JOC The Journal of Organic Chemistry

Note

Visible-Light Induced C (sp3)–H Functionalization of Tosylhydrazones: Synthesis of Polysubstituted Pyrroles under Metal-free Conditions

N Naresh Kumar Reddy, Deepa Rawat, and Subbarayappa Adimurthy

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00878 • Publication Date (Web): 19 Jul 2018

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

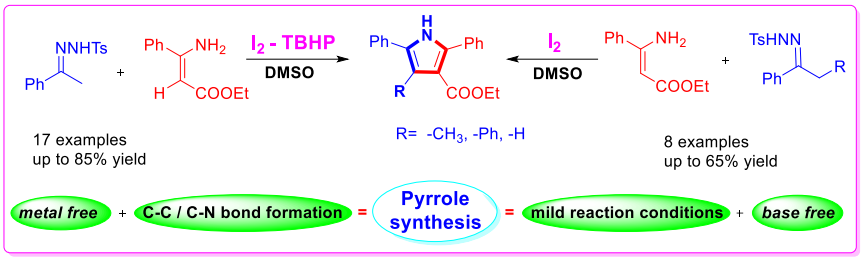
Visible-Light Induced C (sp^3)–H Functionalization of Tosylhydrazones: Synthesis of Polysubstituted Pyrroles under Metal-free Conditions

N. Naresh Kumar Reddy, Deepa Rawat, Subbarayappa Adimurthy*

Academy of Scientific & Innovative Research, CSIR–Central Salt & Marine Chemicals Research Institute, G.B. Marg, Bhavnagar-364 002. Gujarat (INDIA).

*E-mail: adimurthy@csmcri.res.in

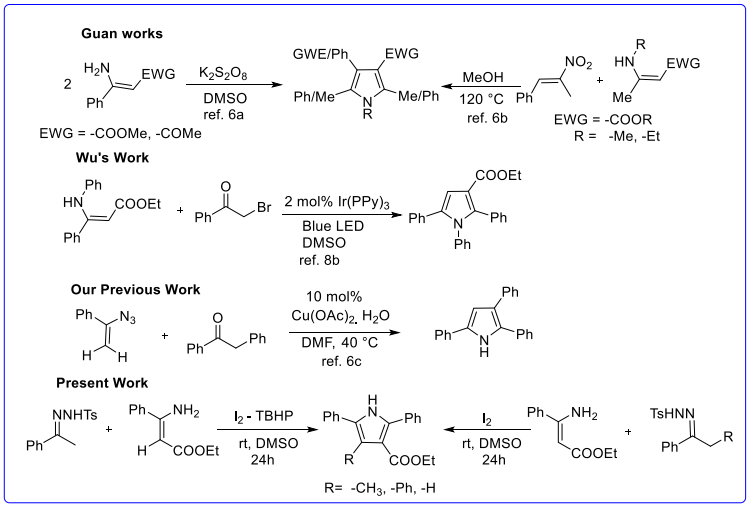
ABSTRACT:



Iodine catalysed C (sp^3)–H functionalization of tosylhydrazones with β-enamino esters under visible light irradiation for the synthesis of tri-substituted pyrroles has been described. The present method is also applicable to α- substituted tosylhydrazones to yield the tetra-substituted pyrroles.

Pyrroles are important synthetic building blocks in chemistry due to their numerous applications such as preparation of pharmaceuticals, biologically active molecules, and natural products.[1] Accordingly, the development of new methodologies to access these valuable molecules is continuously gaining the great importance in synthetic organic chemistry. The first synthetic method was reported by Paal and Knorr independently by the condensation of 1, 4- dicarbonyl compounds with primary amines or ammonia.[2] Inspired by the aforementioned methods, particularly in the last decade a significant progress has been made for the synthesis of pyrroles.[3-6] Despite the advances, the development of convenient and practical method for synthesis of pyrroles under transition metal-free, cheaper and catalytic conditions still holds its relevance, hence it is a highly desirable and yet to be a challenging task. In particular, the exploration of novel reagents and strategies for the synthesis of pyrroles under mild conditions with good functional-group tolerance is vital. From the view point of green chemistry, it is desirable to update the synthetic transformation of pyrroles under operationally simple and environmentally benign conditions.

As part of our ongoing research interest on the development of new methods for the synthesis of various aza-heterocycles through visible-light induced as well as under metal-free conditions,[7] we report herein a novel visible-light-induced synthesis of highly substituted pyrrole derivatives (**Scheme 1**). After careful survey of literature, our attention has been drawn to employ inexpensive and readily available substrates for the synthesis of pyrroles. We report herein a novel visible-light-induced iodine catalysed synthesis of highly substituted pyrrole derivatives (**Scheme 1**).

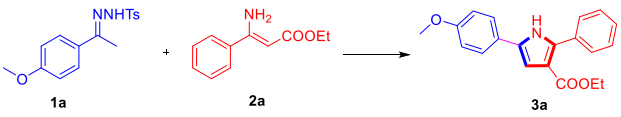


Scheme 1 Synthetic strategies for pyrrole synthesis

We have started our studies on pyrrole syntheses with tosylhydrazones and β-enamino esters. To optimize the conditions we have chosen (E)-N'-(1-(4-methoxyphenyl) ethylidene)-4-methyl benzene sulfonohydrazide (**1a**) and ethyl-3-amino-3-phenylacrylate (**2a**) as the model substrates with catalytic amount of iodine (10 mol %), aqueous TBHP (1.0 equiv.) and DMF as solvent at room temperature under visible light (12W Blue LED) conditions (Table 1). Under these conditions the desired product **3a** was obtained in 10% isolated yield after 24 h reaction time (Table 1, entry 1).When the reaction was carried out in DMSO as solvent under the same conditions, 51% of **3a** was isolated (Table 1, entry 2). To improve the yield of the product, K_2CO_3 was added to the reaction mixture, but the yield was declined (Table 1, entry 3). No product formation was observed with other solvents (NMP, DCE, CH_3CN, THF, H_2O and 1, 4-dioxane) tested for the reaction (Table 1, entries 4-9). The conditions of entry 2 was performed under inert atmosphere, the desired product **3a** yield was increased to 63% (Table 1, entry 10). As the yield was improved under inert atmosphere, based on this observation, the reaction was performed with TBHP in decane instead of water, unexpectedly the yield was dropped to 41% (entry 11). Keeping the solvent as DMSO, the reaction was screened

with different oxidants (DTBP, $K_2S_2O_8$, molecular oxygen, and H_2O_2) and other iodine sources (NIS, TBAI, KI) but the reaction was unsuccessful under these conditions (entries 12−18). To our delight, by increasing the oxidant TBHP to 1.5 equivalents, the product yield was increased to 69% (entry 19). Furthermore, when the reaction was performed with 2.0 equivalents of TBHP, the yield of **3a** was also increased to 79% (entry 20). When the reaction was performed without catalyst, without oxidant and without irradiation of LED light no product formation was observed (entries 21– 23). Finally, the reaction conducted with one and two equivalents of iodine but without TBHP, the comparable yields (61% and 72%) of desired product **3a** was obtained (Table 1, entries 24 & 25).

