 0.38 (EtOAc:hexane, 1:3). IR (KBr): 3426, 2980, 2865, 1634, 1382, 1127, 1046 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 3.38 (dd, $J=17.2$ and $J=6.4$, 1H, CHH), 3.73 (dd, $J=17.2$ and $J=8.4$ Hz, 1H, CHH), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.00 (t, $J=7.2$ Hz, 1H, CH), 5.97 (bs, 1H, C(3)H), 6.09 (bs, 1H, C(4)H), 6.64 (bs, 1H, C(5)H), 6.89-6.93 (m, 2H, ArH), 7.09 (d, $J=7.6$ Hz, 1H, ArH), 7.20-7.24 (m, 1H, ArH), 8.25 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 33.23, 44.12, 52.83, 55.33, 105.40, 108.08, 111.03, 117.00, 121.16, 128.13, 128.58, 130.52, 133.05, 156.44, 161.25, 192.41. Anal. Calcd for $C_{16}H_{17}NO_4$ (287.31): C 66.89, H 5.96, N 4.88. Found: C 66.61, H 5.93, N 4.52.

Methyl 4-(4-fluorophenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (3e): Yield: 0.160 g (58%); light yellow viscous oil; R_f 0.37 (EtOAc:hexane, 1:3). IR (KBr): 3452, 2976, 2862, 1636, 1504, 1446, 1379, 1121, 991 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 3.43 (dd, $J=18.0$ and $J=6.8$ Hz, 1H, CHH), 3.65 (dd, $J=18.0$ and $J=7.6$ Hz, 1H, CHH), 3.87 (s, 3H, OCH_3), 4.60 (t, $J=7.2$ Hz, 1H, CH), 5.92 (bs, 1H, C(3)H), 6.08 (bs, 1H, C(4)H), 6.63 (bs, 1H, C(5)H), 6.98-7.03 (m, 2H, ArH), 7.20-7.24 (m, 2H, ArH), 7.95 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 38.34, 45.66, 52.89, 105.88, 108.45, 115.67(d, $J_{CF}=21.3$ Hz), 117.59, 129.49(d, $J_{CF}=7.9$ Hz), 132.84, 137.88, 161.07, 161.90(d, $J_{CF}=245.0$ Hz), 192.07. Anal. Calcd for $C_{15}H_{14}FNO_3$ (275.27): C 65.45, H 5.13, N 5.09. Found: C 65.22, H 5.18, N 5.12.

Methyl 4-(4-chlorophenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (3f): Yield: 0.143 g (49%); light brown viscous oil; R_f 0.35 (EtOAc:hexane, 1:3). IR (KBr): 3403, 2965, 2929, 2862, 1729, 1644, 1487, 1443, 1257, 1091 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 3.42 (dd, $J=18.4$ and $J=6.8$ Hz, 1H, CHH), 3.64 (dd, $J=18.0$ and $J=7.6$ Hz, 1H, CHH), 3.84 (s, 3H, OCH_3), 4.58 (t, $J=7.2$ Hz, 1H, CH), 5.94 (bs, 1H, C(3)H), 6.09 (bs, 1H, C(4)H), 6.60 (bs, 1H, C(5)H), 7.18 (d, $J=8.4$ Hz, 2H, ArH), 7.27-7.30 (m, 2H,

ArH), 8.03 (bs, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 38.38, 45.39, 52.88, 105.87, 108.38, 117.64, 128.74, 128.88, 132.45, 132.93, 140.71, 160.95, 191.94. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{ClNO}_3$ (291.73): calcd. C 61.76, H 4.84, N 4.80. Found: C 61.93, H 4.83, N 4.65.

