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# Gadolinium triflate catalyzed alkylation of pyrroles: efficient synthesis of 3-oxo-2,3-dihydro-1*H*-pyrrolizine derivatives

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**Abstract**—Novel 2-alkylated pyrrole derivatives were synthesized regioselectively by $Gd(OTf)_3$ catalyzed addition reactions of pyrrole to substituted dimethyl 2-benzylidenemalonate derivatives under mild reaction conditions. 2-Alkylated pyrrole derivatives are used for the construction of the 3-oxo pyrrolizine skeleton. Intramolecular cyclization of alkylated pyrrole derivatives afforded new diastereoselective 3-oxo-2,3-dihydro-1*H*-pyrrolizine derivatives with good to high yields.
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## 1. Introduction

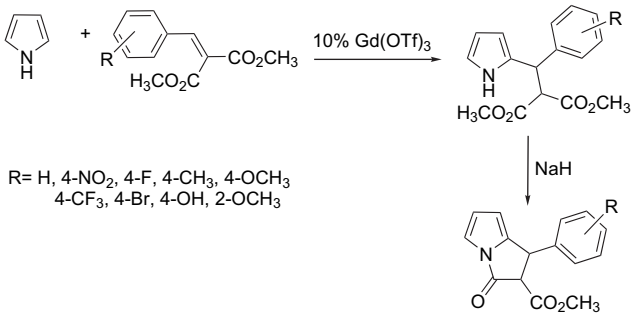
The Friedel–Crafts alkylation reaction is a powerful C–C bond-forming process in organic synthesis.[1] Recently, $M(OTf)_x$ (M=Yb, Sc, Cu, Zn, Dy, etc.) have been used in this transformation as mild, water tolerant, high yielding and environmentally benign Lewis acid catalysts.[2]

Synthesis of pyrrole derivatives and bridgehead nitrogen heterocycles are of interest because they often display biological activity and are important as precursors in the synthesis of many biologically active compounds.[3] A variety of methods have been developed for the alkylation of pyrrole[4] and to generate bicyclic [5-5] systems with one ring junction nitrogen atom.[5] Consequently, interest has been ongoing in the synthesis of pyrrole and pyrrolizine derivatives.

Recently our studies have revealed that metal triflates are very suitable Lewis acids for the direct alkylation of pyrrole compounds. We have reported that the metal triflate catalyzed conjugate addition of pyrrole to α,β-unsaturated esters and *N*-tosyl imines proceeded in good yields.[6] With our ongoing research, we have become interested in the construction of the 3-oxo pyrrolizine skeleton from alkylated pyrroles themselves obtained from the addition of pyrrole to electron-deficient alkenes with a metal triflate catalyst.

A previously published method for the synthesis of pyrrolizine-3-ones involves the cyclization of the condensation product of pyrrole 2-carboxyaldehyde and malonic acid in very low yield.[7] The formation of pyrrolizine-3-one by flash vacuum pyrolysis of the condensation product of pyrrole 2-carboxyaldehyde with Meldrum's acid at 600 °C with high yield has been reported by McNab.[8] The products were further used in the synthesis of 1,2-dihydropyrrolizine-3-one derivatives.[9] Recently, the alkylation product of pyrrole with α,β-unsaturated 2-acyl imidazole[10] and a radical reaction product of pyrrole and α-haloesters[11] were used in the synthesis of oxo-2,3-dihydro-1*H*-pyrrolizine derivatives.

In this work, we describe the gadolinium triflate catalyzed regioselective addition of pyrrole to substituted dimethyl 2-benzylidenemalonates and their intramolecular cyclization affording 3-oxo-2,3-dihydro-1*H*-pyrrolizine derivatives (Scheme 1).




**Scheme 1**.

*Keywords*: 3-Oxo-pyrrolizine derivatives; Pyrrolizine derivatives; Metal triflate; Pyrrole derivatives; Lewis acid catalysis.
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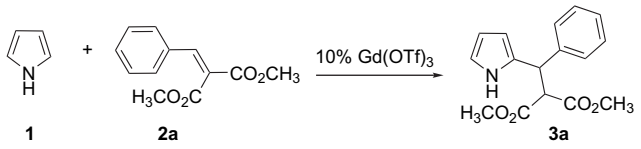
## 2. Results and discussion

Dimethyl 2-benzylidenemalonate (**2a**) was synthesized from benzaldehyde and dimethylmalonate, via the classic Knoevenagel condensation, with piperidine as a catalyst in toluene at reflux. It is known that the high reactivity of pyrrole allows addition to electron-deficient alkenes. Dimethyl 2-benzylidinemalonate (**2a**) seems to be a good acceptor for the addition reactions of pyrrole (**1**) (Scheme 2).