Table 1 Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	catalyst (mmol)	oxidant (mmol)	solvent	yield (%)
1[b]	I_2 (0.05)	TBHP (aq) (0.2)	DMF	10
2[b]	I_2 (0.05)	TBHP (aq) (0.2)	DMSO	51
3[b,c]	I_2 (0.05)	TBHP (aq) (0.2)	DMSO	45
4[b]	I_2 (0.05)	TBHP (aq) (0.2)	NMP	traces
5[b]	I_2 (0.05)	TBHP (aq) (0.2)	DCE	n.d.
6[b]	I_2 (0.05)	TBHP (aq) (0.2)	CH_3CN	n.d.
7[b]	I_2 (0.05)	TBHP (aq) (0.2)	THF	n.d.
8[b]	I_2 (0.05)	TBHP (aq) (0.2)	H_2O	traces
9[b]	I_2 (0.05)	TBHP (aq) (0.2)	Dioxane	n.d.
10	I_2 (0.05)	TBHP (aq) (0.2)	DMSO	63
11	I_2 (0.05)	TBHP (decane) (0.2)	DMSO	41
12	I_2 (0.05)	DTBP (0.2)	DMSO	traces
13	I_2 (0.05)	$K_2S_2O_8$ (0.2)	DMSO	n.d.
14	I_2 (0.05)	O_2 (balloon)	DMSO	traces
15	I_2 (0.05)	H_2O_2 (0.2)	DMSO	n.d.
16	NIS (0.05)	TBHP (aq) (0.2)	DMSO	traces
17	TBAI (0.05)	TBHP (aq) (0.2)	DMSO	n.d.
18	KI (0.05)	TBHP (aq) (0.2)	DMSO	n.d.
19	I_2 (0.05)	TBHP (aq) (0.3)	DMSO	69
20	**I_2 (0.05)**	**TBHP (aq) (0.4)**	**DMSO**	**79**
21	--	TBHP (aq) (0.4)	DMSO	n.d.
22	--	--	DMSO	n.d.
23[d]	I_2 (0.05)	TBHP (aq) (0.4)	DMSO	n.d.
24	I_2 (0.2)	--	DMSO	61
25	I_2 (0.4)	--	DMSO	72

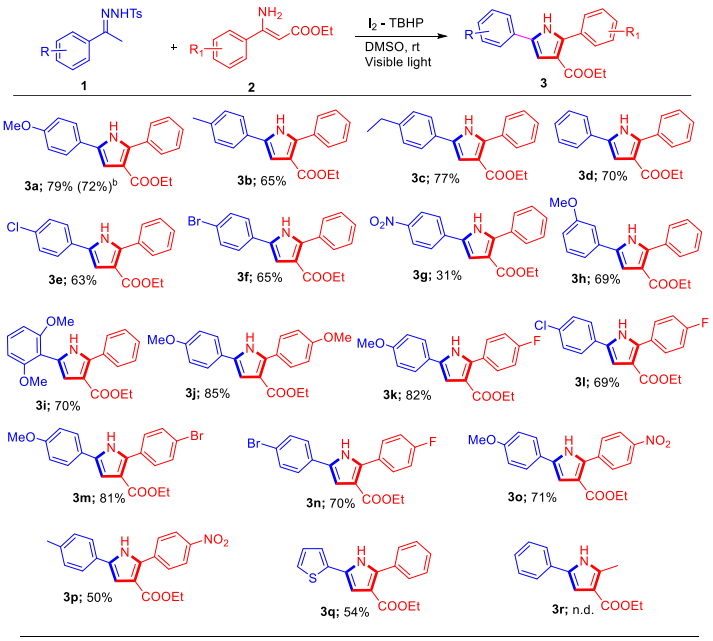
[a]Reaction conditions, unless otherwise stated; 0.2 mmol of **1a**,0.2 mmolof **2a**, 0.05 mmol of I_2, 0.4 mmol of TBHP inH_2O and 2.0 mL of solvent were placed in reaction tube in Ar atmosphere at room temperature, under irradiation of 12 W blue LED strips, 24 h, isolated yields.[b]open air [c] K_2CO_3 was used. [d]without irradiation of 12 W blue LED light.

On the basis of the results obtained, the optimized conditionswere set as 0.2 mmol of **1a**, 0.2 mmol of **2a**, 0.05 mmol of I_2, 0.4 mmol of TBHP in H_2O and 2.0 mL of DMSO as a solvent

under N_2 atmosphere at room temperature with irradiation of 12 W blue LED light for 24 h, for the present transformation.

With the optimized conditions in hand (Table 1, entry 20), we investigated the substrate scope with a diverse set of (E)-N'-(1-arylethylidene)-4-methylbenzenesulfonohydrazides (**1)** and ethyl (Z)-3-amino-3-arylacrylates (**2)** to obtain tri-substituted pyrroles (Scheme 2).

Scheme 2. Substrate scope for the synthesis of tri-substituted pyrroles[a]



[a]Reaction conditions: 0.2 mmol of **1**,0.2 mmolof **2**, 0.05 mmol of I_2, 0.4 mmol of TBHP in H_2O and 2.0 mL of DMSO were placed in reaction tube underAr atmosphere, reaction time 24h, isolated yields. [b]Yield at 1.59 gram scale (5.0 mmol).

Substrates containing either electrondonating (–OMe, –Et, –Me, –H) or withdrawing (–F, –Br) groups at the *para*-position of the phenyl ring **1**, were all tolerated under the standard conditions, and gave the corresponding products (**3a**–**3f**) in good yields (63–79%). One of the products, **3f**, was further confirmed by single crystal X-ray diffraction (Figure 1, CCDC. No.

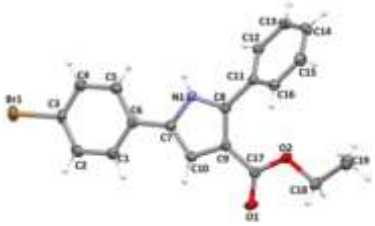
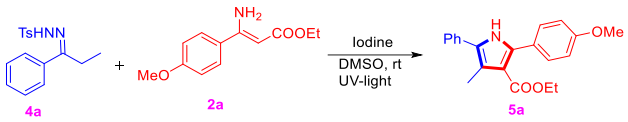


Figure 1. Crystal structure of **3f** (probability 50%)

1835841). In the case of strong electron withdrawing group low yield (31%) of the corresponding product **3g** was observed. The presence of methoxy group at *meta*-position or at either *ortho* position of phenyl ring, gave the good (69% and 70%) yields of products **3h**

and **3i**. The yield of the product **3i** indicates, no steric effect was observed in the present transformation.Then we focused on the reaction of substituted β-enamino esters **2**. The presence of electron donating (–OMe, –Et, –Me, -H) or -withdrawing (–F, –Br, –NO_2) groups at the *para*-position of the phenyl ring **2**, reacted smoothly with representative substrates of **1** and afford the desired tri-substituted pyrroles (**3j**–**3p**) in moderate to good yields (50–85%). The present system is also applicable to heterocyclic derivatives of **1**, and obtained the corresponding product **3q** [ethyl 2-phenyl-5-(thiophen-2-yl)-1H-pyrrole-3-carboxylate], in 54% yield. Unfortunately, with aliphatic enamines it does not yield the desired product **3r**.

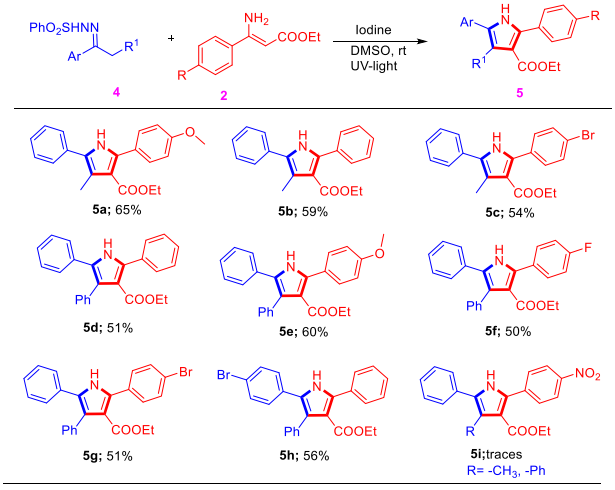
The optimized conditions were then applied for the synthesis of 2, 3, 4, 5- substituted pyrrole **5a** from α-substituted tosylhydrazones [(Z)-N'-(1-phenylpropylidene)-4-methtyl benzene sulfonohydrazide] **4a** and β-enamine ester **2a** (Scheme 3). Under the conditions of scheme 2,



Scheme 3. Synthesis of polysubstituted Pyrroles

only traces of **5a** was observed. We further optimised the conditions by screening various parameters and the best yield of **5a** was obtained with one equivalent of iodine (w.r.t. **2a** and **4a**) in 2.0 mL of DMSO as solvent under argon atmosphere with irradiation of 12 W blue LED light, at room temperature for 24 h (for details see Table S1, supporting information). With these optimised conditions, different tetra-substituted pyrroles were synthesised (Scheme 4).

