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$In(OTf)_3$-catalysed one-pot versatile pyrrole synthesis through domino annulation of α-oxoketene-*N*,*S*-acetals with nitroolefins†

Abhijeet Srivastava,[a] Gaurav Shukla,[a] Anugula Nagaraju,[a] Girijesh Kumar Verma,[a] Keshav Raghuvanshi,[b] Raymond C. F. Jones[c] and Maya Shankar Singh*[a]

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$In(OTf)_3$-catalyzed robust and sustainable one-pot access to previously unknown and synthetically demanding polysubstituted pyrroles *via* [3 + 2] annulation of α-oxoketene-*N*,*S*-acetals with β-nitrostyrenes has been achieved under solvent-free conditions. The merit of this domino Michael addition/cyclization sequence is highlighted by its operational simplicity, short reaction time (5–10 min), good to excellent yields, tolerance of a large variety of functional groups, and efficiency of producing two new (C–C and C–N) bonds and one highly functionalized pyrrole ring in a single operation, which make it an ideal alternative to existing methods.

Introduction

Pyrroles, one of the prominent and ubiquitous privileged N-heterocyclic pharmacophores, exhibit diverse biological and therapeutic activities,[1] and constitute the core structural motif of numerous natural products,[2] medicinal agents,[3] catalysts and conducting polymers.[4] Among the various pharmacological profiles of pyrrole derivatives, their anti-bacterial,[5a] anti-inflammatory,[5b,c] anti-oxidant,[5d,e] anti-tumor,[5f–h] anti-fungal,[5i–k] and immune suppressant activities[5l] seem to be well documented.

Chart 1 constitutes notable privileged medicinal scaffolds having multiple substituted pyrroles.[6] Furthermore, pyrrole based derivatives have broad applications in molecular optics,[7a] electronics,[7b] and as gas sensors for organic compounds.[7c] Moreover, they are also widely employed as versatile building blocks in organic synthesis.[8]

Traditional pyrrole syntheses[9–11] generally require the initial preparation of an intermediate that subsequently undergoes a cyclization reaction. In general, pyrroles are prepared by cycloaddition ([4 + 1] and [3 + 2]) reactions[12] or intramolecular cyclization reactions.[13] Albeit the reported approaches are useful tools, most of them suffer from significant limitations such as multiple steps, functional group compatibility, pre-functionalized substrates, expensive catalysts/reagents, long reaction times and harsh reaction conditions. Recently, a number of strategies[14–18] are employed for the synthesis of pyrroles. Rueping *et al.*[19] reported the synthesis of pyrroles through domino reaction of enaminones with β-bromonitrostyrenes (Scheme 1). The above published protocols not only showcase the power of advances in organic methodology but also provide proof of the vibrant activity in this field. In spite of these outstanding efforts, it is still challenging to prepare polysubstituted pyrroles possessing diverse substituents directly from readily available precursors in a single synthetic operation in an environmentally benign fashion.

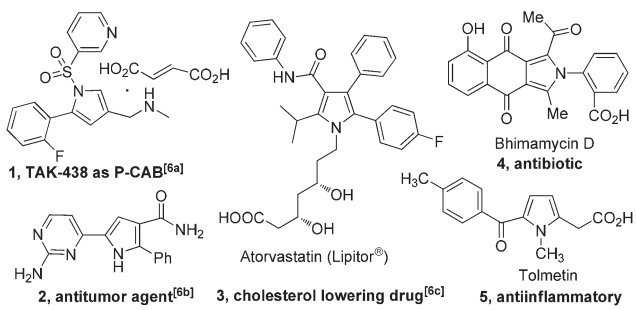

Chart 1 Selected examples of pyrrole-based pharmaceutical compounds.

A possible retrosynthetic analysis for the construction of pyrroles is given in Scheme 2, which comprises the use of simple and easily available synthons such as binucleophilic

[a]*Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi-05, UP, India. E-mail: mssinghbhu@yahoo.co.in; Fax: +91-542-2368127; Tel: +91-542-6702502*
[b]*Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstr. 2, 37077 Göttingen, Germany. E-mail: raghuvanshikeshav@gmail.com*
[c]*Department of Chemistry, Loughborough University, Loughborough, Leics, LE11 3TU, UK. E-mail: r.c.f.jones@lboro.ac.uk*

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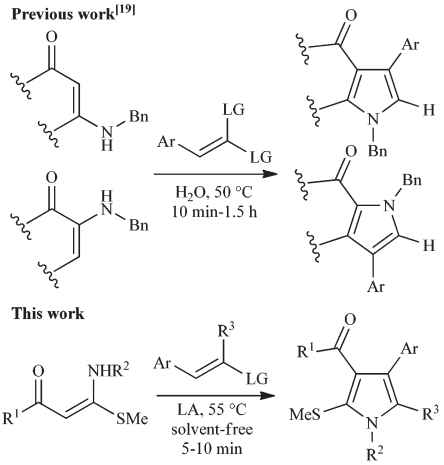
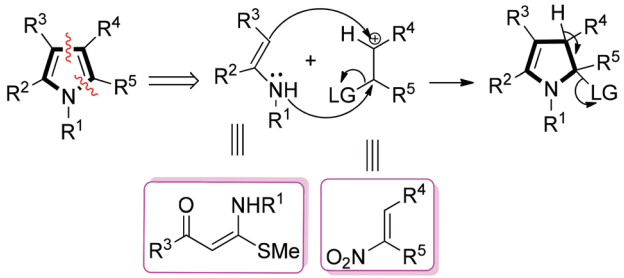
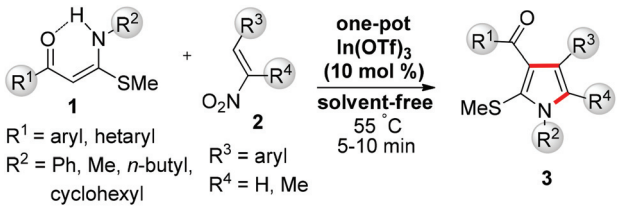


Scheme 1 Synthetic strategies for the construction of pyrroles.



