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A multicomponent pathway-inspired regioselective synthesis of 2,3,4-trisubstituted 1*H*-pyrroles *via* [3+2] cycloaddition reaction†‡

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A copper catalyzed regioselective synthesis of 2,3,4-trisubstituted 1*H*-pyrroles using a novel three-component coupled domino reaction of aldehydes, ketones and alkyl isocyanoacetates is reported. This transformation proceeds through the formation of a chalcone followed by a [3+2] cycloaddition reaction to obtain α-cuprioisocyanide, a cyclic organocopper intermediate, which on copper–hydrogen exchange followed by oxidation exclusively offers 2,3,4-trisubstituted 1*H*-pyrrole.

Introduction

Pyrrole in general and 2,3,4-trisubstituted 1*H*-pyrroles in particular are privileged scaffolds because they are significant structural constituents of various natural products, pharmaceuticals and agrochemicals.[1,2] 2,3,4-Trisubstituted 1*H*-pyrroles that possess ability to form coordinate bond are used in applications such as molecular sensing, semiconducting materials, lasers, image diagnosis, and materials science.[3] Noteworthy is the strong absorption and very intense fluorescence of BODIPY (boron-dipyrromethene) dyes derived from pyrroles.[4] The development of various convenient methods for the synthesis of pyrroles stems from these potential applications.

Several synthetic methodologies have been reported since Hantzsch[5] first prepared pyrroles by the reaction of β-enaminones with α-haloketones. Notable amongst these are the Paal–Knorr synthesis[6] using 1,4-diketones with amines, the Knorr synthesis using α-amino ketones and β-dicarbonyl compounds, the Barton–Zard synthesis using isocyanoacetates and nitroalkenes, and the van Leusen synthesis.[7] In addition to these, some other syntheses have also been reported.[8–12] In spite of their effectiveness, these classical methods suffer from several shortcomings such as functional group non-compatibility, prolonged reaction time, formation of byproducts, poor regiospecificity, harsh reaction conditions, multistep synthetic operation and tedious workup procedures.

In view of the aforementioned difficulties, the development of a cost-effective, mild, convenient, straightforward and regioselective method for the synthesis of pyrroles from easily available chemical entities is highly desirable. Multi-component coupled domino reactions (MCDRs), which involve at least three different substrates reacting in a sequential manner to form a single compound, have provided a most powerful platform to access diversity as well as complexity in a limited number of reaction steps.[13] These reactions can avoid time-consuming and costly processes for the purification of various precursors. In addition, these reactions satisfy the objectives of an ideal synthesis and the principles of green chemistry.[14] Therefore, the design of new MCDRs is a continuing challenge at the forefront of organic chemistry. In this context, in recent years, atom-economical pyrrole synthesis has been accomplished using isocyanides.[15–20] Their unusual reactivity and ability to form multiple bonds through a one-pot procedure offered by tandem or multicomponent reactions has been used to produce an array of heterocycles.[21–22] Ley *et al.* reported the preparation of nitrosubstituted functionalized pyrroles *via* a one-pot three-component coupling of tosyl isocyanide, ethyl chloroformate and nitrostyrene.[23] Uno and co-workers used vinyl sulfones with ethyl isocyanoacetate for the synthesis of 3,4-disubstituted pyrrole-2-carboxylates.[24] 2,3,4-Trisubstituted 1*H*-pyrroles with a tosyl substituent at C-2 position were synthesized from tosylmethyl isocyanide (TOSMIC) and vinyl azides.[25] Nevertheless, the transition-metal-catalyzed cycloadditions of isocyanides with double or triple bonds have received enormous attention. Various groups have reported the synthesis of substituted pyrroles using copper, phosphine and silver catalyzed [3+2] cycloaddition of isocyanides and alkynes.[26–34] Noteworthy is

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† This work is dedicated to Prof. M. M. Salunkhe, Vice Chancellor, Yashwantrao Chavan Maharashtra Open University (YCMOU) on his 60th birthday.

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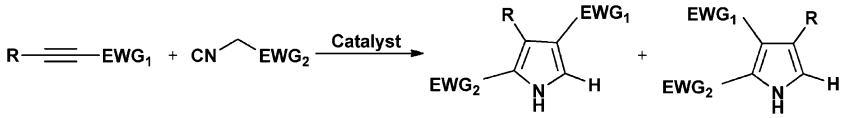
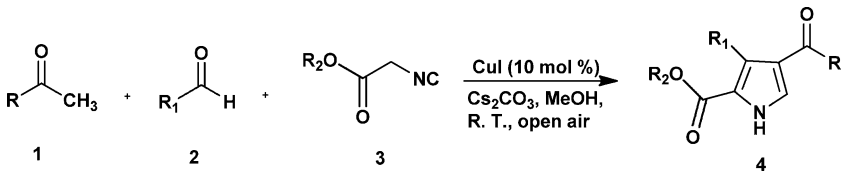
§ These authors contributed equally to this work.



Scheme 1 Formation of mixture of regioisomers.

the formation of 2,4-di-EWG-substituted and 2,3-di-EWG-substituted pyrroles in the presence of copper and phosphine catalysts, respectively. This implies that the regiodifferentiated addition of isocyanides to alkynes is controlled by the catalytic species. However, some of these methods are associated with an inherent drawback of the formation of mixtures of regioisomers (Scheme 1).

Considering the literature reports[35] and as a part of our ongoing research on the development of multicomponent approaches for the synthesis of heterocycles,[36] we herein wish to report a simple, efficient and regioselective synthesis of novel 2,3,4-trisubstituted 1*H*-pyrroles from easily available starting materials. Hitherto, to the best of our knowledge, our attempt is the first one in the direct synthesis of 2,3,4-trisubstituted 1*H*-pyrroles *via* a three-component coupled domino reaction of aldehydes, ketones and alkyl isocyanoacetates (**3**) using a metal catalyst (Scheme 2).