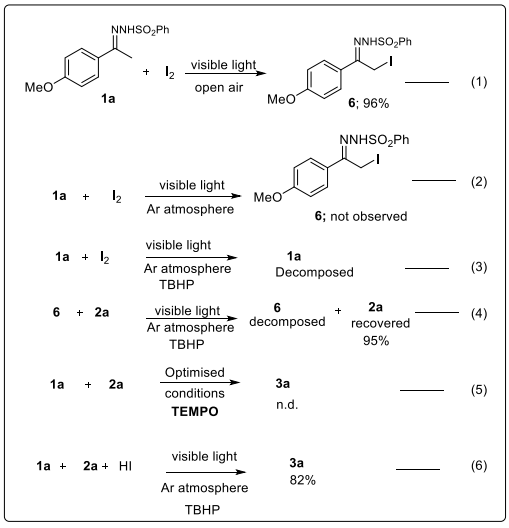
Scheme 4 Substrate scope for the synthesis of tetra-substituted pyrroles[a]



[a]Reaction conditions: 0.2 mmol of **4**, 0.2 mmol of **2**, 0.2 mmol of I_2, 2.0 mL of DMSO were placed in reaction tube under Ar atmosphere, 24h, isolated yields.

The presence of electron donating (–OMe), neutral (–H), and withdrawing (–Br) groups at the *para*-position of the phenyl ring **2**, reacted smoothly with **4a** and afford the tetra substituted pyrroles **5a**–**c** in moderate yields (54-65%). Further the reaction of (Z)-N'-(1, 2-diphenylethylidene)-4-methyl benzene sulfonohydrazide **4b**, with both electron donating and withdrawing substituents of **2**, were also provided the corresponding products **5d**–**g**. Under these conditions, (Z)-N'-(1-(4-bromophenyl)-2-phenylethylidene) benzene sulfonohydrazide **4c** was also reacted with **2** and gave the desired product **5h** in 56% yield. The presence of strong electron withdrawing group ($–NO_2$) on the phenyl ring of β-enamine ester **2** inhibits the reaction. It may be noted that the halogen (Br, Cl, and F) substituted derivatives were well tolerated and could be further applied in traditional cross-coupling reactions. While the yields of these products are moderate, they exemplify the ability to expand the method toward polysubstituted pyrrole synthesis.

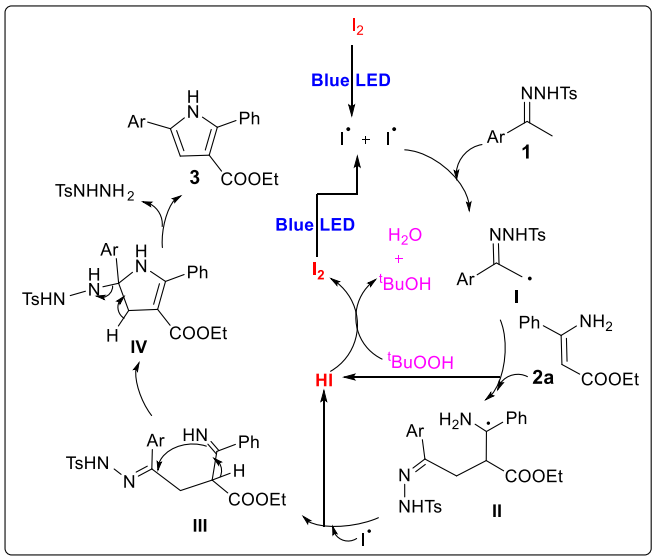
To gain insight into the reaction mechanism we performed some control experiments (Scheme 5). In order to know the reaction intermediate, the reaction of **1a** with stoichiometric amount of I_2 was subjected under visible light conditions in open air and argon atmosphere **(**Scheme 5, eqs. 1 and 2). Under the conditions of eq. 1, the quantitative yield of α-iodo derivative **6** was obtained, however with conditions of eq. 2, **6** was not observed. From the above conditions, in the former case oxygen from air may act as a initiator, in the latter one, due to the lack of initiator, no iodo derivative formation was observed. Addition of 2 equivalents of TBHP to the above conditions, the decomposition of **1a** was observed (eq. 3). Further to know the role of α-iodo derivative **6**, it was reacted with **2a** under the optimised conditions, under these conditions decomposition of **6** was observed with the recovery of **2a** (eq. 4).



Scheme 5. Control experiments

To assess whether the reaction proceed through radical or ionic path, **1a** and **2a** was subjected to the optimised conditions along with TEMPO as a radical scavenger, no desired product **3a** formation was observed (eq. 5). This reaction suggests that, the present reaction may proceed through a radical pathway. Further, when the reaction of **1a** and **2a** was subjected to the optimised conditions with HI (20 mol %) as iodine source, 82% of desired product was isolated (eq. 6). The equation 6 indicates that, TBHP oxidises HI to I_2, which proceeds the reaction in a similar path.

Based on the above results and literature support,[8,9] a plausible reaction mechanism has proposed (Scheme 6). Initially, I_2 in the presence of blue LED generates iodine radical, which may abstract proton from the substrate **1** generates a radical intermediate **I** with the elimination of HI. Reaction of **I** with enamine **2a** generates another intermediate **II**. Intermediate **II** in presence of iodine radical forms intermediate **III** which upon cyclisation forms cyclic intermediate **IV**. With the simultaneous elimination of *p*-toluenesulfonyl hydrazide and aromatisation gives the desired product **3**.



Scheme 6. Plausible mechanism

In conclusion, we have demonstrated a new method for the syntheses of tri and tetra-substituted pyrroles through cyclization of tosylhydrazones and β-enamino esters under metal-free conditions.

EXPERIMENTAL SECTION

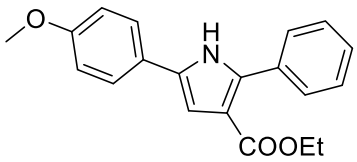
General Information. All commercially available chemicals and reagents were used without anyfurther purification unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded at 600 and 150 MHz, respectively. The spectra were recorded in $CDCl_3$ and DMSO-d_6 as a

solvent. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets), etc. Coupling constants (*J*) were given in Hz. Chemical shifts are reported in δ relative to TMS as an internal standard. The peaks around δ values of 7.26 (^{1}H NMR), 77.0 (^{13}C NMR) correspond to $CDCl_3$.The peaks around δ values of 2.50 (^{1}H NMR), 39.9 (^{13}C NMR) are corresponding to DMSO. The peak around δ values of 3.35 (^{1}H NMR) is corresponding to the H_2O present in DMSO solvent. Progress of the reactions was monitored by thin layer chromatography (TLC). Silica gel 100-200 mesh size was used for column chromatography using a hexane/ethyl acetate eluent unless otherwise indicated.

Experimental Section. General Procedure for 3a: 63.6 mg (0.2 mmol) of (E)-N'-(1-(4-methoxy phenyl)ethylidene)-4-methyl benzene sulfonohydrazide **1a**, 38.2 mg (0.2 mmol) of (ethyl (E)-3-amino-3-phenylacrylate **2a**, 12.65 mg of (0.05 mmol) of I_2 and 36 mg (0.4 mmol) of TBHP were taken in a 10 mL reaction tube; to it 2.0 mL of DMSO at room temperature, argon atmosphere, under irradiation with 12W blue LED strips for 24 h. Then, 15 mL of saturated ($Na_2S_2O_3$) hypo solution was added and extracted with ethyl acetate (3x15 mL) and dried with anhydrous Na_2SO_4. After removal of solvent, the crude mixture was subjected to column chromatography on silica gel, and 79 % yield of the product tri substituted pyrrole (50.9 mg) **3a** was isolated. (All the tosyl hydrazones and β-Enamino esters employed in the present manuscript were prepared by known procedure[10]).