Scheme 2 A retrosynthetic disconnection approach for the synthesis of pyrroles.



Scheme 3 One-pot synthesis of polysubstituted pyrroles.

α-oxoketene-*N*,*S*-acetals and bielectrophilic β-nitrostyrenes. In continuation of our ongoing research for the development of new methodologies for various heterocyclic systems by exploiting the reactions of ketene-*S*,*S*/*N*,*S*-acetals,[20,21] we envisioned to explore α-oxoketene-*N*,*S*-acetals for the construction of highly substituted pyrroles for the first time.

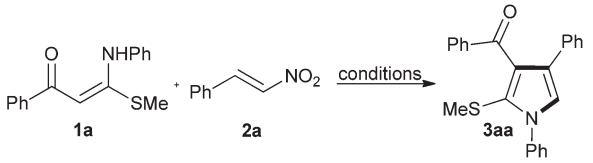
Herein, we report a rapid and efficient one-pot synthesis of highly substituted pyrroles *via* coupling of α-oxoketene-*N*,*S*-acetals with (*E*)-β-nitrostyrenes catalyzed by a Lewis acid under solvent-free conditions at moderate temperature (Scheme 3).

Results and discussion

The feasibility of the coupling reaction was examined using α-oxoketene-*N*,*S*-acetal **1a** and (*E*)-β-nitrostyrene **2a** as the test substrates under different conditions (Table 1). Initially, the equimolar amount of **1a** and **2a** was treated in EtOH at room temperature without any catalyst. The work up of the reaction afforded 3-benzoyl-2-(methylthio)-1,4-diphenylpyrrole **3aa** in 55% yield after 72 h (Table 1, entry 1). In an attempt to increase the yield of **3aa**, the above model reaction was further investigated at 55 °C and in refluxing EtOH. The work up of the reaction provided the desired pyrrole **3aa** in 64% and 68% yields, respectively, reducing the time significantly (Table 1, entries 2 and 3). A brief screen of other protic solvents like MeOH and H_2O afforded **3aa** in 55% and 50% yields, respectively, taking more than double the time (Table 1, entries 4 and 5). Because of the increasing public concern for the harmful effects of organic solvents over environment and human body, we carried out the above model reaction under solvent-free conditions at different temperatures. Notably, the reaction proceeded smoothly at 55 °C furnishing the desired pyrrole **3aa** in 55% yield (Table 1, entry 6). Higher temperatures reduced the yield of **3aa** due to decomposition of the substrates (Table 1, entries 7 and 8).

With a view to optimize the reaction conditions for maximum yield and lesser reaction time, the model reaction was carried out in the presence of Lewis acid (LA) catalysts such as $FeCl_3$, $AlCl_3$, $InBr_3$, $CuBr_2$, $SbCl_3$, $SnCl_4$ and $In(OTf)_3$ under solvent-free conditions at 55 °C (Table 1, entries 9–15). A radical change in reaction time was observed while using various Lewis acids, and to our great pleasure 10 mol% of $In(OTf)_3$ catalyzed the reaction efficiently and afforded the desired pyrrole **3aa** in 92% yield within 5 min (Table 1, entry 15).

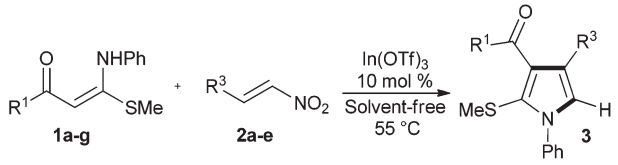
Table 1 Optimization studies



Entry	Solvent	Catalyst (mol%)	*T* (°C)	Time	Yield[a] (%)
1	EtOH	None	rt	72 h	55
2	EtOH	None	55	11 h	64
3	EtOH	None	Reflux	9 h	68
4	MeOH	None	Reflux	20 h	55
5	H_2O	None	Reflux	22 h	50
6	None	None	55	8 h	55
7	None	None	80	6 h	40
8	None	None	100	4 h	15
9	None	$FeCl_3$ (10)	55	30 min	80
10	None	$AlCl_3$ (10)	55	20 min	55
11	None	$InBr_3$ (10)	55	15 min	82
12	None	$CuBr_2$(10)	55	40 min	63
13	None	$SbCl_3$ (10)	55	20 min	85
14	None	$SnCl_4$ (10)	55	15 min	82
15	None	$In(OTf)_3$ (10)	55	5 min	92
16	None	$In(OTf)_3$ (5)	55	10 min	76
17	None	$In(OTf)_3$ (15)	55	5 min	92
18	EtOH	$In(OTf)_3$ (10)	Reflux	5 min	74

[a] Isolated pure yields.

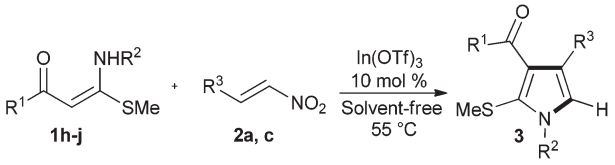
Table 2 Scope of substrates for tetrasubstituted pyrroles



