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Divergent synthesis of 2,3-dihydro-1*H*-pyrroles, 3-alkyl-1*H*-pyrroles and 3-alkenyl-1*H*-pyrroles from 2,4-pentadienenitriles and isocyanides†

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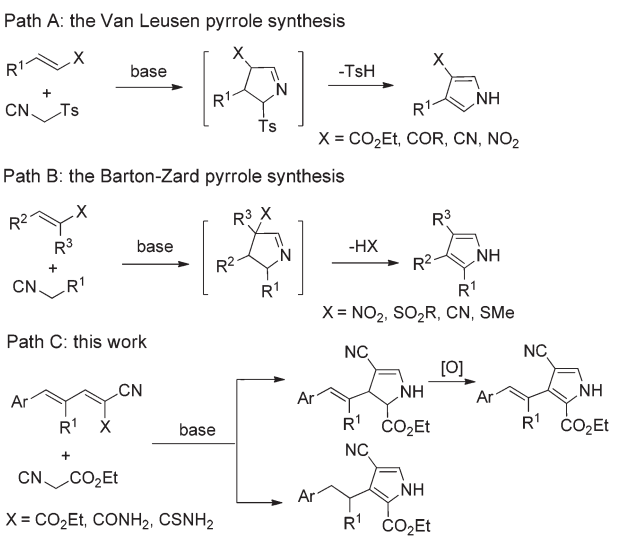
An efficient and divergent one-pot synthesis of 2,3-dihydro-1*H*-pyrroles, 3-alkyl-1*H*-pyrroles and 3-alkenyl-1*H*-pyrroles from readily accessible 2,4-pentadienenitriles with isocyanide based on reaction condition selection has been described. The reaction of 2,4-pentadienenitriles with ethyl isocyanoacetate undergoes a formal [2 + 3] annulation either to generate 2,3-dihydro-1*H*-pyrroles in the presence of DBU (0.3 equiv.) in EtOH at room temperature or to give 3-alkyl-1*H*-pyrroles in the presence of DBU (2.0 equiv.) in EtOH under reflux. Moreover, the 2,3-dihydro-1*H*-pyrroles could be converted to 3-alkenyl-1*H*-pyrroles with DDQ as an oxidant.

Introduction

Pyrroles constitute the core structure of many natural products and synthetic compounds along with a broad range of bio- and pharmacological activities, such as antibiotic, antitumor, antitubercular, multi-drug resistance inhibition and lowering cholesterol.[1] Also, functionalized pyrroles are widely used as versatile building blocks in the synthesis of a wide range of heterocycles, including indoles, indolizidine alkaloids and indolizines.[2] Additionally, pyrroles have found application in functional materials, for instance in glucose sensors, organic semiconductors and BODIPY dyes.[3] Their utilization in organic chemistry, biochemistry, medicinal chemistry and material chemistry has intrigued researchers in search of efficient synthetic approaches for the construction of the skeleton of this type of heterocycle. The classical synthetic methods for pyrroles, including Knorr synthesis,[4] Paal–Knorr synthesis[5] and Hantzsch synthesis,[6] have been established. Recently, transition metal-catalyzed cyclization[7] and multi-component reactions (MCRs)[8] have emerged as attractive and important transformations to the synthesis of pyrroles owing to their high efficiency and selectivity.

On the other hand, isocyanides are recognized as versatile synthons in pyrrole synthesis by reacting with activated alkenes or alkynes.[9] The van Leusen pyrrole synthesis is such a representative organic transformation, in which *p*-toluenesulfonyl methyl isocyanide (TosMIC) was used as a substrate (Scheme 1, Path A).[10] Barton and Zard also achieved the pyrrole synthesis *via* the reaction of isocyanides with nitroalkenes (Scheme 1, Path B).[11] Later on, other alkenes activated by SO_2Ar, CN, and SMe were employed in such pyrrole syntheses.[12]

In the course of our studies on the synthetic utilization of malononitrile and its derivatives, we developed a facile synthesis of highly substituted benzenes[13] from malononitrile



Scheme 1 The reaction of electron-efficient alkenes and isocyanides.