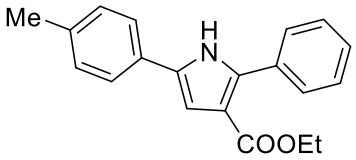
Characterization Data:

Ethyl 5-(4-methoxyphenyl)-2-phenyl-1H-pyrrole-3-carboxylate (3a)



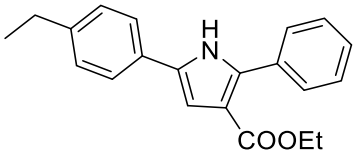
(Eluent: 7% EtOAc/hexane); 79% yield (50.9 mg); pale yellow solid; melting point 158 - 160 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.63 (d, *J* = 6.5Hz, 2H), 7.42 (m, 4H), 7.35 (t, *J* = 6.0 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 2H), 6.88 (s, 1H), 4.22 (q, *J* = 4.5 Hz, 2H), 3.82 (s, 3H), 1.26 (t, *J* = 5.5 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 158.9, 137.2, 132.1, 131.8, 129.0, 128.3, 128.2, 125.5, 124.5, 114.5, 113.7, 108.1, 59.8, 55.5, 14.3. IR: 3433, 3217, 3302, 2939, 1687, 1467, 1296, 1138, 1057, 761, 678, 648. HRMS (ESI-TOF) *m/z*: [M + H]$^+$calcd for $C_{20}H_{20}NO_3$ 322.1443; Found 322.1424.

Ethyl 2-phenyl-5-(p-tolyl)-1H-pyrrole-3-carboxylate (3b)



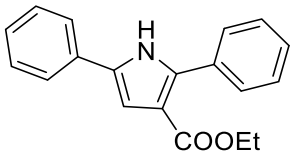
(Eluent: 7% EtOAc/hexane); 65% yield (39.9 mg); white solid; melting point 173 - 175 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.64 (d, J = 6.0Hz, 2H), 7.42 (q, J = 6.0 Hz, 4H), 7.37 (t, J = 6.0 Hz, 1H), 7.20 (d, J = 6.5 Hz, 2H), 6.96 (s, 1H), 4.23 (q, J = 6.0 Hz, 2H), 2.36 (s, 3H), 1.26 (t, J = 6.0 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 137.4, 137.0, 131.9, 129.8, 129.0, 128.4, 128.2, 124.0, 113.3, 108.6, 59.8, 21.2, 14.3. IR: 3476, 3285, 2895, 1664, 1455, 1368, 1265, 1248, 1135, 1039, 822, 745, 701, 623. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$calcd for $C_{20}H_{19}NO_2Na$ 328.1313; Found 328.1306.

Ethyl 5-(4-ethylphenyl)-2-phenyl-1H-pyrrole-3-carboxylate (3c)



(Eluent: 7% EtOAc/hexane); 77% yield (49.1 mg); white solid; melting point 133 - 135 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.63 (d, J = 6.5 Hz, 2H), 7.42 (m, 4H), 7.35 (t, J = 6.0 Hz, 1H), 7.23 (d, J = 6.5 Hz, 2H), 6.96 (s, 1H), 4.22 (q, J = 6.0 Hz, 2H), 2.66 (q, J = 6.5 Hz, 2H), 1.25 (q, J = 6.0 Hz, 6H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 143.3, 137.3, 132.0, 131.9, 129.0, 128.5, 128.3, 128.1, 124.0, 113.6, 108.6, 59.7, 28.5, 15.5, 14.3. IR: 3433, 3318, 2969, 1657, 1447, 1266, 1128, 1057, 761, 678, 648. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$calcd for $C_{21}H_{21}NO_2Na$ 342.1470; Found 342.1468.

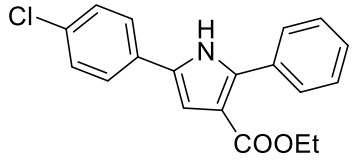
Ethyl 2, 5-diphenyl-1H-pyrrole-3-carboxylate (3d)



(Eluent: 7% EtOAc/hexane); 70% yield (41.0 mg);white solid; melting point 167 - 170 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.64 (d, J = 5.5Hz, 2H), 7.51 (d, J = 6.0 Hz, 2H), 7.41 (q, J = 7.0 Hz, 5H), 7.26 (t, J = 6.0 Hz, 1H), 7.00 (s, 1H), 4.22 (q, J = 6.0 Hz, 2H), 1.26 (t, J = 5.5 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 137.7, 131.9, 131.7, 131.4, 129.0, 128.4, 128.1, 127.0, 124.0, 113.7, 109.1, 59.8, 14.3. IR: 3433, 3302, 2939, 1672, 1455, 1291,

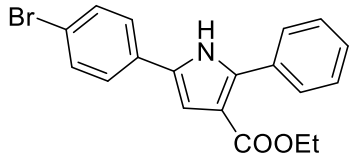
1256, 1138, 1043, 761, 692, 623. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$calcd for $C_{19}H_{17}NO_2Na$ 314.1157; Found 314.1152.

Ethyl 5-(4-chlorophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (3e)



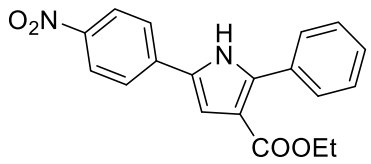
(Eluent: 7% EtOAc/hexane); 63% yield (41.5 mg);white solid; melting point 203 - 205 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.62 (d, J = 5.5Hz, 2H), 7.43 (m, 4H), 7.36 (m, 3H), 6.98 (s, 1H), 4.23 (q, J = 5.5 Hz, 2H), 1.26 (t, J = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 138.1, 132.7, 131.7, 130.7, 130.0, 129.2, 129.0, 128.6, 128.2, 125.2, 113.9, 109.6, 59.9, 14.3. IR: 3456, 3217, 2939, 1687, 1467, 1296, 1378, 1250, 1057, 761, 678, 648. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$calcd for $C_{19}H_{16}ClNO_2Na$ 348.0767; Found 348.0760.

Ethyl 5-(4-bromophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (3f)



(Eluent: 7% EtOAc/hexane); 65% yield (47.8 mg); white solid; melting point 213 - 215 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.62 (d, J = 6.0 Hz, 2H), 7.51 (d, J = 6.5 Hz, 2H), 7.41 (t, J = 6.0 Hz, 2H), 7.37 (d, J = 6.0 Hz, 3H), 6.99 (s, 1H), 4.22 (q, J = 6.0 Hz, 2H), 1.26 (t, J = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 138.1, 132.2, 131.7, 130.6, 130.5, 129.0, 128.6, 128.2, 125.5, 120.7, 114.0, 109.7, 59.9, 14.3. IR: 3419, 3280, 2964, 1658, 1455, 1385, 1286, 1259, 1178, 1143, 1039, 805, 771, 701. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$calcd for $C_{19}H_{16}BrNO_2Na$ 392.0262; Found 392.0260.

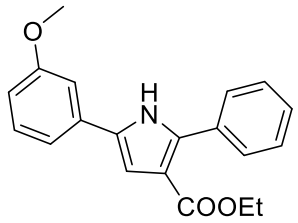
Ethyl 5-(4-nitrophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (3g)



(Eluent: 25% EtOAc/hexane); 31% yield (21.0 mg); yellow solid; melting point 212 - 215 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.1 (s, 1H), 8.18 (d, J = 7.5Hz, 2H), 8.02 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 6.5 Hz, 2H), 7.42 (m, 3H), 7.26 (s, 1H), 4.10 (q, J = 6.5 Hz, 2H), 1.15 (t, J = 5.5 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 145.6, 140.4, 138.3, 130.2, 130.1, 128.8,

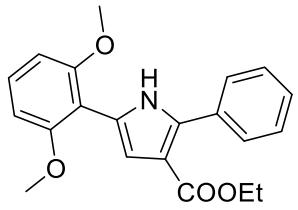
128.2, 125.0, 124.7, 114.1, 112.9, 59.7, 14.6. IR: 3424, 3276, 2947, 1689, 1368, 1265, 1135, 1031, 788. HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $C_{19}H_{15}N_2O_4$ 335.1032; Found 335.1045.