Entry	R^1	R^3	Product	Time (min)	Yield[a] (%)
1	C_6H_5 (**1a**)	C_6H_5 (**2a**)	**3aa**	5	92
2	C_6H_5 (**1a**)	4-MeC_6H_4 (**2b**)	**3ab**	5	94
3	C_6H_5 (**1a**)	4-$OMeC_6H_4$ (**2c**)	**3ac**	5	95
4	C_6H_5 (**1a**)	4-$NO_2C_6H_4$ (**2d**)	**3ad**	8	72
5	4-MeC_6H_4 (**1b**)	4-$NO_2C_6H_4$ (**2d**)	**3bd**	7	73
6	4-$OMeC_6H_4$ (**1c**)	C_6H_5 (**2a**)	**3ca**	5	89
7	4-$OMeC_6H_4$ (**1c**)	4-MeC_6H_4 (**2b**)	**3cb**	5	90
8	4-$OMeC_6H_4$ (**1c**)	4-$NO_2C_6H_4$ (**2d**)	**3cd**	7	70
9	4-$CF_3C_6H_4$ (**1d**)	4-MeC_6H_4 (**2b**)	**3db**	10	62
10	4-PhC_6H_4 (**1e**)	C_6H_5 (**2a**)	**3ea**	6	78
11	4-PhC_6H_4 (**1e**)	4-MeC_6H_4 (**2b**)	**3eb**	6	82
12	4-PhC_6H_4 (**1e**)	4-FC_6H_4 (**2e**)	**3ee**	8	70
13	2-Furyl (**1f**)	C_6H_5 (**2a**)	**3fa**	8	74
14	2-Furyl (**1f**)	4-MeC_6H_4 (**2b**)	**3fb**	6	80
15	2-Furyl (**1f**)	4-$OMeC_6H_4$ (**2c**)	**3fc**	5	87
16	2-Furyl (**1f**)	4-$NO_2C_6H_4$ (**2d**)	**3fd**	9	68
17	2-Thienyl (**1g**)	C_6H_5 (**2a**)	**3ga**	6	72
18	2-Thienyl (**1g**)	4-MeC_6H_4 (**2b**)	**3gb**	6	84

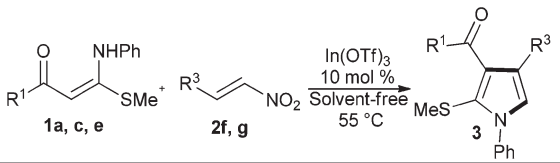
[a] Isolated pure yields.

Table 3 Scope of *N*-substituted α-oxoketene-*N*,*S*-acetals



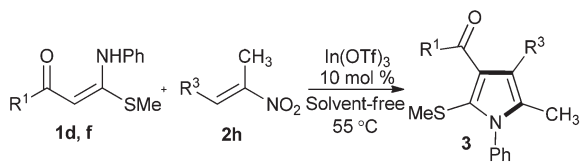
Entry	R^1/R^2	R^3	Product	Time (min)	Yield[a] (%)
1	4-BrC_6H_4/Me (**1h**)	C_6H_5 (**2a**)	**3ha**	5	82
2	3-OHC_6H_4/*n*-butyl (**1i**)	4-$OMeC_6H_4$ (**2c**)	**3ic**	8	77
3	C_6H_5/cyclohexyl (**1j**)	4-$OMeC_6H_4$ (**2c**)	**3jc**	5	84

[a] Isolated pure yields.



Entry	R^1	R^3	Product	Time (min)	Yield[a] (%)
1	4-$OMeC_6H_4$ (**1c**)	2-CH≡CC_6H_4 (**2f**)	**3cf**	5	81
2	4-PhC_6H_4 (**1e**)	2-CH≡CC_6H_4 (**2f**)	**3ef**	6	72
3	C_6H_5(**1a**)	4-$OMeC_6H_4$CH=CH (**2g**)	**3ag**	8	67

Scheme 4 Substrate functionalization on nitrostyrene. [a]Isolated pure yields.



Entry	R^1	R^3	Product	Time (min)	Yield[a](%)
1	4-$CF_3C_6H_4$ (**1d**)	4-$OMeC_6H_4$ (**2h**)	**3dh**	8	66
2	2-Furyl (**1f**)	4-$OMeC_6H_4$ (**2h**)	**3fh**	5	79

Scheme 5 Synthesis of pentasubstituted pyrroles. [a]Isolated pure yields.

Next, reduction in the amount of LA catalyst resulted in lower yield of the desired product, and increasing the catalyst loading did not show any improvement (Table 1, entries 16 and 17). Finally, when the model reaction was carried out in refluxing ethanol in the presence of 10 mol% of $In(OTf)_3$, **3aa** was obtained in 74% yield in 5 h (Table 1, entry 18). Consequently, the optimum reaction condition was achieved by employing equimolar amounts of **1a** and **2a** in the presence of 10 mol% of $In(OTf)_3$ at 55 °C under solvent-free conditions.

Having found an optimum reaction condition, we explored the scope of the substrates and functional group tolerance by synthesizing twenty-six new tetra- and penta-substituted pyrroles with high functionalities from different α-oxoketene-*N*,*S*-acetals (**1a–j**) and (*E*)-β-nitrostyrenes (**2a–h**) as shown in Tables 2 and 3 and Schemes 4 and 5. In all products 2-thiomethyl substituent that stem from α-oxoketene-*N*,*S*-acetals was kept constant. The electron-donating groups at R^3 of nitrostyrenes (**2b**, **2c**) gave a slightly higher yield of the product (Table 2, entries 2, 3, 7, 9, 11, 14, 15, and 18) as compared to electron-withdrawing groups at R^3 of nitrostyrenes (**2d**, **2e**) (Table 2, entries 4, 5, 8, 12, and 16). Similarly, the electron-donating group at R^1 of α-oxoketene-*N*,*S*-acetal (**1c**) provides significantly higher yield as compared with the electron-withdrawing group (**1d**) (Table 2, entry 6 *vs*. entry 9).

To illustrate the broad synthetic utility and generality of our developed methodology, we further treated α-oxoketene-*N*,*S*-acetal bearing extended aromatic ring biphenyl (**1e**), and heteroaryl groups like 2-furyl (**1f**) and 2-thienyl (**1g**) with different (*E*)-β-nitrostyrenes separately under the above optimized conditions to obtain the corresponding tetrasubstituted pyrroles in 68–87% yields (Table 2, entries 10–18).

The scope of α-oxoketene-*N*,*S*-acetal is not limited to R^2 as phenyl only but various substituents have also been screened as shown in Table 3. Methyl, *n*-butyl and cyclohexyl substituents also provided good yields under similar reaction conditions (Table 3).