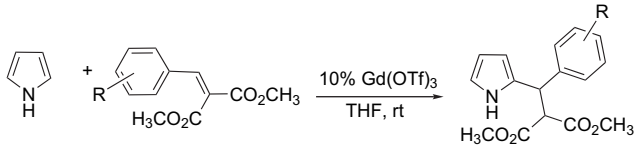

**Scheme 2**.

**Table 1**. Effect of catalyst on the alkylation reaction of pyrrole[a]

| Entry | Catalyst | Yield[b] (%) |
|---|---|---|
| 1 | $Cu(OTf)_2$ | 50 |
| 2 | $Zn(OTf)_2$ | 20 |
| 3 | $Y(OTf)_3$ | 40 |
| 4 | $Yb(OTf)_3$ | 65 |
| 5 | $Nd(OTf)_3$ | 50 |
| 6 | $La(OTf)_3$ | 70 |
| 7 | $Gd(OTf)_3$ | 80 |

[a] Reactions were carried out in THF at rt.
[b] Yield refers to pure product after column chromatography.

**Table 2**. Effect of substituent on the alkylation reaction of pyrrole[a]




| Entry | R | 3 | Yield[b] (%) |
|---|---|---|---|
| 1 | H | **3a** | 80 |
| 2 | 4-$NO_2$ | **3b** | 83 |
| 3 | 4-$CF_3$ | **3c** | 92 |
| 4 | 4-F | **3d** | 81 |
| 5 | 4-Br | **3e** | 84 |
| 6 | 4-$CH_3$ | **3f** | 74 |
| 7 | 4-$OCH_3$ | **3g** | 50 |
| 8 | 4-OH | **3h** | 37 |
| 9 | 2-$OCH_3$ | **3i** | 55 |

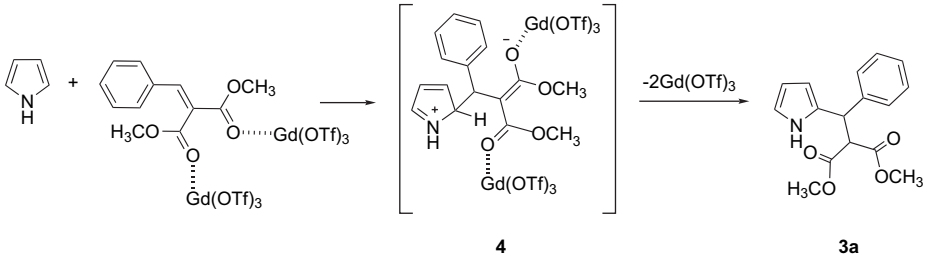
[a] Reactions were carried out in THF at rt.
[b] Yield refers to pure product after column chromatography.

The addition reactions of pyrrole with **2a** in the presence of various metal triflates in THF at rt were subsequently investigated (Table 1). The addition reaction regioselectively provided dimethyl 2-(phenyl(1*H*-pyrroyl)methyl)malonate (**3a**) as product in 80% yield with $Gd(OTf)_3$ (Table 1, entry 7). $Cu(OTf)_2$, $Yb(OTf)_3$, $Nd(OTf)_3$ and $La(OTf)_3$ catalyzed the addition reaction with 50–70% yields (Table 1, entries 1, 4–6). $Zn(OTf)_2$ and $Y(OTf)_3$ were found to be inefficient in improving the yield (Table 1, entries 2 and 3). Of the various organic solvents examined (THF, $CH_2Cl_2$, toluene and acetone) in the presence of 10 mol % $Gd(OTf)_3$ at rt, the best chemical yield (80%) was obtained in THF.