Methyl 4-(4-bromophenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (3g): Yield: 0.212 g (63%); light brown solid; mp 126 °C; R_f 0.46 (EtOAc:hexane, 1:3). IR (KBr): 3424, 2976, 2863, 1636, 1379, 1261, 1122 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 3.43 (dd, $J=18.0$ and $J=6.8$ Hz, 1H, CHH), 3.65 (dd, $J=18.0$ and $J=7.6$ Hz, 1H, CHH), 3.86 (s, 3H, OCH_3), 4.58 (t, $J=7.2$ Hz, 1H, CH), 5.93 (bs, 1H, C(3)H), 6.08 (dd, $J=6.0$ and $J=2.8$ Hz, 1H, C(4)H), 6.63 (bs, 1H, C(5)H), 7.13 (d, $J=8.4$ Hz, 2H, ArH), 7.44 (d, $J=8.4$ Hz, 2H, ArH), 7.94 (bs, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 38.53, 45.40, 52.94, 106.03, 108.52, 117.70, 121.14, 129.70, 131.95, 132.41, 141.19, 161.02, 191.94. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{BrNO}_3$ (336.18): C 53.59, H 4.20, N 4.17. Found: C 53.98, H 4.01, N 4.06.

Methyl 4-(4-nitrophenyl)-2-oxo-4-(1H-pyrrol-2-yl)butanoate (3h): Yield: 0.212 g (70%); brown viscous oil; R_f 0.33 (EtOAc:hexane, 1:2). IR (KBr): 3401, 2956, 2866, 1733, 1605, 1519, 1438, 1348, 1277, 1076 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 3.47 (dd, $J=18.6$ and $J=7.1$ Hz, 1H, CHH), 3.69 (dd, $J=18.6$ and $J=7.3$ Hz, 1H, CHH), 3.82 (s, 3H, OCH_3), 4.70 (t, $J=7.2$ Hz, 1H, CH), 5.95 (bs, 1H, C(3)H), 6.06 (d, $J=3.1$ Hz, 1H, C(4)H), 6.62 (bs, 1H, C(5)H), 7.36 (d, $J=8.7$ Hz, 2H, ArH), 8.03 (d, $J=8.7$ Hz, 2H, ArH), 8.46 (bs, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 38.57, 44.86, 52.90, 105.93, 108.34, 118.04, 123.66, 128.63, 131.24, 146.62, 149.95, 160.67, 191.48. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_5$ (302.28): calcd. C 59.60, H 4.67, N 9.27. Found C 59.27, H 4.97, N 9.12.

General Procedure for the Cyclisation Reactions: 2-Substituted pyrrole derivatives **3a-h** were refluxed in CCl_4 for 6 hours at 75 °C and the reaction was monitored by TLC. ^1H NMR spectra of cyclization products indicated that all C(2)-substituted pyrrole derivatives **3a-h** were converted to **4a-h** quantitatively in 1:1 ratio of diastereomers. To identify the diastereomers, the solvent was removed under reduced pressure and the residue was separated by flash column chromatography (EtOAc:hexane, 1:4).

Methyl 3-hydroxy-1-phenyl-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4a): Light brown solid; mp 64 °C; R_f 0.33 (EtOAc:hexane, 1:3). IR (KBr): 3455, 3030, 2955, 2871, 1740, 1659, 1495, 1453, 1270, 1146, 1068 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.64 (dd, $J=13.6$ and $J=7.7$ Hz, 1H, CHH), 3.39 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.88 (s, 3H, OCH_3), 4.48 (t, $J=8.0$ Hz, 1H, CH), 4.64 (bs, 1H, OH), 5.75 (bs, 1H, pyrH), 6.31 (bs, 1H, pyrH), 6.62 (bs, 1H, pyrH), 7.24-7.37 (m, 5H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 42.08, 50.14, 53.73, 87.18, 101.20, 110.70, 115.00, 126.93, 127.65, 128.65,

139.16, 142.72, 172.02. Anal. Calcd for $C_{15}H_{15}NO_3$ (257.28): C 70.02, H 5.88, N 5.44. Found: C 69.72, H 5.86, N 5.44.