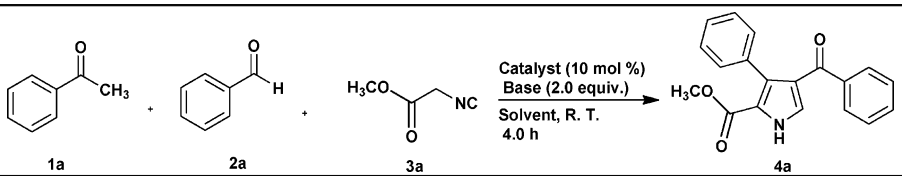


Scheme 2 General regioselective one-pot synthesis of 2,3,4-trisubstituted 1*H*-pyrrole.

Results and discussion

To establish the optimized reaction condition, we first investigated the reaction between acetophenone (**1a**), benzaldehyde (**2a**) and methyl 2-isocyanoacetate (**3a**) using different catalysts, bases and solvents. To our surprise, the combination of 10 mol% CuI and Cs_2CO_3 in methanol at room temperature in open air solely produced methyl 4-benzoyl-3-phenyl-1*H*-pyrrole-2-carboxylate (**4a**) regioselectively with an excellent yield (Table 1, entry 11). Moderate

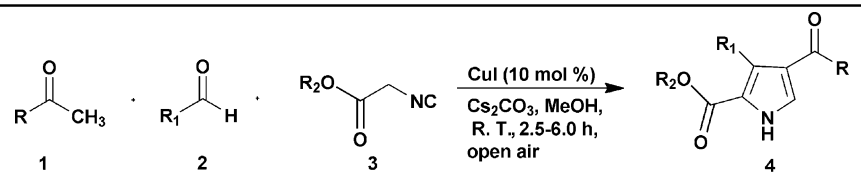
Table 1 Optimization of reaction conditions[a]

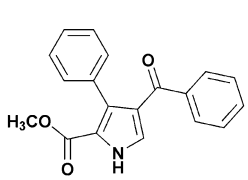


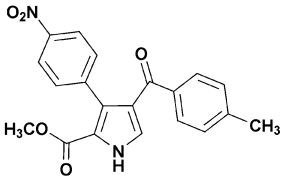
Entry	Catalyst (mol%)	Base	Solvent	Yield[d] (%)
1	CuI	Cs_2CO_3	DCE	62
2	CuI	Cs_2CO_3	DME	68
3	CuI	Cs_2CO_3	Dioxane	57
4	CuI	Cs_2CO_3	THF	51
5	CuI	Cs_2CO_3	CH_3CN	27
6	CuI	K_2CO_3	MeOH	53
7	CuI	K^{t}BuO	MeOH	45
8	CuI	NaOEt	MeOH	48
9	CuI	DBU	MeOH	10
10	CuI	2,6-Lutidine	MeOH	13
11	CuI	Cs_2CO_3	MeOH	83
12[b]	CuI	Cs_2CO_3	MeOH	N.D.
13[c]	CuI	Cs_2CO_3	DMF	Trace
14[c]	CuI	Cs_2CO_3	MeOH	Trace
15	CuCl	Cs_2CO_3	MeOH	44
16	CuBr	Cs_2CO_3	MeOH	34
17	$CuCl_2$	Cs_2CO_3	MeOH	24
18	$CuBr_2$	Cs_2CO_3	MeOH	27
19	$Cu(OAc)_2$	Cs_2CO_3	MeOH	30

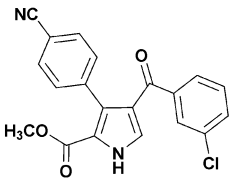
[a] Reaction conditions: acetophenone **1a** (1.0 mmol), benzaldehyde **2a** (1.3 mmol) and base (2.0 mmol) in 3 mL of solvent were stirred at R.T. for 3.5 h; then, catalyst (10 mol%) and methyl 2-isocyanoacetate **3a** (1.0 mmol) in 2 mL solvent were added and stirring was continued for 0.5 h in open air. [b] Reaction conditions: acetophenone **1a** (1.0 mmol), benzaldehyde **2a** (1.3 mmol), CuI (10 mol%), methyl 2-isocyanoacetate **3a** (1.0 mmol) and Cs_2CO_3 (2.0 mmol) in 5 mL of MeOH were stirred at R.T. for 4.0 h in open air. [c] Under N_2. [d] Isolated yields. N.D. = Not Detected.

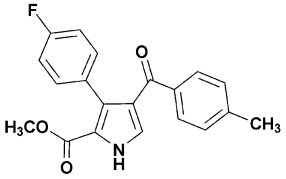
Table 2 Scope of the formation of 2,3,4-trisubstituted 1*H*-pyrroles[a,b]

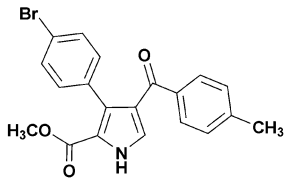


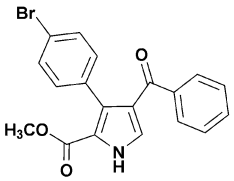

4a (4.0 h, 83%)

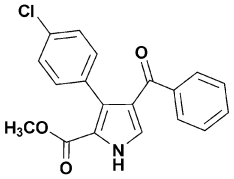

4b (2.5 h, 90%)

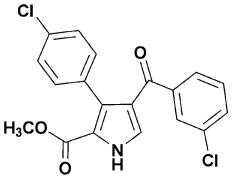

4c (2.5 h, 88%)