Ethyl 5-(3-methoxyphenyl)-2-phenyl-1H-pyrrole-3-carboxylate (3h)



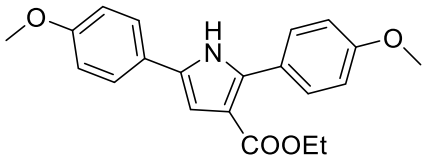
(Eluent: 5% EtOAc/hexane); 69% yield (44.3 mg); white solid; melting point 123 - 125 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.65 (d, J = 7.0 Hz, 2H), 7.43 (t, J = 6.5 Hz, 2H), 7.38 (t, J = 6.0 Hz, 1H), 7.31 (t, J = 7.0 Hz, 1H), 7.09 (d, J = 6.5 Hz, 1H), 7.05 (s, 1H), 7.01 (d, J = 2.5 Hz, 1H), 6.82 (m, 1H), 4.25 (q, J = 6.5 Hz, 2H), 3.85 (s, 3H), 1.28 (t, J = 6.5 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 160.2, 137.7, 131.9, 130.2, 129.0, 128.5, 128.2, 116.4, 113.8, 112.6, 109.9, 109.4, 59.8, 55.4, 14.3. IR: 3433, 3345, 2937, 1677, 1467, 1296, 1138, 1057, 761, 678, 648. HRMS (ESI-TOF) *m/z*: $[M + H]^+$calcd for $C_{20}H_{20}NO_3$ 322.1443; Found 322.1452.

Ethyl 5-(2, 6-dimethoxyphenyl)-2-phenyl-1H-pyrrole-3-carboxylate (3i)



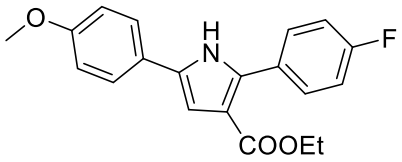
(Eluent: 5% EtOAc/hexane); 70% yield (49.0 mg); white solid; melting point 138 - 140 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.67 (d, J = 6.0 Hz, 2H), 7.43 (t, J = 6.5 Hz, 2H), 7.37 (m, 1H), 7.23 (t, J = 6.0 Hz, 1H), 7.10 (s, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.74 (m, 1H), 4.24 (q, J = 5.5 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 1.29 (t, J = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 154.3, 149.5, 136.4, 132.4, 129.6, 129.1, 128.95, 128.90, 128.2, 120.5, 113.1, 113.0, 112.7, 111.7, 109.8, 59.8, 56.5, 55.8, 14.4. IR: 3450, 3311, 2947, 1699, 1498, 1378, 1230, 1135, 1031, 761. HRMS (ESI-TOF) *m/z*: $[M + H]^+$calcd for $C_{21}H_{22}NO_4$ 352.1549; Found 352.1530.

Ethyl 2, 5-bis (4-methoxyphenyl)-1H-pyrrole-3-carboxylate (3j)



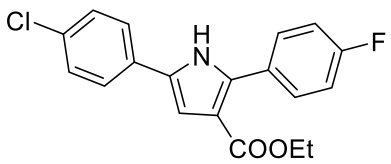
(Eluent: 5% EtOAc/hexane); 85% yield (59.7 mg); yellow liquid; melting point 183 - 185 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.56 (d, J = 6.5Hz, 2H), 7.43 (d, J = 5.0 Hz, 2H), 6.93 (m, 4H), 6.85 (s, 1H), 4.22 (q, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 1.27 (t, J = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 159.7, 158.8, 137.3, 131.4, 130.3, 125.4, 124.5, 114.5, 113.7, 113.1, 107.9, 59.7, 55.4, 14.4. IR: 3476, 3217, 2939, 1687, 1467, 1296, 1138, 1057, 770, 678, 621. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$calcd for $C_{21}H_{21}NO_4Na$ 374.1368; Found 374.1358.

Ethyl 2-(4-fluorophenyl)-5-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate (3k)



(Eluent: 5% EtOAc/hexane); 82% yield (55.8 mg); white solid; melting point 168 - 170 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.58 (d, J = 5.5Hz, 2H), 7.43 (d, J = 6.0 Hz, 2H), 7.07 (t, J = 6.0 Hz, 2H), 6.91 (d, J = 6.0 Hz, 2H), 6.85 (s, 1H), 4.20 (q, J = 6.0 Hz, 2H), 3.82 (s, 3H), 1.26 (t, J = 5.5 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 163.5, (d, J = 247.5 Hz), 161.9, 159.0, 136.2, 131.9, 130.97, (d, J = 9.0 Hz), 130.91, 128.1, 125.5, 124.4, 115.2, (d, J = 22.5 Hz), 115.1, 114.5, 113.7, 108.0, 59.8, 55.4, 14.3. IR: 3477, 3227, 2941, 1647, 1467, 1296, 1138, 1057, 729, 647. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{18}FNO_3Na$ 362.1168; Found 362.1162.

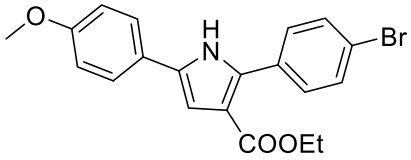
Ethyl 5-(4-chlorophenyl)-2-(4-fluorophenyl)-1H-pyrrole-3-carboxylate (3l)



(Eluent: 5% EtOAc/hexane); 69% yield (47.6 mg); white solid; melting point 208 - 210 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.60 (m, 2H), 7.42 (d, J = 6.0 Hz, 2H), 7.36 (d, J = 6.5 Hz, 2H), 7.10 (t, J = 6.5 Hz, 2H), 6.96 (s, 1H), 4.21 (q, J = 5.5 Hz, 2H), 1.25 (t, J = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 163.7 (d, J = 247.5 Hz), 162.1, 137.1, 132.9, 131.0, (d, J = 9.0 Hz), 130.9, 130.7, 129.9, 129.3, 127.8, 125.2, 115.4, (d, J = 21.0 Hz), 115.2, 114.0, 109.5, 60.0, 14.3. IR: 3423, 3332, 2940, 1672, 1467, 1296, 1138, 1057, 761,

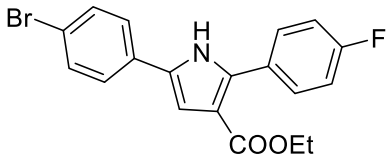
678, 648. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{16}ClFNO_2$ 344.0854; Found 344.0844.

Ethyl 2-(4-bromophenyl)-5-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate (3m)



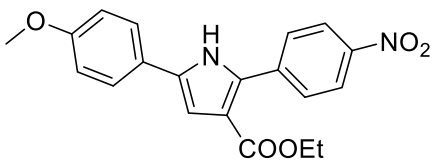
(Eluent: 5% EtOAc/hexane); 81% yield (65.0 mg); white solid; melting point 223 – 230 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.52 (q, *J* = 7.0 Hz, 4H), 7.42 (d, *J* = 7.0 Hz, 2H), 6.92(q, *J* = 7.0 Hz, 2H), 6.87 (s, 1H), 4.22 (q, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 1.28 (t, *J* = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 159.0, 135.8, 131.4, 130.5, 125.6, 124.2, 122.5, 114.5, 114.0, 108.2, 59.9, 55.4, 14.4. IR: 3420, 3119, 2965, 1658, 1455, 1386, 1289, 1259, 1174, 1143, 1039, 805, 772, 699. HRMS (ESI-TOF) *m/z*: $[M + H]^+$calcd for $C_{20}H_{19}BrNO_3$ 400.0548; Found 400.0545.

Ethyl 5-(4-bromophenyl)-2-(4-fluorophenyl)-1H-pyrrole-3-carboxylate (3n)



(Eluent: 5% EtOAc/hexane); 70% yield (54.5 mg); white solid; melting point 218 - 220 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.58 (m, 2H), 7.51 (d, *J* = 6.5 Hz, 2H), 7.36 (m, 2H), 7.09 (t, *J* = 7.0 Hz, 2H), 6.97 (s, 1H), 4.20 (q, *J* = 5.5 Hz, 2H), 1.26 (t, *J* = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 163.7 (d, *J* = 246.0 Hz), 162.1, 137.1, 132.2, 131.0 (d, *J* = 6.0 Hz) 130.9, 130.7, 130.4, 125.5, 120.8, 115.3 (d, *J* = 21.0 Hz), 115.2, 114.1, 109.6, 60.0, 14.3. IR: 3419, 3280, 2939, 1687, 1455, 1378, 1296, 1138, 1057, 761, 678, 648. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{16}BrFNO_2$ 388.0348; Found 388.0354.