Methyl 3-hydroxy-1-phenyl-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4a'): Light brown solid; mp 96-97 °C; R_f 0.27 (EtOAc:hexane, 1:3). IR (KBr): 3460, 3100, 3024, 2955, 2911, 1733, 1493, 1275, 1202, 1115, 1069, 1041 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 3.00-3.08 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.32 (bs, 1H, OH), 4.65 (t, $J=8.1$ Hz, 1H, CH), 5.78 (bs, 1H, pyrH), 6.31 (bs, 1H, pyrH), 6.59 (bs, 1H, pyrH), 7.24-7.34 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 41.60, 50.82, 53.68, 86.93, 101.58, 110.99, 115.04, 126.94, 127.71, 128.62, 139.81, 142.46, 171.39.

Methyl 3-hydroxy-1-p-tolyl-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4b): Light brown solid; mp 111-111.5 °C; R_f 0.49 (EtOAc:hexane, 1:3). IR (KBr): 3446, 3004, 2953, 2923, 1738, 1513, 1454, 1268, 1180, 1146, 1103, 1069 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 2.37 (s, 3H, CH_3), 2.59 (dd, $J=13.6$ and $J=8.0$ Hz, 1H, CHH), 3.33 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.88 (s, 3H, OCH_3), 4.42 (t, $J=8.0$ Hz, 1H, CH), 4.49 (bs, 1H, OH), 5.71 (bs, 1H, pyrH), 6.29 (bs, 1H, pyrH), 6.58 (bs, 1H, pyrH), 7.12 (d, $J=8.0$ Hz, 2H, ArH), 7.23 (d, $J=8.0$ Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 21.10, 42.68, 50.16, 53.70, 87.04, 101.03, 110.49, 114.90, 127.49, 129.27, 136.22, 139.34, 139.64, 172.07. Anal. Calcd for $C_{16}H_{17}NO_3$ (271.31): C 70.83, H 6.32, N 5.16. Found: C 70.48, H 6.03, N 4.76.

Methyl 3-hydroxy-1-p-tolyl-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4b'): Light brown viscous oil; R_f 0.41 (EtOAc:hexane, 1:3). IR (KBr): 3455, 2977, 2917, 2869, 1740, 1658, 1513, 1455, 1262, 1206, 1098, 1073 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 2.38 (s, 3H, CH_3), 2.97-3.03 (m, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.21 (bs, 1H, OH), 4.60 (t, $J=8.1$ Hz, 1H, CH), 5.75 (bs, 1H, pyrH), 6.29 (bs, 1H, pyrH), 6.56 (bs, 1H, pyrH), 7.13 (d, $J=7.9$ Hz, 2H, ArH), 7.22 (d, $J=8.0$ Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 21.10, 41.16, 50.81, 53.62, 86.82, 101.35, 110.77, 114.92, 127.51, 129.21, 136.21, 139.33, 140.02, 171.37.

Methyl 3-hydroxy-1-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4c): Light brown solid; mp 116.5-117.5 °C; R_f 0.33 (EtOAc:hexane, 1:3). IR (KBr): 3479, 3008, 2954, 2841, 1738, 1615, 1513, 1455, 1251, 1190, 1109, 1035 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 2.58 (dd, $J=13.6$ and $J=7.6$ Hz, 1H, CHH), 3.34 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.42 (t, $J=8.0$ Hz, 1H, CH), 4.52 (bs, 1H, OH), 5.71 (bs, 1H, pyrH), 6.29 (bs, 1H, pyrH), 6.59 (bs, 1H, pyrH), 6.85 (d, $J=8.6$ Hz, 2H, ArH), 7.26 (d, $J=8.6$ Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 41.39, 50.35, 53.57, 55.11, 87.14, 101.04, 110.60, 114.08, 114.96, 128.62, 134.77, 139.58, 158.66, 172.10. Anal. Calcd for $C_{16}H_{17}NO_4$ (287.31): C 66.89, H 5.96, N 4.88. Found: C 67.12, H 6.33, N 4.56.