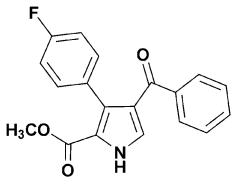

4d (4.0 h, 78%)

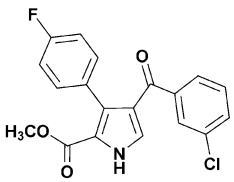

4e (4.0 h, 76%)

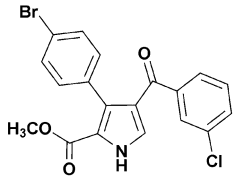

4f (4.0 h, 80%)

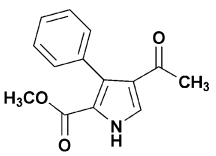

4g (4.0 h, 79%)

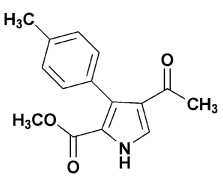

4h (4.0 h, 82%)

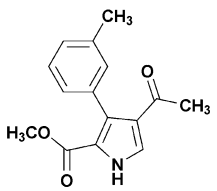

4i (4.0 h, 80%)

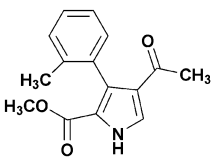

4j (4.0 h, 86%)

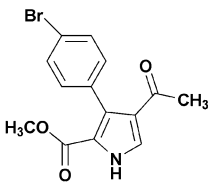

4k (4.0 h, 84%)

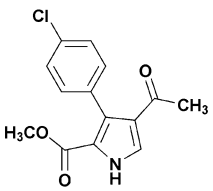

4l (4.5 h, 62%)

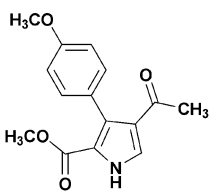

4m (4.5 h 63%)

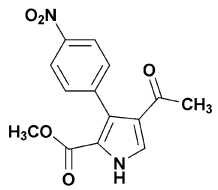

4n (4.5 h, 60%)

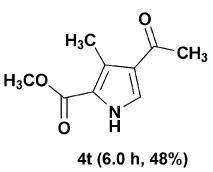

4o (5.0 h, 57%)

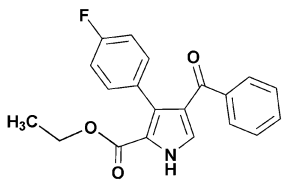

4p (4.5 h, 68%)

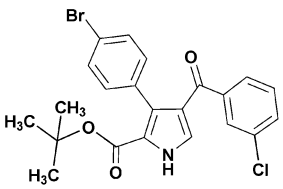

4q (4.5 h, 70%)

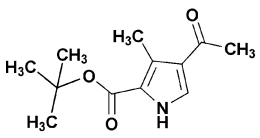

4r (5.5 h, 55%)


4s (3.5 h, 76%)


4t (6.0 h, 48%)


4u (4.5 h, 87%)


4v (4.0 h, 82%)


4w (6.0 h, 53%)

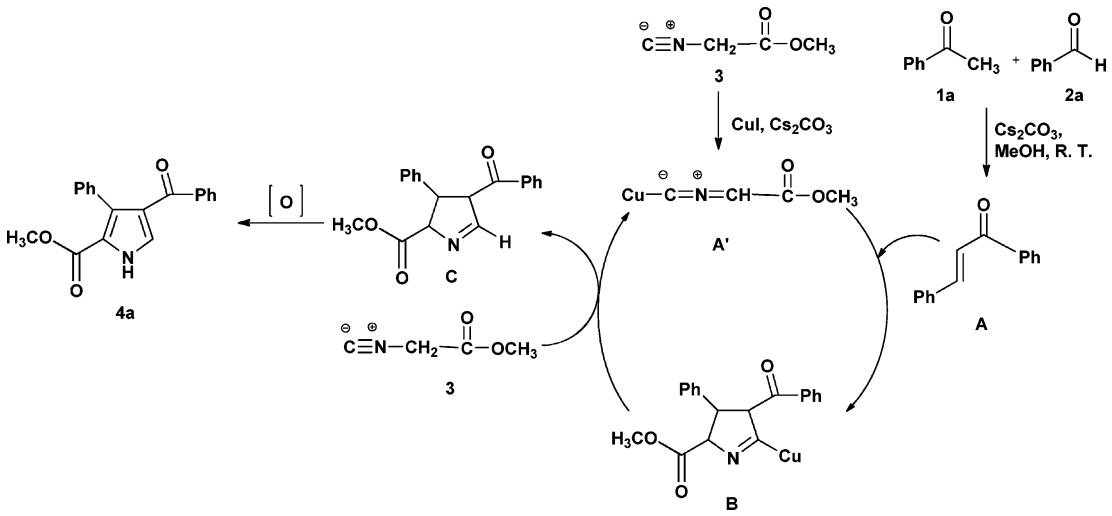
[a] Reaction conditions: ketones **1** (1.0 mmol), aldehydes **2** (1.3 mmol) and Cs_2CO_3 (2.0 mmol) in methanol (3 mL) were stirred at R.T. for 2.0–5.5 h; then, CuI (10 mol%) and alkyl isocyanoacetate **3** (1.0 mmol) in methanol (2 mL) were added and stirring was continued for 0.5 h in open air. [b] Isolated yields.