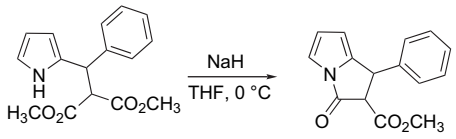
Substituted dimethyl 2-benzylidenemalonates **2b–i** were synthesized to examine the effect of substituents on the addition reaction. Employing $Gd(OTf)_3$ in THF at rt, the influence of the substituent on the alkylation efficiency was examined (Table 2). Addition reactions of pyrrole to **2g**, **2h** and **2i** with electron donating substituents gave the product with low yield (37–55%) (Table 2, entries 7–9). Weakly electron donating methyl substituted **2f** yielded **3f** in 74% yield (Table 2, entry 6). Electron-withdrawing substituents improved the efficiency of the alkylation reaction, and **3b**, **3d** and **3e** were obtained in high yields (83%, 81% and 84%, respectively) (Table 2, entries 2, 4 and 5). Compound **2c** with $CF_3$ gave the addition product **3c** with the highest yield (92%). The structure of **3a–i** was identified by $^1H$ NMR, $^{13}C$ NMR and elemental analysis. The position of the substituent was assigned by COSY spectra and by comparing the $^1H$ NMR spectra with those of the known 2-alkylated pyrroles.[4a,12]

The following reaction mechanism is proposed for $Gd(OTf)_3$ catalyzed addition reaction of pyrrole to substituted dimethyl 2-benzylidenemalonates (Scheme 3). Coordination of $Gd(OTf)_3$ activates the structure of 2-benzylidenemalonate, then addition of pyrrole to activated dimethyl 2-benzylidenemalonate affords **3a** through the intermediate **4**. When the reaction was performed without $Gd(OTf)_3$, the addition product was not obtained. Consequently, $Gd(OTf)_3$ has a crucial function in the addition reaction of pyrrole to dimethyl 2-benzylidenemalonate.

For the synthesis of the [5-5] membered ring system of pyrrolizine, alkylated novel pyrrole derivatives **3a–i** are suitable functional five-membered ring equivalents. Intramolecular cyclizations of **3a** were carried out in the presence of NaH in dry THF under argon (Scheme 4). The reaction mixture was stirred at 0 °C and monitored by TLC. Intramolecular cyclization of dimethyl 2-benzylidenemalonate (**3a**) diastereoselectively furnished lactam product **5a** in 74% yield (Table 3, entry 1). The same method was applied to



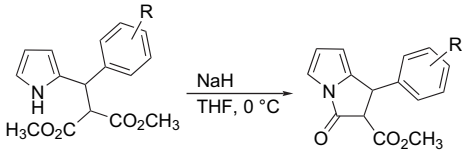

**Scheme 3**.




3a 5a

**Scheme 4**.

**Table 3**. Intramolecular cyclization products **5a–i** of **3a–i**




3a-i 5a-i

| Entry | R | 5 | Yield[a] (%) |
|---|---|---|---|
| 1 | H | **5a** | 74 |
| 2 | 4-$NO_2$ | **5b** | 78 |
| 3 | 4-$CF_3$ | **5c** | 68 |
| 4 | 4-F | **5d** | 70 |
| 5 | 4-Br | **5e** | 77 |
| 6 | 4-$CH_3$ | **5f** | 76 |
| 7 | 4-$OCH_3$ | **5g** | 73 |
| 8 | 4-OH | **5h** | 76 |
| 9 | 2-$OCH_3$ | **5i** | 65 |

[a] Yield refers to pure product after column chromatography.

intramolecular cyclization of **3b–i**. Alkylated pyrrole derivatives **3b**, **3e**, **3f** and **3h** gave, respectively, the cyclization products **5b** (78%), **5e** (77%), **5f** (76%) and **5h** (76%) with comparable yields (Table 3, entries 2, 5, 6 and 8). Compound **5d** was obtained with 70% yield (Table 3, entry 4). Compounds **5c** and **5i** were formed in 68% and 65% yield, respectively (Table 3, entries 3 and 9). 3-Oxo-2,3-dihydro-1*H*-pyrrolizine derivatives **5a–i** formed diastereoselectively.