Methyl 3-hydroxy-1-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4c'): Light brown viscous oil; R_f 0.28 (EtOAc:hexane, 1:3). IR (KBr): 3441, 2977, 2866, 1743, 1613, 1512, 1447, 1383, 1252, 1179, 1118, 1036, 939 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.98-3.01 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.23 (bs, 1H, OH), 4.59 (t, $J=8.4$ Hz, 1H, CH), 5.74 (bs, 1H, pyrH), 6.29 (bs, 1H, pyrH), 6.56 (bs, 1H, pyrH), 6.85 (d, $J=8.4$ Hz, 2H, ArH), 7.23-7.28 (m, 2H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 40.90, 51.02, 53.73, 55.16, 86.92, 101.41, 110.89, 114.06, 115.00, 128.67, 134.44, 140.27, 158.70, 171.47.

Methyl 3-hydroxy-1-(2-methoxyphenyl)-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4d): Light brown solid; mp 111-111.5 $^{\circ}\text{C}$; R_f 0.49 (EtOAc:hexane, 1:3). IR (KBr): 3470, 2954, 2872, 1740, 1625, 1492, 1459, 1385, 1289, 1245, 1146, 1108, 1049 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.21 (dd, $J=12.8$ and $J=9.1$ Hz, 1H, CHH), 3.48 (dd, $J=13.8$ and $J=8.7$ Hz, 1H, CHH), 3.89 (bs, 6H, OCH_3), 4.45 (s, 1H, OH), 4.77 (t, $J=7.7$ Hz, 1H, CH), 5.78 (bs, 1H, pyrH), 6.32 (bs, 1H, pyrH), 6.61 (bs, 1H, pyrH), 6.87-6.91 (m, 2H, ArH), 7.22-7.36 (m, 1H, ArH), 7.34 (d, $J=7.5$ Hz, 1H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 35.73, 48.63, 53.65, 55.35, 87.26, 101.16, 110.32, 110.73, 114.81, 120.89, 127.84, 128.01, 131.18, 138.50, 156.92, 172.05. Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_4$ (287.31): C 66.89, H 5.96, N 4.88. Found: C 66.49, H 5.72, N 4.94.

Methyl 3-hydroxy-1-(2-methoxyphenyl)-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4d'): Light brown viscous oil; R_f 0.41 (EtOAc:hexane, 1:3). IR (KBr): 3442, 2955, 2869, 1739, 1599, 1492, 1459, 1439, 1245, 1107, 1050, 1027 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.84 (dd, $J=13.5$ and $J=7.2$ Hz, 1H, CHH), 3.17 (dd, $J=13.6$ and $J=8.3$ Hz, 1H, CHH), 3.80 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.21 (bs, 1H, OH), 4.95 (t, $J=7.7$ Hz, 1H, CH), 5.82 (bs, 1H, pyrH), 6.33 (bs, 1H, pyrH), 6.60 (bs, 1H, pyrH), 6.87-6.91 (m, 2H, ArH), 7.19-7.24 (m, 1H, ArH), 7.32 (d, $J=7.6$ Hz, 1H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 35.73, 48.63, 53.65, 55.35, 87.26, 101.70, 110.07, 110.84, 114.96, 120.58, 127.77, 127.84, 130.83, 138.88, 157.35, 171.75.

Methyl 1-(4-fluorophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4e): Light brown solid; mp 121-122 $^{\circ}\text{C}$; R_f 0.45 (EtOAc:hexane, 1:3). IR (KBr): 3447, 2978, 2871, 2361, 1741, 1604, 1510, 1456, 1270, 1223, 1148, 1100, 1067, 1013 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.57 (dd, $J=13.6$ and $J=6.2$ Hz, 1H, CHH), 3.39 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.88 (s, 3H, OCH_3), 4.45 (t, $J=7.9$ Hz, 1H, CH), 4.60 (bs, 1H, OH), 5.72 (bs, 1H, pyrH), 6.30 (bs, 1H, pyrH), 6.60 (bs, 1H, pyrH), 6.99-7.04 (m, 2H, ArH), 7.30-7.34 (m, 2H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 41.39, 50.20, 53.85, 87.11, 101.23, 110.80, 115.14, 115.52 (d, $J_{\text{CF}}=21.3$ Hz), 129.15 (d, $J_{\text{CF}}=7.9$ Hz), 138.51, 139.06,

161.86 (d, $J_{\text{CF}}=244.1$ Hz), 171.97. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{FNO}_3$ (275.27): C 65.45, H 5.13, N 5.09. Found: C 65.10, H 5.23, N 5.29.