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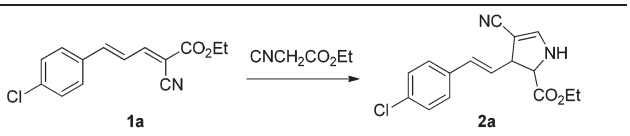
and chalcones in ionic liquids and an efficient synthesis of multi-substituted pyridines[14] *via* a MCR of malonitrile, β-oxo amides and aromatic aldehydes in alcohols. Very recently, we achieved the synthesis of aminopyridines *via* a MCR of 2-[(amino)methylene]malononitriles, sulfonyl azides and alkynes,[15] and a formal [5C + 1N] annulation of 2,4-pentadienenitriles with hydroxyl amine, respectively.[16] In connection with these research studies and the aim to establish novel synthetic approaches for heterocycles, we explored the reaction of 2,4-pentadienenitriles **1** with isocyanides under different conditions. As a result of these studies, we achieved divergent synthesis of 2,3-dihydro-1*H*-pyrroles, 3-alkyl-1*H*-pyrroles and 3-alkenyl-1*H*-pyrroles *via* [2 + 3] cycloaddition of readily accessible 2,4-pentadienenitriles with ethyl isocyanoacetate under different conditions (Scheme 1, Path C). Herein, we report our experimental results and propose a mechanism involved in these reactions.

Results and discussion

The substrates, 2,4-pentadienenitriles **1**, were prepared by the Knoevenagel condensation of commercially available nitriles with cinnamaldehydes in the presence of piperidine in ethanol in excellent yields according to our previous reported procedure.[16] Then, we selected ethyl 5-(4-chlorophenyl)-2-cyanopenta-2,4-dienoate **1a** as the model compound to examine its reaction behavior. The reaction of **1a** with ethyl isocyanoacetate was initially attempted in the presence of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU, 2.0 equiv.) in *N*,*N*-dimethylformamide at room temperature for 12.0 h, and a complex mixture was formed (Table 1, entry 1). A similar phenomenon was observed when **1a**, ethyl isocyanoacetate and DBU were subjected to acetonitrile or tetrahydrofuran (Table 1, entries 2 and 3). To our delight, the reaction proceeded smoothly in ethanol at room temperature and furnished a product, which was characterized as (*E*)-ethyl 3-(4-chlorostyryl)-4-cyano-2,3-dihydro-1*H*-pyrrole-2-carboxylate **2a** on the basis of its spectra and analytical data (Table 1, entry 4). Other bases, such as piperidine, triethylamine and K_2CO_3, were also tested but proved to be less active than DBU (Table 1, entries 5–7). Subsequent experiments revealed that 0.3 equivalent of DBU was effective for the reaction of **1a** with ethyl isocyanoacetate to form **2a** (Table 1, entries 8–10).

Table 1 Reactions of **1a** with ethyl isocyanoacetate under different conditions[a]

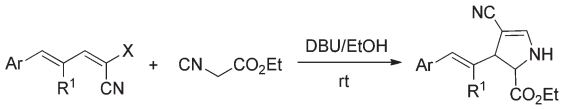


1a **2a**

Entry	Base (equiv.)	Solvent	Time (h)	Yield[b] (%)
1	DBU (2.0)	DMF	12.0	Mixture
2	DBU (2.0)	CH_3CN	12.0	Mixture
3	DBU (2.0)	THF	12.0	Mixture
4	DBU (2.0)	EtOH	0.5	83
5	Piperidine (2.0)	EtOH	0.5	57
6	Et_3N (2.0)	EtOH	6.0	20(15)
7	K_2CO_3 (2.0)	EtOH	0.5	69
8	DBU (1.0)	EtOH	0.5	84
9	**DBU (0.3)**	**EtOH**	**0.5**	**85**
10	DBU (0.1)	EtOH	2.0	72(18)[c]

[a] Reagents and conditions: **1a** (1.0 mmol), ethyl isocyanoacetate (1.0 mmol), solvent (10.0 mL), rt. [b] Isolated yields. [c] Recovery of **1a** in parentheses.

Table 2 Reaction of 2,4-pentadienenitriles **1** with ethyl isocyanoacetate to 2,3-dihydro-1*H*-pyrroles **2**[a]



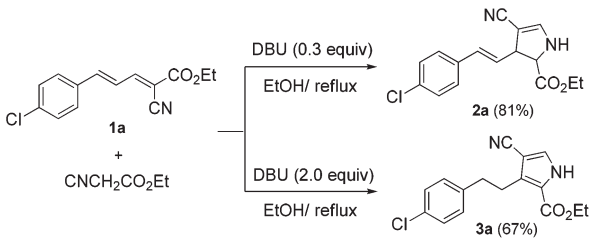
1 **2**

Entry	**1**	Ar	R^1	X	**2**	Yield[b] (%)
1	**1a**	4-ClC_6H_4	H	CO_2Et	**2a**	85
2	**1b**	4-MeC_6H_4	H	CO_2Et	**2b**	79
3	**1c**	4-$MeOC_6H_4$	H	CO_2Et	**2c**	82
4	**1d**	3-$MeOC_6H_4$	H	CO_2Et	**2d**	77
5	**1e**	2-$MeOC_6H_4$	H	CO_2Et	**2e**	80
6	**1f**	C_6H_5	H	CO_2Et	**2f**	74
7	**1g**	C_6H_5	Me	CO_2Et	**2g**	81
8	**1h**	4-ClC_6H_4	H	$CONH_2$	**2a**	76
9	**1i**	4-ClC_6H_4	H	$CSNH_2$	**2a**	78