yields of **4a** (53%, 45% and 48%) were obtained in the presence of K_2CO_3, K^tBuO and NaOEt (Table 1, entries 6–8, respectively). The use of DBU and 2,6-lutidine (Table 1, entries 9 and 10) also resulted in low yields (10% and 13%, respectively) of the product **4a**. We next carried out this domino reaction by adding all the reagents at the same time, but could not detect the formation of product **4a** (Table 1, entry 12). This clearly highlights the significance of step-wise addition. The superior catalytic activity of CuI was observed in open air as compared to that in N_2 (Table 1, entries 13 and 14). Trace amounts of product formation was observed in N_2 atmosphere because oxygen present in the solvent drives the oxidation of pyrroline to pyrrole. Various copper salts were tested under these conditions for their catalytic activity but none were found to be as effective as CuI (Table 1, entries 15–19). Thus, firstly the Aldol condensation reaction involving the acetophenone (**1a**) and benzaldehyde (**2a**) was carried out in the presence of the base. When the reaction was completed and the corresponding α,β-unsaturated ketone was generated in the reaction media, the second reaction step ([3+2] cycloaddition) was carried out by adding catalyst and methyl 2-isocyanoacetate (**3a**) to the reaction media.

To investigate the scope and limitations of this novel three-component coupled domino reaction of various aromatic or aliphatic ketones (**1**), aromatic or aliphatic aldehydes (**2**) and alkyl isocyanoacetates (**3**) were examined (Table 2). The reaction worked well and the corresponding pyrroles (**4a–4w**) were obtained in 48–90% yield within 2.5–6.0 hours. Electron neutral or weakly deactivated acetophenones (4-CH_3 and 3-Cl), or substituted benzaldehydes bearing electron withdrawing (4-NO_2, 4-CN) substituents on the phenyl ring and methyl 2-isocyanoacetate (**3a**) offered excellent yields of the product (Table 2, entries **4b** and **4c**). The rate of chalcone formation followed by 1,3-dipolar cycloaddition reaction was highest (2.5 h) for the aforementioned substrates. Acetophenones (**1**) and benzaldehydes (**2**) bearing halogens, electron neutral substituents on the phenyl ring and methyl 2-isocyanoacetate (**3a**) gave the corresponding 2,3,4-trisubstituted 1*H*-pyrroles in good to excellent yields (Table 2, entries **4d–4k**). Then, the substituted benzaldehydes, acetone and methyl 2-isocyanoacetate (**3a**) were studied for the three-component coupled domino reaction. Benzaldehydes bearing halogens, electron neutral substituents in the phenyl ring, acetone and methyl 2-isocyanoacetate (**3a**) offered moderate to good yields of the products (Table 2, entries **4l–4q**). The steric hindrance near the double bond of chalcones generated *in situ* from benzaldehydes (4-CH_3, 3-CH_3, 2-CH_3) and acetone, followed by [3+2] cycloaddition with methyl 2-isocyanoacetate (**3a**) reduced the yield of the products as well as rate of reactions, and the reactivity order was found to be *p*- > *m*- > *o*-isomer (Table 2, entries **4m**, **4n** and **4o**). As expected, benzaldehyde with an electron withdrawing 4-NO_2 group, acetone and methyl 2-isocyanoacetate (**3a**) had required a significantly shorter reaction time (3.5 h) and gave a higher yield of the product (Table 2, entry **4s**, 76%) than that offered by its methoxy counterpart (Table 2, entry **4r**, 55%). Interestingly, acetaldehyde, acetone and methyl 2-isocyanoacetate (**3a**) also underwent the three-component coupled domino reaction to afford methyl 4-acetyl-3-methyl-1*H*-pyrrole-2-carboxylate (**4t**) in 48% yield.

The scope of this domino reaction was extended to ethyl 2-isocyanoacetate (**3b**). The acetophenone (**1a**), 4-fluorobenzaldehyde and ethyl 2-isocyanoacetate (**3b**) under optimal conditions gave pyrrole (Table 2, entry **4u**) in 87% yield. To further extend the scope of this protocol, we carried out the reaction between acetophenone (**1a**), 4-bromobenzaldehyde and *tert*-butyl 2-isocyanoacetate (**3c**) to furnish the corresponding product (Table 2, entry **4v**) in 82% yield. Similarly, the reaction of acetone, acetaldehyde and *tert*-butyl 2-isocyanoacetate (**3c**) gave *tert*-butyl 4-acetyl-3-methyl-1H-pyrrole-2-carboxylate (Table 2, entry **4w**) in 53% yield.

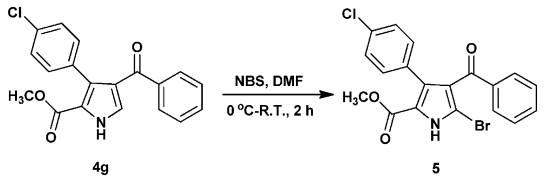
A possible mechanistic pathway of the multicomponent coupled domino reaction is depicted in Scheme 3. First chalcone (**A**) is formed by the cross Aldol condensation of acetophenone (**1a**) and benzaldehyde (**2a**), followed by the reaction of methyl 2-isocyanoacetate (**3a**) with copper iodide to obtain α-cuprioisocyanide (**A′**). Then, [3+2] dipolar cycloaddition of α-cuprioisocyanide (**A′**) and chalcone (**A**) gives a cyclic organocopper intermediate (**B**), which on



Scheme 3 Proposed mechanism.

copper hydrogen exchange affords 3,4-dihydro-2*H*-pyrrole (**C**). The oxidation of the latter gives methyl 4-benzoyl-3-phenyl-1*H*-pyrrole-2-carboxylate (**4a**).[37]

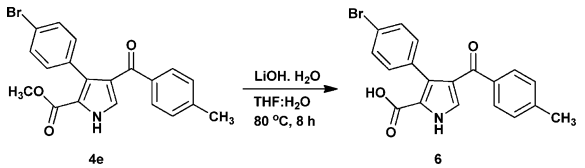
Since the core objective of our research is to prepare 2,3,4-trisubstituted and 2,3,4,5-tetrasubstituted 1*H*-pyrroles for various promising applications, we explored the possibility of carrying out the electrophilic substitution of 2,3,4-trisubstituted 1*H*-pyrrole (**4g**) at the C-5 position. It was interesting to observe that the 5-bromo product (**5**) was obtained on treating pyrrole (**4g**) with *N*-bromosuccinimide in DMF at room temperature (Scheme 4). Thus, pyrrole (**4g**) is a possible intermediate for BODIPY dyes.