Methyl 1-(4-fluorophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4e'): Light brown solid; mp 78-79 °C; R_f 0.38 (EtOAc:hexane, 1:3). IR (KBr): 3400, 2977, 2871, 1743, 1663, 1510, 1263, 1223, 1121, 1074, 1014 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.98 (dd, $J=13.4$ and $J=8.0$ Hz, 1H, CHH), 3.05 (dd, $J=13.4$ and $J=8.0$ Hz, 1H, CHH), 3.88 (s, 3H, OCH_3), 4.29 (bs, 1H, OH), 4.62 (t, $J=8.0$ Hz, 1H, CH), 5.75 (bs, 1H, pyrH), 6.30 (bs, 1H, pyrH), 6.57 (bs, 1H, pyrH), 6.99-7.04 (m, 2H, ArH), 7.28-7.32 (m, 2H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 40.80, 50.81, 53.67, 86.78, 101.47, 111.01, 115.27, 115.38 (d, $J_{\text{CF}}=21.1$ Hz), 129.06 (d, $J_{\text{CF}}=7.7$ Hz), 138.07, 139.54, 161.85 (d, $J_{\text{CF}}=244.4$ Hz), 171.18.

Methyl 1-(4-chlorophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4f): Light brown viscous oil; R_f 0.39 (EtOAc:hexane, 1:3). IR (KBr): 3459, 3100, 2977, 2955, 2873, 1741, 1659, 1491, 1456, 1410, 1266, 1203, 1148, 1092, 1014 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.57 (dd, $J=13.7$ and $J=7.4$ Hz, 1H, CHH), 3.39 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.87 (s, 3H, OCH_3), 4.45 (t, $J=7.9$ Hz, 1H, CH), 4.71 (bs, 1H, OH), 5.73 (bs, 1H, pyrH), 6.31 (bs, 1H, pyrH), 6.62 (bs, 1H, pyrH), 7.27-7.30 (m, 4H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 41.42, 50.70, 53.78, 87.10, 101.23, 110.88, 115.08, 128.42, 128.98, 132.77, 138.67, 141.26, 171.80. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{ClNO}_3$ (291.73): calcd. C 61.76, H 4.84, N 4.80. Found: C 61.44, H 4.75, N 4.73.

Methyl 1-(4-chlorophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4f'): Light brown viscous oil; R_f 0.34 (EtOAc:hexane, 1:3). IR (KBr): 3443, 2978, 2872, 1743, 1657, 1491, 1455, 1409, 1263, 1208, 1121, 1092, 1014 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.97 (dd, $J=13.4$ and $J=8.0$ Hz, 1H, CHH), 3.05 (dd, $J=13.4$ and $J=8.1$ Hz, 1H, CHH), 3.88 (s, 3H, OCH_3), 4.29 (bs, 1H, OH), 4.61 (t, $J=8.0$ Hz, 1H, CH), 5.75 (bs, 1H, pyrH), 6.30 (bs, 1H, pyrH), 6.57 (bs, 1H, pyrH), 7.26-7.30 (m, 4H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 41.03, 50.77, 53.82, 86.89, 101.67, 111.19, 115.20, 128.83, 129.18, 132.89, 139.29, 141.03, 171.26.