[a] Reagents and conditions: **1** (1.0 mmol), ethyl isocyanoacetate (1.0 mmol), DBU (0.3 mmol), EtOH (10.0 mL), rt, 0.5–1.0 h. [b] Isolated yields.

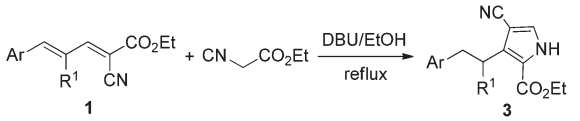
Under the same reaction conditions as for **2a** in entry 9 (Table 1), a range of reactions of substrates **1** with ethyl isocyanoacetate was carried out to determine the scope and limitation of the 2,3-dihydro-1*H*-pyrrole synthesis, and some of the results are summarized in Table 2. The efficiency of the cyclization proved to be suitable for 2,4-pentadienenitriles **1b–g** bearing varied substituents Ar and R^1 on their double bond to afford the corresponding trisubstituted dihydropyrroles **2b–g** in good yields (Table 2, entries 2–7). When 2-carbamoyl-2,4-pentadienenitriles **1h** and **1i** were employed under identical conditions, dihydropyrrole **2a** was obtained in good yield (Table 2, entries 8 and 9). In the ^1H NMR spectra of **2a**, a triplet peak at δ 3.88 and a doublet peak at 4.33 were assigned to the 3-H and the 2-H of the dihydropyrrole. The correlation between 3-H and 2-CO_2CH_2 as well as that between 2-H and 3-CH indicated a *trans* configuration of **2a** (see ESI†). Actually, 2,3-dihydro-1*H*-pyrroles constitute the core structure of many natural products and synthetic compounds along with a broad range of bioactivities, and serve as versatile building blocks for the synthesis of functionalized pyrrolidines and pyrroles.[17] In the present work, we provided a facile and efficient synthesis of 2,3-dihydro-1*H*-pyrroles of type **2** in a diastereoselective manner.

Next, we investigated the reaction of 2,4-penta-dienenitriles **1** and ethyl isocyanoacetate in EtOH under reflux. It was found that the reaction of **1a** and ethyl isocyanoacetate (1.0 equiv.) in



Scheme 2 Reaction of **1a** with ethyl isocyanoacetate under reflux.

Table 3 Reaction of 2,4-pentadienenitriles **1** with ethyl isocyanoacetate to 3-alkylpyrroles **3**[a]



Entry	1	Ar	R^1	3	Yield[b] (%)
1	**1a**	4-ClC_6H_4	H	**3a**	67
2	**1b**	4-MeC_6H_4	H	**3b**	65
3	**1c**	4-$MeOC_6H_4$	H	**3c**	58
4	**1d**	3-$MeOC_6H_4$	H	**3d**	60
5	**1e**	2-$MeOC_6H_4$	H	**3e**	63
6	**1f**	C_6H_5	H	**3f**	61
7	**1g**	C_6H_5	Me	**3g**	72

[a] Reagents and conditions: **1** (1.0 mmol), ethyl isocyanoacetate (1.0 mmol), DBU (2.0 mmol), EtOH (10.0 mL), reflux, 5.0–6.0 h. [b] Isolated yields.

the presence of DBU (0.3 equiv.) could be completed within 20 min and **2a** was obtained in 81% yield (Scheme 2). It was interesting to note that when **1a**, ethyl isocyanoacetate (1.0 equiv.) and DBU (2.0 equiv.) were subjected to EtOH under reflux for 5.0 h, the reaction furnished a main product, which was characterized as ethyl 3-(4-chlorophenethyl)-4-cyano-1*H*-pyrrole-2-carboxylate **3a** (Scheme 2).

In the same fashion, the reactions of **1b–g** with ethyl isocyanoacetate (1.0 equiv.) and DBU (2.0 equiv.) were carried out in EtOH under reflux. All the reactions proceeded smoothly to afford the corresponding 3-alkyl-1*H*-pyrroles **3b–g** in moderate yields (Table 3, entries 2–7). The structure of **3a** was established by its X-ray single crystal analysis (Fig. 1).