## 3. Conclusion

In summary, we report that addition reaction of pyrrole to dimethyl 2-benzylidenemalonate derivatives regioselectively produced novel 2-alkylated pyrrole derivatives **3a–i** in the presence of $Gd(OTf)_3$ under mild reaction conditions. The isolated yields are highly dependent on the substituent. The products are almost formed with high yield excepting the OH and $OCH_3$ substituents. 2-Alkylated pyrrole derivatives **3a–i** are convenient precursors for the synthesis of 3-oxo-2,3-dihydro-1*H*-pyrrolizine derivatives. The synthesis of these heterocycles can be achieved by intramolecular cyclization of 2-alkylated pyrrole derivatives **3a–i**. Novel diastereoselective 3-oxo-2,3-dihydro-1*H*-pyrrolizine derivatives are obtained in good to high yield.

## 4. Experimental

### 4.1. General

Commercially available reagents and solvents were used without further purification. Anhydrous tetrahydrofuran used for intramolecular cyclization was freshly distilled from sodium benzophenone. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Brucker ultra shield FT NMR spectrometer using $CDCl_3$ and DMSO-$d_6$ as solvents and $SiMe_4$ as an internal standard. Chemical shifts (parts per million) were reported relative to $SiMe_4$. Coupling constants are expressed as *J* values in hertz. Infrared spectra were recorded on a Unicam Mattson 1000 FTIR spectrometer. Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. Reactions were monitored by thin layer chromatography using precoated silica plates (Kiesel 60, F254, E. Merck), visualized with UV light ($\lambda$=254 nm). Flash column chromatography was performed on silica gel (230–400 mesh, E. Merck).

### 4.2. General procedure for the synthesis of compounds 3a–i

A mixture of dimethyl benzylidenemalonate derivatives (0.5 mmol) and $Gd(OTf)_3$ (0.03 g, 0.05 mmol) in THF (5 mL) was stirred for 0.5 h at rt. Pyrrole (0.33 g, 5.0 mmol) was added instantly via syringe pump. The resulting mixture was stirred for 12 h at rt and monitored by TLC. Five millilitres of water was added to the solution and the mixture was then extracted with diethylether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography.

**4.2.1. Dimethyl 2-(phenyl(1*H*-pyrrol-2-yl)methyl)malonate (3a).** White tiny prisms; mp: 112–113 °C; $R_f$ 0.38 (1:3 EtOAc/hexane); IR (KBr): 3379, 2952, 1744, 1601, 1558, 1508, 1432, 1258, 1148 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.49 (s, 3H, $OCH_3$), 3.71 (s, 3H, $OCH_3$), 4.19 (d, 1H, *J*=10.4, CH), 4.82 (d, 1H, *J*=10.4, CH), 5.95 (br s, 1H, C3-H), 6.05–6.08 (m, 1H, C4-H), 6.63 (br s, 1H, C5-H), 7.21–7.32 (m, 5H, Ar-H), 8.52 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 44.4, 52.3, 52.7, 57.6, 106.5, 108.2, 117.6, 127.2, 128.2, 128.5, 130.6, 139.8, 167.7, 168.9. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.17; H, 5.82; N, 4.52.

**4.2.2. Dimethyl 2-((4-nitrophenyl)(1*H*-pyrrol-2-yl)-methyl)malonate (3b).** Pale yellow powder; mp: 170–171 °C; $R_f$ 0.33 (1:3 EtOAc/hexane); IR (KBr): 3370, 2951, 1739, 1559, 1509, 1434, 1299, 1256, 1173 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.55 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 4.19 (d, 1H, *J*=9.8, CH), 4.92 (d, 1H, *J*=9.8, CH), 5.90 (br s, 1H, C3-H), 6.06–6.09 (m, 1H, C4-H), 6.69 (br s, 1H, C5-H), 7.45 (d, 2H, *J*=8.7, Ar-H), 8.17 (d, 2H, *J*=8.7, Ar-H), 8.74 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 44.0, 52,8, 53.0, 57.2, 107.6, 108.8, 118.4, 123.8, 128.8, 129.1, 147.2, 147.3, 167.4, 168.6. Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 58.10; H, 4.87; N, 8.25.