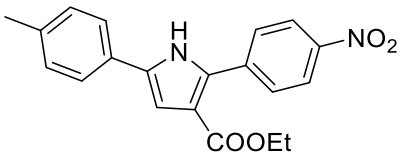
Ethyl 5-(4-methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrole-3-carboxylate (3o)



(Eluent: 25% EtOAc/hexane);71% yield (52.0 mg); yellow solid; melting point 218 - 220 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.26 (d, *J* = 6.0 Hz, 2H), 7.83 (d, *J* = 6.0 Hz, 2H), 7.48 (d, *J* = 7.5 Hz, 2H), 6.93 (m, 3H), 4.27 (q, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 1.32 (t, *J* = 6.0

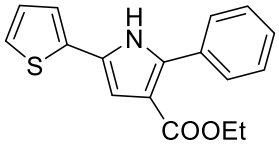
Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 159.4, 147.1, 133.9, 133.6, 129.4, 125.8, 123.7, 123.5, 117.0, 115.7, 114.6, 109.1, 55.4, 14.4. IR: 3424, 3295, 2947, 1689, 1368, 1265, 1298, 1135, 1031, 788, 692, 623. HRMS (ESI-TOF) *m/z*: $[M + H]^+$calcd for $C_{20}H_{19}N_2O_5$ 367.1294; Found 367.1277.

Ethyl 2-(4-nitrophenyl)-5-(p-tolyl)-1H-pyrrole-3-carboxylate (3p)



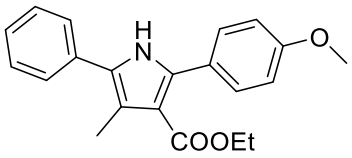
(Eluent: 25% EtOAc/hexane); 49% yield (34.5 mg); yellow solid; melting point 207 - 210 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.23 (d, *J* = 7.5Hz, 2H), 7.79 (d, *J* = 7.0 Hz, 2H), 7.43 (d, *J* = 6.5 Hz, 2H), 7.23 (t, *J* = 7.0 Hz, 2H), 6.98 (s, 1H), 4.26 (q, *J* = 6.5 Hz, 2H), 2.38 (s, 3H), 1.31 (t, *J* = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 147.0, 138.1, 137.7, 134.1, 133.7, 129.9, 129.5, 128.1, 124.2, 123.5, 115.6, 109.5, 60.3, 21.3, 14.4. IR: 3425, 3276, 2947, 1691, 1383, 1265, 1281, 1135, 1031, 788, 690, 630. HRMS (ESI-TOF) *m/z*: $[M +Na]^+$calcd for $C_{20}H_{18}N_2O_4Na$ 373.1164; Found 373.1156.

Ethyl 2-phenyl-5-(thiophen-2-yl)-1H-pyrrole-3-carboxylate (3q)



(Eluent: 5% EtOAc/hexane); 54% yield (32.2 mg); grey solid; melting point 158 - 160 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.59 (d, *J* = 5.5Hz, 2H), 7.36 (m, 3H), 7.19 (s, 1H), 7.09 (s, 1H), 7.02 (s, 1H), 6.87 (s, 1H), 4.19 (q, *J* = 5.5Hz, 2H), 1.24 (t, *J* = 5.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 137.5, 134.7, 131.7, 129.1, 128.5, 128.2, 127.8, 126.5, 123.7, 122.0, 113.6, 109.7, 59.9, 14.3. IR: 3441, 3276, 1668, 1368, 692. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$calcd for $C_{17}H_{15}NO_2SNa$ 320.0721; Found 320.0717.

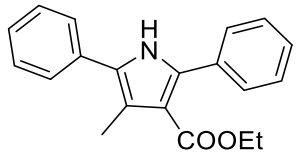
Ethyl 2-(4-methoxyphenyl)-4-methyl-5-phenyl-1H-pyrrole-3-carboxylate (5a)



(Eluent: 3% EtOAc/hexane); 65% yield (43.6 mg); white solid; melting point 130 - 132 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.46 (d, *J* = 7.5Hz, 2H), 7.42 (m, 4H), 7.29 (m,

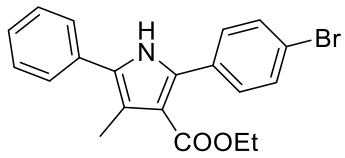
1H), 6.92 (d, *J* = 7.5 Hz, 2H), 4.19 (q, *J* = 6.5 Hz, 2H), 3.82 (s, 3H), 2.41 (s, 3H), 1.20 (t, *J* = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 159.6, 137.0, 132.6, 130.3, 129.1, 128.8, 127.5, 127.0, 125.3, 118.8, 113.5, 112.7, 59.5, 55.4, 14.3, 11.9. IR: 3449, 3330, 2947, 1689, 1469, 1357, 1286, 1225, 1057, 761, 678, 648. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$calcd for $C_{21}H_{21}NO_3Na$ 358.1419; Found 358.1415.

Ethyl 4-methyl-2, 5-diphenyl-1H-pyrrole-3-carboxylate (5b)



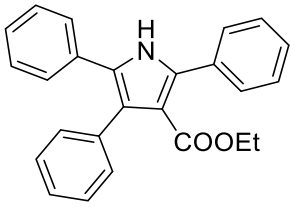
(Eluent: 3% EtOAc/hexane); 59% yield (36.2 mg); white solid; melting point 118 - 120 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.53 (d, *J* = 6.0 Hz, 2H), 7.40 (m, 6H), 7.34 (t, *J* = 6.0 Hz, 1H), 7.31 (m, 1H), 4.19 (q, *J* = 5.5 Hz, 2H), 2.43 (s, 3H), 1.18 (t, *J* = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 136.8, 132.9, 132.5, 129.5, 129.0, 128.8, 128.1, 127.5, 127.1, 119.0, 113.2, 59.6, 14.2, 11.8. IR: 3450, 3311, 2947, 1699, 1499, 1357, 1296, 1245, 1138, 1057, 761, 678, 648. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$calcd for $C_{20}H_{19}NO_2Na$ 328.1313; Found 328.1306.

Ethyl 2-(4-bromophenyl)-4-methyl-5-phenyl-1H-pyrrole-3-carboxylate (5c)



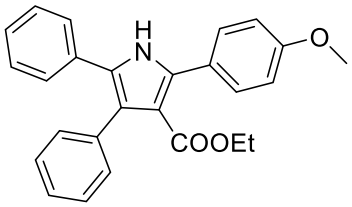
(Eluent: 3% EtOAc/hexane); 54% yield (41.5 mg); white solid; melting point 187 - 189 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.43 (d, *J* = 3.0 Hz, 4H), 7.40 (d, *J* = 6.5 Hz, 2H), 7.31 (m, 1H), 4.21 (q, *J* = 6.0 Hz, 2H), 2.40 (s, 3H), 1.21 (t, *J* = 6.5 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 135.4, 132.3, 131.6, 131.2, 130.5, 129.9, 128.8, 127.5, 127.2, 122.2, 119.1, 113.4, 59.6, 14.2, 11.8.8. IR: 3469, 3250, 2948, 1702, 1498, 1357, 1296, 1245, 1138, 1056, 761, 677, 647. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{18}BrNO_2Na$ 406.0419; Found 406.0405.

Ethyl 2, 4, 5-triphenyl-1H-pyrrole-3-carboxylate (5d)[3f]



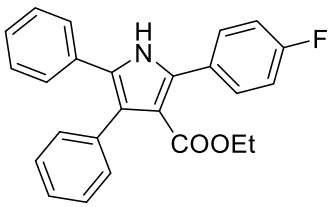
(Eluent: 3% EtOAc/hexane); 51% yield (37.5 mg); white solid; melting point 143 - 145 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.62 (d, J = 6.0 Hz, 2H), 7.41 (d, J = 6.0 Hz, 2H), 7.38 (m, 1H), 7.29 (m, 5H), 7.21 (m, 5H), 3.97 (q, J = 5.5 Hz, 2H), 0.89 (t, J = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 136.1, 135.4, 132.1, 131.9, 130.6, 129.2, 128.7, 128.5, 128.28, 128.24, 127.7, 127.0, 126.5, 124.1, 113.7, 59.7, 13.6. IR: 3450, 3311, 2947, 2500, 1696, 1479, 1357, 1290, 1236, 1138, 1057, 882.