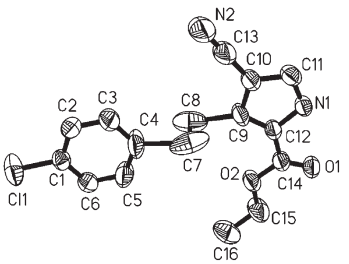
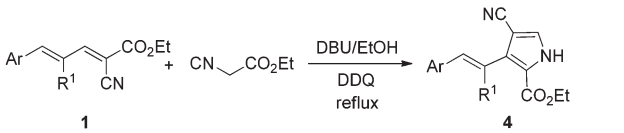


Fig. 1 ORTEP drawing of **3a**.

It should be mentioned that the richness of the functionality of the 2,3-dihydropyrroles **2** may render them versatile precursors in further synthetic transformations. Encouraged by this, we successfully synthesized multi-substituted pyrroles **4** in good yields by a one-pot, two-step procedure: the reactions of **1** and ethyl isocyanoacetate (1.0 equiv.) were performed in EtOH in the presence of DBU (0.3 equiv.) at room temperature for 0.5–1.0 h, and then stirred under reflux for 1.0–2.0 h after the addition of DDQ (1.0 equiv.) (Table 4, entries 1–7). The structure of **4d** was elucidated by means of the X-ray single crystal analysis (Fig. 2) and supported by its spectral and analytical data. Indeed, 3-alkenylpyrrole was first synthesized from pyrroles in five steps by Salvadori and coworkers.[18] Therefore, we provided an alternative and straight route to 3-alkenyl pyrrole of type **4** from open chain precursors.

On the basis of the results obtained together with the reported literature,[11,12,19] a mechanism for the divergent synthesis of 2,3-dihydro-1*H*-pyrroles **2**, 3-alkylpyrroles **3** and 3-alkenylpyrrole **4** is proposed as depicted in Scheme 3. The overall transformation is triggered by the deprotonation of ethyl isocyanoacetate in the presence of DBU at room temperature, and followed by a formal [2 + 3] cycloaddition with 2,4-pentadienenitrile **1** to form a 3,4-dihydro-2*H*-pyrrole inter-

Table 4 Reaction of 2,4-pentadienenitriles **1** with ethyl isocyanoacetate to 3-alkenylpyrroles **4**[a]



Entry	1	Ar	R^1	4	Yield[b] (%)
1	**1a**	4-ClC_6H_4	H	**4a**	81
2	**1b**	4-MeC_6H_4	H	**4b**	76
3	**1c**	4-$MeOC_6H_4$	H	**4c**	73
4	**1d**	3-$MeOC_6H_4$	H	**4d**	75
5	**1e**	2-$MeOC_6H_4$	H	**4e**	77
6	**1f**	C_6H_5	H	**4f**	72
7	**1g**	C_6H_5	Me	**4g**	78

[a] Reagents and conditions: (i) **1** (1.0 mmol), ethyl isocyanoacetate (1.0 mmol), DBU (0.3 mmol), EtOH (10.0 mL), rt, 0.5–1.0 h; (ii) reflux, 1.0–2.0 h. [b] Isolated yields.

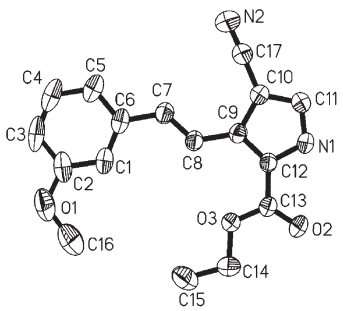
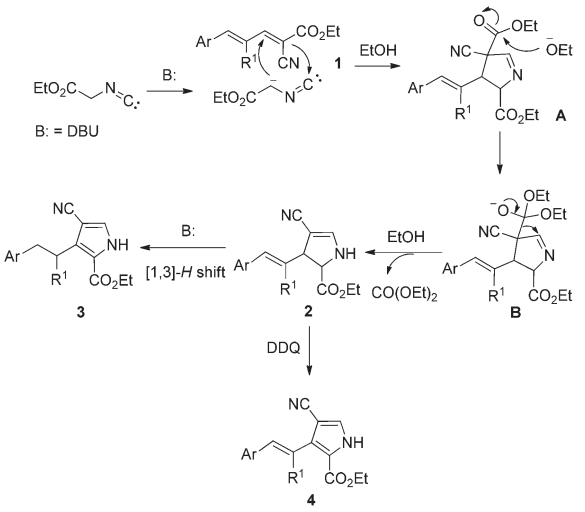


Fig. 2 ORTEP drawing of **4d**.