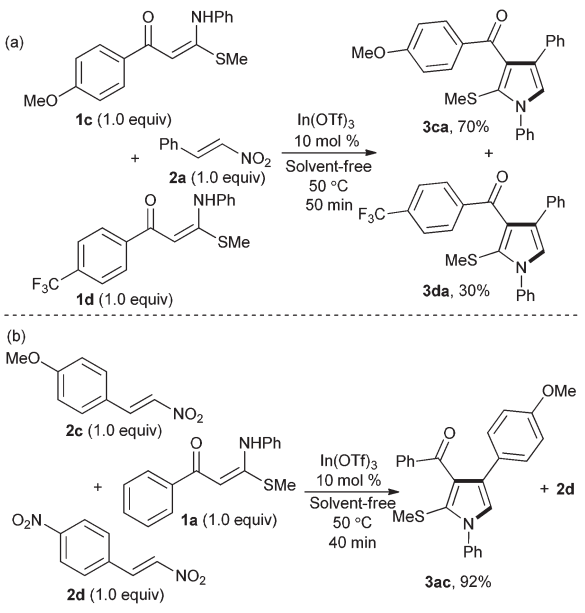
In order to further derivatise the pyrrole moiety, we prepared functionally rich nitrostyrenes **2f** and **2g** from 2-ethynylbenzaldehyde and *p*-methoxycinnamaldehyde, respectively. Treatment of α-oxoketene-*N*,*S*-acetals **1c** and **1e** with the nitrostyrene **2f** provided pyrroles **3cf** and **3ef** in 81% and 72% yields, respectively. Treatment of α-oxoketene-*N*,*S*-acetal **1a** with (*E*)-β-nitrostyrene **2g** gave pyrrole **3ag** in 67% yield

(Scheme 4). These three examples also exhibited functional group tolerance towards the Lewis acid catalyst.

Next, we turned our attention to expand the diversity of this protocol for the synthesis of pentasubstituted pyrroles. Thus, upon treatment of (*E*)-β-methyl-β-nitrostyrene **2h** with α-oxoketene-*N*,*S*-acetals **1d** and **1f** under previously described one-pot optimised reaction conditions furnished pentasubstituted pyrroles **3dh** and **3fh** in 66% and 79% yields, respectively (Scheme 5).

Considering the high electronic efficacy exerted by the various electron-rich and electron-deficient substituents, we performed intermolecular competition experiments with two different α-oxoketene-*N*,*S*-acetals, first containing an electron-donating group **1c** and second an electron-withdrawing group **1d** with simple β-nitrostyrene **2a** in an equimolar ratio. It has been observed that the product pyrrole **3ca** derived from α-oxoketene-*N*,*S*-acetal **1c** was major (70%) and **3da** formed from **1d** was minor (30%) revealing an electron-rich substrate to be more readily functionalized (Scheme 6a). In the next attempt, we performed the reaction of α-oxoketene-*N*,*S*-acetal **1a** with two different (*E*)-β-nitrostyrenes **2c** and **2d** in an equimolar ratio (Scheme 6b). Exclusively, we found only one pyrrole **3ac** in 92% yield derived from nitrostyrene with an electron-donating group **2c**. Unused starting material **2d** was recovered in 90% yield highlighting the electron-rich (*E*)-β-nitrostyrene to be converted more preferentially.

The structures of all the newly synthesized pyrroles **3** were deduced from their satisfactory spectral (IR, ^{1}H &^{13}C NMR, and HRMS) studies and unequivocally established by the X-ray single crystal diffraction analysis of two representative compounds **3ga** and **3eb** (Fig. 1).[22] The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values.



Scheme 6 Intermolecular competition reactions.

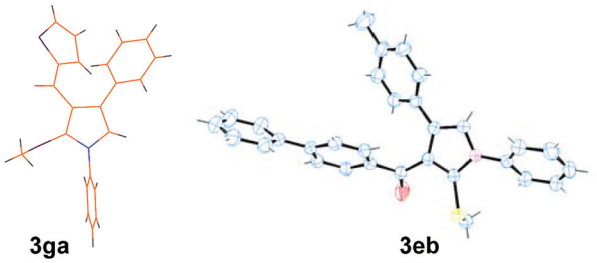
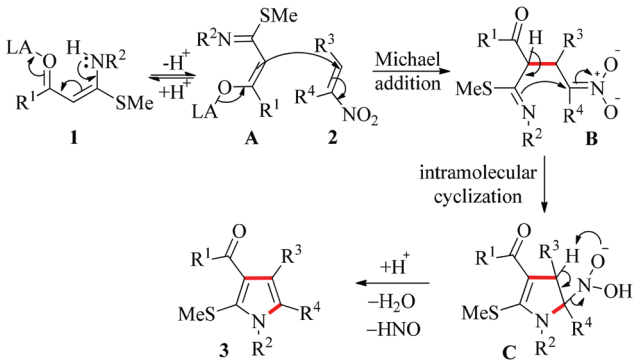


Fig. 1 ORTEP diagrams of **3ga** and **3eb**.



Scheme 7 Plausible mechanism for formation of pyrroles **3**.

On the basis of the above experimental results together with the related reports, a plausible reaction scenario for domino [3 + 2] heteroannulation is outlined in Scheme 7. We speculate that the reaction occurs as a tandem Michael addition/intramolecular ring closure/elimination process. The first step in the mechanism is believed to be the Michael addition of α-oxoketene-*N*,*S*-acetal **1** through its Lewis acid activated enolate form **A** to β-nitrostyrene **2** to generate the open-chain Michael adduct intermediate **B**. Next, the Michael adduct intermediate **B** undergoes successive intramolecular N-cyclization followed by elimination of H_2O and nitroxyl (HNO) *via* intermediate **C** leading to the desired pyrrole **3**.