Methyl 1-(4-bromophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4g): Light brown solid; mp 80-81 °C; R_f 0.49 (EtOAc:hexane, 1:3). IR (KBr): 3474, 2949, 1721, 1458, 1284, 1200, 1147, 1098, 1054 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) (δ ppm): 2.58 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.41 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.88 (s, 3H, OCH_3), 4.46 (t, $J=8.0$ Hz, 1H, CH), 4.57 (bs, 1H, OH), 5.76 (bs, 1H, pyrH), 6.35 (bs, 1H, pyrH), 6.65 (bs, 1H, pyrH), 7.25 (d, $J=8.8$, 2H, ArH), 7.46 (d, $J=8.4$ Hz, 2H, ArH). ^{13}C NMR (100 MHz, CDCl_3) (δ ppm): 41.46, 49.91, 53.90, 87.03, 101.21, 110.85, 115.05,

120.83, 129.33, 131.74, 138.63, 141.74, 171.86. Anal. Calcd for $C_{15}H_{14}BrNO_3$ (336.18): C 53.59, H 4.20, N 4.17. Found: C 53.32, H 4.07, N 4.15.

Methyl 1-(4-bromophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4g'): Light brown viscous oil; R_f 0.44 (EtOAc:heksan, 1:3). IR (KBr): 3497, 2949, 1738, 1476, 1265, 1085, 1023 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 2.99 (dd, $J=13.6$ and $J=8.0$ Hz, 1H, CHH), 3.07 (dd, $J=13.6$ and $J=8.0$ Hz, 1H, CHH), 3.87 (s, 3H, OCH_3), 4.39 (bs, 1H, OH), 4.62 (t, $J=8.0$ Hz, 1H, CH), 5.79 (bs, 1H, pyrH), 6.35 (bs, 1H, pyrH), 6.64 (bs, 1H, pyrH), 7.22 (d, $J=8.4$ Hz, 2H, ArH), 7.47 (d, $J=8.4$ Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 40.97, 50.63, 53.80, 86.84, 101.53, 111.18, 115.03, 120.78, 129.36, 131.74, 139.19, 141.45, 171.17.

Methyl 1-(4-nitrophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4h): Light brown solid; mp 111.5-112.5 $^{\circ}C$; R_f 0.36 (EtOAc:hexane, 1:2). IR (KBr): 3448, 2978, 2869, 1736, 1648, 1518, 1456, 1348, 1267, 1109, 1072, 1014 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 2.59 (dd, $J=14.0$ and $J=7.2$ Hz, 1H, CHH), 3.47 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.90 (s, 3H, OCH_3), 4.57 (t, $J=7.6$ Hz, 1H, CH), 4.66 (bs, 1H, OH), 5.74 (bs, 1H, pyrH), 6.32 (t, $J=2.8$ Hz, 1H, pyrH), 6.63 (bs, 1H, pyrH), 7.52 (d, $J=8.7$ Hz, 2H, ArH), 8.19 (d, $J=9.1$ Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 41.74, 49.60, 54.01, 87.11, 101.65, 111.33, 115.41, 124.00, 128.53, 137.71, 147.20, 150.38, 171.55. Anal. Calcd for $C_{15}H_{14}N_2O_5$ (302.28): C 59.60, H 4.67, N 9.27. Found: C 59.14, H 4.81, N 8.90.

(Methyl 1-(4-nitrophenyl)-3-hydroxy-2,3-dihydro-1H-pyrrolizine-3-carboxylate (4h')): Light brown solid; mp 97.5-98.5 $^{\circ}C$; R_f 0.31 (EtOAc:hexane, 1:2). IR (KBr): 3394, 2900, 1743, 1637, 1518, 1473, 1348, 1263, 1121 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) (δ ppm): 3.02 (dd, $J=13.6$ and $J=7.6$ Hz, 1H, CHH), 3.13 (dd, $J=13.6$ and $J=8.4$ Hz, 1H, CHH), 3.90 (s, 3H, OCH_3), 4.36 (bs, 1H, OH), 5.78 (bs, 1H, pyrH), 6.33 (bs, 1H, pyrH), 6.61 (bs, 1H, pyrH), 7.51 (d, $J=8.7$ Hz, 2H, ArH), 8.21 (d, $J=8.7$ Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 41.37, 51.41, 53.95, 86.88, 101.99, 111.59, 115.46, 123.96, 128.56, 138.15, 147.28, 150.13, 170.96.

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