4g 5

Scheme 4 Electrophilic substitution at the C-5 position.

Furthermore, the ester group in **4e** can be easily hydrolysed to carboxylic acid (**6**), thus offering a possible conjugation site for linking fluorophores available from such 2,3,4-trisubstituted 1*H*-pyrroles with biomolecules (Scheme 5).



4e 6

Scheme 5 Hydrolysis of ester group.

Conclusions

In conclusion, we have developed an operationally simple and highly efficient methodology for the synthesis of 2,3,4-trisubstituted 1*H*-pyrroles *via* a novel three-component coupled domino reaction. The striking feature of this protocol is the use of a wide range of ketones, aldehydes and alkyl isocyanoacetates to obtain the structural diversity of pyrroles at room temperature. This tandem process provides moderate to excellent yields of the products (48–90%). Further use of these pyrroles in the synthesis of BODIPY dyes and their conjugation with biomolecules is currently underway in our laboratory.

Experimental section

General methods

Chemical reagents were obtained from commercial companies. All the reactions were performed in round bottom flasks and monitored by TLC performed on aluminium plates (0.25 mm, E. Merck) precoated with silica gel Merck 60 F-254. Developed TLC plates were visualized under a short-wavelength UV lamp. Reactions were conducted under open air and N_2 atmosphere in solvents such as acetonitrile, DCE, DME, dioxane, MeOH, THF, and DMF. Yields refer to spectroscopically (^{1}H, ^{13}C NMR) homogeneous material obtained after column chromatography. Column chromatography was performed on silica gel (100–200 mesh size) supplied by S. D. Fine Chemicals Limited, India. IR spectra were recorded on a JASCO–FT/IR-4100 LE with attenuated total reflection (ATR) method. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD and DMSO-d_6 solutions with Agilent 300, 500 and Brüker 400 MHz spectrometers. Chemical shifts (δ) are reported relative to $SiMe_4$ (δ = 0.0) as an internal standard. The number of protons (n) for a given resonance is indicated by nH. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; br, broad; J, coupling constant in Hz. High-resolution mass spectra were obtained using positive as well as negative electrospray ionization (ESI) by the time of flight (TOF) method.

General experimental procedure for three-component coupled domino reaction

A round bottom flask was charged with ketone **1** (1.0 mmol), aldehyde **2** (1.3 mmol) and Cs_2CO_3 (2.0 mmol) in methanol (3 mL) at room temperature. TLC indicated the quantitative formation of chalcone after 2.0–5.5 h; subsequently, alkyl isocyanoacetate **3** (1.0 mmol) and CuI (0.1 mmol) in methanol (2 mL) were added. The reaction mixture was stirred at room temperature under open air atmosphere for 0.5 h. The solvent was removed under reduced pressure, the obtained residue was dissolved in ethyl acetate (30 mL) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100–200 mesh size) with *n*-hexane : ethyl acetate (75 : 25) as eluent to afford the desired product **4a–4w**.

Methyl 4-benzoyl-3-phenyl-1*H*-pyrrole-2-carboxylate 4a. Off white solid, mp 140–142 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3256, 1724, 1694, 1632, 1508, 1264 and 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (bs, 1H), 7.72 (dd, J = 7.2, 1.2 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.36–7.32 (m, 5H), 7.29–7.23 (m, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.20, 161.40, 138.97, 133.12, 132.49, 132.00, 130.32, 129.41, 128.02, 127.74, 127.30, 127.21, 125.15, 120.44, 51.65; HRMS (ESI): calc. for $[(C_{19}H_{15}NO_3)H]$ $[M + H]^-$ 306.1131, found 306.1130.

Methyl 4-(4-methylbenzoyl)-3-(4-nitrophenyl)-1*H*-pyrrole-2-carboxylate 4b. Pale yellow solid, mp 162–164 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3421, 1720, 1695, 1627, 1601, 1509, 1437,1341 and 855; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (bs, 1H), 8.15 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 3.2 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 3.73 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.19, 160.86, 146.96, 143.42, 140.89, 136.07, 131.32, 130.08, 129.56, 129.10, 127.90, 125.09, 122.67, 121.03, 51.99, 21.66; HRMS (ESI): calc. for $[(C_{20}H_{16}N_2O_5)H]$ $[M + H]^+$ 365.1137, found 365.1111.

Methyl 4-(3-chlorobenzoyl)-3-(4-cyanophenyl)-1*H*-pyrrole-2-carboxylate 4c. Off white solid, mp 182–184 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3273, 2234, 1727, 1707, 1644, 1517 and 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (bs, 1H), 7.59 (distorted t, J = 7.2 Hz, 4H),

7.42 (distorted d, J = 7.6 Hz, 4H), 7.31 (t, J = 8.0, 7.2 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.12, 160.77, 140.31, 138.41, 134.46, 132.33, 131.21, 130.35, 129.78, 129.41, 128.17, 127.28, 124.48, 121.21, 119.12, 111.04, 52.06; HRMS (ESI): calc. for $[(C_{20}H_{13}ClN_2O_3)H]$ $[M + H]^+$ 365.0693, found 365.0665.