Scheme 3 Plausible mechanism for the synthesis of 2,3-dihydro-1*H*-pyrroles **2**, 3-alkylpyrroles **3** and 3-alkenylpyrroles **4**.

mediate **A**. By the attack of the ethoxide ion, **A** is converted into intermediate **B**, which might shed diethyl carbonate in ethanol to give 2,3-dihydro-1*H*-pyrrole **2**. The process is different from the Barton–Zard reaction in which a pyrrole would be formed directly. Further treated by DBU at higher temperature, 2,3-dihydro-1*H*-pyrrole **2** undergoes double [1,3]-*H* shifts to afford 3-alkylpyrrole **3**. In another way, **2** could be oxidized to 3-alkenylpyrrole **4** by DDQ.

Conclusions

In summary, a facile and divergent synthesis of 2,3-dihydro-1*H*-pyrroles, 3-alkyl-1*H*-pyrroles and 3-alkenyl-1*H*-pyrroles has been developed *via* a formal [2 + 3] annulation of 2,4-pentadienenitriles and ethyl isocyanoacetate by variation of reaction conditions. The protocol is associated with readily available starting materials, very mild conditions, moderate to good yields and structural diversity of products. The potential utilization and extension of the scope of the methodology and the evaluation of biological activity of the novel products are currently under investigation in our laboratory.

Experimental

General

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz, 400 MHz and 100 MHz, respectively, with TMS as an internal standard. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400–4000 cm^{-1}. Petroleum ether (PE) used was the fraction boiling in the range 60–90 °C.

Typical procedure for the synthesis of 2,3-dihydro-1*H*-pyrroles 2 (2a as an example)

A mixture of ethyl 5-(4-chlorophenyl)-2-cyanopenta-2,4-dienoate **1a** (1.0 mmol, 262 mg), ethyl isocyanoacetate (1.0 mmol, 113 mg) and DBU (0.3 mmol, 45.6 mg) in ethanol (10.0 mL) was stirred under room temperature for 0.5 h, and then poured into saturated aqueous NaCl (50 mL), which was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography (silica gel, petroleum ether–ethyl acetate = 2 : 1) to give **2a** as a colorless oil (257 mg, 85%); ^{1}H NMR (400 MHz, DMSO): δ 1.22 (t, J = 7.2 Hz, 3H), 3.88 (q, J = 7.2 Hz, 1H), 4.13–4.21 (m, 2H), 4.33 (d, J = 6.4 Hz, 1H), 6.31 (dd, J_1 = 16.0 Hz, J_2 = 8.4 Hz, 1H), 6.54 (d, J = 16.0 Hz, 1H), 7.31 (s, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 14.1, 49.4, 61.1, 65.2, 77.7, 119.1, 128.2, 128.7, 129.7, 130.1, 132.1, 135.3, 151.8, 171.3; Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.73; H, 4.98; N, 9.20.

Typical procedure for the synthesis of 3-alkyl-1*H*-pyrroles 3 (3a as an example)

A mixture of ethyl 5-(4-chlorophenyl)-2-cyanopenta-2,4-dienoate **1a** (1.0 mmol, 262 mg), ethyl isocyanoacetate (1.0 mmol, 113 mg) and DBU (2.0 mmol, 304 mg) in ethanol (10.0 mL) was stirred under reflux for 5.0 h, and then poured into saturated aqueous NaCl (50 mL), which was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography (silica gel, petroleum ether–ethyl acetate = 2 : 1) to give **3a** as a white solid (204 mg, 67%); mp 157–158 °C; ^{1}H NMR (400 MHz, DMSO): δ 1.28 (t, J = 7.2 Hz, 3H), 2.81 (q, J = 8.4 Hz, 2H), 3.04 (q, J = 8.4 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 3.6 Hz, 1H), 12.51 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.2, 27.2, 35.4, 60.2, 94.6, 115.3, 119.8, 128.2, 129.6, 130.1, 130.6, 133.0, 139.8, 159.8; IR (KBr): ν = 3273, 3128, 2226, 1676, 1418, 1283, 1153, 1014, 783 cm^{-1}; Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.22; H, 5.01; N, 9.28.

Crystal data for **3a**: $C_{16}H_{15}ClN_2O_2$, white crystal, M = 302.76, monoclinic, $P21/c$, a = 13.476(5) Å, b = 6.865(3) Å, c = 17.826(7) Å, α = 90.00°, β = 104.27(1)°, γ = 90.00°, V = 1598.23(306) Å^3, Z = 4, T = 298 K, $F000$ = 624.0, $F000'$ = 624.29, R = 0.0834(1482), wR_2 = 0.2409(3163). CCDC deposition number: 968815.