**4.2.3. Dimethyl 2-((1*H*-pyrrol-2-yl)(4-(trifluoromethyl)-phenyl)methyl)malonate (3c).** White powder; mp: 94–95 °C; $R_f$ 0.45 (1:3 EtOAc/hexane); IR (KBr): 3380, 2955, 1747, 1617, 1432, 1331, 1260, 1153 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.54 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 4.18 (d, 1H, *J*=10.0, CH), 4.87 (d, 1H, *J*=10.0,

CH), 5.91 (br s, 1H, C3-H), 6.07 (br s, 1H, C4-H), 6.67 (br s, 1H, C5-H), 7.40 (d, 2H, $J$=8.0, Ar-H), 7.57 (d, 2H, $J$=8.0, Ar-H), 8.56 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 44.1, 52.6, 52.9, 57.3, 107.3, 108.6, 118.1, 124.1 (q, $^1J_{C-F}$=270.2), 125.5 (q, $^3J_{C-F}$=3.7), 128.6, 129.6 (q, $^2J_{C-F}$=32.2), 129.9, 144.0, 167.5, 168.7. Anal. Calcd for $C_{17}H_{16}F_3NO_4$: C, 57.47; H, 4.54; N, 3.94. Found: C, 57.21; H, 4.64; N, 3.92.

**4.2.4. Dimethyl 2-((4-fluorophenyl)(1*H*-pyrrol-2-yl)-methyl)malonate (3d).** White powder; mp: 131–132 °C; $R_f$ 0.43 (1:3 EtOAc/hexane); IR (KBr): 3378, 2955, 1739, 1507, 1429, 1296, 1250 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.52 (s, 3H, $OCH_3$), 3.71 (s, 3H, $OCH_3$), 4.13 (d, 1H, $J$=10.4, CH), 4.80 (d, 1H, $J$=10.4, CH), 5.92 (br s, 1H, C3-H), 6.07 (br s, 1H, C4-H), 6.65 (br s, 1H, C5-H), 6.96–7.01 (m, 2H, Ar-H), 7.23–7.26 (m, 2H, Ar-H), 8.67 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 43.7, 52.4, 52.8, 57.7, 106.6, 108.4, 115.4 (d, $^2J_{C-F}$=21.2), 117.8, 129.8 (d, $^3J_{C-F}$=7.9), 130.5, 135.6 (d, $^4J_{C-F}$=3.3), 161.9 (d, $^1J_{C-F}$=244.8), 167.7, 168.8. Anal. Calcd for $C_{16}H_{16}FNO_4$: C, 62.94; H, 5.28; N, 4.59. Found: C, 62.65; H, 5.40; N, 4.70.

**4.2.5. Dimethyl 2-((4-bromophenyl)(1*H*-pyrrol-2-yl)-methyl)malonate (3e).** White powder; mp: 158–160 °C; $R_f$ 0.35 (1:3 EtOAc/hexane); IR (KBr): 3385, 2952, 1752, 1436, 1352, 1307, 1256, 1142 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.54 (s, 3H, $OCH_3$), 3.71 (s, 3H, $OCH_3$), 4.13 (d, $J$=10.2, 1H, CH), 4.77 (d, $J$=10.2, 1H, CH), 5.90 (br s, 1H, C3-H), 6.05–6.07 (m, 1H, C4-H), 6.65 (br s, 1H, C5-H), 7.15 (d, $J$=8.4, 2H, Ar-H), 7.42 (d, $J$=8.4, 2H, Ar-H), 8.53 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 43.8, 52.6, 52.9, 57.4, 106.9, 108.4, 117.9, 121.3, 130.0, 131.7, 139.0, 167.6, 168.8. Anal. Calcd for $C_{16}H_{16}BrNO_4$: C, 52.48; H, 4.40; N, 3.82. Found: C, 52.21; H, 4.20; N, 3.89.

**4.2.6. Dimethyl 2-((1*H*-pyrrol-2-yl)(*p*-tolyl)methyl)malonate (3f).** White powder; mp: 133–134 °C; $R_f$ 0.46 (1:3 EtOAc/hexane); IR (KBr): 3381, 2936, 1739, 1632, 1558, 1509, 1432, 1252 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.34 (s, 3H, $CH_3$), 3.52 (s, 3H, $OCH_3$), 3.71 (s, 3H, $OCH_3$), 4.16 (d, 1H, $J$=10.6, CH), 4.78 (d, 1H, $J$=10.6, CH), 5.93 (br s, 1H, C3-H), 6.04–6.06 (m, 1H, C4-H), 6.62 (br s, 1H, C5-H), 7.06–7.16 (m, 4H, Ar-H), 8.58 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.1, 44.0, 52.3, 52.6, 57.7, 106.4, 108.2, 117.5, 128.0, 129.2, 130.9, 136.5, 136.8, 167.7, 168.9. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.50; H, 6.42; N, 4.50.