Methyl 3-(4-fluorophenyl)-4-(4-methylbenzoyl)-1*H*-pyrrole-2-carboxylate 4d. White solid, mp 128–130 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3316, 1728, 1692, 1634, 1517, 1263 and 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (bs, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.34 (s, 1H), 7.28 (distorted t, J = 6.4. 6.0 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 6.95 (t, J = 8.4, 8.0 Hz, 2H), 3.74 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.74, 162.26 (d, J_{C-F} = 248.3 Hz), 161.25, 143.01, 136.26, 132.04 (d, J_{C-F} = 8.0 Hz), 131.99, 131.45, 129.65, 129.03, 128.88, 127.36, 125.34, 120.52, 114.40 (d, J_{C-F} = 21.4 Hz), 51.78, 21.64; HRMS (ESI): calc. for $[(C_{20}H_{16}FNO_3)H]$ $[M + H]^+$ 338.1192, found 338.1163.

Methyl 3-(4-bromophenyl)-4-(4-methylbenzoyl)-1*H*-pyrrole-2-carboxylate 4e. Pale yellow solid, mp 166–168 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3262, 1730, 1692, 1636, 1504, 1261 and 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (bs, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 2.4 Hz, 1H), 7.20–7.15 (dd, J = 8.4, 8.0 Hz, 4H), 3.73 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.57, 161.21, 143.10, 136.23, 132.21, 132.04, 131.21, 130.57, 129.64, 128.94, 127.49, 125.19, 121.59, 120.54, 51.84, 21.66; HRMS (ESI): calc. for $[(C_{20}H_{16}BrNO_3)H]$ $[M + H]^+$ 398.0392, found 400.0354.

Methyl 4-benzoyl-3-(4-bromophenyl)-1*H*-pyrrole-2-carboxylate 4f. Off white solid, mp 162–164 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3275, 1723, 1695, 1632, 1505, 1262 and 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (bs, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.40–7.34 (m, 5H), 7.19 (d, J = 8.0 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.88, 161.20, 138.92, 132.28, 132.14, 132.03, 131.25, 130.57, 129.42, 128.25, 127.87, 124.99, 121.63, 120.69, 51.87; HRMS (ESI): calc. for $[(C_{19}H_{14}BrNO_3)H]$ $[M + H]^+$ 384.0235, found 386.0194.

Methyl 4-benzoyl-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate 4g. Off white solid, mp 148–150 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3276, 1722, 1689, 1631, 1505, 1263 and 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (bs, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.48 (distorted t, J = 7.2, 6.8 Hz, 1H), 7.36 (distorted t, J = 7.6, 7.2 Hz, 3H), 7.25 (s, 4H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.89, 161.19, 138.91, 133.33, 132.27, 131.71, 131.63, 131.24, 129.42, 128.23, 127.78, 127.64, 125.08, 120.72, 51.86; HRMS (ESI): calc. for $[(C_{19}H_{14}ClNO_3)H]$ $[M + H]^+$ 340.0740, found 340.0714.

Methyl 4-(3-chlorobenzoyl)-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate 4h. White solid, mp 110–112 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3282, 1724, 1691, 1637, 1507, 1258 and 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (bs, 1H), 7.62 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.30–7.23 (m, 5H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.52, 161.11, 140.42, 134.30, 133.48, 132.10, 131.68, 131.42, 131.09, 129.61, 129.49, 127.83, 127.69, 127.34, 124.72, 120.88, 51.92; HRMS (ESI): calc. for $[(C_{19}H_{13}Cl_2NO_3)H]$ $[M + H]^+$ 374.0350, found 374.0321.

Methyl 4-benzoyl-3-(4-fluorophenyl)-1*H*-pyrrole-2-carboxylate 4i. White solid, mp 128–130 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3275, 1718, 1686, 1631, 1510, 1264 and 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (bs, 1H), 7.69 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 6.8 Hz, 1H), 7.37–7.25 (m, 5H), 6.94 (t, J = 8.0 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 192.40, 162.10 (d, J_{C-F} = 243.7 Hz), 161.06, 139.18, 132.11 (d, J_{C-F} = 8.1 Hz), 131.86, 131.41, 129.92, 128.99, 128.86, 127.90, 124.13, 120.83, 113.53 (d, J_{C-F} = 21.5 Hz), 50.47; HRMS (ESI): calc. for $[(C_{19}H_{14}FNO_3)H]$ $[M + H]^+$ 324.1036, found 324.1005.

Methyl 4-(3-chlorobenzoyl)-3-(4-fluorophenyl)-1*H*-pyrrole-2-carboxylate 4j. Off white solid mp 104–106 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3296, 1715, 1686, 1637, 1513, 1260 and 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (bs, 1H), 7.61 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 3.2 Hz, 2H), 7.28 (s, 3H), 6.95 (t, J = 8.8, 8.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.74, 162.26 (d, J_{C-F} = 244.8 Hz), 161.18, 140.42, 134.24, 132.08, 132.05 (d, J_{C-F} = 7.9 Hz), 131.31, 129.55, 129.51, 128.79, 127.79, 127.34, 124.83, 120.79, 114.46 (d, J_{C-F} = 21.3 Hz), 51.88; HRMS (ESI): calc. for $[(C_{19}H_{13}ClFNO_3)H]$ $[M + H]^+$ 358.0656, found 358.0623.

Methyl 3-(4-bromophenyl)-4-(3-chlorobenzoyl)-1*H*-pyrrole-2-carboxylate 4k. White solid, mp 144–146 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3298, 1730, 1698, 1630, 1505, 1255 and 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (bs, 1H), 7.62 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.44–7.38 (m, 4H), 7.28 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.48, 161.11, 140.43, 134.31, 132.10, 131.98, 131.93, 131.09, 130.63, 129.63, 129.49, 127.89, 127.34, 124.65, 121.76, 120.85, 51.94; HRMS (ESI): calc. for $[(C_{19}H_{13}BrClNO_3)H]$ $[M + H]^+$ 417.9845, found 417.9822.