Conclusions

In summary, we have designed and developed an operationally simple, highly efficient one-pot direct method for the synthesis of tetra- and pentasubstituted pyrroles under solvent-free mild reaction conditions. Further, we have shown α-oxoketene-*N*,*S*-acetals to be suitable partners in (3 + 2) annulation with β-nitrostyrenes. $In(OTf)_3$ worked very efficiently with various functional group-substituted α-oxoketene-*N*,*S*-acetals and β-nitrostyrenes yielding highly functionalized pyrroles in good to excellent yields. The scope and diversity of the tolerated substrates in this work is rather broad in comparison with the reported ones. These structurally unique molecules synthesized in an environmentally benign manner may reveal potential application in future drug discovery and

development. A possible reaction mechanism was proposed to account for the coupling reaction.

Experimental section

General procedure for synthesis of 3

A 25 mL round bottom flask equipped with a magnetic stirrer was charged with α-oxoketene-*N*,*S*-acetal **1** (1.0 mmol), β-nitrostyrene **2** (1.0 mmol) and 10 mol% of $In(OTf)_3$. The reaction mixture was heated on an oil bath at 55 °C for the stipulated period of time (monitored through TLC). After completion of the reaction, the reaction mixture was extracted with EtOAc, washed with water (2 × 20 mL) followed by brine (1 × 20 mL), and dried over anhydrous sodium sulphate. The solvent was evaporated under vacuum and the crude residue thus obtained was purified by silica gel column chromatography to give pure pyrrole **3**.

3-Benzoyl-2-(methylthio)-1,4-diphenylpyrrole (3aa). Yellow sticky solid. R_f = 0.55 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.2 Hz, 2H), 7.51–7.38 (m, 5H), 7.31–7.04 (m, 9H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1, 138.8, 138.5, 133.9, 132.6, 129.9, 129.0, 128.2, 128.1, 128.0, 127.6, 126.5, 126.2, 122.8, 20.8. IR (KBr) (ν_{max}/cm^{-1}): 2912, 1670, 1222. HRMS (EI) calcd for $C_{24}H_{19}NOS$, m/z: 369.1187, found 369.1193 [M$^+$].

3-Benzoyl-2-(methylthio)-1-phenyl-4-(*p*-tolyl)pyrrole (3ab). Yellow sticky solid. R_f = 0.55 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.2 Hz, 2H), 7.51–7.24 (m, 8H), 7.15–7.10 (m, 2H), 6.96 (d, J = 7.8 Hz, 2H), 2.23 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.3, 138.9, 138.5, 135.8, 132.5, 130.9, 129.9, 128.9, 128.7, 128.3, 128.08, 128.00, 127.4, 127.0, 126.5, 126.19, 126.11, 125.2, 122.6, 20.9, 20.7. IR (KBr) (ν_{max}/cm^{-1}): 2920, 1656, 1595, 1496, 1225. HRMS (ESI) calcd for $C_{25}H_{21}NOS$, m/z: 383.1344, found 384.1399 [(M + H)$^+$].

3-Benzoyl-4-(4-methoxyphenyl)-2-(methylthio)-1-phenylpyrrole (3ac). Yellow sticky solid. R_f = 0.48 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.2 Hz, 2H), 7.55–7.45 (m, 6H), 7.35 (dd, J = 7.8, 7.2 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.11 (s, 1H), 6.75 (d, J = 8.7 Hz, 2H), 3.74 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.3, 158.1, 138.8, 138.5, 132.5, 129.9, 128.9, 128.7, 127.9, 126.5, 126.1, 125.9, 122.3, 113.7, 55.1, 20.7. IR (KBr) (ν_{max}/cm^{-1}): 2922, 1650, 1340, 1229. HRMS (ESI) calcd for $C_{25}H_{21}NO_2S$, m/z: 399.9293, found 438.1102 [(M + K)$^+$].

3-Benzoyl-2-(methylthio)-4-(4-nitrophenyl)-1-phenylpyrrole (3ad). Yellow (crayola) sticky solid. R_f = 0.50 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.5 Hz, 2H), 7.52–7.45 (m, 9H), 7.39–7.32 (m, 2H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 146.0, 140.8, 138.4, 138.3, 133.1, 129.9, 129.2, 128.7, 128.6, 128.3, 128.1, 127.8, 126.5, 124.2, 124.1, 123.8, 20.6. IR (KBr) (ν_{max}/cm^{-1}): 3064, 2922, 1651, 1595, 1513, 1341, 1228. MS calcd for $C_{24}H_{17}N_2O_3S$, m/z: 414.1038, found 415.2 [(M + H)$^+$].

2-(Methylthio)-4-(4-nitrophenyl)-1-phenyl-3-(*p*-tolyl)pyrrole (3bd). Yellow (crayola) sticky solid. R_f = 0.6 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H), 7.52 (m, 6H), 7.39 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.5 Hz, 2H), 2.36 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.4, 145.9, 144.2, 140.8, 138.4, 135.7, 130.1, 129.19, 129.11, 128.9, 128.5, 127.6, 127.5, 126.5, 123.9, 123.8, 21.7, 20.6. IR (KBr) (ν_{max}/cm^{-1}): 2931, 1653, 1559, 1495, 1340, 1247. MS calcd for $C_{25}H_{20}N_2O_3S$, m/z: 428.1195, found 429.2 [(M + H)$^+$].

3-(4-Methoxybenzoyl)-2-(methylthio)-1,4-diphenylpyrrole (3ca). White solid, mp = 135–137 °C. R_f = 0.48 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.8 Hz, 2H), 7.54–7.46 (m, 5H), 7.32–7.10 (m, 5H), 6.84 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 163.3, 138.9, 134.0, 132.4, 131.5, 129.1, 129.0, 128.4, 128.1, 127.4, 126.6, 126.3, 125.8, 125.6, 122.7, 113.3, 55.4, 20.8. IR (KBr) (ν_{max}/cm^{-1}): 3019, 2920, 1650, 1595, 1494, 1262. HRMS (EI) calcd for $C_{25}H_{21}NO_2S$, m/z: 399.1293, found 400.1367 [(M + H)$^+$].