Typical procedure for the synthesis of 3-alkenyl-1*H*-pyrroles 4a (4a as an example)

A mixture of ethyl 5-(4-chlorophenyl)-2-cyanopenta-2,4-dienoate **1a** (1.0 mmol, 262 mg), ethyl isocyanoacetate (1.0 mmol, 113 mg) and DBU (0.3 mmol, 45.6 mg) in ethanol (10.0 mL) was stirred at room temperature for 0.5 h, followed by the addition of DDQ (1.0 mmol, 227 mg) under reflux for 1.0 h.

After completion of the reaction as indicated by TLC, the reaction mixture was poured into saturated aqueous NaCl (50 mL), which was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, petroleum ether–ethyl acetate = 2 : 1) to give **4a** as a yellow solid (244 mg, 81%); mp 222–223 °C; ^{1}H NMR (300 MHz, DMSO): δ 1.34 (t, J = 7.2, 3H), 4.33 (q, J = 7.2 Hz, 2H), 7.36 (d, J = 16.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 16.8 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H), 12.81 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.2, 60.6, 90.7, 116.4, 120.1, 120.4, 127.9, 128.9, 129.5, 131.9, 132.5, 135.6, 159.7; IR (KBr): ν = 3263, 3136, 2216, 1670, 1420, 1271, 962, 808, 608 cm^{-1}; Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.67; H, 4.37; N, 9.27.

2b: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 2.34 (s, 3H), 4.02 (dd, J_1 = 8.1 Hz, J_2 = 5.1 Hz, 1H), 4.18 (d, J = 5.1 Hz, 1H), 4.23–4.31 (m, 2H), 4.68 (s, 1H), 6.12 (dd, J_1 = 15.6 Hz, J_2 = 5.1 Hz, 1H), 6.59 (d, J = 15.6 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.1, 49.5, 62.1, 65.9, 84.1, 117.5, 126.4, 129.2, 132.4, 137.7, 149.3, 171.6; Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.02; H, 6.45; N, 9.96.

2c: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 3.81 (s, 3H), 4.00 (dd, J_1 = 7.8 Hz, J_2 = 5.7 Hz, 1H), 4.18 (d, J = 5.1 Hz, 1H), 4.22–4.29 (m, 2H), 4.71 (s, 1H), 6.04 (dd, J_1 = 15.6 Hz, J_2 = 8.4 Hz, 1H), 6.56 (d, J = 15.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 49.0, 54.8, 61.6, 65.6, 83.5, 113.5, 117.1, 124.9, 127.3, 128.6, 131.5, 148.9, 159.0, 171.1; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.64; H, 6.09; N, 9.32.

2d: orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 3.82 (s, 3H), 4.01–4.04 (m, 1H), 4.19 (d, J = 4.8 Hz, 1H), 4.25–4.28 (m, 2H), 4.70 (s, 1H), 6.17 (dd, J_1 = 16.0 Hz, J_2 = 8.0 Hz, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.99 (d, J = 7.2 Hz, 1H), 7.04 (s, 1H), 7.21–7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 49.4, 55.2, 62.1, 65.9, 84.0, 111.9, 113.7, 117.4, 119.2, 127.8, 129.5, 132.5, 137.7, 149.4, 159.8, 171.5; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.26; H, 6.10; N, 9.35.

2e: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 3.85 (s, 3H), 4.04 (dd, J_1 = 7.6 Hz, J_2 = 5.6 Hz, 1H), 4.20 (d, J = 5.2 Hz, 1H), 4.23–4.31 (m, 2H), 6.21 (dd, J_1 = 16.0 Hz, J_2 = 8.0 Hz, 1H), 6.86–6.96 (m, 3H), 7.03 (d, J = 2.4 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 49.4, 55.2, 62.1, 65.9, 84.0, 111.9, 113.7, 117.4, 119.2, 127.8, 129.5, 132.5, 137.7, 149.4, 159.8, 171.5; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.19; H, 6.05; N, 9.45.

2f: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H), 4.04 (dd, J_1 = 8.1 Hz, J_2 = 5.1 Hz, 1H), 4.20 (d, J = 5.1 Hz, 1H), 4.23–4.32 (m, 2H), 4.67 (s, 1H), 6.18 (dd, J_1 = 15.9 Hz, J_2 = 8.1 Hz, 1H), 6.63 (d, J = 15.9 Hz, 1H), 7.05–7.06 (m, 1H), 7.28–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 49.5, 62.2, 66.0, 84.1, 117.6, 126.7, 127.5, 128.0, 128.7, 132.7, 136.4, 149.5, 171.7; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.89; H, 6.04; N, 10.41.