Methyl 4-acetyl-3-phenyl-1*H*-pyrrole-2-carboxylate 4l. White solid, mp 170–172 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3250, 1728, 1697, 1638, 1512, 1270 and 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (bs, 1H), 7.54 (d, J = 3.5 Hz, 1H), 7.37–7.34 (m, 3H), 7.30–7.28 (m, 2H), 3.63 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.43, 161.27, 134.02, 131.33, 129.83, 127.56, 127.47, 126.80, 126.37, 120.79, 51.49, 29.06; HRMS (ESI): calc. for $[(C_{14}H_{13}NO_3)]$ $[M]^-$ 243.0895 found 243.0817.

Methyl 4-acetyl-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate 4m. White solid, mp 184–186 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3253, 1726, 1694, 1642, 1516, 1268 and 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (bs, 1H), 7.52 (d, J = 3.4 Hz, 1H), 7.24–7.15 (m, 4H), 3.64 (s, 3H), 2.37 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.61, 161.24, 137.11, 131.55, 130.83, 129.70, 128.33, 126.81, 126.41, 120.69, 51.44, 29.10, 21.24; HRMS (ESI): calc. for $[(C_{15}H_{15}NO_3)–H]$ $[M - H]^-$ 256.0973, found 256.0977.

Methyl 4-acetyl-3-(*m*-tolyl)-1*H*-pyrrole-2-carboxylate 4n. White solid, mp 170–172 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3259, 1732, 1696, 1635, 1508, 1260 and 772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (bs, 1H), 7.54 (d, J = 3.5 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.10–7.08 (m, 2H), 3.65 (s, 3H), 2.36 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.51, 161.13, 137.05, 133.79, 131.49, 130.48, 128.28, 127.47, 127.05, 126.90, 126.01, 120.69, 51.46, 29.10, 21.32; HRMS (ESI): calc. for $[(C_{15}H_{15}NO_3)–H]$ $[M - H]^-$ 256.0973, found 256.0974.

Methyl 4-acetyl-3-(*o*-tolyl)-1*H*-pyrrole-2-carboxylate 4o. White solid, mp 162–164 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3248, 1731, 1687, 1629, 1502, 1255 and 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (bs, 1H), 7.61 (d, J = 3.5 Hz, 1H), 7.27–7.16 (m, 3H), 7.11 (d, J = 7.9 Hz, 1H), 3.61 (s, 3H), 2.07 (s, 3H), 1.92 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 194.36, 161.19, 136.39, 134.05, 130.53, 129.53, 129.49, 127.72, 126.72, 126.49, 125.26, 120.70, 51.52, 28.54, 19.94; HRMS (ESI): calc. for $[(C_{15}H_{15}NO_3)–H]$ $[M - H]^-$ 256.0973, found 256.0972.

Methyl 4-acetyl-3-(4-bromophenyl)-1*H*-pyrrole-2-carboxylate 4p. Off white solid, mp 150–152 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3275, 1734, 1690, 1640, 1513, 1250 and 765; ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (bs, 1H), 7.51 (d, J = 3.3 Hz, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 3.65 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.76, 161.09, 132.88, 131.61, 130.63, 129.90, 126.78, 126.19, 121.65, 120.96, 51.59, 28.92; HRMS (ESI): calc. for $[(C_{14}H_{12}BrNO_3)]$ $[M]^-$ 321.0001 found 320.9922.

Methyl 4-acetyl-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate 4q. Off white solid, mp 134–136 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3278, 1728, 1689, 1637, 1510, 1253 and 773; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (bs, 1H), 7.44 (d, J = 3.3 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 3.57 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.71, 161.06, 133.45, 132.35, 131.28, 129.90, 127.72, 126.62, 126.35, 121.01, 51.59, 28.93; HRMS (ESI): calc. for $[(C_{14}H_{12}ClNO_3)H]$ $[M + H]^-$ 278.0585, found 278.0584.

Methyl 4-acetyl-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate 4r. White solid, mp 132–134 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3251, 1720, 1694, 1625, 1501, 1254 and 763; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (bs, 1H), 7.52 (d, J = 3.5 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.65 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.53, 161.24, 159.00, 131.19, 131.05, 126.85, 126.34, 125.89, 120.75, 113.05, 55.09, 51.47, 29.09; HRMS (ESI): calc. for $[(C_{15}H_{14}NO_4)–H]$ $[M - H]^-$ 272.0922 found 272.0923.

Methyl 4-acetyl-3-(4-nitrophenyl)-1*H*-pyrrole-2-carboxylate 4s. Pale yellow solid, mp 144–146 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3415, 1724, 1698, 1632, 1605, 1513, 1443, 1345 and 858; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (bs, 1H), 8.20 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 3.3 Hz, 1H), 7.45 (d, J = 8.6 Hz, 2H), 3.65 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.72, 160.67, 147.08, 141.28, 130.99, 128.68, 126.98, 125.72, 122.54, 121.36, 51.77, 28.47; HRMS (ESI): calc. for $[(C_{14}H_{12}N_2O_5)H]$ $[M + H]^-$ 289.0825, found 289.0824.

Methyl 4-acetyl-3-methyl-1*H*-pyrrole-2-carboxylate 4t. White solid, mp 130–132 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3254, 1732, 1690, 1633, 1505, 1261 and 763; ^1H NMR (400 MHz, $CDCl_3$) δ 9.47(bs, 1H), 7.43 (d, J = 3.4 Hz, 1H), 3.85 (s, 3H), 2.59 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.04, 162.02, 129.17, 127.20, 125.54, 121.16, 51.46, 28.25, 11.58; HRMS (ESI): calc. for $[(C_9H_{11}NO_3)H]$ $[M + H]^-$ 182.0818, found 182.0817.