3-(4-Methoxybenzoyl)-2-(methylthio)-1-phenyl-4-(*p*-tolyl) pyrrole (3cb). White solid, mp = 109–111 °C. R_f = 0.35 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.7 Hz, 2H), 7.51–7.24 (m, 6H), 7.18–7.14 (m, 2H), 7.00–6.95 (m, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 2.24 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.2, 163.3, 139.0, 135.8, 132.4, 131.5, 131.0, 129.1, 129.0, 128.0, 127.3, 126.6, 126.3, 125.8, 125.2, 122.6, 113.6, 113.4, 55.4, 21.1, 20.8. IR (KBr) (ν_{max}/cm^{-1}): 3010, 2933, 1650, 1575, 1482, 1254. HRMS (ESI) calcd for $C_{26}H_{23}NO_2S$, m/z: 413.1449, found 414.1522 [(M + H)$^+$].

3-(4-Methoxybenzoyl)-2-(methylthio)-4-(4-nitrophenyl)-1-phenylpyrrole (3cd). Yellow sticky solid. R_f = 0.50 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H), 7.51–7.39 (m, 8H), 6.84 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.3, 176.7, 173.7, 140.9, 132.3, 129.1, 128.5, 127.5, 126.5, 123.9, 113.6, 55.4, 20.6. IR (KBr) (ν_{max}/cm^{-1}): 3005, 2941, 1666, 1580, 1442, 1338, 1262, 1211. HRMS (EI) calcd for $C_{25}H_{20}N_2O_4S$, m/z: 444.1144, found 444.1137 [M$^+$].

2-(Methylthio)-1-phenyl-4-(*p*-tolyl)-3-(4-trifluoromethyl) pyrrole (3db). White solid, mp = 105–107 °C. R_f = 0.60 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.44–7.28 (m, 6H), 6.94 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.3, 168.8, 143.4, 137.7, 132.9, 132.48, 132.0, 131.6, 129.1, 127.3, 126.8, 125.3, 20.8, 14.7. IR (KBr) (ν_{max}/cm^{-1}): 3077, 2921, 1557, 1537, 1480, 1386, 1103. HRMS (EI) calcd for $C_{26}H_{20}F_3NOS$, m/z: 451.1218, found 451.1229 [M$^+$].

1,4-Diphenyl-2-(methylthio)-3-(4-phenylbenzoyl)pyrrole (3ea). White crystalline solid, mp = 103–105 °C, R_f = 0.60 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.4 Hz, 2H), 7.58–7.08 (m, 18H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.7, 145.1, 140.0, 138.8, 137.2, 133.9, 130.6, 129.0, 128.8, 128.3, 128.1, 127.9, 127.6, 127.2,

126.7, 126.5, 126.3, 126.2, 122.8, 20.8. IR (KBr) (ν_{max}/cm^{-1}): 3029, 2921, 1651, 1600, 1496, 1228. HRMS (ESI) calcd for $C_{30}H_{23}NOS$, *m*/*z*: 445.1500, found 446.1561 [(M + H)$^+$].

2-(Methylthio)-1-phenyl-3-(4-phenylbenzoyl)-4-(*p*-tolyl) pyrrole (3eb). White crystalline solid, mp = 131–133 °C. R_f = 0.55 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.1 Hz, 2H), 7.58–7.35 (m, 12H), 7.23–7.12 (m, 3H), 6.98 (d, *J* = 7.8 Hz, 2H), 2.22 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.8, 145.1, 140.0, 138.9, 137.2, 135.9, 130.9, 130.6, 129.0, 128.9, 128.7, 128.0, 127.9, 127.4, 127.2, 126.7, 126.5, 126.1, 122.6, 21.0, 20.8. IR (KBr) (ν_{max}/cm^{-1}): 3030, 2926, 1643, 1602, 1495, 1446, 1229. HRMS (ESI) calcd for $C_{31}H_{25}NOS$, *m*/*z*: 459.1657, found 460.1733 [(M + H)$^+$].

4-(4-Fluorophenyl)-2-(Methylthio)-1-phenyl-3-(4-phenyl benzoyl)pyrrole (3ee). Yellow crystalline solid, mp = 149–152 °C. R_f = 0.55 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.4 Hz, 2H), 7.59–7.36 (m, 12H), 7.25–7.21(m, 2H), 7.11 (s, 1H), 6.90–6.85 (m, 2H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 184.7, 166.5, 145.4, 140.0, 138.8, 137.1, 130.5, 129.2, 129.0, 128.8, 128.2, 128.0, 127.2, 126.7, 126.5, 125.2, 122.8, 115.4, 115.1, 20.7. IR (KBr) (ν_{max}/cm^{-1}): 2920, 1634, 1494, 1461, 1211. HRMS (EI) calcd for $C_{30}H_{22}FNOS$, *m*/*z*: 463.1406, found 463.1426 [M$^+$].

1,4-Diphenyl-2-(methylthio)-3-(2-furoyl)pyrrole (3fa). White crystalline solid, mp = 148–150 °C. R_f = 0.40 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.41 (m, 6H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.24–7.09 (m, 4H), 6.93 (d, *J* = 3.3 Hz, 1H), 6.34 (d, *J* = 1.8 Hz, 1H), 2.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.7, 153.4, 146.4, 138.8, 134.1, 129.0, 128.3, 128.2, 127.9, 127.4, 127.2, 126.5, 126.2, 126.0, 122.8, 119.8, 112.0, 111.9, 20.9. IR (KBr) (ν_{max}/cm^{-1}): 3116, 2917, 1633, 1492. HRMS (EI) calcd for $C_{22}H_{17}NO_2S$, *m*/*z*: 359.0980, found 359.0973 [M$^+$].