**4.2.7. Dimethyl 2-((4-methoxyphenyl)(1*H*-pyrrol-2-yl)-methyl)malonate (3g).** White block crystals; mp: 112–113 °C; $R_f$ 0.27 (1:3 EtOAc/hexane); IR (KBr): 3381, 2952, 1747, 1609, 1512, 1431, 1307, 1257, 1142 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.51 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 4.12 (d, 1H, $J$=10.6, CH), 4.76 (d, 1H, $J$=10.6, CH), 5.92 (br s, 1H, C3-H), 6.03–6.06 (m, 1H, C4-H), 6.61 (br s, 1H, C5-H), 6.81 (d, 2H, $J$=8.7, Ar-H), 7.18 (d, 2H, $J$=8.7, Ar-H), 8.48 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 43.6, 52.3, 52.7, 55.0, 57.8, 106.2, 108.2, 113.9, 116.1, 117.5, 129.2, 131.1, 131.8, 158.6, 167.8, 168.9. Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.52; H, 6.13; N, 4.60.

**4.2.8. Dimethyl 2-((4-hydroxyphenyl)(1*H*-pyrrol-2-yl)-methyl)malonate (3h).** White powder; mp: 164–165 °C; $R_f$ 0.30 (1:3 EtOAc/hexane); IR (KBr): 3378, 2952, 1746, 1432, 1215, 1258, 1146 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.41 (s, 3H, $OCH_3$), 3.52 (s, 3H, $OCH_3$), 4.25 (d, $J$=12.0, 1H, CH), 4.52 (d, $J$=12.0, 1H, C*H*), 5.84 (br s, 1H, C3-H), 5.92 (s, 1H, C4-H), 6.53 (br s, 1H, C5-H), 6.62 (d, $J$=8.5, 2H, Ar-H), 7.06 (d, $J$=8.5, 2H, Ar-H), 9.27 (s, 1H, OH), 10.58 (br s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 44.0, 52.7, 52.8, 57.3, 104.3, 107.6, 115.3, 117.2, 129.3, 131.7, 132.4, 156.4, 165.2, 168.0. Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.47; H, 5.64; N, 4.54.

**4.2.9. Dimethyl 2-((2-methoxyphenyl)(1*H*-pyrrol-2-yl)-methyl)malonate (3i).** White powder; mp: 85–86 °C; $R_f$ 0.30 (1:3 EtOAc/hexane); IR (KBr): 3339, 2954, 1720, 1512, 1437, 1320, 1240, 1157 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.51 (s, 3H, $OCH_3$), 3.65 (s, 3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 4.51 (d, $J$=10.8, 1H, CH), 5.13 ($J$=10.4, 1H, CH), 5.95 (br s, 1H, C3-H), 6.03–6.05 (m, 1H, C4-H), 6.63 (br s, 1H, C5-H), 6.90–6.93 (m, 2H, Ar-H), 7.19–7.23 (m, 2H, Ar-H), 9.12 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 39.8, 52.3, 52.9, 55.5, 55.6, 107.8, 108.1, 111.0, 116.8, 121.1, 128.1, 128.9, 129.6, 130.3, 156.5, 167.8, 169.0. Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.62; H, 6.09; N, 4.53.

### 4.3. General procedure for the synthesis of 5a–i

The following process was used for the synthesis of the above-mentioned compounds. Dimethyl 2-(phenyl(1*H*-pyrrol-2-yl)methyl)malonate (**3a**) (0.29 g, 1.00 mmol) was dissolved in THF (3 mL) under argon and cooled to 0 °C. Sodium hydride (0.04 g, 1.5 mmol) was added to the solution and the mixture was stirred at 0 °C for 8 h and monitored by TLC. The mixture was then poured into pH 7 phosphate buffer (5 mL) and the product was extracted with EtOAc (3×10 mL). After removal of the solvents under reduced pressure, the residue was purified by flash silica gel column chromatography.