Ethyl 4-benzoyl-3-(4-fluorophenyl)-1*H*-pyrrole-2-carboxylate 4u. White solid, mp 132–134 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3278, 1716, 1685, 1629, 1512, 1266 and 736; ^1H NMR (500 MHz, $CDCl_3$) δ 9.49 (bs, 1H), 7.70 (distorted dd, J = 8.0, 1.5 Hz, 2H), 7.47 (tt, J = 7.5, 1.5 Hz, 1H), 7.38 (d, J = 3.0 Hz, 1H), 7.34 (t, J = 8.0, 7.5 Hz, 2H), 7.31–7.27 (m, 2H), 6.95 (tt, J = 9.0, 3.0, 2.5, 2.0 Hz, 2H), 4.21 (q, J = 7.0 Hz, 2H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.77, 162.30 (d, $J_{C–F}$ = 248.0 Hz), 161.28, 143.04, 136.30, 132.07 (d, $J_{C–F}$ = 8.0 Hz), 131.48, 129.69, 129.07, 128.92, 127.40, 125.38, 120.55, 114.42 (d, $J_{C–F}$ = 21.0 Hz), 61.24, 13.85; HRMS (ESI): calc. for $[(C_{20}H_{16}FNO_3)H]$ $[M + H]^+$ 338.1192, found 338.1197.

***tert*-Butyl 3-(4-bromophenyl)-4-(3-chlorobenzoyl)-1*H*-pyrrole-2-carboxylate 4v.** Light yellow solid, mp 158–160 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3296, 1726, 1696, 1632, 1501, 1252 and 739; ^1H NMR (400 MHz, $CDCl_3$) δ 9.68 (bs, 1H), 7.61 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.43–7.37 (m, 4H), 7.27 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.47, 161.10, 140.42, 134.30, 132.09, 131.97, 131.92, 131.09, 130.62, 129.62, 129.48, 127.88, 127.33, 124.64, 121.75, 120.84, 81.82, 28.83; HRMS (ESI): calc. for $[(C_{22}H_{19}BrClNO_3)H]$ $[M + H]^+$ 460.0315, found 460.0317.

***tert*-Butyl 4-acetyl-3-methyl-1H-pyrrole-2-carboxylate 4w.** White solid, mp 138–140 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3251, 1730, 1694, 1629, 1501, 1265 and 760; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49(bs, 1H), 7.45 (d, J = 3.2 Hz, 1H), 2.61 (s, 3H), 2.41 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.06, 162.04, 129.18, 127.23, 125.55, 121.18, 81.72, 29.02, 28.26, 11.60; HRMS (ESI): calc. for $[(C_{12}H_{17}NO_3)H]$ $[M + H]^+$ 224.1286, found 224.1289.

Experimental procedure for bromination of 4g

A round bottom flask was charged with methyl 4-benzoyl-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate **4g** (1.0 mmol), *N*-bromosuccinimide (1.2 mmol) and 5 mL DMF. The reaction mixture was stirred at 0 °C-room temperature for 2 h under nitrogen atmosphere. The reaction mixture was quenched with water (10 mL), extracted using ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine solution and dried over Na_2SO_4 to afford a crude product. The crude product was purified by column chromatography on silica gel (100–200 mesh size) with *n*-hexane : ethyl acetate (80 : 20) as eluent to afford the desired product **5**.

Methyl 4-benzoyl-5-bromo-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate 5. Yield 88%, white solid, mp 172–174 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3287, 1711, 1515, 1439, 1282, and 783; ^1H NMR (300 MHz, $CDCl_3$) δ 10.16 (bs, 1H), 7.68–7.65 (m, 2H), 7.47–7.41 (m, 1H), 7.31–7.26 (m, 2H), 7.19–7.12 (m, 4H) 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.47, 160.72, 137.57, 133.76, 133.14, 131.78, 131.70, 130.88, 129.93, 128.32, 127.83, 125.28, 120.41, 107.81, 52.13; calc. for $[(C_{19}H_{13}BrClNO_3)H]$ $[M + H]^+$ 417.9845, found 417.9875.

Experimental procedure for hydrolysis of 4e

A round bottom flask was charged with methyl 3-(4-bromophenyl)-4-(4-methylbenzoyl)-1*H*-pyrrole-2-carboxylate **4e** (1.0 mmol), $LiOH·H_2O$ (10.0 mmol) and 5 mL THF : H_2O [1 : 1]. The reaction mixture was heated at 80 °C for 8 h. The reaction mixture was cooled to room temperature, diluted with water (5 mL) and extracted using ethyl acetate (3 × 10 mL). The dried organic layer was concentrated under reduced pressure to afford the desired product **6**.

3-(4-Bromophenyl)-4-(4-methylbenzoyl)-1*H*-pyrrole-2-carboxylic acid 6. Yield 85%, brown solid, mp 214–216 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3214, 1690, 1629, 1603, 1500, 1402, and 754; ^1H NMR (300 MHz, DMSO-d_6) δ 12.04 (bs, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.25–7.17 (m, 6H), 7.03 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.00, 165.29, 141.71, 137.23, 134.92, 133.06, 129.36, 129.07, 128.78, 127.58, 126.83, 125.78, 122.55, 118.86, 21.15; HRMS (ESI): calc. for $[(C_{19}H_{14}BrNO_3)H]$ $[M + H]^+$ 384.0235, found 386.0249.

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