2g: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J = 7.2 Hz, 3H), 1.84 (s, 3H), 4.26–4.33 (m, 2H), 4.52 (dd, J_1 = 7.8 Hz, J_2 = 2.1 Hz, 1H), 5.23 (d, J = 7.5 Hz, 1H), 6.61 (s, 1H), 7.06 (d, J = 1.5 Hz 1H), 7.28–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 13.6, 61.4, 71.4, 85.7, 126.7, 127.7, 128.2, 128.5, 133.0, 135.9, 156.1, 170.1; Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.13; H, 6.41; N, 9.97.

3b: yellow solid: mp 132–134 °C; ^{1}H NMR (300 MHz, DMSO): δ 1.30 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 2.74–2.79 (m, 2H), 3.00–3.06 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 3.3 Hz, 1H), 12.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.0, 20.4, 27.4, 35.7, 60.0, 94.4, 115.2, 119.7, 127.9, 128.7, 129.3, 133.3, 134.7, 137.7, 159.7; IR (KBr): ν = 3269, 3128, 2224, 1682, 1420, 1283, 1155, 1018, 787 cm^{-1}; Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.16; H, 6.40; N, 9.98.

3c: yellow solid: mp 121–123 °C; ^{1}H NMR (300 MHz, DMSO): δ 1.30 (t, J = 7.2 Hz, 3H), 2.72–2.77 (m, 2H), 2.99–3.04 (m, 2H), 3.71 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 3.3 Hz, 1H), 12.51 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.1, 27.5, 35.3, 54.9, 60.0, 94.5, 113.6, 115.2, 119.7, 129.0, 129.3, 132.8, 133.3, 157.5, 159.8; IR (KBr): ν = 3269, 3126, 2224, 1678, 1417, 1285, 1155, 1041, 789 cm^{-1}; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.11; H, 6.09; N, 9.34.

3d: yellow solid: mp 100–101 °C; ^{1}H NMR (300 MHz, DMSO): δ 1.30 (t, J = 7.2 Hz, 3H), 2.76–2.81 (m, 2H), 3.03–3.08 (m, 2H), 3.72 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 6.71–6.77 (m, 3H), 7.19 (t, J = 7.8 Hz, 1H), 7.72 (d, J = 3.3 Hz, 1H), 12.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.1, 27.3, 36.2, 54.8, 60.2, 94.5, 111.4, 113.7, 115.4, 119.8, 120.4, 129.3, 129.5, 133.3, 142.4, 159.2, 159.9; IR (KBr): ν = 3273, 3126, 2224, 1678, 1418, 1285, 1155, 1032, 783 cm^{-1}; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.76; H, 6.06; N, 9.37.

3e: white solid: mp 141–143 °C; ^{1}H NMR (300 MHz, DMSO): δ 1.29 (t, J = 7.2 Hz, 3H), 2.76–2.82 (m, 2H), 3.00–3.05 (m, 2H), 3.77 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 6.82 (t, J = 7.2 Hz, 1H), 6.91–7.00 (m, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.68 (d, J = 3.3 Hz, 1H), 12.48 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.1, 25.6, 30.9, 55.0, 60.1, 94.7, 110.5, 115.3, 119.8, 120.0, 127.4, 128.7, 129.4, 133.7, 157.2, 159.9; IR (KBr): ν = 3302, 3128, 2226, 1686, 1418, 1285, 1036, 764 cm^{-1}; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.15; H, 6.10; N, 9.33.

3f: white solid: mp 118–120 °C; ^{1}H NMR (400 MHz, DMSO): δ 1.30 (t, J = 7.2 Hz, 3H), 2.79–2.83 (m, 2H), 3.04–3.08 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 7.15–7.20 (m, 3H), 7.26–7.29 (m, 2H), 7.71 (d, J = 3.2 Hz, 1H), 12.50 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.2, 27.4, 36.3, 60.2, 94.5, 115.3, 119.8, 126.0, 128.1, 128.2, 129.5, 133.3, 140.9, 159.9; IR (KBr): ν = 3279, 3126, 2224, 1682, 1420, 1285, 1157, 1028, 781 cm^{-1}; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.34; H, 6.02; N, 10.36.

3g: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34–1.42 (m, 6H), 2.96–3.12 (m, 2H), 3.94–4.02 (m, 1H), 4.30 (t, J = 7.2 Hz, 2H), 7.12–7.23 (m, 5H), 7.29 (d, J = 3.6 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 19.7, 32.7, 42.6, 60.9, 94.3, 115.9, 119.8, 125.9, 128.0, 128.7, 128.9, 138.8, 140.3, 160.5; Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.56; H, 6.46; N, 9.97.