Ethyl 2-(4-methoxyphenyl)-4, 5-diphenyl-1H-pyrrole-3-carboxylate (5e)



(Eluent: 3% EtOAc/hexane); 60% yield (48.0 mg); white solid; melting point 128 – 130 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.57 (d, J = 6.5 Hz, 2H), 7.30 (m, 4H), 7.24 (m, 3H), 7.17 (m, 3H), 6.97 (d, J = 7.0 Hz, 2H) 3.97 (q, J = 5.5 Hz, 2H), 3.84 (s, 3H), 0.89 (t, J = 5.5 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 159.7, 135.7, 130.7, 130.2, 128.8, 128.6, 127.8, 127.0, 126.9, 126.5, 124.7, 124.1, 113.8, 59.7, 55.4, 13.7. IR: 3433, 3302, 2936, 2467, 1672, 1479, 1357, 1290, 1236, 1138, 1057, 880, 761. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$calcd for $C_{26}H_{23}NO_3Na$ 420.1576; Found 420.1569.

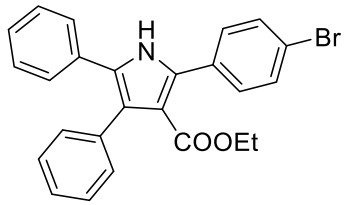
Ethyl 5-(4-nitrophenyl)-2, 4-diphenyl-1H-pyrrole-3-carboxylate (5f)



(Eluent: 3% EtOAc/hexane); 50% yield (38.5 mg); white solid; melting point 183 - 185 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.59 (t, J = 4.5Hz, 2H), 7.30 (m, 5H), 7.22 (m, 2H), 7.18 (t, J = 7.0 Hz, 3H), 7.10 (t, J = 7.0 Hz, 2H), 3.97 (q, J = 6.0 Hz, 2H), 0.88 (t, J = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 163.5, (d, J = 225 Hz), 162.0, 135.4(d, J = 15 Hz), 135.3, 131.8, 130.75, (d, J = 7.5 Hz), 130.70, 130.6, 129.3, 128.5, 128.3, 127.7,

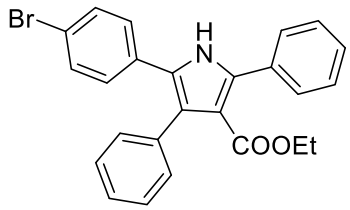
127.0, 126.5, 124.2, 115.3, 115.2, 113.7, 59.7, 13.6. IR: 3426, 3280, 2939, 1687, 1455, 1378, 1296, 1138, 1057. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$calcd for $C_{25}H_{20}FNO_2Na$ 408.1376; Found 408.1378.

Ethyl 2-(4-bromophenyl)-4, 5-diphenyl-1H-pyrrole-3-carboxylate (5g)



(Eluent: 3% EtOAc/hexane); 51% yield (45.6 mg); white solid; melting point 172 - 175 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.50 (m, 2H), 7.30 (m, 4H), 7.22 (m, 6H), 4.00 (q, J = 6.0 Hz, 2H), 0.90 (t, J = 6.0 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 135.2, 134.8, 131.6, 131.4, 130.5, 130.3, 129.6, 128.6, 127.1, 127.0, 126.6, 124.3, 122.4, 114.0, 59.8, 13.6. IR: 3426, 3278, 2970, 2478, 1660, 1457, 1357, 1290, 1236, 1138, 1039. HRMS (ESI-TOF) *m/z*: $[M + H]^+$calcd for $C_{25}H_{21}BrNO_2$ 446.0756; Found 446.0745.

Ethyl 5-(4-bromophenyl)-2, 4-diphenyl-1H-pyrrole-3-carboxylate (5h)



(Eluent: 3% EtOAc/hexane); 56% yield (49.9 mg); white solid; melting point 183 - 185 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.61 (d, J = 6.0 Hz, 2H), 7.42 (t, J = 6.0 Hz, 2H), 7.38 (t, J = 6.0 Hz, 1H), 7.31 (m, 3H), 7.29 (m, 4H), 7.02 (d, J = 7.5 Hz, 2H), 3.97 (q, J = 6.0 Hz, 2H), 0.88 (t, J = 5.5 Hz, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 136.6, 135.2, 132.0, 131.8, 130.8, 130.6, 128.8, 128.5, 128.4, 128.3, 126.8, 124.8, 120.9, 113.9, 59.8, 13.6. IR: 3426, 3278, 2971, 2478, 1658, 1455, 1357, 1290, 1236, 1138, 1039. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$calcd for $C_{25}H_{20}BrNO_2Na$ 468.0575; Found 468.0571.

Associated Content

Supporting Information

Copies of NMR spectra for all compounds and HRMS spectra for new compounds, and crystallographic data for **3f** (CCDC No. 1835841). This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgements

CSIR-CSMCRI Communication No. 40/2018. N.N.K.R thankful to AcSIR for his Ph.D. enrolment and the "Analytical Discipline and Centralized Instrumental Facilities" for providing instrumentation facilities. We thank DST, Government of India (EMR/2016/000010), and CSIR-CSMCRI (MLP-027 and OLP-088) for financial support.

References

1. (a) Huffman, J. W. Cannabimimetic indoles, pyrroles and indenes.Curr. Med. Chem. **1999**, *6*, 705. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms. *Chem. Rev.* **2008**, *108*, 264. (c) Young, I. S.; Thornton, P. D.; Thompson, A. Synthesis of natural products containing the pyrrolic ring. *Nat. Prod. Rep.* **2010**, *27*, 1801. (d) Liu, R.; Liu, Y.; Zhou, Y.-D.; Nagle, D. G. Molecular-Targeted Antitumor Agents. 15. Neolamellarins from the Marine Sponge *Dendrillanigra* Inhibit Hypoxia-Inducible Factor-1 Activation and Secreted Vascular Endothelial Growth Factor Production in Breast Tumor Cells. *J. Nat. Prod.* **2007**, *70*, 1741. (e) Jansen, R.; Sood, S.; Mohr, K. I.; Kunze, B.; Irschik, H.; Stadler, M.; Müller, R. Nannozinones and Sorazinones, Unprecedented Pyrazinones from Myxobacteria. *J. Nat. Prod.* **2014**, *77*, 2545.

2. (a) Paal, C.; Synthese von Thiophen- und Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367. (b) Knorr, L.; Synthese von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1884**, **17**, 1635. (c) Hantzsch, A.; NeueBildungsweise von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.

3. (a) Tsai, A-I.; Chuang, C-P. Synthesis of highly substituted pyrroles via oxidative free radical reactions of β-aminocinnamates. *Tetrahedron*, **2006**, *62*, 2235. (b) Rakshit, S.; Patureau, F. W.; Glorius, F. Pyrrole Synthesis via Allylic sp^3 C−H Activation of Enamines Followed by Intermolecular Coupling with Unactivated Alkynes. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (c) Ran, L.; Ren, Z-H.; Wang Y-Y.; Guan, Z-H. Copper-catalyzed homo coupling of ketoxime carboxylates for synthesis of symmetrical pyrroles. *Green Chem.* **2014**, *16*, 112. (d) Daw, P.; Chakraborty, S.; Garg, J. A.; David, Y. B. Milstein, D. Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines

Catalyzed by Cobalt Pincer Complexes. *Angew. Chem. Int. Ed.* **2016**, *55*, 14373. (e) Amombo, G. M. O.; Flogel, O.; Kalai, S. K. D.; Schoder, S.; Warzok, U.; Reissig, H-U. Efficient Syntheses of 2, 5-Dihydropyrroles, Pyrrolidin-3-ones, and Electron-Rich Pyrroles from *N*-Tosylimines and Lithiated Alkoxyallenes. *Eur. J. Org. Chem.* **2017**, *2017*, 1965. (f) Zhao, M-N.; Liang, H.; Ren, Z-H.; Guan, Z-H. Iron-Catalyzed Tandem One-Pot Addition and Cyclization of the Blaise Reaction Intermediate and Nitroolefins: Synthesis of Substituted NH-Pyrroles from Nitriles. *Adv. Synth. Catal.* **2013**, *355*, 221.