3-(2-Furoyl)-2-(methylthio)-1-phenyl-4-(*p*-tolyl)pyrrole (3fb). Yellow amorphous, mp = 127–129 °C. R_f = 0.42 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.44 (m, 6H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.06–7.01 (m, 3H), 6.93 (d, *J* = 3.0 Hz, 1H), 6.35 (dd, *J* = 1.8, 1.8 Hz, 1H), 2.27 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.8, 153.5, 146.3, 138.8, 135.8, 131.1, 129.0, 128.9, 128.1, 127.3, 126.9, 126.5, 125.9, 122.6, 119.8, 112.0, 111.9, 20.9. IR (KBr) (ν_{max}/cm^{-1}): 3099, 2972, 1656, 1442, 1202. HRMS (EI) calcd for $C_{23}H_{19}NO_2S$, *m*/*z*: 373.1136, found 373.1139 [M$^+$].

3-(2-Furoyl)-4-(4-methoxyphenyl)-2-(methylthio)-1-phenyl pyrrole (3fc). White solid, mp = 140–143 °C. R_f = 0.40 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.45 (m, 7H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 3.6 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.36 (dd, *J* = 1.65, 1.8 Hz, 1H), 3.75 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.8, 158.2, 153.5, 146.4, 138.8, 129.0, 128.6, 128.1, 126.7, 126.5, 125.6, 122.5, 122.4, 119.9, 113.8, 112.1, 112.0, 55.2, 20.9. IR (KBr) (ν_{max}/cm^{-1}): 3010, 2982, 1643, 1446, 1236. HRMS (EI) calcd for $C_{23}H_{19}NO_3S$, *m*/*z*: 389.1086, found 389.1076 [M$^+$].

3-(2-Furoyl)-2-(methylthio)-4-(4-nitrophenyl)-1-phenyl pyrrole (3fd). Brown solid, mp = 87–89 °C. R_f = 0.45 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.7 Hz, 2H), 7.51–7.43 (m, 9H), 7.04 (d, *J* = 3.3 Hz, 1H), 6.42 (d, *J* = 2.1 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.0, 153.2, 146.7, 145.9, 141.0, 138.2, 129.1, 128.7, 128.6, 127.5, 126.4, 124.0, 123.7, 120.0, 112.3, 20.6. IR (KBr) (ν_{max}/cm^{-1}): 3100, 2915, 1665, 1555, 1465, 1421, 1224. HRMS (EI) calcd for $C_{22}H_{16}N_2O_4S$, *m*/*z*: 404.0831, found 404.0830 [M$^+$].

1,4-Diphenyl-2-(methylthio)-3-(2-thienoyl)pyrrole (3ga). White crystalline solid, mp = 152–154 °C. R_f = 0.45 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.41 (m, 8H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.24–7.18 (m, 2H), 7.11 (s, 1H), 6.90 (m, 1H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.0, 145.6, 138.8, 134.9, 133.9, 129.0, 128.4, 128.1, 127.7, 127.5, 126.5, 126.3, 125.6, 122.8, 21.0. IR (KBr) (ν_{max}/cm^{-1}): 3082, 2916, 1616, 1488, 1465, 1405, 1279, 1229. HRMS (EI) calcd for $C_{22}H_{17}NOS_2$, *m*/*z*: 375.0752, found 375.0758 [M$^+$].

2-(Methylthio)-1-phenyl-3-(2-thienoyl)-4-(*p*-tolyl)pyrrole (3gb). White crystalline solid, mp = 157–159 °C. R_f = 0.40 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.53 (m, 5H), 7.51–7.46 (m, 2H), 7.25 (s, 1H), 7.13 (s, 1H), 7.06 (d, *J* = 8 Hz, 2H), 6.95 (dd, *J* = 4.8, 4.0 Hz, 1H), 2.28 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 145.7, 138.9, 136.0, 135.0, 134.0, 131.0, 129.2, 129.1, 128.9, 128.2, 127.9, 127.4, 126.6, 125.9, 125.6, 122.7, 22.7, 21.1. IR (KBr) (ν_{max}/cm^{-1}): 3077, 2914, 1617, 1495, 1406, 1230. HRMS (EI) calcd for $C_{23}H_{19}NOS_2$, *m*/*z*: 389.0908, found 389.0902 [M$^+$].

3-(4-Bromobenzoyl)-4-phenyl-2-(methylthio)-1-methylpyrrole (3ha). Brown sticky solid. R_f = 0.48 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, 2H, *J* = 8.4 Hz), 7.36 (d, 2H, *J* = 8.4), 7.13–7.08 (m, 5H), 6.92 (s, 1H), 3.80 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.8, 137.4, 134.1, 131.3, 131.1, 128.2, 127.7, 127.3, 126.1, 125.8, 122.4, 34.0, 21.0. HRMS (EI) calcd for $C_{19}H_{16}BrNOS$, *m*/*z*: 385.0136, found 386.0219 [(M + H)$^+$].

3-(3-Hydroxybenzoyl)-4-(4-methoxyphenyl)-2-(methylthio)-1-(*n*-butyl)pyrrole (3ic). Brown solid, mp = 114–116 °C. R_f = 0.60 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.13 (m, 2H), 7.00–6.98 (m, 3H), 6.79–6.74 (m, 2H), 6.60–6.57 (d, 2H, *J* = 8.7 Hz), 4.32 (s, 0.35H), 4.04 (2H, dd, *J* = 7.5, 7.2 Hz), 3.61 (s, 3H), 2.19(s, 3H), 1.73–1.71 (m, 2H), 1.37–1.18 (m, 2H), 0.93–0.80 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 157.9, 156.7, 155.7, 140.1, 132.1, 130.0, 129.0, 128.7, 127.0, 126.2, 125.7, 123.0, 122.3, 120.7, 119.9, 116.0, 114.4, 113.6, 55.1, 46.7, 33.6, 21.5, 19.9, 13.6, 0.9. HRMS (EI) calcd for $C_{23}H_{25}NO_3S$, *m*/*z*: 395.1555, found 418.1480 [(M + Na)$^+$].