4b: yellow solid: mp 218–220 °C; ^{1}H NMR (400 MHz, DMSO): 1.34 (t, J = 7.2, 3H), 2.32 (s, 3H), 4.33 (q, J = 7.2 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 16.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 16.8 Hz, 1H), 7.87 (d, J = 3.2 Hz, 1H), 12.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.2, 20.8, 60.6, 90.5, 116.6, 118.3, 120.0, 126.2, 128.5, 129.6, 130.9, 131.9, 133.9, 137.8, 159.8; IR (KBr): ν = 3267, 3134, 2216, 1672, 1420, 1265, 1163, 962, 800 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.48, H, 5.77; N, 10.04.

4c: yellow solid: mp 207–208 °C; ^{1}H NMR (400 MHz, DMSO): 1.34 (t, J = 7.2, 3H), 3.79 (s, 3H), 4.32 (q, J = 7.2 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 16.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 16.8 Hz, 1H), 7.86 (s, 1H), 12.72 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.2, 55.2, 60.5, 90.4, 114.4, 116.6, 117.0, 119.8, 127.6, 128.8, 129.2, 130.6, 131.8, 159.4, 159.8; IR (KBr): ν = 3248, 3119, 2222, 1676, 1420, 1271, 1171, 1038, 779 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.26; H, 5.42; N, 9.42.

4d: yellow solid: mp 188–189 °C; ^{1}H NMR (400 MHz, DMSO): 1.35 (t, J = 7.2 Hz, 3H), 3.81 (s, 3H), 4.33 (q, J = 7.2 Hz, 2H), 6.89–6.92 (m, 1H), 7.04 (s, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.31–7.38 (m, 2H), 7.72 (d, J = 16.8 Hz, 1H), 7.89 (s, 1H), 12.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.1, 55.0, 60.6, 90.7, 111.1, 114.1, 116.5, 118.8, 119.7, 120.3, 128.1, 130.0, 130.8, 131.9, 138.1, 159.7, 159.8; IR (KBr): ν = 3244, 3119, 2218, 1680, 1421, 1271, 1169, 966, 777 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.70; H, 5.43; N, 9.47.

Crystal data for **4d**: $C_{17}H_{16}N_2O_3$, white crystal, M = 296.32, monoclinic, $P21/c$, a = 8.8199(8) Å, b = 12.7684(12) Å, c = 13.8563(13) Å, α = 90.00°, β = 91.733(2)°, γ = 90.00°, V = 1559.7(3) Å^3, Z = 4, T = 298 K, $F000$ = 624.0, $F000'$ = 624.29, R = 0.0545-(2132), wR_2 = 0.1276(3070). CCDC deposition number: 968816.

4e: white solid: mp 197–199 °C; ^{1}H NMR (400 MHz, DMSO): 1.34 (t, J = 7.2, 3H), 3.84 (s, 3H), 4.32 (q, J = 7.2 Hz, 2H), 6.98–7.07 (m, 2H), 7.29–7.33 (m, 1H), 7.52–7.54 (m, 1H), 7.72 (s, 2H), 7.86 (s, 1H), 12.73 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.2, 55.7, 60.5, 90.5, 111.6, 116.5, 119.5, 120.0, 120.8, 125.3, 126.0, 129.0, 129.5, 131.9, 156.7, 159.8; IR (KBr): ν = 3250, 3128, 2226, 1676, 1420, 1277, 1026, 978, 743 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.67; H, 5.45; N, 9.39.

4f: orange solid: mp 186–187 °C; ^{1}H NMR (300 MHz, DMSO): 1.35 (t, J = 7.2, 3H), 4.33 (q, J = 7.2 Hz, 2H), 7.30–7.53 (m, 6H), 7.74 (d, J = 16.8 Hz, 1H), 7.90 (d, J = 3.3 Hz, 1H), 12.81 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.2, 60.6, 90.6, 116.5, 119.3, 120.2, 126.2, 128.2, 128.9, 130.9, 131.9, 136.6, 159.8; IR (KBr): ν = 3248, 3144, 2220, 1672, 1423, 1269, 1169, 964, 775 cm^{-1}; Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.82; H, 5.32; N, 10.56.

4g: white solid: mp 77–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 7.2 Hz, 3H), 2.19 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 6.52 (s, 1H), 7.27–7.45 (m, 5H), 7.82 (s, 1H), 12.73 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.1, 19.5, 60.3, 94.2, 115.6, 119.3, 126.9, 128.3, 128.8, 129.4, 129.7, 130.8, 136.9, 136.9, 159.4; IR (KBr): ν = 3279, 3126, 2220, 1674, 1418, 1271, 1175, 1018, 689 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.56; H, 5.74; N, 9.97.

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