4. (a) D. J; Shrinivas, Uttam, A. M.; Venkatrao, H. K.; Tejraj, M. A. Pyrrole: Chemical Synthesis, Microwave Assisted Synthesis, Reactions and Applications: A Review. *Curr. Org. Chem.* **2013**, *17*, 2279. (b) Trofimov, B. A.; A. I.; Mikhaleva.; Schmidt, E. Y.; Sobenina, L. N.Chemistryof Pyrroles. *CRC Press*, **2014**. (c) Estevez, V.; Villacampa, M.; Menendez, J. C. Recent advances in the synthesis of pyrroles by multi component reactions. *Chem. Soc. Rev.* **2014**, *43*, 4633. (d) Zhou, N-N.; Zhu, H-T.; Yang, D-S.; Guan, Z-H. Recent developments in the group-1B-metal-catalyzed synthesis of pyrroles. *Org. Biomol. Chem.* **2016**, *14*, 7136.
5. (a) Bhunia, N.; Das, B. One-Pot Synthesis of Penta substituted Pyrroles from Propargylic Alcohols, Amines, and Dialkyl Acetylenedicarboxylates; Tandem Amination, Propargylation and Cycloisomerization Catalyzed by Molecular Iodine. *Synthesis*, **2013**, *45*, 1045. (b) Wang, Y.; Jiang, C-M.; Li, H-L.; He, F-S.; Luo, X.; Deng, W-P. Regioselective Iodine-Catalyzed Construction of Polysubstituted Pyrroles from Allenes and Enamines. *J. Org. Chem.* **2016**, *81*, 8653. (c) Cheng, B-Y.; Wang, Y-N.; Li, T-R.; Lu, L-Q.; Xiao, W-J. Synthesis of Polysubstituted Pyrroles through a Formal [4 + 1] Cycloaddition/E1cb Elimination/Aromatization Sequence of Sulfur Ylides and α, β-Unsaturated Imines. *J. Org. Chem.* **2017**, *82*, 12134. (d) Xuan, J.; Xia, X-D.; Zeng, T-T.; Feng, Z-J.; Chen, J-R.; Lu, L-Q.; Xiao, W-J. Visible-Light-Induced Formal [3+2] Cycloaddition for Pyrrole Synthesis under Metal-Free Conditions. *Angew. Chem. Int. Ed.* **2014**, *53*, 5653.
6. (a) Gao, P.; Wang, J.; Bai, Z-J.; Shen, L.; Yan, Y-Y.; Yang, D-S.; Fan, M-J.; Guan, Z-H. Synthesis of Polycarbonyl Pyrroles via $K_2S_2O_8$ Mediated Oxidative Cyclization of Enamines. *Org. Lett.* **2016**, *18*, 6074. (b) Guan, Z – H.; Li, L.; Ren, Z-H.; Li, J.; Zhao, M-N. A facile and efficient synthesis of multisubstituted pyrroles from enaminoesters and nitroolefins. *Green Chem.* **2011**, *13*, 1664. (c) Donthiri, R. R.; Samanta, S.; Adimurthy, S.

Copper-catalyzed C (sp^3)–H functionalization of ketones with vinyl azides: synthesis of substituted-1H-pyrroles. *Org. Biomol. Chem.* **2015**, *13*, 10113.

7. (a) Samanta, S.; Ravi, C.; Joshi, A.; Venkatanarayana, P.; Adimurthy, S.Visible-light-induced aerobic dioxygenation of styrenes under metal- and additive-free ambient conditions. *Tetrahedron Lett.* **2017**, *58*, 721. (b) Samanta, S.; Ravi, C.; Rao, S. N.; Joshi, A.; Adimurthy, S. Visible-light-promoted selective C–H amination of hetero arenes with heteroaromatic amines under metal-free conditions. *Org. Biomol. Chem.* **2017**, *15*, 9590. (c) Reddy, N. N. K.; Rao, S. N.; Ravi, C.; Adimurthy, S. Catalyst-free synthesis of 2, 4-disubstituted-1-H-imidazolesthrough [3+2] cyclisation of vinyl azides with amidines. *ACS Omega* **2017**, *2*, 5235. (d) Rao, S. N.; Reddy, N. N. K.; Samanta, S.; Adimurthy, S. I_2 - Catalyzed Oxidative amidation of benzyl amines and benzyl cyanides under mild conditions. *J. Org. Chem.* **2017**, *82*, 13632. (e) Venkatanarayana, P.; Ravi, C.; Samanta, S.; Adimurthy, S.Oxidative Amidation of Methylarenes and Heteroamines under Metal-Free Conditions. *ChemistrySelect* **2017**, *2*, 5887.

8. (a) Zhong, X.; Lv, J.; Luo, S. Oxidative Radical Addition–Cyclization of Sulfonyl Hydrazones with Simple Olefins by Binary Acid Catalysis. *Org. Lett.* **2016**, *18*, 3150. (b) Lei, T.; Liu, W-Q.; Li, J.; Huang, M-Y.; Yang, B.; Meng, Q-Y.; Chen, B.; Tung, C-H Wu, L-Z. Visible Light Initiated Hantzsch Synthesis of 2, 5-Diaryl-Substituted Pyrroles at Ambient Conditions. *Org. Lett.* **2016**, *18*, 2479.

9. (a) Inturi, S. B.; Kalita, B.; Ahamed, A. J. I_2-TBHP-catalyzed one-pot highly efficient synthesis of 4,3-fused 1,2,4-triazoles from N-tosylhydrazones and aromatic N-heterocycles via intermolecular formal 1,3-dipolar cycloaddition. *Org. Biomol. Chem.* **2016**, *14*, 11061. (b) Panda, S.; Maity, P.; Manna, D. Transition Metal, Azide, and Oxidant-Free Homo- and Hetero coupling of Ambiphilic Tosylhydrazones to the Regioselective Triazoles and Pyrazoles. *Org. Lett.* **2017**, *19*, 1534. (c) Gao, Q.; Wu, X.; Liu, S.; Wu, A. I_2-Promoted Selective Oxidative Cross-Coupling/Annulation of 2-Naphthols with Methyl Ketones: A Strategy To Build Naphtho [2, 1-*b*]furan-1(2*H*)-ones with a Quaternary Center.*Org. Lett.* **2014**, *16*, 1732. (d) Mohammed, S.; Vishwakarma, R. A.; Bharate, S. B. Iodine Catalyzed Oxidative Synthesis of Quinazolin-4(3*H*)-ones and Pyrazolo [4, 3-*d*] pyrimidin-7(6*H*)-ones via Amination of Sp^3 C–H Bond. *J. Org. Chem.* **2015**, *80*, 6915. (e) Zhang, J.; Wu, X.; Gao, Q.; Geng, X.; Zhao, P.; Wu, Y-D.; Wu, A.

Diamination/Oxidative Cross-Coupling/Bicyclization of Anilines And Methyl Ketones: Direct I_2– Promoted Synthesis of 1, 2-Fused Oxindoles. *Org. Lett.* **2017**, *19*, 408.

10. (a) Huang, F.; Liu, Z.; Wang, Q.; Lou, J.; Yu, Z. Copper-Catalyzed Formal Carbene Migratory Insertion into Internal Olefinic C═C Bonds with *N*-Tosylhydrazones To Access Iminofuran and 2(3*H*)-Furanone Derivatives. *Org. Lett.* **2017**, *19*, 3660. (b) Ye, J.; Wang, C.; Chen, L.; Wu, X.; Zhou, L.; Sun, J. Copper-Catalyzed Remote C-H Amination of Quinolines with N-Fluorobenzenesulfonimide. *Adv. Synth. Catal.* **2016**, *338*, 1042.