**4.3.1. Methyl 3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5a).** Viscous oil; $R_f$ 0.48 (1:3 EtOAc/hexane); IR (KBr): 2952, 1762, 1571, 1455, 1398, 1289, 1251, 1164, 1082 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.88 (s, 3H, $OCH_3$), 3.94 (d, 1H, $J$=5.1, CH), 4.92 (d, 1H, $J$=4.6, CH), 6.00 (br s, 1H, Pyr-H), 6.53 (t, 1H, $J$=3.2, Pyr-H), 7.11 (d, 1H, $J$=3.2, Pyr-H), 7.27–7.34 (m, 5H, Ar-H). $^{13}$C NMR (100 MHz, $CDCl_3$): 43.0, 53.1, 62.3, 106.3, 111.9, 119.8, 127.3, 127.9, 128.9, 129.2, 140.1, 165.0, 167.6. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.36; H, 5.10; N, 5.16.

**4.3.2. Methyl 1-(4-nitrophenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5b).** Viscous oil; $R_f$ 0.54 (1:3 EtOAc/hexane); IR (KBr): 2866, 1732, 1641, 1517, 1461, 1397, 1344, 1287, 1124 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.91 (br s, 4H, $OCH_3$, CH), 5.07 (d, 1H, $J$=5.2, CH), 6.04 (br s, 1H, Pyr-H), 6.58 (t, 1H, $J$=3.2, Pyr-H), 7.15 (br s, 1H, Pyr-H), 7.47 (d, 2H, $J$=8.7, Ar-H), 8.24 (d, 2H, $J$=8.7, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 42.5, 53.4, 61.7, 106.8, 112.6, 119.9, 120.1, 124.5, 128.4, 138.3,

147.1, 147.9, 162.0, 167.6. Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.17; H, 4.05; N, 9.12.

**4.3.3. Methyl 3-oxo-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5c).** Viscous oil; $R_f$ 0.71 (1:3 EtOAc/hexane); IR (KBr): 2957, 1760, 1653, 1618, 1404, 1324, 1165, 1068 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.86 (s, 3H, $OCH_3$), 3.91 (d, 1H, $J$=5.2, CH), 4.99 (d, 1H, $J$=5.2, CH), 6.01 (br s, 1H, Pyr-H), 6.55 (t, 1H, $J$=3.2, Pyr-H), 7.14 (d, 1H, $J$=3.2, Pyr-H), 7.41 (d, 2H, $J$=8.1, Ar-H), 7.63 (d, 2H, $J$=8.1, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 42.6, 53.3, 61.9, 106.6, 112.3, 120.1, 126.1 (q, $^3J_{C-F}$=3.7), 126.6 (q, $^1J_{C-F}$=270.3), 127.8, 130.4 (q, $^2J_{C-F}$=32.3), 139.0, 144.1, 164.4, 167.2. Anal. Calcd for $C_{16}H_{12}F_3NO_3$: C, 59.45; H, 3.74; N, 4.33. Found: C, 59.48; H, 4.01; N, 4.44.

**4.3.4. Methyl 1-(4-fluorophenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5d).** Viscous oil; $R_f$ 0.60 (1:3 EtOAc/hexane); IR (KBr): 2953, 1760, 1605, 1570, 1508, 1464, 1231, 1162 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.87 (br s, 4H, $OCH_3$, CH), 4.91 (d, 1H, $J$=4.9, CH), 5.99 (br s, 1H, Pyr-H), 6.52 (t, 1H, $J$=3.2, Pyr-H), 7.01–7.05 (m, 2H, Ar-H), 7.10 (br s, 1H, Pyr-H), 7.22–7.26 (m, 2H, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 42.3, 53.1, 62.3, 106.4, 112.0, 116.1 (d, $^2J_{C-F}$=21.3), 119.8, 129.0 (d, $^3J_{C-F}$=8,1), 135.8 (d, $^4J_{C-F}$=3.4), 139.8, 162.4 (d, $^1J_{C-F}$=245.9), 164.7, 167.4. Anal. Calcd for $C_{15}H_{12}FNO_3$: C, 65.93; H, 4.43; N, 5.13. Found: C, 65.60; H, 4.47; N, 5.24.