3-Benzoyl-4-(4-methoxyphenyl)-2-(methylthio)-1-cyclohexyl pyrrole (3jc). Brown solid, mp = 111–113 °C. R_f = 0.60 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.76 (m, 2H), 7.40–7.35 (m, 1H), 7.27–7.22 (m, 2H), 7.11–7.08 (m, 2H), 6.94 (s, 1H), 6.66 (d, 2H, *J* = 8.1 Hz), 3.69 (s, 3H), 2.26 (s, 3H), 2.07–1.91 (m, 4H), 1.80–1.56 (m, 2H), 1.52–1.20 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.5, 157.8, 138.8, 132.2, 129.9, 128.8, 128.6, 127.8, 127.2, 126.9, 125.4, 124.8, 117.7, 117.6, 113.5, 55.3, 34.7, 25.8, 25.3, 21.7. HRMS (EI) calcd for $C_{25}H_{27}NO_2S$, *m*/*z*: 405.1762, found 428.1689 [(M + Na)$^+$].

4-(2-Ethynylphenyl)-2-(methylthio)-3-(4-methoxyphenyl)-1-phenylpyrrole (3cf). Yellow (crayola) sticky solid. R_f = 0.45 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 7.8 Hz, 2H), 7.42–6.94 (m, 10H), 6.65 (d, J = 7.8 Hz, 2H), 3.66 (s, 3H), 3.01 (s, 1H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9, 162.8, 138.8, 136.7, 133.3, 132.2, 131.3, 129.9, 129.5, 128.8, 128.4, 127.9, 126.4, 126.1, 126.0, 124.79, 124.72, 123.8, 120.2, 112.9, 112.8, 83.5, 80.4, 55.2, 20.7. IR (KBr) (ν_{max}/cm^{-1}): 3279, 2921, 1643, 1596, 1497, 1461, 1253. HRMS (EI) calcd for $C_{27}H_{21}NO_2S$, m/z: 423.1293, found 422.1182 [$(M - H)^+$].

4-(2-Ethynylphenyl)-2-(methylthio)-1-phenyl-3-(4-phenylbenzoyl)pyrrole (3ef). Yellow (crayola) sticky solid. R_f = 0.45 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.1 Hz, 2H), 7.51–7.27 (m, 14H), 7.16–7.09 (m, 2H), 7.01 (d, J = 7.2 Hz, 1H), 3.11 (s, 1H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.6, 144.5, 140.0, 138.8, 137.2, 136.8, 133.3, 130.5, 130.0, 129.2, 128.9, 128.8, 128.6, 128.5, 128.0, 127.8, 127.0, 126.4, 126.2, 126.1, 124.7, 124.2, 120.4, 83.5, 80.5, 20.7. IR (KBr) (ν_{max}/cm^{-1}): 3281, 3058, 2921, 1645, 1599, 1497, 1227. HRMS (ESI) calcd for $C_{32}H_{23}NOS$, m/z: 469.1500, found 470.1572 [$(M + H)^+$].

3-Benzoyl-4-((*E*)-(4-methoxystyryl))-2-(methylthio)-1-phenylpyrrole (3ag). Brown sticky solid. R_f = 0.45 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.5 Hz, 2H), 7.53–7.41 (m, 9H), 7.17 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 10.2 Hz, 2H), 3.74 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.8, 158.7, 139.2, 138.7, 132.5, 130.3, 129.9, 128.9, 128.1, 127.1, 127.0, 126.5, 123.7, 121.9, 118.1, 113.8, 55.1, 20.5. IR (KBr) (ν_{max}/cm^{-1}): 2921, 1596, 1509, 1249. MS calcd for $C_{27}H_{23}NO_2S$, m/z: 425.1449, found 424.1 [M^+].

4-(4-Methoxyphenyl)-5-methyl-2-(methylthio)-1-phenyl-3-(4-trifluoromethyl)pyrrole (3dh). Brown solid, mp = 164–166 °C. R_f = 0.55 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.1 Hz, 2H), 7.53–7.46 (m, 5H), 7.35 (d, J = 6.6 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 3.69 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6, 158.0, 141.8, 137.7, 133.6, 133.2, 132.8, 132.3, 130.7, 130.0, 129.9, 129.1, 128.7, 128.5, 126.7, 126.4, 125.5, 125.1, 124.6, 123.0, 113.5, 55.1, 21.1, 12.0. IR (KBr) (ν_{max}/cm^{-1}): 3058, 3043, 2921, 1643, 1557, 1482, 1386, 1212, 1172. HRMS (ESI) calcd for $C_{27}H_{22}F_3NO_2S$, m/z: 481.1323, found 481.1326 [$(M + Na)^+$].

3-(2-Furoyl)-4-(4-methoxyphenyl)-5-methyl-2-(methylthio)-1-phenylpyrrole (3fh). White solid, mp = 185–188 °C. R_f = 0.38 (19 : 1 hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.49 (m, 3H), 7.39 (dd, J = 8.4, 6.8 Hz, 3H), 7.18 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 3.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 2H), 6.35 (dd, J = 3.4, 1.6 Hz, 1H), 3.77 (s, 3H), 2.09 [s, 6H, {3H each of 5-methyl and 2-methylthio}]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.9, 157.8, 153.6, 146.1, 137.8, 130.5, 129.8, 129.1, 128.69, 128.64, 128.0, 127.2, 125.6, 122.3, 119.4, 113.6, 111.9, 55.2, 21.3, 12.2. IR (KBr) (ν_{max}/cm^{-1}): 2920, 1629, 1471, 1249. HRMS (EI) calcd for $C_{24}H_{21}NO_3S$, m/z: 403.1242, found 403.1250 [M^+].

Copies of ^{1}H, ^{13}C and MS/HRMS are listed in ESI.†

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