**4.3.5. Methyl 1-(4-bromophenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5e).** White tiny prisms; mp: 66–68 °C; $R_f$ 0.63 (1:3 EtOAc/hexane); IR (KBr): 2966, 1754, 1612, 1512, 1454, 1401, 1254, 1168, 1118 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.87 (br s, 4H, $OCH_3$, CH), 4.89 (d, 1H, $J$=4.9, CH), 5.98 (br s, 1H, Pyr-H), 6.55 (t, 1H, $J$=3.2, Pyr-H), 7.09 (br s, 1H, Pyr-H), 7.15 (d, 2H, $J$=8.5, Ar-H), 7.46 (d, 2H, $J$=8.5, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 42.4, 53.1, 61.9, 106.3, 112.0, 119.9, 121.9, 129.0, 132.2, 139.0, 139.3, 164.5, 167.2. Anal. Calcd for $C_{15}H_{12}BrNO_3$: C, 53.91; H, 3.62; N, 4.19. Found: C, 53.54; H, 3.56; N, 4.17.

**4.3.6. Methyl 3-oxo-1-*p*-tolyl-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5f).** Viscous oil; $R_f$ 0.60 (1:3 EtOAc/hexane); IR (KBr): 2950, 1754, 1644, 1571, 1511, 1462, 1400, 1088 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 2.37 (s, 3H, $CH_3$), 3.87 (s, 3H, $OCH_3$), 3.91 (d, 1H, $J$=5.1, CH), 4.88 (d, 1H, $J$=5.2, CH), 5.98 (br s, 1H, Pyr-H), 6.52 (t, 1H, $J$=3.2, Pyr-H), 7.10 (d, 1H, $J$=3.2, Pyr-H), 7.14 (br s, 4H, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 21.2, 42.8, 53.1, 62.4, 106.2, 111.8, 119.9, 127.2, 129.8, 137.2, 137.5, 140.4, 165.2, 167.6. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.17; H, 5.43; N, 5.27.

**4.3.7. Methyl 1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5g).** Viscous oil; $R_f$ 0.46 (1:3 EtOAc/hexane); IR (KBr): 2951, 1755, 1609, 1571, 1509, 1461, 1292, 1247, 1171, 1030 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.81 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 3.89 (d, 1H, $J$=5.2, CH), 4.87 (d, 1H, $J$=5.0, CH), 5.96–5.98 (m, 1H, Pyr-H), 6.52 (t, 1H, $J$=3.2, Pyr-H), 6.85 (d, 2H, $J$=8.6, Ar-H), 7.09 (br s, 1H, Pyr-H), 7.16 (d, 2H, $J$=8.6, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 42.4, 53.0, 55.2, 62.5, 106.1, 111.7, 114.5, 119.8, 128.4, 132.0, 140.5, 159.3, 165.1, 167.6. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 66.97; H, 5.29; N, 4.91.

**4.3.8. Methyl 1-(4-hydroxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5h).** Viscous oil; $R_f$ 0.61 (1:3 EtOAc/hexane); IR (KBr): 2955, 1771, 1571, 1474, 1398, 1292, 1165, 1080 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.86 (s, 3H, $OCH_3$), 3.89 (d, 1H, $J$=5.2, CH), 4.86 (d, 1H, $J$=4.9, CH), 5.74 (br s, 1H, Pyr-H), 5.97 (br s, 1H, Pyr-H), 6.52 (t, 1H, $J$=3.2, Pyr-H), 6.78 (d, 2H, $J$=8.6, Ar-H), 7.10 (d, 2H, $J$=8.5, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 42.4, 53.2, 62.6, 106.3, 111.8, 115.3, 120.1, 128.5, 131.8, 140.5, 155.7, 165.6, 167.8. Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.20; H, 5.10; N, 5.08.

**4.3.9. Methyl 1-(2-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5i).** Viscous oil; $R_f$ 0.65 (1:3 EtOAc/hexane); IR (KBr): 2951, 1631, 1584, 1399, 1292, 1247, 1160, 1085 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.77 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 3.90 (d, 1H, $J$=4.2, CH), 5.01 (d, 1H, $J$=4.0, CH), 5.99–6.01 (m, 1H, Pyr-H), 6.52 (t, 1H, $J$=3.2, Pyr-H), 6.87–6.93 (m, 2H, Ar-H), 7.10 (br s, Pyr-H), 7.25–7.28 (m, 2H, Ar-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): 39.2, 52.8, 55.3, 61.0, 106.0, 110.0, 111.7, 119.7, 120.8, 128.0, 128.2, 129.1, 140.0, 157.2, 166.0, 168.3. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.10; H, 5.25; N, 4.98.

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